OPTIMIZING INVESTMENTS IN MOLDOVA'S TUBERCULOSIS RESPONSE

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Optima TB

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ABBREVIATIONS

AE	allocative efficiency
AIDS	acquired immune deficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral drug
DALY	disability-adjusted life year
DS	drug susceptible
ECA	Europe and Central Asia
EUR	Euro
FSW	female sex worker
GBD	global burden of disease
GDP	gross domestic product
GGHE	general government health expenditure
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IMF	International Monetary Fund
LPA	line probe assay
LRI	lower respiratory infection
LTBI	latent tuberculosis infection
MDG	Millennium Development Goals
MDR	multi-drug resistant
NASA	National AIDS Spending Assessment
NHA	national health accounts
NTD	neglected tropical disease
PLHIV	people living with HIV
PWID	people who inject drugs
SDG	sustainable development goals
STI	sexually transmitted infections
TB	tuberculosis
TST	tuberculin skin test
THE	total health expenditure
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNDP	United Nations Development Programme
UNGASS	United Nations General Assembly Special Session
USAID	United States Agency for International Development

WHO	World Health Organization
XDR	extensively drug resistant
YLL	years of life lost

KEY MESSAGES

Current TB interventions are projected to result in a continued steady decline in new TB infections by approximately 10% by 2035 while the number of active cases and TB-related deaths are projected to remain relatively steady over the same period. This allocative efficiency study identified how to best reallocate resources to accelerate the projected decline of the TB epidemic in Moldova by decreasing the average time to diagnosis and providing additional cost-effective treatment. The same budget available for TB-related activities in 2016 (17.5 million EUR) could – if optimally allocated – achieve the following, relative to 2016 values:

- reduce TB incidence by 5% by 2020 and by 20% by 2035,
- reduce TB prevalence by 10% by 2020 and by 50% by 2035,
- reduce TB-related deaths by 10% by 2020 and by 50% by 2035,

thereby accelerating progress towards the End TB Stategy targets. Although additional funding and new technologies will be needed to achieve global 2035 targets in Moldova.

Despite these improvements optimized allocation of current TB resources would be insufficient to achieve global TB targets set for 2035 and new technologies, as well as strategies to address latent TB, will be required to achieve 2035 targets.

To achieve optimized allocation of current TB resources, specific reallocations are required across TB interventions and modalities. Transitioning from hospital care to ambulatory care could reduce treatment cost by up to 24% and free up approximately 2.4 million EUR for reallocation towards higher impact interventions.

Resources freed up by changing treatment modalities should be invested in high-impact cost-effective interventions and delivery solutions. These include provision of incentives for providers of ambulatory TB care, procurement of new, more efficacious drug regimens for MDR-TB and XDR-TB, scale up of rapid molecular diagnostics, enhanced active case finding among high-risk populations and enhanced contact tracing.

Despite progress made in reducing TB incidence and deaths, Moldova's TB response continues to face challenges, particularly in relation to increases in drug resistant TB and relatively late diagnosis of active TB. This modeling study will demonstrate that a shift towards more active TB case finding could lead to earlier diagnoses.

EXECUTIVE SUMMARY

This report summarizes the findings of an allocative efficiency study of Moldova's Tuberculosis (TB) response, which was conducted in 2017 using the Optima TB model.

STATUS OF THE TB EPIDEMIC AND THE RESPONSE

Currently in Moldova most TB notifications are among people aged 18-64 years with specific risk groups including prisoners, migrants, and people coinfected with HIV. Importantly, most infections within the general population are sensitive to TB treatment. However, the incidence of MDR-TB has steadily increased from 2005 to 2012, where it appears to have stabilized; except among prisoners having increased prevalence of MDR-TB since 2015. While the exact number of latent-TB cases in Moldova is unknown, it appears that cases of latent TB may have decreased over time amongst the general population, but remained high amongst prisoners, migrants, and people living with HIV. Moldova has set ambitious targets within their 2016-2020 national TB strategy. These target are aligned with WHO End TB Strategy targets (WHO 2014). Targets to be achieved by 2020 include a 35% reduction in TB mortality, 20% reduction in TB incidence, reduction in HIV/TB co-infection rates to under 5%, and implementation of cost protection measures for patients and families to ensure costs borne for treatment are reduced by 50%.

Epidemic projections generated using the Optima TB model suggest that under current TB and HIV care coverage, TB-related deaths within the general population would gradually decline through to 2035 with the exception of increased active TB infections among migrants during the same period. Despite this decline, it was found that current resource and coverage levels will not be sufficient to meet national 2020 targets or international 2035 targets to reduce TB incidence and deaths, and to achieve successful treatment coverage levels.

ALTERNATIVE TB RESPONSE SCENARIOS

Mathematical modeling analyses suggest that alternative program scale up scenarios and different service delivery modalities could improve outcomes of the TB response:

- Meeting the care cascade targets and these sustaining achievements is projected to yield significant reductions in the total number of active TB cases of up to 45%. It is projected that substantial improvements would be made by improving linkage to treatment and improved adherence. Improvements in the treatment outcomes for MDR-TB cases is projected to yield the greatest impact, while an increase in linkage to care is estimated to significantly reduce the total number of both MDR-TB and XDR-TB cases.
- A shift from the current model of hospital-based care to a model of extended ambulatory care would reduce TB treatment cost by up to 24% (2.8 million EUR) with the same treatment outcomes. The largest relative proportion of this saving comes from MDR and XDR treatment programs which have the longest duration of treatment programs at a duration of 18-24 months.
- With the low treatment success rates for extensively drug resistant (XDR) TB in the most recently reported data, even increased diagnosis and treatment coverage for XDR-TB, would only lead to moderate reductions in XDR-TB. Improving treatment success rates

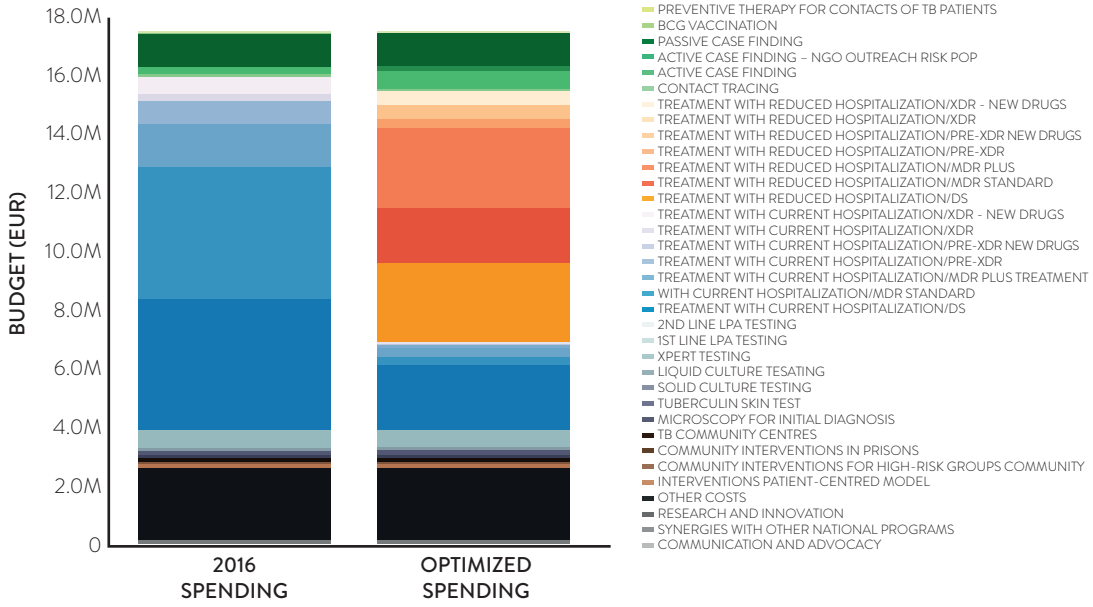
through the expanded introduction of new drugs such as bedaquiline (BDQ) is projected to have a greater impact in reducing the prevalence of active XDR-TB by 2035 compared to scale up with the drugs previously used.

- Current treatment failure rates are high, however reducing treatment failure rates due to lack of adherence and less than ideal treatment regimens could reduce treatment initiation for DS-TB by 170 cases per year and for DR-TB by 200 cases per year. This would result in a savings of 267,000 EUR from averted re-initiation for DS-TB cases and 1.6-1.8 million EUR from averted re-initiation in DR-TB cases annually.
- From this modelling study, migrants are the only population forecasted to increase in number of active-TB cases through to 2035 even with maintenance of 2016 resources and coverage levels of programs accessed by this population group. This is assuming that current trends in increasing numbers of migration continue. Scale up of testing and treatment for migrants is indicated for reducing the number of active TB-infections; however, these increases are estimated to be insufficient for reversing the projected increase in active-TB cases on their own.
- Improving links between HIV ART treatment and TB treatment leading to reaching 90-90-90 targets would result in reduced active TB prevalence of 30% and reduced TB-related deaths by 50% amongst people living with HIV.

OPTIMIZED ALLOCATIONS

Optimization analysis was carried out using a formal mathematical algorithm to establish, which mix of TB response interventions is expected to produce the largest reductions in TB incidence, prevalence and deaths. Figure ES.1 shows current allocations of resources and the optimized allocation of resources.

FIGURE ES.1 CURRENT AND OPTIMIZED TB RESOURCE ALLOCATIONS FOR MOLDOVA



Source: Populated using the Optima TB model for Moldova.

The optimized budget allocation differs from most recent allocations across several different areas including; shifts from hospital-focused towards ambulatory treatment modalities; introduction of new drug regimens for DR-TB including BDQ for pre-XDR and XDR; and increased funding towards active case finding programs.

Modelling shows that with the same amount of funding allocated optimally, it is possible to invest into cost effective treatment programs to increase coverage of the number of people treated for both DS-TB and DR-TB for less spending overall and allow for reinvestment of the remaining amount into testing programs to increase the number of notified cases and ensuring patient linkage into treatment.

Optimal allocation of funding could make further progress towards 2020 national strategy targets by reducing the total number of TB deaths by 10%, reducing new active TB infections by up to 5%, increasing MDR-TB treatment by up to 38%, and meet or exceed the targets for MDR-TB detection.

By 2035, if 2016 funding levels were optimally allocated the number of new active TB infections could be reduced by 20% and the number of TB-related deaths and the TB prevalence each by 50%.

Increases in resourcing alone are insufficient to reach the End TB 2035 targets.

CONCLUSIONS AND RECOMMENDATIONS

Based on the analyses conducted, nine conclusions and recommendations were formulated (see chapter 7 for details):

1. **Transitioning from hospital-focused to ambulatory treatment modalities** could reduce the cost of TB treatment by up to 24% and free up resources for reallocation to high-impact interventions.
2. **If 2016 funding levels are retained, allocation of resources to screening and diagnostic programs would need to increase by 25% to reduce late diagnoses of active TB.** Moldova's 43% late diagnosis rate indicates the need to identify new active cases earlier through active case finding methods.
3. Currently low treatment success rates are projected to lead to a 50% increase in XDR-TB by 2020. **Expanded application of new DR-TB drug regimens for pre-XDE and XDR TB could reduce active XDR-TB prevalence by 33% by 2035.**
4. Decreasing current rates of treatment failure and patient loss-to-follow up to 10% could save in treatment costs and avert TB-related deaths. **Current adherence support strategies, including patient incentives and psycho-social servies should be sustained and new approaches for improving adherence should be explored and impacts tracked to inform future decision making.**
5. There is a need to evaluate additional active case finding interventions within **prison populations.** Prisoners show higher levels of latent prevalence but better treatment outcomes than the general population which indicates that early diagnosis could successfully prevent transmission.
6. Migrants are the only population currently projected to have increasing levels of active-TB should current migration trends continue. **Innovative interventions targeted towards migrant populations should be considered to directly address TB infection rates amongst migrant populations.**
7. **Enhanced integration of TB programs with other health programs would improve health outcomes for TB patients.** Interventions such as alcohol screening and support services and programs designed for at-risk populations, including ART adherence programs for HIV+ populations would reduce TB incidence and TB-related deaths.
8. Further exploration of the geographic, social, economic and other risk factors underlying Moldova's TB epidemic is needed to understand and focus on key risk groups.
9. **Moldova should sustain current TB investment and consider a phased approach towards achieving a sustainable and largely domestically financed TB response.**

1. INTRODUCTION: WHY ALLOCATIVE EFFICIENCY ANALYSIS NOW?

1.1 NECESSITY FOR ALLOCATIVE EFFICIENCY

Adoption of the sustainable development goals (SDGs) agenda (UNGASS 2015) and the World Health Organization's End TB Strategy (WHO 2015a) have introduced a new era for national TB responses. While the Millennium Development Goals (MDGs) had aimed to halt and reverse the epidemics of HIV, tuberculosis (TB) and malaria, the SDG agenda sets out a more ambitious pathway towards ending TB (Lönnroth 2016). This has been translated into ambitious targets of reducing TB incidence by 80% (or to less than 20/100,000) and TB-related deaths by 90% by 2030. The WHO End TB strategy has set additional targets with a longer time frame of 2035 aiming for a 90% reduction in TB incidence (or <10/100,000) and a 95% reduction in TB-related deaths.

The 2015 WHO Global TB report (WHO 2015b) demonstrated that TB responses needed to be scaled-up if these targets were to be achieved. The decline in global TB incidence was negligible (then estimated at only 1.5% annually), despite doubled TB funding in 2015 compared to 2006. It was also reported that there were now more global TB-related deaths than AIDS deaths, and that there was a large gap between knowledge of what works and implementation of effective programmes.

These new international frameworks have highlighted the need for national TB responses to scale up programs for screening, diagnosis and treatment to achieve substantially higher coverage and treatment success rates than in the past. Since the majority of TB epidemics affect low- and middle-income countries, national TB responses are commonly faced with resource constraints. While enhanced domestic and international resource mobilization for health continues to be desirable, international assistance for disease response programs has stagnated and domestic financing remains constrained by competing health, social and other financing priorities. Focused design and efficiency in TB program delivery and implementation efficiencies are therefore essential to ensure that national programs can do more with available heath funding.

There is wide consensus that better outcomes could be achieved in many settings with a given amount of TB funding; or that given outcomes could be achieved with less TB funding if resources are distributed optimally or if resources are used most efficiently. Mathematical modelling is one way to estimate the optimized TB resource allocation and assist national program partners on the best ways to reach their health goals with the funding that is available.

2. REPORT METHODOLOGY

WHAT ARE THE KEY QUESTIONS AND HOW WILL THIS REPORT ANSWER THEM?

This section outlines the main steps taken and tools applied to carry out the analyses presented in this report. Additional details are available in appendices A and B.
To support the national strategy priorities and assist Moldova in meeting its set targets, this report answers the following questions:

1. **What is the estimated future trend of Moldova's TB response?**
2. **How could different program implementation scenarios affect Moldova's future TB epidemic?**
    - How will the trajectory of Moldova's TB epidemic change through achieving program specific targets through implementation of the following programs?
        - Treatment scale-up related to missing cases
        - Hospital-focused vs. ambulatory treatment
        - Enhanced XDR treatment
        - Different case finding modalities
        - Adherence targets
3. **What is the impact of optimized TB spending during the current national strategy from 2018 to 2020 and up to 2035?**
4. **What is the effect of different levels of TB spending on the achievement of targets?**
    - What would be the effect of reduced or increased TB spending on TB incidence, deaths and prevalence if most recently reported resources were allocated optimally?
        - With reduced funding to 50-90% of 2016 TB spending
        - With increased funding to 110-120% of 2016 TB spending

2.1 OPTIMA TB MODEL

Optima TB, a mathematical model of TB transmission and disease progression integrated with an economic and program analysis framework was used to carry out the analyses. Optima TB incorporates evidence on biological transmission probabilities, detailed infection progression and population mixing patterns, within a compartmental model that disaggregates populations into different compartments including *susceptible, vaccinated, early latent (infection <5 years), late latent (infection >5 years), undiagnosed active TB, diagnosed active TB, on treatment and recovered* populations. Compartments are further disaggregated by TB drug resistance types including drug susceptible (DS), multi-drug resistant (MDR) and extensively drug resistant (XDR) TB. A more detailed illustration of the compartmental model structure is included in appendix A.

To assess how incremental changes in spending affects the TB epidemic in a given context and to estimate the optimized funding allocation, the model parameterizes relationships between the cost of TB intervention programs, the coverage level attained by these programs, and the resulting outcomes, known as cost functions. Cost functions are specific to the country, population, and intervention program being considered.

Using cost functions coupled with the epidemic module of the Optima TB model, it is possible to determine how incremental changes in the level of funding allocated to each program will impact the overall epidemic outcomes. Furthermore, a unique feature of the Optima TB model is the optimization algorithm, which allows determination of the optimized allocation of funding across different TB programs. Additional details about the Optima TB model are included in appendices A and B.

2.2 ANALYTICAL FRAMEWORK

The Republic of Moldova engaged the Optima Consortium for Decision Science, in partnership with the World Bank, to carry out an Optima TB study. An in-country group was formed involving TB Institute/ NTP, PR Center PAS, PR UCIMP, SDC and Ministry of Health, Moldova. Country-specific objectives of the analysis and parameters were outlined in a Scope of Work document. Epidemiological, program, and cost data were collected by in-country experts in collaboration with international experts using an adapted MS-Excel-based Optima data entry spreadsheet. 2016 expenditure data was provided. This data was triangulated with other unit cost data to establish estimated TB spending by intervention. Input data, model calibration and cost-coverage-outcome relations were reviewed and validated by the in-country group. The team then consulted with other in-country partners on the preliminary results, as summarized in this report.

TABLE 2.1 MODEL PARAMETERS

CATEGORY	PARAMETERIZATION IN THE OPTIMA MODEL	DESCRIPTION/ASSUMPTIONS
Populations defined in the model	1. General population (0-4 years) 2. General population (5-14 years) 3. General population (15- 17 years) 4. General population (18-64 years) 5. General population (65+) 6. PLHIV (18+) 7. Prisoners (15+) 8. Migrants (all ages)	1. Male and Female Children aged 0-4 2. Male and Female Young Population aged 5-14 3. Male and Female Adult Population aged 15-17 4. Male and Female Adult Population aged 18-64 5. Male and Female Elderly Population aged 65+ 6. Males and Females aged 18+ living with HIV 7. Male and Female prison populations aged 15+ Assumed to be equivalent to the total national prison population 8. Male and Female migrants* all ages
Program expenditure areas defined in the model and included in optimization analysis	1. BCG Vaccination 2. Preventive therapy for contacts of TB patients 3. Preventive therapy for HIV positive individuals 4. Contact tracing 5. Active case finding 6. Active case finding - NGO outreach for high-risk populations 7. Passive case finding	1. Vaccination with Bacillus Calmette-Guérin targeting the 0-4 population 2. Preventive therapy for contacts of TB patients 3. Preventive therapy for HIV positive individuals 4. Investigation and testing of TB-contacts 5. Active case-finding by targeted screening of high-risk groups with chest X-rays 6. Active case-finding by targeted screening and selective testing of high-risk groups via outreach conducted by non-governmental organizations 7. Diagnosis package for people who present to the health facility with symptoms; includes a Chest X-ray, X-pert, two Sputum Smear Microscopies and two Culture tests or culture couple with LPA

CATEGORY	PARAMETERIZATION IN THE OPTIMA MODEL	DESCRIPTION/ASSUMPTIONS
Program expenditure areas defined in the model and included in optimization analysis	8. Enhanced contact tracing 9. Enhanced active case finding 10. Treatment with current hospitalization DS MDR standard MDR plus[1] Pre-XDR Pre-XDR new drugs XDR XDR new drugs 11. Treatment with reduced hospitalization DS MDR standard MDR plus Pre-XDR Pre-XDR new drugs XDR XDR new drugs	8. Enhanced contact tracing 9. Enhanced active case finding 10. Current treatment delivery implemented in Moldova including the current number of hospitalization days for each specific drug regimen targeted at each type of DS/MDR/XDR-TB 11. WHO recommended outpatient service delivery, with a reduced number of days hospitalized. Hospital based only during the intensive phase of a given regimen or until smear conversion. Specified as separate programs for each specific drug regimen targeted at each type of DS/MDR/XDR-TB.
Expenditure areas not optimized	The components of TB spending that will not be included in the optimization analysis include: 1. Prisoner screening 2. Microscopy for initial diagnosis 3. Tuberculin skin test 4. Solid culture testing 5. Liquid culture testing 6. GeneXpert testing 7. LPA testing • First Line • Second Line 8. Community interventions patient-centred model 9. Community interventions for high-risk groups 10. Community interventions in prisons 11. TB community centres 12. Communication & advocacy 13. Synergies with other national programs 14. Research & innovation 15. Other costs	Non-targeted program costs, also called enablers and synergies, have not been optimized (as they either do not have measurable epidemic impact or are components of another program) but instead were fixed agreed amounts. This was done for different reasons including either due to a program's effect on TB incidence, morbidity or mortality is not clear, or because the expenditure is central systems expenditure that is essential for several program areas, or because no country data to estimate effects was available. 1. Prisoner screening 2. Microscopy for initial diagnosis 3. Cost of conducting TST test to diagnose LTBI 4. Cost of solid culture testing to identify and confirm resistance types of MDR-TB and XDR-TB 5. Liquid culture testing 6. GeneXpert testing 7. Cost of LPA testing to identify and confirm resistance types of MDR-TB and XDR-TB 8. Community interventions patient-centered model 9. Community interventions for high-risk groups 10. Community interventions in prisons 11. TB community centers 12. Communication & advocacy 13. Synergies with other national programs 14. Research & innovation 15. Other costs

CATEGORY	PARAMETERIZATION IN THE OPTIMA MODEL	DESCRIPTION/ASSUMPTIONS
Timeframes over which the optimization was considered	2000 – starting year for data entry 2018-2020 (government's timeline for achievements of national strategic plan targets) 2025/2035 (interim accelerated and standard timeline for international targets set by End TB Strategy) 2030 (new Stop TB horizon for ending TB)	
Baseline scenario funding	Based on a combination of sources	Sources include WHO databases and reports, national TB reports for the WHO and MoH, and NTP records.

**Migrants are defined as people who have previously spent at least 3 months in a foreign country during any 12-month period*

1 MDR plus is treatment with re-purposed medications such as Linezolid (LNZ), IMEPINEM,/Cilastatin, and Amoxicillin/Clavulanic acid

Calibrations and cost functions were produced in collaboration with national experts and are further explained in appendix B, while unit costs are included in appendix C.

2.3 NATIONAL TARGETS AND HOW THEY WERE TRANSLATED IN OPTIMA

The strategic goals under the National Tuberculosis Plan (NTP) 2016-2020 include: (i) reduce TB mortality by 35%; (ii) decrease TB incidence by 25%; (iii) reduce HIV co-infection rates amongst TB cases to under 5%; (iv) implement cost protection programs that will reduce related costs borne by affected families by 50%; (v) achieve TB detection rate of more than 85% amongst MDR-TB cases; (vi) achieve more than 85% treatment success rates among new cases of bacteriologically confirmed pulmonary TB; (vii) achieve more than 75% treatment success rates amongst MDR-TB cases; (viii) provide for integrated patient-centered health care services to improve adherence to therapy and (ix) provide for program sustainability including capacity building for efficient program management.

We examined of long-term trends by comparing against global targets including 2025 milestones, 2030 SDG goals and 2035 End TB Strategy targets.

INDICATOR	BASELINE VALUE	2020 (NTP TARGET)	2025 (END TB TARGET)	2030 (SDG TARGET)	2035 (END TB TARGET)
Reduction in TB-related deaths	11 in 100,000	35%	75%	90%	95%
Reduction in TB incidence rate (per 100,000)	90 in 100,000	25%	50%	80%	90%
Reduction in number of MDR-TB notifications	892	797	30%	50%	75%
Treatment success rate among MDR-TB patients	50%	75%	80%	85%	90%

2.4 LIMITATIONS OF THE ANALYSIS

As for any mathematical modeling analysis, this study is based on a number of assumptions, which necessarily imply specific limitations:

- As for all complex modelling studies of diseases, there are some gaps in data. As such, assumptions surrounding estimation of the population size for undiagnosed populations were necessary.
- Unlike HIV, no standardized national TB spending assessments are undertaken in countries. Moreover, current templates for national health accounts including TB sub-accounts do not provide sufficiently detailed breakdowns of costs by intervention area. As noted above, estimations of TB spending had to be made based on unit costs derived from program records.
- In particular, prospective unit costs for treatment of multi-drug resistant TB with Bedaquiline (BDQ) were based on the supply costs in European countries, but there is considerable uncertainty surrounding future procurement and the associated cost per person reached with the BDQ regimen for Moldova. Any changes in this or other unit costs will have a meaningful impact on the allocation projections.
- The modelling approach used to calculate relative cost-effectiveness among programs includes assumptions concerning the impact of increases or decreases in funding for programs. These assumptions are partially based on cost per person reached and observed relationships among outcomes of program coverage and the amount of money spent on programs in the past or in other contexts
- The analysis did not determine the implementation efficiency of several programs. Gains in implementation efficiency were mainly considered when analysing delivery models for TB treatment. Actualization of additional implementation efficiencies, such as reductions in drug prices, could result in different unit costs, which would affect optimal resource allocation predictions.
- Modelling the optimization of allocative efficiencies depends critically on the availability of evidence-based parameter estimates of the effectiveness of individual interventions. Although these estimates were derived from a global systematic literature review, they may vary in specific countries and populations depending on various factors; in particular the quality of implementation and levels of adherence to interventions. Programs and spending categories for which such parameters could not be obtained were not included within the mathematical optimization. Because these programs are still important to the TB response, they were treated as fixed costs and, in some specific scenarios, adjusted with specific justifications.
- Effects outside the TB endpoints are complex to consider (such as non-TB health benefits and non-health benefits of different TB treatment modalities). Given the complexity of interactions among interventions and their non-TB benefits the model does not seek to consider 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.
- Migration and TB rates amongst migrant populations are of concern in Moldova. The model is not structured to predict migration trends, which are dependent on a variety of domestic and international geo-political factors. Assumptions regarding the continuation of current migration trends were made based on available trend data to estimate future impacts related to this group.
- Latent TB infection is of concern in Moldova. While there have been some domestic studies done to estimate latent TB rates, these studies had relatively small sample sizes. Modelling was conducted using observed active TB rates that aligned with small scale domestic studies.

3. WHAT ARE THE CURRENT TRENDS OF THE TB EPIDEMIC?

Chapter 3 summarizes the status of the TB epidemic in Moldova. The model assumed that current conditions would continue until 2018, i.e. that the coverage of individual interventions would remain constant.

3.1 SUMMARY OF KEY NATIONAL DATA AND ESTIMATES ON THE STATUS OF THE TB EPIDEMIC

As shown in Table 3.1, WHO estimated that 4,134 incident TB infections (including both new and relapse as well as HIV+TB) and an estimated 320 TB related deaths occurred in Moldova in 2016. (WHO 2017)

TABLE 3.1 KEY TB EPIDEMIOLOGICAL DATA FOR MOLDOVA, 2016

ESTIMATES OF TB BURDEN, 2016	NUMBER (THOUSANDS)		RATE (PER 100 000 POPULATION)	
Mortality (excludes HIV+TB)	0.26	(0.24–0.27)	6.3	(5.9-6.7)
Mortality (HIV+TB only)	0.06	(0.046-0.08)	1.5	(1.1-2)
Incidence (includes HIV+TB)	4.1	(3.5–4.7)	101	(87–117)
Incidence (HIV+TB only)	0.37	(0.31–0.43)	9.2	(7.8-11)
Incidence (MDR/RR-TB)	2.3	(1.9-2.6)	56	(47-65)

ESTIMATED TB INCIDENCE BY AGE AND SEX (THOUSANDS), 2016						
	0-14 YEARS		> 14 YEARS		TOTAL	
Females	0.19	(0.16–0.23)	1	(0.86–1.2)	1.2	(1–1.4)
Males	0.21	(0.18–0.25)	2.7	(2.3–3.1)	2.9	(2.5–3.3)
Total	0.4	(0.34–0.46)	3.7	(3.1–4.3)	4.1	(3.3–4.7)

TB CASE NOTIFICATIONS, 2016	
Total cases notified	4,134
Total new and relapse	3,571
% tested with rapid diagnostics at time of diagnosis	51%
% with known HIV status	94%
% pulmonary	91%
% bacteriologically confirmed among pulmonary	62%

Source: Prepared based on WHO TB epidemic profile for 2016 (WHO 2017b)

Moldova recorded 4,134 total notified TB cases in 2016, of which 3,571 were new and relapse cases. Among notified TB cases, 51% were tested using rapid molecular diagnostics at the time of diagnosis and 94% were tested for HIV. Overall, 91% of notified cases were pulmonary TB cases, among which 62% were bacteriologically confirmed.

AN EPIDEMIC HIGHLY AFFECTING MEN

Approximately 66% of incident TB cases are estimated to occur among males 15 and older, with 24% in females 15 and older and 10% in children (similar across both genders) (WHO 2017). The sex-disaggregated data suggests that there are specific risk factors among men causing increased incidence of active TB. These are likely to include higher use of alcohol, higher HIV prevalence, higher drug use, higher likelihood of imprisonment and potentially a range of other factors.

HIGH LEVELS OF DRUG RESISTANCE

Moldova experiences high levels of TB drug resistance. In 2016, there were 1,400 MDR/RR-TB cases among notified TB cases and MDR/RR-TB cases represented 26% of new cases and 56% of previously treated cases. In the same year, 58% of new cases and 65% of previously treated cases were tested for rifampicin resistance (WHO 2017) . Within the 1,400 notified MDR-TB cases in 2016, 862 were tested for resistance to second-line drugs and 72 were confirmed as XDR-TB.

TABLE 3.2 DRUG RESISTANCE STATUS

DRUG-RESISTANT TB CARE, 2016	NEW CASES	PREVIOUSLY TREATED CASES	TOTAL NUMBER
Estimated MDR/RR-TB cases among notified pulmonary TB cases		1,400 (1,300–1,400)	
Estimated % of TB cases with MDR/RR-TB	26% (24–28)	56% (51–60)	
% notified tested for rifampicin resistance	58%	65%	2,491
MDR/RR-TB cases tested for resistance to second-line drugs			862

Source: Prepared based on WHO TB epidemic profile for 2016 (WHO 2017b)

LARGE VARIATION IN TREATMENT OUTCOMES

Moldova has relatively high diagnosis with 87% of the estimated incident TB cases being diagnosed in 2016 (Table 3.3) and a number of notifications (including retreatment) approximately equal to the number of estimated incidence cases. Based on WHO's global TB database (WHO 2017) a summary of the TB cascade was prepared for 2016 (Figure 3.1 a). Additional analysis based on the WHO database is presented for specific TB treatment cohorts. These TB treatment cohort cascades use the people initiated on treatment as the denominator.

When considering new and relapse TB cases, the losses in the TB cascade from initiation of treatment to completion are 20% and attributable to a combination of loss-to-follow up, death, treatment failure and lack of evaluation (Figure 3.1 b) leading to a treatment success rate of 80%.

Among TB patients with known HIV status 9% were HIV positive and 66% on antiretroviral therapy in 2016. An analysis of the TB treatment cohort cascade for 2015 suggests that treatment outcomes for HIV positive patients were substantially less favourable than for HIV negative TB patients with a success rate of 55% and death being the largest breakpoint in the treatment cohort cascade. (Figure 3.1c)

Among people with MDR-TB, there are major losses in the TB-treatment cohort cascade. Reported data suggest that loss-to-follow up, death and treatment failure are major breakpoints in the cascade, which contributed to a treatment success rate of 50% in 2014. (Figure 3.1d)

The treatment cohort cascade for XDR-TB for 2014 was based on a very small sample of nine people, of whom three were successfully treated (Figure 3.1e).

TABLE 3.3 KEY TREATMENT INDICATORS

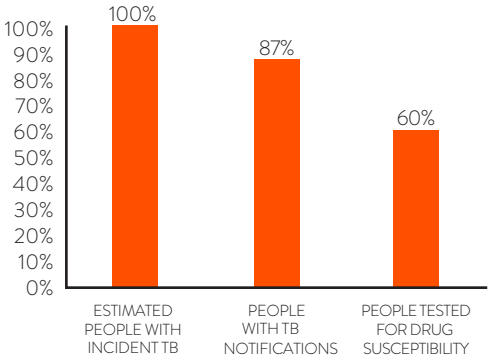
UNIVERSAL HEALTH COVERAGE AND SOCIAL PROTECTION			
TB treatment coverage (notified/estimated incidence), 2016		87% (75%–100%)	
TB case fatality ratio (estimated mortality/estimated incidence), 2016		0.08 (0.07–0.09)	
TB/HIV CARE IN NEW AND RELAPSE TB PATIENTS, 2016		**NUMBER**	**PERCENT**
Patients with known HIV-status who are HIV-positive		293	
On antiretroviral therapy		193	66%
Laboratory-confirmed cases		MDR/RR-TB: 1 031, XDR-TB: 72	9%
People started on treatment*		MDR/RR-TB: 1 037, XDR-TB: 67	
TREATMENT SUCCESS RATE AND COHORT SIZE		**SUCCESS RATE**	**COHORT SIZE (N)**
New and relapse cases registered in 2015		80%	2,992
Previously treated cases, excluding relapse, registered in 2015		47%	217
HIV-positive TB cases, all types, registered in 2015		55%	227
MDR/RR-TB cases started on second-line treatment in 2014		50%	919
XDR-TB cases started on second-line treatment in 2014		33%	9
TB PREVENTIVE TREATMENT, 2016			**PERCENT**
% of HIV-positives (newly enrolled in care) on preventive treatment			0%
% of children (aged < 5 years) household contacts of bacteriologically-confirmed TB cases on preventive treatment			0%

*Including patients diagnosed before 2016 and patients who were not laboratory-confirmed

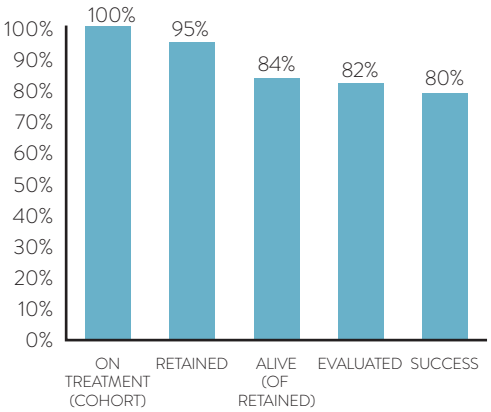
Source: Prepared based on WHO TB epidemic profile for 2016 (WHO 2017)

FIGURE 3.1 TB TREATMENT CASCADE AND TREATMENT COHORT CASCADES FOR MOLDOVA

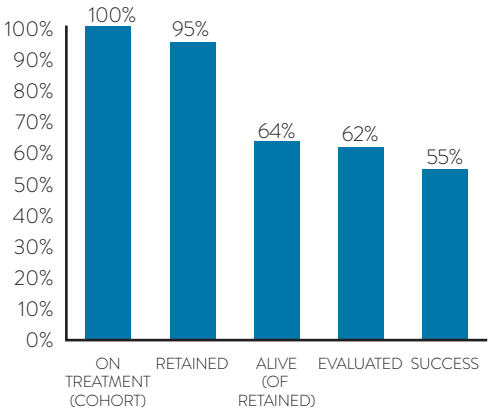
a) TB care cascade of all incident cases (new and relapse cases), first part from infection to diagnosis 2015. The 60% of people tested for drug susceptibility among estimated people with incident TB reflects 58% of new cases and 65% of previously treated cases being tested for rifampicin resistance (WHO 2017), including all patients with positive culture results (country reported).



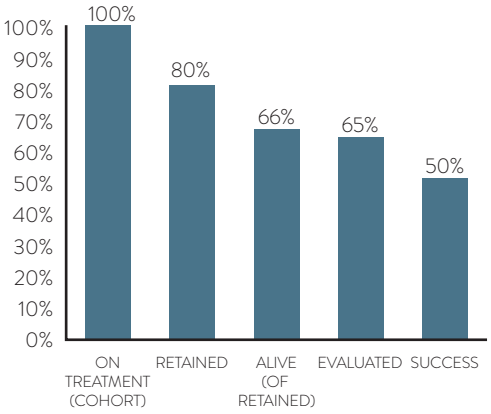
b) TB Treatment cohort (n=2992) cascade, all new and relapse cases, 2015



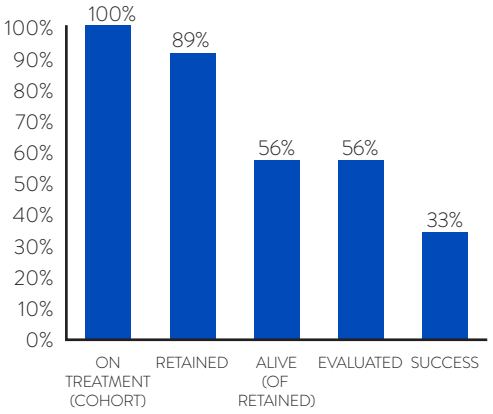
c) TB Treatment cohort (n=227) cascade, PLHIV, 2015



d) TB Treatment cohort (n=919) cascade, MDR-TB, 2014



e) TB Treatment cohort (n=9) cascade, XDR-TB, 2014



Source: Prepared by authors based on WHO global TB database (WHO 2018)

3.2 EPIDEMIC TRENDS ESTIMATED USING OPTIMA TB

The Optima TB model was used to estimate trends of TB prevalence, incidence and mortality in Moldova. Estimates were made based on detailed epidemiological and program data received, which are summarized in the appendix B of this report.

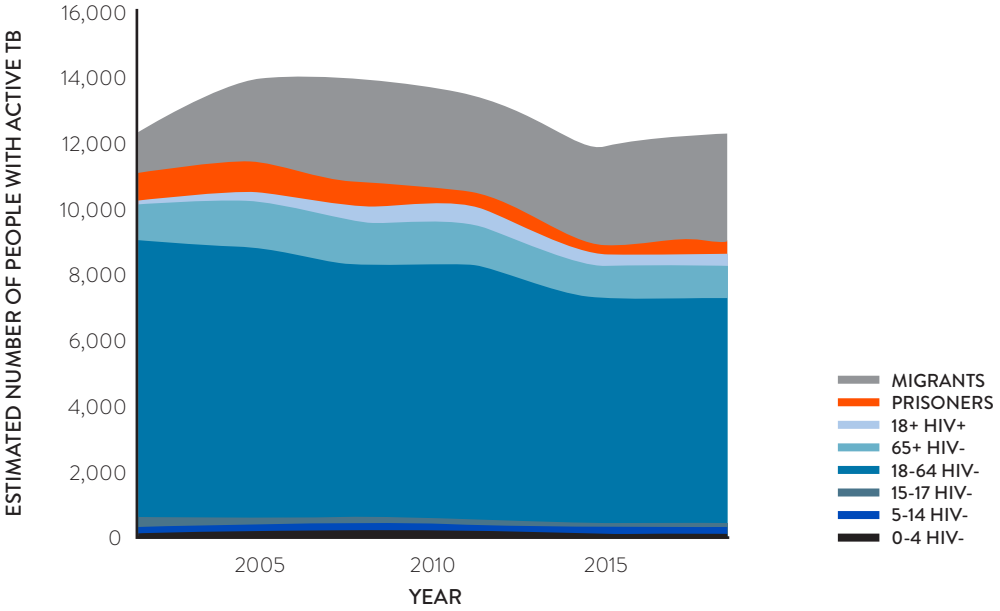
THE PREVALENCE OF ACTIVE TB REMAINED STEADY SINCE 2000

Optima TB results suggest that the number of active TB cases across the entire population peaked from 2005 to 2007 and has been gently declining until 2016. Within specific populations, active TB cases have been decreasing in the general population aged 18-64 years without HIV and decreasing in the prisoner population, but this has been balanced by an increase in the cases of active TB among the growing populations of people living with HIV and migrants (Figure 3.2). The epidemic trend with a declining number of new infections is in line with reported notifications which peaked in 2007 and have been declining until the present (Figure 3.3).

While drug-resistant types of TB were at very low levels prior to 2002, the MDR-TB epidemic showed a steady increase from 2005 to 2012, which appears to have stabilized at just over 30% of all active TB cases (Figure 3.4) including the very small proportion of XDR-TB cases.

The overall trend in the estimated number of people with active TB in Moldova decreased from approximately 14,000 active cases in 2004 to 12,000 in 2014. From 2015 it was estimated that there was a rebound in active cases up to approximately 12,500 in 2018. From this analyses, general population adults aged 18 to 64 years represent the majority of active cases, exhibiting a gradual and mostly steady decline in the active cases from 9,000 cases estimated in 2000 to 7,000 in 2018. This is not surprising as this population represents 52% of the total population. There was with a slight leveling of cases in the population group from 2015 to 2018. Migrants represented approximately 25% of the total estimated active TB cases since around 2005 after seeing a rise in cases from 2000 to 2005. In 2018 there were an estimated 3,500 active TB cases among migrants.

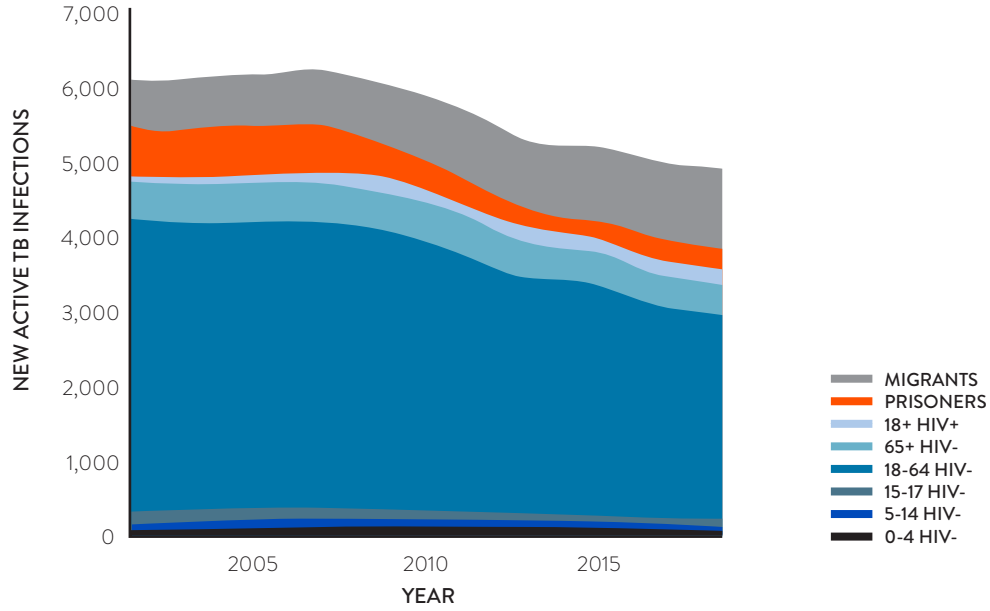
FIGURE 3.2 TRENDS IN THE ESTIMATED NUMBER OF PEOPLE WITH ACTIVE TB IN MOLDOVA BY POPULATION, 2002–2018



Source: Populated using the Optima TB model for Moldova

Overall, the estimated number of new active TB infections have been declining in Moldova since 2005. With approximately 6,400 new active infections in 2006 to 5,000 in 2018. As with active cases, the majority of active infections were estimated to be among the largest group by population, adults aged 18 to 64 years of age. The number of active infections among prisoners have declined since 2003; with approximately 730 new infections in 2003, to 270 in 2018. Migrants also account for a large proportion of new TB infections, with an increase in infections from 2003 (650 new TB infections) through to 2018 (1,100 new infections).

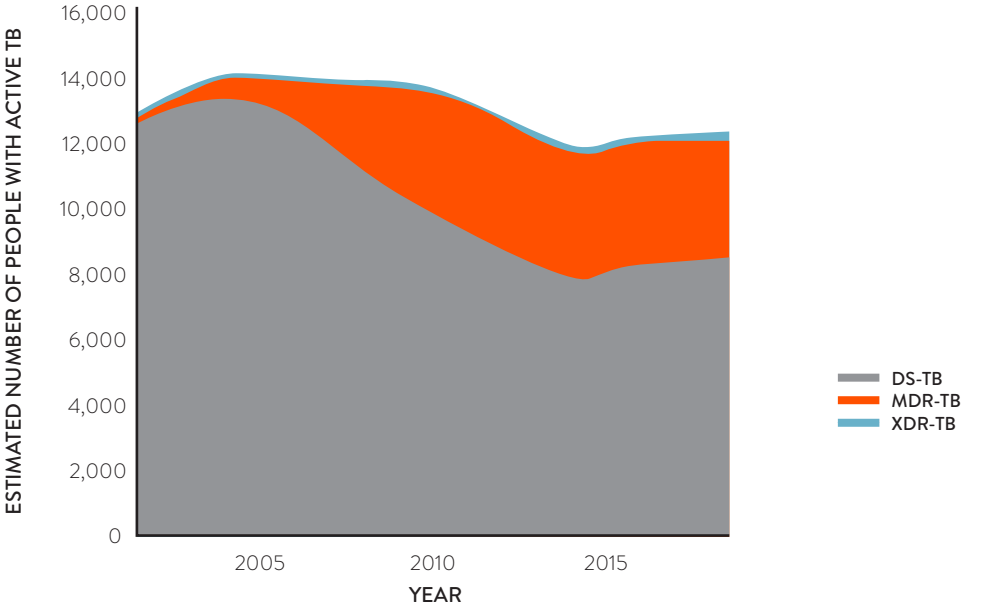
FIGURE 3.3 TRENDS IN THE ESTIMATED NUMBER OF NEW ACTIVE TB CASES IN MOLDOVA BY POPULATION, 2002–2018



Source: Populated using the Optima TB model for Moldova

In 2000 it was estimated that DR-TB represented less than 1% of all active TB cases; in contrast prevalence grew to 31% (3,800 DR-TB active cases) by 2018. The largest proportion of DR-TB are MDR-TB. It was estimated that the prevalence of active MDR-TB cases have been dramatically increasing in Moldova from 1,100 in 2005 to 3,900 in 2011 with stabilization to 3,600 in 2018. The number of XDR-TB cases is small but has risen from just 10 in 2006 to 180 in 2018.

FIGURE 3.4 TRENDS IN THE ESTIMATED NUMBER OF PEOPLE WITH ACTIVE TB IN MOLDOVA BY DRUG RESISTANCE TYPE, 2002–2018



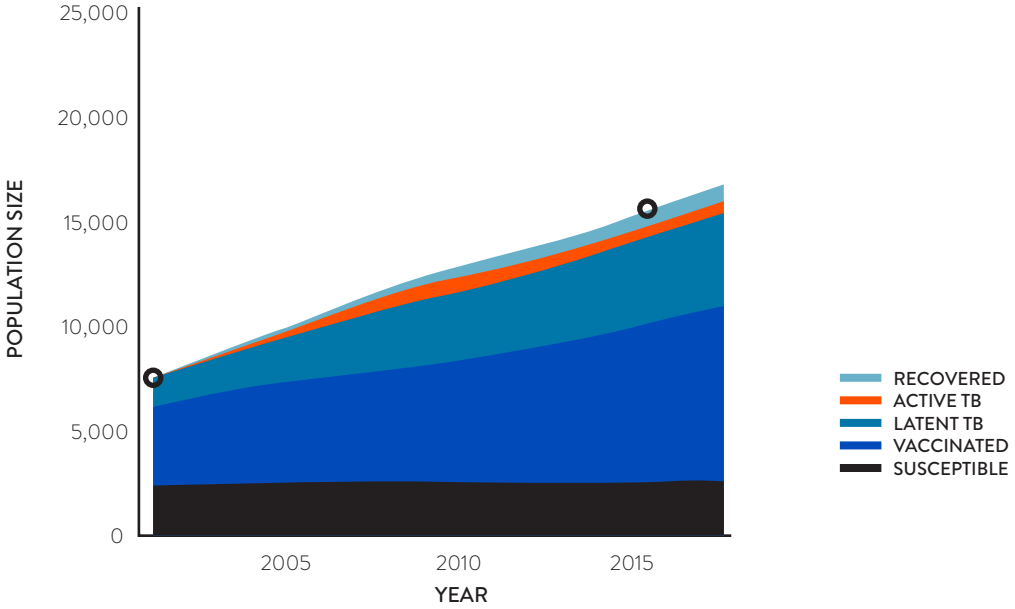
Source: Populated using the Optima TB model for Moldova

AN INCREASING CONTRIBUTION OF HIV TO THE TB EPIDEMIC

While the prevalence of TB has remained relatively steady between 2000 and 2016, Moldova's HIV epidemic has approximately doubled over the same period from an estimated 7,500 people living with HIV in 2000 to over 15,000 in 2015, although significant uncertainty exists over these figures (UNAIDS 2016). Figure 3.5 illustrates the growing number of PLHIV in Moldova by TB disease status. Optima projections suggest that the proportion of people with active TB who are HIV positive increased from less than 2% of people with active TB in 2000 to approximately 4% in 2016 and this proportion will continue increasing in the future.

It is estimated that 48% of PLHIV with active TB as of 2016 have a drug resistant type, compared with 30% in the entire population (Figure 3.6). The estimated number of people living with HIV co-infected with TB was shown to increase from under 200 in 2000 to 500 in 2018. The prevalence of active TB cases among PLHIV peaked at 5% in 2008 and in 2018 is 3%.

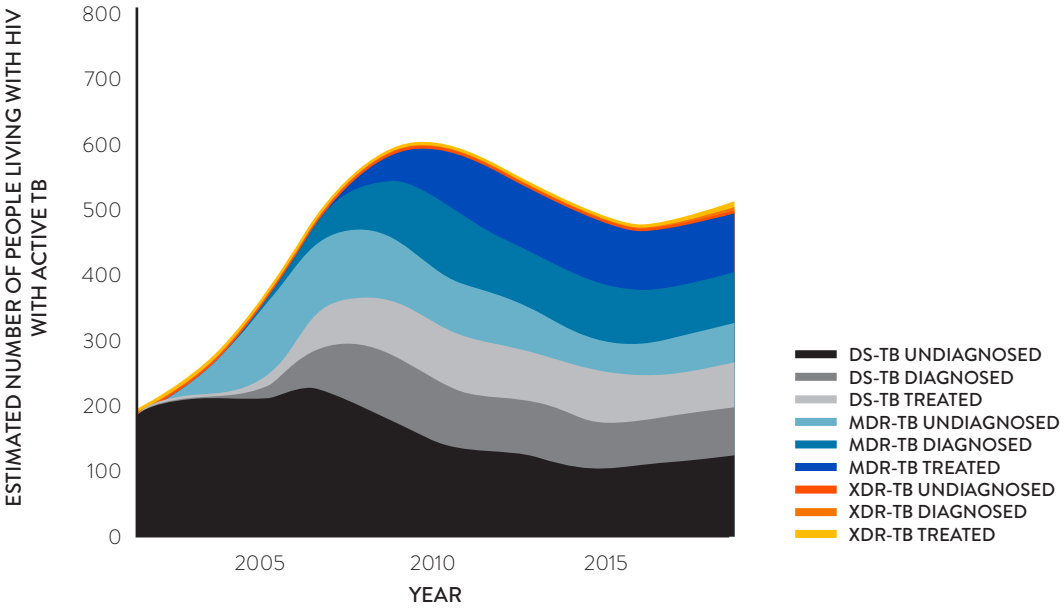
FIGURE 3.5 PEOPLE LIVING WITH HIV BY TB DISEASE STATUS IN MOLDOVA, 2000–2018



Source: Populated using the Optima TB model for Moldova

In 2016 approximately half of the 500 PLHIV with active TB cases were drug-resistant. This is a dramatic increase from the estimated 200 people co-infected with HIV-TB in 2000 (less than 1% were estimated to be drug-sensitive) and the 350 people co-infected with HIV-TB in 2005 among whom 33% were estimated to be drug-sensitive, but undiagnosed.

FIGURE 3.6 ESTIMATED NUMBER OF PEOPLE LIVING WITH HIV WHO HAVE ACTIVE TB IN MOLDOVA BY DRUG RESISTANCE TYPE, 2002–2018



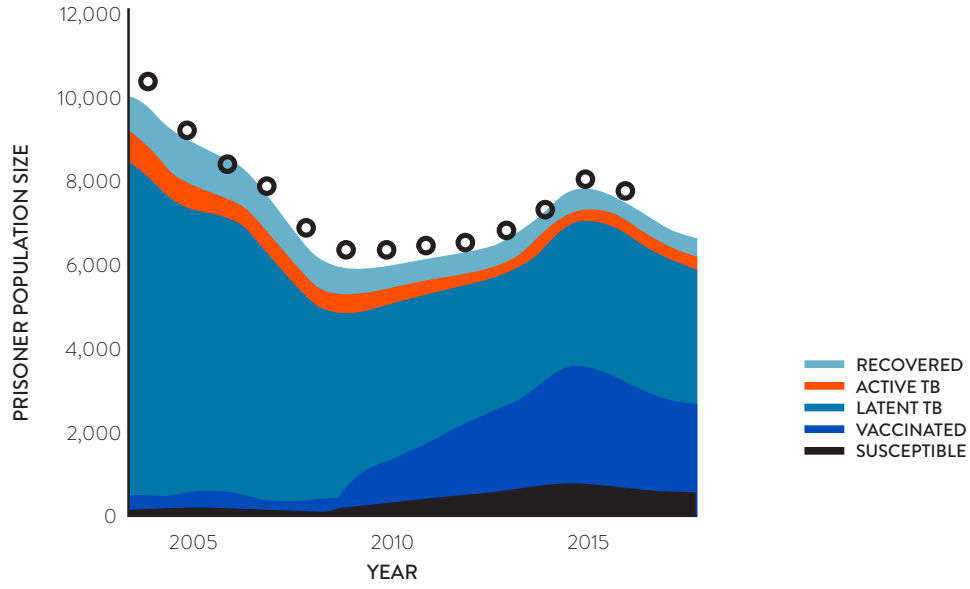
Source: Populated using the Optima TB model for Moldova

A DECREASING CONTRIBUTION OF PRISONERS TO THE TB EPIDEMIC

In 2000, prisoners are estimated to have accounted for 6% of all active TB cases and peaked at 7% in 2004, but by 2016 this has decreased to 3% of active TB cases and is projected to slowly decrease further. This can be explained both through a diminishing prison population (nearly 30% smaller over the same period) as well as a variety of programs targeting TB among prisoners such that fewer new prisoners entering the system are becoming infected with latent TB or progressing to active TB during their incarceration as a result. Figures 3.7 and 3.8 illustrate the changing characteristics of active TB in the prison population.

Prisoners who were vaccinated for TB increased from approximately 5% in 2008 to a peak of 39% in 2014. Inversely, the number of prisoners with latent TB decreased from 9,000 in 2000 to a stable range of 3,000 to 3,400 after 2011.

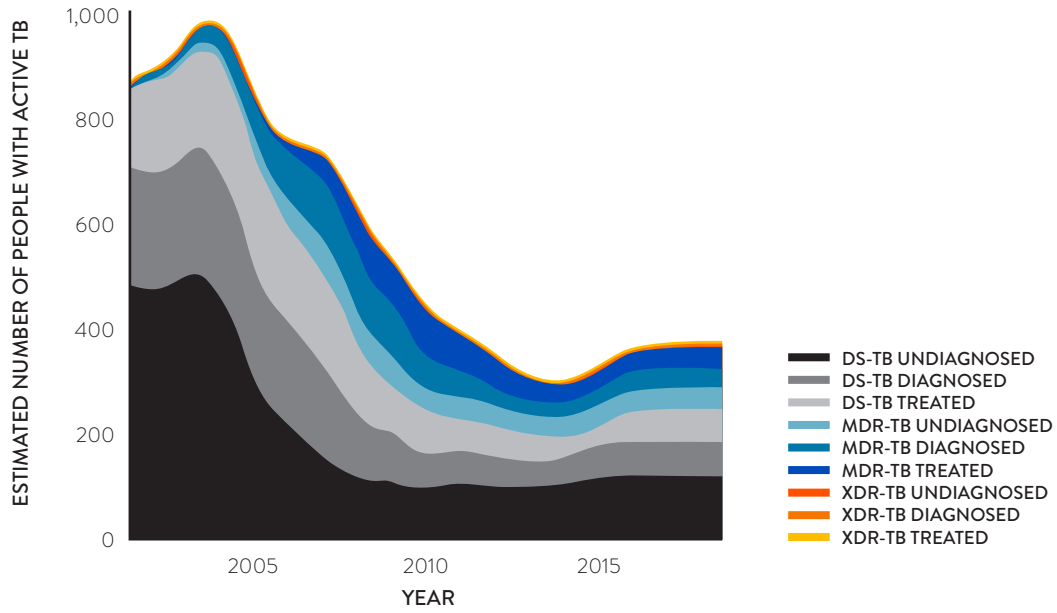
FIGURE 3.7 PRISONER POPULATION BY TB DISEASE STATUS IN MOLDOVA, 2003–2018



Source: Populated using the Optima TB model for Moldova

TB drug-resistance among prisoners increased from 10% (of total active TB among prisoners (in 2004 to 33% in 2018.

FIGURE 3.8 PRISONERS WHO HAVE ACTIVE TB BY DRUG RESISTANCE TYPE IN MOLDOVA, 2002–2018



Source: Populated using the Optima TB model for Moldova

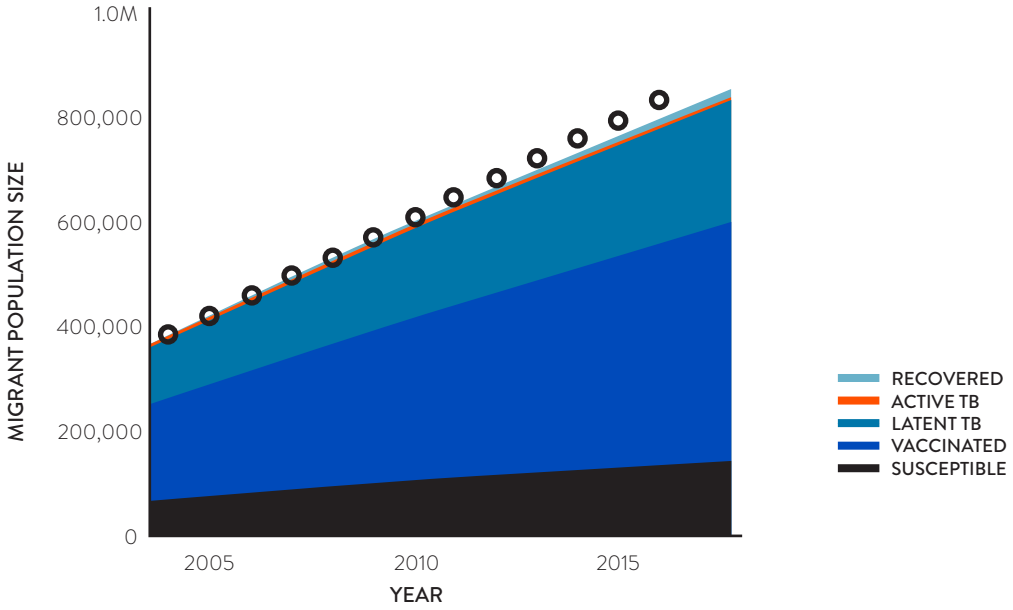
MIGRATION AS A FORCE CONTINUING THE TB EPIDEMIC

The population of migrants has continued to increase over time due to the large number of Moldovans who emigrate, primarily to the Commonwealth of Independent States (CIS) and European Union (EU) for work.

While incident cases are decreasing in most populations, an increasing proportion of the total active TB infections are attributed to the migrant population, from 10% in 2001 to 25% in 2016 and projected to increase further in the future. This is exacerbated by the challenges of both reaching migrants to test them as well as lower and/or slower uptake rates for treatment among migrants compared to the general population. It is estimated that only 28% of migrants who have been diagnosed and are aware of their active TB status were being treated for TB in 2016. Figures 3.9 and 3.10 illustrate the changing characteristics of active TB in the migrant population.

In 2018, the proportion of active TB cases among the 900,000 migrants was 0.4%, those with latent TB was 28%.

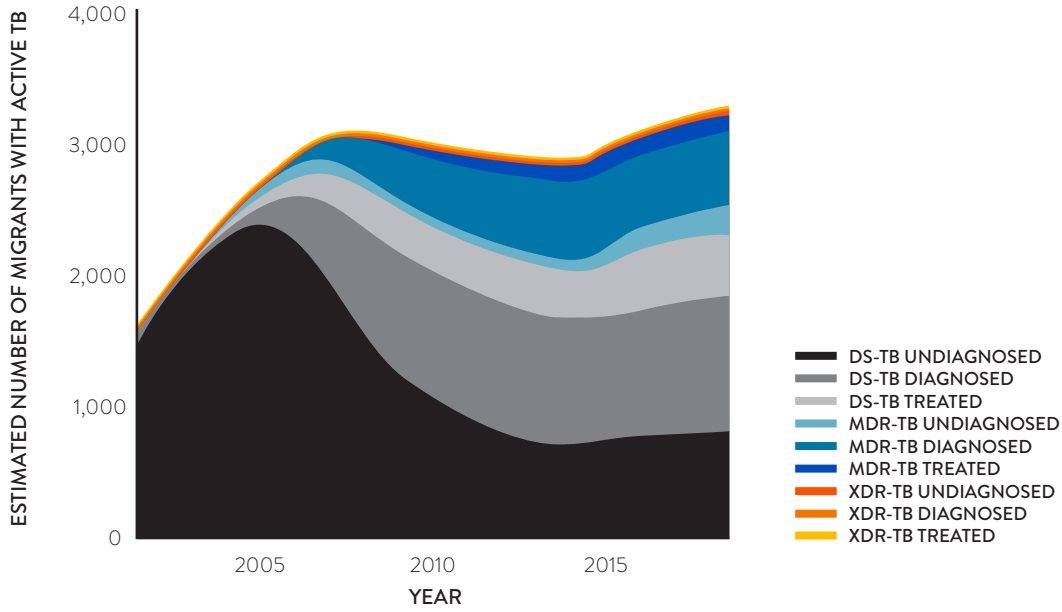
FIGURE 3.9 MIGRANT POPULATION BY TB DISEASE STATUS IN MOLDOVA, 2003–2018



Source: Populated using the Optima TB model for Moldova

TB drug-resistance among migrants increased from 2004 (3% of total active TB among migrants) to 29% in 2018.

FIGURE 3.10 MIGRANTS WITH ACTIVE TB BY DRUG RESISTANCE TYPE IN MOLDOVA, 2002–2018

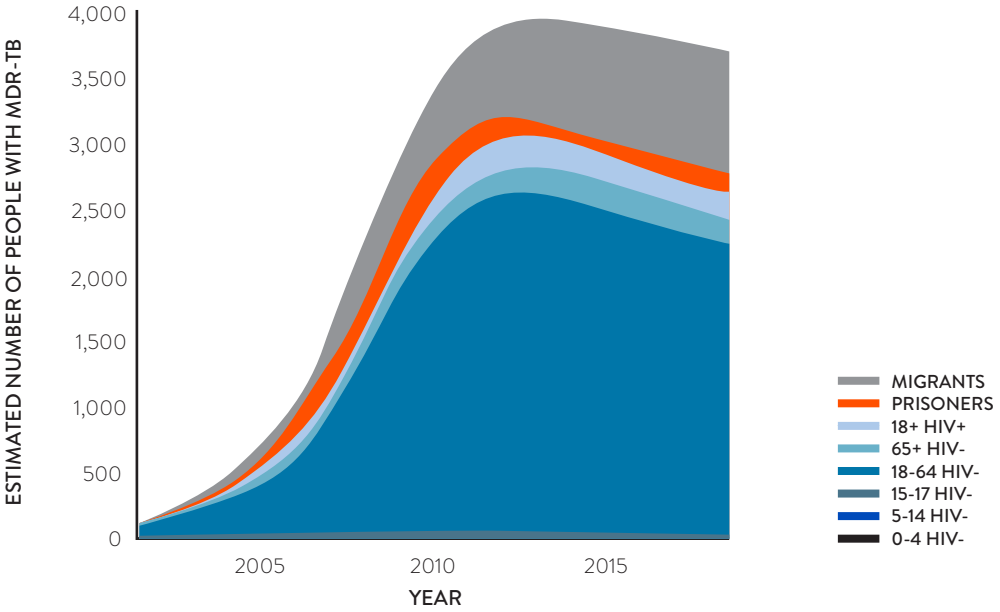


Source: Populated using the Optima TB model for Moldova

HIGH PREVALENCE OF MDR-TB

Optima TB projections suggest that the number of people with MDR-TB continued to increase up to 3,900 cases in 2012, but has declined to 3,600 in 2018 (Figure 3.11). New active cases of MDR-TB peaked earlier in 2008 (Figure 3.12).

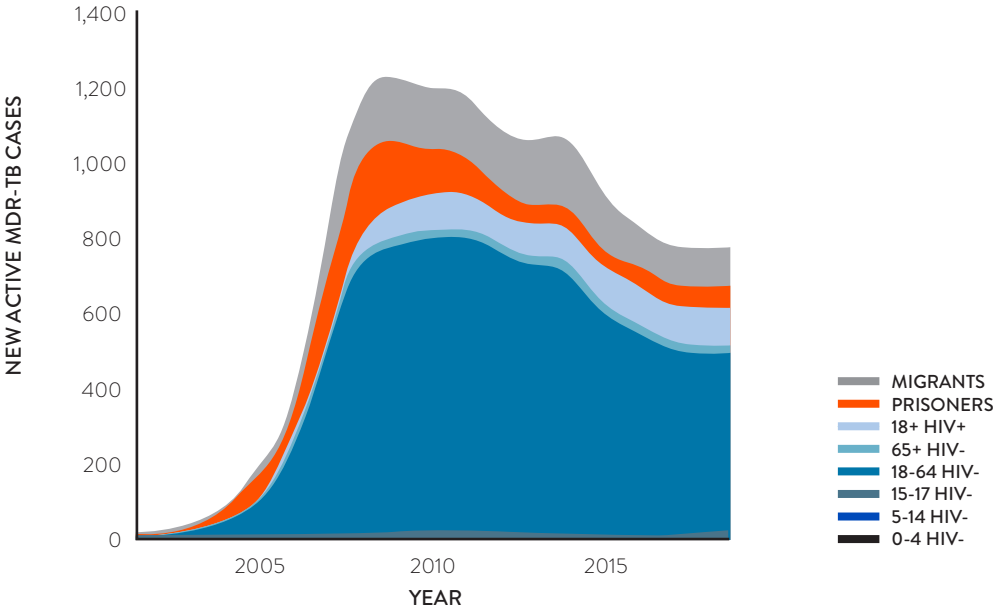
FIGURE 3.11 PEOPLE WITH ACTIVE MDR-TB IN MOLDOVA, 2002–2018



Source: Populated using the Optima TB model for Moldova

New active MDR-TB increased to 1,200 cases in 2008, and thereafter declined to 800 in 2018. This increase in MDR-TB from 2000 coincides with shortages of health resources, including the lack and inconsistent availability of TB drugs in the early 2000s (Soltan 2008). Poor treatment adherence and the risk of transmission during hospitalized based care contributed to the rise of MDR-TB (Soltan 2008, Jenkins 2014). The subsequent decline is consistent with the roll-out of rapid MTB/RIF testing using Xpert technology between 2012 and 2014 (Harvard Medical School 2016).

FIGURE 3.12 NEW ACTIVE MDR-TB IN MOLDOVA, 2002–2018



Source: Populated using the Optima TB model for Moldova

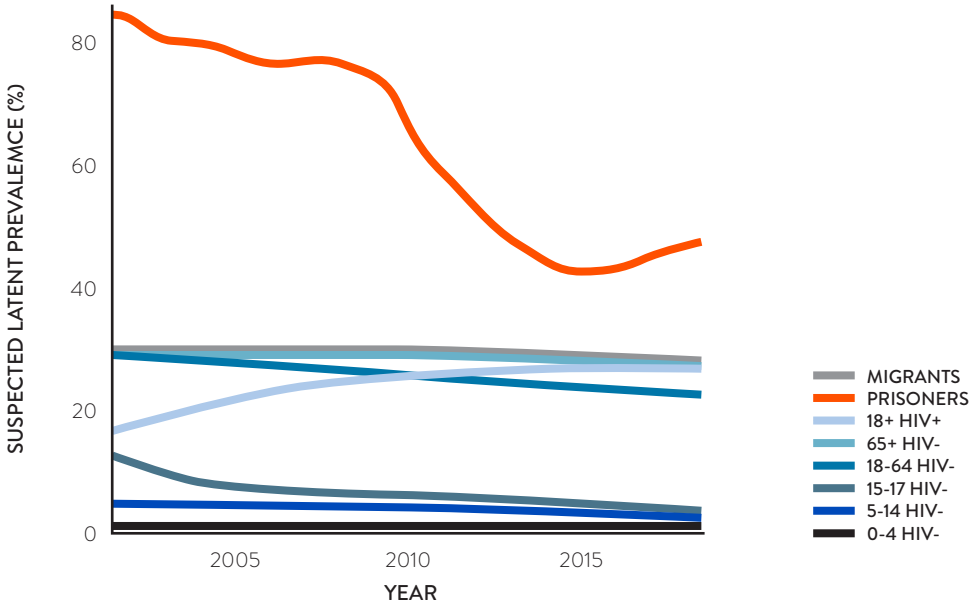
LATENT TB: THE RESERVOIR SUSTAINING THE TB EPIDEMIC

The actual prevalence of latent TB in Moldova is currently unknown. While earlier estimates suggested that up to one third of the world's population was infected with latent TB, the most recent global estimate suggests that global latent TB prevalence is less than 25% (Houben 2016).

Estimates of the prevalence of latent TB in Moldova have been produced using the Optima TB model, based on observed active TB cases. Optima TB estimates the number of latent TB cases to be approximately 850,000 in 2016, with the prevalence of latent TB infections stable in most populations in Moldova (Figure 3.13). There is a continuing slow decrease in general populations and a very significant decrease in the prisoner population as new infection rates have been reduced. Independent estimates suggest that the number of people with latent TB in Moldova is between 611,000 and 882,000 (Houben 2016).

Prisoners have the highest suspected latent prevalence of TB in Moldova; however, the prevalence has decreased from 84% in 2000 to a low of 42% in 2015, with a reversion to 48% suspected in 2018.

FIGURE 3.13 SUSPECTED LATENT TB PREVALENCE IN MOLDOVA, 2002–2018



Source: Populated using the Optima TB model for Moldova

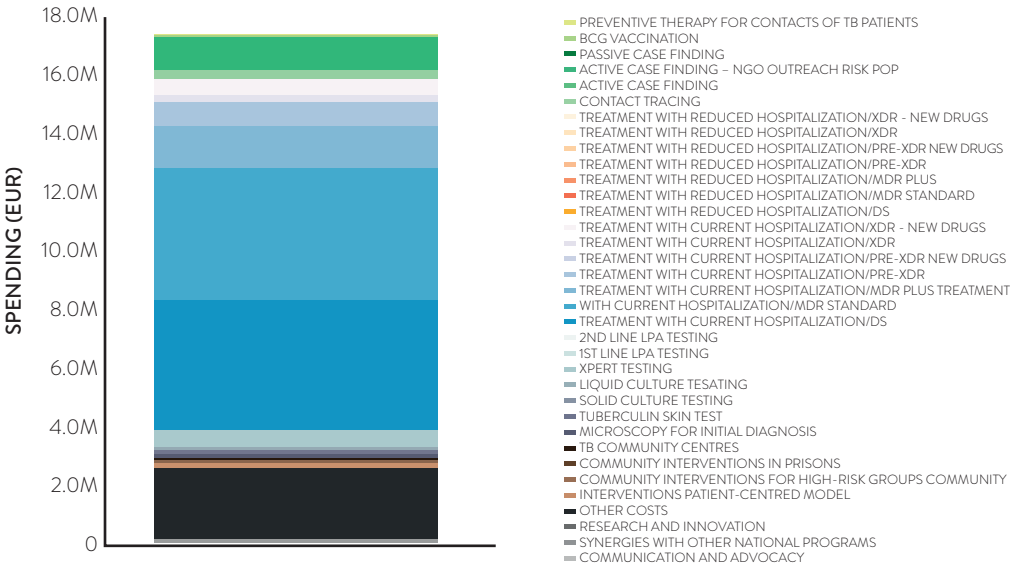
4. WHAT ARE THE IMPACTS OF CURRENT TUBERCULOSIS SPENDING?

This chapter describes the programmatic focus of the 2016 TB response in Moldova and the corresponding epidemiological outcomes if current spending patterns were sustained.

4.1 FOCUS OF CURRENT TB PROGRAMS IN MOLDOVA

The total spending in 2016 for Moldova's TB response was 17.5 million EUR. Figure 4.1 shows the 2016 allocation of funding across various TB interventions in Euro.

FIGURE 4.1 SPENDING BY TB PROGRAM IN MOLDOVA, 2016



Source: Prepared by authors based on Ministry of Health reports and program records

TABLE 4.1 TB PROGRAMS AND UNIT COSTS (EUR), 2016

DIAGNOSIS AND PREVENTIVE TB PROGRAMS	UNIT COST (PER TEST OR PERSON-YEAR, EUR) 2016
BCG vaccination	0.89
DIAGNOSTIC COMPONENTS	
Tuberculin skin test	2.73
Chest X-ray	4.56
Microscopy for initial diagnosis	2.01
Solid culture testing	3.22
Liquid culture testing	28.06
GeneXpert testing	15.12
1st Line LPA	8.76
2nd Line LPA	7.64
PROGRAMS	
Contact tracing	7.06
Active case finding	7.06
Active case finding –outreach in high risk areas	12.06
Passive case finding	7.06
Extended contact tracing	8.18
Extended active case finding	8.18

Of the total budget, only 1.7 million EUR was spent on testing programs to identify new cases in 2016. This figure accounts for both the screening and diagnostics components of testing programs. Table 4.2 outlines the 2016 program types, costs and yields demonstrating that 83% of current diagnoses were made through passive case finding. From a cost perspective, passive case finding is cost effective (Table 4.2); however, passive case finding will not address the missing cases which are currently contributing to Moldova's sizable population of latent TB.

TABLE 4.2 TB TRACING MODALITIES ON DIAGNOSES YIELD

MODALITIES	TOTAL SCREENED	TOTAL DIAGNOSED	YIELD %	SHARE OF TOTAL	TOTAL COST (EUR)
Contact tracing	23,047	277	1.2%	6.5%	162,703
Active case finding	36,672	348	1.0%	8.2%	258,891
Acting case finding NGO outreach risk population	10,000	95	1.0%	2.2%	120,891
Passive case finding	157,832	3,515	2.2%	83.0%	1,114,233
TOTAL	227,552	4,235	1.9%	100%	1,656,423

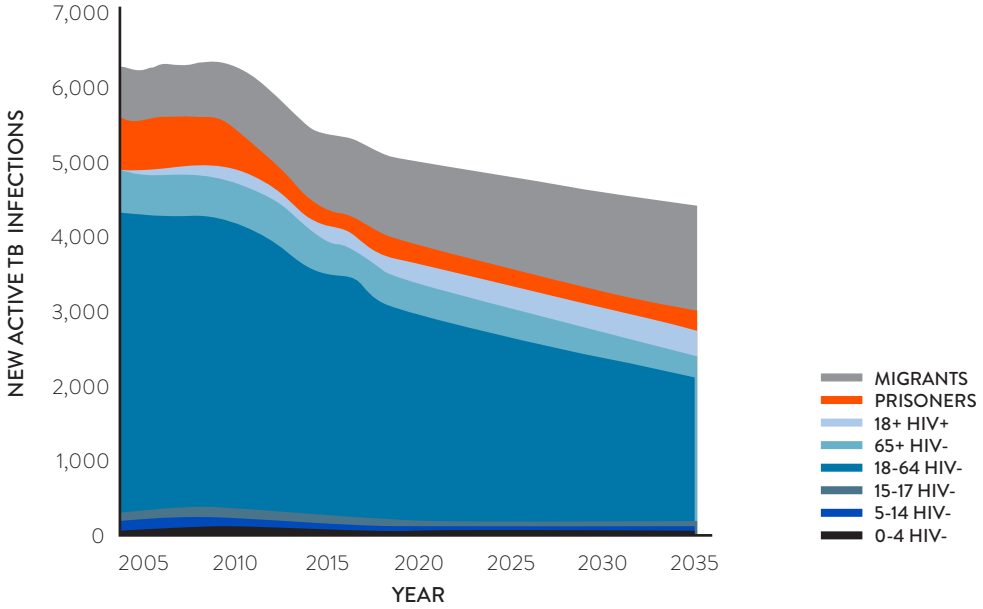
4.2 CONTINUATION OF CURRENT CARE AND COVERAGE LEVEL: NEW ACTIVE TB INFECTIONS

A scenario analysis was performed to assess the ongoing impact of existing TB programs to 2035. This analysis assumed that the level of 2016 resources would be sustained up to 2035 and that care and coverage levels would remain constant with 2016 levels.

The scenario analysis suggests that under 2016 current funding for TB programs, there would be a continued reduction in new TB infections in every population group except for migrants, up to 2035.

Under 2016 levels of TB spending, it was projected that new active TB infections would decline from 5,100 in 2016 to 4,300 in 2035, representing a 15% decline. Thus not achieving the national targets specified in Section 2.3. The proportion of new active TB infections among migrants is projected to increase from 12% (750) in 2006 to 33% (1,400) in 2035.

FIGURE 4.2 PROJECTED NUMBER OF NEW ACTIVE TB INFECTIONS UNDER 2016 BUDGET BY POPULATION IN MOLDOVA, 2005–2035

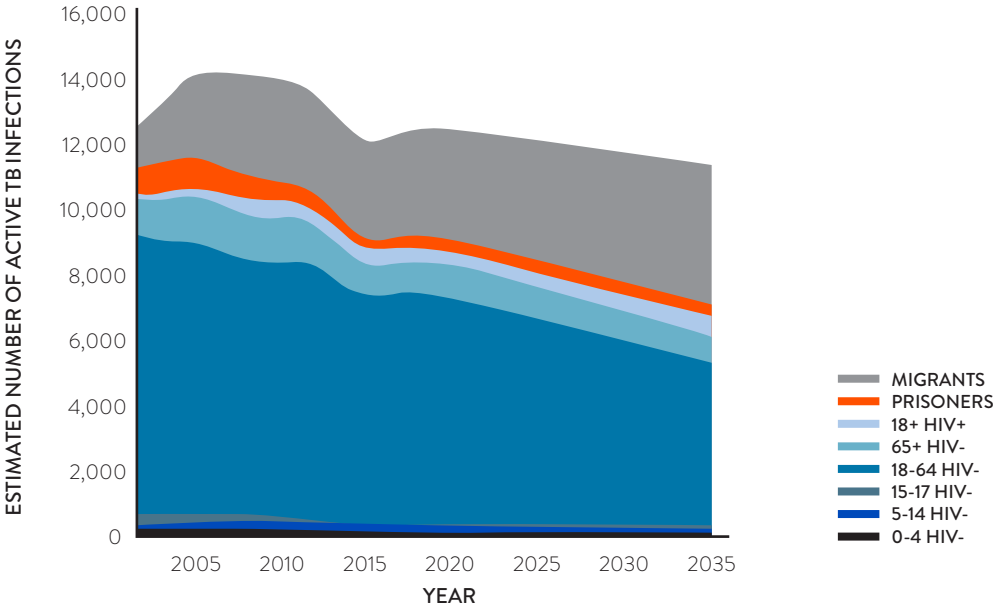


Source: Populated using the Optima TB model for Moldova

In terms of active TB infections, with 2016 resource and coverage levels, all active TB infections are also expected to gradually decrease to 2035 in all populations except for migrant populations. Among migrants, an increase in active infections to 2035 it is expected, assuming the increasing trend for migrant population size continues.

Overall the number of all active TB infections were projected to decline from 14,200 in 2005 to 12,000 in 2035. The proportion of all active TB infections among migrants is projected to continue increasing from 26% (3,200) in 2016 to 38% (4,200) in 2035.

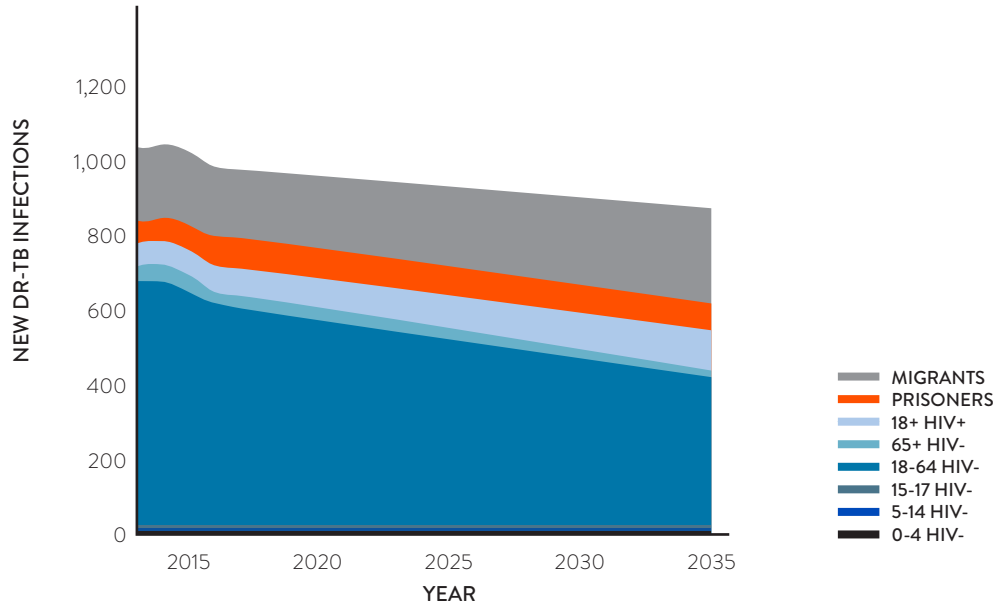
FIGURE 4.3 PROJECTED NUMBER OF ALL ACTIVE TB INFECTIONS UNDER 2016 BUDGET BY POPULATION IN MOLDOVA, 2000–2035



Source: Populated using the Optima TB model for Moldova

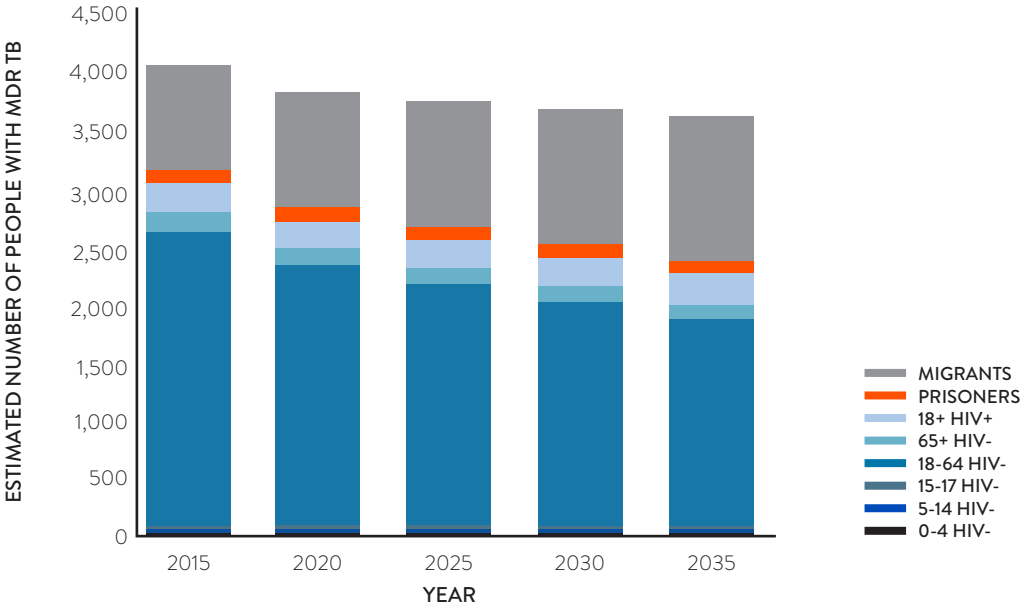
If 2016 resourcing, allocation, and coverage levels are maintained to 2035, modeled numbers of people with new DR-TB infections and active MDR-TB infections are also projected to decrease across all population groups from 1,000 in 2015 to 860 in 2035, except for migrant and adults living with HIV.

FIGURE 4.4 ESTIMATED NEW ACTIVE DR-TB INFECTIONS BY POPULATION, 2012–2035



Source: Populated using the Optima TB model for Moldova

FIGURE 4.5 MODELED NUMBER OF ACTIVE MDR-TB CASES, 2015–2035



Source: Populated using the Optima TB model for Moldova

5. WHAT WILL BE THE IMPACT OF DIFFERENT PROGRAM IMPLEMENTATION SCENARIOS?

This chapter summarizes different scenario analyses, which were conducted to understand the effect that specific programmatic changes would have on Moldova's TB epidemic. Specifically, it will examine how the trajectory of Moldova's TB epidemic would change through achieving program specific targets through the implementation of the following programs;

- Treatment scale-up related to missing cases
- Hospital-focused versus ambulatory treatment
- Enhanced XDR-TB treatment
- Different TB case finding modalities
- Treatment adherence targets
- Improving testing and treatment among migrants
- Impact of targeting comorbidities

5.1 SCENARIO 1: IMPACT OF ACHIEVING THE TB CARE CASCADE TARGETS

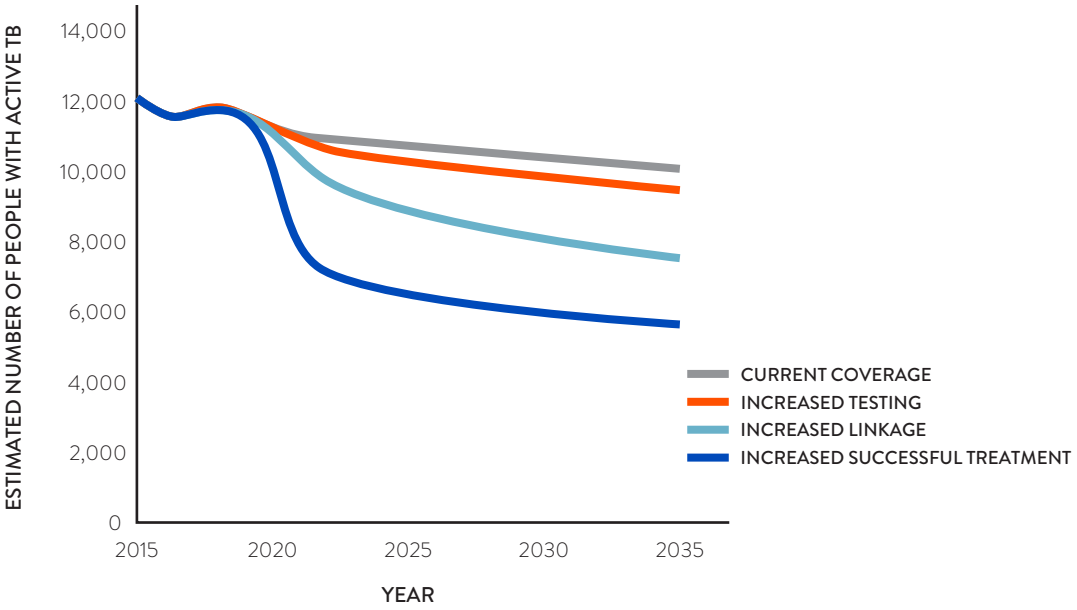
A scenario analysis was performed to understand the level of changes to the TB epidemic that would occur if global targets were achieved by 2035. Table 5.1 summarizes the most recently reported care conditions, as well as targets for testing, linkage to care, and treatment success by 2035.

TABLE 5.1 SCENARIO 1 PARAMETERS – ACHIEVING TB CARE CASCADE TARGETS BY 2035

SCENARIO 1: IMPROVED CARE CASCADE	MOST RECENT CONDITIONS (2015)	INCREASED TESTING	INCREASED LINKAGE TO CARE	INCREASED TREATMENT SUCCESS
Diagnosis of prevalent cases	84%	90%	90%	90%
DS-TB CARE				
Treatment initiation	80%	80%	90%	90%
Treatment success	85%	85%	85%	90%
MDR-TB CARE				
Treatment initiation	50%	50%	90%	90%
Treatment success	50%	50%	50%	90%
XDR-TB CARE				
Treatment initiation	50%	50%	90%	90%
Treatment success	50%	50%	50%	90%

Figure 5.1 illustrates the effect of meeting and sustaining the care cascade targets through improvements from diagnosis to linkage to treatment and successful completion of treatment. It is estimated that improved care cascade linkages could reduce the number of active TB cases in Moldova by up to 45% annually by 2035, from 10,000 projected in 2035 under current coverage to 6,000 with increased testing, linkage to care, and treatment success rates.

FIGURE 5.1 MODELED NUMBER OF ACTIVE TB CASES, 2015–2035

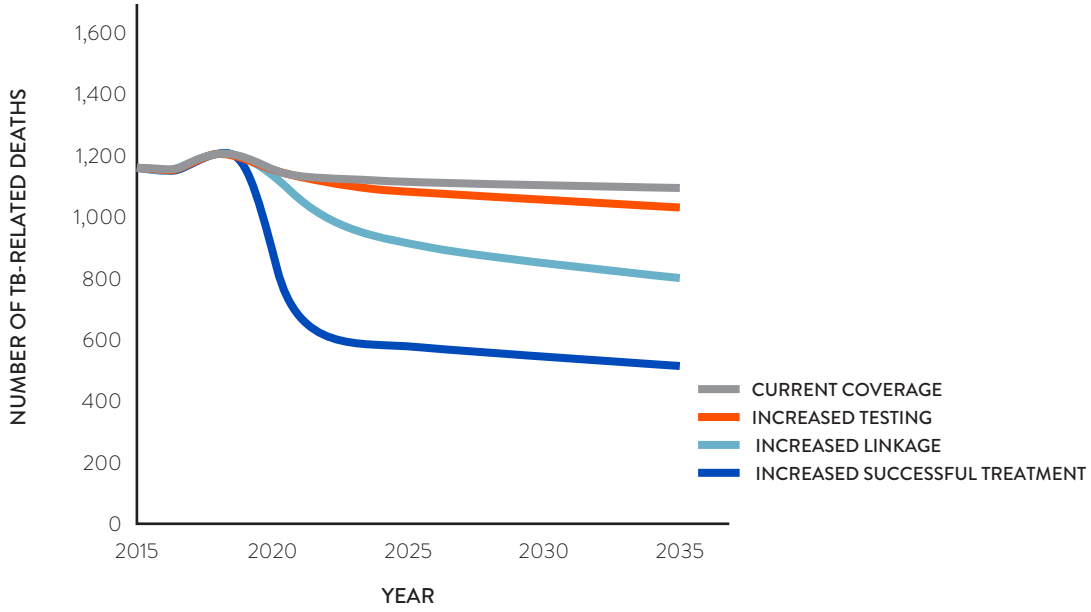


Source: Populated using the Optima TB model for Moldova

There was discussion as to why there was such a large potential for increases in relation to linkage to care. For MDR-TB, retention over the entire treatment period may be an issue, but for DS-TB it seems that most people diagnosed are already initiated and retained in case (WHO 2017).

Figure 5.2 shows the effect of the same scenarios on TB-related deaths. With current coverage of interventions from 2016, the overall number of TB-related deaths per year would remain relatively stable from 1,200 in 2016 to 1,100 in 2035. With increased testing, linkage to care and treatment success rates, 49,000 (50%) of cumulative TB-related deaths could be averted from 2016 to 2035.

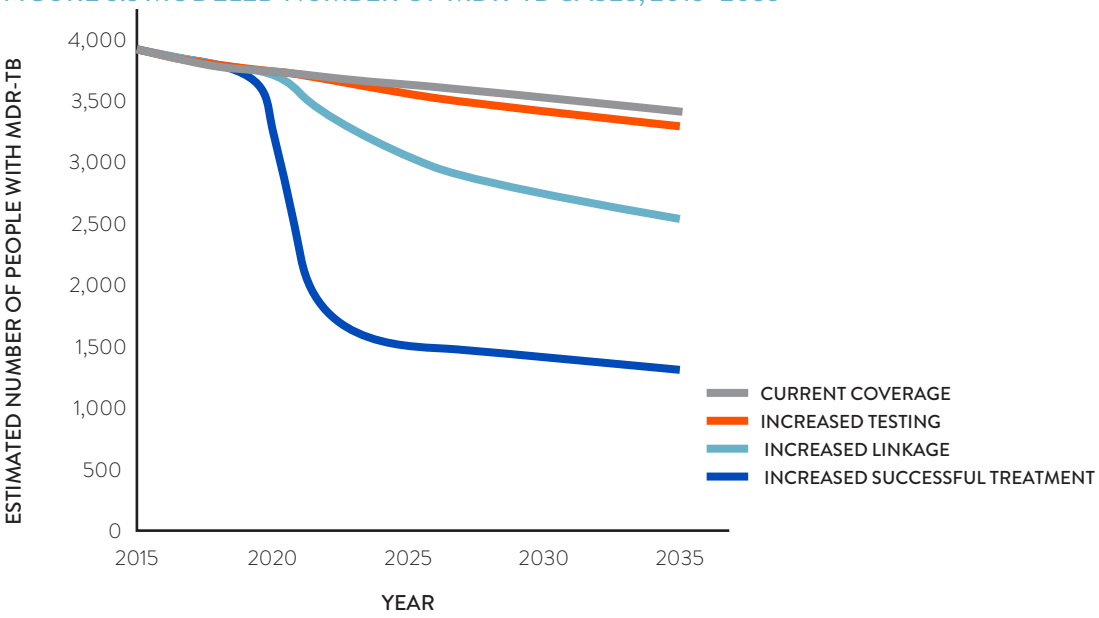
FIGURE 5.2 MODELED NUMBER OF TB-RELATED DEATHS, 2015–2035



Source: Populated using the Optima TB model for Moldova

Figure 5.3 shows the effect of the same care cascade scenarios on the number of cases of MDR-TB in the total population of Moldova. By 2035, meeting and sustaining the 90-90-90 targets could result in a 59% reduction in active cases of MDR-TB from 3,800 in 2016 to 1,300 in 2035 where a continuation of interventions from 2016 is projected to lead to a more modest decrease to 3,100 active MDR-TB cases by 2035. Improvements in the treatment outcomes for MDR-TB cases are projected to yield the greatest impact, while increases in testing and linkage to care are estimated to significantly reduce the active cases of MDR-TB by 33% (2,500 projected MDR-TB cases in 2035).

FIGURE 5.3 MODELED NUMBER OF MDR-TB CASES, 2015–2035



Source: Populated using the Optima TB model for Moldova

5.2 SCENARIO 2: SHIFTING FROM HOSPITAL FOCUSED TO AMBULATORY CARE TB MODALITIES

This scenario explores the projected effects of transition from hospital focused to ambulatory focused (with reduced hospitalization) for people infected with TB. For the purposes of this analysis, the same coverage levels were assumed for all drug regimens, with only the service modality varied.

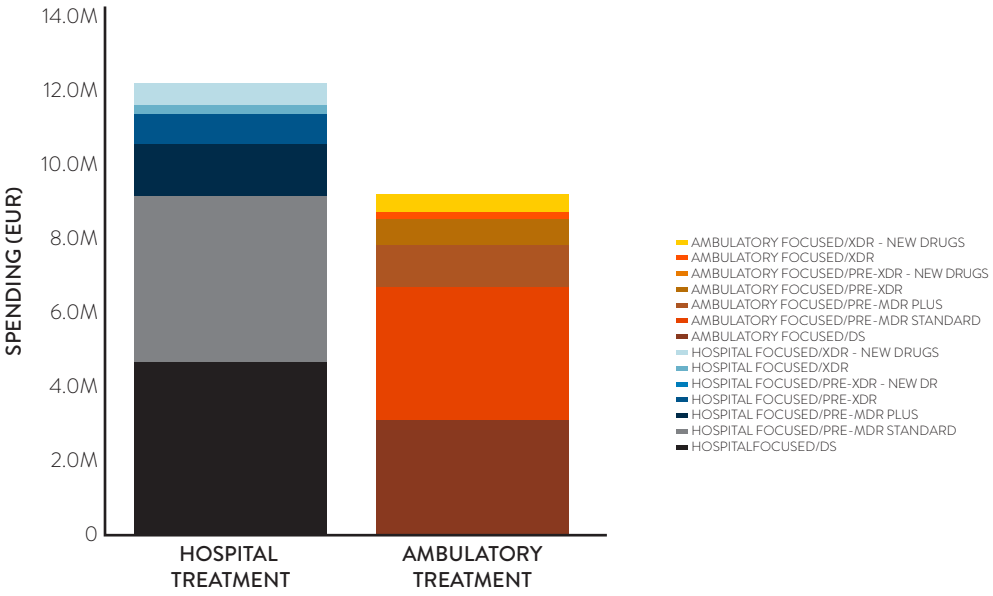
Table 5.2 summarizes the durations and costs of TB-treatment, which were assumed for the different treatment modalities. The assumed reduction in in-patient days for ambulatory modalities corresponds to the estimated time required to achieve smear conversion suggesting that the patient is no longer highly infectious.

TABLE 5.2 SCENARIO 2 PARAMETERS – SHIFTING FROM HOSPITAL FOCUSED TO AMBULATORY CARE TB MODALITIES

PROGRAM	REGIMEN	LENGTH OF TREATMENT DURATION IN DAYS	DRUG REGIMEN COST (FULL COURSE, EUR)	INPATIENT		OUTPATIENT/DOTS	
				INPATIENT DAYS	TOTAL INPATIENT COSTS (EUR)	OUTPATIENT DAYS	TOTAL OUTPATIENT COSTS (EUR)
Treatment with current hospitalization	DS	201	28.70	40	835.18	161	525.56
	MDR standard	570	1 826.15	127	2,621.58	444	1,501.00
	MDR plus	570	2,637.48	127	2,621.58	444	1,501.00
	Pre-XDR	720	2,637.48	160	3,311.47	560	1,896.00
	Pre-XDR new drugs	570	5,874.00	127	2,621.58	444	1,501.00
	XDR	880	2,637.48	195	4,047.35	685	2,317.34
	XDR- new drugs	720	8,658.51	160	3,311.47	560	1,896.00
Treatment with reduced hospitalization	DS	201	28.70	14	290.14	187	611.57
	MDR standard	570	1,826.15	60	1,243.44	510	1,726.07
	MDR plus	570	2,637.48	60	1,243.44	510	1,726.07
	Pre-XDR	720	2,637.48	60	1,243.44	660	2,233.74
	Pre-XDR new drugs	570	5,874.00	60	1,243.44	510	1,726.07
	XDR	880	2,637.48	60	1,243.44	820	2,775.25
	XDR-new drugs	720	8,658.51	60	1,243.44	660	2,233.74

Figure 5.4 shows program spending for treatment programs for hospital and ambulatory service modalities in Euros. We estimate that shifting from hospital focused treatment, which costs approximately 7-times more per day compared with outpatient care, would result in a 24% (2.8 million EUR) reduction in treatment costs per annum. In absolute terms, the single largest saving can be made by reducing hospitalization for DS-TB treatment from 40 to 14 days. In relative terms, large savings can also be made by reducing hospitalization due to DR-TB, because of the particularly long current hospitalization.

FIGURE 5.4 SPENDING FOR HOSPITAL AND AMBULATORY TB SERVICE MODALITIES



Source: Populated using the Optima TB model for Moldova

5.3 SCENARIO 3: ENHANCED DRUG REGIMENS AND COVERAGE OF XDR-TB TREATMENT

As outlined earlier in this report, rising levels of drug resistance are the key challenge for Moldova's TB response. In 2016, Moldova made a concerted effort to initiate XDR cases onto Bedaquiline (BDQ) regimens, which have been shown to have higher efficacy than older treatments. Expert opinion suggests that approximately 70% of current XDR patients would be eligible for BDQ regimens. This scenario explores the effects of continuing the transition to newer XDR-TB treatments and scaling up XDR treatment coverage levels.

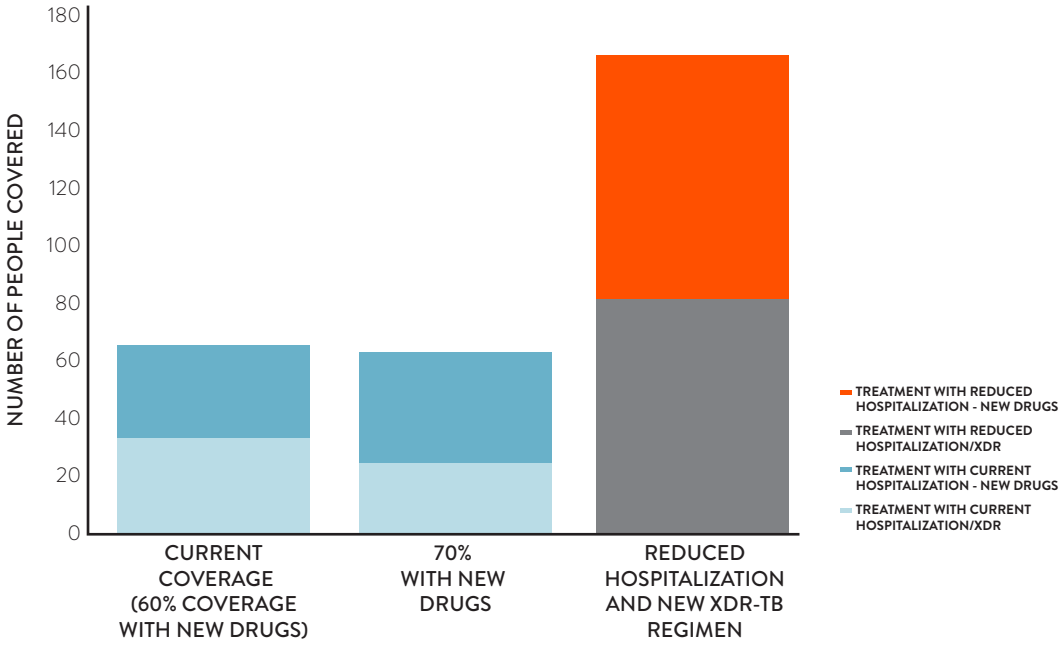
TABLE 5.3 COMPARISON OF XDR-TB TREATMENT REGIMENS

XDR-TB TREATMENT REGIMEN	CURRENT TREATMENT INITIATIONS (2017)	INCREASING COVERAGE OF BDQ	REDUCED HOSPITALIZATION
Treatment service modality	Hospital focused	Hospital focused	Ambulatory focused
Budget (EUR)	791,403	791,403	791,403
Proportion on standardized XDR-TB regimen	40%	30%	30%
Proportion on new XDR-TB regimen	60%	70%	70%

Currently, BDQ-based regimens are more expensive than standard XDR drug regimens. Increasing coverage of BDQ could mean that 70% of eligible people receive the new XDR-TB regimen; however, this will require an increase in budget.

Figure 5.5 demonstrates how a shift away from hospital-based treatment modalities can reduce total costs to allow for a 2.5-fold increase in BDQ-based treatment coverage under existing budget level.

FIGURE 5.5 TREATMENT COVERAGE ATTAINABLE WITH THE 2017 XDR-TB BUDGET

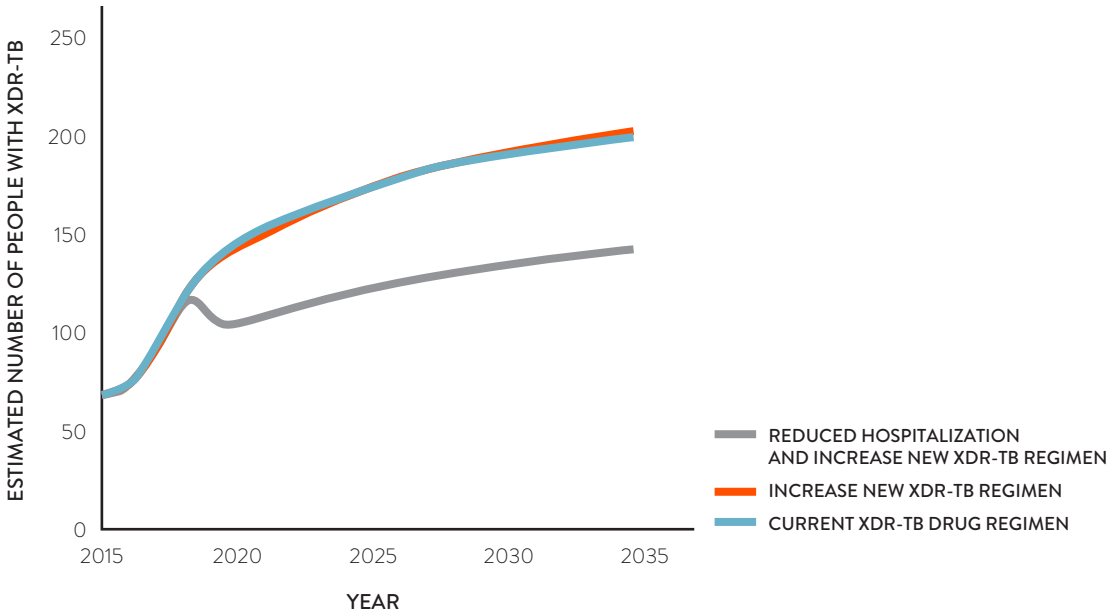


Source: Populated using the Optima TB model for Moldova

Under this scenario, 60% of funding will be allocated to new drugs regimens, but this is coupled with the increases in coverage for those being treated with old drugs. The same for the 70% coverage scenario, whereby there will be an increase in coverage of people with new drug regimens (light blue shaded area), but more people will also be treated with the old drugs (dark blue shaded area).

Shifting from 60% to 70% of cases on BDQ-XDR-TB treatment regimens does not lead to substantial gains as while the efficacy of the new drugs is much higher (93% success in completed treatments as opposed to 61% with standard XDR drug regimens), the higher cost results in fewer cases being treated in total and treatment adherence levels are assumed to remain quite low, at only 55% (source: Optima TB model input). However, reduced hospitalization within the same budget constraints allows for increased coverage where over double the number of patients could be initiated onto XDR treatment per year. Even with the current low levels of treatment adherence, doubling the number of XDR-TB infected individuals initiated onto treatment would lead to a significant reduction in the number of XDR cases. While this shift would reduce the number of XDR cases, reducing the number of XDR-TB infections would require additional increases in coverage.

FIGURE 5.6 MODELED NUMBER OF ACTIVE XDR-TB INFECTIONS UNDER VARIOUS DR-TB REGIMENS, 2015–2035



5.4 SCENARIO 4: EFFICIENT SCREENING AND DIAGNOSIS OF ACTIVE TB

As shown in chapter 3 of this report, late stage diagnosis is a significant concern within Moldova, with 47% of all notified cases occurring at a late stage and 43% of new and relapse cases are diagnosed late. Earlier identification would likely require a shift towards more active case finding to diagnose cases earlier reducing sequelae, treatment intensity and overall costs. This scenario explores the project costs of alternative TB screening strategies. While the estimated costs of shifting towards active case finding would require increased spending and programmatic support, it would also likely increase the number of earlier diagnoses which could reduce overall treatment costs and complications. While the current focus on passive case finding is less expensive in the short-term, it ultimately leads to later diagnoses and therefore more transmission and higher treatment costs in the long-term.

In a resource constrained setting, sustaining costly BDQ based regimens will not be a given with anticipated withdrawal of international funding. A subsequent scenario analysis could be designed to compare zero funding, and thus zero (0%) drug coverage, rather than using the 60% current coverage as a baseline. Nevertheless, it has been shown that while the new drug regimens are more expensive than the old drugs, they have better anticipated outcomes. Therefore, re-allocating funds towards increased coverage of new drugs, and as a consequent away from funding towards old drugs will mean that a few more people are successfully treated in the short term, but long-term the overall lower number of people on treatment (due to more costly regimens) is expected to result in more people becoming infected with TB. With either option, we do not predict the difference, considering inherent uncertainty of modelling projections, on the health impact to be substantial.

5.5 SCENARIO 5: PROMOTING ADHERENCE AND REDUCING TB TREATMENT FAILURE

As shown in chapter 3, treatment failure rates are high in Moldova. Treatment failure appears to be mainly due to two factors. The first factor being lack of treatment adherence, which leads to 50%-57% of all treatment failure and may also contribute to the need of re-treatment at a later stage. The second factor is a result of unsuccessful treatment regimens, due in part older drug regimens with lower efficacy levels, which have been in use until recently. However, in 2016 Bedaquiline was introduced. More recently Linezolid is also used more widely now with 65% of regimens including Linezolid in 2017. T able 5.4 shows current treatment failure rates and compares those rates to national targets.

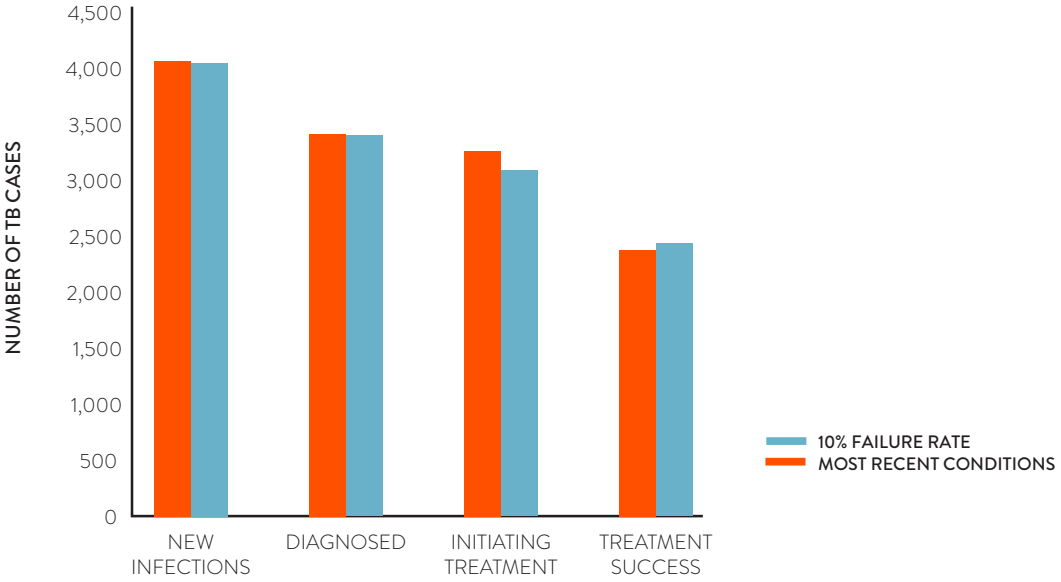
TABLE 5.4 MOST RECENT AND TARGET FAILURE RATES BY TB DRUG RESISTANCE TYPE

TREATMENT MODALITIES	MOST RECENT CONDITIONS	FAILURE RATE TARGETS
DS-TB treatment failure rate	11%	6%
MDR-TB treatment failure rate	35%	20%
XDR-TB treatment failure rate	35%	20%

The reduction of treatment failure through the dual promotion of treatment adherence and the implementation of customized drug regimens could effectively address high treatment failure rates. Modeling demonstrates that meeting the annual treatment failure rate target of 10% would lead to a reduction in the need for treatment initiation for DS-TB cases by 170 cases per year, for DR-TB by 200 cases per year, and would equate to an annual saving of up to 2 million EUR.

Figure 5.7 shows an annual cost-savings of 267,000 EUR that could be achieved by reaching the 10% annual treatment failure rate target for DS-TB across the general population.

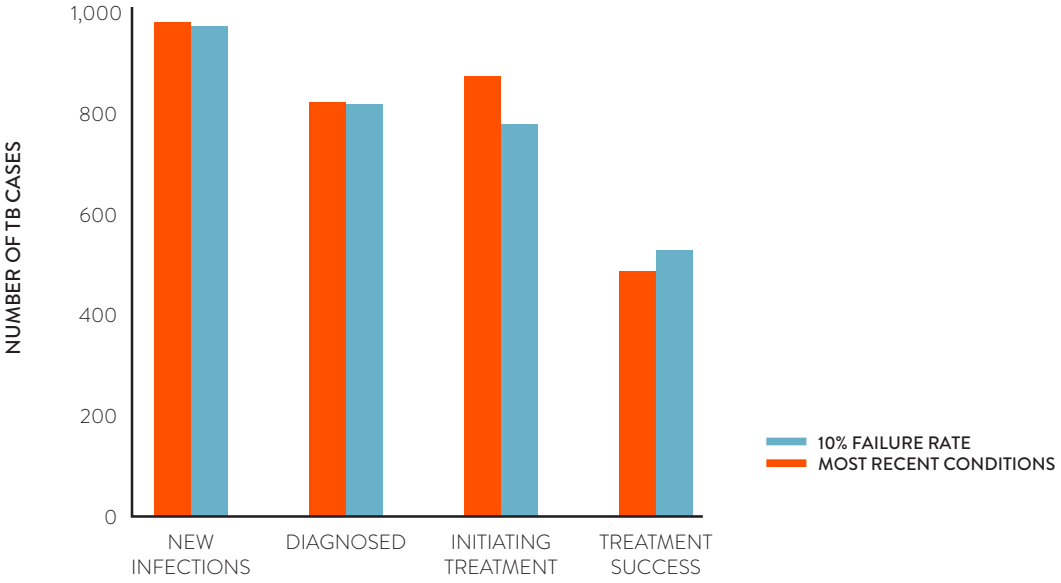
FIGURE 5.7 MODELED DS-TB CARE CASCADE, 2020



Source: Populated using the Optima TB model for Moldova

Figure 5.8 shows cost savings that could be gleaned by reaching the 10% treatment failure rate targets for DR-TB across the general population, with estimated savings of 1.6-1.8 million EUR from averting re-initiation onto treatment.

FIGURE 5.8 MODELED DR-TB CARE CASCADE, 2020

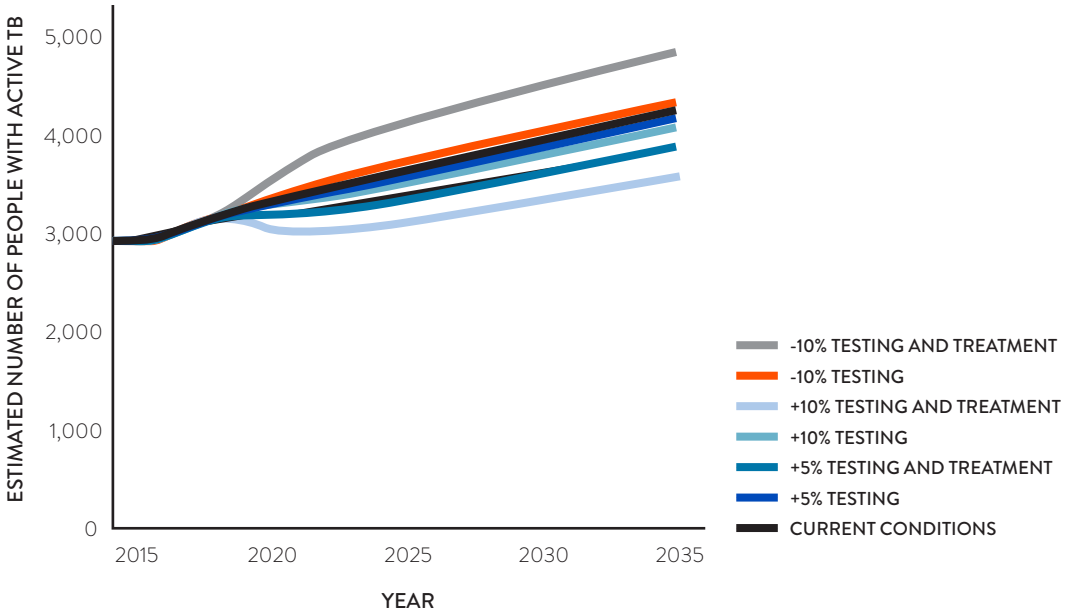


Source: Populated using the Optima TB model for Moldova

5.6 SCENARIO 6: IMPROVING IMPACT IN MIGRANT POPULATIONS

While the overall burden of disease within Moldova has decreased across the general population, the number of active TB cases within migrant populations appears to be increasing. Modeling shows that if current migration trends continue, the number of migrants infected with active TB would increase from 3,100 in 2016 through to 4,200 in 2035. While increases in testing and treatment are projected to reduce the number of infections within migrant populations, these programs would be insufficient to reverse the overall projected burden of disease. Figure 5.9 shows the modeled number of people with active TB within migrant populations

FIGURE 5.9 MODELED NUMBER OF MIGRANTS WITH ACTIVE TB, 2015–2035



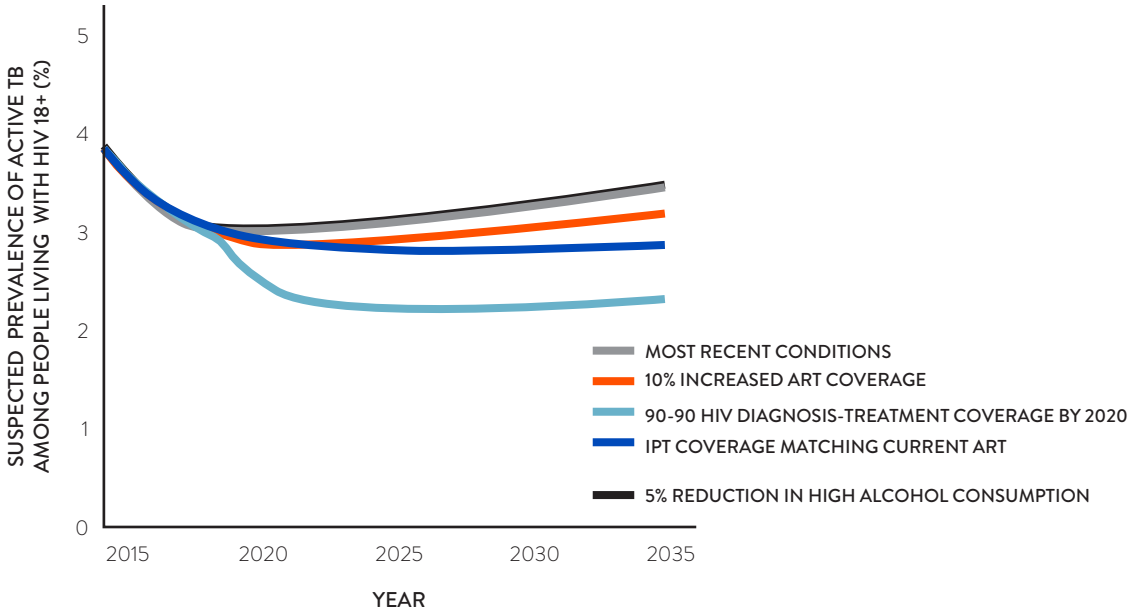
Source: Populated using the Optima TB model for Moldova

5.7 SCENARIO 7: TARGETING COMORBIDITIES

Within HIV-TB co-infected patients, co-morbidities of high alcohol consumption (HAC) and HIV are known to affect TB infection susceptibility, disease progression and increase risk of mortality and poor treatment outcomes. Modeling showed that reducing HAC from current levels of 10% within the adult 18-64 population had a negligible effect on mortality and on disease risk. The most substantial impact came from reaching the 90-90-90 global targets for ART treatment coverage which reduced TB-related deaths by 50% and reduced active TB prevalence by 30% as demonstrated in figures 5.10 and 5.11 below.

Importantly, our model does not reflect any changes in HIV incidence that are likely to be the result of achieving the 90-90-90 HIV targets, and any such changes would indirectly effect TB mortality rates. In other words, it is likely that the impact demonstrated in the light blue curve for 90-90 ART coverage achieved by 2020 in figure 5.11 at 2.4% by 2035 may be an underestimation in the reduction of active prevalence of TB.

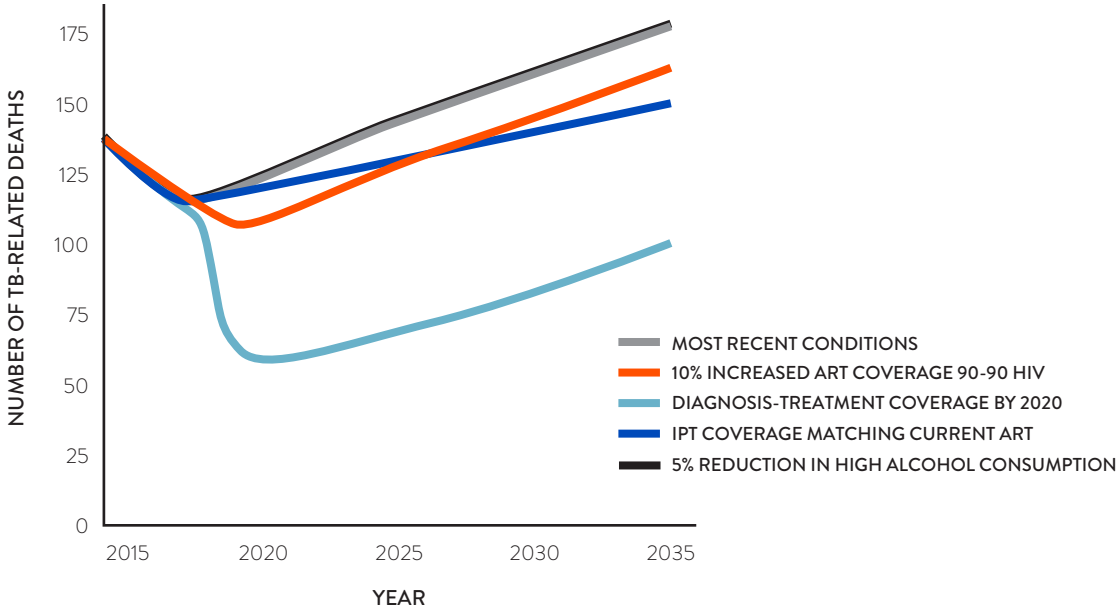
FIGURE 5.10 MODELED SUSPECTED PREVALENCE OF ACTIVE TB AMONG PEOPLE LIVING WITH HIV AGED 18 YEARS AND OLDER, 2015–2035



Source: Populated using the Optima TB model for Moldova

For the modeled scenario with a reduction from 10% to 5% in high alcohol consumption, there is very little change in the estimated number of TB-related deaths (corresponding to the black curve in figure 5.11) as it is essentially the same as the baseline for the most recent conditions (grey curve in this figure). Achieving 90-90 ART coverage by 2020 is projected to result in a 60% reduction in mortality per 100,000 from 2016 to 2035 (from 780 per 100,000 PLHIV to 320 per 100,000 PLHIV). As noted above, the absolute number of TB-related deaths is predicted to continue rising if rates of HIV incidence continued at 2016 levels, but meeting the 90-90 ART coverage by 2020 would also reduce HIV incidence and have a greater impact on TB-related deaths.

FIGURE 5.11 MODELED NUMBER OF TB-RELATED DEATHS AMONG PEOPLE LIVING WITH HIV AGED 18 YEARS AND OLDER, 2015–2035



Source: Populated using the Optima TB model for Moldova

6. WHAT MIGHT BE GAINED FROM OPTIMIZED ALLOCATION OF CURRENTLY AVAILABLE FUNDING?

The analysis presented in this chapter answers the core questions of this allocative efficiency study. Previous chapters have identified the effects and costs of specific programmatic changes. This chapter analyses the TB response holistically and answers the question of how to best allocate resources to maximize health outcomes and reach national and international goals. The results presented in this chapter were generated using an optimization algorithm mentioned earlier in this report and described in detail in appendix A. Briefly, within the Optima TB model the optimization algorithm is used to determine the optimal distribution of resources projected to lead to the most cost-efficient, targeted programs to maximize the desired health outcomes.

As outlined in chapter 4 of this report, the current allocation of resources in Moldova is projected to lead to continued moderate declines in TB incidence, prevalence and mortality in most population groups. The scope of this chapter is to explore to what extent and how further reductions could be achieved during the remaining period of the national strategic plan (2018-2020) and during the timeline towards achieving global TB targets (2025 and 2035).

6.1 OPTIMIZED ALLOCATION OF RESOURCES TO MINIMIZE INCIDENCE, PREVALENCE, AND DEATHS

In general, optimized allocations of resources are only optimal relative to a specific set of objectives and given timeframe. To reflect the different dimensions of the TB response, optimization analysis was performed for a combination of three objectives with equal weighting to:

- avert new TB infections;
- further reduce TB prevalence of active TB; and
- prevent TB-related deaths.

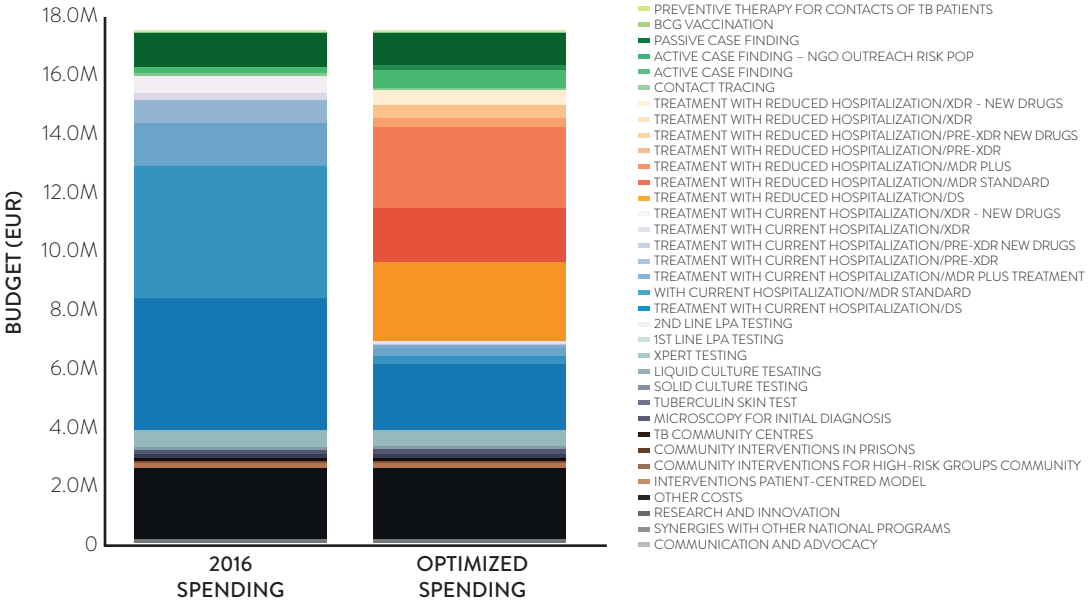
In addition, optimizations for specific objectives were run to explore to what extent optimized allocations would differ for different sets of objectives.

HOW TO REALLOCATE RESOURCES?

The overall optimized allocation of resources to minimize TB incidence, prevalence and deaths is shown in figure 6.1. In this analysis it was assumed that the same 17.5 million EUR that were available for TB-related programs in 2016 would remain available on an annual basis up to 2035. The optimized budget allocation differs from most recent allocations across several different areas. The re-allocation decreased funding to hospital-based treatment modalities while increasing funds to:

- ambulatory treatment modalities;
- new drug regimens for DR-TB including BDQ for pre-XDR and XDR-TB; and
- active case finding and screening programs.

FIGURE 6.1 MOST RECENT AND OPTIMIZED ALLOCATIONS OF TB RESOURCES TO MINIMIZE CUMULATIVE TB INCIDENCE, PREVALENCE, AND TB-RELATED DEATHS IN MOLDOVA BY 2035

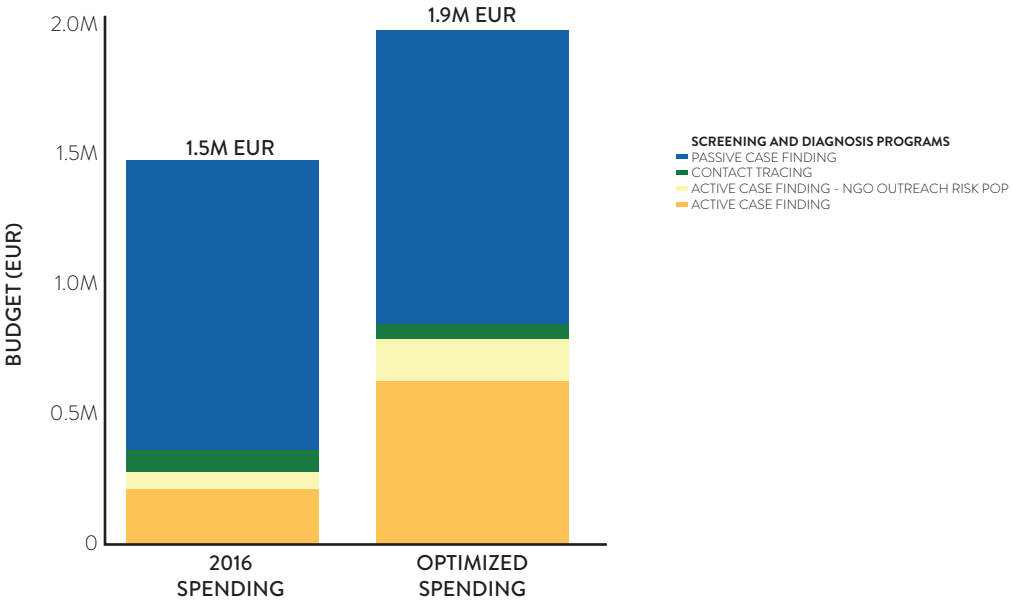


Source: Populated using the Optima TB model for Moldova

SHIFTS WITHIN TESTING AND DIAGNOSIS PROGRAMS

Gaps in diagnosis represents a major break point in the TB care cascade in most countries, including in Moldova where high rates of late diagnoses contribute to high rates of DR-TB as outlined in chapter 3. According to Optima TB projections to minimize incidence, prevalence and deaths, optimized allocation of resources would imply an 35% increase in funding towards diagnostic interventions including and additional EUR +0.4M for normal active case finding and an additional EUR+0.1M for active case finding targeting specific high-risk populations. Figure 6.2 shows current and optimized investment into diagnostic interventions. Compared to the current diagnostic approach, which primarily builds on an increase of active case finding to assist in the timely detection of active TB cases.

FIGURE 6.2 MOST RECENT ALLOCATION AND OPTIMIZED ALLOCATIONS OF RESOURCES FOR TB DIAGNOSIS TO MINIMIZE TB INCIDENCE, PREVALENCE, AND TB-RELATED DEATHS IN MOLDOVA

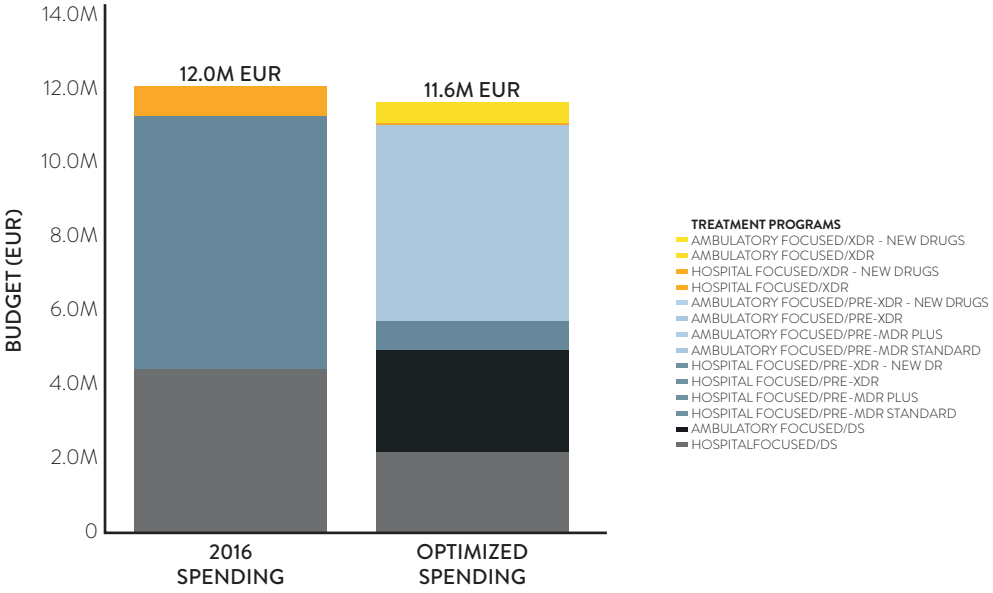


Source: Populated using the Optima TB model for Moldova

SHIFTS WITHIN TREATMENT AND CARE PROGRAMS

TB treatment and care (including hospital, ambulatory and palliative care absorbed most of Moldova's TB spending in 2016. Optimization analysis suggests that large reallocations are indicated within TB treatment and care programs. Optimized allocations imply that a combination of shifts towards ambulatory-focused delivery for DS-TB and DR-TB along with new drug regimens for pre-XDR would provide care for most of TB patients.

FIGURE 6.3 MOST RECENT AND OPTIMIZED ALLOCATIONS IN TB TREATMENT AND CARE TO MINIMIZE TB INCIDENCE, PREVALENCE, AND DEATHS IN MOLDOVA



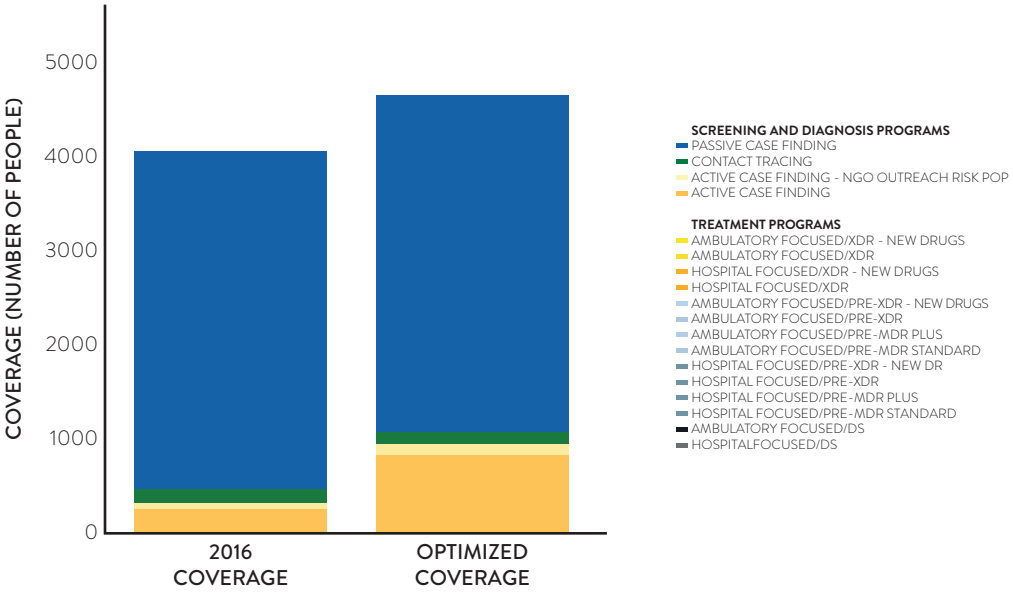
Source: Populated using the Optima TB model for Moldova

IMPROVED OUTCOMES UNDER OPTIMIZED RESOURCE ALLOCATION

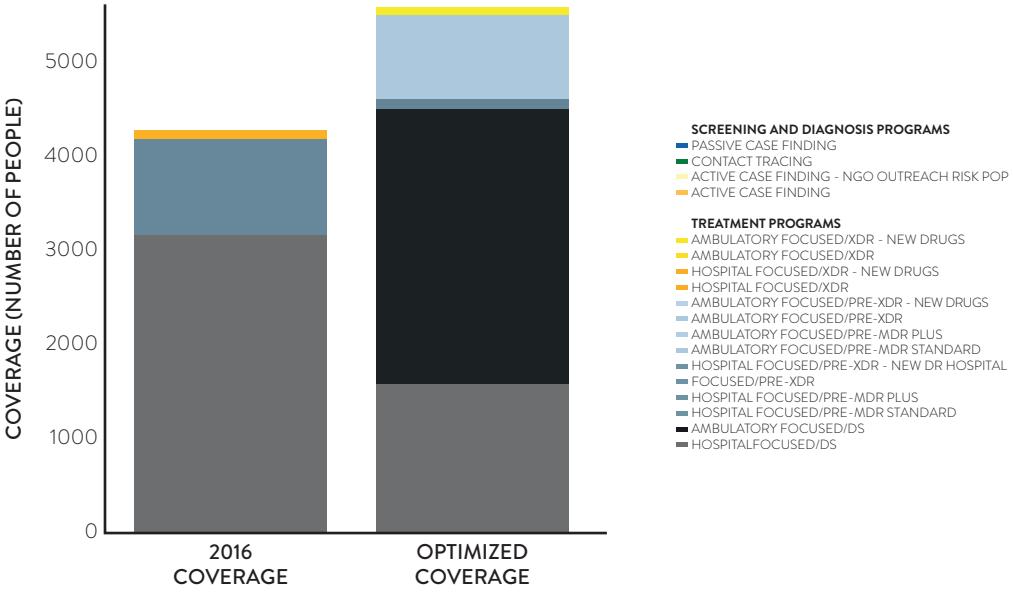
Optimized resource allocation, as shown in figure 6.1, would have substantial effect on the TB response and epidemic in Moldova. Figure 6.4 illustrates coverage for TB diagnosis and screening, as well as treatment initiation programs considered in the model among the general population aged 15-64 years under 2016 or optimized allocations.

FIGURE 6.4 COVERAGE OF TB DIAGNOSIS AND TREATMENT AMONG THE GENERAL POPULATION AGED 15-64 YEARS, UNDER 2016 AND OPTIMIZED ALLOCATIONS, MOLDOVA 2016–2035

a. Total number of people aged 15-64 years diagnosed with TB, 2016-2035



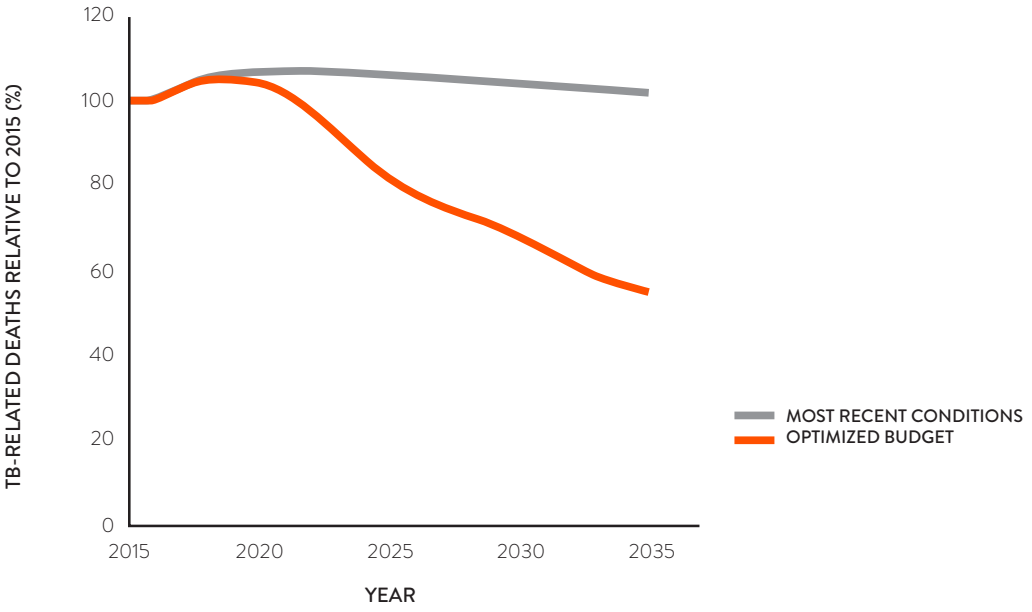
b. Total number of people aged 15-64 years initiated on TB treatment, 2016-2035



Source: Populated using the Optima TB model for Moldova

Figure 6.5 shows the impact of optimized funding allocation on TB-related deaths. With the same level of annual funding as reported in 2016, but with optimal allocation there could be a 50% reduction in annual TB-related deaths across all populations by 2035.

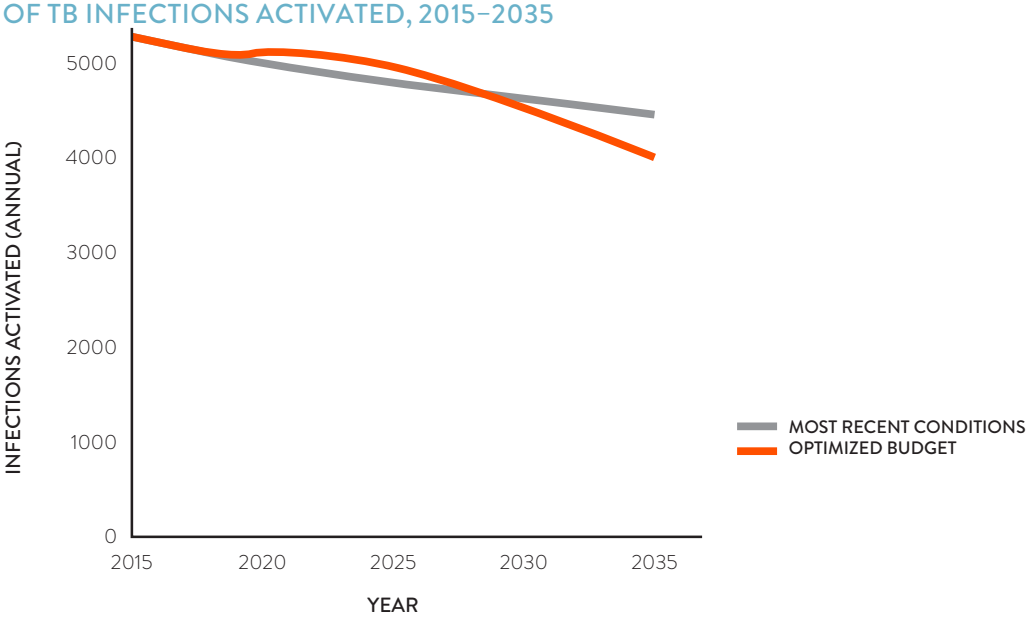
FIGURE 6.5 IMPACT OF OPTIMIZED FUNDING ALLOCATION ON TB-RELATED DEATHS RELATIVE TO 2015 THROUGH TO 2035



Source: Populated using the Optima TB model for Moldova

Figure 6.6 shows the impact of optimized funding on the number of active TB cases estimated in Moldova. Across all populations, with the same levels of annual funding as reported in 2016, optimal allocation of funding could lead to a 20% reduction in the number of new TB cases from 2016 values by 2035, accelerating the existing downward trend.

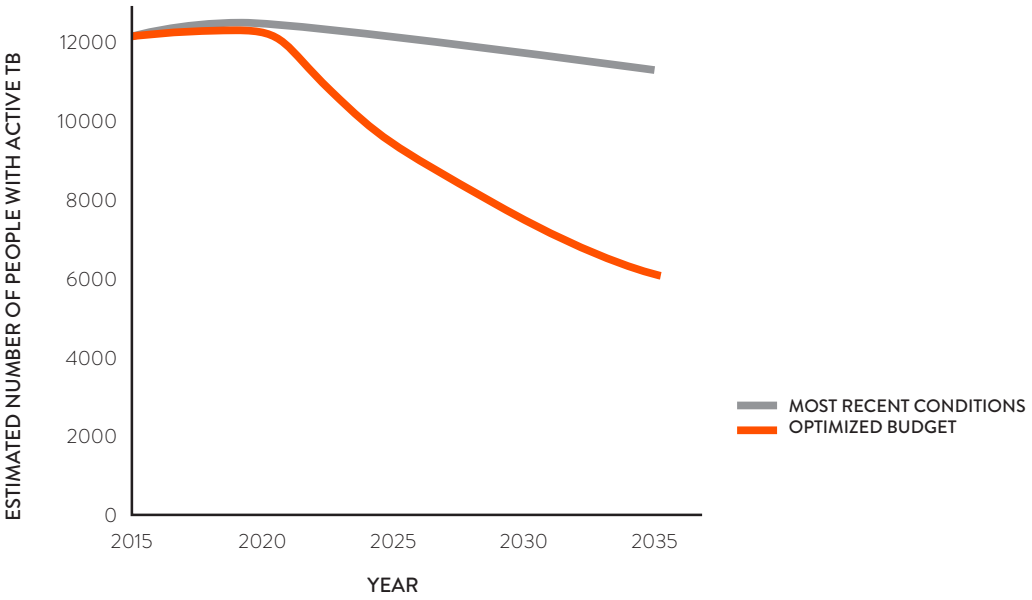
FIGURE 6.6. IMPACT OF OPTIMIZED FUNDING ALLOCATION ON THE NUMBER OF TB INFECTIONS ACTIVATED, 2015–2035



Source: Populated using the Optima TB model for Moldova

Figure 6.7 shows the impact of optimized funding on all active TB cases. Optimal allocation of 2016 levels in funding could lead to a 50% reduction in the number of active TB infections due to more rapid diagnosis and treatment of active TB cases.

FIGURE 6.7 ESTIMATED NUMBER OF PEOPLE WITH ACTIVE TB , 2015–2035



Source: Populated using the Optima TB model for Moldova

6.2 WILL OPTIMIZED ALLOCATIONS OF CURRENT RESOURCES ACHIEVE NATIONAL AND GLOBAL TARGETS?

This section explores to what extent the optimized allocations shown in previous chapters will achieve national and global targets with the level of resources available in 2016 (17.5 million EUR), if funding were reduced to 50%-90% of 2016 TB spending and if funding was increased to 110%-120% of 2016 levels.

IMPACT OF OPTIMIZED ALLOCATION OF 2016 TB FUNDING LEVELS

The question remains whether optimal allocation of funding can lead to the achievement of Moldova's desired TB targets. Results for the optimization analysis showed that with 2016 funding levels, but with optimized allocation the following progress could be made towards national targets by 2020 including:

- a reduction in TB-related deaths by up to 10%;
- a reduction in new active TB infections by up to 5%;
- meeting or exceeding national targets for MDR-TB detection rates; and
- increasing treatment success for MDR-TB by up to 38%.

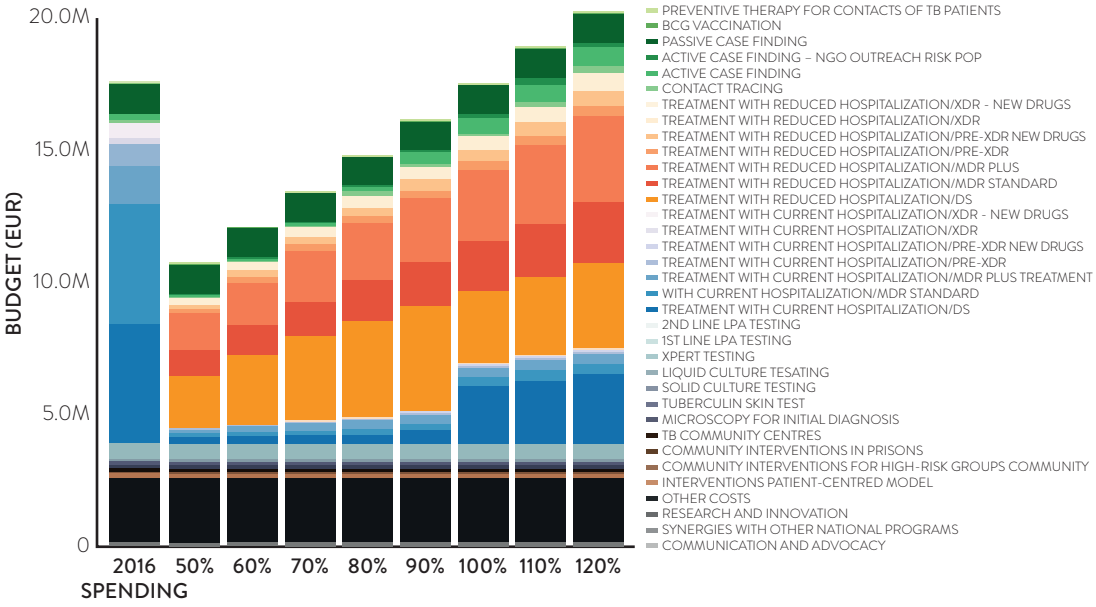
In terms of international goals, resource optimization showed that with 2016 funding levels the following could be achieved by 2035:

- a reduction in the number of new active TB infections by up to 20%;
- a reduction in the number of active TB infections by up to 50%; and
- a reduction of TB-related deaths by up to 50%.

THE IMPACT OF OPTIMIZED RESOURCE ALLOCATION ACROSS VARYING FUNDING LEVELS

Figure 6.8 summarizes the optimal allocation across TB programs with variable levels in funding from 50% to 120%compared with 2016 spending and allocation.

FIGURE 6.8 DIFFERENT OPTIMAL ALLOCATIONS WITH VARIABLE LEVELS IN FUNDING

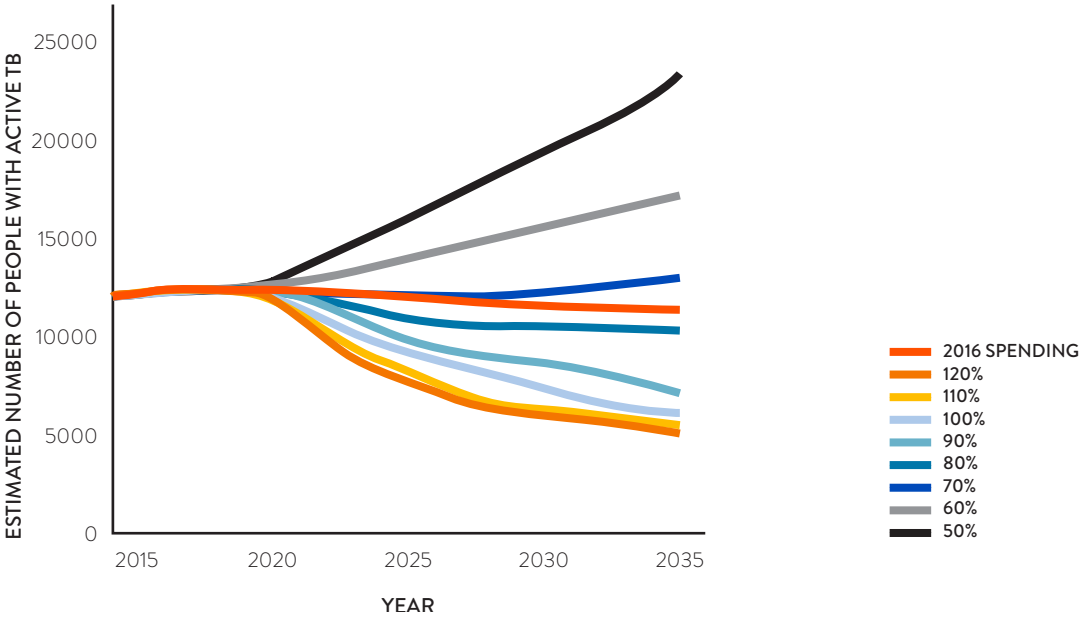


Source: Populated using the Optima TB model for Moldova

IMPACT OF DIFFERENT SPENDING AMOUNTS ON TB OUTCOMES

Figure 6.9 illustrates the health impact of different optimally allocated TB budget amounts. If resources were optimally allocated, model projections suggest significant reductions in active TB infections and TB-related deaths. However, similar reductions could also be attained even if there were minor decreases to 2016 funding (to 90% or 80%), as it was estimated that screening, diagnosis, and treatment coverage would be retained by targeting resources towards the most cost-effective programs. Importantly, it was projected that reductions of over 10% in funding would lead to increases in the numbers of TB infections and deaths. Conversely, increasing spending by 10% or more would allow for targets to be reached before 2035, by reaching larger proportions of people who can then be linked to care. In terms of specific international targets, however, modeling showed that for Moldova, increases in spending alone will not be sufficient to meet the 2035 End TB targets. Beyond resource optimization and optimized increases in funding, new approaches and innovative technologies will be required if targets are to be met.

FIGURE 6.9 IMPACT ON ACTIVE TB CASES OF OPTIMIZATION OF VARIABLE LEVELS OF 2016 SPENDING, 2015–2035



Source: Populated using the Optima TB model for Moldova

7. CONCLUSIONS AND RECOMMENDATIONS

Optima TB analyses identified and illustrated several options to improve the allocative efficiency of Moldova's TB response. The allocative efficiency analysis of Moldova's TB response found that optimized allocation of the 15 million EUR spent on TB in 2016 could lead to a:

- 5% reduction in TB incidence by 2020 and 20% by 2035;
- 10% reduction in TB prevalence by 2020 and 50% by 2035; and
- 10% reduction in TB-related deaths by 2020 and 50% by 2035.

Optimized allocation could accelerate process towards End TB targets; however, additional funds and new technologies will be needed to achieve global 2035 goals.

1 **Transition from hospital-focused to ambulatory treatment modalities could reduce the cost of TB treatment by 24% and free up 2.8 million EUR for reallocation to highest-impact TB interventions.** High and long hospitalization is the primary cost driver of the TB response in Moldova. Evidence suggests that hospital-based treatment does not have clinical benefits over ambulatory treatment. The duration of hospitalization could be reduced substantially from 40 to 14 days on average for DS-TB treatment to align with international practice. For MDR-TB, hospitalization could be reduced from 127–195 to 60 days.

2 **If the same level of overall TB funding remains available, allocation to screening and diagnostic programs should be increased by an estimated 25% to reduce late diagnoses of active TB.** It is estimated that Moldova has a 43% prevalence of late diagnosis among new and relapsed cases, which suggests the need for increased investment to identify new cases earlier. While enhanced active case finding (ACF) is already part of performance-based financing, analyses indicate that should funding remain at 2016 levels, investment in TB screening and diagnosis should be increased by 25% from 1.5 million EUR to 1.9 million EUR. This should also be coupled with increased focus on ACF methods over passive case finding to identify more missing cases that may not be otherwise be reached within the health system in a timely manner.

3 **Expanded application of new DR-TB drug regimens for pre-XDR- and XDR-TB could lead to a 33% reduction of active XDR-TB prevalence by 2035.** With current drug regimens, Moldova is facing low DR-TB treatment success with a projected 50% increase in XDR-TB by 2020. Reduced hospitalization from between 127 and 195 days to 60 days for XDR-TB cases would allow for increasing coverage by up to 153% which would in principle allow nearly every person with XDR-TB who is aware of their status to be on treatment with new BDQ-based XDR and pre-XDR regimens where eligible or standard regimens where not eligible.

4 **Findings show that current TB treatment adherence support strategies, including patient incentives, should be sustained and new approaches for improving adherence should be explored.** It is estimated that a decrease in the most recent rates in treatment failure and loss-to-follow of up to 10% would save an estimated 1.6-1.8 million EUR in treatment costs and avert 170 DS-TB and 200 DR-TB cases annually. Current patient treatment incentive rates were found to be both effective in addressing loss-to-follow up and cost-effective within the optimization analyses and should therefore be retained. Additionally, while options for increasing treatment adherence such as abbreviated treatment regimens, expanded patient incentives and community support interventions could not be assessed in the model due to insufficient data, these interventions should be explored, and benefits tracked to inform future analyses.

5 **There is a need to evaluate additional active case finding interventions within prison populations.** Modeled latent prevalence is over 40% in the prison population, due to higher exposures to active TB and upon infection, faster progression from early-latent to active TB within the prison system, compared with 25% in the general population. However, treatment outcomes for prisoners are better than for the general population. This combination of results suggests that the emphasis should fall on early diagnoses and cure to prevent transmission. The current policy of entry and exit screening for all prisoners should be maintained; however, additional approaches, including active case finding, contact tracing of diagnosed cases and IPT for reducing infection and progression of TB in penitentiaries should be considered.

6 **Innovative interventions targeted at migrant populations should be considered for reducing TB infection rates.** Model findings suggest that the proportion of new active TB cases among migrants could increase from 18% in 2016 to 35% in 2030 if current trends in migration continues. While the model is not geared to predict trends in migration, which are grounded in many international and national geopolitical factors, assumptions were made for the purposes of this study that the current trends would continue. Migrants currently have lower rates of diagnosis and awareness of their TB risk relative to other populations groups. Opportunities for targeting TB interventions among migrants include enhanced screening including through a multisectoral partnership with border control, as well as community appropriate support mechanisms including information provision through emails, SMS, newsletters and outreach.

7 **Enhancing integration of TB interventions within other health programs to improve outcomes.** Low cost, best practice interventions such as alcohol screening and support services for all TB patients should be considered along. Additional programs for groups at high-risk of acquiring TB infection should also be considered, such as improving linkage to HIV care and treatment in line with global 2020 90-90-90 targets among HIV positive populations. This could result in a 30% decrease in TB incidence and 50% decrease in TB-related deaths within this population.

8 **Further exploration of the geographic, social, economic and other risk factors underlying Moldova's TB epidemic is needed to understand and target key risk groups.** Moldova already has strong database systems which could enhance epidemiological investigations to target active case finding and early diagnoses in high incidence areas and with key risk population groups. Innovative analysis of key populations and key locations could inform active case finding and expanded contact tracing interventions.

9 **Moldova should sustain current TB investment and consider a phased approach towards achieving a sustainable and largely domestically financed TB response.** Modelling studies indicate that a 50% reduction in funding, even if with optimal resource allocation, would result in a doubling of active TB cases. While sustaining 2016 funding levels and reallocating according to optimal allocations could lead to a 20% reduction in TB incidence and 50% reduction in TB-related deaths by 2035. Continued international support and local exploration of implementation efficiencies could further bolster these trends. In the short-term preparing for sustainability will require optimized allocation of resources and enhanced implementation efficiency. In the medium-term opportunities for more integrated TB care could be explored. In the long run, reduced disease burden will be the key to sustainability of the response.

APPENDICES

APPENDIX A.
TECHNICAL SUMMARY OF THE OPTIMA TB MODEL

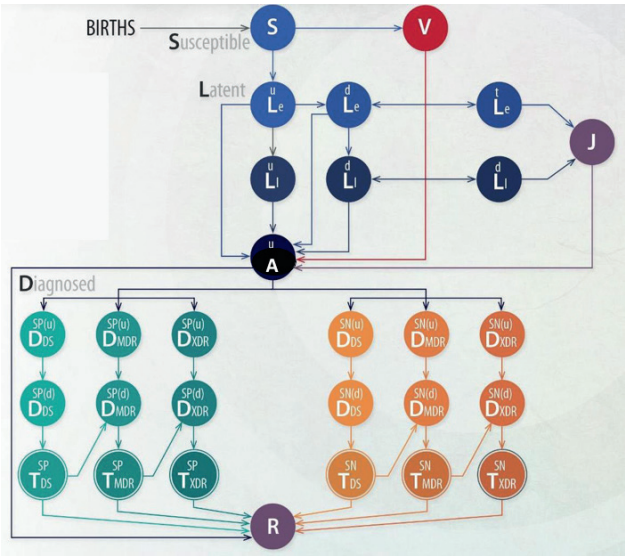
Appendix A provides a brief technical overview of the Optima model. The Optima mathematical modelling suite was designed to support decision-makers in prioritization, resource allocation and planning to maximize impact of health interventions. Optima HIV was the most widely used component of the Optima modelling suite. A more detailed summary of the model and methods is provided elsewhere (Kerr 2016).

Optima TB is a mathematical model of TB transmission and disease progression integrated with an economic and program analysis framework. Optima uses TB epidemic modeling techniques and incorporates evidence on biological transmission probabilities, detailed infection progression and population mixing patterns. Optima TB is a compartmental model, which disaggregates populations into different model compartments including susceptible, vaccinated, early latent, late latent, undiagnosed active TB, diagnosed active TB, on treatment and recovered populations. In addition, compartments are further disaggregated by drug resistance type into drug susceptible (DS), multi-drug resistant (MDR) and extensively drug resistant (XDR).

Optima TB is based on a dynamic, population-based TB model. Figure A.1 shows the basic disease progression implemented in the model at the time it was applied in Moldova.

The model uses a linked system of ordinary differential equations to track the movement of people among health states. 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.

FIGURE A.1 SCHEMATIC DIAGRAM OF THE HEALTH STATE STRUCTURE OF THE OPTIMA TB MODEL



S = Susceptible

L=Latent TB
e=early (infection <5 years)
l=late (infection >5 years)

u=undiagnosed
d=diagnosed

A= Active TB
u=Undiagnosed
d=Diagnosed
t=On treatment

R=Recovered

DS=Drug susceptible
MDR=Multi-drug resistant
XDR=Extensively drug resistant
SP=Smear positive
SN=Smear negative

Source: Prepared based on Optima TB model structure

Note: each compartment represents a single population group with a specified health state. Each arrow represents the movement of many 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.

Each compartment (figure A.1, circular shaped items) corresponds to a single differential equation in the model, and each rate (figure A.1, arrows) corresponds to a single term in that equation. Table A.1 lists the parameters used in the Optima TB model; most of these are used to calculate the force of infection. Empirical estimates are interpreted for model parameters in Bayesian terms as previous distributions. The model is then calibrated: finding posterior distributions of the model parameter values so that the model generates accurate estimates of TB prevalence, the number of people on treatment, as well as using any other available epidemiological data or estimates, such as the number of estimated number of TB-related deaths. Model calibration and validation normally should be performed in consultation with country governments for which the model is being applied.

TB RESOURCE OPTIMIZATION AND PROGRAM COVERAGE TARGETS

A novel component of the Optima approach is the capability to determine the optimal resource allocation to 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 coverage levels required to achieve these targets, Optima can be used to inform TB strategic planning in this regard.

The key assumptions of resource optimization are relationships among (1) the cost of TB programs for specific target populations, (2) the resulting population specific coverage levels targeted by these programs, and (3) how changes in TB program coverage levels targeted populations will influence clinical outcomes. Defining such relationships is necessary to estimate how incremental changes in spending (i.e. marginal costs) will affect the trend of the TB epidemic in a given context.

To perform the optimization, Optima uses a global parameter search algorithm, which is an adaptive stochastic descent algorithm (Kerr et al. 2017) This algorithm is similar to simulated annealing in that it makes stochastic downhill steps in parameter space from an initial starting point. However, unlike simulated annealing, the algorithm chooses future step sizes and directions based on the outcome of previous steps. For certain classes of optimization problems, the team has shown that the algorithm can determine optimized solutions with fewer function evaluations than traditional optimization methods, including gradient descent and simulated annealing.

UNCERTAINTY ANALYSES

Optima uses a Markov chain Monte Carlo (MCMC) algorithm for performing automatic calibration and for computing uncertainties in the model calibration to epidemiological data. With this algorithm, the model is run many times (typically 1,000–10,000 times) to generate a range of epidemic projections. Differences in projections 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, referred to as cost functions. To incorporate uncertainty surrounding these curves, users define upper and lower limits for both coverage and behaviour for two scenarios, (1) zero spending and (2) very high spending levels to achieve a maximum or saturation coverage.[2]

[2]All available historical spending data and achieved outcomes of spending, data from comparable settings, experience, and extensive discussion with stakeholders in the country of application can be used to inform these ranges. All logistic curves within these ranges then are allowable and are incorporated in the uncertainty analyses. These cost-coverage and coverage-outcome curves are thus reconciled using epidemiological and biological data in a Bayesian optimal way, thereby enabling the calculation of unified uncertainty estimates.

APPENDIX B.
OPTIMA TB MODEL CALIBRATION

This appendix describes the calibration process for the Optima TB study conducted for Moldova, and specific modifications were necessary to include to best calibrate the model to the TB epidemic for Moldova.

DEMOGRAPHICS

Demographics are calculated for each key population within the model by considering:

- initial population size;
- annual birth rates;
- annual mortality rates;
- transfers in and out of population groups due to aging; and
- other transfers in and out of population groups, due to non-aging effects, such as migration or incarceration.

Population size, number of births and deaths are directly reported by the country government, while transfers between population groups can either be at rates that are calculated using values similarly specified following known data, or due to aging, where a proportion of a key population is moved to the next population, assuming a uniform distribution of ages within a key population. As these values are directly reported by the country with considerable confidence, the model output is usually consistent with known data values for demographics, with no modification required.

PEOPLE LIVING WITH HIV

As population size and HIV comorbidity are considered more significant than risk of acquiring TB infection due to age, it was agreed that all HIV-positive populations over the age of 18 would be combined into one population, as well as because the HIV-positive numbers for children, prisoners, and migrants were not sufficiently high to justify including these as separate population groups. It was estimated that there are only around 40 prisoners living with HIV who are not currently on ART (Doltu 2015).

HIV incidence rates were taken from UNAIDS estimates (UNAIDS AIDSinfo).

HIGH ALCOHOL CONSUMPTION (HAC)

High alcohol consumption was only a comorbidity with >5% of notifications. Prevalence of HAC was reported by the country to be approximately 12% in the 18+ population, and is modeled as effecting the latent progression rates – both doubling the early latent departure rate and making it significantly more likely that an early latent TB case will progress directly to active TB (93% of the time as for those with untreated HIV, compared to 0.177 in cases without comorbidities).

MIGRATION

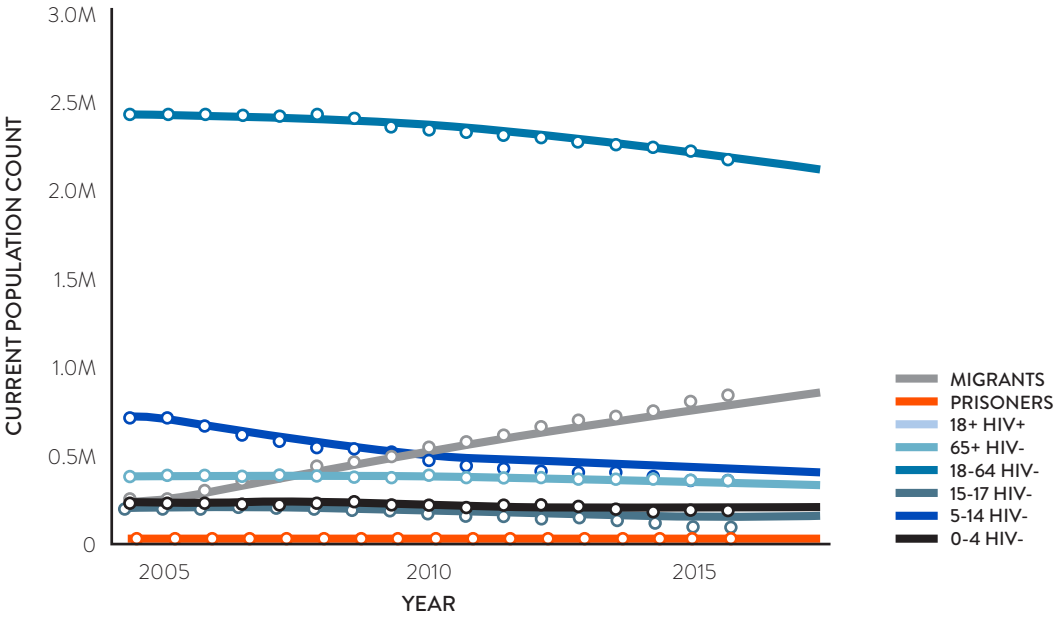
The population of Moldovan nationals who emigrate primarily for work to foreign countries (primarily to the Commonwealth of Independent States (CIS) and European Union (EU)) and thereafter return to country is of importance to the TB epidemic in Moldova. This however, presents a significant modeling challenge as the modeled characteristics of this population could be interpreted in multiple ways.

In consultation with the country team, it was decided that the transition for migrants would be a one-way transition to capture all long-term outcomes for migrants returning to country, but without migrants ever returning to the general population. The inclusion criterion was that migrants had “spent a minimum of three months overseas during any single previous 12-month period”.

POPULATION SIZE

There was some uncertainty expressed by the country team over the total population size for Moldova. Without a clear and recent population census or consensus on how to account for the population from the Left Bank of Moldova, United Nations Population Division population size estimates for the general population were used and adjusted to subtract key population size estimate values (United Nations Population Division, 2017).

FIGURE B.1 ANNUAL POPULATION SIZES IN MODEL COMPARED TO REPORTED DATA, 2005–2018



Source: Populated using the Optima TB model for Moldova

DISEASE PROGRESSION USING EPIDEMIOLOGICAL MODEL

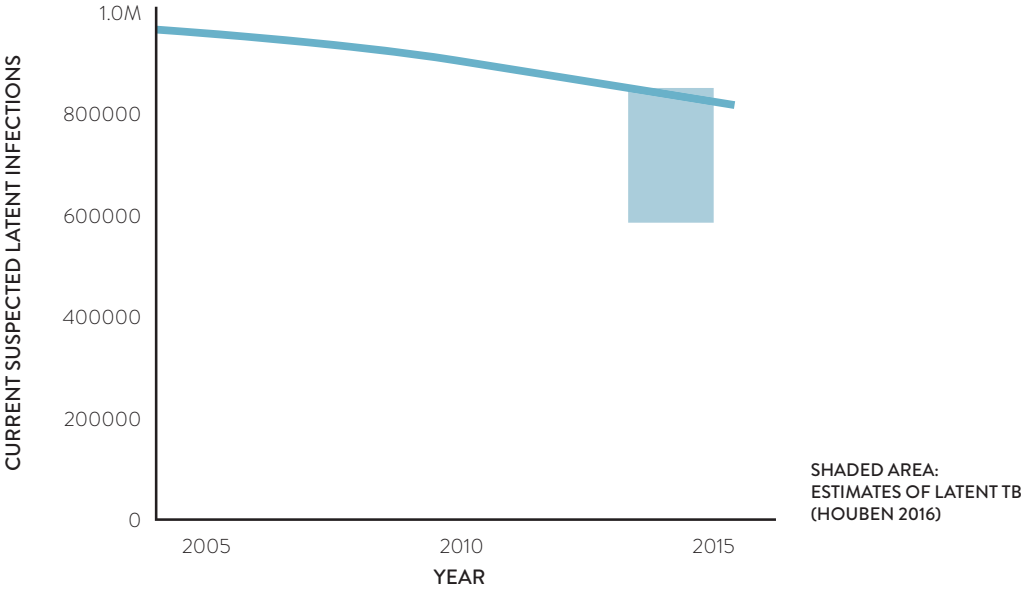
Progression rates for TB were obtained for natural progression of the disease and in response to treatment for values such as disease duration and fatality. The model was set-up to replicate these experiments by considering an overall population that began with the same disease state (i.e. susceptible), and examined how quickly people progressed to subsequent disease states or death.

Using this process, we generally found good agreement with the values for case fatality and disease duration for the HIV-negative population, for both natural progression of the HIV disease and when on antiretroviral treatment (Table B.1; Figure B.2).

LATENT TB

Significant uncertainty exists over latent TB prevalence in the general population of Moldova, with in-country discussions suggesting that latent cases could be much higher, but the best available estimates are between 611,000 and 882,000 in 2014 (Houben 2016). Latent rates were estimated to be just within the upper end of this range in 2015 at 859,000 latent TB infections (LTBI). This equates to approximately 30% prevalence of LTBI among the adult population aged 18+, far lower among children, and over 70% in the prisoner population, but with a decreasing trend overall in recent years (figure B.2).

FIGURE B.2 MODELED NUMBER OF LATENT TB INFECTIONS, 2002–2018



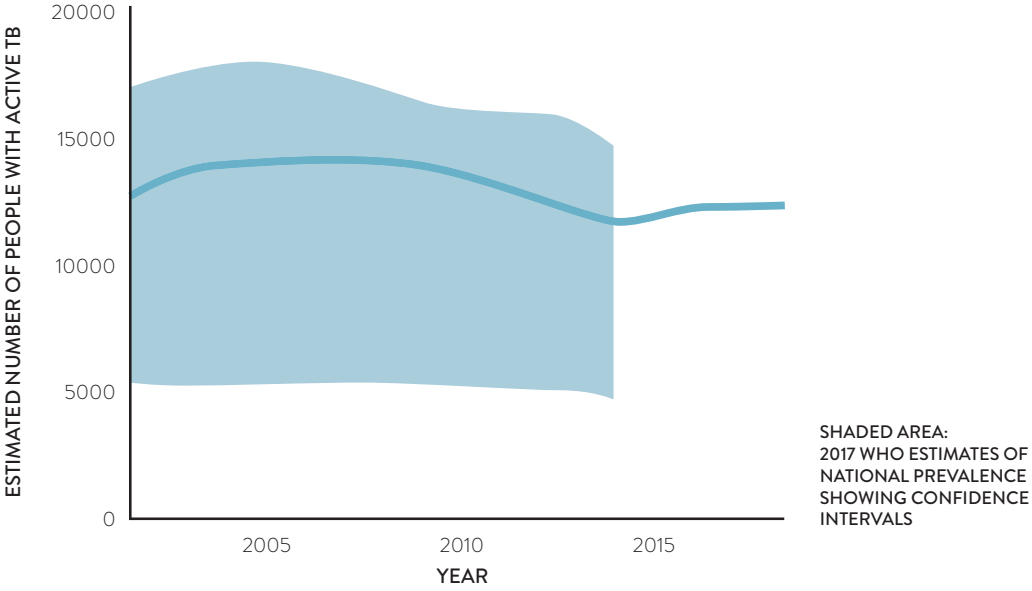
Source: Populated using the Optima TB model for Moldova

PREVALENCE ESTIMATES FROM NOTIFIED CASES FOR TOTAL ACTIVE TB

Data provided by Moldova included the yearly numbers of registered notified new TB cases, but not estimates in absolute numbers for TB incidence or prevalence. Estimates for these were calibrated to match the latest ECDC/WHO report. The estimated number of active TB cases in Optima TB (Figure B.3) is slightly higher than the WHO TB prevalence estimates for Moldova, but well within the confidence bounds of those estimates. Incidence estimates in Optima TB (Figure B.4) are higher than the WHO TB estimates for Moldova but in keeping with trends.

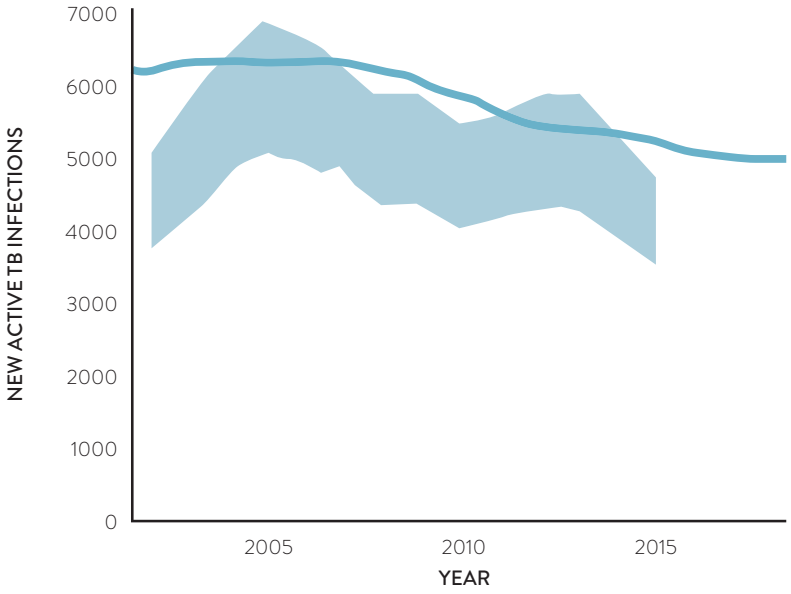
Higher estimates of TB prevalence from the Optima TB model, compared with prevalence estimates reported using routine surveillance, are likely due to different disease input assumptions on parameters such as disease duration, which in Moldova is relatively long in duration due to the high prevalence of drug-resistant TB and a relatively large number of people in palliative care who do not access any form of treatment for TB.

FIGURE B.3 MODELED NUMBER OF PREVALENT ACTIVE TB INFECTIONS, 2002–2018



Source: Populated using the Optima TB model for Moldova

FIGURE B.4 MODELED NUMBER OF INCIDENT ACTIVE TB INFECTIONS, 2000–2018



Source: Populated using the Optima TB model for Moldova

Disaggregation into the different age and risk categories was done on the assumption that notification rates (smoothed to a three-year rolling average) were representative of the number of infections in each category, with children less likely to be diagnosed (35% in infants, 80% and 60% respectively in older children) and thus assumed to have a proportionally higher incidence and prevalence relative to the number of notifications.

The need to disaggregate prevalence according to TB smear-status and drug resistance-type was also addressed using proportions based on the numbers of notified cases reported by the country. The respective age and risk-group estimates were multiplied by the proportions of smear-positive and smear-negative cases out of the total number of recorded notified cases by age and risk-group. Similarly, to disaggregate by drug resistance-type, the proportions of DS-TB, MDR-TB, or XDR-TB as fractions of the total notified cases of a given smear-status in an age group, was multiplied by the smear-status prevalence estimates of their respective age group.

The assumptions used to initialize the model, for year 2000, were individually calibrated to best match consistent trends for population specific prevalence.

PROGRESSION FROM LATENT TO ACTIVE TB

To evaluate the outflow of people moving from the early latent compartment to both the late latent and active TB compartments we based our analysis on a review paper (Andrews 2012). In this work, several studies from the pre-chemotherapy era were analyzed where healthy individuals were in contact with actively infected individuals. There was follow-up of subjects for a variable amount of time and the number of new active cases were recorded. Due to high-levels of TB exposure it was assumed that people who came in contact with people actively infected with TB were themselves infected with latent TB. Using statistical analysis (i.e. the survival model) we were able to infer the probability that latent cases would develop active TB during the first five years after infection (i.e. the timeframe for early latent TB).

We applied the same methodology to derive the probability for these individuals with latent TB of not developing active TB after five years and, combining these two values, we were able to estimate the rate of early latent progression.

FIGURE B.5 DISEASE PROGRESSION

A. Determining disease states following progression from the initial state. Here, births and population migration were not allowed. Depending on the investigation, testing and treatment rates were disabled to represent the natural progression of the disease without intervention, or set to the calibrated version if testing and treatment were included. This specific example shows those HIV-negative individuals who were treated for TB. The population is aged 15-64 years.

B. Disease progressions were used to determine average disease duration and case fatality rates, as well as other characteristics such as percentage of people who spontaneously self-heal. Abbreviations include: 5-year (5yr) and 10-year (10yr).

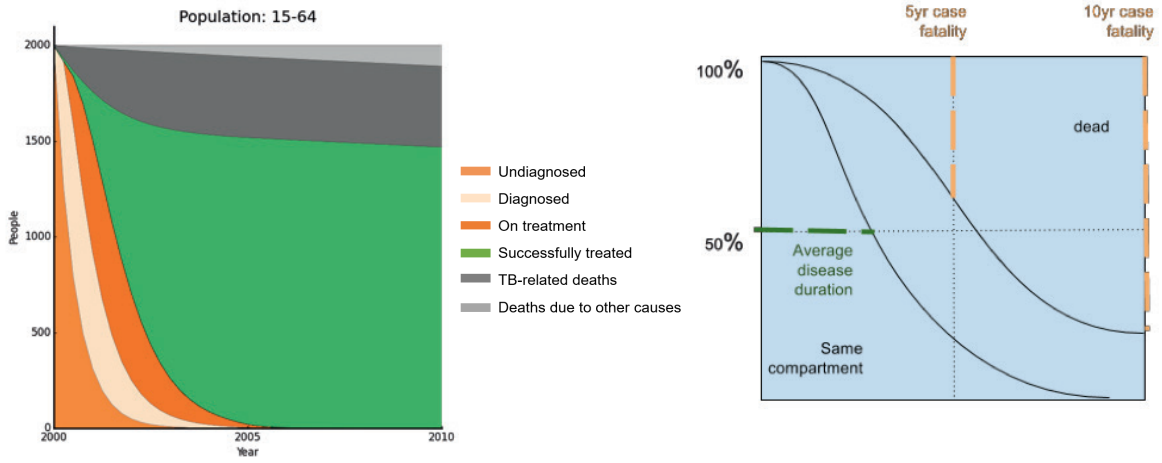
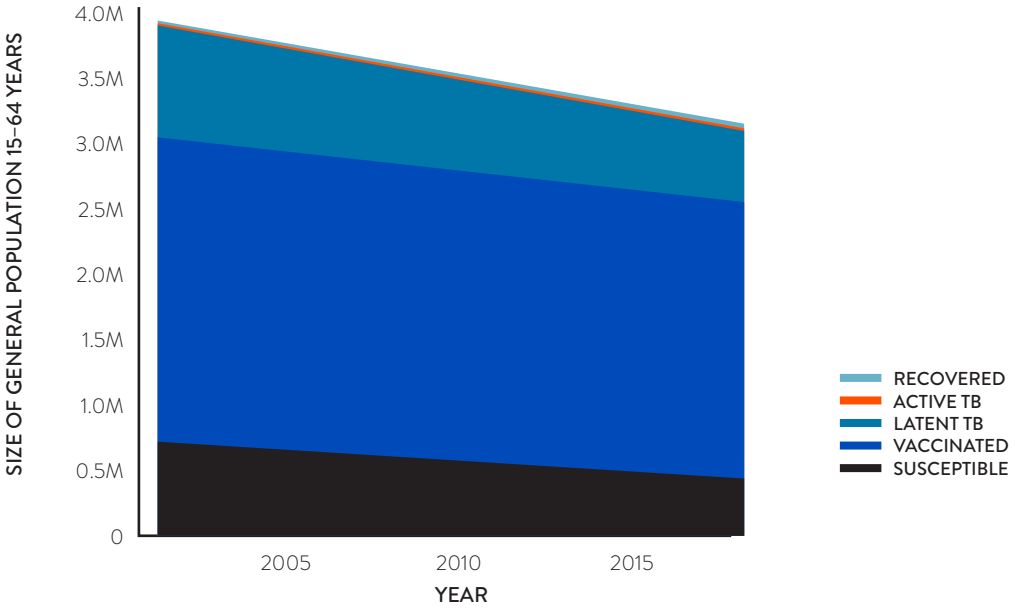


TABLE B.1 RATES OF NATURAL DISEASE PROGRESSION AND DISEASE PROGRESSION ON TREATMENT

NATURAL DISEASE PROGRESSION		MODEL OUTPUT	SOURCE
Untreated, HIV-negative	**Disease duration** 1-4 years 3 years	3.25-3.50 years	WHO Tiemersma 2011
	Smear positive case fatality Case fatality rate 70% 5-year case fatality 55% 10-year case fatality 72%	 46% at 5 years 66% at 10 years	 WHO Tiemersma 2011 Tiemersma 2011
	Smear negative case fatality Case fatality rate 20% 10 year[4] case fatality 20%	 15% at 10years	 WHO Tiemersma 2011
Untreated, HIV-positive	Disease duration: 0.01-0.2 years SP Case fatality rate: 83% SN Case fatality rate: 74%		WHO 2017, 2018
DISEASE PROGRESSION ON TREATMENT		**MODEL OUTPUT**	**SOURCE**
Treated, HIV-	Disease duration: 0.2-2 years	0.25-2.00 years	WHO 2017, 2018
Treated, HIV+	Disease duration: 0.01-1 year		WHO 2017, 2018

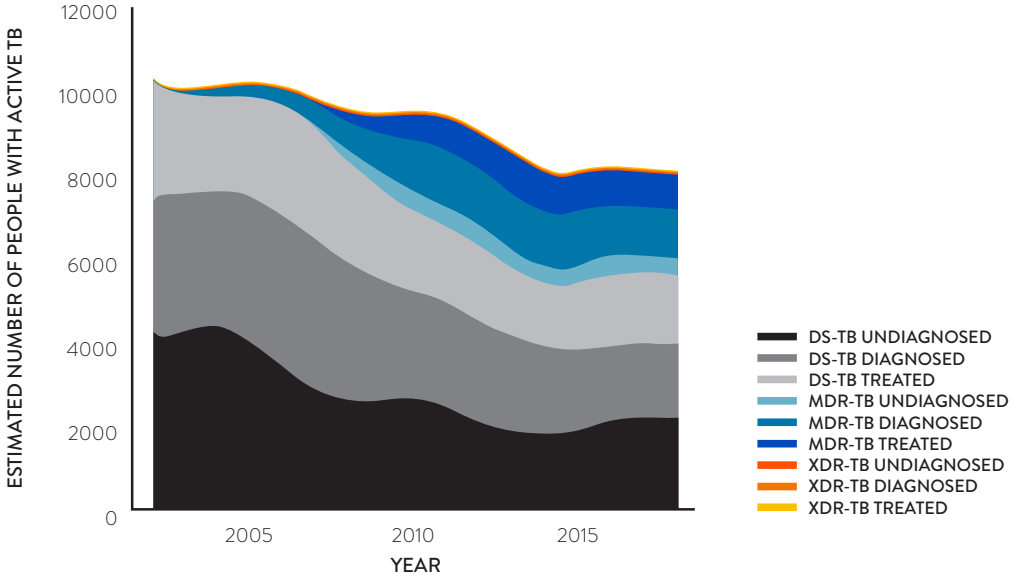
[4]*Reported as 'lifetime case fatality', although in the same study the authors refer to a maximum window of 10 years.*

FIGURE B.6 SAMPLE CALIBRATION OF THE GENERAL POPULATION 15–64 YEARS BY TB STATUS, 2000–2018



Source: Populated using the Optima TB model for Moldova

FIGURE B.7 SAMPLE CALIBRATION FIGURE, ACTIVE TB INFECTIONS BY CARE STATUS: GENERAL POPULATION 15–64 YEARS, 2000–2018



Source: Populated using the Optima TB model for Moldova

APPENDIX C.
KEY DATA INPUTS USED TO INFORM THE MODEL

DEMOGRAPHIC INPUTS

TABLE C.1 POPULATION SIZES

POPULATION	2000	2005	2010	2015	2016
0-4	234,213	192,852	201,919	198,384	192,245
5-14	719,505	539,320	409,382	360,938	351,249
15-17	209,572	207,500	148,340	85,998	91,656
18-64	2,431,471	2,425,418	2,310,985	2,219,976	2,168,134
65+	385,318	391,454	382,464	377,817	379,184
18+ HIV-positive*	7,500				15,488
Prisoners†	10,923	9,225	6,324	8,054	7,761
Migrants†	231,776	421,131	610,486	799,841	837,712

Source: Prepared by authors based on UN World Population Prospects (United Nations, Department of Economic and Social Affairs, Population Division, 2015)

**18+ HIV-positive population for 2000 was cited in the Analysis of the epidemiological impact of tuberculosis in the Republic of Moldova, 2017 study and from the UNAIDS AIDSinfo repository for the 2016 values. (UNAIDS AIDSinfo 2017) The model then interpolates population size values for years 2001 to 2015.*

†Population sizes for prisoner and migrant groups were supplied by country.

TABLE C.2 BACKGROUND MORTALITY (PERCENTAGE OF PEOPLE WHO DIE ANNUALLY)

POPULATION	2000	2005	2010	2015	2016
0-4	0.440%	0.378%	0.362%	0.282%	0.282%
5-14	0.059%	0.059%	0.059%	0.059%	0.059%
15-17	0.048%	0.049%	0.049%	0.049%	0.049%
18-64	0.649%	0.636%	0.529%	0.561%	0.562%
65+	7.292%	7.900%	8.800%	9.400%	9.200%
18+ HIV-positive (off ART)	6.149%	4.636%	6.529%	6.561%	6.562%
18+ HIV-positive (on ART)		Assumed the same as for the population aged 18-64 years			
Prisoners					
Migrants					

Source: Prepared by authors based on United Nations Population Division data, accessed 22 December 2017

TABLE C.3 NEWLY NOTIFIED TB INFECTIONS BY POPULATION

POPULATION GROUPS	2000	2005	2010	2015	2016
0-4 years	31	67	39	43	36
5-14 years	59	122	100	62	67
15-17 years	68	103	56	42	40
18-64 years	2764	4929	3756	2795	2704
65 years and older	183	311	248	219	265
18 years and older HIV positive	0	48	301	383	373
Prisoners	289	685	270	153	208
Migrants	1	47	769	604	542

Source: Vital Registration System, accessed 22 December 2017

TABLE C.4 NEWLY NOTIFIED TB INFECTIONS BY POPULATION AND DRUG TYPE

		2000	2005	2010	2011	2012	2013	2014	2015	2016
0-4	Total	31	67	39	52	48	38	44	43	36
0-4	DS-TB	31	67	39	52	46	37	44	42	34
0-4	MDR-TB	0	0	0	0	2	1	0	1	2
0-4	XDR-TB	0	0	0	0	0	0	0	0	0
5-14	Total	59	122	100	105	96	93	69	62	67
5-14	DS-TB	59	121	97	103	93	90	66	60	64
5-14	MDR-TB	0	1	3	2	3	3	3	2	2
5-14	XDR-TB	0	0	0	0	0	0	0	0	1
15-17	Total	68	103	56	70	54	48	44	42	40
15-17	DS-TB	68	101	45	55	48	41	40	39	30
15-17	MDR-TB	0	2	11	15	5	7	4	3	10
15-17	XDR-TB	0	0	0	0	1	0	0	0	0
18-64	Total	2764	4929	3756	3687	3575	3366	3047	2795	2704
18-64	DS-TB	2760	4759	2939	2890	2844	2615	2445	2192	2177
18-64	MDR-TB	4	167	802	775	719	733	589	560	485
18-64	XDR-TB	0	3	15	22	12	18	13	43	42
65+	Total	183	311	248	222	250	258	250	219	265
65+	DS-TB	183	309	229	210	232	235	223	202	246
65+	MDR-TB	0	2	19	12	16	23	27	17	18
65+	XDR-TB	0	0	0	0	2	0	0	0	1

		2000	2005	2010	2011	2012	2013	2014	2015	2016
18+ HIV+	Total	0	48	301	284	305	316	341	383	373
18+ HIV+	DS-TB	0	35	185	202	223	207	248	256	256
18+ HIV+	MDR-TB	0	13	115	82	81	107	90	118	106
18+ HIV+	XDR-TB	0	0	1	0	1	2	3	9	11
Prisoners	Total	289	685	270	209	226	193	159	153	208
Prisoners	DS-TB	288	615	177	146	176	145	111	105	152
Prisoners	MDR-TB	1	70	93	63	50	47	48	44	54
Prisoners	XDR-TB	0	0	0	0	0	1	0	4	2
Migrants	Total	1	47	769	823	878	852	780	604	542
Migrants	DS-TB	1	41	600	665	698	666	626	503	439
Migrants	MDR-TB	0	6	167	156	177	181	150	99	97
Migrants	XDR-TB	0	0	2	2	3	5	4	2	6

Source: Vital Registration System, accessed 22 December 2017

TABLE C.5 NEWLY NOTIFIED TB INFECTIONS BY SMEAR STATUS AND DRUG TYPE AMONG PEOPLE AGED 18–64 YEARS

			2000	2005	2010	2011	2012	2013	2014	2015	2016
18-64	Smear-	Total	1940	2562	2113	2067	2035	1409	1184	998	992
18-64	Smear-	DS-TB	1940	2553	1907	1868	1809	1375	1158	979	974
18-64	Smear-	MDR-TB		9	205	197	220	33	26	19	18
18-64	Smear-	XDR-TB			1	2	6	1			
18-64	Smear+	Total	824	2367	1643	1620	1540	1957	1863	1797	1712
18-64	Smear+	DS-TB	820	2206	1032	1022	1035	1240	1287	1213	1203
18-64	Smear+	MDR-TB	4	158	597	578	499	700	563	541	467
18-64	Smear+	XDR-TB		3	14	20	6	17	13	43	42

Source: Vital Registration System, accessed 22 December 2017

COST DATA

TABLE C.6 UNIT COSTS FOR TB PROGRAMS FOR MOLDOVA

DIAGNOSIS & PREVENTIVE PROGRAMS	UNIT COST (PER TEST OR PER PERSON PER YEAR), 2016, US$
BCG vaccination	$1.13
Preventive therapy for contacts of TB patients	$2.41
Preventive therapy for HIV positive individuals	$2.41
Contact tracing	$305.44
Active case finding	$610.03
Active case finding - NGO outreach risk population	$660.10
Passive case finding	$275.78
PROGRAMS TREATED AS FIXED COST	**ANNUAL COST**
Microscopy for initial diagnosis	$153,748
Tuberculin skin test	$112,201
Solid culture testing	$11,829
Liquid culture testing	$107,772
GeneXpert testing	$564,991
1st line LPA testing	$20,677
2nd line LPA testing	$6,739
Community interventions patient-centred model	$160,000
Community interventions for high-risk groups	$48,000
Community interventions in prisons	$30,000
TB community centres	$105,225
Communication & advocacy	$81,770
Synergies with other national programs	$48,548
Research & innovation	$605
Other costs	$2,457,501

Source: Country reported

TABLE C.7 TREATMENT DURATION AND COST OF CARE BY MODALITY AND DRUG RESISTANCE TYPE

TREATMENT DURATION (IN DAYS)					UNIT COST PER DAY US$		COST OF CARE
MODALITY	REGIMEN	INPATIENT	OUTPATIENT	TOTAL	INPATIENT	OUTPATIENT	TOTAL US$
CURRENT PRACTICE							
Current hospitalization	DS treatment	40	161	201	$20.72	$3.27	$1,392.30
Current hospitalization	MDR standard	127	444	570	$20.72	$3.38	$6,131.35
Current hospitalization	MDR plus	127	444	570	$20.72	$3.38	$7,023.81
Current hospitalization	Pre-XDR	160	560	720	$20.72	$3.38	$8,108.70
Current hospitalization	Pre-XDR new drugs	127	444	570	$20.72	$3.38	$10,583.98
Current hospitalization	XDR	195	685	880	$20.72	$3.38	$9,265.92
Current hospitalization	XDR – new drugs	160	560	720	$20.72	$3.38	$14,731.84
ALTERNATIVE MODALITIES							
Reduced hospitalization	DS treatment	14	187	201	20.72	3.27	933.27
Reduced hospitalization	MDR standard	60	510	570	20.72	3.38	4,978.27
Reduced hospitalization	MDR plus	60	510	570	20.72	3.38	5,870.73
Reduced hospitalization	Pre-XDR	60	660	720	20.72	3.38	6,378.40
Reduced hospitalization	Pre-XDR new drugs	60	510	570	20.72	3.38	9,430.91
Reduced hospitalization	XDR	60	820	880	20.72	3.38	6,919.91
Reduced hospitalization	XDR – new drugs	60	660	720	20.72	3.38	13,001.54

Source: Prepared by authors based on national program records

GLOSSARY

Allocative efficiency (AE)	Within a defined resource envelope, AE of health or TB-specific interventions provides the right intervention to the right people at the right place in the correct way to maximize targeted health outcomes.
Effectiveness	Degree of achievement of a health outcome in a real-world setting.
Efficiency	Achievement of an output with the lowest possible input without compromising quality.
Financial sustainability	Ability of government and its partners to continue spending on a health or TB outcome for the required duration and to meet any cost of borrowing without compromising the government's, household's, or other funding partner's financial position.
TB incidence	Estimated total number (or rate) of new (total number of diagnosed and undiagnosed) TB infections in a given period.
TB prevalence	Percentage of people who are infected with TB at a given point in time.
Implementation efficiency	Set of measures to ensure that programs are implemented in a way that achieves outputs with the lowest input of resources. In practical terms, improving implementation efficiency means identifying better delivery solutions. Doing so requires improving planning, designing service delivery models, and assessing and addressing service delivery "roadblocks." Implementation efficiency will improve the scale, coverage, and quality of programs.
Model	Computer system designed to demonstrate the probable effect of two or more variables that might be brought to bear on an outcome. Such models can reduce the effort required to manipulate these factors and present the results in an accessible format.
Program effectiveness	Program effectiveness incorporates evaluations to establish what works and impacts disease and/or transmission intensity, disseminating proven practice, and improving the public health results of programs.
Program sustainability	Ability to maintain the institutions, management, human resources, service delivery, and demand generation components of a national response until impact goals have been achieved and maintained over time as intended by the strategy.
Saturation	Maximum level of coverage that a program can achieve.
Technical efficiency	Delivery of a (health) service in a way that produces maximum output at the lowest possible unit cost while according with operational quality standards.
Universal health coverage	Universal health coverage (UHC), is defined as ensuring that all people have access to the promotive, preventive, curative, rehabilitative, and palliative health services that they need, of sufficient quality to be effective, while ensuring that the use of these services does not expose the user to financial hardship.

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