Annexes

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Annex 1. Measuring progress towards targets

The Stop TB Partnership will measure progress towards the 90-(90)-90 targets, the milestones for research and development, and the funding goals set out in the Plan.

The three 90-(90)-90 high-level targets are summarized below:

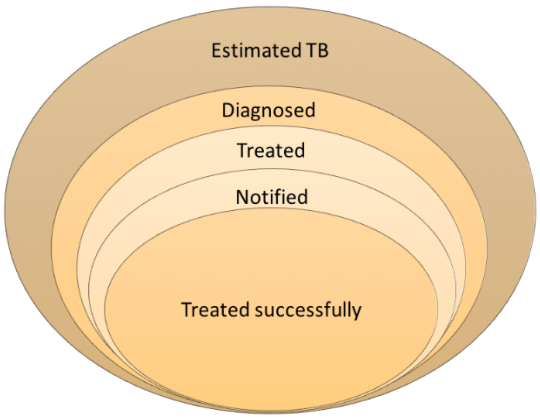
1.	Reach at least 90% of all people with TB and place all of them on appropriate therapy: first-line, second-line, and preventive therapy, as required.
2.	As a part of this approach, reach at least 90% of the key populations, the most vulnerable, underserved, at-risk populations.
3.	Achieve at least 90% treatment success for all people diagnosed with TB through affordable treatment services, adherence to complete and correct treatment, and social support.

These targets need to be reached as early as possible, but no later than 2025.

WHO has developed more detailed indicators and targets for the End TB Strategy (see tables below). These indicators have been prioritized into a list of "Top-10" indicators. The remaining indicators serve as examples of each pillar of the End TB Strategy. These are mentioned below.

The Global Plan recommends:

1. Additional process-oriented indicators and targets should be developed to track progress against elements related to the paradigm shift described in the Plan. This should include but not be limited to numbers tested for TB, community systems, key populations, private sector care, and so on.
2. Data collected to measure progress against all indicators and targets should be appropriately disaggregated for adults and children, sex, and relevant key populations.
3. As part of the paradigm shift, the way data are collected and used needs to change. The following changes are recommended:
    a. All diagnosed TB patients should be notified. Currently, in many high-burden countries, only a subset of diagnosed TB cases start treatment and are notified.
    b. TB programmes need to be accountable for all diagnosed TB patients, and all of them should be included when reporting treatment outcomes. The third 90 calls for at least 90% treatment success for diagnosed TB patients. Currently, in many countries, no data are collected systematically on the gap between the number of patients diagnosed and the number of those initiated on treatment. This gap has been documented to be as high as 10–20% in settings where data are available. The figure below shows the different gaps that currently exist between the estimated number of people with TB and those who ultimately receive successful treatment.



    c. Data need to be made available at subnational, national and global levels much earlier than they are now. Electronic systems, case-based data and more frequent reporting cycles will help drive progress in this direction.
    d. More qualitative real-time data need to be collected from frontline workers, patients and communities, and used for improving services through the use of social media and crowd-sourcing techniques.
    e. Countries need to make greater use of subnational quantitative and qualitative data for identifying local issues, hot spots and barriers to access.
    f. Vital registration systems should be strengthened and used.
    g. TB information systems should be integrated into district health information system initiatives.

h. Communities need to be involved in programme monitoring and evaluation, and data need to be converted into simple, actionable information for use by communities for advocacy.

Table 1. Top-10 priority indicators (not ranked) for monitoring and implementation of the End TB Strategy at global and national levels, with recommended target levels that are applicable to all countries

	Indicator	Recommended target level*	Main rationale for inclusion in top-10
1	TB treatment coverage *Number of new and relapse cases that were notified and treated, divided by the estimated number of incident TB cases in the same year, expressed as a percentage*	≥90%	High-quality TB care is essential to prevent suffering and death from TB and to cut transmission. High coverage of appropriate treatment is a fundamental requirement for achieving the milestones and targets of the End TB Strategy. In combination, it is likely that these two indicators will be used for monitoring progress towards universal health coverage (UHC) within the post-2015 Sustainable Development Goals (SDGs).
2	TB treatment success rate *Percentage of notified TB patients who were successfully treated. The target is for drug-susceptible and drug-resistant TB combined, although outcomes should also be reported separately.*	≥90%	
3	Percentage of TB-affected households that experience catastrophic costs due to TB *Number of people treated for TB (and their households) who incur catastrophic costs (direct and indirect combined), divided by the total number of people treated for TB.*	0%	One of the End TB Strategy's three high-level indicators; key marker of financial risk protection and progress towards UHC and social protection for TB-affected households.
4	Percentage of newly notified TB patients diagnosed using WHO-recommended rapid tests *Number of newly notified TB patients diagnosed with WHO-recommended rapid tests, divided by the total number of newly notified TB patient.*	≥90%	Accurate diagnosis is a fundamental component of TB care. Rapid tests help to ensure early detection and prompt treatment.
5	LTBI treatment coverage *Sum of the number of people living with HIV newly enrolled in HIV care and the number of children who are contacts of cases started on LTBI treatment, divided by the number eligible for treatment, expressed as a percentage*	≥90%	Treatment for latent TB infection (LTBI) is the main treatment intervention available to prevent development of active TB disease in those already infected with *M. tuberculosis*.
6	Contact investigation coverage *Number of contacts of people with bacteriologically-confirmed TB who were investigated for TB divided by the number eligible, expressed as a percentage*	≥90%	Contact investigation is a key component of early TB detection and TB prevention, especially in children.
7	DST coverage for TB patients *Number of TB patients with DST results divided by the number of bacteriologically confirmed cases in the same year, expressed as a percentage. DST coverage includes results from molecular (e.g. Xpert MTB/RIF) as well as conventional phenotypic DST results.*	100%	Drug susceptibility testing (DST) is essential to provide the right treatment for every person diagnosed with TB.
8	Treatment coverage, new TB drugs *Number of TB patients treated with regimens that include new TB drugs, divided by the number of notified patients eligible for treatment with new TB drugs, expressed as a percentage*	≥90%	An indicator that is relevant to monitoring the adoption of innovations in all countries. *NB. Indicators related to the development of new tools are needed at global level but are not appropriate for monitoring progress in all countries.*
9	Documentation of HIV status among TB patients *Number of new and relapse TB patients with documented HIV status divided by the number of new and relapse TB patients notified in the same year, expressed as a percentage*	100%	One of the core global indicators used to monitor collaborative TB/HIV activities. Documentation of HIV status is essential to provide the best care for HIV-positive TB patients, including anti-retroviral treatment (ART)
10	Case fatality ratio (CFR) *Number of TB deaths (from a national VR system)divided by estimated number of incident cases in the same years, expressed as a percentage*	≤5%	This is a key indicator for monitoring progress towards 2020 and 2025 milestones. A CFR of 6% is required to achieve the 2025 global milestone for reductions in TB deaths and cases.

*target level to be reached by 2025 at the latest.

Examples of indicators to monitor End TB Strategy implementation: Pillar 1

Indicator	Requirements for measurement	References
Component A: early diagnosis, universal drug susceptibility testing (DST) and systematic screening		
DST* coverage for TB patients (%) *Number of TB patients with DST results divided by the number of notified cases in the same year*	Routine recording and reporting system consistent with 2013 WHO recording and reporting framework.	6
Contact tracing coverage (%) *Number of contacts of TB cases who were investigated for TB divided by the number eligible*	Requires additional routine data collection compared with 2013 WHO recording and reporting framework. Adding variables is easier if case-based electronic recording and reporting is in place.	7, 8
Component B: treatment of all people with TB, including MDR-TB		

Number of notified TB cases NB: could also be expressed as a rate Number of notified cases of drug resistant TB (RR or MDR-TB)	Routine recording and reporting system consistent with 2013 WHO recording and reporting framework	6
TB treatment coverage (%) *Number of new and relapse cases that were notified and treated, divided by the estimated number of incident TB cases in the same year*	For notifications, routine recording and reporting system consistent with WHO recording and reporting framework. TB incidence is estimated by WHO using methods that are periodically reviewed by an expert group convened under the umbrella of the WHO Global Task Force on TB Impact Measurement. The main reasons for a gap between incidence and notifications are: 1) under-reporting of detected cases; 2) under-diagnosis of cases. Levels of under-reporting can be measured using an inventory study. Levels of under-diagnosis require assessment of factors associated with under-diagnosis, such as the extent to which UHC and social protection are in place. This indicator can only be estimated with reasonable precision once UHC and social protection are in place.	6, 9
Enrolment on treatment for detected cases of drug-resistant TB (%) *Number of RR/MDR-TB patients started on treatment, divided by the number of RR/MDR-TB cases detected in the same period* Treatment success rate	Routine recording and reporting system consistent with 2013 WHO recording and reporting framework. The treatment success rate can be reported separately for drug-susceptible and drug-resistant TB.	6
Case fatality ratio (CFR) *Number of TB deaths divided by estimated number of incident cases in the same years, expressed as a percentage.*	National (or sample) vital registration system of high coverage and quality for measurement of TB deaths. For TB incidence, see explanation for Treatment Coverage above. Notifications can be used as a proxy for incidence when target levels for treatment coverage, catastrophic costs and under-reporting are reached.	1, 3, 4, 9
Component C: collaborative TB/HIV activities, and management of co-morbidities		
Documentation of HIV status among TB patients (%) *Number of new and relapse TB patients with documented HIV status divided by number of new and relapse notified cases* ART coverage, HIV-positive TB patients (%)	Routine recording and reporting system consistent with 2013 WHO recording and reporting framework and the 2015 WHO guide on monitoring and evaluation of collaborative TB/HIV activities.	1, 3, 4, 9, 10
Component D: preventive treatment of persons at high risk, and TB vaccination		
LTBI treatment coverage (%) *Sum of the number of people living with HIV and children who are contacts of cases started on LTBI treatment, divided by the total number eligible for treatment*	Routine R&R system for people in HIV care, including specific reporting for treatment of LTBI. Collection of data on number of children eligible for treatment and the number initiated on treatment.	10, 11
BCG vaccination coverage at 1 year (%)	Routine immunization reports, vaccine coverage surveys	13

Examples of indicators to monitor End TB Strategy implementation: Pillar 2

Indicator	**Requirements for measurement**	**References**
Component A: political commitment with adequate resources for TB care and prevention		
Proportion of annual budget defined in TB national strategic plans that is funded (%)	Budget data and data on available sources of funding	
Component B: engagement of communities, civil society organizations, and public and private care providers		
Case reporting coverage (%) *Proportion of detected TB cases that were reported to national health authorities*	An inventory study that measures the level of under-reporting is required. Inventory studies require a case-based electronic reporting system to be in place or the establishment of such a system, to allow cross-checking of cases detected by all care providers with those notified to national authorities. It is not expected that inventory study would be implemented every	1, 12

	year.	
Component C: universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control		
Health insurance coverage *Percentage of population covered by health insurance (or equivalent)*	Surveys or routine data. Clear definitions of the types of services that are covered, and to what extent the full service cost is covered, are needed.	
Public health spending per capita (US$)	National health account data produced according to the system of health accounts (SHA).	15
Percentage of total health expenditures (THE) accounted for by out-of-pocket (OOP) expenditures	National health account data produced according to the system of health accounts (SHA). Along with adequate public health spending per capita, it has been suggested that OOPs need to be ≤15% of THE for UHC to be considered in place.	14, 15
Percentage of TB patients and their households that experience catastrophic costs due to TB	Special surveys are required. See section 2.3.4 for further details.	5
Case notification is mandated by law (yes/no)	Review of relevant laws.	X
Vital registration (VR) system in place that meets international standards of coverage and quality (yes/no)	There are standard methods for evaluating the coverage and quality of cause of death VR data.	1, 3, 4
Component D: social protection, poverty alleviation and actions on other social determinants		
Percentage of people with TB who receive appropriate social protection	Surveys or routine data; "appropriate" needs to be clearly defined according to the country setting. Can also be measured through assessment of the indicator on catastrophic costs.	
Percentage of population adequately nourished	Routine assessment is done by the Food and Agricultural Organization and the World Food Programme.	16

Examples of indicators to monitor End TB Strategy implementation: Pillar 3

Indicator	**Requirements for measurement**	**References**
Component A: discovery, development and rapid uptake of new tools, interventions and strategies		
Percentage of TB patients tested using WHO-recommended rapid tests	Requires additional routine data collection compared with 2013 WHO recording and reporting framework. Case-based electronic recording and reporting systems facilitate the addition of new variables to routine data collection efforts.	17
Enrolment on treatment with new TB drugs (%) *Number of TB patients treated with regimens that include new TB drugs, divided by the number of patients eligible for treatment with new TB drugs, expressed as a percentage*		

Annex 2. Modelling the impact of the 90-(90)-90 strategy

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Contents

Abbreviations

CDR	Case detection ratio
CFP	Case-finding proportion
COE	Complex operating environment
CSP	Case-survival proportion
DALY	Disability adjusted life year
GP	TB Global Plan 2016–2020
GTB	Global TB Programme
LE	Life expectancy
PCA	Principal Component Analysis
PSC	Program support costs
ROI	Return on investment
TIME	TB Impact Model and Estimates
VSL	Value of a statistical life
VSLY	Value of a statistical life year
YLD	Years lost due to disability
YLL	Years of life lost to due to premature death
Standard investment plan	TB interventions are scaled up in an s-shape, reaching coverage targets by 2025
Accelerated investment plan	TB interventions are scaled up in an s-shape, reaching coverage targets by 2020

Modelling the impact of the Global Plan

This document details the methodology developed for modelling the impact of the Global TB Plan.

The impact modelling methods can be summarized as a framework for adjusting trends in key TB indicators, such as TB incidence, mortality, notification and so on, in order to reflect the epidemiological impact of the programmatic implementation of key TB intervention and control strategies, as defined by the GP 90-(90)-90 strategy.

Epidemiological impact was estimated by applying the modelling framework of the TB Impact Model and Estimates (TIME) model to capture the potential impact of the GP 90-(90)-90 targets in nine countries. These countries were chosen to represent a range of contexts as described below.[1] The estimated impact of the GP 90-(90)-90 strategy in these countries was then applied to GTB epidemiological trends for an additional 152 countries[2], using a statistical method of extrapolation. This framework produced a set of global results for the epidemiological impact of the GP 90-(90)-90 strategy, as a downward deviation of trends through GTB data for the same indicators.

The methods are presented in eleven sections: 1) a brief overview of the epidemiological data and trends; 2) a description of the regression method used to estimate TB/HIV incidence; 3) a brief overview of the TIME model; 4) a description of the implementation of the GP strategy in the TIME model; 5) an outline of scale-up patterns used in the TIME model; 6) a statistical analysis of TB country groups/contexts; 7) schematic of modeling process; 8) a summary of impact results; 9) summary tables showing impact; 10) DALYs averted and 11) details of return on investment.

GTB epidemiological data and trends

The TB burden analysis of the GP relies strongly on incidence and notification data reported to GTB. This section provides a short overview of the data processing methods, discussing a few aspects of TB data reporting that result in uncertainty in incidence estimates.

The most successful and most widely used approach for estimating TB incidence at the national level is the employment of routine surveillance systems, from which reports of notified new and relapse cases are prepared. Generally, countries with universal health coverage have near complete notification reports, providing a reliable proxy for TB incidence.

However, surveillance systems often fail to provide reliable estimates of TB incidence, the leading reasons being laboratory errors, lack of notification by public and private providers, failure of health care staff to recognize TB signs and symptoms among people accessing health services, and lack of access to health services. These factors all contribute to uncertainty over the TB incidence estimates obtained from case notification data. At the same time, the reliance on expert opinion to estimate incidence in countries with weak surveillance and health systems often results in biases and considerable uncertainty in TB estimates, as mentioned in the Global TB Report.

[1] The TIME modelling framework was developed by The London School of Hygiene and Tropical Medicine and Avenir Health.

[2] The 152 countries comprise a GP result set determined by the intersection of the GTB country-level data and the UNAIDS country-level Spectrum AIM/EPP files. Spectrum AIM/EPP is the software used by UNAIDS to produce country-level estimates of HIV burden and resource needs.

The prevalence of HIV among reported new and relapse TB cases is used as a proxy for HIV prevalence among incident TB. Sources of data at country level include nationwide representative HIV serological surveys among a sample of reported TB cases, data from HIV sentinel groups, and results from routine testing of TB patients where testing coverage of newly reported cases is high.

The TIME Estimates submodel projects current trends in key epidemiological indicators using cubic splines (penalized B-splines in particular) – a technique widely used for projecting trends forward in time. The same method was used as one of the techniques for shaping the force of HIV infection in the EPP model.3 Its application here to produce TB estimates is described in detail in a recent publication4 and summarized in this section.

In simple terms, the spline regression approach can be explained as a regression method that estimates the coefficients of a set of cubic-spline functions arranged by the user to cover the estimation period of interest, i.e. between 1990, when GTB data start for most countries, and 2025, the final year of projection in the GP analysis. By forming linear combinations of the cubic-spline functions, most continuous and smooth trends over the specified interval can be represented. For the GP analysis, our main focus was trends in TB incidence, the split into HIV-negative and HIV-positive TB, TB mortality, and notification. Trends for different case types, e.g. new, re-treatment, drug-susceptible, and drug-sensitive TB, were determined by applying the 2013 distribution of case types to the projected notification trend.

The trends thus obtained form the basis of the counterfactual to trends under the GP 90-(90)-90 strategy, should it be fully implemented within the timeframe of the Plan. Despite the aforementioned limitations and uncertainties associated with the global TB dataset published by GTB, it is the most complete and readily accessible dataset available for the assessment of the global TB burden.

A regression method to estimate TB/HIV incidence

Once overall TB incidence was estimated, the projected TB incidence was then treated as simulated data, together with reported TB/HIV data, to estimate a disaggregation of the total number of TB incident cases into three assumed components: HIV-negative, HIV-positive not on ART, and HIV-positive on ART. This disaggregation method was also based on cubic-spline regression, combining data from the GTB and UNAIDS at country level.

The CD4 decline and ART status information were drawn from the UNAIDS dataset. The TB/HIV data came from three sources that countries report to GTB: nationwide representative HIV serological surveys among a sample of reported TB cases, data from HIV sentinel groups, and results from routine testing of TB patients where testing coverage of newly reported cases is high.

We modelled the risk of TB disease as a simple, two-parameter function of CD4 decline – one parameter controlling the HIV-positive risk of TB at high CD4 count (>500 cells/uL), and the second parameter controlling the increase in risk per unit of CD4 count decline. The values of these two

[3] Hogan D, Zaslavsky A, et al. Flexible epidemiological model for estimates and short-term projections in generalised HIV/AIDS epidemics. Sex Transm Infect. 2010;86(Suppl_2):ii84–ii92.
[4] Pretorius C, Glaziou P, Dodd PJ, et al. Using the TIME model in Spectrum to estimate tuberculosis-HIV incidence and mortality. AIDS. 2014;28 Suppl 4:S477–87.

parameters, together with the cubic spline coefficients determining the overall incidence trend, were produced by regressing the reported data.

TB mortality is affected by a complex relationship between active TB disease and many clinical variables. We approximated these variables in a simple functional relationship between incidence and case fatality ratios (CFR). The eight categories of CFRs (HIV negative, HIV positive not on ART, HIV positive on ART <6m, and HIV positive on ART for >=6m, by notification status) were clinical states that were both clinically relevant and possible to estimate from available data. Using this approach, TB mortality was calculated as a product of incidence and case fatality ratios.

Overview of the TIME model

The TIME model is comprised of two submodels: TIME Estimates and TIME Impact. TIME Estimates is used to produce trends in the distribution of case types. As described above, it is a statistical model that uses a cubic-spline method to produce trends in TB incidence, mortality and notifications, and uses a simple two-parameter model to partition these trends into three HIV components (HIV-negative, HIV-positive not on ART, and HIV-positive on ART).

TIME Impact is a comprehensive dynamic compartment model of TB that can be used by programme planners during policy discussions to help inform strategic planning at the national or subnational level. The model works in parallel with DemProj, AIM, and other modules in the Spectrum suite of policy tools that are currently used by international organizations to estimate disease burden and plan optimal strategies for a variety of programmes.5

TIME Impact is a dynamic model that captures essential TB processes of primary infection, infection with latent disease, reactivation, reinfection, the presence of a generalized MDR strain (with a differential fitness and acquisition rate with respect to non-MDR), TB mortality, and the role of HIV in TB incidence and mortality.

It uses more than 1000 compartments: two for sex, seventeen for age (in five-year bins), two for MDR status, nine for TB status, two for treatment history, three for ART status, and eight for the HIV/CD4 category. It receives demographic information from DemProj (which in turn uses data from the UN Population Division) and HIV information from AIM/EPP (which is used by UNAIDS to produce country-level estimates of HIV burden). Then, it automatically calibrates a large number of the model's compartments.

TB epidemiology is represented in TIME Impact by a set of natural history parameters, which are varied as little as possible within a range of plausible values determined by a comprehensive literature review. TB programmes are represented by a sequence of processes that define a cascade from detection, to linkage to care, to treatment. These sets of user inputs are adjusted until a good fit is obtained for TB incidence, prevalence, mortality and notification data, as well as data related to the disaggregation of TB by HIV and MDR status.

[5] http://www.avenirhealth.org/software-spectrum.php

The implementation of the GP strategy in the TIME model

The Global Plan (GP) is structured around the implementation of the so-called 90-(90)-90 strategy, through which several key service delivery areas are brought to scale **by 2025**. These scale-up targets are:

- Target 1: Find at least 90% of people with TB in the population and place all of them on appropriate and effective treatment.
- Target 2: As a part of the effort to reach Target 1, make a special effort to reach at least 90% of the key populations: the most vulnerable, underserved, at-risk populations in countries.
- Target 3: Reach at least 90% treatment success for all people diagnosed with TB, through affordable treatment services, the promotion of adherence, and social support.

1. First 90: This package of interventions promotes the early diagnosis of all TB patients and linking all eligible individuals to effective and appropriate treatment for drug-susceptible TB, drug-resistant TB, and ART with CPT. Once diagnosed, all TB patients should be offered appropriate treatment. To select the correct TB treatment, all patients should have DST results at the time of diagnosis. TB/HIV patients not on ART should be initiated on ART care irrespective of CD4-based eligibility criteria. For TB/HIV cases where active TB was ruled out, patients must be provided with preventive treatment for TB.

2. Second 90: This package of interventions promotes increased action to reach people who are at increased risk of getting TB, more vulnerable to the impact of TB, currently underserved by health systems and/or face barriers to accessing TB care.

3. Third 90: This package of interventions promotes good-quality and appropriate TB treatment for all forms of TB: drug-susceptible, drug-resistant and HIV-associated TB. Countries have demonstrated that achieving a treatment success of 90% for first-line treatment is feasible. Countries have so far not had the same level of treatment success with second-line treatment, with the global average below 50%.

The GP 90-(90)-90 strategy was adopted as the basis of the Global Plan analysis in order to provide insight into the ambitious scale-up of TB programmes in line with these three dimensions. As part of the Global Plan analysis, the details of implementation, and especially the selection of appropriate interventions to reach the 90-(90)-90 targets, were specified at the country level by TB programme experts.

Several modelling decisions were made in order to apply this approach in TIME. The first deals with the overall case detection objectives of the GP. The CDR (the ratio between notifications and incidence) is widely used as the target for similar diagnostic objectives. However, the CDR does not remain at a fixed level when interventions are implemented, as incidence rates respond immediately to intervention, according to dynamic TB models. It would require a continuously increasing detection rate to maintain CDR at any fixed level, and this adjustment would vary by country.

To this end, we adopted a specific definition of case detection, based on two different ratios: the case-finding proportion (CFP) and the case-survival proportion (CSP), where:

CFP = notifications / (notifications + TB deaths + TB self-recovery), and

CSP = (notifications + TB self-recovery) / (notifications + TB deaths + TB self-recovery)

Here, "notification" is the total notification (of all case types, and, implicitly in the model structure, successful treatment); TB deaths is the total number of TB-related deaths (of all case types); and TB self-recovery is the total number of people who recover from an active TB episode without treatment.

CFP is the average probability that an active TB episode will end through notification rather than in death or self-recovery.6 The concept is one of "competing risks" to end an active TB episode. CSP is identical to CFP, except that self-recovery and notification are both considered satisfactory ends to an active TB episode.

The first two 90s were modelled as reaching a CSP of 90% and a CFP of 81%, with CFP set at the lower limit of 90% case detection and 90% linkage to care. Since these probabilities are ratios of probabilities, they reach a stable level for a choice of TB control parameters.

The utility of CFP and CSP is that they provide an umbrella mechanism for achieving overall case detection objectives, with subpopulations implicitly reached. This characteristic indirectly addresses a limitation of the TIME model caused by the lack of epidemiological and transmission data regarding TB burden in different, interacting high-risk TB groups; except for HIV, no other comorbidities or risk-factors were explicitly modelled.

In practice, reaching an overall CSP of 90% may require the implementation of ACF campaigns in certain vulnerable and high-risk groups. We consider these activities to be part of the approach to reaching the first two 90s. In fact, as CFP moves towards 90%, the general case-detection process effectively moves from enhanced passive case-finding to active case-finding. In effect, cases will have to be found in a matter of months for the "first-90" condition to be met. The distinction becomes one of programmatic implementation and cost-efficiency.

A further motivation for using an umbrella mechanism is the specification of "100% linkage to appropriate care" as part of the 90-(90)-90 strategy. Since the product of case detection and linkage to care is the effective parameter in TIME, the 90% CSP objective serves again to accommodate a range of linkage to care and case-detection realities.

Other elements of the 90-(90)-90 strategy were directly specified in TIME. Treatment success was specified separately for non-MDR and MDR-TB, and separately for HIV-negative and HIV-positive not on ART or on ART. Most of the significant programme elements implied by "100% linkage to appropriate care" were directly implemented in TIME: 100% of re-treatment cases received a drug sensitivity test; 100% of new pulmonary cases received a drug-sensitivity test; 100% of notified TB/HIV cases not receiving ART were linked to ART care; 100% of confirmed TB-latent, HIV-positive cases were linked to preventive care for TB; and 100% of cases exposed to an index case were found via a household screening mechanism and placed on preventive therapy when confirmed to have latent TB infection. Note that only the preventive therapy aspect of HH contact tracing was modelled, as the active case element forms part of the diagnostic element of the GP.

The TIME parameters directly used in the implementation of the GP are listed in Table 1.

[6] Within the TIME model, when treatment fails, people remain in a state of active TB.

Table 1. TIME model parameters related to the 90-(90)-90 Global Plan strategy

Parameters Directly Related to 90-(90)-90 Strategy	
Parameter/Field	**Note**
Relative detection rate smear negative	Adjusted to fit data
Diagnostic rate	
HIV-	Adjusted to fit data, then adjusted to achieve CSP of 90%
HIV+	Adjusted to fit data, then adjusted to achieve CSP of 90%
Linkage to care	Set at 100%
Treatment success	
HIV-	Adjusted to fit data, then to 90% by 2025/2020
HIV+	Adjusted to fit data, then to 90% by 2025/2020
HIV+ on ART	Adjusted to fit data, then to 90% by 2025/2020
Parameters Directly Related to the "100% Linkage to Appropriate Care" Requirement	
Proportion of cases tested for MDR-TB	
HIV- cases	
Among new cases (all forms)	Adjusted to fit MDR data, then to 100% among pulmonary cases by 2025/2020
Among re-treated cases (all types)	Adjusted to fit MDR data, then to 100% by 2025/2020
HIV+ cases	
Among new cases (all forms)	Adjusted to fit MDR data, then to 100% among pulmonary cases by 2025/2020
Among re-treated cases (all types)	Adjusted to fit MDR data, then to 100% by 2025/2020
General interventions	
Coverage of INH	Increased to 90% (100% of the 90% detected) by 2025/2020
IPT for HIV+ on ART	
Coverage of INH	Increased to 90% (100% of the 90% detected) by 2025/2020
Household screening	
Coverage of household screening of notified TB cases	Increased to 90% (100% of the 90% detected) by 2025/2020
Proportion linked to IPT care	Set at 100%
Proportion of u5s that complete IPT	Assumed at 30%
HIV testing and ART initiation	
Coverage of HIV testing	Set to GTB data, then to 90% by 2025/2020
Proportion linked to ART	Set at 100%

Scale-up patterns used in the TIME model

One of the objectives of the GP is to reach the End TB milestones: reductions of 20%, 50%, 80% and 90% in TB incidence by 2020, 2025, 2030 and 2035, respectively, and reductions of 35%, 75%, 90% and 95% in TB deaths by 2020, 2025, 2030 and 2035, respectively. These impact targets are based on an assumed trajectory of reductions in TB incidence and CFR, as depicted in Fig. 1.

The trajectory assumes that the effect of progress towards universal health coverage (and the implementation of new diagnostics and drugs currently in the pipeline) will intensify around 2020 and achieve its full potential by 2025.

These principles were applied to the scale-up patterns used in the GP analysis, namely that the intervention scale-up will progress initially at a modest pace, intensify around 2020, and achieve maximal coverage in 2025. This scenario is often called **the standard investment plan** below. A second scenario, called the **accelerated investment plan**, calls for a more aggressive scale-up, reaching full scale in 2020; this second scenario was also considered.

Fig. 2 shows an example of two scale-up patterns for treatment success coverage: one reaching scale in 2025 and one in 2020. The properties of each curve, i.e. the parameters of a logistic curve (rate of increase, location of maximal rate of increase), were applied to all interventions of a corresponding scenario. A scenario is thus defined by the interventions that are scaled up (Table 1) and the pattern or shape of the scale-up, which can be summarized by the location and acceleration of scale-up and the year (2020 or 2025) in which maximal coverage is reached.

Figure 1: Shape of assumed change in incidence (annual rate of decline) and CFR, 2015–2035, used in the WHO End TB Strategy

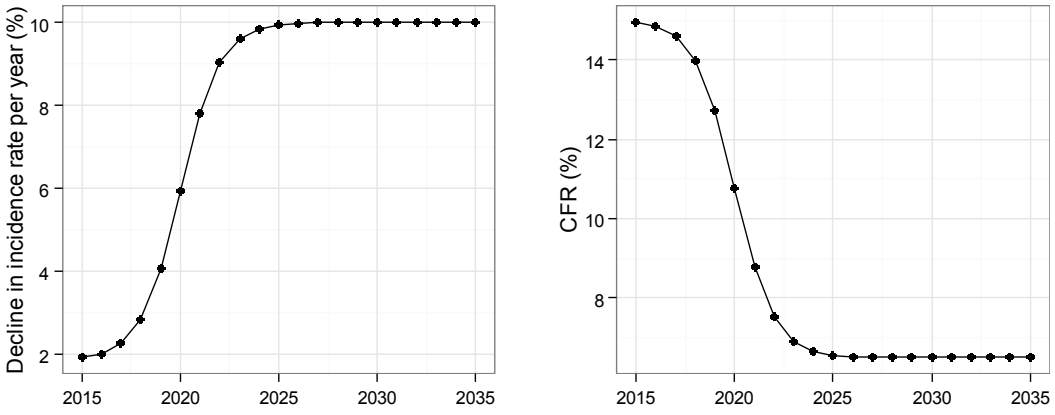
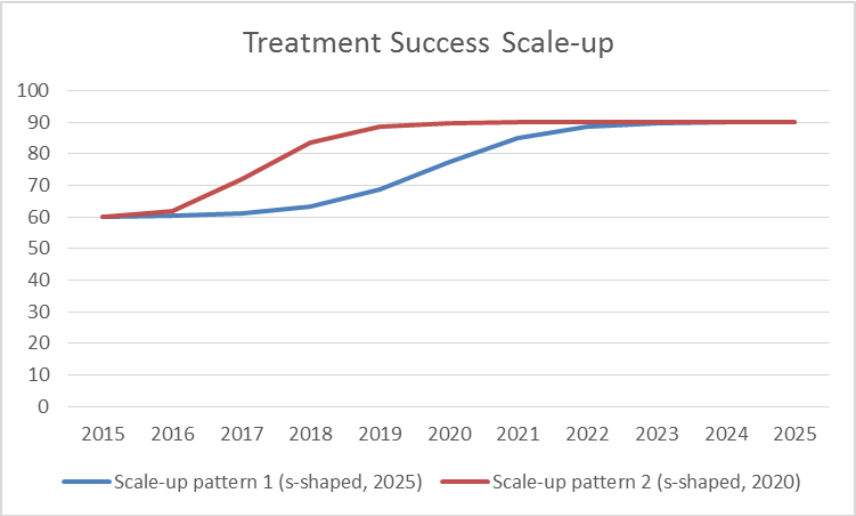


Figure 2. Intervention scale-up patterns used in the TIME model of the GP



Statistical analysis of TB country groups/contexts

The impact of the GP in nine countries, representing about 50% of the global TB burden, was directly modelled using the TIME model. To produce global estimates, an extrapolation method was required. A decision was made that the extrapolation method should be based on the general TB context, represented by a group of countries having similar TB burden, TB programmes, socioeconomic situation and other characteristics. These country groups are based on a multivariate analysis of TB-related variables, as described in this section.

Multivariate TB data

Several datasets were collated to produce the country-level data required both for the multivariate analysis and for the model calibration with the TIME model. These datasets included:

- GTB: TB burden, notification, treatment outcomes, MDR burden, treatment outcomes
- World Development Indictors (WDI): measures of wealth and health access and coverage
- Millennium Development Goals (MDG): measures of development such as coverage of child vaccinations
- UNPop: Population data including population size and TFR
- UNDP: Human development indices
- FFP: Fragile state indices
- UNAIDS: HIV data including ART coverage and PMTCT coverage
- WHO Health Systems: data focused on health financing

Several hundred indicators were processed in the search for a representative multivariate dataset and indicators common to most countries. A number of indicators were found in 120 countries, with most but not all data points reflecting values in the year 2012. The variables represented aspects of socioeconomic standing (e.g. GDP per capita, Human Development Index, Fragile State Index), TB service delivery (e.g. TB treatment success), health systems capacity and efficiency (e.g. infant immunization coverage), and general health systems financing (e.g. per capita health expenditure). The fields and their data sources are shown in Table 2.

Table 2. GP multivariate analysis variables

Field	Code	Description	Source
TB-related			
TBinc	V1	TB incidence per 100K population	GTB
TBnoti	V2	TB notification per 100K population	GTB
TBincHP	V3	Percentage of TB incidence cases who are HIV-positive	GTB
TBmortALL	V4	TB mortality rate per 100K population	GTB
TBmortHN	V5	TB mortality rate per 100K HIV-negative population	GTB
TBmortHP	V6	TB mortality rate per 100K HIV-positive population	GTB
TBmdr	V7	Percentage of MDR-TB notification	GTB
TB service delivery			
NEWSPts	V8	TS for new cases	GTB
CDR	V9	TB case-detection ratio	GTB
General health service delivery			
Imun	V10	Percentage of children 1 years old immunized against measles	MDG
ART_Cov	V11	ART coverage of total HIV-positive population	Spectrum AIM
Socioeconomic			
GNIperCAP	V12	GNI per capita (2011 PPP)	WDI
HDI	V13	Human development index	UNDP
FS	V14	Fragile state index	UNPop
Health systems			
ExpGDP	V15	Total expenditure on health as a percentage of gross domestic product	WHO HS
Gov_vs_Tot	V16	General government expenditure on health as a percentage of total government expenditure	WHO HS
PerCapHlth	V17	Per capita total expenditure on health (PPP int. $)	WHO HS

Some variables related to health systems, such as population density of medical lab personnel, proved to be useful variables for TB category discrimination. However, these data are recorded in too few countries to be used in a representative multivariate analysis. We did, however, include a measure of child immunization coverage, which has been shown to be closely related to health systems capacity and service delivery measures. The statistical properties of this dataset will be explored in subsequent sections.

The first seven variables are TB 'target' variables that are expected to be "explained" by the remaining explanatory variables. The statistical question is how these variables are explained. We will partially answer this question using multivariate analysis techniques.

Country classification

Countries can naturally be grouped in many ways depending on the purpose of the grouping. We illustrate this principle by comparing classification the thresholds used in the Post-2015 Global TB Strategy to the thresholds derived through a statistical approach.

A presentation of the Post-2015 Global TB Strategy classifies countries according to Table 3.

Table 3. TB classification in Post-2015 Global TB Strategy

Classification	Threshold
Pre-elimination	TB mortality < 1/100,000 population
Concentrated	1< TB mortality < 20/100,000 population
Endemic	TB mortality > 20/100,000 population
High-MDR	MDR in new TB > 5%
High-HIV	HIV in TB > 20%

For the purposes of the GP, which advocates high-impact strategies tailored to epidemic contexts, a classification of TB into pre-elimination, concentrated and endemic does not seem immediately useful. However, mortality is a consequence of TB incidence, case detection, and treatment outcomes. Threshold levels of the first three variables are therefore tied to a high-level classification of TB epidemiology and TB programme performance.

We may first investigate whether the thresholds stated in Table 3 achieve the maximal separation of groups of countries. This can be achieved through a clustering method that is applied to each variable in order to maximize their separation. Table 4 shows the outcome of such a procedure, showing the mean value of the two clusters (based on k-means clustering[7]), the mid-point between the two clusters, the mean and median of the variable across all countries, and the threshold levels of the Post-2015 Global TB Strategy for each variable. The difference between the mean and median is a measure of asymmetry in the data. The difference between the Post-2015 Global TB Strategy thresholds and the mid-point of the maximally separated clusters shows the degree to which the Post-2015 Global TB Strategy thresholds can separate countries.

This comparison shows that the Post-2015 Global TB Strategy thresholds do not maximally separate countries. Instead, they are normative thresholds. However, they do not differ too much from the thresholds that would achieve maximal separation.

[7] K-means clustering is a technique that minimizes the total distance of all countries to the within-group centroids. Here, 'distance' is defined in the multivariate space by the variables in Table 3

Table 4. Threshold levels according to a 'two-mean' clustering method

	Variable	Cluster1	Cluster2	Mid-Point	Mean	Median	
TBinc	V1	657.2	97.9	377.5	144.5	83.555	
TBnoti	V2	59.0	355.5	207.3	93.6	58.09	
TBincHP	V3	48.4	7.2	27.8	12.4	6.29	
TBmortALL	V4	23.1	378.2	200.7	29.0	11.625	
TBmortHN	V5	57.0	9.4	33.2	17.7	9.49	
TBmortHP	V6	399.1	2089.4	1244.3	666.7	397.295	
TBmdr	V7	2.8	30.5	16.7	5.2	2.45	
NEWSPts	V8	84.9	65.1	75.0	79.3	81	
CDR	V9	57.8	82.1	69.9	72.8	75.265	
Imun	V10	94.0	70.7	82.3	88.1	93	
ARTcov	V11	52.3	21.7	37.0	33.2	32.685	
GNIpercap	V12	31732.4	6799.3	19265.8	13240.3	8192.37	
HDI	V13	0.8	0.5	0.6	0.7	0.68	
FS	V14	4083.1	8400.0	6241.6	7140.9	7665	
HExpGDP	V15	5.2	9.4	7.3	6.9	6.5	
GovVsTotal	V16	15.4	8.6	12.0	11.5	11.25	
PerCapHealth	V17	463.8	3437.1	1950.5	959.4	443.25	

The clustering method outlined above is a very practical way of grouping countries. The method can be used to distinguish countries along the lines of high or low TB-burden, the role of HIV, high or low MDR-burden, measures of health system performance, and so on. As a result, the method provides a practical level of granularity and can be responsive to the intervention strategies implemented to address the different challenges TB programmes face.

However, despite using the median of each indicator as the level that discriminates between the groups, there remains arbitrariness in the variables chosen and in the number of levels for each variable. The question is whether these distinctions can be made in a way that is statistically objective, using available data. Other requirements include that a distinction must be based on the most informative indicators and that it can be used for extrapolating modelled impact results to countries that will not be explicitly modelled.

Principal Component Analysis (PCA)

Principal Component Analysis (PCA) is a widely used technique for finding descriptions in the dataset that explain most variance. The idea is to express new variables, called Principal Components (PCs), in terms of the 20 variables in Table 2 in such a way that the new variables are mutually orthogonal, and thus serve as an abstract coordinate system. Furthermore, the technique must ensure that the variables are numerated in the sense that the first PC dimension explains most variance, the second dimension the second most variance, and so on.

A PCA was performed, producing the results shown in Fig. 3–5. Fig. 3 is a Pareto plot showing the percentage of variance in the dataset explained by each principal component. This plot shows that the first few PCs explain most of the variance in the dataset, i.e. variation in relationships, for example

between wealth, health system coverage and TB burden. The results suggest that there are not many independent dimensions in the dataset.

Fig. 4 and 5 show the country data (red dots representing each country) and the original collinear axes (blue lines representing each of the original 20 variables) projected into the new space formed by the PCs, forming the axes in the new space. These charts give an idea of the correlation between the original 27 variables. For example, in Fig. 4, we show PC1 against PC2. The "development" variables (or measures thereof, such as GDP per capita, ART coverage, and so on) have positive PC1 coordinates, whereas the "TB-burden" variables have negative PC1 coordinates. These results obviously suggest that "development" variables are negatively correlated with "TB-burden" variables, as we might expect.

However, further PCA revealed more subtle differences among countries. Fig. 5, for example, shows that component 3 is an MDR-distinguishing variable. Each PC distinguishes another feature or combination of features of the country-level TB data.

Using the PC coordinates to re-express the original data in the new space, clusters or groups are formed that are epidemiologically meaningful. Statistical methods are readily available to detect clusters or groups. We used k-means clustering with nine groups.

A few of the groups make immediate sense: Groups 7 and 9 represent medium and high TB/HIV-burden countries; groups 3 and 8 represent "developed" countries, which have mostly a low TB burden and are close to TB elimination; group 5 represents countries with high MDR-TB burden. The validity of these groups can be verified quantitatively to some extent using the results shown in Tables 5 and 6, stating the average value of each TB variable in each group.

The PCA could be further refined to highlight the role that macroeconomic or development variables, along with health system variables, play in TB and MDR-TB burden. This step involved searching for more variables to include in the analysis, as well as experimenting with the number of clusters in the k-means clustering. Initial investigations showed that six to nine groups with clear geographic and epidemiological characteristics could be distinguished from the multivariate dataset. It should be noted that this classification or grouping approach cannot replace expert opinion on how countries may be grouped. It is a statistical method and therefore subject to noise, which can lead to outlier and erroneous classifications. Experts, however, are less likely to make such errors due to their expert knowledge of TB programmes. In any case, it is important that the number of groups not be too large, as the size of the dataset will produce outliers (as individual groups) if a large number of groups is selected.

Figure 3. Percentage of variance explained by PCs

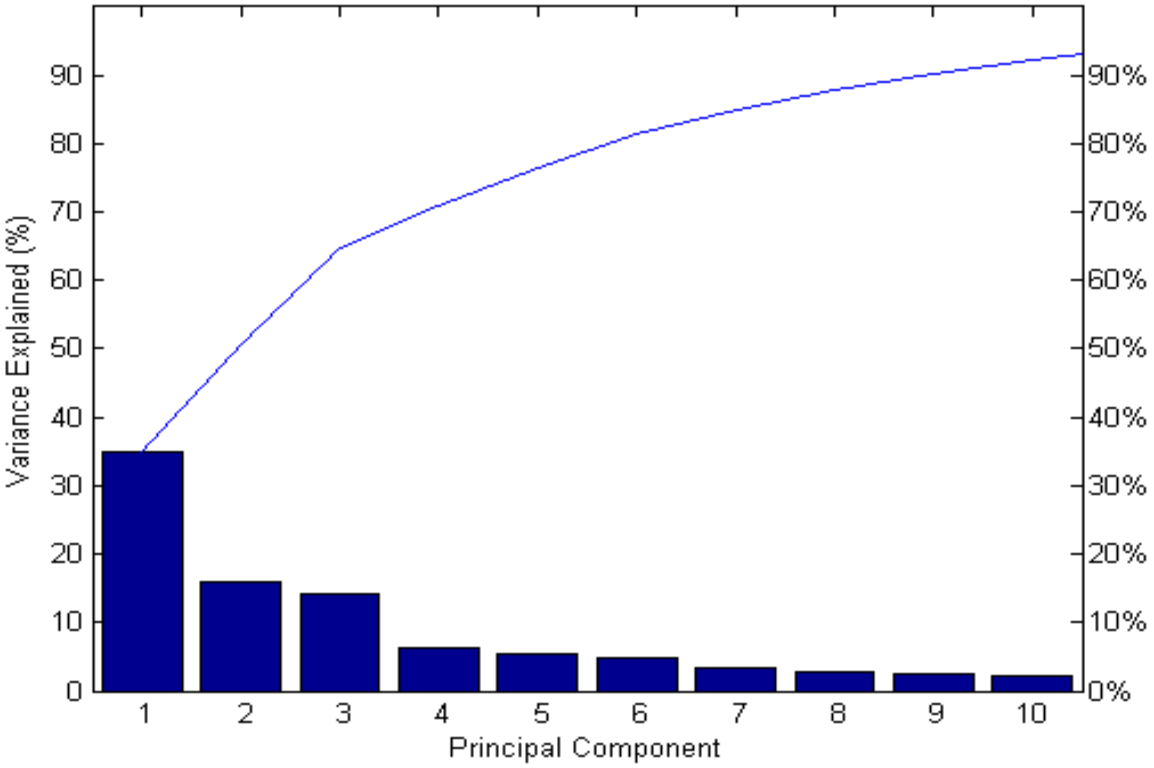


Figure 4. PC1 against PC2

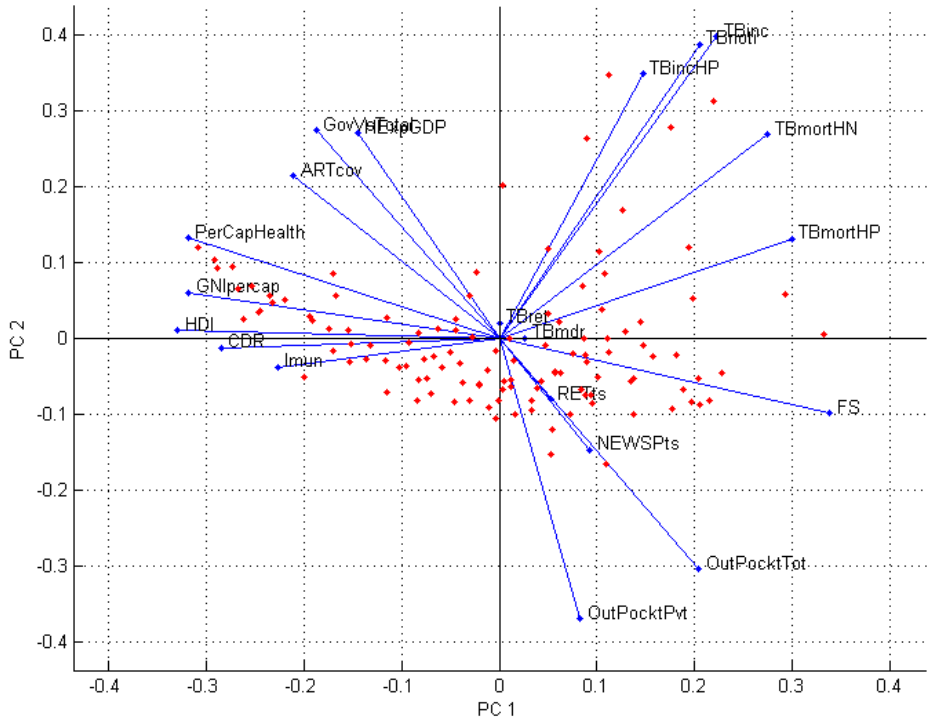


Figure 5. PC2 against PC3

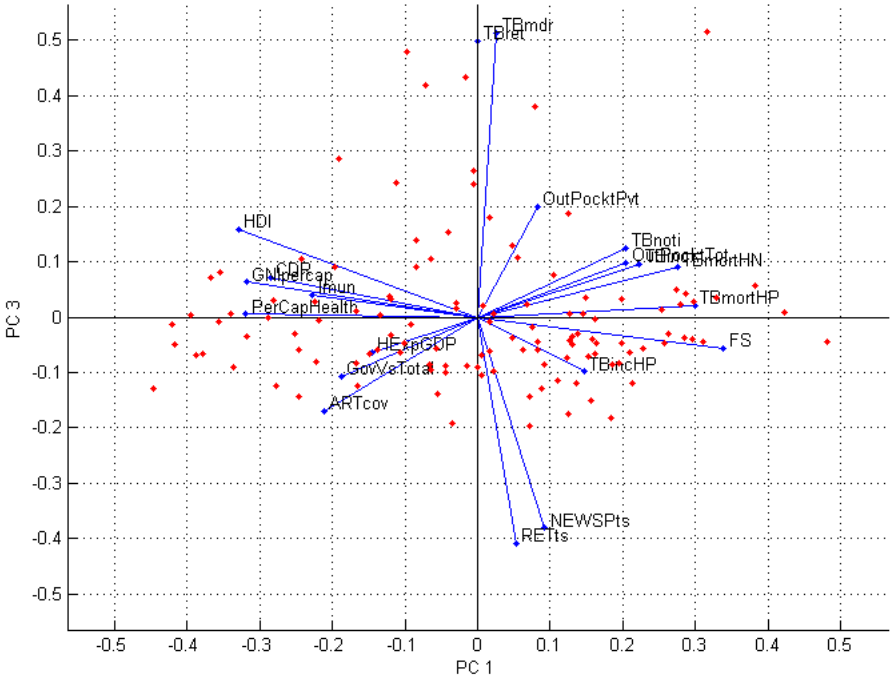


Table 5. Group averages: TB-related

Group	TBinc	TBnoti	TBincHP	TBmortALL	TBmortHN	TBmortHP	TBmdr	NEWSPts	CDR
1	118.4	88.7	4.2	15.8	15.0	536.9	3.9	86.5	71.9
2	42.9	35.2	5.9	4.6	4.0	215.4	2.8	85.5	83.1
3	18.3	16.1	3.0	1.5	1.4	38.7	1.4	74.0	87.2
4	296.9	172.0	14.4	65.6	49.9	1,843.0	2.9	80.1	56.2
5	87.4	68.7	6.7	10.6	9.6	582.0	29.1	65.4	79.5
6	138.4	92.3	21.0	25.7	17.3	711.5	2.7	82.4	63.4
7	974.4	559.7	66.0	267.9	67.8	1,546.2	4.9	77.5	59.6
8	17.2	14.1	10.3	1.9	1.6	48.7	1.7	64.5	80.2
9	221.9	146.8	29.9	42.6	28.1	1,161.3	1.9	87.0	67.6

Table 6. Explanatory variables

Group	Imun	ARTcov	GNIpercap	HDI	FS	HExpGDP	GovVsTotal	PerCapHealth
1	91.6	17.1	8,362.5	0.67	78.2	5.4	7.8	341.4
2	95.9	36.2	15,116.9	0.74	68.5	7.1	12.7	886.7
3	94.7	61.2	38,825.3	0.89	30.7	9.5	15.4	3,725.1
4	73.0	23.1	3,666.4	0.50	95.6	4.8	8.3	125.3
5	91.0	14.7	15,448.6	0.76	66.7	6.3	10.4	819.6
6	83.2	38.1	3,931.2	0.51	86.2	6.0	10.4	181.9
7	82.0	38.1	7,326.9	0.58	75.6	9.3	14.9	568.8
8	94.3	35.2	19,442.7	0.80	47.5	7.7	15.6	1,650.0
9	86.8	34.8	1,171.3	0.43	91.0	12.6	17.9	133.4

Extrapolation of TIME impact results using country groups

With only nine countries directly modelled, a method was needed to extrapolate the impact results to the countries not directly modelled. A simple approach using the statistically determined country groups was used for this purpose.

One of the countries directly modelled was first assigned to each of the statistical groups. Ideally, the centroid of the group should be modelled, but this of course is a virtual country for which we know only the properties reflected in Table 2.

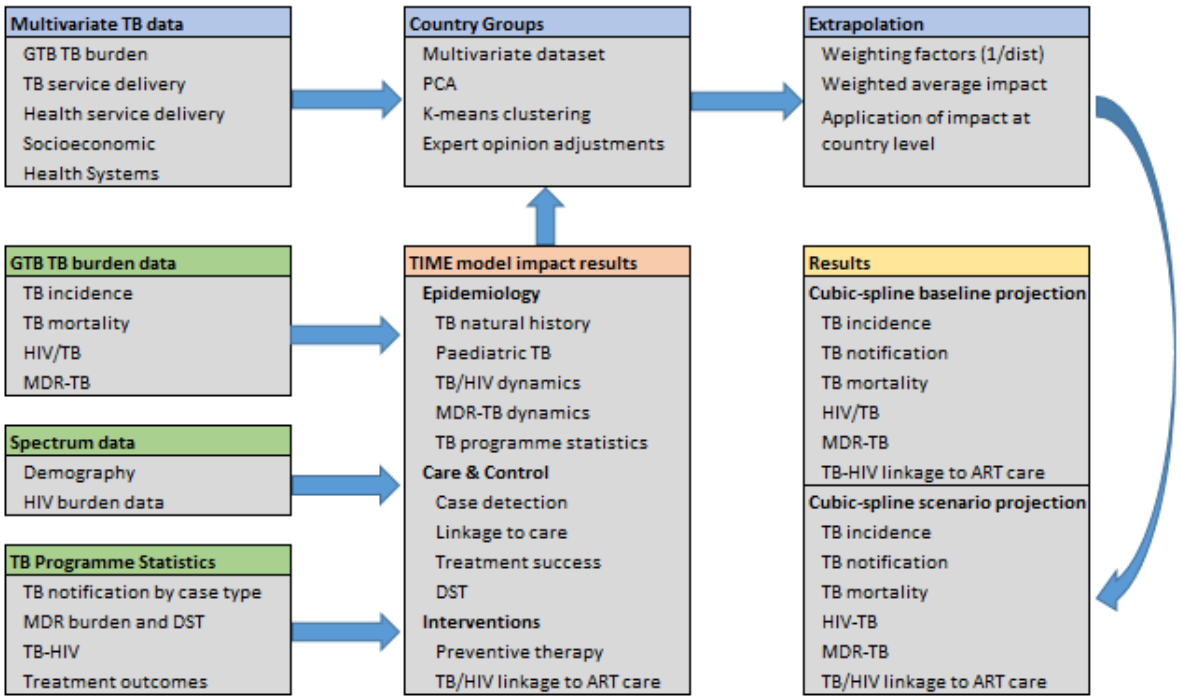
The next step was to relate all countries to each of the group centroids. The inverse distance of each country to the centroid of each country group was used to obtain a normalized weighting factor for each country. These weighting factors could be used to represent the degree to which a country was like group 1, group 2, and so on – each representing an identifiable context.

The impact of the 90-(90)-90 strategy on the epidemiology of each country not modelled could thus be obtained as a weighted average impact of the countries directly modelled. These average impact factors were then applied to the incidence, notification and mortality trends prepared through the GTB data.

Schematic of the GP impact modelling process

The schematic in Fig. 6 shows how the different modelling processes were combined to produce global results. The TIME impact model was informed by GTB data, population data from the UN Population Division and HIV data from UNAIDS. The country groups and weighting factors were produced from a multivariate TB dataset. Impact factors were then applied to cubic spline trends through GTB data in order to map TIME-modelled deviations onto these trends. The adjusted trends ultimately led to an estimate of epidemiological and cost impacts between baseline (continuation of current service levels) and scale-up scenarios.

Figure 6. Schematic of GP impact modelling process



Impact results

The machinery described above was employed to produce GP impact results for 152 countries. The results were collected in a database, from which the following outputs are presented first at the global level and then for each of the nine countries directly modelled (country results in GP report only).

Incidence

A chart shows GTB incidence data (dots), a cubic spline trend through the data (blue line), a projected deviation from the trend following the implementation of the GP (brown line), and a sequence of milestones depicting the post-2015 WHO targets (red dots) as defined by the WHO Secretariat's 'Global strategy and targets for tuberculosis prevention, care and control after 2015'. The targets are 20%, 50%, 80% and 90% reductions in TB incidence by 2020, 2025, 2030 and 2035, respectively.

Mortality

A chart shows GTB incidence data (dots), a cubic spline trend through the data (blue line), a projected deviation from the trend following the implementation of the GP (brown line), and a sequence of milestones depicting the post-2015 WHO milestones (red dots) as defined by the WHO Secretariat's 'Global strategy and targets for tuberculosis prevention, care and control after 2015'. The targets are 35%, 75%, 90% and 95% reductions in TB deaths by 2020, 2025, 2030 and 2035, respectively.

Notification

A chart shows GTB incidence data (dots), a cubic spline trend through the data (blue line), and a projected deviation from the trend following the implementation of the GP (red line). Generally, the projected increase in notification is short-lived due to the sharp reduction in incidence following the implementation of the GP. No explicit milestones have been set.

MDR treatment initiation

A chart shows projections of global new MDR treatment initiates and the expected increase in the volume of MDR patients as a result of the GP guidelines for testing new and re-treatment cases reported. This increase in volume of patients is a key driver of cost increases under the GP. Under the GP there will be a substantial increase in the costs that result from MDR treatment and health service utilization for MDR patients.

Factors that influence the modelled epidemiological impact

Several factors influence the impact of the GP at country level, and the results have been aggregated in order to produce global impact estimates.

Baseline trends

Baseline TB burden trends are informed by GTB reported data. For each country directly modelled, an attempt has been made to produce the best possible calibration of the TIME model to the GTB data and in particular to the TB country profile published by WHO. For several countries, a more refined calibration was possible, notably for China, India and South Africa, as we were able to draw on work from another project (the Post-2015 Targets project).

Calibration

The TIME model cannot fit all the calibration data precisely and several decisions have to be made in order to provide a fit that captures the most important aspects of each country's TB profile. Most emphasis is given to recent notification and incidence data, based on the assumption that recently reported data have improved in quality. Prevalence estimates from recent surveys also receive substantial weight. These data also form the basis of current budgeting efforts. Although misfits to past data could influence the relative distribution of TB incidence by infection versus activation of previous TB episodes, the GP does not aim to be precise in this regard.

Flat coverage going forward

An important assumption underlying the baseline scenario is that TB and HIV interventions and programmes will be kept at current coverage levels for all future years of the analysis. For TB programmes, this means no further increases in treatment success or case detection rates, and thus no further direct decreases in the average time a person with active TB spends exposing others to the risk of TB infection. For HIV, this assumption means foremost that there will be no further ART coverage increases going forward, and thus no dramatic change in the distribution of HIV cases receiving ART.

The consequence is that the TB epidemic in many countries will tend to rebound slowly from current levels. Impact is measured relative to this potentially increasing baseline TB-burden trend.

Impact

The relative decrease in incidence and consequently mortality at country level is a function of the baseline calibration and the future trend of the baseline, as described above. This calibration is based on the adjustment of the care and control parameters outlined in Table 1. The baseline level of these parameters, as informed by country data, implies a maximal coverage change in order to reach the 90-(90)-90 milestones of the GP. Impact thus decreases relative to improved reporting of TB programme functions: countries with low levels of coverage and case detection should expect a large impact on the epidemic resulting from reaching the GP coverage objectives, whereas countries that have already reached high coverage levels can expect a relatively lower degree of impact.

Country-group-based averaging

The statistical description of each country as a certain fraction, as with group 1, group 2, and so on, is used to produce an average impact for each country. This results, to some extent, in the impact regressing to the mean, although for a particular country group, impact is dominated by the representative country of its group, and by one or two other groups with which it shares aspects of its epidemic (as quantified in Table 2).

Global results

Fig. 7 demonstrates one of the key motivations for setting an ambitious TB control strategy. TB incidence is declining slowly from a global level estimated to be above 9 million, at a rate of approximately 1.5% annually. The rate of decline is clearly inadequate in terms of achieving the End TB impact milestones.

The projected impact of the implementation of the standard investment plan (i.e. scale-up by 2025) is a strong function of the shape of the scale-up of the interventions described by the 90-(90)-90 framework. By adjusting the initial increase in coverage, the location of rapid increase, and the year at which final and full coverage levels are reached, an impact curve can be generated that is commensurate with the End TB Strategy impact milestones.

A modelled result can also be obtained that demonstrates the possibility of earlier impact. Fig. 7 shows a second scenario wherein the scale-up patterns are brought to scale under the accelerated investment plan (i.e. scale-up by 2020). Under such a scenario, the projected impact of the implementation of the GP strategy is dramatic. In fact, the impact would exceed the End TB milestones, which are considered maximal, in that a greater decline was not observed in Western Europe following a sustained period of post-WWII socioeconomic development and improved health care access and service delivery. It must however be noted that the TIME model, unlike a general dynamic TB model, has context-specific intrinsic impact limits. The projected impact results simply reflect the result of scale-up strategies used in the model.

The resulting decline in TB mortality follows a similar pattern as shown in Fig. 8. The 2020 mortality impact targets of the End TB Strategy can be reached with appropriate scale-up, particularly through the accelerated investment scenario.

Figure 7. Global TB Incidence

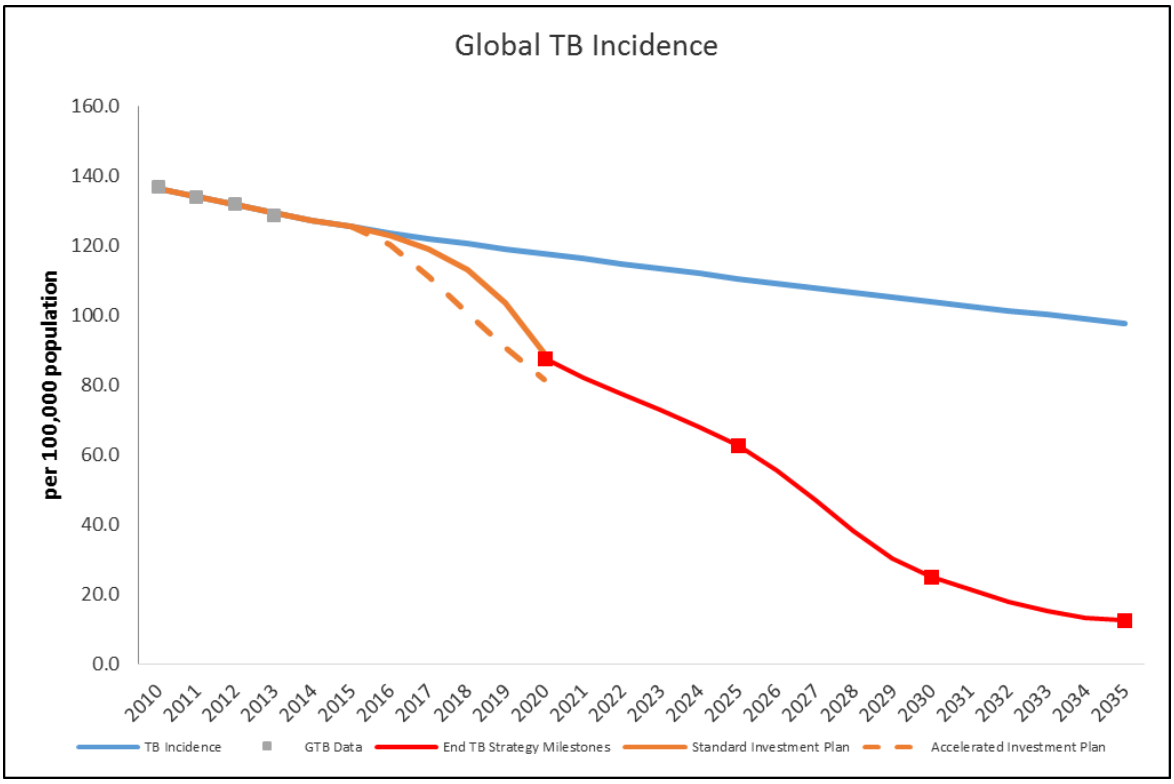
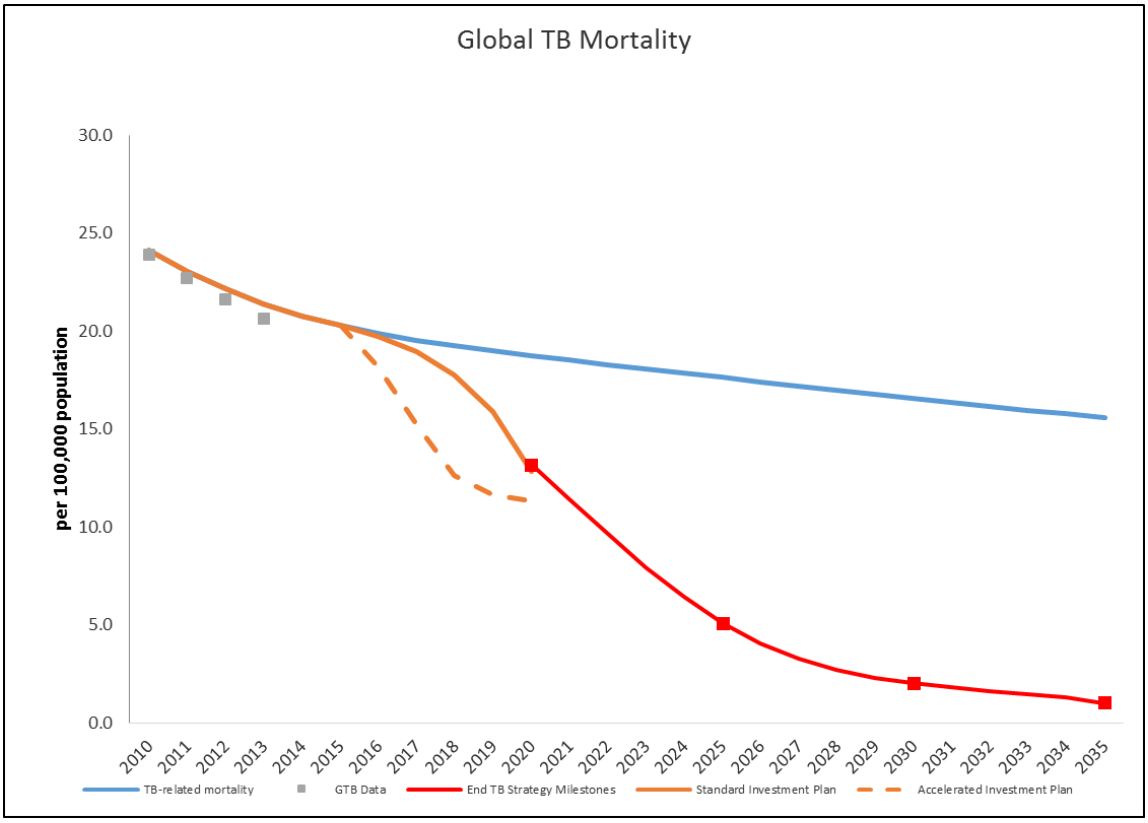


Figure 8. Global TB mortality



Impact summary tables

Tables 6 and 7 show the impact achieved in terms of reducing TB incidence and TB deaths in 2020 relative to the projected 2015 levels – the year relative to which GP and End TB Targets in 2020 are measured.

Table 8 shows the cumulative number of TB cases and deaths for the period 2015–2020 that are projected to be averted under the two GP scenarios: scaling up by 2025 and scaling up more ambitiously by 2020. The difference represents the cost of inaction.

Impact in 2020

Table 6. TB incidence results

TB Incidence			
	TB Incidence 2015	TB Incidence 2020	Reduction by 2020
Countries			
Afghanistan	57,000	44,000	24.2%
Belarus	6,500	5,000	18.5%
Brazil	94,000	71,000	24.2%
China	985,000	773,000	21.5%
DRC	218,000	143,000	34.4%
India	2,077,000	1,486,000	28.4%
Indonesia	456,000	346,000	24.0%
Nigeria	599,000	411,000	31.4%
South Africa	451,000	369,000	18.2%
Country Groups			
High MDR Burden, Centralized Care	279,000	227,000	18.7%
High TB/HIV, SADC	954,000	767,000	19.6%
High TB/HIV, Outside SADC	1,249,000	900,000	27.9%
Moderate Burden, COE	536,000	383,000	28.6%
High Burden, Private Sector	2,117,000	1,579,000	25.4%
Moderate Burden, Middle Income	492,000	374,000	24.0%
India	2,077,000	1,486,000	28.4%
China	985,000	773,000	21.5%
Low Burden, High Income	164,000	124,000	24.3%
Global	8,853,000	6,613,000	**25.3%**

Table 7. TB mortality results

TB Mortality			
	TB Mortality 2015	TB Mortality 2020	Reduction by 2020
Countries			
Afghanistan	12,500	8,000	33.6%
Belarus	900	700	22.2%
Brazil	6,700	5,000	31.3%
China	43,000	25,000	41.6%
DRC	51,000	32,000	37.1%
India	294,000	200,000	32.2%
Indonesia	68,000	47,000	30.1%
Nigeria	237,000	150,000	36.8%
South Africa	89,000	57,000	36.1%
Country Groups			
High MDR Burden, Centralized Care	37,000	26,000	29.9%
High TB/HIV, SADC	225,000	146,000	35.0%
High TB/HIV, Outside SADC	359,000	233,000	35.1%
Moderate Burden, COE	120,000	79,000	34.2%
High Burden, Private Sector	304,000	208,000	31.4%
Moderate Burden, Middle Income	40,000	27,000	33.7%
India	294,000	200,000	32.2%
China	43,000	25,000	41.6%
Low Burden, High Income	10,000	7,000	30.6%
Global	1,432,000	951,000	33.6%

Cumulative impact and opportunity cost

Table 8. Opportunity costs: Cases not averted and lives not saved by delayed implementation of GP

Cumulative Impact for Period 2015–2020 (thousands)	Standard Investment Plan		Accelerated Investment Plan	
	Cases Averted	TB Deaths Averted	Cases Averted	TB Deaths Averted
Country Settings				
High MDR Burden, Centralized Care	100	20	260	50
High TB/HIV, SADC	330	140	880	300
High TB/HIV, Outside SADC	570	210	1,510	490
Moderate Burden, COE	270	70	730	170
High Burden, Private Sector	960	170	2,700	450

Moderate Burden, Middle Income	220	20	590	60
India	1,130	160	3,030	400
China	410	30	950	60
Low Burden, High Income	70	10	180	10
Global (thousands)	4,050	830	10,820	2,000

DALYs averted

DALYs averted (between baseline and scale-up) were calculated with the TIME model using a standard life table.8 The calculation was done only for the nine workshop countries and three additional countries, thus totaling 12 countries representing about 50% of the world's population and 50% of the world's TB burden.

To estimate DALYs averted for the remaining countries, an extrapolation scheme was used, similar to the method explained in the section 'Extrapolation of TIME impact results using country groups'. For each modelled country, a ratio between TB-related deaths and DALYs averted, as modelled by the TIME model, was calculated. Each remaining country was expressed as a percentage of the group-representative countries. TB-related deaths averted for each country in the 2015–2020 period were then multiplied by the average 'DALYS averted per TB death inverted' (i.e. the average of the nine ratios) to obtain country-specific estimates.

Results for the standard and accelerated investment plans are shown in Table 9. Globally, averting one TB death would lead to approximately 62 DALYs when evaluating the impact period 2015–2020. A discount rate of 3% was applied to the DALY estimates.

Table 9. DALYs averted with the standard and accelerated investment plans for the period 2015–2020 by country setting, applying a global discount rate of 3%.

Cumulative Impact for Period 2015–2020 (thousands)	Standard Investment Plan	Accelerated Investment Plan
	DALYs Averted	DALYs Averted
Country Settings		
High MDR Burden, Centralized Care	900	2,700
High TB/HIV, SADC	7,800	21,000
High TB/HIV, Outside SADC	13,100	37,400
Moderate Burden, COE	4,700	13,400
High Burden, Private Sector	10,700	31,100
Moderate Burden, Middle Income	1,300	3,700
India	10,600	30,400
China	2,000	4,800
Low Burden, High Income	80	200
Global (thousands)	51,200	144,700

[8] Also used by Global Burden of Disease: the so-called Coale and Demeny West level 26 life table, with life expectancy at birth set at 82.5 years for women and 80 years for men.

Return on Investment

When a TB programme prevents or treats cases and thereby prevents death and disability, it is quite reasonable to assume that the populations affected (i.e. those who would otherwise have died or incurred a disability, and their families) experience corresponding economic benefits. First, it is possible that the prevention of TB cases may save household expenditure on health care. Second, when cases are prevented (or effectively treated), household members are able to continue (or return to) productive work. These are real monetary benefits that people with TB and their households can experience.

Studies focusing on productivity gains or household economic impact for the target population (i.e. those affected by the disease) may measure plausible economic benefits of disease prevention and treatment (e.g. less absenteeism from work, higher earnings, fewer missed days of school, fewer children dropping out of school because they have become orphaned, etc.). Although these are real economic gains for affected households, we should be cautious about assuming that such gains translate into equivalently large gains at the societal level.

It is much less clear whether investments in these disease programmes lead to monetary economic benefits for the society (i.e. at the country level). This is because many of the societies affected by TB are not at full employment, have large informal sectors, and often rely heavily on extractive industries (i.e. mining) for the bulk of their GDP. In these settings, if a worker dies or leaves the workforce due to disability, his or her household may be worse off, but another person who steps into the job may be better off. Meanwhile, the society does not feel much impact in terms of productivity. As a result, preventing the death of an individual may not impact the GDP of the country, and is even less likely to positively impact the GDP per capita.

Value of statistical life

Another increasingly common way to measure return on investment was recently highlighted by the Global Health 2035 Lancet Commission[9]. This approach involves assigning a monetary value to health gains. This method is based on the "full income" approach to measuring a society's economic welfare. Comparing countries' economic status using GDP per capita alone misses important aspects of social welfare such as life expectancy[10]. "Full income" accounting monetizes life expectancy gains and combines them with consumption gains in order to get a fuller picture of improvements in welfare.

The methods for estimating the monetary value of a life year gained (or DALY averted) are complicated, since there are no "markets" where life years can be bought and sold. Typically, monetary values for health gains are derived from studies of the wage premiums workers command for dangerous jobs in the United States and other rich countries. For example, a 35-year-old person might accept US$ 630 a year in additional pay in order to do a job that has a 1 in 10 000 higher risk of fatality. This would imply that preventing a fatality (often called "value of a statistical life" (VSL)) is worth US$ 6.3 million. An incremental mortality risk shifts an individual's survival curve and changes his or her life expectancy. Likewise, preventing a fatality can be translated into a quantity of additional life years, and the US$ 6.3 million VSL could be spread across those life years to calculate a monetary

[9] Jamison D, et al, Global health 2035: a world converging within a generation. The Lancet, 2013, Vol 282 No 9908.
[10] Nordhaus WD, The health of nations. The contribution of improved health to living standards. Working paper. http://www.econ.yale.edu/~nordhaus/homepage/health_nber_w8818.pdf

value of a statistical life year (VSLY). Although theory predicts that the value of life years should vary with age, the most common approach to estimating VSLY assumes that all years of life gained are of equal value.

The Lancet Commission Global Health 2035 paper assumes that VSL in all countries is 180*GDP per capita (generalizing from the United States). Then, the authors use life tables to estimate reductions in the age-specific mortality risk corresponding to historical changes in life expectancy. They assume the value of a standard unit of mortality risk (i.e. a 1 in 10 000 risk) varies proportionally with remaining life expectancy. (This is equivalent to assuming that all life years gained are of equal value.) The value of all age-specific mortality risk reductions are summed, and the results are normalized to the value of a one-year gain in life expectancy (VLY). Finally, as mortality risk reductions are assumed to be permanent, the value of these risk reductions in all future years is calculated assuming a discount rate of 3% per year. Ultimately, the Lancet Commission estimates that one life year gained is, on average, worth 2.3 times GDP per capita in low- and middle-income countries. This valuation is roughly in line with earlier claims of the Commission on Macroeconomics and Health that a life year gained is worth one to three times GDP per capita[11].

To estimate the return on investment of the GP, we adapted the method used by the Lancet Commission on Investing in Health to the 12 countries for which health gains were modelled with TIME. Like Jamison et al., we assumed that a mortality risk reduction was proportional to remaining life expectancy. This means that a mortality risk reduction at younger ages is typically worth more than the same risk reduction at older ages. We followed the Jamison approach in using life tables to estimate the age-specific mortality risk reductions corresponding to life expectancy gains observed over the past 13 years (2000–2013). However, for our analysis, we used WHO country-specific life tables, instead of historical Japanese life tables as in Jamison et al, because it was not possible to find a good proxy for some of the focus countries using the historical life tables of Japan. In the Jamison et al. base case analysis, life years gained among children age 0 to 4 were arbitrarily discounted by 50%. Because the health impacts of TB programmes primarily benefit persons older than 4-years-old, we did not adopt this assumption. The effect was that greater monetary value was given to the average life year gained in a country (since any gains in early childhood were not down-weighted). This made the valuation a better proxy for the value of the adult years gained due to TB interventions. The results are shown in Table 10.

To further tailor the approach to the GP, it would be useful to estimate the age-specific mortality risk reductions resulting from the GP. It might be possible to derive these estimates from the TIME model output of age-specific YLL averted. To the extent that the TB plan averts deaths at older ages, the ROI will be somewhat smaller.

There are two drivers of differences in VLY as a multiple of GDP per capita between countries. First, the ratio of life expectancy gain to a standardized mortality unit (SMU) is not constant. The same life expectancy gain can translate to different amounts of SMUs, depending on the age distribution of the SMUs. Second, the values of the SMUs depend on the remaining life expectancy at the age at which the SMUs occur.

[11]The Commission on Macroeconomics and Health (CMH) was established by WHO in January 2000 to assess the contribution of health to global economic development. http://www.who.int/trade/glossary/story008/en/

EXAMPLE:

Belarus gained 2.85 years between 2000 and 2013, translating to 5.57 SMUs per LY. Because these SMUs accrued to older ages, the remaining life expectancy (RLE)-adjusted SMUs were 3.47 per LY

Afghanistan gained 6.35 years between 2000 and 2013, translating to 5.06 SMUs per LY. Because these SMUs accrued to younger ages, the RLE-adjusted SMUs were 6.75 per LY.

A limitation of the current approach to estimating ROI is that we have not accounted for YLDs. However, more than 90% of the TB DALYs averted by the STOP TB Plan are attributable to mortality reductions (YLL averted). As such, we somewhat underestimate ROI in our analysis. Our ROI estimate is computed by multiplying VLY by the number of DALYs averted. However, the life year that is valued in the VLY calculation is not a life year in perfect health, but rather a life year lived in age-specific average health. Averting a DALY is more valuable than gaining a life year of age-specific average health. Average levels of disability by age are not readily available for the 12 focus TB countries. However, a rough estimate from U.S. studies indicates that ROI is underestimated by 10–30% due to the lack of accounting for disability.

Table 10. VLY estimates as multiple of GDP per capita

Country	LE gain 2000 to 2013	SMU * n(a) / LE change	SMU*n(a)*e(a)/e(35) / LE change	GDP per capita 2013	VLY as multiple of GDP per capita
Afghanistan	6.4	5.3	6.7	665	4.2
Belarus	2.9	4.5	3.5	7,722	1.7
Brazil	4.5	4.2	2.7	11,939	2.0
China	4.2	4.5	2.9	6,992	2.2
DRC	3.8	6.6	8.3	445	5.2
India	4.8	4.6	4.8	1,487	3.2
Indonesia	4.0	8.4	3.8	3,644	2.5
Kazakhstan	5.0	4.9	4.3	13,612	2.6
Nigeria	7.1	7.4	8.3	2,966	6.0
South Africa	1.8	8.0	5.5	6,886	6.5
Uganda	13.8	6.9	7.3	657	5.4
UK	3.1	8.2	2.5	41,777	1.4

ROI projections resulting from GP investments

To obtain VLY estimates for the countries not modelled, we used the same weighted averaging approach as for the extrapolations of DALYs averted and TB cases and deaths averted. The original country group classification variables were not specifically chosen to capture countries with respect to life-table variables; these elements are therefore at best only indirectly accounted for in the classification.

To obtain the return of investment projections for the period 2015–2020, we multiplied VLY (as multiples of GNI per capita 2013[12]) by DALYs averted over this period, thus assuming a constant GNI per capita. The results are shown in Table 11.

The overall return on investment was about US$ 535 billion (or US$ 1.2 trillion) in return for the incremental TB investment of the standard (or accelerated) investment plans of US$ 21.3 billion (or US$ 20.4 billion). The return on investment ratios are 25 and 85 respectively.

ROI of the GP is positive in all country groups, ranging from ratios below 10 in settings such as high-MDR and fragile-state settings, to the high ratio of 90 in high TB/HIV settings in SADC countries, with the standard investment plan.

Table 11. Return on investment estimates for the GP in the 2015–2020 period, by country setting and globally

By Country Group	GNI per capita 2013 (AVG)	ROI for standard investment plan (USD millions)	ROI for accelerated investment plan (USD millions)
High MDR Burden, Centralized Care	9,000	15,000	1,700
High TB/HIV, SADC	3,200	185,000	7,800
High TB/HIV, Outside SADC	1,500	159,000	41,200
Moderate Burden, COE	800	12,000	158,500
High Burden, Private Sector	2,400	60,500	41,000
Moderate Burden, Middle Income	8,200	16,200	407,200
India	1,600	52,900	364,000
China	6,700	29,200	52,600
Low Burden, High Income	40,900	3,000	134,500
Total	11,000	533,000	1,208,500

[12] World Bank. GNI per capita, 2013 Atlas method data.

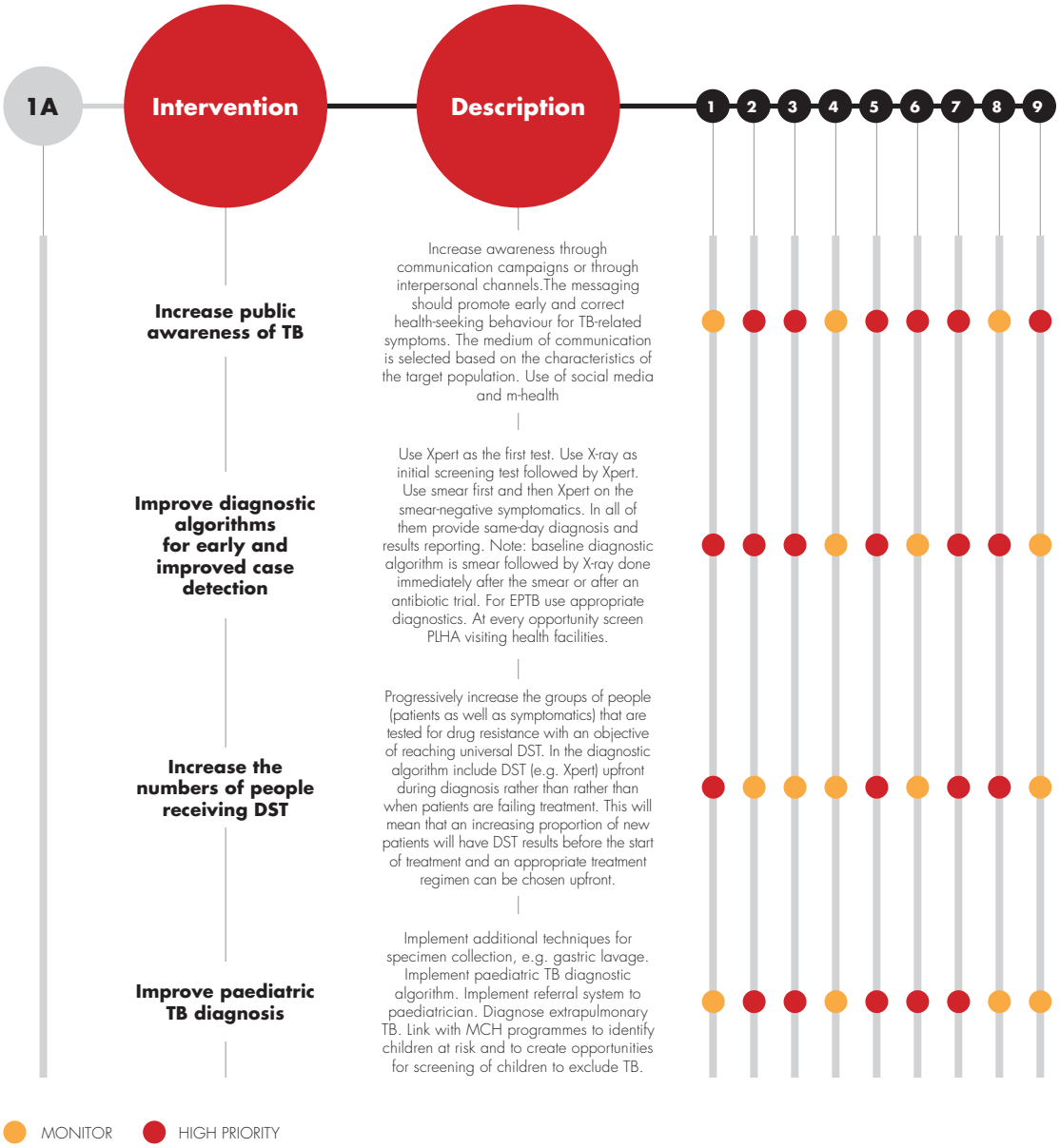
INVESTMENT PACKAGES BY COUNTRY SETTING

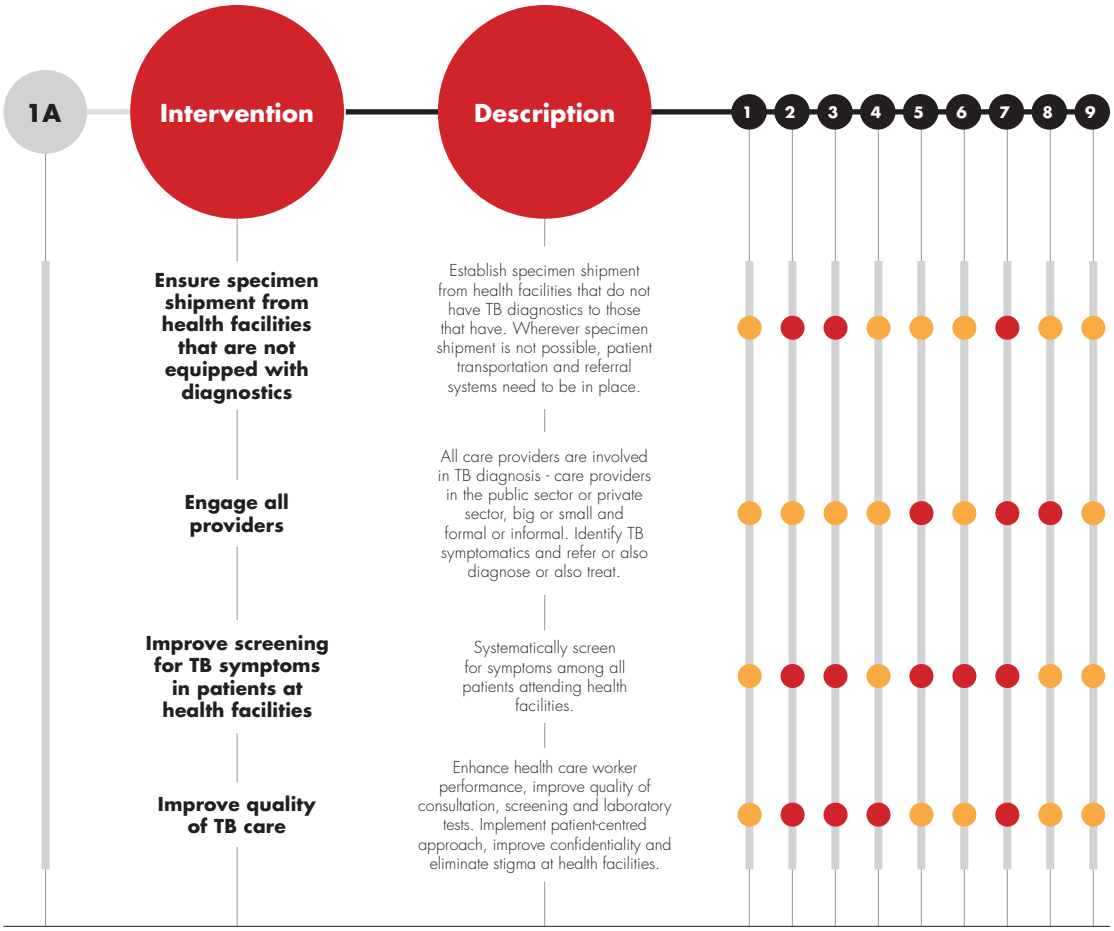
SETTINGS

1. EECA countries with high MDR and centralized care
2. Southern Africa SADC countries
3. Non-SADC countries in Africa with high HIV-associated TB
4. Fragile states affected by conflict and with weak health systems
5. High to moderate burden of TB with large proportion in private care
6. Remaining middle-income and moderate-burden countries
7. India
8. China
9. Low burden and on the verge of eliminating TB

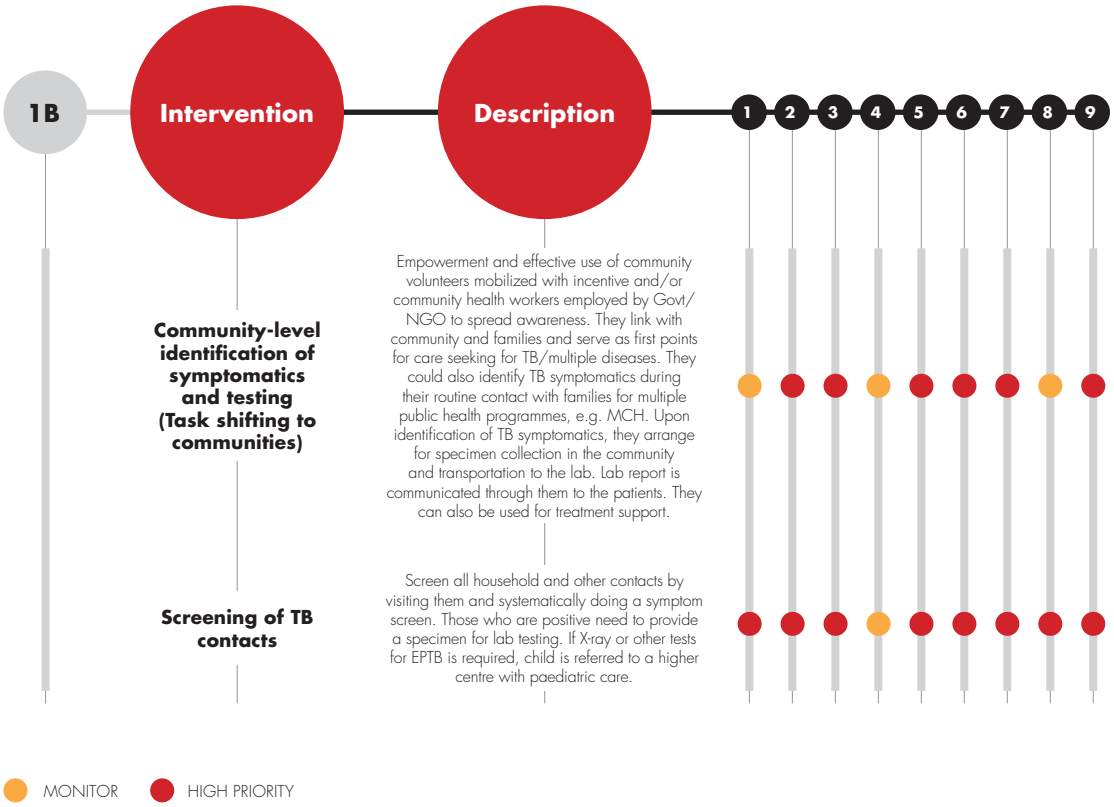
DIAGNOSIS

Improve passive case finding

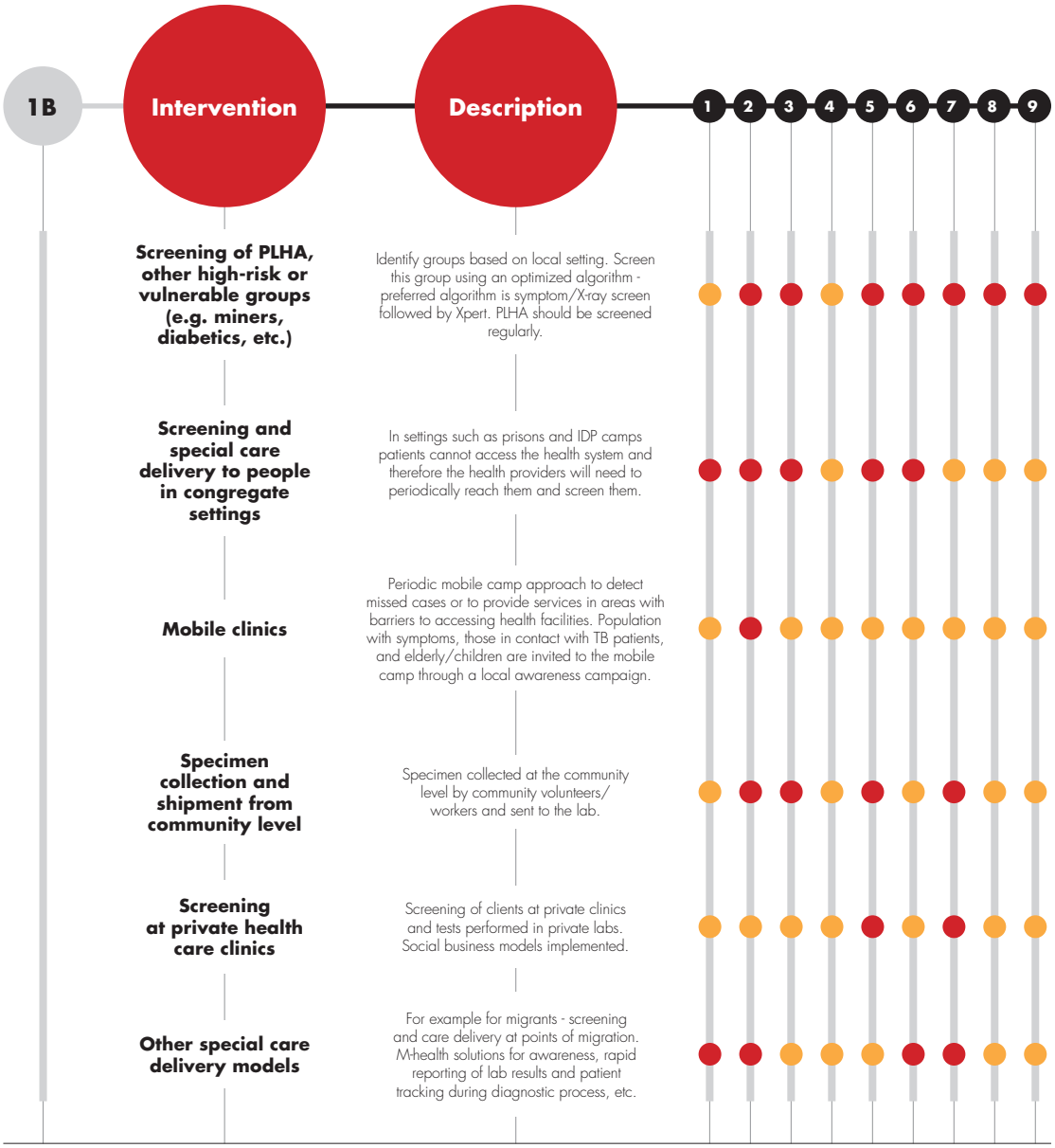




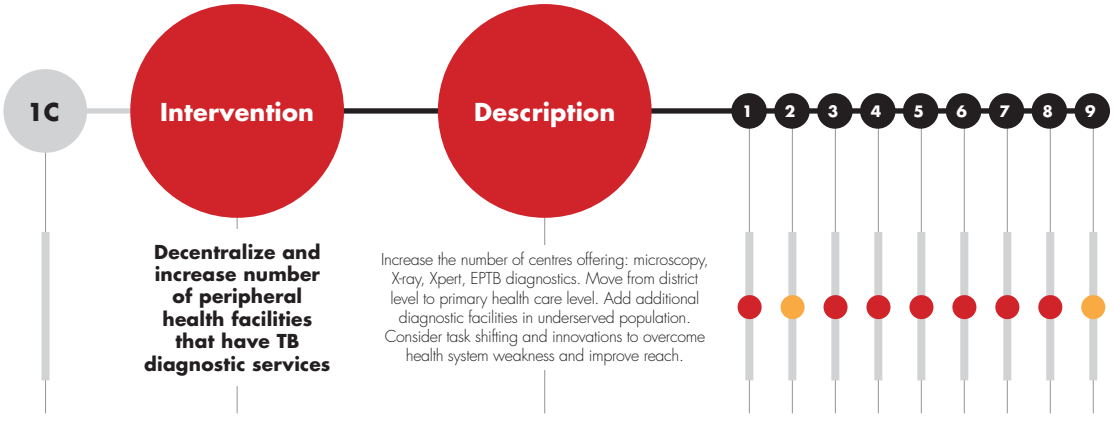
Ensure active case finding



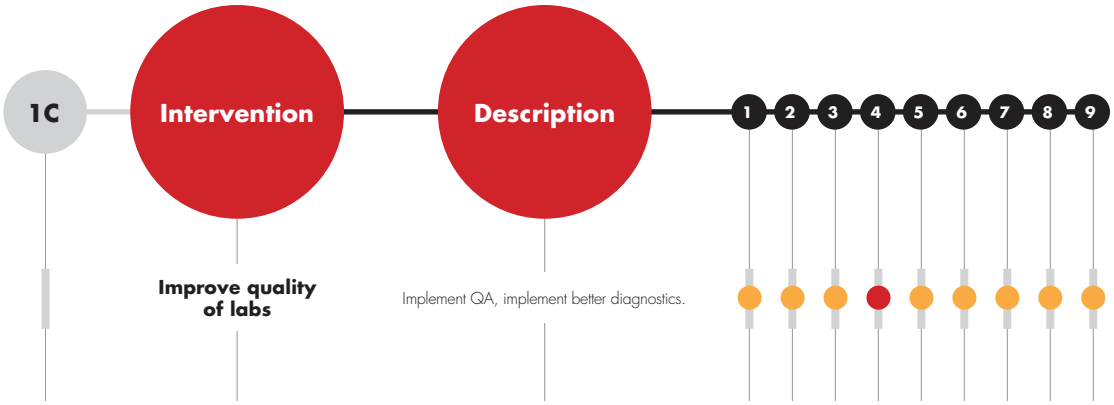
MONITOR HIGH PRIORITY



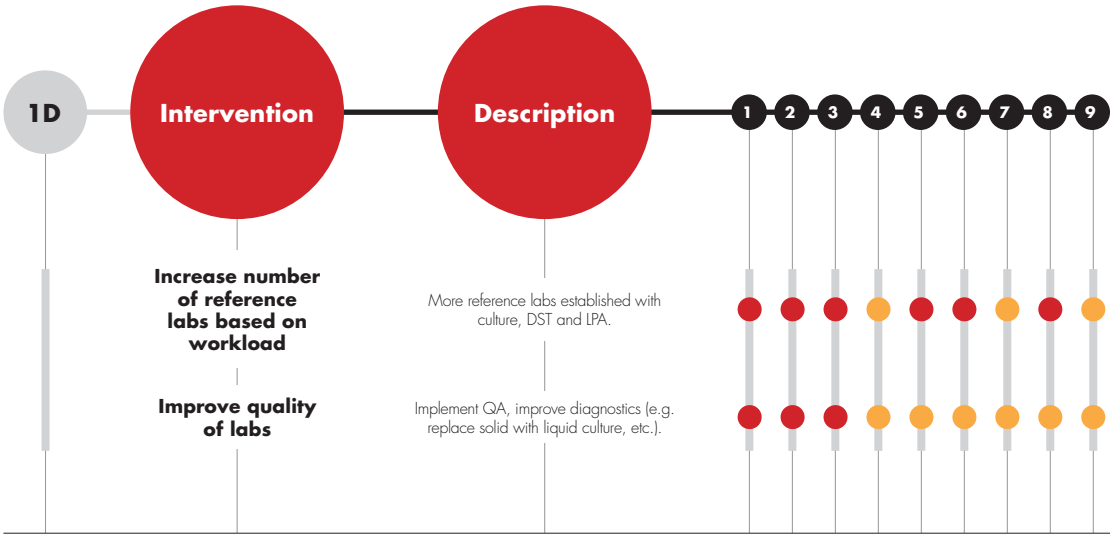
Introduce/scale up/optimize diagnostics in peripheral labs



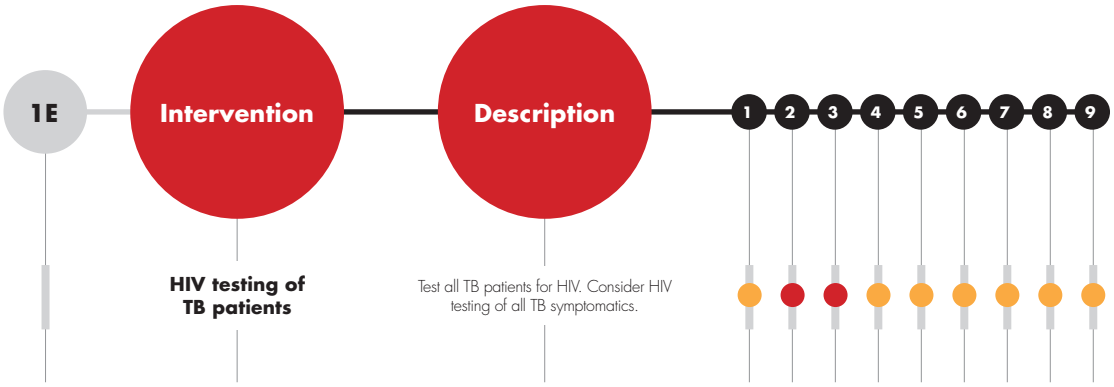
MONITOR HIGH PRIORITY



Introduce/scale up/optimize diagnostics in reference labs

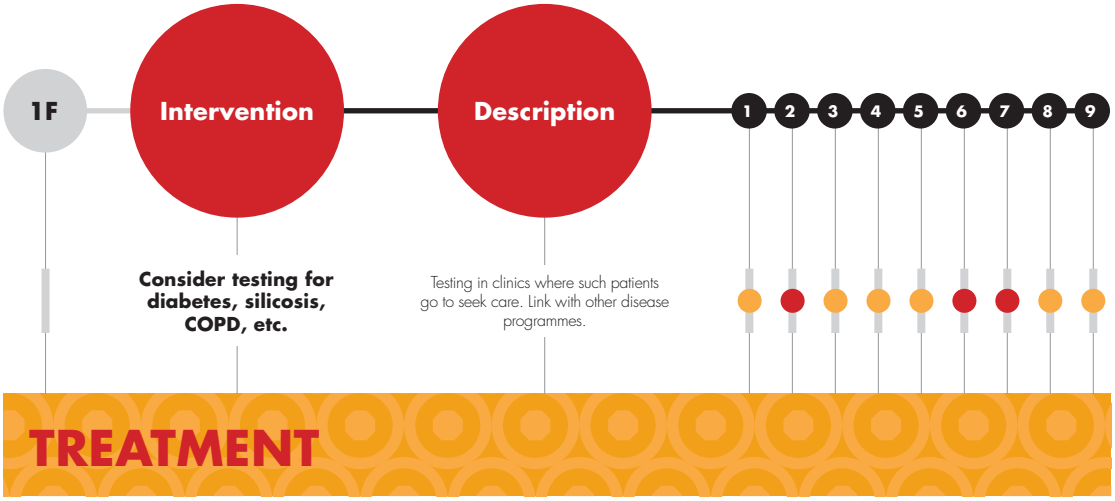


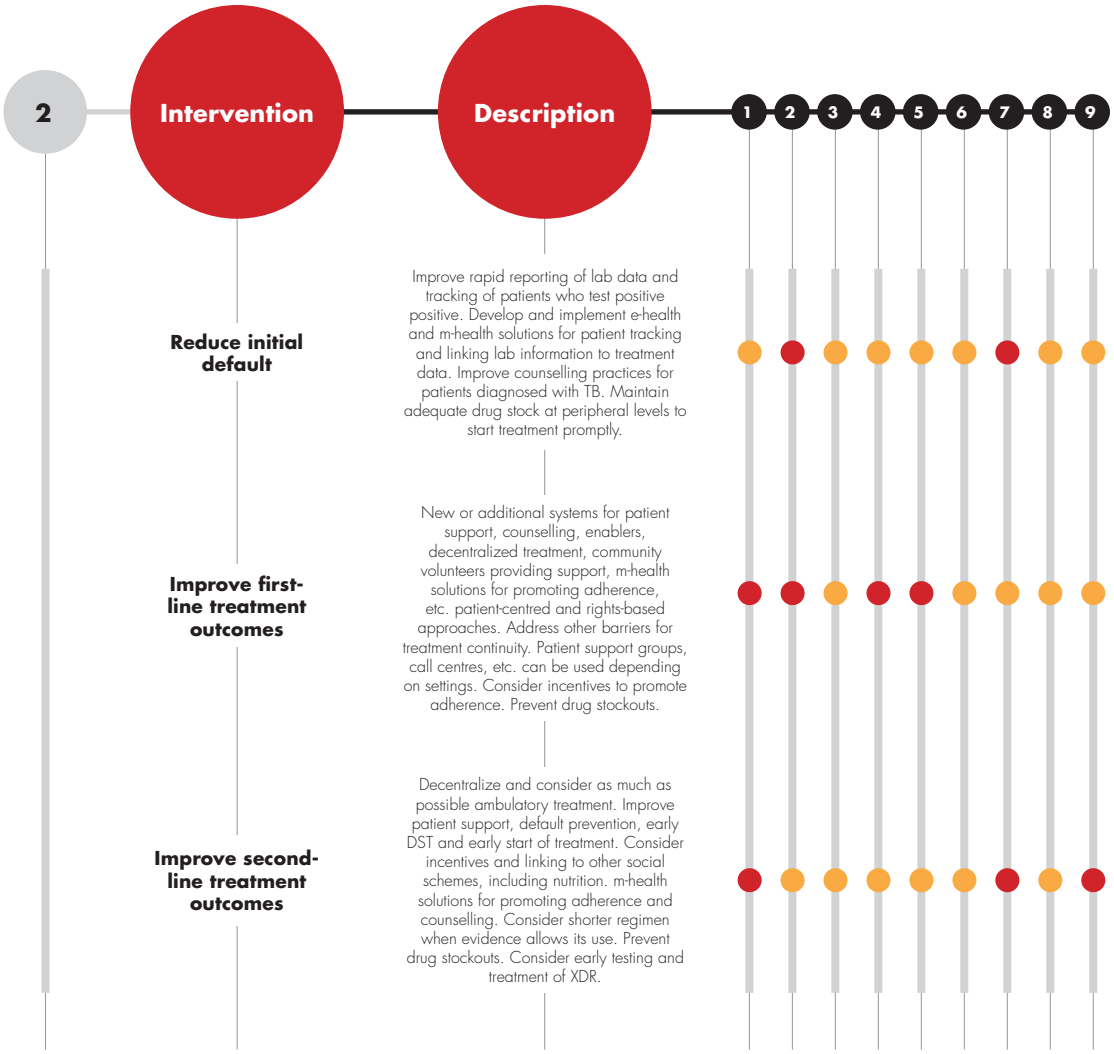
Scale up HIV testing



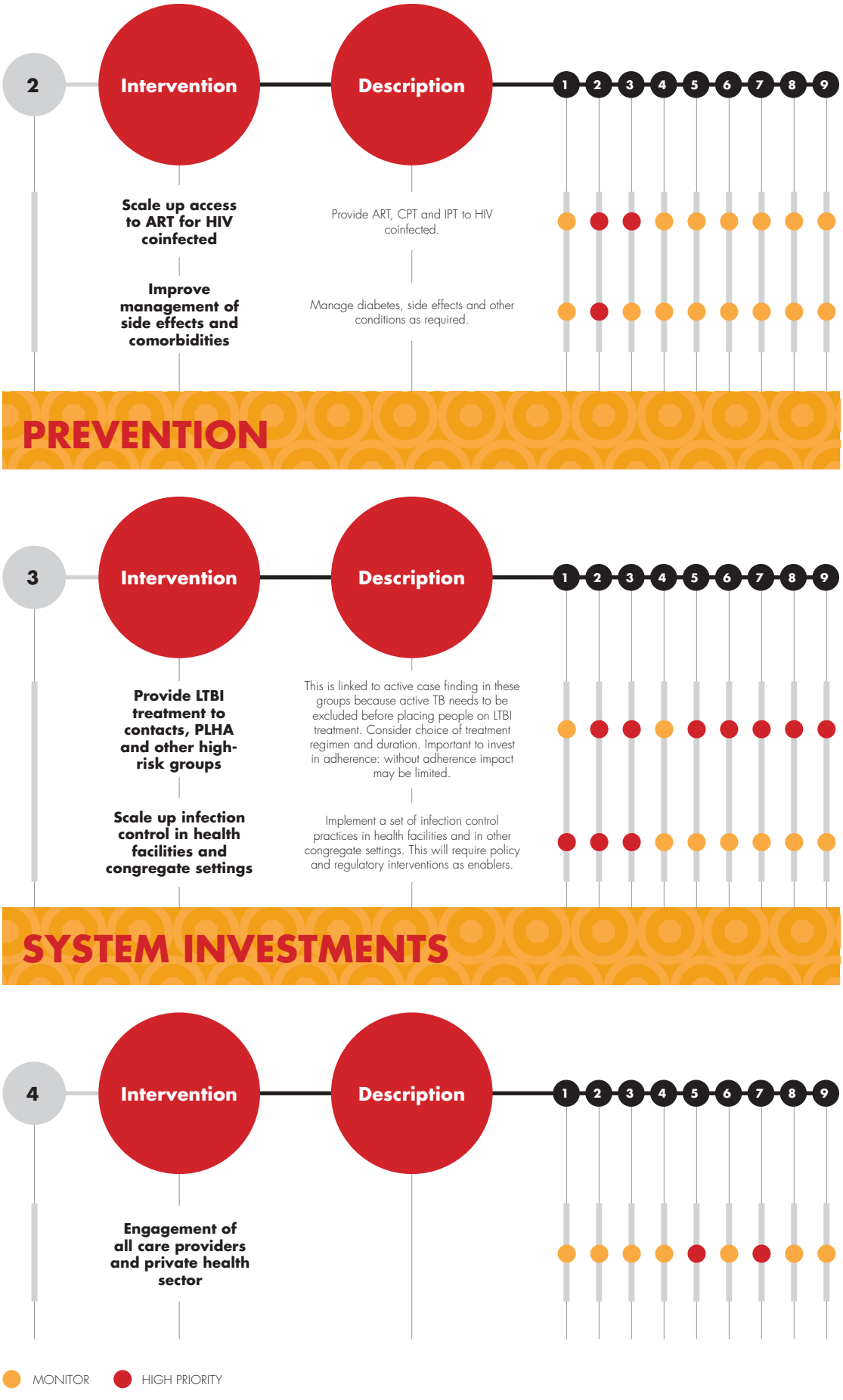
MONITOR HIGH PRIORITY

Scale up testing for comorbidities

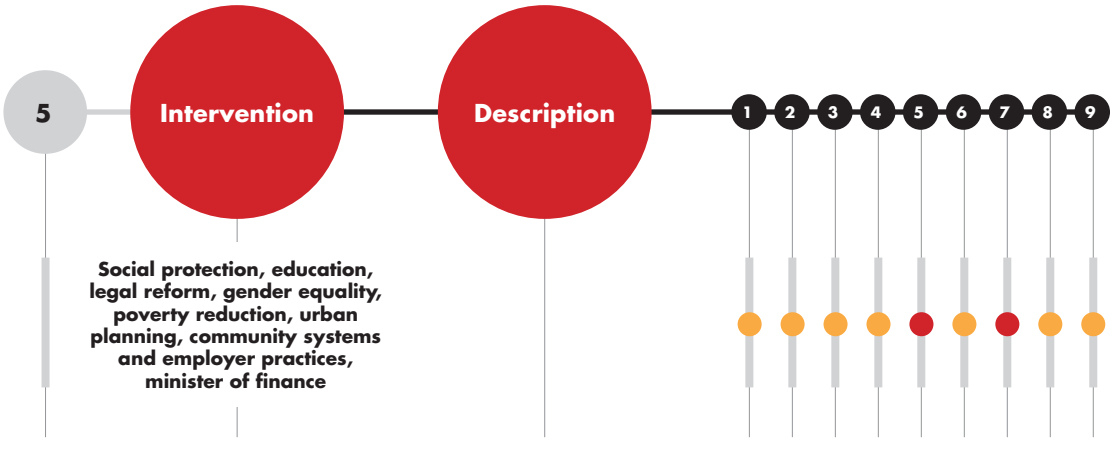




MONITOR HIGH PRIORITY


2
Intervention
Description
1 2 3 4 5 6 7 8 9
Scale up access to ART for HIV coinfected
Provide ART, CPT and IPT to HIV coinfected.
Improve management of side effects and comorbidities
Manage diabetes, side effects and other conditions as required.
PREVENTION
3
Intervention
Description
1 2 3 4 5 6 7 8 9
Provide LTBI treatment to contacts, PLHA and other high-risk groups
This is linked to active case finding in these groups because active TB needs to be excluded before placing people on LTBI treatment. Consider choice of treatment regimen and duration. Important to invest in adherence: without adherence impact may be limited.
Scale up infection control in health facilities and congregate settings
Implement a set of infection control practices in health facilities and in other congregate settings. This will require policy and regulatory interventions as enablers.
SYSTEM INVESTMENTS
4
Intervention
Description
1 2 3 4 5 6 7 8 9
Engagement of all care providers and private health sector
MONITOR
HIGH PRIORITY

ENABLERS AND SYNERGIES WITH THE DEVELOPMENT SECTOR



MONITOR HIGH PRIORITY

Annex 4. Country strategies

Setting 1: Eastern European and central Asian settings that have a high proportion of drug-resistant TB and a hospital-based care delivery system

Belarus country strategy 2016–2020

Targets

By 2020, Belarus aims to screen 90% of people in key populations for TB, diagnose and start treatment for 90% of people estimated to have TB, successfully treat 90% of people with drug-sensitive TB, and ensure that 100% of TB patients and their families avoid catastrophic costs. Belarus also aims to reduce the number of multidrug-resistant TB (MDR-TB) cases by 12% by 2020, compared to 2013 levels, and achieve a 75% treatment success rate among people with MDR-TB. The country aims to achieve 95% coverage of antiretroviral therapy and preventive therapy among people with TB/HIV coinfection.

Key populations

Belarus has made significant progress in implementing rapid diagnostic techniques and increasing treatment success rates. The traditional system of active case finding based on chest X-ray (including mobile digital X-ray devices) has been supplemented with new, rapid diagnostics (Xpert MTB/RIF). This enables the national TB programme to better diagnose drug-sensitive and drug-resistant TB among vulnerable groups, including people living with HIV, migrants, prisoners, the homeless, people who suffer from alcohol-related problems and people who use drugs.

Key interventions

The following key interventions are planned:

1. Ensure universal access to high-quality, rapid laboratory diagnosis for all forms of TB, including drug-resistant TB.
2. Enhance coverage for people with drug-resistant TB by providing high-quality treatment, including the early implementation of new drugs for effective treatment of extensively drug-resistant TB.
3. Improve drug-resistant TB treatment outcomes with appropriate patient-centred support, including patients from high-risk groups and vulnerable populations.
4. Improve the management of HIV-associated TB.
5. Strengthen the health system by introducing new funding models for ambulatory TB care. A portion of funding for the hospital sector will be reallocated to support ambulatory models of care, including providing enablers (transportation reimbursement) and incentives (food parcels) to TB patients, and to primary care workers who support treatment. In 2015, the Ministry of Health passed a new order to provide social support for TB patients during the ambulatory phase of treatment.

Setting 2: Southern and central African settings where HIV and mining are key drivers of the epidemic

South Africa country strategy 2016–2020

Targets

By 2020, South Africa aims to screen for TB among 90% of people in key populations, providing preventive therapy to 90% of people who need it. South Africa also aims to diagnose and start treatment for 90% of the estimated number of people with TB, ensuring that 90% of people with TB/HIV coinfection are also provided with antiretroviral treatment. The country aims to successfully treat 90% of people with drug-sensitive TB and 75% of people with drug-resistant TB.

Key populations

While the TB epidemic in South Africa has largely been driven by the HIV epidemic, there are few communities that are untouched by TB. The disease was the leading cause of death in South Africa in 2013 (8.8% of deaths). Key populations in South Africa who are particularly vulnerable to TB include: people living with HIV; people with diabetes; household contacts of people with TB; pregnant women and children under the age of 5; miners, former miners, and people working and living near mines; prison inmates and prison employees; and health care workers.

Key interventions

The following key interventions are planned:

1. Mass TB screening. Persons living within informal, poor and at-risk communities will be reached through a combination of intensified case-finding and active case-finding.
2. Improved linkage to care. South Africa is focusing on the treatment cascade and linkages to care across the health system, including in programmes for TB, HIV, and maternal, newborn and child health. Additionally, for drug-resistant TB, South Africa will continue efforts to decentralize and deinstitutionalize treatment.
3. Improved treatment for drug-resistant TB. South Africa will roll out and monitor newly available and registered second-line drugs, and implement earlier and more comprehensive detection of second-line drug resistance.
4. Increased prevention of TB. Preventive therapy will be given to people with a high risk of becoming ill with TB, including people living with HIV, miners with silicosis and young children who are TB contacts. Coverage of preventive therapy will increase from 5% to 90% to prevent TB disease.

Setting 3: African settings with moderate to high HIV where mining is not a significant driver

Nigeria country strategy 2016–2020

Targets

The Nigeria National Strategic Plan (2015–2020) aims to find 90% of all people with TB and achieve at least a 90% treatment success rate among people who are provided with first-line anti-TB drugs. In addition, Nigeria aims to provide HIV testing for all people who are diagnosed with TB, ensure that all TB patients who are HIV positive are provided with antiretroviral therapy and preventive therapy, and provide at least 80% of people living with HIV with preventive therapy. Furthermore, the country aims to provide access to drug-sensitivity testing for all people who are thought to have drug-resistant TB and to provide all people with drug-resistant TB with appropriate treatment.

Key populations

To achieve a rapid increase in TB case-finding, the Nigeria National Strategic Plan recommends a departure from a predominantly passive TB case-finding approach to a more active approach. The Plan targets key populations that are at an increased risk of developing TB disease and/or do not currently have access to TB services. These key populations include people living with HIV, contacts of people with TB, people living in urban slums, nomads, migrants and internally displaced people, prisoners, people with diabetes, children, and health care workers, especially those in in-patient facilities, HIV and TB clinics, and laboratories.

Key interventions

The following key interventions are planned:

1. Inform the public about TB facts, how to access services, how to get cured, and what their rights and responsibilities are in order to support demand for universal access to services.
2. Engage with various primary contact points – including patent medicine vendors, community pharmacists, private providers, faith-based organizations, community providers and community-based organizations – in the identification of people who may have TB and the diagnosis, notification and treatment of TB patients.
3. Shift from passive to active case-finding in key populations.
4. Scale up rapid TB diagnostic technologies to serve groups at risk of missed or delayed diagnosis, including people living with HIV, children, and people with smear-negative TB, extra-pulmonary TB or presumptive drug-resistant TB.
5. Expand services for drug-resistant TB patients based on an ambulatory model, with rigorous supervision and community-based patient support.
6. Design and implement an electronic reporting system that captures and analyses TB data for use in timely programme monitoring.

Setting 4: Settings with severely under-resourced health systems or settings with challenging operating environments

Afghanistan country strategy 2016–2020

Targets

To reach the 90-(90)-90 targets by 2025, Afghanistan aims to:

- Expand health services to the most remote areas, finding and treating 90% of people with TB in these areas by 2025
- Involve all private health facilities and general practitioners in TB control activities by 2025
- Ensure that at least 90% of people are aware of TB and that TB services are provided free of charge at public health facilities
- Trace all contacts of people with infectious TB by 2020
- Target all key populations
- Provide drug-resistant TB screening to all people previously treated for TB, 50% of new cases by 2020 and 100% of all cases by 2025.

Key populations

Key populations in Afghanistan include prisoners, people living with HIV, malnourished children, people with diabetes, internally displaced people, returnees, refugees, nomads, and women in reproductive age groups. The priority populations are prisoners, people living with HIV, severely malnourished children, people with diabetes, and women of reproductive age who are attending school or university or who are employed in a workplace. Two thirds of TB cases are among women in Afghanistan.

Key interventions

The following key interventions are planned:

1. Expand health services to the most remote areas to reach missed TB cases.
2. Encourage private health practitioners and general practitioners to refer or diagnose people with suspected TB and provide treatment as guided by the national TB programme.
3. Advocate for greater support from other sectors and enhance general awareness of public health facilities that provide TB services.
4. Engage in active case-finding, focused on contact tracing and screening vulnerable groups in the community.
5. Reach key populations.
6. Expand the programmatic management of drug-resistant TB.

Setting 5: Settings with a high to moderate burden of TB with a large proportion in private sector care

Indonesia country strategy 2016–2020

Targets

In its current National Strategic Plan 2015–2019, Indonesia's national TB programme and stakeholders have set ambitious targets to be reached by 2015. These are to decrease TB deaths by 30% compared to 2014 and to decrease incidence by 15% compared to 2014. The Plan also aims to accelerate the rate of annual decline in incidence (1% in 2014) to 4% a year by 2017, and to increase access to universal health coverage and social protection so that by 2019 no individuals or families will suffer from catastrophic costs due to TB.

Key populations

Indonesia will target efforts to find and treat people with TB in marginalized population groups, such as those living in urban slums, people living with HIV, people with drug-resistant TB, prisoners, people with diabetes and people who smoke.

Key interventions

The key interventions in Indonesia's National Strategic Plan are to:

1. Increase the case notification rate for all forms of TB from 131 per 100 000 population in 2013 to 236 per 100 000 population by 2019.
2. Ensure that treatment success rates in hospitals and the private sector, as well as in the public sector, reach 90% by 2019.
3. Increase the prevention, diagnosis and reporting of TB in children.
4. Increase coordination between TB and HIV/AIDS programmes across programmes and sectors at all levels to reduce the TB and HIV burdens in the community.
5. Ensure universal access to diagnosis and treatment for drug-resistant TB by 2019.
6. Ensure political commitment at the national, provincial and local levels for the allocation of sufficient resources and enforcement of existing and new regulations that support efforts against TB.
7. Expand and strengthen infrastructure, human resources, and management processes to implement the national strategy successfully.
8. Expand and strengthen data collection and surveillance systems to capture strategic information on TB cases diagnosed and treated in all sectors, and analyse that information for programme improvement.

Setting 6: Middle-income country settings with a moderate TB-burden

Brazil country strategy 2016–2020

Targets

Brazil aims to remove all barriers to the universal coverage of diagnosis and treatment that is already provided through the Brazilian Unified Health System. Brazil's targets for 2020 are in accordance with the End TB Strategy: a 35% reduction in the number of TB deaths and a 20% reduction in the TB incidence rate compared to 2015. The country is currently developing a National TB Plan with operational targets and specific recommendations aligned with the Global Plan.

Key populations

In Brazil, key populations include indigenous peoples, prisoners, people who are coinfected with TB/HIV, health professionals, people living in poor conditions and the homeless. The country has specific national recommendations for these population groups and is scaling up existing recommendations for vulnerable populations, as well as developing clinical delivery and new approaches that consider social protection and community engagement.

Key interventions

The following key interventions are planned:

1. Specific TB strategies to improve access to health facilities and the treatment success rate among key populations
2. Specimen shipment from health facilities that are not equipped with diagnostic capabilities
3. Introduction of strategies for social protection, including incentives to increase treatment adherence
4. The increase of treatment success rate through a focus on people lost to follow up
5. The improvement of first-line and second-line treatment outcomes.

Setting 7: India setting

India country strategy 2016–2020

Targets

India aims to find 90% of people who are ill with TB and achieve a 90% treatment success rate for drug-sensitive TB. India also aims to offer drug-sensitivity testing to at least 90% of people with TB and provide treatment to 90% of people with multidrug-resistant TB (MDR-TB). India aims to ensure HIV testing for 90% of TB patients and will offer preventive treatment and antiretroviral therapy to 90% of people living with HIV who have TB. India's TB programme aims to initiate active case-finding in key populations in at least 90% of its programme management units. India aims to reach these scale-up objectives before 2020.

Key populations

India will prioritize socially vulnerable, marginalized population groups, as well as clinically high-risk groups, for increased service delivery. Active case-finding will be intensified among the urban poor, in settings such as prisons, in tribal and remote areas, among people with diabetes and among people who use tobacco or alcohol.

Key interventions

The following key interventions are planned:

1. Implementing an efficient diagnostic algorithm with higher sensitivity tools and x-ray screening
2. Improving long-term treatment outcomes by using better first-line regimens, improving treatment adherence and patient support, and providing treatment for drug-resistant TB that is guided by drug-sensitivity testing.
3. Active case finding in high-risk groups, including contact investigation and screening in high-risk population groups and settings
4. Establishing a TB surveillance system that utilizes call centres, online technology and GIS mapping of TB cases to inform corrective local action
5. Engaging the private sector in notification, diagnosis and treatment, as per international standards, and using innovative methods such as interface agencies and information technology-based treatment adherence options.

Setting 8: China setting

China country strategy 2016–2020

Targets

By 2020, China aims to screen 90% of people in key populations for TB, diagnose and start treatment for 90% of the number of people estimated to have TB, and successfully treat 90% of people with drug-sensitive TB.

Key populations

The following key populations will be prioritized for increased service delivery: people with multidrug-resistant TB, people with TB/HIV coinfection, people with diabetes, prisoners, migrants, and poor people who may not have adequate health insurance.

Key interventions

China's strategy focuses on interventions in the following key areas:

1. Hospital-based TB service delivery
2. Improved patient management
3. Improved detection and treatment for drug-resistant TB
4. Increased detection of TB in vulnerable groups
5. Elimination of catastrophic costs.

Annex 5. Strategic frameworks for research and development for new tools for TB

New Drugs Strategic Framework 2016–2020

Vision: To develop shorter, more effective drugs and regimens for all age groups and populations affected by TB			
Goals: Introduction of a new regimen with a shorter duration (2–3 months) and containing three or four new drugs without pre-existing resistance to treat both drug-susceptible and drug-resistant TB			
Objective	Milestone(s)	Major Activities	Funding Required 2016–2020 (US$ millions)
Sustaining the pipeline through basic discovery for TB drugs	New clinical candidates entering Phase I	Accelerate screening and optimization of new chemical entities; validate biomarkers; develop animal models that are more predictive of clinical efficacy; identify new drug targets	1050
Maintaining trial site capacity	Increased number of GCP/GLP compliant sites available for TB drug trials	Identify, maintain and provide training at GCP/GLP-compliant sites	300
Developing a shorter regimen for DS-TB	Complete Phase III of a 2–4 month regimen for DS-TB	Conduct trials in pK studies, Phase I, Phase II (EBA, SSCC, drug-interaction studies), and Phase III to advance two to three new shorter regimens	1400
Developing a safer, higher efficacy and shorter regimen for MDR-TB	Complete Phase III of a shorter regimen for MDR-TB	Conduct trials in pK studies, Phase I, Phase II, and Phase III to advance two to three new shorter regimens	600
Improving treatment for children in parallel to efforts in adults	Complete formulation and clinical testing in children in conjunction with any new regimen advancing in adults	Include children in trials early on for new regimens; develop safe, reliable and user-friendly regimens for all forms of TB in children early in the development process; conduct drug-interaction studies	150
Developing a safer, high-efficacy	Complete Phase III of a safer, high-	Conduct Phase III trials of new regimens for latent TB	90

regimen for latent TB	efficacy regimen for latent TB	with the aim of a shorter duration of treatment	
Ensuring adoption of new TB drugs and regimens at the country level	Patients access newly approved drugs and regimens, especially in high-burden countries	Include new drugs and regimens in national policies and guidelines; implement mechanisms to expedite regulatory processes in countries; engage key stakeholders; conduct extensive training of health providers	500
Engaging community and civil society in the entire process of drug development and access	Community and civil society are represented in all decision-making processes and forums along the drug discovery and development pipeline	Include community and civil society representatives in advisory committees, protocol and study design, scientific networks, and other forums related to TB drug development	65
		Grand Total	**4155**

New Diagnostics Strategic Framework 2016–2020

Vision: Achieve early and universal diagnosis of all patients with all forms of TB to foster progress towards TB elimination, by making appropriate and affordable diagnostic solutions available in the right setting and ensuring that diagnostic results are linked to treatment.			
Goals: 1. Improve TB case detection through accurate tests, enabling patient-centred use at all levels of the health care system for all populations, including children and those living with HIV, as well as innovative diagnostic strategies that will ensure better outreach to patients. 2. Enable timely and effective treatment to reduce mortality and ongoing transmission, and prevent antimicrobial resistance by rapidly and simply detecting resistance to existing and future drugs. 3. Reliably identify individuals at risk of progression from latent infection to active TB disease in order to introduce targeted preventive therapy and cut transmission.			
Objective	**Milestone(s)**	**Major Activities**	**Funding Required 2016–2020 (US$ millions)**
Ensure that the critical knowledge enabling the development of new diagnostic tools and solutions is available and explore alternative approaches for case finding	Undertake discovery science and build/improve capacity for such discovery research to identify and validate new markers	Support consortia on biomarker discovery using different platforms and approaches targeting: a. Detection of active TB at POC b. Identification and characterization of mutations c. Progression to active disease d. Treatment monitoring e. Validation of promising biomarkers f. Development of a biomarker database	134.5
	Ensure increased access to clinical reference materials that are critical for the development and validation of new TB diagnostics	Specimen collection, maintenance and expansion of repositories, data management and QA/QC for: a. Specimen bank b. Strain bank c. Paediatric specimen bank d. Extra-pulmonary TB specimen bank e. Specimen bank for treatment monitoring	31
	Support assessment of MTB genetic variants to inform the development of	Development and maintenance of a centralized repository of global genomic and clinically relevant data,	110

	molecular tests for the detection of drug-resistant TB	review for quality and standardization	
	Increase efficiency of early development pipeline and support decisions before large-scale trials	Conduct studies for evaluation/ demonstration studies planned under objective 3 to assess potential impact and help plan those studies in the most effective way	5
	Undertake research and consultations to support development of e-health solutions	Definition of patient charter/ethical criteria, and consensus-building on patient identifier	0.7
Total Objective 1 – Addressing knowledge gaps			281.2
Develop a portfolio of new diagnostic tools coupled with a package of accompanying solutions to ensure that results translate into patient treatment	Develop tests and solutions for the diagnosis of active TB at the point-of-care level in all patient populations, including children and people living with HIV	Support test development and technical and clinical validation during development for: a. Smear-replacement tests and solutions b. Biomarker-based non-sputum-based tests and solutions c. Triage referral tests and solutions	75
	Develop tests and solutions for rapid and simple detection of resistance to existing and future drugs	Support test development and technical and clinical validation during development for: a. Next-generation DST at peripheral levels b. DST for new drugs and new drug regimens c. Next-generation sequencing directly from sputum	36
	Develop tests and solutions for predicting the risk of disease progression	Development, endorsement and revision of TPPs; test development, and technical and clinical validation during development, including validation and qualification of immune activation biomarkers	20.2

	Develop tests to support syndromic approaches to help differentiate between pathogens and reduce antibiotic overtreatment	Validation and qualification of suitable biomarkers for syndromic tests for patients with respiratory symptoms on first visit to primary health care services providing a clinically actionable answer	16
	Develop tests and solutions for treatment monitoring/test of cure	Test development, and technical and clinical validation during development, including molecular candidate as well as validation and qualification of suitable biomarkers	6
	Develop e-health and connectivity solutions to facilitate access by patients to tests listed above	Development, endorsement and revision of TPPs; integration of connectivity in diagnostic technologies; development of e-health applications and aggregation platforms	4.3
Total Objective 2 – Development of a portfolio of new tests and solutions			157.5

Evaluate the portfolio of new diagnostic tools and solutions, including new detection strategies, approaches for optimized use, and innovative delivery mechanisms; demonstrate patient benefits and predict likely impact within the entire health system	Conduct evaluation in clinical trials and demonstration studies for new tests and solutions identified above, as well as for syndromic approaches	a. Evaluation of tests for active TB and for drug-susceptibility testing (MDR/XDR TB) b. Demonstration studies of TB tests and DST c. Demonstration studies of tests targeting paediatric TB d. Demonstration studies of tests targeting extrapulmonary TB e. Evaluation and demonstration of syndromic approaches f. Demonstration studies of e-health solutions and platforms for connected diagnostics	86
	Predict patient impact from the use of improved diagnostics on TB detection rate, transmission and mortality	a. Develop mathematical modelling b. Conduct impact and cost–effectiveness studies to evaluate new technologies and innovative strategy/approach	70
	Conduct market analysis and estimate potential for new diagnostics	Update and expand existing market assessments	2
Total Objective 3 – Evaluation, demonstration and impact			164.5
Ensure that fully validated new diagnostic tools and solutions are widely available and appropriately used in endemic countries	Roll-out of new tools and solutions	Procurement of devices and consumables for the roll-out of at least one new technology to support the detection of active TB in 90% of new cases and drug resistance in 100% of cases in high-risk groups	2300
	Strengthening laboratory capacity for appropriate scale-up of new tools	Training; QA and accompanying measures; ongoing assistance; training assistance for supply management aspects	224.2
	Patient-centred diagnosis and decentralization of testing	a. Xpert referral system (sample transportation, results delivery to patients/clinic, follow-up with patients) b. m/e-health solutions / transmission of results	76.7

	c. Incentive systems for patients to compensate for time required for diagnosis	
TB/HIV laboratory integration (TB testing in HIV settings)	Demonstration projects and operational research on how the new viral load test could be used as a predictor to screen for TB	24
Private sector integration	a. Incentives for private sector to use endorsed new tools b. Laboratory strengthening and EQA for tools in use in the private sector	8
Maintain speed of national policy change and in-country regulation processes	a. Harmonize regulatory processes in countries with problematic mechanisms: China, Russia, and Brazil to some extent b. Support national policy change and adoption (local cost–effectiveness and validation studies)	33
Sensitize stakeholders	Coordinate with advocacy groups; organize workshops with NTPs, MoHs, technical, procurement and funding agencies, and patient representatives	10
Conduct operational research on how best to deliver diagnostic services in routine programmatic settings to ensure a patient-centred approach, and to estimate costs and resources used by NTPs	Conduct studies covering different test categories and scenarios, as well as different settings, i.e. low/high-MDR, low/high-HIV, different geographies	30
Scale up manufacturing and other market interventions	Investment in commercialization and successful scale-up	75

	Introduction in countries of DST for new drugs and for additional group V drugs as of 2017	Introduction of appropriate testing strategies and protocols, and EQA for phenotypic testing and molecular detection	33.9
	Expanded sequencing capacity in countries as of 2017	Training and support in sequencing analysis at reference laboratory level	12.5
Total Objective 4 – Availability and appropriate use of new tests (incl. roll-out) without roll-out			2827.373
Grand Total			**3430.5 (with roll-out)** **676.2 (without roll-out)**

New Vaccines Strategic Framework 2016–2020

Vision: To develop new, more effective vaccines that will directly and safely prevent TB in all age groups and populations

Goals: Prevent TB disease and interrupt transmission through the development of new vaccines that would prevent infection, reactivation or reinfection; incorporate and consider access strategies throughout the TB vaccine development process; and strengthen community engagement in TB vaccine R&D.

Objective	Milestone(s)	Major Activities	Funding Required 2016–2020 (US$ millions)
Continue to advance the clinical pipeline of TB vaccine candidates	Advance candidate and candidate concepts through clinical trials, utilizing portfolio management and common stage-gating criteria	Initiate at least one Phase III trial and conduct Phase I/IIa/IIb trials on vaccine candidates that meet criteria	250
	Explore and implement novel Phase II clinical trial designs to identify the most promising vaccines as early as possible in development and optimize use of resources	Conduct trials using prevention of infection and prevention of recurrence study designs	75
	Ensure sufficient capacity to support large-scale clinical trials	Scale up manufacturing to support large-scale (Phase IIb/III) clinical trials; maintain capacity trial sites in different regions to conduct clinical trials at GCP standards	200
	Conduct epidemiological research at trial sites to inform site selection and trial design	Conduct incidence and prevalence of TB infection studies; incidence of disease studies; and cross-sectional prevalence of disease studies in multiple regions	12
Total Objective 1 – Clinical pipeline			537
Enhance knowledge through experimental medicine	Develop and test a human challenge model to speed TB vaccine R&D	Support consortium to advance human challenge model through development and preclinical phase, and initiate clinical phase	20
	Complete human studies in parallel with NHP challenge in order to learn about protective immune responses	Conduct NHP challenge studies to determine correlates of protective immunity	100

	Test key hypotheses about protective immune responses	Conduct multiple experimental medicine studies to test different hypotheses	100
Total Objective 2 – Experimental medicine			220
Increase emphasis on early-stage and discovery research	Develop biomarkers	Identify immune correlates of protection and disease	60
	Identify novel vaccine targets	Identify and advance novel vaccine targets	40
	Investigate new approaches to mount an effective response	Conduct unconventional studies to induce protective immune responses	100
Total Objective 3 – Early-stage anddiscovery research			200
Improve animal models	Develop and optimize fit for purpose animal models, including natural transmission models, and an optimal model to test prevention of infection or disease	Enhance infrastructure; qualify and validate models in different animal species	150
Total Objective 4 – Animal models			150
Improve preclinical and clinical readouts	Standarize reagents and harmonize assays	Gather stakeholder input and come to consensus on path forward	1
		Continue and expand on programmes to provide reagents to laboratories and research facilities	30
		Develop necessary assays based on stakeholder consensus	40
Total Objective 5 – Reagents and assays			71
Lay the groundwork for adolescent and adult vaccination campaigns	Conduct strategic access and implementation research, including studies of cost-of goods, TB cost–effectiveness, country vaccine readiness, and vaccine landscape		12
Total Objective 6 – Conduct strategic access research			12
Engage communities in TB vaccine R&D (see table below)			60
		Grand Total	**1250**

Strategic Framework for R&D Advocacy and Community Engagement

Objective	Milestones	Activities	Funding Required 2016–2020 (millions)
Build support for TB vaccine R&D through an enhanced advocacy and community engagement framework	Increase funding for TB R&D advocacy	NGOs, community-based organizations, and other civil society and advocacy groups receive financial support for conducting advocacy at the global, regional, country, and local levels.	60
	Include advocates in decision-making structures and scientific forums	TB research conferences and meetings take steps to enable the active participation of civil society and community representatives in program settings, including relevant tracks for abstract submission and funding to support participation.	
	Strengthen community engagement in research	Clinical trials have community advisory/engagement plans and involve community representatives in the design, conduct and dissemination of research.	Costing for community engagement is included in the Strategic Frameworks for Drugs Diagnostics, and Vaccines
		Diagnostic, vaccine and drug developers actively engage community stakeholders in the R&D process, from early-stage research to clinical trials and licensure.	

Annex 6. Estimating the cost of the 90-(90)-90 strategy

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Contents

Abbreviations

ART	Antiretroviral therapy
COE	Complex operating environment
DC	Direct cost
DST	Drug susceptibility tests
FLD	First-line drug
GP	Global Plan
GTB	Global TB Programme
TB/HIV	TB and HIV collaborative activities
HS	Health systems
LAB	Laboratory and diagnostic cost
MDR	Multidrug resistance
PSC	Programme support cost
SLD	Second-line drug

Standard investment plan	TB interventions are scaled up in an s-shape, achieving coverage targets by 2025
Accelerated investment plan	TB interventions are scaled up in an s-shape, achieving coverage targets by 2020

Costing the Global Plan

This document details the methodology developed for estimating the cost of the Global TB Plan.

Two complementary methods are used. The first method is based entirely on a database of TB financing information. Around 120 countries report this information to WHO GTB annually. Using the WHO TB data to cost the GP can follow two different approaches: using 2013 expenditure data or using 2013 budget data (i.e. the budget estimates for 2014). A second method allows for more detailed reporting of expected direct costs by using information collected at a costing workshop held December 2014 in Geneva.

WHO financing data, an overview

WHO maintains a detailed database of TB financing elements that were utilized in this analysis:

- We use a number of variables from this database to estimate both the unit costs for direct cost categories and the level of programme support (i.e. indirect costs) at country level.
- We obtain unit costs per patient hospitalization and ambulatory care costs from the WHO Choice dataset.
- We also use the WHO TB financing data to estimate procurement and distribution costs for first-line drugs, second-line drugs, and labs and diagnostics (see Table 1 below for descriptions).

The costing tool allows us to derive unit costs from either expenditure data or budget data. Both are required for estimating the resource requirements of the GP. Expenditure-derived unit costs are used to project the continuation of the 'baseline' (or business as usual), whereas budget-derived unit costs are used to cost the implementation of the GP.

Expenditures are capped by funding realities, while budgets are based on national strategic TB plans. As such, budgets are aspirational and typically include requests for improved diagnostic tools, equipment, and programme implementation structures. In effect, budgets are based on the types of TB programme improvements that are required in order to achieve the ambitious targets set out by the GP. However, the information available does not allow for a direct mapping between budgets reported to WHO and TB programme elements implied by the GP.

Note that either the expenditure-derived or the budget-derived unit costs are used for all unit costs and countries, with the higher of the two unit costs being selected. Expenditure-derived unit costs may exceed budget-derived unit costs in cases where higher than expected case notification targets are proposed in the budget section of the questionnaire. This assumption may inflate the unit costs of certain countries. This deviation is acceptable with respect to the objectives of the cost analysis, the primary one being to estimate a reasonable lower bound for the resources required to implement the GP.

It must be noted that costing methods that depend on the WHO TB financing data will be subject to the known and unknown limitations of the data, such as completeness and accuracy. Nevertheless, the WHO TB database represents a detailed and complete financial reference database, which is routinely used in similar costing work for global TB costing and funding projections.

Direct costs and programme support costs

Within the WHO dataset, all cost categories consist of direct and indirect costs. The only cost categories that are predominantly direct in nature are the first-line and second-line treatment costs. All other cost categories are predominantly indirect in nature. However, it is not necessary to make a sharp distinction between direct and indirect costs in this analysis, since all cost categories are developed into unit costs in terms of case numbers of different types, for example, total notifications or MDR cases initiating treatment.

Standalone cost categories

It is a somewhat arbitrary choice as to which cost categories should be handled individually and which should simply be grouped together. In this analysis, five categories are treated as standalone cost categories, since they are connected to distinct case categories. The standalone cost categories are shown in Table 1.

Table 1. Standalone cost categories

Cost Category	Description
First-line drugs (FLDs)	Anti-TB drugs, excluding drugs to treat multidrug-resistant (MDR) TB. Includes all first-line drugs (including buffer stock) used to treat category I, II and III cases, i.e. all new (including children) and re-treatment cases.
Second-line drugs (SLDs)	Second-line drugs include drugs procured through the Global Drug Facility (GDF) and through other mechanisms. Includes buffer stock.
MDR-management (MDR-M)	Management of MDR-TB (excluding anti-TB drugs for MDR-TB). Includes contact investigation, drugs for adverse events, regulatory fees and other elements.
Labs and diagnostics (LAB+D)	Laboratory supplies and equipment for smears, cultures, DST, line probe assays and Xpert MTB/RIF.
Collaborative TB/HIV activities (TB/HIV)	Activities involving collaboration between TB and HIV programmes aimed at reducing the impact of HIV-related TB. These include TB/HIV coordinating bodies, joint TB/HIV training and planning, HIV testing for TB patients, HIV surveillance among TB patients, TB screening for people living with HIV/AIDS, isoniazid preventive therapy and joint TB/HIV information/education/communication.

We calculate a unit cost for each country using the 2013 expenditure reports and 2014 budget estimates, together with denominators drawn from the impact analysis, e.g. the total number of drug-susceptible, MDR, TB/HIV cases, and so on. The global average unit cost is calculated as [total cost] / [total number of cases], where these totals are computed using data from countries with complete data for all variables. Tables 2 and 3 show the unit costs at the global level and according to the nine country settings of the GP. Note that the global average unit costs are not used in the analysis. In cases where countries have no data or incomplete data, **a unit cost is taken from the country setting group of which they are a part**.

Table 2. Unit cost percentiles (US$)

Unit Cost Type	FLD	SLD	MDR-M	LAB+D	TB/HIV
Expenditure-based unit costs	60	1,490	460	70	330
Budget-based unit costs	60	1,250	1,510	150	400

Table 3. Expenditure-based unit costs by Global Plan country group

Global Plan Groups	FLD	SLD	MDR-M	LAB+D	TB/HIV
High MDR Burden, Centralized Care	30	2,480	2,400	80	250
High TB/HIV, SADC	80	3,310	790	170	240
High TB/HIV, Outside SADC	40	5,110	6,850	30	110
Moderate Burden, COE	30	5,440	4,300	40	170
High Burden, Private Sector	30	2,480	2,400	80	250
Moderate Burden, Middle Income	50	2,780	5,270	100	260
India	70	2,290	200	20	170
China	50	2,040	5,540	50	650
Low Burden, High Income	40	1,150	3,250	180	640

Table 4. Budget-based unit costs by Global Plan country group

Global Plan Groups	FLD	SLD	MDR-M	LAB+D	TB/HIV
High MDR Burden, Centralized Care	50	3,380	4,770	110	370
High TB/HIV, SADC	80	1,920	620	180	300
High TB/HIV, Outside SADC	30	3,460	6,130	100	140
Moderate Burden, COE	30	6,540	4,370	50	150
High Burden, Private Sector	40	2,850	2,470	100	650
Moderate Burden, Middle Income	50	3,380	4,770	110	370
India	60	1,030	90	20	170
China	40	1,000	2,710	50	640
Low Burden, High Income	40	1,390	3,830	160	3090

Tables 3 and 4 contain apparent discrepancies, such as higher than expected unit costs for MDR-related costs and lower than expected unit costs for countries in high-income settings. These values are the result of several factors. High-income countries do not report all their expenditures to WHO. For example, India reports elements of MDR case management under general programme management categories. For low-burden countries, the unit costs are based on a small number of countries and are likely to underestimate the true unit costs for high-income countries.

Furthermore, SLD costs reflect more than the commodity or actual drug costs. The unit cost also reflects upfront-procurement and buffer-stock costs. Carrying these forward in the GP cost projections introduces a bias, since the nature of the unit cost is likely to change. High costs may well have to continue under the GP as MDR treatment is rapidly expanded, particularly over the 2016–2020 period,

which is the focus period of the costing estimates. The assumption of large upfront costs for expanding MDR programmes may not apply in low MDR-burden settings, but, as pointed out, MDR-related costs in these settings are expected to be much higher than in other settings for a number of reasons. (Note, however, the main purpose of the analysis concerns resource needs estimates for non-OECD countries.)

Programme support costs (PSCs)

The remaining categories are predominantly indirect in nature and grouped into a single category for which the unit cost is expressed relative to the total notifications. Note that MDR-related management is handled separately as a standalone cost category.

The programme support cost descriptions are given in Table 5. Individual programme support cost categories are combined into a single category, representing total programme support costs (PSCs), and then projected forward.

Table 5. Programme support costs

Cost Category	Description
Staff	Staff cost for staff working on TB activities only at central and peripheral levels (for example, provincial TB coordinators, district TB coordinators, etc.)
Programme management	Management and supervision of the TB control programme. Examples are training, policy development, meetings, visits for supervision, fuel for supervision, purchase of office equipment/vehicles, construction of buildings for use by programme staff, recording and reporting, and drug management and distribution.
Public–private mix (PPM)	Management of PPM, e.g. meetings related to PPM, development of guidelines, and any payment/contractual scheme that might exist.
Community strengthening and involvement	Budget for activities related to community involvement; community TB care, including policy development, incentives and enablers.
Advocacy, communication and social mobilization	Activities related to advocacy, communication and social mobilization; community mobilization, including policy development, incentives and enablers.
Operational research	Operational research designed to answer question relating to the performance of routine data collections and management.
Surveys	Periodic surveys to measure the burden of TB and the impact of TB control, e.g. disease prevalence surveys, surveys of TB mortality, drug resistance surveys, etc.
Other	Activities not included above, including technical assistance.

Direct costs are linked to cases and therefore grow in line with the GP scale-up scenarios to reach 90% coverage for different forms of TB. The growth in PSCs is more difficult to estimate, and several assumptions can be made about how PSCs are expected to grow:

1) PSCs will grow so as to maintain the base year fraction of total costs and hence a relative relationship to direct costs.
2) PSCs will grow independently of direct costs at a specified rate.
3) A portion of the PSCs will grow with the direct costs, while the remaining portion will grow independently of direct costs at a specified rate.

Although the most intuitive option is 3, the split cannot be determined with the available data. Detailed PSC expenditure data would be needed to estimate this split, and such data are not available.

Therefore, we use a variation of option 1, developing a PSC unit cost per case from the GTB financing data by assuming that PSCs will grow at a rate that is proportional to the total number of notified cases. Option 2 is an equally valid choice, as annual growth in programme support structures could simply be stated based on expert opinion (noting that it is essentially not possible to cost PSCs directly within the scope of the analysis). Considering all of the uses of the cost estimates, however, our variation of option 1 emerges as the best assumption.

Hospitalization and ambulatory care

While costs resulting from TB patient health utilization (i.e. hospitalization and ambulatory care) do not typically represent a direct cost to the TB programme, this is a significant cost that is related to TB case management and that needs to be planned for, even if its costs accrue in another health budget. These costs include patient in-day and out-day costs. To estimate these costs at country level, WHO uses estimates for average per-day hospitalization costs drawn from the Choice database and frequency of visit information reported as part of the WHO finance questionnaire.

The global percentiles and averaged for health system utilization costs are shown in Table 6. Group averages are shown in Table 7. Low-burden countries do not report this data in sufficient quantities for the average to be estimated. China reports this data in categories used for programme and case management (as does Russia).

For this unit cost, we use the global average for countries with no data.

Table 6. Patient health system utilization costs (US$)

Percentile	Non-MDR HS Utilization	MDR HS Utilization
Average	140	2,720

Table 7. Patient health system utilization costs (US$) by country group

Global Plan Groups	HS non-MDR	HS MDR
High MDR Burden, Centralized Care	960	4,290
High TB/HIV, SADC	240	18,870
High TB/HIV, Outside SADC	40	4,350
Moderate Burden, COE	60	1,560
High Burden, Private Sector	100	1,380
Moderate Burden, Middle Income	370	4,870
India	100	2,350
China (*)	N/A	N/A
Low Burden, High Income (*)	N/A	N/A

* reported in other categories or reported by too few countries to obtain an estimate

For high MDR-burden countries in the WHO Europe region, we adopt the European regional plan of advocating 90 days of hospitalization for all MDR cases. A proportional adjustment is made to high-MDR countries in this region by taking the ratio between 90 days and the country's reported number of hospitalization days, which typically far exceeds 90 days. This decrease is applied in a linear manner to reach its full effect by 2020. This is an important efficiency gain captured by the GP resource needs estimate.

Time trends in unit costs

The analysis anticipates an increase in unit costs for two reasons:

1) The existing financial data (2008–2013) show unit cost growth over this period. The costing for the GP assumes that this trend will continue for at least the next five years due to the fact that large programmatic gaps still exist in most countries. Some adjustments in the baseline growth rates of unit costs are made, as discussed below.
2) Unit costs are also expected to grow because of the paradigm shift proposed in the GP. This shift is essential to break away from slow progress and to reach the GP targets of 90-(90)-90. The End TB Strategy targets include universal DST, high coverage for rapid tests, and zero catastrophic costs for patients. All of these targets will increase unit costs. Currently, patients bear significant out-of-pocket expenses in many high-burden countries, e.g. for X-rays and private sector care. These out-of-pocket expenses need to be eliminated and transferred to TB programme budgets. It is also expected that as coverage levels increase towards 90%, the unit cost per case will increase because of the extra effort and increased testing required to access the unreached TB and MDR-TB cases.

Recognizing the limitations posed by the lack of financial data on developing new approaches and the paradigm shift required, this costing work takes a more pragmatic approach, using adjusted growth rates of different types of unit costs to account for the changes expected in TB programmes over the next five years.

Some of the unit costs, such as for drugs, are unlikely to grow beyond standard inflation rates, unless a new drug is added to the regimen. Other unit costs, such as for laboratories, are likely to grow at higher rates in order to ensure universal access to DST, the scale-up of new rapid molecular tests, etc. Other unit costs, such as health system utilization costs, are unlikely to increase. Moreover, in the European and Central Asian region these costs are likely to decrease, as explained above.

Table 8 summarizes the unit cost increases estimated for the 2008–2013 period, using six years of GTB data for a restricted group of countries. Note that FLD and SLD costs and health system utilization costs are not considered here, as they are subject to US$-based inflation due to the reasons explained above.

Table 8. Unit costs and average annual increases

Unit Costs	Description	Unit Cost in 2008	Unit Cost in 2013	Avg. Annual Growth Rate
Budget-PSC	PS unit costs from budget	$ 404.7	$ 504.4	4.6%
Exp-PSC	PS unit costs from expenditure	$ 127.7	$ 219.6	12.0%
Budget-MDR-M	MDR management unit costs from budget	$ 903.7	$ 4,472.2	42.0%
Budget-Lab & Diagnostics	Average LAB unit costs from budget	$ 35.4	$ 64.7	7.9%
Budget-HIV	HIV unit costs from budget (excludes ART)	$ 19.3	$ 33.8	13.8%
Exp-MDR-M	MDR management unit costs from expenditure	$ 771.2	$ 4,566.4	43.2%
Exp-Lab & Diagnostics	Average LAB unit costs from expenditure	$ 8.4	$ 18.6	14.5%
Exp-HIV	HIV unit costs from expenditure (excludes ART)	$ 10.0	$ 3.9	0.0%

The estimated annual growth rates in unit costs are calculated using countries with data for all six years (2008 to 2013). Since the countries used are not the same for the various unit cost estimates, and since the estimates are sensitive to the choice of countries, the values are not directly comparable. Nevertheless, there is a clear upward trend in all of the unit costs.

There are also clear upward trends in global expenditure and budgets (despite a drop in cases globally). It is reasonable to assume that these trends will continue in the short term, as program restructuring costs are carried forward and increased further to achieve the impact milestones of the GP. However, there is also an unknown level of implementation inefficiency, which should not be carried forward, as explained in the main Global Plan report.

The exponential trend in PSC unit costs, fit to the PSC data, expenditure and budget (i.e. the first two rows of Table 8), is shown in Fig. 1 and 2.

Figure 1. Fitting and exponential increase in budgeted programme support unit costs for the period 2008–2013. The average increase per year is 4.6%. Trend based on a restricted set of countries.

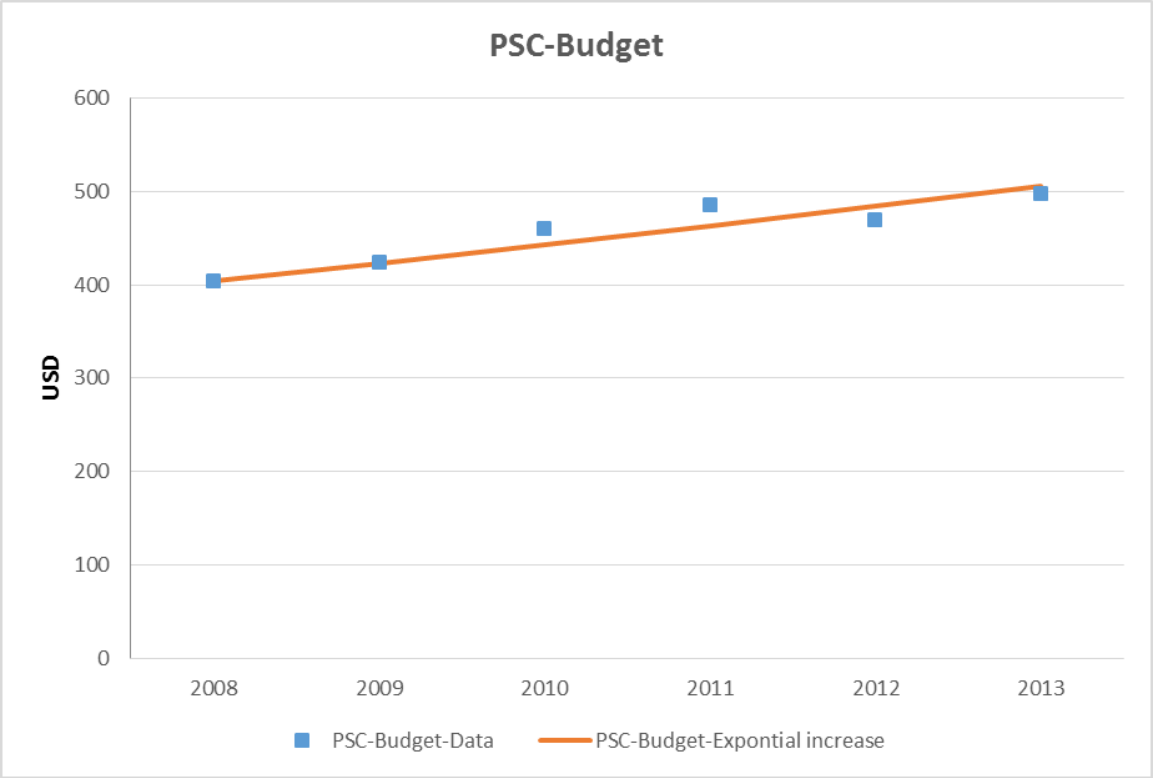
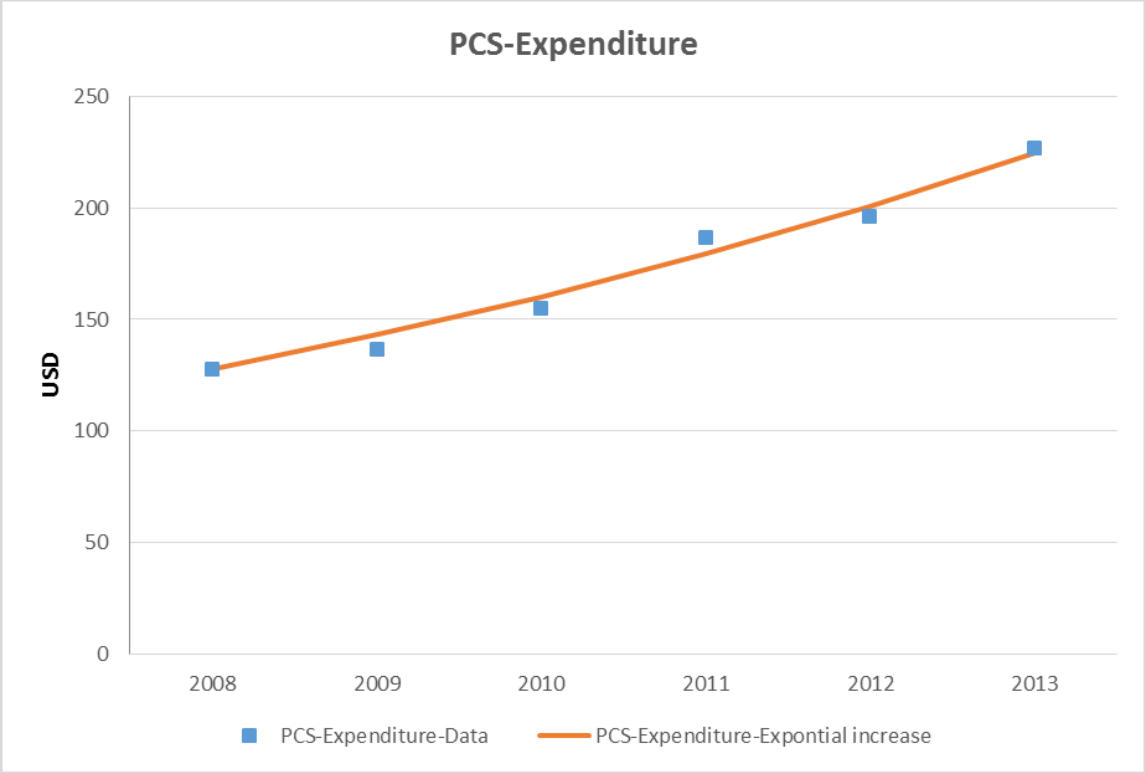


Figure 2. Fitting and exponential increase in reported expenditures in programme support unit costs for the period 2008–2013. The average increase per year is 12.0%. Trend based on a restricted set of countries.



The following practical and simplifying assumptions are made in order to estimate annual growth in unit costs, with different assumptions pertaining to different unit costs:

Inflation-based unit cost increases

- FLD and SLD costs will grow at 3% US$-based inflation starting in 2015. (In reality, the unit costs likely increased in 2014 as well, but the analysis uses 2014 as part of the baseline.) The estimate of 3% is based on the fact that FLD costs have been stable for several years. Any new FLD or regimen that is introduced is unlikely to be used at scale by 2020. If this happens, however, the GP budget should be updated at that point in time. GDF data show that SLD costs have declined in recent years. There are two new SLDs, new drug donation programmes, and a shorter MDR-TB regimen undergoing testing. If any new information or guidance emerges in the future, the GP budget should be updated at that point.
- We have no historical data for the Choice health services utilization data and thus cannot study trends. Therefore, we make the assumption that these unit costs will also grow at 3% US$-based inflation. While this type of expenditure contains elements that are subject to country-specific inflation, which is typically higher than 3% in countries with significant TB burden, there are also expected savings to be realized through the decentralization of care, as promoted by the GP, especially in Eastern Europe and Central Asia.

Unit cost increases related to the paradigm shift of the GP – above-inflation unit costs

- Programme support unit costs will grow at 12% per year due to reasons cited above. Being the most significant cost category, it is reasonable to assume that previous unit cost growth rates will not only be matched, but exceeded. At the same time, inefficiencies will need to be addressed in order to achieve the paradigm shift promoted by the GP. Represented in this category is community and private sector involvement, which should expand significantly under the GP.
- TB/HIV collaboration will grow at 12% per year, starting in 2015. This assumption is based on the notion that the category carries a significant programme support component, with the GP's recommendations for increased screening for TB among HIV cases and a drastic increase in preventive therapy for TB/HIV cases. ART for TB patients is not included in this cost category.
- Lab and diagnostics unit costs will grow at 14.5% per year. The continued increase seen in this cost category in Table 8 likely underestimates what is actually needed to achieve the targets of the GP and the End TB Strategy. Both strategies call for a significant increase in DST coverage and rapid molecular testing, which are more expensive than conventional diagnostic methods. Furthermore, patients in many settings make a significant degree of out-of-pocket payments for X-ray tests. These should be included in formal planning.
- MDR case management unit costs will grow at 5% per year. While historical trends show a much larger increase for this cost category, as many programmes develop their MDR elements, it is expected that a change in MDR management approaches will result in savings. In addition, in many countries, the MDR management infrastructure and systems development is currently used to treat small numbers of MDR-TB patients,

which inflates the unit costs. Going forward, as MDR-TB patient cohorts expand rapidly, the unit costs are expected to decline.

Eventual decline in unit costs

All the unit costs above inflation are then expected to drop in a linear fashion to 5% growth per year by 2025, starting in 2015. There is no way to justify these assumptions about eventual unit cost growth quantitatively, but qualitative arguments include:

- The current growth rate is high due to programmatic restructuring and approaches to increasing coverage. These cannot continue for many years and account for an element of inefficiency, which should be reduced under the implementation of the GP.
- Eventually, expenditures will respond to programme designs as reflected in budgets and will drop to a level no higher than the budgeted unit cost for increased PSCs, the dominant cost category.
- Unit costs will eventually be governed by economic growth rates for which a global rate of 5% is optimistic.

As part of our analysis, we constructed scenarios in which unit cost growth rates varied in order to study variation in costs (see Fig. 7).

Health system costs

One of the requirements of the costing method is to provide so-called health systems estimates. We use a simple approach to extract these from our cost estimates:

- Hospitalization and ambulatory care costs are HS costs.
- A norm used by WHO is that 15% of FLD and SLD costs are required for procurement, distribution and the management of buffer stock. For LAB costs (consumables and reagents), health system costs are between 10% and 15%; we use 12.5%. A second calculation is possible for FLD and SLD HS costs: by comparing the relative difference between a separate per patient expenditure estimate (also from the WHO database) and the unit costs derived using the above methods, and using that value if it exceeds 15%. A similar method is being developed for LAB costs, but the method is not yet available.
- The health system portion of the PSCs is small and omitted from this calculation.

GP workshop data

A workshop was held in December 2014 to collect unit costs for nine countries representing the nine GP country setting groups.

In order to use these results in a comparable framework, we calculated the total costs of FLDs and SLDs, MDR-patient management, LAB, and TB/HIV collaboration, and built in a mechanism to replace the corresponding values from the WHO database with these estimates, i.e. to produce an alternative set of unit costs. Since the nine countries represent more than 50% of the global TB burden, the final figures from the workshop costing workbooks influenced the final cost estimates for the GP.

Treatment volumes

The direct cost elements of the GP are driven largely by TB treatment and MDR initiation projections, as shown in Tables 9–12 below, to which unit costs are applied. For the MDR treatment initiation estimates, we assume that the GTB estimated burden of MDR among notified cases will continue. In reality, the surge in TB treatment and preventive therapy will likely alter and perhaps increase MDR burden over the short term. However, a detailed analysis of the consequences of a large increase in FL treatment volumes on MDR burden cannot be performed at this time.

Table 9. Projection of the number of cases treated under the standard investment scenario

Notification by Country Group	2016	2017	2018	2019	2020	Total
High MDR Burden, Centralized Care	259,000	256,000	253,000	244,000	223,000	**1,235,000**
High TB/HIV, SADC	623,000	621,000	630,000	641,000	603,000	**3,118,000**
High TB/HIV, Outside SADC	557,000	568,000	603,000	663,000	663,000	**3,054,000**
Moderate Burden, COE	315,000	330,000	364,000	400,000	367,000	**1,776,000**
High Burden, Private Sector	1,534,000	1,573,000	1,649,000	1,743,000	1,573,000	**8,072,000**
Moderate Burden, Middle Income	422,000	425,000	430,000	412,000	364,000	**2,053,000**
India	1,489,000	1,539,000	1,646,000	1,753,000	1,476,000	**7,903,000**
China	829,000	811,000	782,000	732,000	658,000	**3,812,000**
Low Burden, High Income	149,000	149,000	149,000	141,000	124,000	**712,000**
Total	**6,177,000**	**6,272,000**	**6,506,000**	**6,729,000**	**6,051,000**	**31,735,000**

Table 10. Projection of the number of cases treated under the accelerated investment scenario

Notification by Country Group	2016	2017	2018	2019	2020	Total
High MDR Burden, Centralized Care	264,000	257,000	227,000	191,000	162,000	**1,101,000**
High TB/HIV, SADC	651,000	709,000	639,000	537,000	457,000	**2,993,000**
High TB/HIV, Outside SADC	602,000	747,000	734,000	552,000	414,000	**3,049,000**
Moderate Burden, COE	339,000	452,000	396,000	286,000	206,000	**1,679,000**
High Burden, Private Sector	1,671,000	1,927,000	1,637,000	1,234,000	930,000	**7,399,000**
Moderate Burden, Middle Income	443,000	453,000	387,000	304,000	243,000	**1,830,000**
India	1,610,000	1,940,000	1,571,000	1,120,000	784,000	**7,025,000**
China	845,000	793,000	686,000	583,000	522,000	**3,429,000**
Low Burden, High Income	152,000	147,000	124,000	98,000	77,000	**598,000**
Total	**6,577,000**	**7,425,000**	**6,401,000**	**4,905,000**	**3,795,000**	**29,103,000**

Table 11. Projection of MDR treatment initiation under the standard investment scenario

MDR Tx Initiation by Country Group	2016	2017	2018	2019	2020	Total
High MDR Burden, Centralized Care	47,000	49,000	53,000	58,000	61,000	**268,000**
High TB/HIV, SADC	12,000	13,000	15,000	18,000	21,000	**79,000**
High TB/HIV, Outside SADC	3,000	4,000	7,000	11,000	14,000	**39,000**
Moderate Burden, COE	2,000	2,000	5,000	8,000	10,000	**27,000**
High Burden, Private Sector	12,000	16,000	26,000	40,000	47,000	**141,000**
Moderate Burden, Middle Income	4,000	5,000	7,000	9,000	10,000	**35,000**
India	20,000	23,000	27,000	33,000	35,000	**138,000**
China	7,000	11,000	18,000	25,000	30,000	**91,000**
Low Burden, High Income	2,000	2,000	2,000	3,000	3,000	**12,000**
Total	**109,000**	**125,000**	**160,000**	**205,000**	**231,000**	**830,000**

Table 12. Projection of MDR treatment initiation under the accelerated investment scenario

MDR Tx Initiation by Country Group	2016	2017	2018	2019	2020	Total
High MDR Burden, Centralized Care	50,000	61,000	65,000	63,000	60,000	**299,000**
High TB/HIV, SADC	13,000	20,000	23,000	22,000	21,000	**99,000**
High TB/HIV, Outside SADC	4,000	12,000	17,000	14,000	11,000	**58,000**
Moderate Burden, COE	2,000	9,000	11,000	9,000	7,000	**38,000**
High Burden, Private Sector	16,000	44,000	53,000	45,000	36,000	**194,000**
Moderate Burden, Middle Income	5,000	10,000	11,000	10,000	9,000	**45,000**
India	23,000	35,000	43,000	40,000	35,000	**176,000**
China	10,000	27,000	34,000	32,000	30,000	**133,000**
Low Burden, High Income	2,000	3,000	3,000	3,000	3,000	**14,000**
Total	**125,000**	**221,000**	**260,000**	**238,000**	**212,000**	**1,056,000**

Costs calculation

With these TB cost elements prepared and a few assumptions made, it is straightforward to calculate TB costs at baseline (i.e. the continuation of the current level of TB services) and with scale-up under the GP. The steps are as follows:

- Produce two result sets (baseline and scale-up under GP) that, among other things, contain projections of population-in-need volumes, i.e. projections of non-MDR notified TB, notified MDR-TB, MDR-TB treatment initiation, all TB notifications, and notified TB/HIV cases.
- Multiply the volumes by the country-specific estimates of unit costs for these categories in order to produce an estimate of costs for each category and a total cost across all categories.
- Apply the health services unit costs to the non-MDR and MDR-TB projected notifications and add the estimates to the total. (Since China and Russia report these costs as part of their programme support costs, the estimates for these two countries have been removed from the HS section.)

- Estimate the proportion of FLD, SLD, and LABs that represents procurement and distribution (i.e. part of health systems).
- Group results by GP setting, OECD status, WB income status, Global Fund eligibility, and BRICS participation.
- Apply projections of domestic contributions to GF-eligible countries in order to estimate the GF funding gap.

The cost of the Global Plan

Fig. 3 shows the cost of the GP (brown line) under the standard investment plan (i.e. interventions are scaled up by 2025), using budget-derived unit costs relative to the cost of continuing the current level of service. Fig. 3 also depicts the current relationship between expenditures and services (blue line), using expenditure-derived unit costs. The 2013–2015 benchmark for total TB expenditure is about US$ 6.3 billion and about US$ 8.1 billion for TB budgets. These figures form the basis of our needs estimate (which is inflated in our analysis due to always using the maximum values for expenditure and programme support-based unit costs). Note that the baseline trend is increasing at about 7% per year, a balance between the initial increase in unit costs and the projected slow drop in cases under the baseline scenario.

Fig. 3 further shows the projected cost of the standard and accelerated investment plans, corresponding to the GP's 90-(90)-90 coverage objectives to be achieved by 2025 and 2020, respectively.

The standard investment plan has a maximum resource needs estimate of about US$ 13.6 billion (in 2020) and the accelerated investment plan has a maximum resource needs estimate of about US$ 12.3 billion (in 2018). The standard investment plan requires US$ 58.5 billion and the accelerated investment plan US$ 56 billion over the five years of the GP.

One qualitative insight from Fig. 3 is that when the overall price tag is modelled as being dependent on case notifications, as we have done through our unit cost assumptions, the results reflect a tradeoff between a decline in case numbers and the anticipated increase in unit costs that is required to achieve the paradigm shift represented by the GP. In effect, the total cost curve is essentially a temporarily increasing direct cost curve superimposed on an increasing PSC curve. In the case of the baseline (business as usual), the cost curve keeps increasing due to the modest expected impact of case notifications as business as usual continues.

The second qualitative insight from Fig. 3 is that implementing the accelerated investment plan leads to a much earlier reduction in case notifications. The accelerated plan thus represents cost savings relative to the standard investment plan.

Tables 13 and 14 are summaries of the total financial resource requirements for the period 2016–2025 by income status, GFATM eligibility status and GP country group.

Disaggregation of total costs

A disaggregation of the total budget for the 2016–2020 period for the standard investment plan is shown in Table 15. Table 16 shows a similar disaggregation for the accelerated plan. Fig. 4 (all countries) and 5 (non-OECD countries) also depict this disaggregation, where PSCs include overall support (staff, programme management, among other categories; see Table 5), MDR case management, advocacy, community and private sector involvement, and TB/HIV collaboration, which

consists predominantly of programme support elements. (IPT is a small expense, and ART is not costed here.) FLD, SLD, and Labs include all direct costs for FLDs, SLDs, and LABs (i.e. all forms of diagnosis, screening, tests for treatment, monitoring tests and DST). Health systems consist of hospitalization and ambulatory care costs, together with the procurement and distribution costs of FLD, SLD, and Labs.

We estimate that globally 3.4% of total budgets are earmarked for community involvement. An assumption is made that this should increase to 5% by 2020. Globally, 1.6% of budgets are allocated to private sector involvement. For the "High Burden, Private Sector" settings and India, however, this figure is 5%. An assumption is made that globally this relative investment will increase to 5% of total budgets, whereas in the "High Burden, Private Sector" settings and India, it will increase to 10%. It is stipulated that 1% of the total budget for the period 2016–2020 be allocated to advocacy (at the global, regional and national levels).

These increases are adjusted within the total estimated need, i.e. amounts are not added separately on top of the estimated need.

Funding gap for GF-eligible countries

Fig. 6 depicts the funding gap to meet the resource requirements of the GP standard investment plan under assumptions of optimistic domestic financing forecasts, optimistic non-GF external financing forecasts, and US$ 0.7 billion annual GF TB financing. The resulting gap can arguably only be financed by external donors, since domestic forecasts are already projected at optimistic levels, and the GF contribution is unlikely to increase significantly from the previous average annual allocation of US$ 0.7 billion.

Figure 3. The cost of the TB Global Plan (US$ millions)

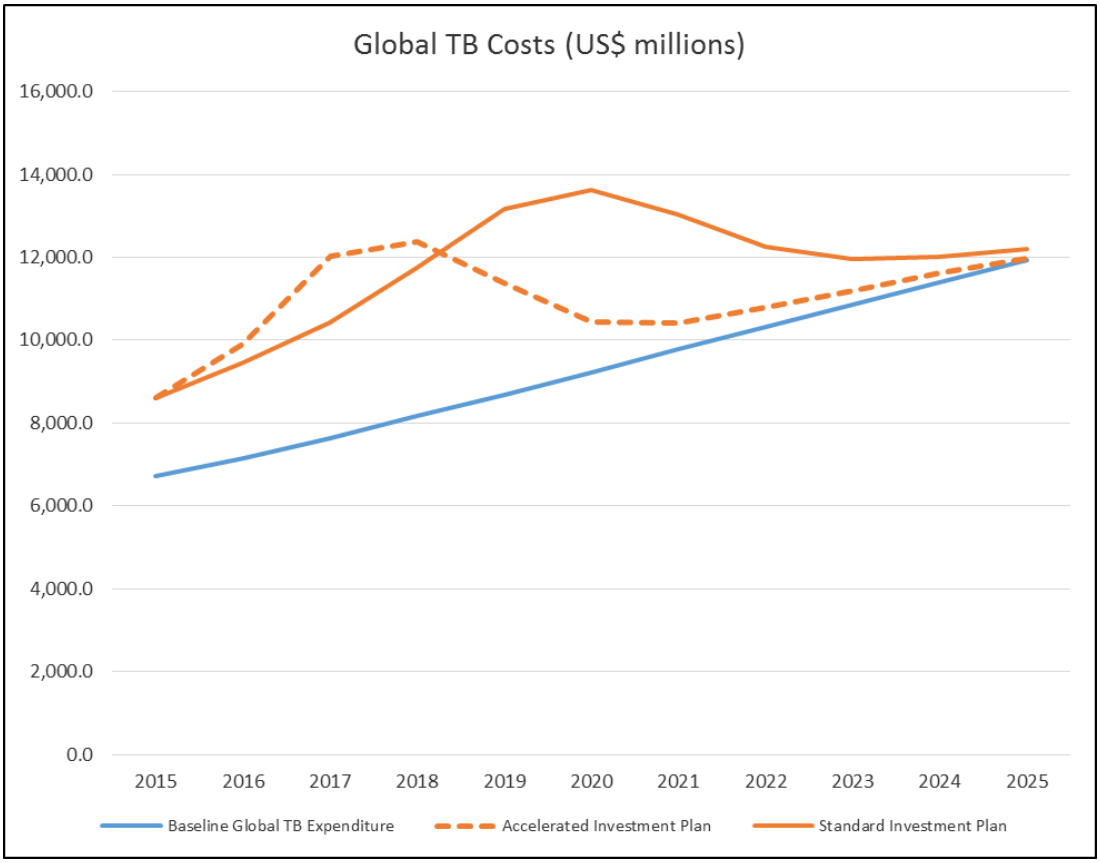


Table 13. Cost of the TB Global Plan, standard investment plan (i.e. 2025 scale-up strategy): Summary, US$ billions

Total resource requirements when scaling up Global Plan by 2025 (US$ billions)						
	2016	2017	2018	2019	2020	Total
Global Total						
Total (Global, including OECD countries)	9.5	10.4	11.7	13.2	13.6	**58.4**
Total (Global, excluding OECD countries)	8.3	9.2	10.4	11.8	12.2	**51.9**
By Income Status						
Low income	0.9	1.0	1.3	1.6	1.7	**6.5**
Lower-middle income	2.2	2.5	2.9	3.4	3.5	**14.4**
Upper-middle income	2.5	2.7	2.9	3.2	3.3	**14.6**
High income	3.8	4.2	4.7	5.0	5.2	**22.9**
GFATM Eligible Countries, by Income Status						
Low income	0.9	1.0	1.3	1.6	1.7	**6.5**
Lower-middle income	2.2	2.5	2.9	3.4	3.5	**14.4**
Upper-middle income	1.5	1.6	1.7	1.8	1.9	**8.5**
High income	0.0	0.0	0.0	0.0	0.0	**0.0**
Total	**4.6**	**5.1**	**5.8**	**6.8**	**7.1**	**29.4**
Global Plan Country Settings						
High MDR Burden, Centralized Care	3.9	4.2	4.6	5.0	5.1	**22.7**
High TB/HIV, SADC	0.9	1.0	1.1	1.2	1.2	**5.4**
High TB/HIV, Outside SADC	0.5	0.6	0.7	0.9	1.0	**3.7**
Moderate Burden, COE	0.2	0.3	0.3	0.4	0.5	**1.7**
High Burden, Private Sector	0.9	1.1	1.3	1.7	1.7	**6.7**
Moderate Burden, Middle Income	0.7	0.8	0.9	1.0	1.0	**4.4**
India	0.6	0.6	0.7	0.8	0.7	**3.4**
China	0.5	0.6	0.7	0.7	0.8	**3.3**
Low Burden, High Income	1.2	1.3	1.5	1.5	1.5	**7.1**
BRICS (BRA,CHN,IND,RUS,ZAF)						
Total	4.4	4.9	5.4	6.0	6.2	**26.9**

Table 14. Cost of the TB Global Plan, accelerated investment plan (i.e. 2020 scale-up strategy): Summary, US$ billions

Total resource requirements when scaling up Global Plan by 2020 (US$ billions)						
	2016	2017	2018	2019	2020	Total
Global Total						
Total (Global, including OECD countries)	9.9	12.0	12.4	11.4	10.4	**56.1**
Total (Global, excluding OECD countries)	8.7	10.8	11.2	10.2	9.4	**50.3**
By Income Status						
Low income	1.0	1.6	1.6	1.4	1.2	**6.8**
Lower-middle income	2.4	3.2	3.3	2.9	2.5	**14.3**
Upper-middle income	2.6	2.9	2.8	2.7	2.5	**13.5**

High income	3.9	4.4	4.6	4.4	4.2	**21.5**
GFATM Eligible Countries, by Income Status						
Low income	1.0	1.6	1.6	1.4	1.2	**6.8**
Lower-middle income	2.4	3.2	3.3	2.9	2.5	**14.3**
Upper-middle income	1.6	1.8	1.8	1.7	1.6	**8.5**
High income	0.0	0.0	0.0	0.0	0.0	**0.0**
Total	**5.0**	**6.5**	**6.7**	**6.0**	**5.3**	**29.6**
Global Plan Country Settings						
High MDR Burden, Centralized Care	4.0	4.5	4.6	4.5	4.3	**21.9**
High TB/HIV, SADC	1.0	1.2	1.2	1.1	1.1	**5.5**
High TB/HIV, Outside SADC	0.6	0.8	1.0	0.8	0.7	**3.9**
Moderate Burden, COE	0.3	0.5	0.5	0.4	0.3	**1.9**
High Burden, Private Sector	1.0	1.5	1.6	1.4	1.2	**6.7**
Moderate Burden, Middle Income	0.8	0.9	0.9	0.8	0.7	**4.1**
India	0.6	0.8	0.7	0.6	0.6	**3.3**
China	0.5	0.5	0.5	0.5	0.5	**2.5**
Low Burden, High Income	1.3	1.4	1.3	1.2	1.1	**6.3**
BRICS (BRA,CHN,IND,RUS,ZAF)						
Total	4.5	5.3	5.4	5.2	4.9	**25.3**

Table 15. Cost of the TB Global Plan by cost category, standard investment plan, US$ billions

Total resource requirements when scaling up Global Plan by 2025 (US$ billions)						
Cost Category	2016	2017	2018	2019	2020	Total
Programme Support (*)	**4.5**	**4.9**	**5.2**	**5.5**	**5.3**	**25.3**
MDR case management	0.9	1.0	1.4	1.8	2.1	**7.1**
Advocacy	0.1	0.1	0.1	0.1	0.1	**0.6**
Community strengthening and involvement (**)	0.2	0.3	0.4	0.5	0.5	**1.9**
Private sector involvement	0.2	0.3	0.5	0.7	0.8	**2.5**
Predominantly Direct Costs	**1.4**	**1.6**	**1.9**	**2.2**	**2.2**	**9.3**
First-line drugs	0.3	0.3	0.3	0.3	0.3	**1.6**
Second-line drugs	0.3	0.4	0.5	0.6	0.7	**2.5**
LAB	0.6	0.7	0.8	0.9	0.9	**3.8**
TB/HIV collaboration	0.3	0.3	0.3	0.3	0.4	**1.6**
Health Systems Costs	**2.1**	**2.2**	**2.3**	**2.5**	**2.5**	**11.7**
FL hospt. and ambltry. care	1.4	1.4	1.4	1.5	1.5	**7.1**
SL hospt. and ambltry. care	0.5	0.5	0.4	0.4	0.4	**2.2**
Procurement and distribution	**0.3**	**0.4**	**0.5**	**0.6**	**0.7**	**2.4**
First-line drugs	0.1	0.1	0.1	0.1	0.1	**0.5**
Second-line drugs	0.1	0.2	0.2	0.4	0.4	**1.3**
LAB	0.1	0.1	0.1	0.1	0.1	**0.5**
Total	**9.5**	**10.4**	**11.7**	**13.2**	**13.6**	**58.4**

Table 16. Cost of the TB Global Plan by cost category, accelerated investment plan, US$ billions

Total resource requirements when scaling up Global Plan by 2020 (US$ billions)						
Cost Category	2016	2017	2018	2019	2020	Total
Programme Support (*)	**4.6**	**5.1**	**4.8**	**4.1**	**3.5**	**22.0**
MDR case management	0.9	1.5	1.9	1.8	1.7	**7.9**
Advocacy	0.1	0.1	0.1	0.1	0.1	**0.6**
Community strengthening and involvement (**)	0.2	0.3	0.4	0.4	0.4	**1.8**
Private sector involvement	0.2	0.4	0.5	0.6	0.6	**2.3**
Predominantly Direct Costs	**1.5**	**2.1**	**2.1**	**1.9**	**1.7**	**9.3**
First-line drugs	0.3	0.4	0.3	0.2	0.2	**1.4**
Second-line drugs	0.4	0.6	0.8	0.7	0.7	**3.1**
LAB	0.6	0.8	0.8	0.7	0.6	**3.4**
TB/HIV collaboration	0.3	0.3	0.3	0.3	0.2	**1.4**
Health Systems Costs	**2.2**	**2.5**	**2.6**	**2.5**	**2.5**	**12.3**
FL hospt. and ambltry. care	1.4	1.4	1.5	1.5	1.5	**7.4**
SL hospt. and ambltry. care	0.5	0.5	0.4	0.4	0.4	**2.2**
Procurement and distribution	**0.3**	**0.6**	**0.7**	**0.6**	**0.5**	**2.7**
First-line drugs	0.1	0.1	0.1	0.1	0.1	**0.5**
Second-line drugs	0.2	0.4	0.5	0.4	0.3	**1.7**
LAB	0.1	0.1	0.1	0.1	0.1	**0.5**
Total	**9.9**	**12.0**	**12.4**	**11.4**	**10.4**	**56.1**

* – excludes MDR case management, and community and private sector involvement

** – excludes advocacy

Figure 4. Disaggregation of the total cost over the period 2016–2020 for the standard investment plan

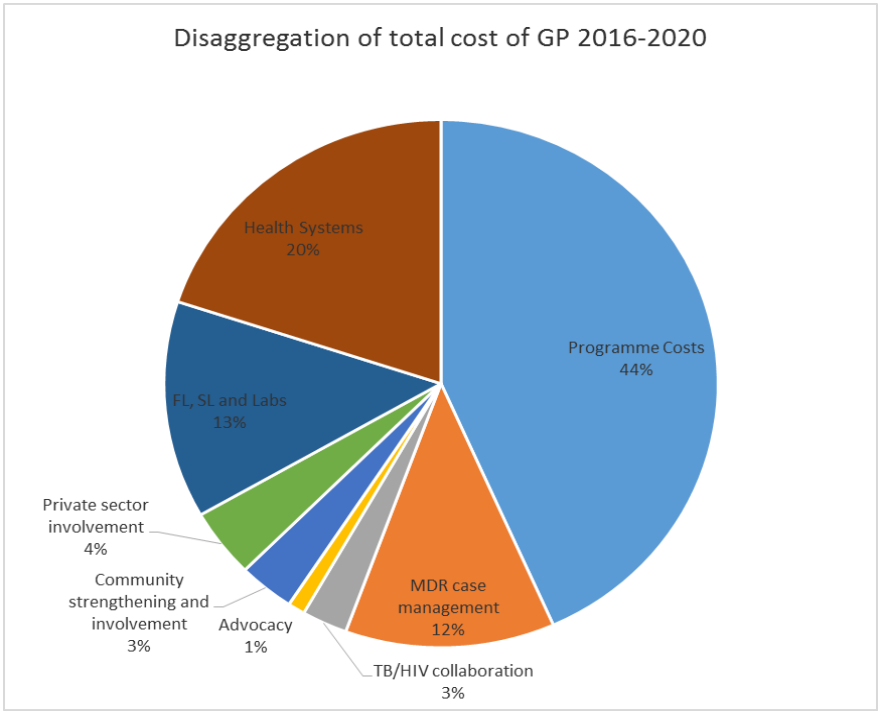


Figure 5. Disaggregation of the total cost over the period 2016–2020 for the standard investment plan, restricted to non-OECD countries

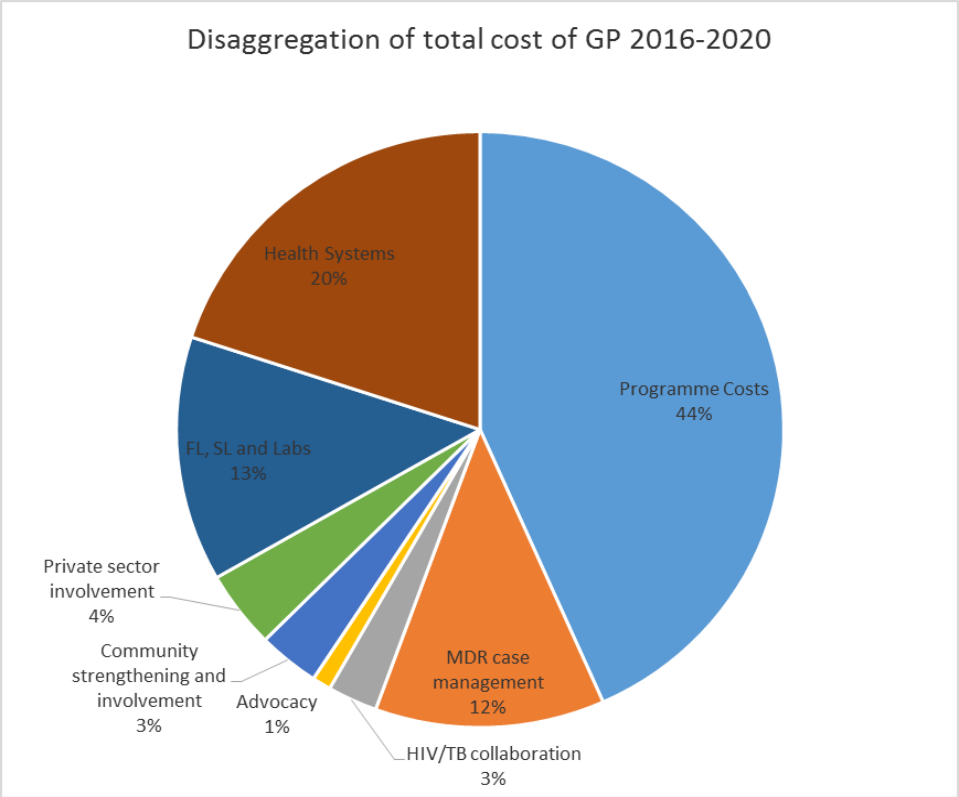
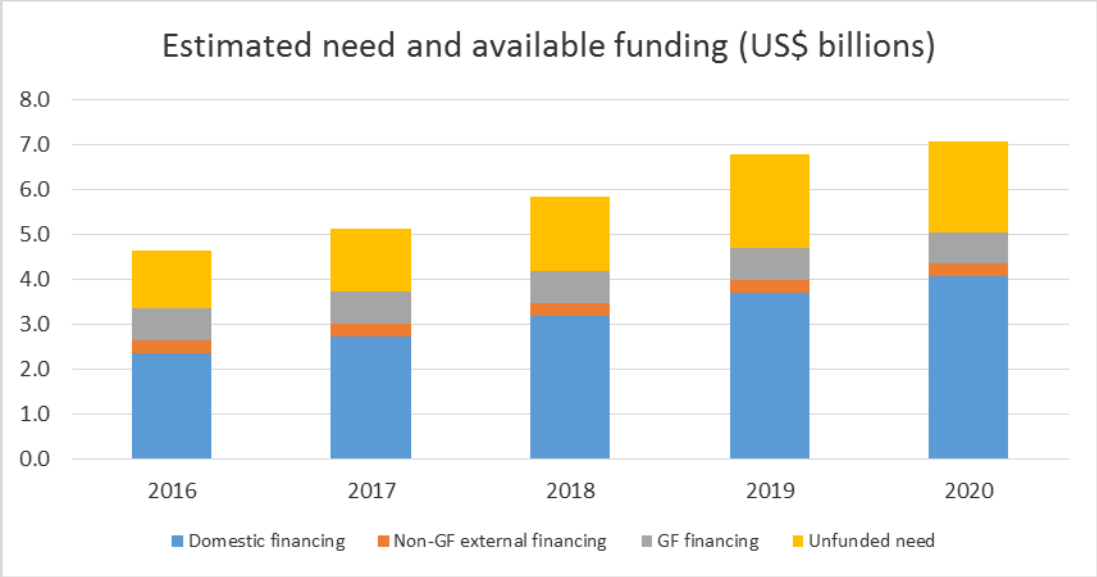


Figure 6. Domestic financing (optimistic forecast), non-GF external financing, GF financing (continuation of US$ 0.7 billion annual financing), and unfunded need to meet the funding requirements projected by the standard investment plan in GF-eligible countries



Total cost sensitivity analysis

We conducted a simple sensitivity analysis of the GP cost projections by varying the assumptions about unit cost growth. Five scenarios were constructed:

- S1 – All unit costs grow as defined by the GP, 2025 scale-up or standard investment plan
- S2 – Same as S1, with PSCs at 10% increase per year
- S3 – Same as S1, with PSCs at 15% increase per year
- S4 – Same as S3, with Labs and diagnostics at 20% increase per year
- S5 – Same as S4, with MDR case management at 10% increase per year

The scenarios are summarized in Tables 17 (unit cost increases in 2015) and 18 (unit cost increases in 2025). The results are depicted in Fig. 7. The global price tag would be significantly higher (more than US$ 15 billion in 2020) if PSCs grew at a rate of 15%. It is not clear if this level of increase is required to achieve the paradigm shift represented by the GP, but historical trends suggest that levels this high have not been reached in the past.

Table 17. Unit cost growth rate scenarios, growth rate at 2015

	S1	S2	S3	S4	S5
PS	12.0%	10.0%	15.0%	15.0%	15.0%
FLD	3.0%	3.0%	3.0%	3.0%	3.0%
SLD	3.0%	3.0%	3.0%	3.0%	3.0%
MDRMGT	5.0%	5.0%	5.0%	5.0%	10.0%
LAB	14.5.%	14.5%	14.5%	20.0%	20.0%
TB/HIV	12.0%	12.0%	12.0%	12.0%	12.0%
Health Services non-MDR	3.0%	3.0%	3.0%	3.0%	3.0%
Health Services MDR	3.0%	3.0%	3.0%	3.0%	3.0%

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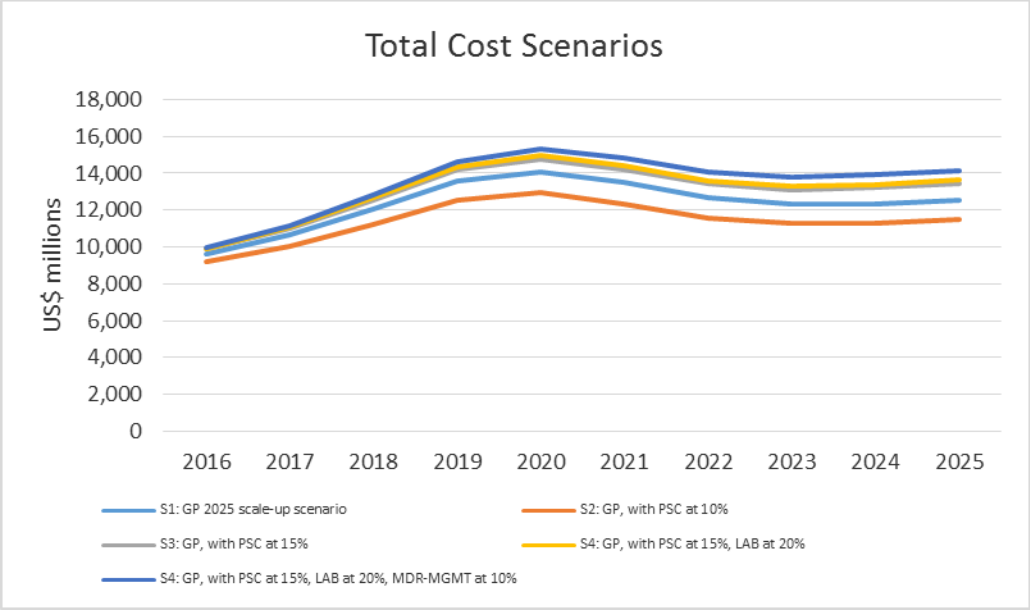
Table 18. Unit cost growth rate scenarios, growth rate at 2025

	S1	S2	S3	S4	S5
PS	5.0%	5.0%	5.0%	5.0%	5.0%
FLD	3%	3%	3%	3%	3%
SLD	3%	3%	3%	3%	3%
MDRMGT	5.0%	5.0%	5.0%	5.0%	5.0%
LAB	5.0%	5.0%	5.0%	5.0%	5.0%
TB/HIV	5.0%	5.0%	5.0%	5.0%	5.0%
Health Services non-MDR	3%	3%	3%	5.0%	3%
Health Services MDR	3%	3%	3%	5.0%	3%

Figure 7: Total cost curves for the 2025 scale-up GP scenario, for different unit cost trend assumptions



Limitations of approach to costing Global Plan

Several limitations to the costing approach should be recognized. These limitations lead to uncertainty in the cost projections, which can only be studied in a limited sense by conducting a sensitivity analysis of the known uncertain elements in the analysis.

Data from GP costing workshop

The use of two datasets to calculate TB costs – one based on the WHO's financing questionnaire and the other drawn from a GP workshop held in December 2014 – posed a significant challenge to the analysis. Neither dataset captures the key elements required for a more detailed analysis. Nevertheless, the WHO costing database was found to be the most complete global database available for the analysis, and thus formed the basis of the costing analysis.

The GP workshop focused strongly on intervention and case/patient-based costing. Programme support elements were reported as part of the GP workshop questionnaire. However, these elements were ultimately taken from the WHO data so as to make this dominant element more comparable between the two sources of data and to more effectively produce estimates for countries that were not part of the GP workshop. Thus, only direct cost elements were taken from the workshop costing data for the countries participating in the workshop.

Linking costs to the number of notified cases

The approach of linking costs to notified cases leads directly to a projection of costs declining as cases decline – as they are projected to do following the implementation of the GP. In reality, there are elements of TB programmes that are independent of case notification. These include elements of programme support structures, case management utilizing services in the general health system, expansion of health insurance and social protection, and other elements that could lead to the continued growth in costs in many settings.

Unit cost trends

The assumptions of unit cost growth are based on past trends in a selected set of countries and then applied globally. The extent to which these increases reflect global estimates should naturally be questioned.

The GP does not stipulate how countries should reach the targets of the strategy. Therefore, key programme elements were not modelled or costed at country level. The assumed increases in unit costs, especially those related to programme support, are an attempt to capture these elements indirectly. They are seen to be necessary, given past trends. At the same time, they are likely to be underestimated, given that the new elements defining the GP's paradigm shift have not been explicitly added. Since the estimates are based on budgets reported to WHO, which are ambitious in terms of expanding the coverage of existing methods, a clear map to the GP package of interventions cannot be established.

The eventual decline in unit costs is also difficult to verify. An assumption is made that budget-based unit costs are much closer to inflation than observed trends in expenditure-based unit costs. As such, increases will eventually become a reality, once the TB burden is reduced to more manageable levels.

Several caveats are noted in the section detailing unit cost increases. However, the list is not exhaustive and may not reflect context-specific challenges related to the unit cost increase estimates.

Cost trends

The two assumptions above – deriving a case-based unit cost for all cost categories and assuming above-inflation unit cost increases for some cost categories (most importantly in the programme support category) – combined with case and volume increases modelled over the short term lead to an increase in costs up to a point where cases and unit costs have been sufficiently reduced. At that point, costs start to drop, although this is conditional upon the described decreases occurring first. The sharp increase in cases, and in particular MDR case volumes, accounts for a significant part of the projected cost increases.