Maximising value for money of tuberculosis investment in the Philippines

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Contents

Contributors ........................................................................................................ iii
Acknowledgements ............................................................................................ iv
Abbreviations ..................................................................................................... xii
Executive summary ............................................................................................ 1
  Background and context ................................................................................... 1
  Epidemiology of TB in the Philippines ........................................................... 2
  Existing efforts to control TB in the Philippines ............................................. 2
  Questions for the AuTuMN analysis ............................................................... 3
  Interventions simulated and scenarios analysed ............................................ 3
  Cost-effectiveness analysis ............................................................................. 4
  Optimisation ..................................................................................................... 4
  Conclusions ...................................................................................................... 4

Chapter 1. Introduction ....................................................................................... 7
  1.1 Motivation for this work ........................................................................... 7
  1.2 Capabilities of the AuTuMN analysis ...................................................... 7
  1.3 Objectives of AuTuMN in the Philippines ................................................ 8

Chapter 2. Background .................................................................................... 9
  2.1 Global setting ........................................................................................... 9
  2.2 TB epidemiology in the Philippines ........................................................ 10
    2.2.1 Incidence .......................................................................................... 10
    2.2.2 Age distribution .............................................................................. 11
    2.2.3 Geographical distribution ................................................................ 11
    2.2.4 Private sector ................................................................................... 12
    2.2.5 TB Mortality .................................................................................... 12
    2.2.6 Multidrug-resistant TB ................................................................. 13
  2.3 Existing TB control programs in the Philippines ..................................... 14
    2.3.1 Directly Observed Treatment Short-Course (DOTS) .................... 14
    2.3.2 TB management in children ............................................................ 15
    2.3.3 Programmatic management of MDR-TB ....................................... 15
    2.3.4 High risk population groups ............................................................ 15
Chapter 2. Diagnosis and laboratory testing ........................................ 16

Chapter 3. Modelling objectives and constraints .................................. 19

3.1 Time horizons and goals of the NTP ............................................ 19

3.2 Epidemiology, programs and expenditure at baseline .................... 19

3.3 Approach and brief summary of methods .................................... 20

3.3.1 Epidemiology of the model .................................................. 20

3.3.2 Model fitting and model uncertainty .................................... 21

3.3.3 Economic model ............................................................... 21

3.3.4 Optimisation ................................................................. 22

Chapter 4. Projected epidemiological impact of control programs .......... 24

4.1 Model calibration .................................................................... 24

4.2 Baseline carried forward predictions ....................................... 26

4.3 Scenarios ............................................................................. 28

4.3.1 Scenario 1: Engagement of providers not compliant to NTP protocol ...... 29

4.3.2 Scenarios 2: Replacing smear microscopy with GeneXpert as the primary diagnostic test ..................................................... 30

4.3.3 Scenario 3: Systematic screening in high risk groups ............... 32

4.3.4 Scenarios 4 and 5: Preventive therapy .................................. 35

4.3.5 Scenario 6: Promoting awareness ....................................... 37

4.3.6 Scenario 7: Short-course regimen for MDR-TB ..................... 39

4.3.7 Combination of scenarios 1, 2, 3, 4, 5, 6, 7 .................................. 40

4.3.8 Poverty reduction ............................................................ 42

Chapter 5. Projected cost and financial commitment ......................... 44

5.1 By year .............................................................................. 44

5.2 By program .......................................................................... 45

5.2.1 Engagement of health care providers not compliant to NTP protocol ...... 45

5.2.2 GeneXpert replacing smear microscopy .................................. 46

5.2.3 Short-course regimen for MDR-TB ...................................... 46

5.2.4 Systematic screening in high risk groups .................................. 47

5.2.5 Preventive therapy for LTBI ............................................... 48

Chapter 6. Cost-effectiveness ............................................................ 49

Chapter 7. Optimising resource allocation ......................................... 52
Appendix 4.  Calculations of cost inputs.................................................................86
   A4.1  BCG vaccination .......................................................................................86
   A4.2  Preventive for children contacts ...............................................................86
   A4.3  Short-course regimen for MDR-TB ............................................................87
   A4.4  Gene X-pert ..............................................................................................88
   A4.5  Systematic screening in high risk groups ....................................................89

References .............................................................................................................91
List of figures

Figure 1. World and Philippines maps ......................................................... 9
Figure 2. Notifications of TB by year, all forms, 1990-2014 .......................... 10
Figure 3. Total number of TB cases and the proportion by case classification, 2003-2011 .... 10
Figure 4. Proportion of all new smear-positive cases by age groups, 2003-2011 ........ 11
Figure 5. TB case notification and mortality rates by province, 2011-2013 ............. 11
Figure 6. Health seeking behaviour of presumptive TB who sought care ............ 12
Figure 7. Trend of CNR and TB mortality ...................................................... 13
Figure 8. Trend of CNR and TB mortality ...................................................... 13
Figure 9. Health spending by source of financing in the Philippines, 1995-2014 (USD) .... 17
Figure 10. Estimated financing requirements by year, in billions PHP, 2010-2022 .......... 18
Figure 11. Share of TB funding for the Philippines by sources .......................... 18
Figure 12. Example of approach to fitting time-variant model parameters to data ....... 21
Figure 13. Diagram depicting the events in the optimisation algorithm .................. 23
Figure 14. Manually adjusted case detection rate ........................................... 25
Figure 15. Baseline model outputs ............................................................... 25
Figure 16. Model predictions of MDR-TB burden if baseline conditions are carried forward 27
Figure 17. Impact of engagement of health care providers who are not compliant to NTP protocol ........................................................................ 30
Figure 18. Impact of GeneXpert replacing smear as primary diagnostic tool on overall TB burden ........................................................................ 31
Figure 19. Impact of GeneXpert replacing smear as primary diagnostic tool on MDR-TB burden ........................................................................ 31
Figure 20. Matrix of population mixing ......................................................... 32
Figure 21. Impact of systematic screening on overall TB burden ....................... 34
Figure 22. Impact of systematic screening on TB burden in the targeted risk groups ... 35
Figure 23. Impact of preventive therapy on overall TB burden .......................... 36
Figure 24. Impact of preventive therapy on age-group-specific TB burden ............ 37
Figure 25. Impact of awareness program on TB burden ................................... 38
Figure 26. Impact of short-course MDR-TB regimen on MDR-TB burden ............ 39
Figure 27. Impact of short-course MDR-TB regimen on overall TB burden .......... 40
Figure 28. Impact of combining all interventions on overall TB burden .............. 41
Figure 29. Impact of combining all interventions on MDR-TB burden ................. 41
Figure 30. Impact of reducing the proportion of urban and rural poor by 50% .......... 42
Figure 31. Yearly costs of 7 TB programs ...................................................... 44
Figure 32. Proportion of total spent on each program for year 2022 as an example .... 45
Figure 33. Cost of engagement of providers not compliant to NTP protocol .......... 45
Figure 34. Cost of GeneXpert replacing smear microscopy .............................. 46
Figure 35. Yearly cost of short-course regimen for MDR-TB ............................ 47
Figure 36. Cost of systematic screening program in different risk groups .......... 48
Figure 37. Cost of preventive therapy. .................................................................48
Figure 38. Incremental costs and active TB cases averted over 19 years (2017 – 2035). ....50
Figure 39. Tuberculosis incidence and mortality in 2035 under the conditions of program allocation based on achieving optimal incidence...............................................................54
Figure 40. Optimal spend when minimising incidence in 2035, proportion of funds allocated to each program when considering different annual envelopes. ........................................55
Figure 41. The modular structure of the AuTuMN software platform...............................58
Figure 42. Disease dynamic model. ........................................................................61
Figure 43. Example of cost-coverage curve. ................................................................68
Figure 44. Diagram depicting the events in the optimisation algorithm. .........................69
List of tables

Table 1. Number of presumptive TB cases tested by smear microscopy and outcomes
Table 2. Baseline parameters
Table 3. Model predictions if baseline conditions are carried forward
Table 4. Summary of the scenarios
Table 5. Summary of the effects of interventions on overall TB burden
Table 6. Incremental costs and active TB cases averted over 19 years (2017 – 2035)
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>3HP</td>
<td>3 months of weekly rifapentine plus isoniazid for preventive therapy</td>
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<tr>
<td>ACF</td>
<td>Active case finding</td>
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<td>CNR</td>
<td>Case notification rate</td>
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<tr>
<td>DOTS</td>
<td>Directly observed therapy short-course</td>
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<tr>
<td>DST</td>
<td>Drug susceptibility testing</td>
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<tr>
<td>Global Fund</td>
<td>The Global Fund to Fight AIDS, TB and Malaria</td>
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<tr>
<td>IPT</td>
<td>Isoniazid-based treatment of latent <em>M.tb</em> infection for prevention of tuberculosis</td>
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<tr>
<td>MDR</td>
<td>Multidrug-resistant</td>
</tr>
<tr>
<td><em>M.tb</em></td>
<td><em>Mycobacterium tuberculosis</em></td>
</tr>
<tr>
<td>NSP</td>
<td>National Strategic Plan</td>
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<tr>
<td>NTP</td>
<td>National Tuberculosis Programme</td>
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<tr>
<td>PLHIV</td>
<td>People living with HIV/AIDS</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
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<tr>
<td>TST</td>
<td>Tuberculin skin test</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Executive summary

This report summarises findings from an epidemiological and economic analysis conducted for the Department of Health of the Republic of the Philippines by the AuTuMN (Australian Tuberculosis Modelling Network) team, through the Global Fund’s Special Initiative of Optimizing Value for Money and Financial Sustainability. This work was conducted with contributions from partners in the National Tuberculosis Program of the Philippines and the Universities and Institutes associated with the AuTuMN Team (Australian Institute of Tropical Health and Medicine, James Cook University, University of Melbourne and Monash University). It used AuTuMN, a software platform specially designed for the purpose of supporting decision-making and strategic investment planning for tuberculosis (TB). The platform is able to perform epidemic scenario analyses, economic analyses including cost-effectiveness and financial commitment, and optimisation of health resource allocation.

Background and context

The international spending on the three pathogens creating the world’s greatest health burden (HIV, Malaria and TB) has slowed, and countries are now investigating ways of maximising the impact of every available health dollar. The Global Fund has established and launched the Special Initiative of Optimizing Value for Money and Financial Sustainability (the Special Initiative) in 2014 to support countries to optimise value for money of the health investment including that of the Global Fund. As part of the Special Initiative, this project aims to help countries quantify and compare the epidemiological and economic impact of different intervention scenarios, enabling to improvements in the efficiency of their national strategic plans (NSPs) and their use of Global Fund grants.

Tuberculosis is today the world’s leading infectious diseases killer. In the Philippines, TB remains a major endemic problem with an estimated 324,000 new cases per year (322 cases per 100,000 population). The country has one of the highest burdens of multidrug-resistant TB (MDR-TB) in the world, with 2.6% and 29% of new TB cases and previously treated TB cases respectively exhibiting this resistance pattern. HIV has not become highly prevalent in the Philippines, with an estimated prevalence of less than 0.1%, and malaria has been eliminated. By contrast diabetes is considered as the most important comorbidity for TB patients. The Department of Health of the Philippines has undertaken to achieve the Sustainable Development Goals for the End TB strategy. These are to reduce the incidence of TB by 90% and the mortality from TB by 95% by 2035, as an interim measure to eliminating TB by 2050. These aims underpin the time horizons and outcome measures used in this report.

Various publicly available databases were used to populate the AuTuMN model, which is a standard feature of our analyses. These sources included the World Health Organization
Global Tuberculosis Report, the World Bank, Unicef and published literature. Data provided by the country were also used where available or where locally-specific information was more appropriate. Demographic data including age distribution, fertility and life expectancy rates were included, along with burden of disease, access to health care, coverage of existing programs and epidemiological data on TB incidence and mortality trends over time. Additionally, we accessed data at the level of the Department of Health and the NTP to populate the model with financial information regarding existing and proposed future programs.

**Epidemiology of TB in the Philippines**

With an estimated 322 cases per 100,000 population, the Philippines is a high-burden country for TB. Although rates of drug resistance are comparable to global estimates, the Philippines is also among the countries with the highest burden of MDR-TB in the world due to its high case numbers, with an estimated 2.6% of new TB cases and 29% of previously treated TB cases being MDR-TB. TB notifications in the Philippines have declined gradually from 1990 to 1994; however this is likely to reflect poor case detection and reporting during these years, rather than a change in underlying incidence. The implementation of the Directly Observed Treatment Short-course (DOTS) strategy resulted in a significant increase in TB notifications in 1996. Increased efforts in case finding and engagement of the private sector in TB care are believed to account for the increase in case notifications after 2010.

**Existing efforts to control TB in the Philippines**

A number of interventions are in place to control and manage TB in the Philippines. DOTS, as advocated by the WHO, was first implemented in the country in 1997 and limited to the public sector at the time. This program was expanded in 2002 by the NTP engaging private sector such as private hospitals, clinics and pharmacies in the TB control efforts. TB control in children was introduced in 2004 with household contacts under 5 years old being assessed for latent TB and provided with isoniazid preventive therapy (IPT) if latent TB infection (LTBI) is diagnosed. However, this activity has only achieved a limited coverage of around 14% to date. Six-month daily IPT regimen has been used for LTBI treatment among children, with plans to switch to 3-month of weekly rifapentine plus isoniazid regimen (3HP) are underway.

Programmatic management of MDR-TB was officially integrated into the NTP in 2008. It involves provision of diagnosis and treatment services to all MDR-TB cases through health centres dedicated to MDR-TB care across the country. To improve adherence, a daily allowance, food packages and milestone incentives are also provided to patients. The recommended regimen is a 20-month regimen; however conversion to a 9-month short-course regimen is being planned.
Currently the NTP is considering a number of measures to improve detection and control of the disease. These include engagement of health care providers who are currently not compliant to NTP protocol, use of GeneXpert to replace sputum smear microscopy as a primary diagnostic, systematic screening in high risk population groups (including prisoners, rural poor, urban poor, people with diabetes and people living with HIV/AIDS [PLHIV]), and awareness raising campaigns.

**Questions for the AuTuMN analysis**

To guide TB decision-making and strategic planning, the AuTuMN analysis aims to provide answers to the following important policy questions that the country is currently facing.

1. What is the epidemic trajectory of TB as a result of current TB interventions?
2. What is the likely epidemiological impact of different TB invention scenarios and how will TB trends change under these scenarios?
3. Can the Philippines achieve the NSP and End TB targets for TB incidence and mortality, and if so how long might it take to reach these targets?
4. What are the costs and cost-effectiveness of TB programs? How should TB programs be prioritised based on their cost-effectiveness?
5. For the current level of funding, how should resources be allocated across different programs to maximise health outcomes? How will optimal allocation of resources change with different funding envelops?

**Interventions simulated and scenarios analysed**

We investigated six different programs under different implementation models to develop 14 scenarios. Each of these is based on programs being considered by the NTP and are summarised as follows.

Scenario 1. Engagement of health care providers who are currently not compliant to NTP protocol.

Scenario 2. GeneXpert replacing sputum smear microscopy as the primary diagnostic tool. This involves purchasing new GeneXpert machines, investing in facilities such as computers, internet access, and training for staff.

Scenario 3. Systematic screening in high risk groups. This includes active case finding using mobile clinics in rural poor (including indigenous) communities, urban poor communities and prisoners; and intensified case finding among people with diabetes and PLHIV when they visit health facilities for regular check-ups.
Scenarios 4 and 5 are the use of 3HP for treatment of LTBI with the aim of preventing active TB. This was examined under two scenarios; improving the coverage for the 0-5 year olds (scenario 4) and scaling up coverage for adults (15 years and above) (scenario 5).

Scenario 6 is awareness campaigns to improve understanding of the disease, change patients and the community’s attitude towards TB, TB care seeking behaviour.

Scenario 7 involves replacing the conventional 20-month regimen for MDR-TB with a short-course 9-month regimen.

Scenario 8 is a combination of all the above scenarios.

Cost-effectiveness analysis

Total costs and total cases of active TB averted were estimated over the period 2017-2035 inclusive. Values for cost per active TB case averted were calculated over this time. Incremental cost-effectiveness ratio (ICER) charts produced show both the cost-effectiveness, indicated by the slope of the line from the origin to the point, and the total epidemiological impact and cost, indicated by the magnitude of the point form the X and Y axes respectively. Following this, we examined complex combinations of scenarios to determine the optimal mix of scenarios and order of implementation.

Optimisation

The total costs of each program were measured from 2017 to 2035 inclusive, covering a 19 year period. Combinations of programs were permitted and allowed for potential interacting effects in the epidemiology model and efficiencies and savings due to reduced burden of TB. For a specific financial bundle, we investigated the greatest impact on incidence at year 2035, and optimise the mix of programs within that financial constraint. We also performed another optimisation with minimisation of mortality at year 2035 as the criterion for optimisation.

Conclusions

Although TB in the Philippines has declined over recent years, dramatic improvements in disease burden will be required if the country is to achieve its disease-related goals. Baseline projections for continuing the current programmatic response in the Philippines predicted a gradual decline in disease burden, which would meet country’s target for incidence for 2022 but would fall far short of meeting country’s target from mortality for 2022 or global targets for both indicators for 2035. Moreover, MDR-TB is predicted to constitute a rapidly increasing proportion of cases with time if programs specifically directed at this strain are not implemented.
Systematic screening in all risk groups including prisoners, urban poor, rural poor, PLHIV and diabetes is the most impactful intervention. Engagement of providers not compliant to NTP protocol and GeneXpert replacing smear microscopy as primary diagnostic are the second and third most impactful interventions, respectively. Expanded preventive therapy for children contacts under 5 years old and preventive therapy for adult contacts (15 years of age or above) had a small impact on the overall disease burden. Changing from conventional to short-course MDR-TB regimens is predicted to have a marked impact on improving MDR-TB burden and to be cost-saving. This translates to a small reduction in overall incidence, due to MDR-TB constituting a relatively small proportion of all incident cases in the Philippines. Implementation of all the above programs together results in substantial reductions in disease burden, with a reduction in incidence to almost half of that currently observed and a reduction in mortality and prevalence to around half of current levels by 2035.

Systematic screening in PLHIV and people with diabetes was the most cost-effective single intervention, followed by preventive therapy for children contacts; while systematic screening in rural poor appeared least cost-effective. Optimisation revealed that systematic screening for PLHIV and people with diabetes, moving to GeneXpert as the main first-line diagnostic, preventive therapy for children, engagement of the low-quality health sector should all be considered at all levels of funding envelope. As available funding increases and these most cost-effective programs reach saturation and approach full funding, additional funds should then be diverted to systematic screening in prisons and urban poor.
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Chapter 1. Introduction

1.1 Motivation for this work

To maximise impact - a core focus of the 2012-2016 strategy and New Funding Model of the Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund) - countries need reliable estimates of the epidemiological and financial impact of disease control interventions to identify an optimal mix of interventions. The Special Initiative for Optimizing Value for Money and Financial Sustainability (the Special Initiative) was created with the approval of the Global Fund Board in early 2014 to support countries to maximise value for money of health investment and to enhance the efficiency of disease control and prevention programs. As part of the Special Initiative, AuTuMN has been invited to provide modelling support to assist countries to quantify and compare the costs and impact of different intervention scenarios to guide optimal allocation of resources for tuberculosis (TB), thus to improve the efficiency of their TB investment.

The aim of this modelling project is to improve program efficiency and strengthen epidemiological understanding underpinning the National Strategic Plans (NSPs), concept notes, briefing notes and grant agreements, in close collaboration with respective Global Fund country teams. That is, the AuTuMN team will provide analytical support to apply AuTuMN to enhance country TB programs through the following three main stages of a Global Fund grant cycle: (1) NSP and concept note development stage; (2) concept note review and grant signing stage; and (3) grant implementation stage. The Philippines is developing a new funding request and considering options for funding programs for submission to and review by the Global Fund, following the completion of the current Global Fund grant by the end of 2016. The Global Fund is keen to assist the country with using modelling results to identify its most efficient programs and develop the funding request.

1.2 Capabilities of the AuTuMN analysis

Health care expenditure should be allocated in such a way that leads to the best health outcomes. The objective of the AuTuMN analysis is to provide a tool to guide TB strategic investments. AuTuMN is a software package that is flexible enough to address the key practical questions around policy decisions being weighed by policy makers; particularly at the national program level. It is relevant to funders, governments and program implementers. AuTuMN provides TB epidemic trajectory under various intervention and funding scenarios, enabling policy makers to gain a better understanding of their countries’ epidemic and evaluating and prioritising TB programs from both epidemiological and financial perspectives. It is able to assess the ability of current programs to reach sustainable development goals and...
country-specific goals, and to compare the current programs with proposed new programs or improved programs; allowing comparison over a pre-defined period (such as 2016 to 2035) and over different outcomes (such as mortality from TB versus number of new active cases of TB). AuTuMN also informs countries how to best allocate resources across different TB control activities to maximise health outcomes. It can do this with different time horizons (e.g. to 2025 or to 2035) and with different key outcomes to be considered (e.g. minimising incidence or minimising mortality). The results of the analysis will help policy makers and the NTP to design tailored strategic plans that are effective in reducing TB burden in the country. For a given financial commitment, AuTuMN determines the optimal mix of programs. It also provides cost estimates required to achieve a set outcome.

1.3 Objectives of AuTuMN in the Philippines

Three missions to the Philippines by the AuTuMN team involved consultation with the NTP, the Global Fund, the WHO, other stakeholders from the Ministry of Health of the Philippines to determine the purpose and objectives of the AuTuMN analysis. The principal purpose of the analysis was to prioritise TB control program spending. Specifically, AuTuMN assists the country with answering the following important policy questions:

1. What is the epidemic trajectory of TB as a result of current TB interventions?
2. What is the likely epidemiological impact of different TB invention scenarios and how will TB trends change under these scenarios?
3. Can the Philippines achieve the NSP and End TB targets for TB incidence and mortality, and if so how long might it take to reach these targets?
4. What are the costs and cost-effectiveness of TB programs? How should TB programs be prioritised based on their cost-effectiveness?
5. For the current level of funding, how should resources be allocated across different programs to maximise health outcomes? How will optimal allocation of resources change with different funding envelops?
Chapter 2. Background

2.1 Global setting

Tuberculosis is now the leading infectious disease killer globally, with 10.4 million new cases and 1.8 million deaths attributed to TB (including TB-HIV) in 2015.¹ The Western Pacific Region (WPRO) and the South-East Asia Region (SEARO) together make up over half the global burden of TB.¹ Drivers and threats to TB control include HIV, multidrug-resistant TB (MDR-TB), weak health care services and missing cases.¹ The End TB targets are ambitious and will require renewed efforts to address TB. The Philippines (Figure 1) is a high burden country with an estimated incidence of 322 (277 – 370) per 100,000 (324 [279 – 373] thousand cases), with high rates of drug resistance (2.6% new cases and 29% previously treated cases).¹ These high rates, combined with the country’s high population make for a very high absolute case burden. The country is committed to the End TB goals of TB elimination by 2050. This includes interim milestones, reduction in incidence rate of 45% by 2022 and 90% by 2035, reduction in mortality cases by 90% by 2022 and mortality rate by 95% by 2035 (baseline 2015 WHO TB estimates), maintaining treatment success rates above 95% for drug-susceptible (DS-TB) and above 75% for MDR-TB throughout.

Figure 1. World and Philippines maps (source: WHO Global Tuberculosis Report 2016¹).
2.2 TB epidemiology in the Philippines

2.2.1 Incidence

TB notifications in Philippines have shown a gradual decline from 1990 to 1994 (Figure 2). In 1996, TB notifications increased significantly because of the implementation of the Directly Observed Treatment Short-course (DOTS) strategy. Increased efforts in case finding and the engagement of the private sector are believed to account for the increase in case notifications after 2010. Approximately 55% of new TB cases are smear-positive, 40% are smear-negative and the remaining cases are extrapulmonary. The proportion by case classification has remained steady over the years (Figure 3).

![Figure 2](image1.png)

*Figure 2. Notifications of TB by year, all forms, 1990-2014. Data source: World Health Organization.*

![Figure 3](image2.png)

*Figure 3. Total number of TB cases and the proportion by case classification, 2003-2011.*

2
2.2.2 Age distribution

The most represented groups are the 25-34, 35-44, and 45-54 years old, each contributing 20-22% of all new smear-positive cases in the country from 2003 to 2011 (Figure 4). Only 1% of new smear-positive cases was found in children during this period.

![Figure 4. Proportion of all new smear-positive cases by age groups, 2003-2011.](image)

2.2.3 Geographical distribution

Between 2011 - 2013, among the 17 divisions of the Philippines, on average the highest case notification rate (CNR) was in the Autonomous Region of Muslim Mindanao (ARMM) region (400 cases per 100,000 population) while the lowest in Cagayan Valley (Region 2, 155 cases per 100,000 population) (Figure 5). The names of the 17 regions are listed in Appendix 1.

![Figure 5. TB case notification and mortality rates by province, 2011-2013.](image)
2.2.4 Private sector

The Philippines has a large private sector, with 20,000-30,000 private medical practitioners and more than a thousand private hospitals of various sizes. Anti-TB drugs are widely available in the private market in the Philippines. According to the 2007 TB prevalence survey (latest TB prevalence survey available), of those who had presumptive TB, 25% took no action, 40% self-medicated and 35% sought treatment. Although TB diagnosis and treatment is free in the public sector, approximately 40% of those who sought treatment did so from private physicians or private hospitals (Figure 6). Notifying TB cases to the NTP is not mandatory to the private sector. Indeed, from 2008 to 2011, only 5.7% of the TB cases reported to the NTP were from the private sector (38,565 out of 676,081). The majority of health care providers who are not compliant to NTP protocol come from the private sector. Their TB care service is usually considered to be of lower quality compared to those who are compliant to NTP protocol.

![Figure 6. Health seeking behaviour of presumptive TB who sought care. Reproduced from Celina Garfin, TB burden in the Philippines, 2016.](image)

2.2.5 TB Mortality

TB mortality in the period 1999-2014 has been steadily declining – from 55 per 100,000 in 1999 to 10 per 100,000 in 2014 at an average rate of 5% per year. In the period from 2000 onwards, unlike CNR which remained fairly constant and all death rate which gradually increases, TB-related mortality decreases (Figure 7). This may suggest the impact of strengthening TB control from 2000 on the reduction of TB mortality.
Depending on the register, missing deaths can occur. Using the vital register, a death can be missed if the NTP does not communicate with the vital registry and a cause of death other than TB is given. Similarly, missing deaths can occur when a case of TB is not notified to the NTP, and only diagnosed post-mortem, and not communicated with the NTP. Indeed, it is reported that the deaths recorded by the NTP only correspond to 60% of deaths captured in the vital registry.³

2.2.6 Multidrug-resistant TB

The Philippines has one of the highest burdens of MDR-TB in the world, with approximately 2.6% of newly diagnosed cases and 29% of previously treated cases being MDR-TB. Although these proportions are comparable to those reported at a global level, the high absolute case numbers in the Philippines mean that it is necessary to seriously address the significant burden of MDR-TB in the country. Alarmingly, only 19% of MDR-TB cases are diagnosed and treated. Treatment success rates for MDR-TB have fluctuated over the years as shown in Figure 8.
2.3  Existing TB control programs in the Philippines

2.3.1  Directly Observed Treatment Short-Course (DOTS)

The DOTS strategy for TB control commenced in 1997 and nationwide coverage (100%) was achieved in 2003. The DOTS strategy has 5 core elements: (1) strong political commitment to support and sustain the program; (2) diagnosis by quality assured bacteriologic examination that is accessible and affordable to all; (3) uninterrupted supply of quality-assured anti-TB drugs and laboratory supplies; (4) treatment with standardised short-course regimens that are administered under the direct observation of a responsible treatment partner; and (5) standardised recording and reporting system that allows monitoring and evaluation of the program and of each patient under treatment. There are currently more than 3,000 DOTS centres across the country. A review of the achievements of DOTS reported that, from 2003 to 2011, more than four million symptomatic TB cases were examined by microscopy, and a total of 1,379,390 cases of TB all forms were diagnosed and treated. Since the implementation of DOTS in 1997 until 2011, the country has achieved a 32% reduction in the prevalence of culture-positive TB and 29% reduction in the prevalence of smear-positive TB.²
2.3.2 TB management in children

In 1998, the NTP began to address the problem of paediatric TB with the establishment of the Task Force on Childhood Tuberculosis. In 2004, the first Guidelines for Implementing TB Control in Children were developed, which paved the way for the expansion of the childhood TB program throughout the country. For household contacts under 5 years old with no evidence of active disease, assessment for latent TB infection (LTBI) is recommended and 6-month of daily isoniazid is given if latent TB infection (LTBI) is diagnosed. To date, however only 14% of eligible children under 5 years of age receive isoniazid preventive therapy. Changing from the conventional 6-month of daily isoniazid regimen to 3-month of weekly rifapentine plus isoniazid regimen (3HP regimen) is under consideration.

2.3.3 Programmatic management of MDR-TB

Programmatic management of MDR-TB was officially integrated into the NTP in 2008. It involves provision of diagnosis and treatment services to all MDR-TB cases through treatment centres. There are more than 600 health centres qualified to provide MDR-TB care across the country, including treatment centres, satellite treatment centres and iDOTS health centres. To improve adherence, a daily allowance (PHP 150/day for the entire treatment duration), food packages (PHP 100/day for the entire duration of treatment) and milestone incentives (PHP 5,000 on 6th month, PHP 5,000 on 12th month, PHP 10,000 upon completion) are provided to patients. In 2015, only 24% of estimated MDR-TB cases have been provided with quality assured second line anti-TB drugs. The recommended regimen is the 20-month regimen, but transition to a 9-month short-course regimen is currently underway.

2.3.4 High risk population groups

Diabetes is now considered as the most important comorbidity for TB in the Philippines. Approximately 6% of the general population aged 20 years and above have diabetes; whereas diabetes is rare in people less than 20 years old. It is estimated that people with diabetes are about 3.11 times more likely to develop TB compared to those without diabetes. HIV is another important comorbidity in TB patients, increasing the risk of TB reactivation 36.7 times compared to those without HIV. However, the prevalence of HIV in the country is very low (<0.1%). In the Philippines, other high risk groups including prisoners, urban poor and rural poor (including indigenous) communities. Urban poor and rural poor are estimated to each account for 21% of the total population (21.5 million out of 101 million). The TB burden in urban poor and rural poor communities is estimated to be 20 times higher than in the general population. Although prisoners only account for 0.1% of the population (109,000); TB burden among prisoners is 4-5 times higher than that in the general population.
2.3.5 Diagnosis and laboratory testing

The current diagnostic algorithm for TB involves sputum smear microscopy for all people with symptoms suggestive of TB, followed by GeneXpert if smear microscopy is positive or chest x-ray if microscopy is negative. For patients undergoing chest x-ray, this will be followed by GeneXpert if x-ray finds abnormalities suggestive of TB. Since mid-2016, GeneXpert has been used as the initial diagnostic for some of the vulnerable populations including children, people living with HIV/AIDS (PLHIV) and prisoners. Using GeneXpert to replace smear microscopy as a first line diagnostic for all is under consideration.

There are currently 186 GeneXpert machines, available mostly at the provincial level or in highly urbanised cities. There are plans to expand to 354 GeneXpert machines by the end of 2017 and 3,000 machines by the end of 2020, with the aim to have at least one machine for each municipality. There are currently on seven centres that can conduct conventional drug susceptibility testing (DST).

Laboratory testing has increased in the country from 558,836 presumptive TB tested in 2010 to 814,321 in 2015; however, the number of positive cases detected has remained fairly constant, with the exception of 2014 when reporting issue might have occurred. This resulted in a positivity rate decreasing from 17% in 2010 to 13% in 2015 (Table 1). Treatment success rates have remained steady at around 90% since 2000.

<table>
<thead>
<tr>
<th>Year</th>
<th>Number tested</th>
<th>Number positive</th>
<th>Positivity rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>558,836</td>
<td>97,648</td>
<td>17%</td>
</tr>
<tr>
<td>2012</td>
<td>643,151</td>
<td>98,192</td>
<td>15%</td>
</tr>
<tr>
<td>2013</td>
<td>664,033</td>
<td>100,014</td>
<td>15%</td>
</tr>
<tr>
<td>2014</td>
<td>681,630</td>
<td>227,914</td>
<td>33%</td>
</tr>
<tr>
<td>2015</td>
<td>814,321</td>
<td>104,012</td>
<td>13%</td>
</tr>
</tbody>
</table>

2.4 Financial context for TB control in the Philippines

Health care expenditure in the Philippines has increased over the past two decades, from PHP 125 billion (USD 2.5 billion, 3.5% GDP) in 1995 to PHP 668 billion (USD 13.4 billion, 4.7% GDP) in 2014. Financing for health care in the country mainly comes from out-of-pocket and government sources, with a smaller contribution from non-out-of-pocket sources in the private sector (i.e. private insurance) (Figure 9). The contributions of patients to health financing in the Philippines have increased markedly over the years. In 2014 for example, 54% of health care was paid out of pocket compared to 40% in 2000.
Figure 9. Health spending by source of financing in the Philippines, 1995-2014 (USD). Data source: World Bank.

Figure 10 shows the estimated financing requirements for TB control activities from 2010 to 2022. Funding for TB programs in the Philippines comes from various sources which can be broadly divided into two categories: domestic including Philippines health insurance corporations, non-government organisations, local government units and out-of-pocket (due to payments to private providers as well as the transportation costs incurred); and international mainly from the Global Fund (Figure 11). Despite known commitments of foreign donors and expected national government funding, funding gaps are expected to persist and rise. It is estimated that the funding shortfall will be around 38% of the total budget required for TB activities in the Philippines (PHP 5 billion, USD 104 million). Of the funded amount (PHP 3 billion, USD 64.5 million), 44% is contributed by international donors, and the remaining is provided domestically (Figure 11).
Figure 10. Estimated financing requirements by year, in billions PHP, 2010-2022.9,10

Figure 11. Share of TB funding for the Philippines by sources.9
Chapter 3. Modelling objectives and constraints

Priority modelling questions for the NTP of the Philippines are presented in the Objectives section above (Section 1.3).

3.1 Time horizons and goals of the NTP

In line with the WHO Sustainable Development Goals and the End TB targets, the Philippines has set ambitious targets to achieve TB elimination by 2050. The interim aims of the program address goals to reduce incidence by 90% and mortality by 95% by 2035.

We have therefore used 2035 as the main time horizon for this exercise and examined the impact on prevalence, incidence of and mortality from TB. For the optimisation exercise, we use incidence of tuberculosis (per 100,000 people per year) at 2035 as the main outcome to be optimised. The input is the cost expended on all of the programs over the whole period from 2017 to 2035, expressed as mean cost per annum of the funding package.

Results from later time horizons are less likely to be reliable, as new technologies and developments in TB control are likely to have occurred over this period to influence predictions. By contrast, time horizons shorter than this period are unlikely to show dramatic changes on an epidemic as slow-moving as TB.

3.2 Epidemiology, programs and expenditure at baseline

Funding at baseline is spread across a number of programs, some of which are compulsory, such as hospitalisation, monitoring and evaluation and first-line drugs for treatment. Others are discretionary and aimed at increased case finding, such as targeting of high-risk groups and community involvement and improving diagnostics. These baseline activities have played an important role over the last five years in reducing TB burden. In the epidemiology chapter, we examine the maximum impact of each scenario individually and then the combined case of all scenarios to look at the greatest possible impact these activities can have given our estimated maximum coverage of the activities. We compare allocation to various defined programs and compare the improvement with the baseline to assess the impact of programs individually. We also use our mechanistic model to allow us to explore synergies across programs and to examine how allocative efficiency (the best possible mix of programs) can lead to greater impact on the incidence of TB in the Philippines.
3.3 Approach and brief summary of methods

A full and detailed description of the model is given in the final section: Methods, here we present a brief description only.

3.3.1 Epidemiology of the model

This analysis is based on a mechanistic model that explicitly simulates the progression of individuals between disease states. That is, we simulate people entering the model through birth (with or without vaccination), being exposed to the organism, becoming infected, progressing to active disease and then interacting with the health care sector to achieve cure. This involves compartments that represent susceptibility to infection, varying levels of immunity, latent infection, active infection, detection, mis-assignment and progression through treatment.

Populations are then further divided according to risk factors (prisoners, rural and urban poor, diabetes, HIV) and age groups. People can transition through TB states and progress through age-groups with time. Transition rates are guided by parameters, such as a rate of moving from latent to active TB, or a rate of ageing from the 0-5 age-group to the 5-15 age-group. Several model parameters change with time – for example, the treatment success rate varies year on year to match reported observations. An example of time variant parameters used in the model is presented in Figure 12 (birth rate and life-expectancy), to illustrate our approach of using splines to fit time-variant functions to input data from the sources described above. The inputs to the epidemiological model include:

- Demographics: age strata and fertility from 1900
- Treatment: historical inputs of commencement of treatment,
- WHO data from 1990 on TB prevalence, incidence, mortality and CNR
- Evidence from the literature on natural history of progression of TB disease
- Peer-review of literature evidence on the impact of programs

The main outputs from the model are mortality from TB, incidence of TB and prevalence of TB. These can be stratified by age or risk group. These outputs can also be used as inputs into the Economic model.
3.3.2 Model fitting and model uncertainty

In the model we allow for uncertainty around the model parameters: transmissibility, natural mortality and duration of active tuberculosis in the absence of treatment. We run a Bayesian Monte Carlo Markov Chain algorithm and accept proposed parameters based on the closeness of the modelled data to historical data on incidence and mortality (taken from WHO reports). The accepted sets of parameters are then used to project the epidemiology forwards in time under the different scenarios.

3.3.3 Economic model

A health economic module is linked to the disease dynamic model to estimate costs of TB programs, and TB epidemic corresponding to different levels of funding. We use a generalised logistic function to describe the association between funding and coverage of a TB program. The epidemic model and the health economic model are linked in both directions. The epidemic model can inform (for example) the size of the population requiring treatment each year, which will in-turn drive the associated costs. By contrast, the economic model can generate an epidemiological input, such as a new case finding program, which both increases treatments of cases in the short-term, but also reduces incidence of new cases in the long-term. Hence there is a complex interaction between these two modules. The economic model
impacts on the epidemic model through a change in a model parameter. In the previous example, increased case notification would increase the rate of individuals moving from active TB in the community, to active TB with diagnosis.

The main inputs for this model are startup costs, unit costs and maximum coverage. Unit costs and start-up costs were supplied by the economist of the NTP, and maximum coverage was mostly defined through expert elicitation. Another input for the health economic model is population size, defined by the model, evidence from peer reviewed sources, expert opinion, and the NTP.

Model outputs can be bidirectional. For example, when the epidemic model feeds into the economic model, output calculations are dollars spent for each program resulting from new cases of TB. When money is spent proactively, money is translated into new programs via changes in parameters based on changes in programmatic activity.

### 3.3.4 Optimisation

The AuTuMN model allows users to choose a set of objectives, such as minimising new infections for a given amount of funding, reaching sustainable development goals for incidence or mortality or to determine targets for the lowest possible spending, minimising TB-related deaths, or minimising long-term financial commitments, and to then determine the optimal resource allocation for meeting those objectives. For this analysis, the NTP is interested in looking at cumulative incidence of cases of TB from 2017 until 2035 inclusive and comparing outcomes over different programs, to determine the optimal mix of spending.

Optimisation then works to find the best resource allocation to TB programmes that achieves the stated objective. We employ a minimisation algorithm aimed at minimising the model predicted cumulative incident cases of TB or mortality from TB from 2017 to 2035. The inputs over which the algorithm searches are the proportion of funds spent on each of the proposed activities, namely:

1. Engagement of providers not compliant to NTP protocol
2. GeneXpert replacing sputum smear as the first-line diagnostic test
3. Systematic screening for TB cases
   a. In the prison population
   b. In the urban poor
   c. People with diabetes and PLHIV

[Of note, we excluded systematic screening in the rural poor from optimisation the analysis because our cost-effectiveness analysis results [see Chapter 6 below]
suggest that it is the least cost-effective intervention with very high cost and low impact).

4. Preventive therapy for children under 5 years old

5. Promoting awareness
   [We plan to add this intervention in later versions of this report if data on program cost are available]

Replacing conventional regimen with short-course regimen for MDR-TB is not included in the optimisation because it is demonstrated to be always cost-saving.

A feedback loop is in place such that if an intervention leads to fewer cases of active TB, the costs of treatment and case management activity, offsets the costs of the effective intervention. For a fixed amount of money spent, the proportion allocated to each program can be adjusted, this will lead to a change in epidemiology and may lead (through feedback loops) to different amounts spent in other programs. A minimisation algorithm finds the optimal proportion of those funds spent on each of the programs (Figure 13).

![Figure 13. Diagram depicting the events in the optimisation algorithm.](image)

It is important to note that the results of optimisation depend entirely on the epidemiological and economic inputs to the model. That is, an intervention that has been assessed as cheaper and that has a marked epidemiological impact will be consistently favoured by any optimisation algorithm. By contrast, an intervention that is more expensive or has limited programmatic benefit will only be incorporated into the optimisation analysis if and when the budget envelope expands sufficiently that other programs have already been fully funded.
Chapter 4.  Projected epidemiological impact of control programs

4.1 Model calibration

For the period 1990 to 2015, we accessed information on incidence, case detection rates, estimated prevalence and notified deaths from TB in the Philippines from WHO reports.\(^{11,12}\) On discussion with the country team, WHO regional adviser and other relevant stakeholders, we felt that the very high rates of case detection (85% in 2015) reported in recent WHO data were likely to be markedly overestimated. Under these (high) case detection rates, patients would spend a relatively short period of time infectious in the community, which seems unrealistic in the context of the Philippines. This is particularly important for this analysis, as interventions that aim to reduce this time period (e.g. systematic screening, awareness raising) are likely to appear relatively ineffective if short undiagnosed periods are simulated.

Given this, it was felt that the reported estimates for incidence and prevalence are more likely to be reliable than the reported case detection rates and these quantities were used for data fitting. To achieve this, we adjusted the case detection rate parameter\(^1\) at multiple time points to fall within a plausible range (Figure 14), while also achieving a steady reduction in disease burden consistent with that reported in the WHO Reports. This approach results in the model calibration displayed in Figure 15. Prevalence of TB was not fitted to data, but was used as a cross validation of the fitting process.

Figure 15 shows that calibration was good to the WHO figures of incidence and prevalence. The fit to notifications is poorer than the other indicators because of the recalibration of case detection rates as explained above. The estimated mortality is similar to the WHO estimates but with some differences. The estimated mortality from 2010 onwards is higher than the WHO estimates as a reaction to lower case detection rates that were used in our model compared to the WHO reported case detection rates as explained above.

These calibration results should be interpreted with the caveat that we assume that a proportion of the TB burden in all countries we model is entirely unrecognised. This is due to the following two factors. First, rates of childhood TB are considerably lower than those predicted by the model when using data from developed country settings, which could be due either to over-diagnosis in such high-income settings or under-diagnosis in resource-poor settings. Second, if we assume case fatality rates consistent with those reported in the pre-

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\(^1\) Note that the “case detection rate” we implement in the model is: the proportion of all cases that would be diagnosed by the high-quality care sector at some point during the course of their disease.
chemotherapy era (see Tiemersma et al.,\textsuperscript{13}) mortality rates are considerably higher than those reported in all countries in which AuTuMN has been used. This likely reflects unrecognised TB-related deaths occurring before presentation to the health system. It is important to note that neither of these issues are specific to the Philippines.

![Graph: Case detection rate](image)

**Figure 14.** Manually adjusted case detection rate.

![Graphs: Incidence, Mortality, Prevalence, Notifications](image)

**Figure 15.** Baseline model outputs.
4.2 Baseline carried forward predictions

The baseline scenario (Table 2) uses results from the current program as at 2015 and assumes that these coverage levels continue until 2035. Outcomes for treatment programs are carried forward as constant from 2015, with treatment success rates at 92% for DS-TB and 50% for MDR-TB, death rates at 2.4% for DS-TB and 20% for MDR-TB, and failure or default rates at 5.6% and 30% for DS-TB and MDR-TB, respectively. Case detection rate is assumed to remain at 62%. Sensitivity of the diagnostic algorithm for passive case detection is assumed to be 90% due to the adoption of GeneXpert. Time from presentation to a health facility to commencing treatment is assumed to be 7 days for smear-positive and 30 days for smear-negative pulmonary TB. BCG coverage remains at 80% of the birth cohort. A more detailed description of the parameters used in the model at baseline can be found in Appendix 2.

Figure 15 above shows predictions of overall epidemic curves assuming current programs as described in 2015 are carried forward in subsequent years. The model suggests that if the TB control program continues as they are, there will be further gradual decline in incidence, prevalence and mortality; however, it will be well short of the NSP and End TB targets, except for incidence which will meet the NSP target for 2022 (Table 3). Figure 16 shows model predictions for MDR-TB if baseline conditions are carried forward. The model predicts an increase in incidence, prevalence and mortality of MDR-TB over time.

Table 2. Baseline parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment success rate (DS-TB, MDR-TB)</td>
<td>92%, 50%</td>
</tr>
<tr>
<td>Mortality on treatment (DS-TB, MDR-TB)</td>
<td>2.4%, 20%</td>
</tr>
<tr>
<td>Default/failure rate (DS-TB, MDR-TB)</td>
<td>5.6%, 30%</td>
</tr>
<tr>
<td>Case detection rate</td>
<td>62%</td>
</tr>
<tr>
<td>Diagnostic sensitivity</td>
<td>90%</td>
</tr>
<tr>
<td>Mean time to diagnosis 16 days</td>
<td>16 days</td>
</tr>
<tr>
<td>Preventive therapy for &lt;5y TST+, uptake</td>
<td>14%</td>
</tr>
<tr>
<td>Proportion of first-line diagnostics using GeneXpert</td>
<td>2.8%</td>
</tr>
<tr>
<td>Proportion of patients accessing care through providers not compliant to NTP protocol</td>
<td>30%</td>
</tr>
</tbody>
</table>
Table 3. Model predictions if baseline conditions are carried forward

<table>
<thead>
<tr>
<th></th>
<th>2022</th>
<th></th>
<th>End TB 2035</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Target</td>
<td>Projected</td>
<td>Target</td>
<td>Projected</td>
</tr>
<tr>
<td>Incidence (rate, /100,000)</td>
<td>243</td>
<td><strong>241</strong></td>
<td>32</td>
<td>226</td>
</tr>
<tr>
<td>Mortality (number of deaths)</td>
<td>7,000</td>
<td>21,000</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mortality (rate, /100,000)</td>
<td>NA</td>
<td>NA</td>
<td>0.5</td>
<td>20</td>
</tr>
</tbody>
</table>

NA, not applicable.

Figure 16. Model predictions of MDR-TB burden if baseline conditions are carried forward.
4.3 Scenarios

Table 4 provides a summary of scenarios examined in this report. Below is an explanation of the programs and the manner in which they have been incorporated into the model. A detailed review of the evidence used to populate the model is presented in Appendix 3.

Table 4. Summary of the scenarios

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Description</th>
<th>Parameter change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scenario 1</td>
<td>Engagement of providers not compliant to NTP protocol</td>
<td>Increase coverage from zero to 80% by 2020</td>
</tr>
<tr>
<td>Scenario 2</td>
<td>Replacing smear with GeneXpert in all diagnostic centres</td>
<td>Increase coverage from 2.8% to 99% in 2020 in line with planned roll-out</td>
</tr>
<tr>
<td>Scenario 3</td>
<td>Systematic screening. This includes active case finding using chest x-ray as screening test followed by GeneXpert equipped in a mobile van in prisoners, urban poor and rural poor; plus intensified case finding using GeneXpert among PLHIV and people with diabetes who visit health facilities for their regular check-ups</td>
<td>99% coverage for prisoners, 80% urban poor, 70% rural poor, 90% PLHIV and diabetic</td>
</tr>
<tr>
<td>Scenario 4</td>
<td>Preventive therapy for children contacts under 5 years old</td>
<td>Increase from 14% coverage at baseline to 90% under intervention scenario</td>
</tr>
<tr>
<td>Scenario 5</td>
<td>Preventive therapy for adult contacts &gt;15 years old</td>
<td>Increase coverage from zero to 90%</td>
</tr>
<tr>
<td>Scenario 6</td>
<td>Awareness raising at 50% coverage</td>
<td>Accelerate rate of presentation to care 1.3-fold for population covered by intervention</td>
</tr>
<tr>
<td>Scenario 7</td>
<td>Short-course MDR-TB</td>
<td>Transition to 9-month regimen in all persons eligible for treatment Treatment outcomes improve to 88% treatment success and 5% treatment-related death</td>
</tr>
<tr>
<td>Scenario 8</td>
<td>Combined implementation of all of the above scenarios</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: MDR-TB, multi-drug resistant TB; NTP, National Tuberculosis Program; PLHIV, people living with HIV/AIDS.
4.3.1 Scenario 1: Engagement of providers not compliant to NTP protocol

Health care providers who are not compliant to NTP protocol provide care that is considered to be of a lower quality than that provided through the government centres coordinated by the NTP. Approximately 60% of care is provided through government centres compliant to NTP protocol, which are considered to be of high quality, with treatment outcomes approximating those reported in national statistics and the WHO. Around 14% of patients are treated in hospitals, which are most often of a high standard, comparable to that of the government centres. The remaining 20-30% of patients have treatment provided through providers who are not compliant to NTP protocol. Of note, our baseline estimate of the proportion of patients accessing care through these providers is deliberately conservative at 30% coverage. Engagement of these providers is an important component of the NSP. The intervention is considered to involve either provision of financial incentives (approximately USD 100 per patient) to these providers to improve care quality or increasing referral to the public sector.

Patients initially receiving care from providers who are not compliant to NTP protocol spend an average of two years under the care of these providers, which is considered to be of low quality, before returning to the infectious pool and seeking treatment for a second time (from either NTP protocol compliant or non-compliant providers). Note that this relatively long average period of time reflects that fact that many patients accessing care through providers not compliant to NTP protocol will never engage with higher-quality NTP protocol-compliant health care, while some may transition from low-quality to high-quality care within a few months. During their engagement with providers who are not compliant to NTP protocol, treatment does not modify patients’ disease course. This scenario simulates scale-up of this intervention to 80% coverage as advised by the Philippines NTP. The effect of this intervention is shown in Figure 17. We estimate that this intervention will reduce TB incidence and mortality in 2035 by 12% and 18%, respectively, compared to baseline.
4.3.2 Scenarios 2: Replacing smear microscopy with GeneXpert as the primary diagnostic test

Although the algorithm for the use of GeneXpert in the Philippines was developed in 2012, the effective coverage of GeneXpert diagnostics has remained relatively low (2.8% in 2012). GeneXpert scale-up is underway, with GeneXpert machines currently available in larger health centres (186 available, 354 to arrive by end 2017) and around 50,000 tests performed each year. Full transition to point-of-care testing is planned, with a large number of the new, cheaper and batter-operated GeneXpert Omni devices ordered from 2017. Complete coverage of the country with 3000 devices is anticipated by the end of 2020. This is planned regardless of the results of this report, but it is nevertheless important to understand the impact of this program. We model the introduction of GeneXpert through the following:

1. Increases the proportion of smear-negative patients diagnosed. Specifically, narrows the gap between smear-negative and smear-positive diagnosis according to its sensitivity for smear-negative disease (67%)
2. Increase the proportion of MDR-TB patients assigned to the correct regimen
3. Decrease in the time to treatment commencement for smear-negative patients

A moderate impact of this intervention is observed on overall disease burden (Figure 18); while the impact of the program on MDR-TB is more substantial (Figure 19). Specifically, GeneXpert as the primary diagnostic test will result in a 27% reduction in MDR-TB incidence and 33% reduction in MDR-TB mortality in 2035 compared with baseline. This is thought to be primarily due to GeneXpert’s effect on improving diagnosis of smear-negative TB.

Figure 18. Impact of GeneXpert replacing smear as primary diagnostic tool on overall TB burden.
4.3.3 Scenario 3: Systematic screening in high risk groups

Systematic screening involves the deployment of a clinical team and mobile van equipped with GeneXpert and chest x-ray machines to search for active cases of TB in prisons, rural poor (including indigenous) communities and urban poor communities (i.e. active case finding). This is complemented by screening for TB cases among PLHIV and people with diabetes who visit health care facilities for their regular check-ups (i.e. intensified case finding).

For implementation of systematic screening and throughout all of the analysis presented here, we no longer make the assumption of homogeneous mixing. For example, the assumption that prisoners mostly contact persons in the general population, rather than other prisoners is very unlikely to be correct. Therefore, we incorporate a “matrix of population mixing”, illustrated below (Figure 20). Here we assume that the rural poor receive 20% of their contacts from the general population (i.e. those who are not rural poor or prisoners), 5% from the urban poor, 5% from the diabetics and the remaining 70% from other rural poor. For prisoners, the proportions are general population 10%, other prisoners 85% and 1% each for the remaining population groups. Similar interpretations for the remaining population groups can be obtained from Figure 20.
Figure 20. Matrix of population mixing

For the finding of TB cases among prisoners, urban and rural communities using mobile diagnostic units, we rely most strongly on information from the Palawan active case finding study (pers comm Rajendra Yadav, Garfin AMC, et al. Bringing state-of-the-art diagnostics to vulnerable populations: the use of mobile screening unit in active case finding for tuberculosis in Palawan, the Philippines. Submitted for publication) and also from the DETECTB study in Harare. The former study is the most directly applicable to this analysis, being data from the Philippines, while the latter has the advantage of having included prevalence surveys before and after the active case finding intervention, such that an estimate of the proportion of all active cases detected can be made.

In the DETECTB study, we estimated that around 23% of undiagnosed patients with active TB would have been detected at each screening round. In the Palawan study, the algorithm employed was clinical assessment plus chest x-ray. Those with abnormal results (predominantly chest x-ray, supplemented by clinical symptoms) provided two sputum specimens and those with positive results on LED-smear or GeneXpert analysis were diagnosed as having TB. We believe this approach is similar to the intervention we have been requested to simulate. It should be noted that all eligible persons were screened in prisons (and schools), but only those who received the study information and voluntarily participated were screened in rural poor and indigenous (and urban poor). The proportion of screened persons diagnosed with TB was: rural poor 2.2%, indigenous 2.9% and prisons 6.2%. However, these figures are likely to be higher than the true prevalence in the rural poor and indigenous groups, due to patient selection. Therefore, based on the above discussion and the high yield
of screening observed in the Palawan study, we assume that the true prevalence of TB in the rural poor and indigenous population is 2% (2000 per 100,000 population), of which we are able to diagnose 50% of cases in each round of active case finding. In the prison population, the prevalence is assumed to be 10% (10,000 per 100,000 population), of which we are able to diagnose 62% of cases.

We estimate that systematic screening in high-risk groups has substantial impact on overall TB burden (Figure 21). In particular, this intervention will reduce overall TB incidence and mortality in 2035 by 19% and 28%, respectively, compared with baseline. The impact of the intervention on the targeted risk groups is even more substantial (Figure 22).

Figure 21. Impact of systematic screening on overall TB burden.
Figure 22. Impact of systematic screening on TB burden in the targeted risk groups.

4.3.4 Scenarios 4 and 5: Preventive therapy

Currently only household contacts aged under five of smear-positive index cases are recommended for preventive therapy. Despite the recommendation, coverage is low with only about 14% of children household contacts receive preventive therapy. The NTP aims to increase coverage to 90% by 2022 among children under 5 years old (scenario 4). We also simulate a scenario in which preventative therapy is given to 90% of adult (>15 years of age) contacts (scenario 5). 6-months of daily isoniazid has been used but plans to switch to 3-months of weekly rifapentine plus isoniazid are underway. Therefore, we simulate the preventive therapy with the latter regimen as advised by the country team.

We model the intervention by increasing the number of people moving from the latent TB compartment to the susceptible (but partially immune) compartment to reflect uptake of preventive therapy of contacts of TB cases with positive TST of 90% and effectiveness of therapy of 60%. We found that preventive therapy for both children and adult contacts has
modest impact on overall TB burden (Figure 23). Preventive therapy for adult contacts is less effective than for children contacts. The modest impact of preventive therapy in children contacts can be explained by the small population size of children relative to the total population; whereas the modest impact in adults can be explained by the fact that, in our model, adults have very low risk of developing active TB (lower than that of children). The effects of both scenarios on TB burden in their respective population age groups are more substantial than on overall TB burden (Figure 24).

Figure 23. Impact of preventive therapy on overall TB burden.
4.3.5 Scenario 6: Promoting awareness

Communication interventions are an essential part of TB programs. In the Philippines, these involve face-to-face and door-to-door campaigns among high-risk population groups such as household contacts and urban and rural poor communities. The program is aimed at reducing stigma, improving knowledge about the disease, greater community awareness, changing health care seeking behaviour and health service utilisation. Due to the lack of efficacy data of this intervention in the Philippines, data derived from the literature were used.

In a study conducted in an indigenous community with high TB burden in Canada in the context of passive case finding, Alvarez et al. found that the number of people presented themselves to the clinic increased by 92% during the four-month community-wide awareness campaigns, compared to the previous periods without the campaign (increased from an average of 26 people per month to 50 per month). This study also found that door-to-door campaign increased the number of new LTBI cases by 34%, and increased the number of newly diagnosed active TB cases by 29.5%. In Columbia, Jaramillo reported that a six week mass media-based health education (radio, television and newspaper) increased the number of smears processed by laboratories by 64% and increased the number of smear-positive
pulmonary TB cases detected and notified by 52%. In both the studies by Alvarez et al. and Jaramillo, the effects of the program were not sustained beyond the period of the intervention. A brief report of an intervention in Odisha (India) involving health worker education, van-mounted loudspeakers and community-based health camps found an increase in the number of detections compared to before the intervention. Although the increase in the total number of TB diagnoses made was not reported, the number of persons screened increased by 87.8% and the number of smear-positive diagnoses made increased by 10.8% (figures which seem consistent with those reported by the studies discussed above).

The extent of the intervention considered by the Philippines is probably more equivalent to that described by Alvarez et al., which involved door-to-door campaign in high risk communities. Therefore, we consider that awareness raising can increase rates of presentation 1.3-fold compared to the baseline. The caveats described above should be borne in mind, as well as the consideration that interventions that are continued for longer periods of time than those studied above may lose their effectiveness with time. For this intervention, we assumed 50% coverage. We estimate a modest reduction in incidence and mortality by 2035 of 6% and 10%, respectively (Figure 25).

**Figure 25.** Impact of awareness program on TB burden.
4.3.6 Scenario 7: Short-course regimen for MDR-TB

As mentioned above, the Philippines has one of the highest burdens of MDR-TB in the world. Currently, the country adopts the conventional 20-month regimen recommended by the WHO. However, this regimen has shown a modest success rate of 50% in the Philippines, comparable to that seen worldwide (44 to 61%). Not only is the current regimen lengthy and incompletely effective, it is also poorly tolerated and expensive. Recently, a nine-month short course regimen has been demonstrated to be highly effective with success rates of 87.9%. In addition, it has been shown to be well-tolerated, inexpensive and not associated with relapses. Adoption of this new regimen in the Philippines is underway. This is envisaged to occur through the expansion of iDOTS centres around the country, each responsible for the management of a relatively small number of MDR-TB patients. It is expected that approximately 90% of MDR-TB patients should be eligible for this regimen. Of note, for the short-course regimen to have such high treatment success rate, making MDR-TB health care services patient-centred is essential. In the context of the Philippines, this would be feasible using the existing successful DOTS network.

This intervention predicts a marked impact on the burden of MDR-TB (the strain against which this intervention is directed, Figure 26). The impact on overall TB burden (Figure 27) is relatively small, due to the fact that MDR-TB only constitutes approximately 3 to 5% of the total TB burden over the period simulated.

Figure 26. Impact of short-course MDR-TB regimen on MDR-TB burden.
Figure 27. Impact of short-course MDR-TB regimen on overall TB burden.

4.3.7 Combination of scenarios 1, 2, 3, 4, 5, 6, 7

Figure 28 shows the impact of all of the interventions combined. Combining all the interventions substantially reduces overall TB incidence by 38% and mortality by 54% in 2035 (by comparison to 2015). Also of note is that improvements in case detection will put a strain on the program with increases in notification in the first five years of the interventions. Substantial reduction in MDR-TB burden is also predicted (Figure 29).
Figure 28. Impact of combining all interventions on overall TB burden.

Figure 29. Impact of combining all interventions on MDR-TB burden.
4.3.8 Poverty reduction

In addition to the above scenarios which are within TB activities, we also simulated the impact of reducing the proportion of urban and rural poor populations by half. This can be interpreted as the results of macro-economic policies to reduce poverty such as sustained economic growth, reduced unemployment, increasing benefits to the poor etc. Our model shows a marked reduction in TB burden (Figure 30). In particular, incidence will be reduced by 2035 by 26% and mortality by 27% compared to baseline. The effects of different scenarios on TB burden are summarised in Table 5.

![Figure 30. Impact of reducing the proportion of urban and rural poor by 50%](image-url)
### Table 5. Summary of effects of different interventions on overall TB incidence

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Incidence rate in 2035 (/100,000)</th>
<th>% reduction relative to 2016</th>
<th>% reduction relative to baseline in 2035</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>226</td>
<td>13%</td>
<td>-</td>
</tr>
<tr>
<td>Engagement of providers not compliant to NTP protocol</td>
<td>199</td>
<td>22%</td>
<td>12%</td>
</tr>
<tr>
<td>GeneXpert replacing smear as primary diagnostic tool</td>
<td>203</td>
<td>21%</td>
<td>10%</td>
</tr>
<tr>
<td>Systematic screening in prisoners, rural poor, urban poor, PLHIV and diabetes</td>
<td>183</td>
<td>28%</td>
<td>19%</td>
</tr>
<tr>
<td>Preventive therapy for children 0-5 years</td>
<td>222</td>
<td>13%</td>
<td>2%</td>
</tr>
<tr>
<td>Preventive therapy for adults &gt;15 years</td>
<td>221</td>
<td>13%</td>
<td>2%</td>
</tr>
<tr>
<td>Awareness raising</td>
<td>212</td>
<td>17%</td>
<td>6%</td>
</tr>
<tr>
<td>Short-course MDR</td>
<td>224</td>
<td>12%</td>
<td>1%</td>
</tr>
<tr>
<td>Poverty reduction</td>
<td>167</td>
<td>35%</td>
<td>26%</td>
</tr>
<tr>
<td>All of the above except poverty reduction</td>
<td>141</td>
<td>45%</td>
<td>38%</td>
</tr>
</tbody>
</table>
Chapter 5. Projected cost and financial commitment

5.1 By year

Total costs of all TB programs implemented together are shown in Figure 31. It shows the maximum additional budget that would be required if all these new TB programs are implemented on top of the existing programs. Of note, short-course regimen for MDR-TB is not included because it replaces an existing program, conventional regimen for MDR-TB. Replacing conventional regimen for MDR-TB with short-course regimen will be cost-saving (see section 5.2.3). Except for the first three years (2017 to 2019), when the programs are being implemented with initial start-up costs, the average total cost for all TB programs combined in the Philippines is projected to be PHP 45 billion (USD 900 million) per year. In 2022 for example, systematic screening in rural poor accounts for the majority of TB costs (48%), followed by systematic screening in urban poor (41% of total cost) and GeneXpert replacing smear microscopy (6%) (Figure 32). Unit cost inputs are shown in Appendix 4.

Figure 31. Yearly costs of 7 TB programs.
5.2 By program

5.2.1 Engagement of health care providers not compliant to NTP protocol

The cost of this intervention is shown in Figure 33. It is assumed that the program will be implemented in 2017 for 80% of health care providers who are currently not compliant to NTP protocol (i.e. 80% coverage). Except for the first 3 years when the program is being set up and has zero coverage, average yearly cost is projected to be PHP 1.3 billion (USD 25.6 million).
5.2.2 GeneXpert replacing smear microscopy

Figure 34 shows the costs of GeneXpert replacing smear microscopy. The program is assumed to be at universal coverage (100%). The cost of the program is highest during the period of 2017 – 2019 when significant start-up cost is required to set-up the program. After this period, yearly cost of the program becomes stable at around PHP 2.5 billion (USD 50.5 million).

![Graph showing the costs of GeneXpert replacing smear microscopy](image)

**Figure 34.** Cost of GeneXpert replacing smear microscopy.

5.2.3 Short-course regimen for MDR-TB

Figure 35 shows yearly cost of short-course regimen (blue line) for MDR in comparison to the conventional regimen (red line). The short-course regimen costs around PHP 3.2 billion per year (USD 65 million) whereas the conventional regimen would cost PHP 4.1 billion (USD 82.6 million). Therefore, replacing the conventional regimen with a short-course regimen for MDR is a cost-saving activity. We estimate that using the short-course regimen will save PHP 1.8 billion (USD 35.3 million) per year (blue bars in Figure 35).
5.2.4 Systematic screening in high risk groups

The costs of systematic screening in different risk groups are shown in Figure 36. Systematic screening implemented in people with diabetes and PLHIV is the cheapest, costing approximately PHP 137 million (USD 2.7 million) per year. Systematic screening in prisoners is the second cheapest, costing around PHP 623 million (USD 12.5 million) a year. Systematic screening in urban poor and rural poor are the most expensive programs with an average yearly cost of PHP 18.4 billion (USD 369 million) and PHP 21.8 billion (USD 439 million), respectively.
5.2.5 Preventive therapy for LTBI

Figure 37 below shows the costs of preventive therapy in children under 5 years of age (blue line) and in adults aged from 15 years or above (red line). Average yearly costs of the program in the two age groups are estimated to be PHP 300 million (USD 6 million) and PHP 1.1 billion (USD 22 million), respectively.
In cost-effectiveness analysis (CEA), the health outcomes of the alternative strategies being considered are measured in relative to their costs. CEA is expressed in terms of a ratio of the difference in cost (incremental cost) over the difference in health outcome (incremental effect) of the two interventions being considered. This ratio is known as the incremental cost-effectiveness ratio (ICER). Assume that a new intervention is being compared to an existing intervention (the comparator); and the total costs and effectiveness of each program are $C_{\text{new intervention}}, C_{\text{comparator}}, E_{\text{new intervention}}, E_{\text{comparator}}$, respectively; the ICER then is defined as:

$$\text{ICER} = \frac{C_{\text{new intervention}} - C_{\text{comparator}}}{E_{\text{new intervention}} - E_{\text{comparator}}}$$

The ICER indicates the cost per additional unit of effect of one intervention relative to another. Given that resources are scarce and that the ultimate goal of resource allocation is to get the best from a defined budget, ICERs can be used to rank mutually exclusive interventions. The intervention that has the smallest ICER is the most cost-effective and hence the most preferred one. In this analysis, the comparator is the baseline carried forward; and effectiveness is measured in terms of the number of new active TB cases.

Figure 38 and Table 6 display the incremental cost, total epidemiological impact and cost-effectiveness of different TB programs taken individually or different bundles of programs taken together over 19 years from 2017-2035. They show a clear choice of short-course regimen for MDR-TB. The regimen is not only cost-saving but also more impactful compared to the conventional regimen. With the exception of short-course regimen for MDR-TB which is a clear choice, systematic screening in PLHIV and people with diabetes is the most cost-effective program. Preventive therapy for children aged 0-5 years is the second most cost-effective intervention; however it has a limited capacity to impact the epidemiology, averting around 4,390 active TB cases per year. A combination of engagement of providers not compliant to NTP protocol plus preventive therapy in children and systematic screening in PLHIV and people with diabetes is the next cost-effective program, followed by engagement of providers not compliant to NTP protocol alone. Systematic screening in rural poor is the least cost-effective program.
Figure 38. Incremental costs and active TB cases averted over 19 years (2017 – 2035).
### Table 6. Incremental costs and active TB cases averted over 19 years (2017 – 2035)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Active TB cases averted</th>
<th>Incremental cost (PHP)</th>
<th>Cost per active TB case averted PHP (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-course MDR-TB</td>
<td>48,196</td>
<td>-21,303,431,693</td>
<td>Cost-saving and impactful. Always recommended</td>
</tr>
<tr>
<td>Systematic screening in PLHIV and diabetes</td>
<td>116,525</td>
<td>1,651,304,822</td>
<td>14,171 (284)</td>
</tr>
<tr>
<td>Preventive therapy for children (0-5 years)</td>
<td>83,423</td>
<td>3,661,600,182</td>
<td>43,892 (881)</td>
</tr>
<tr>
<td>Engagement of providers not compliant to NTP protocol + Preventive therapy in children + Systematic screening in PLHIV and diabetic</td>
<td>471,540</td>
<td>21,442,275,426</td>
<td>45,473 (912)</td>
</tr>
<tr>
<td>Engagement of providers not compliant to NTP protocol</td>
<td>345,321</td>
<td>16,129,370,423</td>
<td>46,708 (937)</td>
</tr>
<tr>
<td>Engagement of providers not compliant to NTP protocol + Preventive therapy in children</td>
<td>393,645</td>
<td>19,790,970,605</td>
<td>50,276 (1,009)</td>
</tr>
<tr>
<td>GeneXpert replacing smear</td>
<td>314,926</td>
<td>30,370,705,932</td>
<td>96,438 (1,935)</td>
</tr>
<tr>
<td>Preventive therapy for adults (&gt;15 years)</td>
<td>90,049</td>
<td>15,209,735,817</td>
<td>168,906 (3,389)</td>
</tr>
<tr>
<td>Systematic screening in prisoners</td>
<td>40,737</td>
<td>7,462,850,065</td>
<td>183,198 (3,676)</td>
</tr>
<tr>
<td>Systematic screening in urban poor</td>
<td>383,199</td>
<td>224,275,553,437</td>
<td>585,272 (11,743)</td>
</tr>
<tr>
<td>Systematic screening in all risk groups</td>
<td>564,383</td>
<td>500,334,203,473</td>
<td>886,515 (17,787)</td>
</tr>
<tr>
<td>Systematic screening in rural poor</td>
<td>122,635</td>
<td>266,944,495,149</td>
<td>2,176,734 (43,674)</td>
</tr>
</tbody>
</table>
Chapter 7. Optimising resource allocation

7.1 Principle and aims

In this section, we aim to answer the following question: “Which mix of programs would lead to the best outcome for a given budget?” The interventions considered in this analysis are:

- Engagement of providers not compliant to NTP protocol
- Xpert as primary diagnostic tool
- Preventive therapy for 0 to 5 year olds
- Systematic screening in prisons
- Systematic screening in urban poor
- Systematic screening in PLHIV and people with diabetes

In the above analyses, we demonstrated that replacing the conventional regimen for MDR-TB with a short-course regimen would lead to improved epidemiological outcomes as well as cost savings. Therefore, this intervention would contribute to enhancing the efficiency of TB control in the Philippines and should always be implemented. Systematic screening in rural poor was found to be the least cost-effective intervention above; therefore it was excluded from the optimisation.

In order to interpret results meaningfully, we need to define three components; time horizon, budget and outcomes. Time horizon has been defined as 2035, given that it fits with the interim targets for End TB. The budget (i.e. total funding envelope) will define the amount of money that is spent for the programs listed above. We consider a total amount of money that has to be spent from 2017-2035. This amount is calculated from an annual spending assumed to be consistent over the period 2017-2035. In 2016, approximately USD 100 million was dedicated to TB control in the Philippines. We wanted to consider a broad range of funding in order to provide insight into the relationship between national TB budget and epidemiological outcomes. The annual envelopes considered in this exercise are USD 25, 50, 75, 100 and 125 million USD. It is important to stress that this budget or envelope is not equal to the total spending on TB in the Philippines for at least two reasons. First, some programs, such as DOTS, are considered to be essential and fully implemented, such that decreases or increases in funding for these programs cannot be considered. Further, optimisation is only useful for programs which both improve epidemiological outcomes and increase costs. Programs that worsen epidemiological outcomes should, of course, not be considered in optimisation. Similarly, programs that both save money and improve epidemiological outcomes should also
not be included, such as short-course treatment regimens for MDR-TB in this analysis. Therefore, the budget should be viewed strictly as the amount of funding available for the six programs listed above, with funding for already implemented programs from the baseline scenario continued.

Two obvious choices for outcome are incidence of tuberculosis cases, which best reflects the overall extent of the epidemic, and mortality, which is arguably the most important ultimate outcome to be considered. In the interest of clarity, we choose to present only the results for minimisation of TB incidence, as the results obtained when minimising TB mortality were found to be very similar (although equivalent results for minimisation of TB mortality can easily be obtained). Although we optimise against incidence, we still present the equivalent mortality estimates for each optimised scenario below.

### 7.2 Results

Figure 39 presents how the main epidemiological indicators (TB incidence and TB mortality in 2035) are affected by the budget allocated to the interventions considered. These results correspond to optimised allocation plans, such as those presented in Figure 40. Therefore, they should be interpreted as the best epidemiological situations that could possibly be achieved when spending the selected amounts of money on the listed interventions.

We observe a decrease in both TB incidence and TB mortality as the total annual budget allocated to the interventions is increased. However, we observe a plateau in both incidence and mortality as the budget allocated to the considered interventions exceeds USD 125 million. At this point, the incidence is predicted to be 167 per 100,000 per year and the mortality recorded in the program is 12 per 100,000 per year. This indicates that it becomes much more difficult to have an impact from additional funding when the annual budget is already at a high level. In contrast, the model suggests that even small increases in funding would significantly affect both TB incidence and TB mortality when the annual budget is relatively small (< USD 75 million).
Figure 39. Tuberculosis incidence and mortality in 2035 under the conditions of program allocation based on achieving optimal incidence.

Figure 40 suggests that engagement of providers not compliant to NTP protocol, use of GeneXpert as a first-line diagnostic tool, systematic screening in PLHIV and people with diabetes, and preventive therapy for children contacts should be prioritised under all levels of funding. These results are in line with our previous findings that highlighted the high cost-effectiveness of these interventions. For any funding envelop, the total budget is spent across the four interventions mentioned above (Figure 40). With a funding envelop of USD 75 million, systematic screening in prisons appears in the optimal spend. Systematic screening in urban poor population is only allocated some proportion of the funds when funding envelop is above USD 100 million. The fact that this intervention was not recommended for lower budgets is explained by the very high costs and poor cost-effectiveness associated with this intervention, as presented in a previous chapter.
Figure 40. Optimal spend when minimising incidence in 2035, proportion of funds allocated to each program when considering different annual envelopes.
Chapter 8. Conclusions

The Philippines is a country with a large total burden of TB due to high rates of disease and a large population. The epidemic is largely driven by community transmission among predominantly HIV-negative populations, including high-risk groups such as prisoners and poor populations – both urban and rural. Although rates of disease have declined over recent years, dramatic improvements in disease burden will be required if the country is to achieve its disease-related goals.

Calibration of the model revealed important insights around the TB transmission dynamics in the Philippines. As for several other countries in which AuTuMN has been implemented, proportion of mortality occurring in the community that is accurately identified and contributes to reported statistics appeared low (unless the case fatality rate of TB has declined dramatically since the pre-chemotherapy era). Although reported case detection rates were consistent with the notification data reported by the country in earlier iterations of model calibration, both these estimates were inconsistent with reported rates of incidence, prevalence and mortality. As the Philippines has conducted a number of prevalence surveys over recent years, it seems reasonable to calibrate more closely to incidence and prevalence than to notifications for this country.

Baseline projections for continuing the current programmatic response in the Philippines predicted a gradual decline in disease burden, which would meet country’s target for incidence for 2022 but would fall far short of meeting country’s target from mortality for 2022 or global targets for both indicators for 2035. Moreover, MDR-TB is predicted to constitute a rapidly increasing proportion of cases with time if programs specifically directed at this strain are not implemented.

In relation to the interventions implemented, systematic screening in all risk groups including prisoners, urban poor, rural poor, PLHIV and diabetes is the most impactful intervention. Engagement of providers not compliant to NTP protocol and GeneXpert replacing smear microscopy as primary diagnostic are the second and third most impactful interventions, respectively. Awareness raising is estimated to have moderate impact on the disease burden.

Expanded preventive therapy for the under 5s had a small impact on the overall disease burden, which is attributable to a relatively small proportion of all TB cases being detected by the high-quality health care sector (whose contacts this intervention is considered to apply to) and less than half of all modelled infections occurring in household contacts. Once efficacy of the treatment regimen is also incorporated, the proportion of all infections that can be averted is relatively small. Moreover, under 5s account for a relatively small proportion of the total population. Despite this, as the intervention is considered to be very cheap and cost-effective, as it requires little more than providing rifapentine and isoniazid to contacts of
patients who are being visited for DOTS anyway, it should not be discounted. Preventive therapy for adult contacts is found to be not impactful and not cost-effective due to the very low risk of TB infection considered in our model.

Changing from conventional to short-course MDR-TB regimens is predicted to have a marked impact on improving MDR-TB burden and to be cost-saving. This translates to a small reduction in overall incidence, due to MDR-TB constituting a relatively small proportion of all incident cases in the Philippines.

Implementation of all the above programs together results in substantial reductions in disease burden, with a reduction in incidence to almost half of that currently observed and a reduction in mortality and prevalence to around half of current levels by 2035.

Systematic screening in PLHIV and people with diabetes was the most cost-effective single intervention, followed by preventive therapy for children contacts; while systematic screening in rural poor appeared least cost-effective. Optimisation revealed that systematic screening for PLHIV and people with diabetes, moving to GeneXpert as the main first-line diagnostic, preventive therapy for children, engagement of the low-quality health sector should all be considered at all levels of funding envelope. As available funding increases and these most cost-effective programs reach saturation and approach full funding, additional funds should then be diverted to systematic screening in prisons and urban poor.
Chapter 9. Model methods

9.1 The AuTuMN software platform

AuTuMN is a flexible framework that can be applied to TB transmission across a diverse range of epidemiological contexts. A novel modular approach to programming for infectious disease control was used for the development of AuTuMN. This approach offers several advantages. First, the modular approach allows independent development of the modules, reusability of modules, combinations of existing modules. Thus, a pool of modules have been developed that can rapidly and efficiently be assembled to create a range of models. Development of new disease modules makes it possible to use an existing model for simulating other diseases. Second, it ensures that changes only affect one specific module, which makes changes, adaptations and improvements easier. A third benefit is that separate validation of the single modules supports validating the whole model. Hence, validated modules might be reused for other projects, which decreases effort and increases accuracy.

The AuTuMN platform comprises seven different modules for disease dynamics, health economics, calibration, uncertainty, data inputs, model outputs and graphical visualisation. These modules are linked to one another through a graphical user interface (GUI) (Figure 41 below). The transmission dynamic, economic and minimisation modules are described in detail in the below sections.

Figure 41. The modular structure of the AuTuMN software platform.
9.2 Structure of the epidemiological model

The structure of the epidemiological model is dynamic and population-based compartmental. The model uses a linked system of ordinary differential equations to track the movements of people between health states. Infections occur through the interaction between infected and susceptible members of the populations. The force of infection is the rate at which uninfected individuals become infected, and depends on the number of individuals infected and how infectious they are, as well as the susceptibility of the uninfected individual and the extent of exposure to the pool of infected people. Force of infection calculations are made separately for each strain included in the model. Within models of infectious diseases, empirical estimates of risk events and their associated infection probabilities are treated as parameters that inform the force-of-infection. For other inter-compartmental flows in the model, transition rates per person are also defined by model parameters. The TB transmission dynamic module is stratified by age-group (0 to 4 years, 5 to 14 years and 15 years and above), strains (DS-TB, MDR-TB, XDR-TB), smear status (smear-positive, smear-negative, extrapulmonary), comorbidities, special populations, access to healthcare, etc. as applicable to each context. In these cases, the compartmental structure is retained, but parameters are modified according to the stratum considered. The model incorporates the following features:

- Differential immunity by past TB infection, treatment and vaccination history
- Partially effective, or “leaky” vaccination
- Up to three strains of TB, differing by drug resistance patterns
- Declining risk of active disease with time from infection
- Differential infectiousness by smear-status
- Treatment of latent infection
- Sensitivity of diagnostic algorithms for TB disease
- Mis-identification of strain type due to lack of available drug resistance testing
- Declining infectiousness with treatment – and
- Amplification of resistance through default from treatment.

Figure 42 below presents an abbreviated pictorial representation of the compartmental model structure, with the parameters used for inter-compartmental flows described in Appendix 2. People are born at a constant rate into either the unvaccinated or vaccinated compartments, with the proportion entering each compartment depending upon BCG vaccination coverage at birth. The rate at which susceptible individuals are infected (i.e. the force of infection) differs by strain, being approximately proportional to the number of individuals currently suffering TB with each strain, although also modified by the infectiousness of those individuals, as described below. From the point of infection onwards, all compartments are sub-divided by strain (i.e. DS-TB and MDR-TB in this case). Individuals first enter an early latent compartment and may progress rapidly to active disease, or enter the respective late latent compartments, from which progression occurs more slowly. Active
disease in the community compartments are further subdivided by smear-status, as well as strain. The three smear-status subgroups are: smear-positive pulmonary, smear-negative pulmonary (conceptually including smear-negative/culture-positive and smear-negative/culture-negative pulmonary) and extrapulmonary. The smear-positive pulmonary subgroup is considered fully infectious, the smear-negative pulmonary subgroup is considered partially infectious and the extrapulmonary subgroup is considered non-infectious. These smear status subgroups are explicitly modelled, rather than employing weighted averages, because interventions will also differ in their impact by subgroups (e.g. sputum-based diagnostics).

Infected individuals with active disease may spontaneously cure (returning to late latency), die and exit the model, or be diagnosed with active disease or be detected by the health system as described below.

Patients seek treatment at a rate determined by local epidemiological information (such as the ratio of incidence to prevalence). After presenting to the health care system, the following processes may occur: 1) being correctly diagnosed as having active TB and correct identification of strain 2) being correctly diagnosed as having active TB and incorrect identification of strain or 3) failure to be identified as having active TB by the health care system (e.g. due to an insufficiently sensitive diagnostic algorithm). Once patients are correctly identified by the health system, they may then commence treatment (if available) or transition back to their respective active disease compartment.

We assume that all DS-TB is treated with an effective regimen, whereas MDR-TB may be either treated inappropriately as DS-TB, or appropriately with second-line therapy. That is, the regimen that each patient commences on is determined by the diagnostic group they have been assigned to as a consequence of the strain identification component of their diagnostic process. Individuals retained on appropriate treatment move from infectious on treatment to non-infectious and on treatment. Patients undergoing inappropriate treatment may transition to the appropriate treatment compartments after a period of several weeks (default value of eight weeks), when the results of conventional drug susceptibility testing become available. The additional TB-specific death rate is also modified by appropriate treatment, but not by inappropriate treatment.

Treated individuals are assigned the same risk of infection as other individuals who have been previously infected with a TB-family organism (i.e. *M. tb* or Bacille Calmette-Guérin [BCG] vaccine). Patients completing their second episode of treatment return to the partially susceptible compartment, with no further duplication of compartments by new/retreatment status. A proportion of defaulting patients from DS-TB regimens amplify to *de novo* MDR-TB.
Figure 42. Disease dynamic model. Recovery to susceptible compartments after successful completion of treatment, default with return to active disease, death and intervention-related non-standard flows are universally implemented but not presented in this Figure. Greater number of overlapping rectangles indicates greater degrees of model stratification, although number of rectangles is arbitrary. Flows presented are: 1, births; 2, infection; 3, progression to active disease; 4 and 5, spontaneous recovery; 6, missed diagnosis due to insensitivity of the diagnostic algorithm; 7, return to care seeking; 8, detection with correct assignment by drug resistance profile; 9, detection with incorrect assignment by drug resistance profile; 10 and 11, commencement on treatment. "Organ involvement" refers to whether patient has smear-positive, smear-negative or extrapulmonary disease.
9.3 Key components captured by the model

9.3.1 Immunisation

The BCG vaccine is known to provide partial protection against infection with TB.\textsuperscript{18} Past models for TB transmission in developed countries have represented this partial immunity as a compartment of fully immune individuals, with the flow entering the compartment proportional to the product of vaccine efficacy and vaccine coverage.\textsuperscript{19} The BCG vaccine may have particular efficacy in preventing disease in the years following vaccination,\textsuperscript{20} although this immunity may be overwhelmed by repeated exposure in highly endemic settings. Therefore, representing vaccination as complete and permanent immunity for a proportion of the population may not be appropriate for highly endemic developing countries. We represent the BCG effect as a proportional reduction in the force of infection for those vaccinated, and as providing no further protective effect after infection has occurred. As the BCG vaccine is administered as a neonatal vaccine, birth cohorts are split between vaccinated and fully susceptible compartments.

9.3.2 Latency

Markedly different rates of progression to active infection are observed in the years following infection with TB, by comparison to subsequent years remote from infection. For example, over the first 23 months following infection by a smear-positive index case confirmed by positive interferon-gamma release assay, 12.9\% of patients progressed to active disease.\textsuperscript{21} By contrast, the rate at which active disease develops once this high-risk period has ended is generally modelled at a much lower rate, such as 5-10\% over 20 years.\textsuperscript{22}

To represent this clinical observation, past models have included both fast and slow pathways from susceptible to actively infected, with a proportion of exposed susceptibles progressing immediately to active infection.\textsuperscript{22,23} This approach allows slight modification of the standard exponential function governing sojourn time in the exposed, non-infectious compartment. Other models have utilized alternative distributions of the latent period, including a stepwise reduction in the rate of progression occurring five years after exposure,\textsuperscript{19} and an arbitrary distribution of the latent period, which was demonstrated to retain important model properties.\textsuperscript{24} However, dual latent compartments linked by constant flow rates are increasingly utilized to represent the high and low risk periods following infection. These compartments may either be included as a sequential progression from early to late latent\textsuperscript{25-28} or allow for bypass of the early latent compartment with immediate entry into the late latent compartment after infection.\textsuperscript{29,30}

We include two sequential latent compartments in our model to simulate the increased risk of progression to active disease in the years immediately following initial infection.
9.3.3 Diagnosis and commencement on treatment

The process of actively infected patients commencing on effective treatment can be divided into multiple compartments, and previous models have separated patient-related pre-health system delays from health system delays, or have distinguished pre-diagnosis delays from delays to treatment after diagnosis. There are many steps in a patient’s transition from symptomatic but yet-to-present in the community through to commencing on treatment, sometimes termed a “care cascade”. However, several previous models have grouped all stages from onset of symptoms to commencement on treatment within a single inter-compartmental transition. Although wishing to retain the most parsimonious approach, we include a separate set of compartments representing those for whom the diagnostic algorithm has failed. This elaboration is included as patients with active TB for whom the diagnostic algorithm has been insufficiently sensitive may differ in at least three ways from yet-to-present patients in the community. First, those who have presented but not been recognised may have a period of increased exposure to health care (e.g. inpatient admission without appropriate infection control). Second, such patients may have a different rate of detection (i.e. they may have either an increased or decreased rate of diagnosis due to the fact that they have recently been determined not to have active TB, which is likely to be setting-specific). Third, these individuals may later be recognized to have active TB once laboratory culture results become available.

By contrast, different components of the diagnostic algorithm that become available close to the time of presentation (i.e. clinical assessment, sputum smear and GeneXpert) are incorporated within the one inter-compartmental transition, as the parameters relating to each stage of diagnosis can be used to calculate a single inter-compartmental flow rate, while there is no important clinical difference between patients who have been detected through different components of the algorithm.

9.3.4 Recovery

Most previous models present a separate compartment for previously treated and spontaneously recovered individuals from the compartments representing individuals who are fully susceptible or previously vaccinated, allowing these individuals to be conferred a different rate of infection. The different approaches to quantifying this modified rate of infection include; assuming no further risk of infection after recovery, assuming all recurrent cases are due to relapse, assuming the same risk modification as for latent infection, assuming the same rate of reinfection as for susceptible individuals, and allowing for both reinfection and relapse after treatment. Therefore, consensus has not been reached as to whether recovered individuals should be conferred no risk, reduced risk, equivalent risk or higher risk than fully susceptible individuals. As a result, we have separated fully susceptible from recovered individuals to allow the greatest model versatility.
9.3.5 Reinfection

Exogenous reinfection following treatment has long been thought to occur in some previously treated immunocompetent patients and has more recently been confirmed with molecular epidemiological techniques. However, the rate with which this occurs, relative to fully susceptible individuals is uncertain. A review of recurrent TB episodes found that the proportion of recurrent cases that were due to subsequent infection – as opposed to relapse with the same strain – varied widely from 0 to 100%. However, the review stressed that relapse and reinfection should be considered separate processes, which is likely to be responsible for the degree of variability in results.

Individual studies from highly endemic regions have found rates of reinfection after treatment to be variable, which likely reflects the degree of continuing exposure after treatment. Our model represents this continued exposure by allowing previously treated individuals to return to a partially susceptible state after completion of effective treatment. As none of the above studies compare risk of infection or disease between cohorts of fully susceptible and previously infected patients, the absolute rate of reinfection after treatment is impossible to directly quantify. Modelling studies based on published epidemiological datasets suggest that although recovered individuals are at increased risk for subsequent disease, this effect is most likely mediated by the population effect of high-risk individuals developing disease more frequently, rather than infection itself leading to increased susceptibility. Therefore, as both the BCG vaccination and past TB disease represent exposure to a TB-family organism, we consider it biologically plausible for both situations to lead to partial immunity, and consider infection rates to be the same among these groups.

Based on the above discussion, we model spontaneously recovering individuals as return to late latency with the equivalent strain. This assumes that those persons remaining within the active disease compartments for three years (the effective sojourn time untreated) remain infected and at risk of future disease.

9.3.6 Reinfection during latency

As immunity following recovery is incomplete, immunity during latency may well be similar, and repeated exposure to infectious TB during latency (i.e. reinfection or superinfection) is likely to occur frequently in highly endemic populations. Some recent TB models incorporate reinfection, either allowing replacement with the infecting strain or the coexistence of multiple strains during latency. Approaches to modelling the rate of reinfection differ, with some models applying the same rate of infection as for those never previously exposed, while others apply a lower rate. Such models have been used to demonstrate that reinfection is likely to have waned in importance during the latter part of the 20th century as TB incidence decreased, implying that reinfection is more important in highly endemic settings.
Applying a lower risk of disease following re-exposure is consistent with animal models demonstrating partial protection from subsequent reactivation following a first infection. Modelling based on epidemiological data from the Netherlands indicates that the risk of developing active TB after reinfection is around 2% per year over the five years following reinfection, by comparison to 5% per year for primary infection. This 0.38 relative risk of reinfection following treatment of past infection observed in the Netherlands is within the confidence intervals of the estimated efficacy of the BCG vaccination. Moreover, a similar risk modification following past infection as after BCG vaccination is biologically plausible, as both situations represent past exposure to a TB-family organism. Therefore, in the absence of evidence for significantly difference risks for these patient groups, we apply the same risk modification to latently infected individuals as for the vaccinated and recovered groups.

9.3.7 Drug resistance

Previous models have considered multiple strains of TB differing by their drug-resistance profile, with the proportion of the population infected with each strain determining the respective force of infection. Earlier models did not include effective treatment of drug-resistant strains, either assuming the resistant strain to be untreatable, or applying a relative reduction in efficacy of standard short-course treatment to the more resistant strain. More recent studies have modelled the emergence of progressively drug-resistant TB, and have further considered the impact of HIV on this process in a setting highly endemic for both infections. Despite this, the modelling literature for drug-resistant TB remains sparse, particularly in relation to programmatic responses to this important problem.

The marked differences in treatment duration and expense associated with MDR-TB regimens make consideration of the response to this strain essential. In developing countries it remains impractical to introduce programmatic responses to XDR-TB before the response to MDR-TB has been considered. Therefore we will not generally be considering programmatic management of XDR-TB as an intervention. Nevertheless it is important to consider the rate at which XDR-TB may emerge under different programmatic responses. Therefore, to best consider the programmatic implications of drug-resistant TB, we present a three strain model; including DS-TB, MDR-TB and XDR-TB.

9.3.8 Default and resistance amplification

By contrast to the situation with previously fully treated patients, most cases of recurrence after default are due to relapse with the same strain. Therefore, our model structure returns defaulting patients to the infectious compartment of the same strain susceptibility, unless amplification occurs.

While our model allows for circulation of MDR-TB strains, we also consider the emergence of new drug-resistance in a strain of TB previously known to be drug-susceptible in response to inappropriate treatment.
Past studies have modelled amplification occurring from the treatment compartment,\textsuperscript{51} and most often consider the rate of amplification to be proportional the rate of treatment of drug-susceptible strains.\textsuperscript{23,33,34,48,52} It has previously been noted that when an amplification pathway is included, the drug-resistant strain no longer requires a basic reproductive number ($R_0$) greater than one for equilibrium to be reached with both strains present.\textsuperscript{53} Other models have allowed amplification to emerge in a constant proportion of patients who were unsuccessfully treated.\textsuperscript{43} As our model structure considers inadequate treatment as a pathway representing default from treatment, we consider amplification to arise at a rate constantly proportional to this rate. With an improved understanding of this process emerging through molecular techniques, this proportion can now be more clearly delineated.\textsuperscript{54,55}

This approach to modelling default and amplification of resistance allows consideration of the programmatic effect of modifying default rates and treatment duration on these processes.

### 9.4 Data used to parameterise the model and time variation

Many parameters used in this model have been sourced from systematic literature reviews and trials based around the world. These apply to general features of TB infection that we have determined are generalizable to other contexts. Many of these values are disease specific but not country specific and include natural history of TB (duration of the latent period, infectious period (with and without treatment), mortality rate when not on therapy, relative infectiousness in different age groups and so on.

Country-specific parameters are required to enable assessment of comorbidities, and interventions being considered. Epidemiological variables of incidence, estimated prevalence and mortality were sourced from WHO reports, whereas many parameters required input from the National Tuberculosis Program database. These include, for example, accuracy of diagnostic algorithm, outcome of treatment, and default rates.

A brief discussion the Philippines-specific parameter values follows:

**Diabetes:** The main modification made to the generic model to specify TB control to the Philippines context was to include diabetes as the primary comorbidity to enable estimation of its contribution to the TB epidemiology. We incorporated it into the model as a risk factor that began in 1990 and gradually increased in prevalence until it was 5.9\% in 2015 as informed by the literature. At an individual level, TB risk begins at age 20 years in the model and is equal between men and women. No ethnic differences were modelled. Diabetes leads to a relative risk of active TB of 3.1 in the model.

Existing TB control programs were incorporated into the model historically; including BCG vaccination, case detection and treatment rates. These involved calibrating the number of
case notifications to the WHO incidence rates: starting from 1990. Treatment success rates provided by the TB control program and WHO of around 85-92% in the last 10 years was also used.

Other data used in the model that is specific to the Philippines is birth rate. These are historical data and were obtained from Unicef (BCG rate), World Bank (birth rate) and WHO (case detection rate, treatment success rate, and TB-related mortality rate). These data are obtained from publicly available databases, and automatically imported into the model using our data input module. The values used are also given in Appendix 2.

### 9.5 Model uncertainty

In the model we allow for uncertainty around the following parameters:

Transmissibility. Defined as the typical number of new cases caused by an undiagnosed, smear positive pulmonary TB cases per annum. For the Philippines the fitted value was 7.9, however we allowed this value to be drawn from a distribution of 5 to 20.

Natural fatality. Here we express the parameter as the proportion of people with smear positive tuberculosis who die over three years if not treated. The fitted value is 0.7, however we allow a range of 0.35 to 0.85.

Duration of active TB. This is the mean duration of untreated active TB cases to remain in the state of active TB before either death or spontaneous cure. The default value is 3 years but we fit from 2 years until 4 years.

### 9.6 Health economic model

A health economic module is linked to the disease dynamic model to estimate costs of TB programs, and TB epidemic corresponding to different levels of funding. We use a generalized logistic function to describe the association between funding and coverage of a TB program. The logistic function takes the following form:

\[
Coverage = A + \frac{Saturation - A}{1 + e^{-B(Cost-Inflection cost)}}^\alpha
\]

where

\[
A = \frac{Saturation}{1 - 2^\alpha}
\]

\[
B = \frac{2^\alpha + 1}{\alpha (Saturation - A)(Unit cost)(Population size)}
\]

\(\alpha\) is a constant.
Logistic functions can incorporate initial start-up costs and allow coverage to saturate at high spending levels, thus better reflecting the program reality. The above function is fitted to available data on coverage levels to estimate costs of TB programs. Conversely, when spending data are known, AuTuMN uses the above equation to estimate the corresponding level of coverage. In doing so, the model can obtain outputs related to both the epidemiological situation and the financial perspective.

![Figure 43. Example of cost-coverage curve.](image)

AuTuMN aimed to use historical data on program costs and coverage levels to derive the relationships between changes in expenditure and changes in model parameters. These data are primarily drawn from high-level national reports, such as NSP reports. Micro-costing frameworks are also used when data are available to better capture program costs. Despite the literature assessing TB interventions, studies still point to a lack of cost data for many key interventions at a country level. When specific cost data were insufficient to calibrate the cost-coverage curve, we used current costs and coverage, and expert opinion regarding coverage saturation point. We also used unit costs of delivering a service to determine the maximum slope of the cost-coverage curve.

Start-up costs were modelled by making the first few years of a new program more expensive than subsequent years. Inflation adjustment is made using CPI from the World Bank figures. The value of USD 1 is set as the value in 2010 and all currency is interpreted in terms of its equivalent value based on the year it was spent. Costs and effectiveness are discounted at 3% for cost-effectiveness analysis.
9.7 Optimisation

The AuTuMN model allows users to choose a set of objectives, such as minimising new infections for a given amount of funding, reaching sustainable development goals for incidence or mortality or to determine targets for the lowest possible spending, minimising TB-related deaths, or minimising long-term financial commitments, and to then determine the optimal resource allocation for meeting those objectives.

For this analysis, the NTP was interested in looking at cumulative incidence of cases of TB from 2016 until 2035 inclusive and comparing outcomes over different programs, to determine the optimal mix of spending.

The way optimisation works is to try to find the best resource allocation to TB programmes that achieves the stated objective. We have used a minimisation algorithm aimed at minimising the model predicted cumulative incident cases of TB from 2017 to 2035. The inputs over which the algorithm searches are the proportion of funds spent on each of the proposed activities.

A feedback loop is in place such that if an intervention leads to fewer cases of active tuberculosis, the costs of treatment and case management activity, offsets the costs of the effective intervention. For a fixed amount of money spent, the proportion allocated to each program can be adjusted, this will lead to a change in epidemiology and may lead (through feedback loops) to different amounts spent in other programs. A minimisation algorithm finds the optimal proportion of those funds spent on each of the programs (Figure 44).

Figure 44. Diagram depicting the events in the optimisation algorithm.
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Appendix 1. List of geographical regions

1  Ilocos Region
2  Cagayan Valley
3  Central Luzon
4A Calabarzon
4B Mimaropa
5  Bicol Region
6  Western Visayas
7  Central Visayas
8  Eastern Visayas
9  Zamboanga Peninsula
10 Northern Mindanao
11 Davao Region
12 Soccsksargen
13 Caraga
CAR Cordillera Administrative Region
NCR National Capital Region
ARMM Autonomous Region of Muslim Mindanao
## Appendix 2. Input parameters

Table A1. Epidemiological input parameters (USD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
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<td>Sensitivity of LTBI test</td>
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<td>Sensitivity of Xpert on smear negative cases</td>
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<td>Relative risk of infection in those already latently infected</td>
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<td>Chest x-ray sensitivity</td>
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<td>program_rate_start_treatment</td>
<td>Inverse of time period that detected patients have to wait before starting treatment</td>
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<td>Rate at which patients who were told they didn't have TB turn up again to the health system</td>
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<td>Rate at which patients change from the low quality to the high quality health system</td>
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<td>Proportion of TB-related deaths not already under treatment that are correctly reported as such</td>
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<td>Proportion of TB-related deaths not already under treatment that are correctly reported as such</td>
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<td>Proportional reduction in adverse outcomes from the treatment support intervention</td>
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<td>program_prop_acf_detections_per_round</td>
<td>Proportion of all undiagnosed cases detected through ACF</td>
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<td>Proportional reduction in duration of MDR-TB treatment with short course treatment (also applies to duration of infectiousness)</td>
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<td>program_prop_treatment_success_shortcourse_mdr</td>
<td>Treatment success under short course MDR-TB regimens</td>
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<td>Probability of treatment success of MDR incorrectly diagnosed as DS</td>
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<td>Probability of treatment success of XDR incorrectly diagnosed as DS</td>
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<td>Probability of treatment success of XDR incorrectly diagnosed as MDR</td>
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<td>Probability of death on treatment if XDR incorrectly diagnosed as MDR</td>
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<td>Duration of a round of ACF</td>
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<td>Number needed to screen to detect one smear-positive case through smear-based ACF</td>
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<td>Number of tests done on persons with diagnoses other than TB for each done on a TB patient</td>
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<td>Best case detection proportion possible under ideal programmatic conditions</td>
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<td>Average household size</td>
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<td>comorb_startage_diabetes</td>
<td>Age at which diabetes is implemented in the model</td>
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<td>comorb_multiplier_diabetes_progression</td>
<td>RR of active TB among diabetics</td>
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<td>RR of active TB among HIV</td>
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### Table A2. Economic input parameters (USD)

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Appendix 3. Review of literature on the epidemiological input parameters

A3.1 Introduction

This document outlines the evidence used in AuTuMN analyses. It consists of a review of the evidence underpinning major model assumptions and the effectiveness of interventions. Currently, the approach to reviewing evidence consists of the authors’ knowledge from previous modelling work combined with further investigation from simple search strategies (e.g. PubMed, GoogleScholar). The list of interventions reviewed will be extended as new interventions are requested by new country applications. As at 8th January 2017, this document includes all evidence relevant to interventions to be implemented in Fiji and the Philippines. In the future, evidence reviews will be further extended with systematic reviews as possible.

A3.2 Epidemiology

A3.2.1 Age differences

Risk of progression to active disease

The natural history of childhood tuberculosis (TB) was described in detail by Marais et al. in their 2004 publication that considered historical publications on this topic in detail. The period from 1920 to 1950 was particularly interesting for the study of the natural history of TB, as chest radiography had become available but effective treatment to modify the natural history had not. Although quantitative estimates of the risk of progression to active disease and subtypes are presented, we prefer the publications by Sloot et al. and Trauer et al., as these two modern estimates are highly consistent with each other.

Infectiousness

Although children are often considered non-infectious, some groups of children are likely to have the potential to transmit infection, including adolescents who more often have adult-type reactivation TB. Other potentially infectious paediatric groups include those with pulmonary cavitation, positive smears for acid fast bacilli (AFBs), laryngeal involvement, widespread pulmonary disease and suspected congenital TB (which tends to be more
extensive). However, younger children, including those with primary pulmonary TB are unlikely to be infectious because of their low bacillary load\(^5\) and inability to generate a sufficiently forceful cough.\(^6\) This is supported by the observation that an infectious adult was consistently identifiable in outbreaks of TB in orphanages and children’s hospitals, while such outbreaks did not occur when only a child was identified with active TB. Eight case reports of transmission from children were identified in a 2001 review, which included four children aged under one (including two with congenital TB), with the others aged 3, 5, 7 and 9. However, the extent of transmission was either limited or incompletely described in most of the six reports considering children aged five and below. Unpublished data recording low rates of tuberculin skin test (TST) conversion in staff of paediatric hospitals also supports this contention.\(^6\)

**Case fatality**

The case fatality rate (a proportion) for children with miliary TB was estimated at 14% in one case series,\(^6\) which is considerably greater than the estimate of 3.5% for all cases from one meta-analysis.\(^6\) However, this is clearly not a direct comparison, as this higher rate is observed only in a subgroup of paediatric cases and may well be offset by lower case fatality rates in other subgroups, such as tuberculous lymphadenitis. Moreover, these estimates consider primarily patients under treatment and so cannot be used to estimate the case fatality of untreated TB (which is of greater relevance to our model parameters).

**Conclusions and recommendations for model implementation**

We use the age-specific progression proportions reported by Trauer \textit{et al.} and are currently undertaking further work to refine these parameters. Although difficult to quantify, we suggest reducing the infectiousness of persons aged under 10, and apply a ten-fold reduction. Case fatality rates will not be modified for age at this stage.

**A3.2.2 Diabetes**

**Burden of disease**

Downloadable estimates for the country-level prevalence of diabetes in 2015 are available from both the World Bank\(^6\) and the International Diabetes Federation’s (IDF) Diabetes Atlas.\(^6\) These estimates are numerically identical and so are presumably obtained from the same source. Many other on-line sources quote prevalence levels that are consistent with the official estimates provided by the World Bank and the IDF. Although the World Health Organization (WHO) also provides country profiles, lists total number of persons with diabetes\(^6\) and has produced a Global Report on Diabetes,\(^6\) no data spreadsheets are available for download. The WHO’s estimates are generally comparable to those of the World Bank, differing by up to around 3% in either direction.
**Effect on TB dynamics**

Diabetes is a major threat to TB control efforts, being responsible for around 15% of the global burden of TB or around one million cases. Potential synergies between efforts to control these two public health threats exist in many low and middle-income settings. A 2014 review of the evidence for the effect of nutritional status found that several different lines of evidence suggest that under-nutrition is associated with a markedly increased risk of tuberculosis. Increased weight is protective, with a dose-response relationship that persists as far as a BMI of 30kg/m², although the effect of increased weight beyond this level is uncertain. Although increased weight is strongly associated with diabetes, diabetes is also an independent risk factor for tuberculosis, with a meta-analysis indicating a 3.11-fold increased risk (2.27 – 4.26).

**Conclusions and recommendations for model implementation**

For estimates of the global burden of diabetes, we use the IDF Diabetes Atlas downloadable spreadsheet, as this source provides widely accepted estimates that are current for 2015 alongside a range of other indicators relevant to diabetes.

**A3.2.3 HIV**

**Effect on TB dynamics**

HIV is considered as the most important predisposing factor for developing TB. In patients co-infected with HIV and TB, the risk of developing active TB varies according to HIV prevalence and is estimated to be 20 - 30 times higher than that in HIV-negative TB patients. Countries with a generalised HIV epidemic have a TB incidence rate ratio (IRR, the relative risk of TB developing in HIV-infected persons compared to that in HIV-uninfected persons) of 20.6. Countries with concentrated HIV epidemics (HIV prevalence between 0.1% and 1%) have a TB IRR of 26.7, and countries with a low prevalence of HIV infection (HIV prevalence < 0.1%) have a TB IRR of 36.7.

Recent evidence also suggests that TB patients co-infected with HIV may be less infectious than those without HIV. A prospective cohort study of over 800 household contacts of 58 HIV-infected and 116 matched HIV-negative index cases with newly diagnosed smear-positive or culture-positive pulmonary TB found that HIV-positive index cases were half as likely as HIV-negative index cases to transmit TB to their close contacts, even after controlling for the degree of smear positivity. Similarly, in another prospective cohort study of 360 contacts of 86 patients with smear positive pulmonary TB, contacts of HIV-infected were found to have a significantly decreased risk of TST conversion in index cases, with an odds ratio of 0.24 (95% CI, 0.09 to 0.65). Less frequent cavitary TB, lower sputum bacillary burden, weakened cough with more severe disease, and greater social isolation are thought to explain for the decreased transmission of TB by HIV-infected patients.
HIV has also been found to affect the duration of TB infectiousness. The direction of such effects depends on access to care and rapidity of diagnosis. Where HIV-infected individuals have access to care and are enrolled in a care program and/or where active TB case finding exists, the mean duration of infectiousness of TB is found to be shorter than that of TB in persons without HIV due to a combination of a higher rate of progression, earlier presentation to the health care system, and more rapid diagnosis. In a cross-sectional and longitudinal cohort study of over 1,600 South African gold miners, Corbett et al. found that the mean duration of infectiousness (defined as smear positivity) in HIV-positive individuals with TB (2 months) was significantly shorted than in HIV-negative TB patients (14 months). In contrast, in patients with poor access to care and/or where active case finding is absent, the duration of TB infectiousness is longer in HIV-positive patients than in HIV-negative patients. A study in slum community in South Africa estimated the duration of infectiousness in TB/HIV patients to be 12 months compared to 9 months in TB patients without HIV infection.

HIV also increases the mortality rates associated with TB. A prospective 12-year study in San Francisco showed that the TB case-fatality rate was significantly higher for patients co-infected with HIV than for HIV-uninfected patients (22% and 10%, respectively) in the era prior to ART and that the higher TB case-fatality rate for HIV-infected patients persisted even after the availability of ART. In resource-limited settings, the reported case fatality rates prior to the availability antiretrovirals were extremely high: in the Central African Republic, the case-fatality rate was as high as 58% for HIV-infected patients, compared to 20% for HIV-uninfected patients at 24 months after the initiation of TB treatment.

### A3.3 TB interventions

#### A3.3.1 Support for patients under treatment

**Background and introduction to DOT**

Direct observation of patients taking treatment has been the mainstay of ensuring high treatment success rates since 1993. A systematic review that identified eleven trials comparing DOT to self-administered treatment found no significant effect of DOT on improving treatment outcomes (RR for cure 1.08, 95% CI 0.91 to 1.27), although outcomes were generally poor in both treatment and control arms. Daily DOT appeared slightly more effective (RR for cure 1.15, 95% CI 1.06 to 1.25), depending on the frequency of contact in the control arm. Little differences were found between treatment administered by health personnel, community workers or family members. Despite this weak evidence base, the WHO continues to recommend DOT as the mainstay of treatment, for a number of reasons, including the absence of longer-term treatment outcomes in the above studies, evidence for high rates of adverse outcomes in the absence of DOT from observational studies and the concern of amplification of drug resistance. Therefore, DOT remains widespread and forms the basis for supporting patients on treatment.
Treatment support for patients with TB

A non-randomised study of patients with smear-positive pulmonary TB in southern Thailand compared the proportions of patients not practising actual DOT (i.e. watching the patient swallow drugs) between those supported by health personnel, community members and family members. The proportions not practising actual DOT (e.g. preparing drugs for the patient, staying with the patient during drug intake or reminding the patient about treatment) in this setting were 11% health personnel, 23% community members and 35% family members. Although this evidence suggests that community and family members are less likely to provide actual DOT to patients, the results are subject to confounding, likely to be setting-specific and cannot be directly translated to rates of adverse treatment outcome.

A cluster-randomised trial of patients with smear-positive pulmonary TB in Senegal considered a multi-factorial intervention aimed to improve treatment adherence. The intervention incorporated four components, namely: improved communication and counselling between health personnel and patients, decentralised treatment to remote health posts and community health workers, allowing patients to choose their DOTS supporter and reinforcing supervision of local treatment from the district health centre. This intervention was compared to a control group who underwent treatment as usual. With this strategy, outcomes for the intervention group (n=778) were 87.7% treatment success (83.4% cure, 4.3% completion), 5.5% default, 3.7% transferred out, 1.5% failure and 1.5% death, while for the control group (n=744), outcomes were 75.7% treatment success (69.9% cure, 5.8% completion), 16.8% default, 3.4% transferred out, 0.8% failure and 3.4% death. Therefore, in the intervention group, for those evaluated (i.e. not those transferred out), death occurred in 1.6%, other adverse outcomes in 7.3% and success in 91.1%, while for those evaluated in the control group, death occurred in 3.5%, other adverse outcomes in 18.2% and success in 78.3%. By contrast to the study in Thailand, patients supervised by family members had higher treatment success rates than those supervised by health personnel (and relatively few [9.1%] were supervised by a community health worker or community member).

Evidence from areas of research outside of TB control

More generally, a systematic review of RCTs considering the effect of interventions to support patients to adhere to any medication (i.e. not limited to TB) was undertaken by Haynes et al. in 1996. This review found 13 studies that considered 15 interventions to improve medication adherence, but interventions were too disparate for results to be pooled. The authors concluded that both adherence and treatment outcomes can be improved by certain (usually complex) interventions, but that further research is needed to fully define the optimal such interventions for a given setting.
Conclusions and recommendations for model implementation

To summarise, despite the lack of evidence for DOT and the unclear effect of the DOT provider, it is likely that carefully constructed, multifactorial interventions to support patients on treatment are effective in improving patient adherence and treatment outcomes. For model implementation, based on the study from Senegal, we suggest a reduction in death on treatment to 1.6% and a reduction in other adverse outcomes to 7.3% (or if this is not considered feasible, a 0.457-fold modification to rates of death on treatment and a 0.401-fold modification to rates of other adverse outcomes on treatment could be considered).

A3.3.2 GeneXpert

Time to treatment commencement for drug-susceptible TB

For patients with drug-susceptible TB, time to treatment initiation may be decreased by comparison to other approaches. The large multi-centre study considering the implementation of GeneXpert across six countries in three continents found a median time to “detection” of zero days for GeneXpert, one day for smear microscopy, 16 days for liquid culture and 30 days for solid culture. However, time to treatment commencement for smear-negative, culture-positive patients decreased from a median 56 days to five days, while for smear-positive patients a non-significant reduction from four to two days occurred.

A study in Johannesburg (641 presentations with possible TB, 69% HIV-infected) found delays to treatment of zero days for GeneXpert, 14 days for clinical or radiological diagnoses and 144 for culture-based diagnoses. Similarly, a study from Saudi Arabia found results for both GeneXpert and smear microscopy were available on the same day, while culture took a median 22 days for results to be available.

Time to treatment commencement for MDR-TB

Roll out of GeneXpert technology has been demonstrated to reduce the time taken for patients to be commenced on treatment for MDR-TB. For example, time to commence treatment decreased from a median 40 days to seven days in Latvia. Similarly, in Cape Town, GeneXpert also decreased time to treatment commencement for MDR-TB by around a month, with median time to commencement falling from 42 to 17 days.

Diagnostic accuracy for the presence of TB

In the large multi-centre study introduced above, pooled results across all centres gave a 98.3% sensitivity for smear-positive TB, 76.9% for smear-negative, culture-positive TB and a specificity of 99.0%. This was associated with a reduction in the proportion of patients with smear-negative, culture-positive disease who remained untreated from 39.3% to 14.7%. These estimates are close to those derived from a 2014 Cochrane review of 27 studies.
(including the study described above), which reported a pooled sensitivity of 98% for smear-positive TB, 67% for smear-negative, culture-positive TB and a specificity of 99%.\textsuperscript{82}

**Yield of GeneXpert**

Studies that investigated the yield of GeneXpert are scarce. In a study conducted among 393 household contacts of pulmonary TB cases in Ethiopia, GeneXpert was estimated to have a yield of 35.9% (14 of 39 presumptive TB cases were confirmed to be TB by GeneXpert). In this study, the number of contacts needed to screen (NNS) to find a single case of TB while using GeneXpert as a diagnostic test was 25; and the number of presumptive TB cases needed to test (NNT) to diagnose a single case of TB while using GeneXpert was 3. In another study in 245 suspected TB cases (205 suspected pulmonary, 40 suspected extrapulmonary TB) in Pakistan, the yield of GeneXpert was estimated to be 45.3%.

**A3.3.3 Promoting awareness**

Cultural, environmental and politico-economic factors are known to be important in driving the TB epidemic, which is more often conceptualised from a biological perspective.\textsuperscript{83} Communication interventions for tuberculosis control have the potential to markedly improve rates of presentation for care, through reduction in stigma, improved understanding of the condition and greater community awareness. Countries such as Peru and Vietnam have used improved awareness as a cornerstone of their control efforts.\textsuperscript{84-86} Although a systematic review was registered in 2014 to consider the effect of mass media interventions on TB knowledge, attitudes and awareness, health care seeking behaviour and health service utilisation, no results are yet available from this study.\textsuperscript{87} Moreover, there are a number of critical considerations to bear in mind in estimating the likely effectiveness of such interventions, including tailoring messages to the context and culture in which they are provided, and ensuring that curative care of a sufficient standard is available to the additional persons presenting for care.

Studies investigating the impact of awareness programs on TB have reported variable results, but have consistently found effects to increase rates of clinic presentation, increase detection of new active and latent cases, and reduce treatment abandonment rate. In a study conducted in an indigenous community with high TB burden in Canada in the context of passive case finding, Alvarez et al. found that the number of people presented themselves to the clinic increased by 92% during the four-month community-wide awareness campaigns, compared to the previous periods without the campaign (increased from an average of 26 people per month to 50 per month).\textsuperscript{15} This study also found that door-to-door campaign increased the number of new LTBI cases by 34%, and increased the number of newly diagnosed active TB cases by 29.5%. In Columbia, Jaramillo reported that a six week mass media-based health education (radio, television and newspaper) increased the number of smears processed by laboratories by 64% and increased the number of smear-positive pulmonary TB cases detected and notified by 52%.\textsuperscript{16} In both the studies by Alvarez and
Jaramillo, the effects of the program were not sustained beyond the period of the intervention. A brief report of an intervention in Odisha (India) involving health worker education, van-mounted loudspeakers and community-based health camps found an increase in the number of detections compared to before the intervention.\textsuperscript{17} Although the increase in the total number of TB diagnoses made was not reported, the number of persons screened increased by 87.8% and the number of smear-positive diagnoses made increased by 10.8% (figures which seem consistent with those reported by the studies discussed above).

**Conclusions and recommendations for model implementation**

The extent of the interventions considered by the countries we are currently engaged with (particularly the Philippines) is probably more equivalent to that described by Jaramillo than to that described by Alvarez, which involved extensive community engagement and mobilisation. Therefore, we consider that mass media-based interventions can increase rates of presentation 1.52-fold compared to the baseline. The caveats described above should be borne in mind, as well as the consideration that interventions that are continued for longer periods of time than those studied above may lose their effectiveness with time.

A3.3.4 Preventive therapy

**Isoniazid preventive therapy (IPT) for DS-TB in HIV-negative patients**

A Cochrane review of IPT was undertaken in 1994, with the 2003 update finding no further citations, such that the authors do not plan to update this review again. The review was limited to randomised trials of appropriately dosed IPT provided for at least six months with follow-up for at least two years. It found IPT to be associated with a risk ratio for active TB of 0.40 (95%CI 0.31 to 0.52).\textsuperscript{88} When six and twelve month courses were considered separately, the respective risk ratios were 0.44 and 0.38, although this difference was not statistically significant. Rates of hepatotoxicity for these two regimen durations were 0.36% and 0.52% respectively. For model implementation, it should be noted that all but one of the studies included in this review analysed by intention-to-treat. Therefore, this estimate does not require a reduction for patient compliance.

**Sensitivity of diagnostics for latent infection**

At least seven meta-analyses have estimated the sensitivity of the tuberculin skin test in diagnosing TB, with results ranging from 0.70 to 0.82.\textsuperscript{89} While meta-analytic estimates for the sensitivity of QuantiFERON range from 0.66 to 0.83 and of T-SPOT from 0.62 to 0.90. Therefore, there is no evidence that any one of these tests has superior sensitivity to that of the others. As all have a sensitivity of around 0.7 to 0.8, a sensitivity of 0.75 is a reasonable estimate for model implementation.
Proportion of close contacts infected

A systematic review and meta-analysis of contacts of patients with active TB found that, in low-middle income countries, 3.1% of all contacts had active TB and 51.5% had latent TB infection. However, this study did not report the number of infected contacts per case of active disease, which is likely to vary based on setting.

Conclusions and recommendations for model implementation

The first step in model implementation is to determine the average household size for the population of interest and to subtract one from this value to estimate the number of close contacts per case of TB. Next, this is multiplied by the proportion of these contacts who were infected (i.e. 51.5% from the evidence summarised above) and then by the sensitivity of the diagnostic test used (i.e. 0.75) and by the effectiveness estimate for IPT (i.e. 60%). This number of individuals are then moved from the early latent compartment to the susceptible vacinated compartment.

A3.3.5 Active case finding

Introduction

Active case finding (ACF) through chest radiography of asymptomatic persons was implemented extensively in developed country settings the 1930s to 1960s. Although this strategy was successful in detecting a significant number of previously undiagnosed cases, the financial expense and logistics were considerable. From the early 1960s, the paradigm began to change in the light of studies finding that most patients with undiagnosed TB had had symptoms for some time and had often sought care previously. These studies indicated that few patients would be missed by restricting ACF to those with symptoms, such as cough for two weeks or more. Therefore, the focus shifted to health system strengthening and ACF was thought to be unnecessary, particularly at a time when TB was thought to be becoming a minor global health problem. Since then, a range of ACF strategies have been studied, although few have been associated with prevalence surveys that could shed light on the proportion of undiagnosed cases that were detected.

DETECTB

One of the most important studies in ACF was DEECTB, which was a cluster randomised study of two alternative approaches to ACF undertaken by Corbett et al. in Harare from 2006 to 2008. This study compared six rounds of ACF at six-monthly intervals, either through the presence of a mobile van in the community for five days (manned by three lay workers equipped with loudspeaker and leaflets) or through door-to-door enquiry at the household level (with each household approached once per ACF round by two teams of three lay workers). Two sputum specimens were collected from individuals with a history of cough for two weeks or longer and analysed with smear microscopy but not culture. The primary
outcome was the yield of smear-positive TB through the two screening methods, while the secondary outcome was the change in culture-positive TB through prevalence surveys performed with the first and last ACF round. The primary outcome detected 255 and 137 in the van and door-to-door interventions respectively, for a cumulative yield of 4.27 and 2.38 smear-positive cases per thousand population over the six rounds of intervention (or 0.71 and 0.40 per round). Given that prevalence was 4.0 smear-positive cases per 1,000 population at the start of the intervention, that 2.3 smear-positive cases per 1,000 per population before the fifth round and that the authors assumed a linear decrease in burden over the study period, the average prevalence of smear-positive disease over the course of the study would have been 3.1 per 1,000. On average, 0.72 smear-positive cases were diagnosed in each round of van-based ACF and 0.40 cases in each round of door-to-door based ACF, which represents 23.2% and 12.8% of undiagnosed cases respectively.

Other recent studies

Sekandi, et al. reported on a single round of ACF undertaken in a peri-urban setting of around 10,000 persons, finding 33 additional cases of smear-positive TB through an algorithm of symptom screening for chronic cough and smear microscopy.\textsuperscript{92} This study was limited by comparison to DETECTB, in that no prevalence surveys were undertaken, such that the proportion of all undiagnosed cases that this represents is difficult to estimate. (Given Uganda’s prevalence of TB of around 150 to 200 per 100,000 with around 60% of notified cases smear-positive, the smear-positive prevalence is likely to be around 100 per 100,000. This suggests at most 10 undiagnosed such cases in a population of 10,000, although the authors acknowledge that the prevalence is likely to be higher in their slum setting.\textsuperscript{93})

Conclusions and recommendations for model implementation

For smear-based ACF, we suggest that van-based ACF implemented with screening rounds at six-monthly intervals can be expected to diagnose around 23.2% of smear-positive cases not previously diagnosed. For GeneXpert-based strategies, the intervention could also be applied to the undiagnosed smear-negative population, but should be multiplied by the sensitivity of GeneXpert for smear-negative disease (i.e. 67%) to give an overall proportion diagnosed of 15.6%. As these strategies generally commence with enquiry as to the presence of cough, no effect on extrapulmonary disease can be expected.
Appendix 4. Calculations of cost inputs

A4.1 BCG vaccination

Data on the unit cost of BCG vaccination in the Philippines are lacking; as such, data reported in the literature were used. A unit cost of US $2.13 was used in the analysis as reported by Ditkowsky and Schwartzman in South Africa.\textsuperscript{93} This is consistent with Trunz et al. who conducted a systematic review of studies that investigated the cost-effectiveness of BCG, and found that the unit costs of BCG ranged from US $2-3 in low- and middle-income countries.\textsuperscript{94} Of note, the unit costs in these studies were estimated from a health provider perspective, and comprised the costs of vaccine production, distribution, administration, personnel and clinic visits. As BCG vaccination is a well-established program that has been implemented for a long time with high coverage levels in the Philippines, start-up cost is assumed to be zero.

A4.2 Preventive for children contacts

The unit cost of IPT in the Philippines was calculated to be US $16 using a micro-costing approach based on country-specific data. This program comprises the following cost ingredients (Table A3):

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<th>Cost component</th>
<th>Unit cost (Peso) (/person/treatment course)</th>
<th>Unit cost (USD) (/person/treatment course)</th>
</tr>
</thead>
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</tr>
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<td>TST screening</td>
<td>57</td>
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<td>Medical supplies</td>
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<td>0.2</td>
</tr>
<tr>
<td>Medical personnel (HCW)</td>
<td>59</td>
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</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>795</strong></td>
<td><strong>16</strong></td>
</tr>
</tbody>
</table>

The country is considering changing to 3HP regimen; however cost data on this new regimen are currently lacking. Although the acquisition cost of rifapentine is considered to be more expensive than that of isoniazid, the duration of 3HP is shorter than isoniazid alone regimen (3 months versus 6 months) and the dosing interval of the new regimen is longer (weekly versus daily), will compensate for the increased acquisition drug cost to some extent. Therefore, unit cost per person of 3HP is assumed to be equal to that of isoniazid alone regimen (USD 16). Of note, the unit cost can be adjusted when country-specific data become available.
The current level of coverage of the program is only 14% and the NTP aims to achieve a high coverage of 90% in 2020. To achieve such a high level of coverage, significant start-up cost will be needed. Using country-specific data, this cost was calculated to be US $265,450 as shown in Table A4.

Table A4. Start-up cost of IPT for children contacts

<table>
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<tr>
<th>Cost component</th>
<th>Cost (Peso)</th>
<th>Cost (USD)</th>
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<tr>
<td>Training for HCW</td>
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<td>36,000</td>
</tr>
<tr>
<td>One-off training for warehouse personnel</td>
<td>129,600</td>
<td>2,600</td>
</tr>
<tr>
<td>Upgrade warehouse facilities</td>
<td>9,500,000</td>
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</tr>
<tr>
<td>Hiring additional warehouse personnel</td>
<td>9,720,000</td>
<td>194,000</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>21,150,000</strong></td>
<td><strong>424,350</strong></td>
</tr>
</tbody>
</table>

A4.3 Short-course regimen for MDR-TB

In the Philippines, a 20-month regimen is currently recommended for all MDR-TB cases. The NTP of the Philippines is considering changing to a shorter 9-month regimen in around 90% of MDR-TB cases (of note, it is estimated that around 10% of MDR-TB cases are clinically not eligible for short-course regimen). Using a micro-costing approach, the cost per patient of this program was calculated to be US $2,927 as follows. Of note, this calculation was based on the assumption that the patient would not require hospitalisation, surgery, and special diagnostic assistance (such as CT scan, audiometry, and ECG) which are not part of the routine care for MDR-TB patients in the country.

The start-up cost of this program was estimated to be 1.14 million USD (57 million Peso), which consists of the costs of 15-day training program for treatment centres (7 million Peso) and upgrading regional centres to enable delivery of MDR-TB treatment (50 million Peso).
Table A5. Cost components of short-course regimen for MDR-TB

<table>
<thead>
<tr>
<th>Cost component</th>
<th>Unit cost per test (Peso)</th>
<th>Frequency per entire course of treatment</th>
<th>Unit cost per patient per course of treatment (Peso)</th>
<th>Unit cost per patient per course of treatment (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening and baseline laboratory test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gene-Xpert</td>
<td>1,308</td>
<td>1</td>
<td>1,308</td>
<td>26</td>
</tr>
<tr>
<td>DSSM</td>
<td>200</td>
<td>2</td>
<td>400</td>
<td>8</td>
</tr>
<tr>
<td>TB culture</td>
<td>1,500</td>
<td>1</td>
<td>1,500</td>
<td>30</td>
</tr>
<tr>
<td>DST</td>
<td>2,000</td>
<td>1</td>
<td>2,000</td>
<td>40</td>
</tr>
<tr>
<td>LPA</td>
<td>3,500</td>
<td>1</td>
<td>3,500</td>
<td>70</td>
</tr>
<tr>
<td>X-ray</td>
<td>250</td>
<td>1</td>
<td>250</td>
<td>5</td>
</tr>
<tr>
<td>Blood chemistry</td>
<td>2,500</td>
<td>1</td>
<td>2,500</td>
<td>50</td>
</tr>
<tr>
<td><strong>Laboratory monitoring</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSSM</td>
<td>200</td>
<td>9</td>
<td>1,800</td>
<td>36</td>
</tr>
<tr>
<td>TB culture</td>
<td>1,500</td>
<td>9</td>
<td>13,500</td>
<td>271</td>
</tr>
<tr>
<td>X-ray</td>
<td>250</td>
<td>2</td>
<td>500</td>
<td>10</td>
</tr>
<tr>
<td>Blood chemistry</td>
<td>2,500</td>
<td>2</td>
<td>5,000</td>
<td>100</td>
</tr>
<tr>
<td><strong>Drug regimen</strong></td>
<td>47,394</td>
<td>1</td>
<td>47,394</td>
<td>951</td>
</tr>
<tr>
<td><strong>Patient enablers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily patient allowance</td>
<td>3,900</td>
<td>9</td>
<td>35,100</td>
<td>704</td>
</tr>
<tr>
<td>Milestone incentives</td>
<td>5,000</td>
<td>1</td>
<td>5,000</td>
<td>100</td>
</tr>
<tr>
<td>Patient food package</td>
<td>2,600</td>
<td>9</td>
<td>23,400</td>
<td>470</td>
</tr>
<tr>
<td><strong>Medical supplies</strong></td>
<td>150</td>
<td>9</td>
<td>1,350</td>
<td>27</td>
</tr>
<tr>
<td><strong>Patient education</strong></td>
<td>75</td>
<td>9</td>
<td>675</td>
<td>14</td>
</tr>
<tr>
<td><strong>Ancillary medicines</strong></td>
<td>277.78</td>
<td>3</td>
<td>833.33</td>
<td>17</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td>146,000</td>
</tr>
</tbody>
</table>

A4.4 Gene X-pert

The cost of performing one X-pert test is estimated to be US $30.26 (1,508 Peso). This includes the costs of operating an X-pert machine (800 Peso), cartridge (500 Peso), sputum cup (8 Peso) and transportation of specimens (200 Peso). As GeneXpert replaces smear microscopy, we deduct the cost of performing one smear microscopy ($4) to calculate the unit cost of
GeneXpert replacing smear microscopy as primary diagnostic test ($26). Rolling-out GeneXpert will require substantial start-up cost, which is estimated to be 11.6 million USD (577 million Peso) for a period of 3 years. This includes the following activities:

Table A6. Start-up cost of Gene X-pert program

<table>
<thead>
<tr>
<th>Cost component</th>
<th>Cost per unit (Peso)</th>
<th>Quantity</th>
<th>Total cost (Peso)</th>
<th>Total cost (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purchase of X-pert machines</td>
<td>150,000</td>
<td>2,814</td>
<td>420,750,000</td>
<td>8,442,000</td>
</tr>
<tr>
<td>Purchase of computers</td>
<td>50,000</td>
<td>2,814</td>
<td>140,700,000</td>
<td>2,823,000</td>
</tr>
<tr>
<td>Purchase of internet routers</td>
<td>1,000</td>
<td>2,814</td>
<td>2,814,000</td>
<td>56,460</td>
</tr>
<tr>
<td>Purchase of uninterruptible power supplies (UPS)</td>
<td>2,000</td>
<td>2,814</td>
<td>5,628,000</td>
<td>113,000</td>
</tr>
<tr>
<td>GXAlert</td>
<td>7,000,000</td>
<td>1</td>
<td>7,000,000</td>
<td>140,450</td>
</tr>
<tr>
<td>Training</td>
<td>18,000</td>
<td>1</td>
<td>18,000</td>
<td>361</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td><strong>577,000,000</strong></td>
<td><strong>11,575,226</strong></td>
</tr>
</tbody>
</table>

A4.5 Systematic screening in high risk groups

In the context of the Philippines, systematic screening consists of active case finding (ACF) using mobile clinics in prisoners, urban and rural poor, and intensified case finding using GeneXpert among PLHIV and diabetes who visit health care clinics for regular check-ups.

Costs calculations for ACF are based on the standard diagnostic algorithm, in which a chest x-ray is performed on all high risk patients identified and GeneXpert is subsequently performed for those who have positive x-ray results. Using results from a study that investigated ACF in the province of Palawan in the Philippines, we calculated the proportion of x-ray screens that are followed by GeneXpert in prisoners and rural poor to be 38.5% and 16%, respectively. We multiplied these proportions with the unit cost of performing one GeneXpert analysis of PHP 1,308 (PHP 800 operating an X-pert machine + PHP 500 cartridge + PHP 8 sputum cup) to calculate the unit cost of GeneXpert for prison and rural poor. The unit cost per patient of ACF program in prison is calculated to be PHP 754 ($15), which is as a sum of the unit cost of chest x-ray (PHP 250) and GeneXpert (PHP 504). The unit costs per patient of ACF rural poor communities are calculated as follows (Table A7). It was advised by the country team that the unit cost of ACF for urban poor should be lower than that of rural poor; and we assumed it to be 30% lower. As shown in Table A7 below, unit cost of ACF in rural poor was estimated to be $28; therefore the unit cost of ACF in urban poor was estimated to be $20.
Country-specific cost data for intensified case finding are lacking. We assumed that the unit cost of this activity to be $24 as reported in the literature.\textsuperscript{95}

Table A7. Unit cost of active case finding in urban and rural poor communities

<table>
<thead>
<tr>
<th>Cost component</th>
<th>Cost (Peso)</th>
<th>Cost (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest x-ray</td>
<td>250</td>
<td>5</td>
</tr>
<tr>
<td>GeneXpert</td>
<td>209</td>
<td>4</td>
</tr>
<tr>
<td>Patient incentive</td>
<td>300</td>
<td>60</td>
</tr>
<tr>
<td>Car hire</td>
<td>58</td>
<td>1</td>
</tr>
<tr>
<td>Doctor from community clinic</td>
<td>5</td>
<td>0.1</td>
</tr>
<tr>
<td>Community presentation-Barangay-level meetings</td>
<td>37.5</td>
<td>0.75</td>
</tr>
<tr>
<td>Community presentation-posters and printing materials</td>
<td>8</td>
<td>0.2</td>
</tr>
<tr>
<td>House-to-house visit: transportation and meals</td>
<td>130</td>
<td>2.6</td>
</tr>
<tr>
<td>House-to-house visit: screening forms</td>
<td>2.5</td>
<td>0</td>
</tr>
<tr>
<td>Laboratory request form</td>
<td>0.44</td>
<td>0</td>
</tr>
<tr>
<td>Purified protein derivative</td>
<td>14</td>
<td>0.28</td>
</tr>
<tr>
<td>Meals for ACF team</td>
<td>64</td>
<td>1.3</td>
</tr>
<tr>
<td>Xpert operator</td>
<td>33</td>
<td>0.66</td>
</tr>
<tr>
<td>Xray operator</td>
<td>33</td>
<td>0.66</td>
</tr>
<tr>
<td>Nurse</td>
<td>33</td>
<td>0.66</td>
</tr>
<tr>
<td>Documented</td>
<td>55</td>
<td>1</td>
</tr>
<tr>
<td>Project team leader</td>
<td>133</td>
<td>2.7</td>
</tr>
<tr>
<td>Post-activity evaluation</td>
<td>37.5</td>
<td>0.75</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>Rural poor: 1,401</strong></td>
<td><strong>28</strong></td>
</tr>
</tbody>
</table>

The total start-up cost for ACF to be implemented in each of the urban and rural population is estimated to be PHP 3.5 million ($70,700) for a period of 3 years. This start-up cost consists of purchase of fully-equipped mobile vans (PHP 3 million), consultation meetings (PHP 6,700), planning workshop (PHP 10,000), and capacity-building training for implementer (PHP 9,000). We assumed no start-up cost required for intensified case finding.
References

7. UNAIDS. HIV and AIDS estimates. 2015.


84. Fernandez Llanos-Zavalaga, Patricia Poppe, Youssef Tawfik, Cathleen Church-Balin. The role of communication in Peru’s fight against tuberculosis. 2004.


