VERSION 2

Bending the Curve

ENDING TB in the WHO South-East Asia Region

World Health Organization
Regional Office for South-East Asia

Bending the Curve - Ending TB in the WHO South-East Asia Region

ISBN: 978-92-9022-574-4

Suggested citation. Bending the Curve - Ending TB in the WHO South-East Asia Region: World Health Organization, Regional Office for South-East Asia; 2017. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

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Abbreviations

AIDS	:	acquired immune deficiency syndrome
ART	:	antiretroviral therapy
ARV	:	antiretrovirals
DOT	:	directly observed treatment
DOTS	:	directly observed treatment, short-course
DRS	:	drug resistance survey
DR-TB	:	drug-resistant tuberculosis
DST	:	drug susceptibility testing
GAVI	:	Global Vaccine Alliance
GF	:	The Global Fund to Fight AIDS, Tuberculosis and Malaria
rGLC	:	regional Green Light Committee
HBC	:	high-burden (TB) country
HRD	:	human resource development
HSS	:	health system strengthening
IC	:	infection control
IPT	:	isoniazid preventive therapy
ISTC	:	International Standards for TB Care
LBC	:	low-burden (TB) country
LTBI	:	latent TB infection
MDGs	:	Millennium Development Goals
MDR-TB	:	multidrug-resistant tuberculosis
NGO	:	nongovernmental organization
PMDT	:	programmatic management of drug-resistant tuberculosis
PPM	:	public-private mix
PTB	:	pulmonary TB
RR-TB	:	rifampicin-resistant TB
SDGs	:	Sustainable Development Goals
SEA	:	South-East Asia
SEAR	:	South-East Asia Region (of WHO)
SLD	:	second-line anti-TB drugs
TA	:	technical assistance
TB	:	tuberculosis
UHC	:	universal Health Coverage
WHA	:	World Health Assembly
WHO	:	World Health Organization
XDR-TB	:	extensively drug-resistant TB

Disclaimer

The results from the modelling work being conducted by WHO SEARO in collaboration with international modelling experts from Imperial College, London, Public Health Foundation of India, Delhi and health economists from eSYS Development pvt Limited, Sydney are being used in the document to demonstrate the feasibility of certain interventions to bend the TB curve. Certain assumptions have been modelled to assess the impact of seven interventions on the TB incidence. The results have been derived after consolidating results of all 11 Member States. The reader's attention is drawn to the following points while interpreting the results:

1. The incidence rate trends in the baseline scenario are projected as per current trends in decline noted in past few years. However, the extent of decline that could be achieved has certain levels of uncertainty going into the future.
2. For mortality, an increase in absolute numbers may be observed in the baseline scenario for certain countries because of increase in population size. However, the mortality rates (per 100 000 population) could still be decreasing for all countries even with current efforts Interventions included in the package 'strengthening existing system' are essential building blocks for any further intervention that needs to be undertaken for improving programme performance. The effect of subsequent packages is cumulative over this package and would not be observed if the basic services are not strengthened. Specifically it is important for countries to adopt new, rapid diagnostics as this will be essential to reduce diagnostic delays, diagnose resistance early for appropriate treatment and improve the efficiency of the Accelerated Case Finding package.
3. The preventive therapy starting in 2025, as used in the model, remains hypothetical. The current available tool, such as isoniazid preventive therapy, is useful for a specific target population but not applicable for the general population. The hypothetical measures could involve a range of possible interventions, including: a transmission-blocking vaccine; infection control in the household and in the community (in addition to existing facility-based infection control practices); and use of a preventive therapy regimen, coupled with a biomarker test to identify those TB infections at greatest risk of development of active disease.
4. The modelling in its current form does not explicitly take into account the impact of other nonprogrammatic interventions such as strengthening social security, improving nutrition, housing conditions, awareness generation activities and addressing co-morbidities that also have an impact on TB epidemiology and programme performance.

Foreword

Tuberculosis (TB) remains the largest cause of death and suffering due to any communicable disease among the most productive groups in the World Health Organization's South-East Asia Region (SEAR). Nearly half of global TB cases emerge in this Region, which is home to one fourth of the total population. It is estimated that TB and TB-HIV co-infection caused 3 deaths every 2 minutes in the Region in 2015. These deaths were entirely preventable with proper treatment of all TB patients, including those infected with drug-resistant strains.

The WHO End TB strategy and corresponding Regional Strategic Plan to end TB targets reductions to the extent of 90% in deaths, and 80% in TB incidence by 2030. This is in alignment with the Sustainable Development Goals (SDGs) to which all countries have committed.

Ending TB is an essential step towards securing good health in Member States because TB plays such an overwhelming role in mortality and lost productive years. We know with certainty that we can bend the TB curve even with the tools available to us; and if we rightfully invest in research, we can end TB by 2030 if not before.

However, the current pace of response needs to be accelerated for achieving the targets of ending TB. To achieve this, the South-East Asia Regional Office of WHO along with Member States and partners are making concerted efforts. A Ministerial Meeting with high-level participation from the 11 Member States of the WHO South-East Asia Region was held on 15–16 March 2017 in New Delhi, India. The purpose of the meeting was to ensure an urgent and extraordinary plan of action to accelerate the effort of TB control towards achievement of WHO End TB targets aligned with SDGs through the highest level of political commitment, and increased funding. The meeting was attended by nine Health Ministers and two senior representatives from Member States along with several partners that included heads of three international agencies. The meeting concluded with the issuance of a "Call for Action" for Member States to accelerate response for ending TB and the allocation of needed resources. WHO SEARO, on its part, has made ending TB one of its flagship projects.

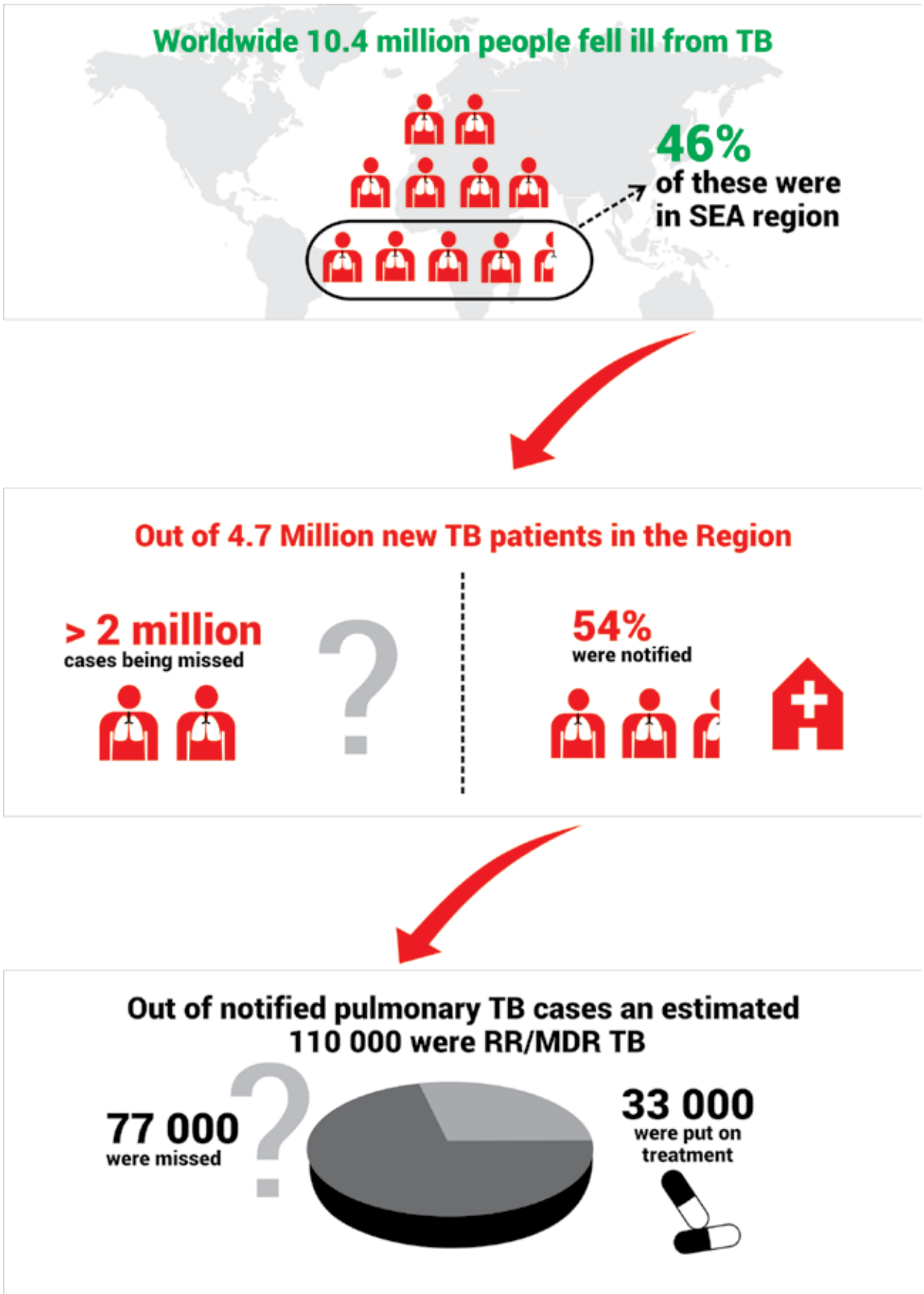
Ending TB is possible and cost-effective, as is also shown by modelling exercises. Investment in ending TB is among the highest cost-effective interventions, yielding a 40 times return for every death averted.

We can end TB with a focus on strengthening current systems, reaching out to all cases in the community with patient-centred approaches, addressing the determinants and investments in research.

Dr Poonam Khetrapal Singh
Regional Director

Disease burden and programme performance

Figure 1: TB burden and progress in the WHO South-East Asia Region (2015)[1]



The WHO SEA Region bears a disproportionately high burden of tuberculosis

Six SEA countries – Bangladesh, DPR Korea, India, Indonesia, Myanmar and Thailand – are among the 30 high TB burden countries globally.

The WHO South-East Asia (SEA) Region bears the highest burden of TB in the world with a human, economic and social impact that is devastating. The Region has nearly half the global burden[1] in terms of new cases appearing (incidence), and close to 40% of the burden in terms of deaths due to TB (mortality) – while about 26% of the global population lives in the Region (Figure 1). The disease takes an unconscionably high toll in human lives and economic development.

In 2015, there were approximately 800 000 deaths from TB and TB-HIV, and 4.7 million new cases of TB disease in the countries included of this Region. India and Indonesia alone have 37% of the global TB burden. Timor- Leste and DPR Korea are among the top 10 countries in the world in terms of proportions of TB cases emerging (incidence rates). In terms of mortality rate in the Region, Timor-Leste (100 per 100 000 population) is followed by DPR Korea (61), Myanmar (49), Bangladesh (45) and Indonesia (40). The total number of new cases that were notified to national TB programmes of the SEA Region was about 2.56 million in 2015 or only about 54% of estimated incidence.

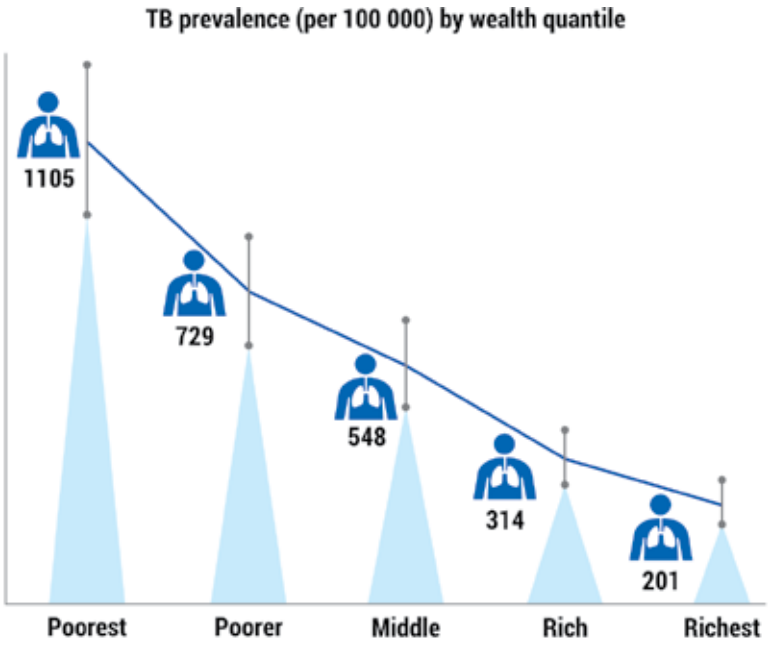
The overall success rate of tuberculosis treatment in the WHO South-East Asia Region stood at 79% in 2015, the lowest in the last 5 years, largely because India's private sector health-care system accounts for a large proportion of TB patients that did not get reported earlier to the national TB programme.

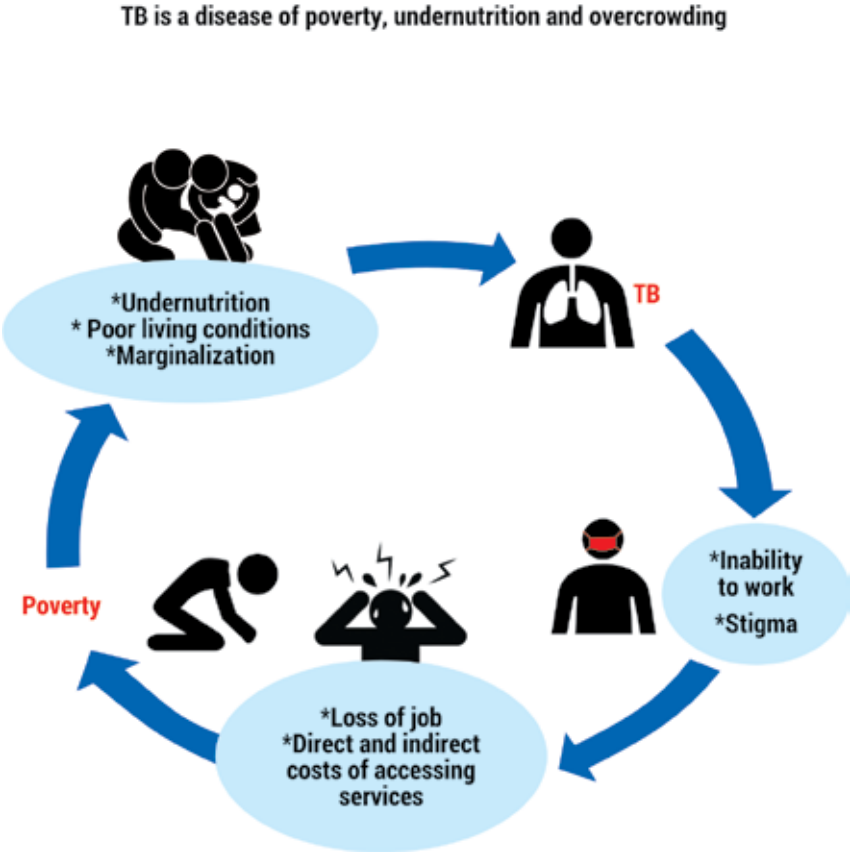
Multidrug resistant and rifampicin-resistant TB (MDR/RR-TB) is a key threat. Its estimated incidence in the Region was 200 000, of which just 32 648 or 16% were started on treatment in 2015. Of those started on treatment in previous years (2013), less than half were successfully treated. Six SEAR nations reported extensively drug-resistant TB (XDR-TB) by 2015.

An estimated 227 000 cases (4.7%) of the 4.7 million incident cases were HIV positive. An estimated 74 000 people died of HIV-linked TB in 2015.

Figure 2: TB is inseparably linked to the Region's development agenda

The poorest are the most affected by TB[2]





Ending TB is a pressing human and development need in the Region

TB is the leading infectious-disease cause of mortality and lost productive years (DALYs) among people aged 15–49 years in the Region as a whole.

Tuberculosis persists as the most destructive infectious disease problem in many of the 11 Member States that constitute WHO's South-East Asia Region.

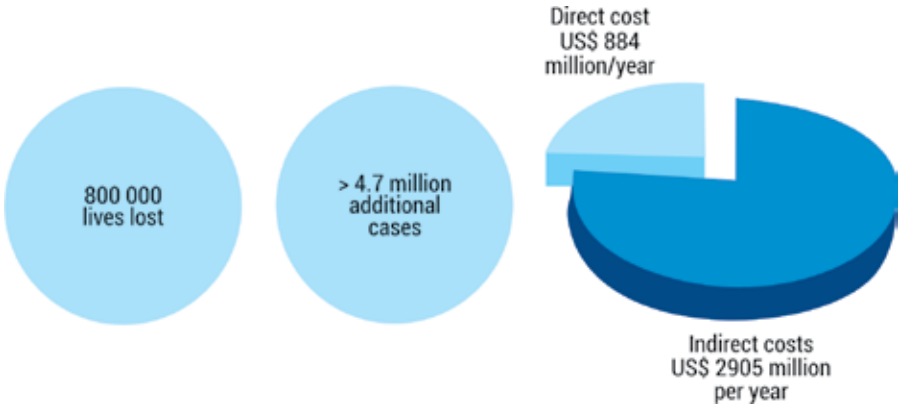
The costs in suffering, premature mortality, impoverishment and foregone development are huge (Figure 2).

- More than 11 million disability adjusted life years (DALYs) lost in the most productive age group (15–49 yrs)[3].
- Modelling exercises estimate that nearly US$ 4 billion is lost in the Region annually as direct and indirect costs to the patients while accessing TB services.

TB perpetuates poverty and poverty increases vulnerability to the disease.

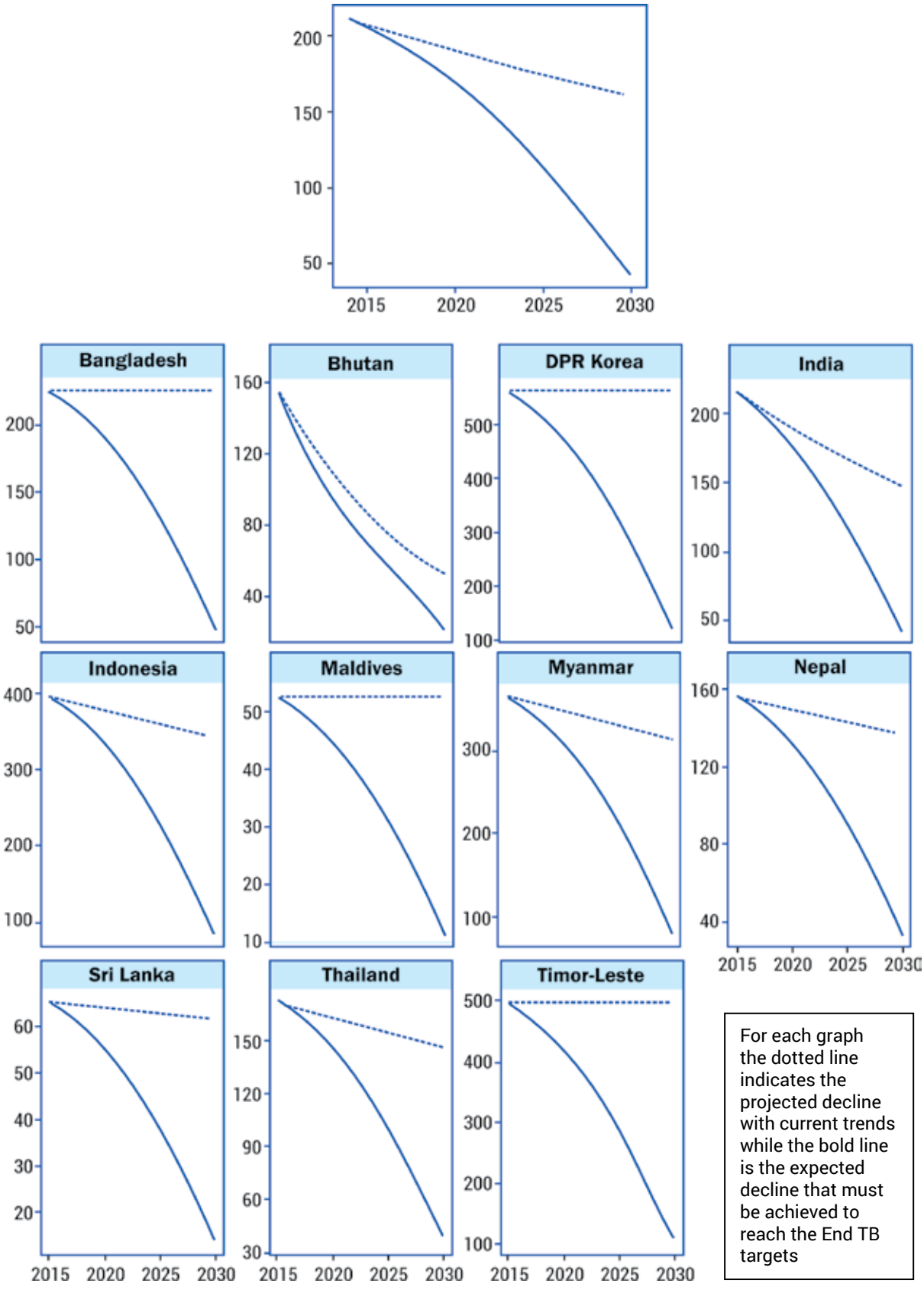
Any amount of this toll is unacceptable because essentially the disease is preventable and curable even with the tools, strategies and resources available today.

Each year's delay means:



Source: Modelling exercise (details available at Annexure)

Figure 3: Projected declines in incidence rates (per 100 000 population) for the SEA Region and Member States[1]



For each graph the dotted line indicates the projected decline with current trends while the bold line is the expected decline that must be achieved to reach the End TB targets

Progress made in this Region will directly determine global TB trends

We will not end TB in this Region at the current level of only 1.5–2% annual decline in TB incidence.

The current rate of decline in TB incidence is grossly insufficient compared with the required decline of at least 10–15% to reach the WHO End TB Strategy targets by 2035 (Figure 3).

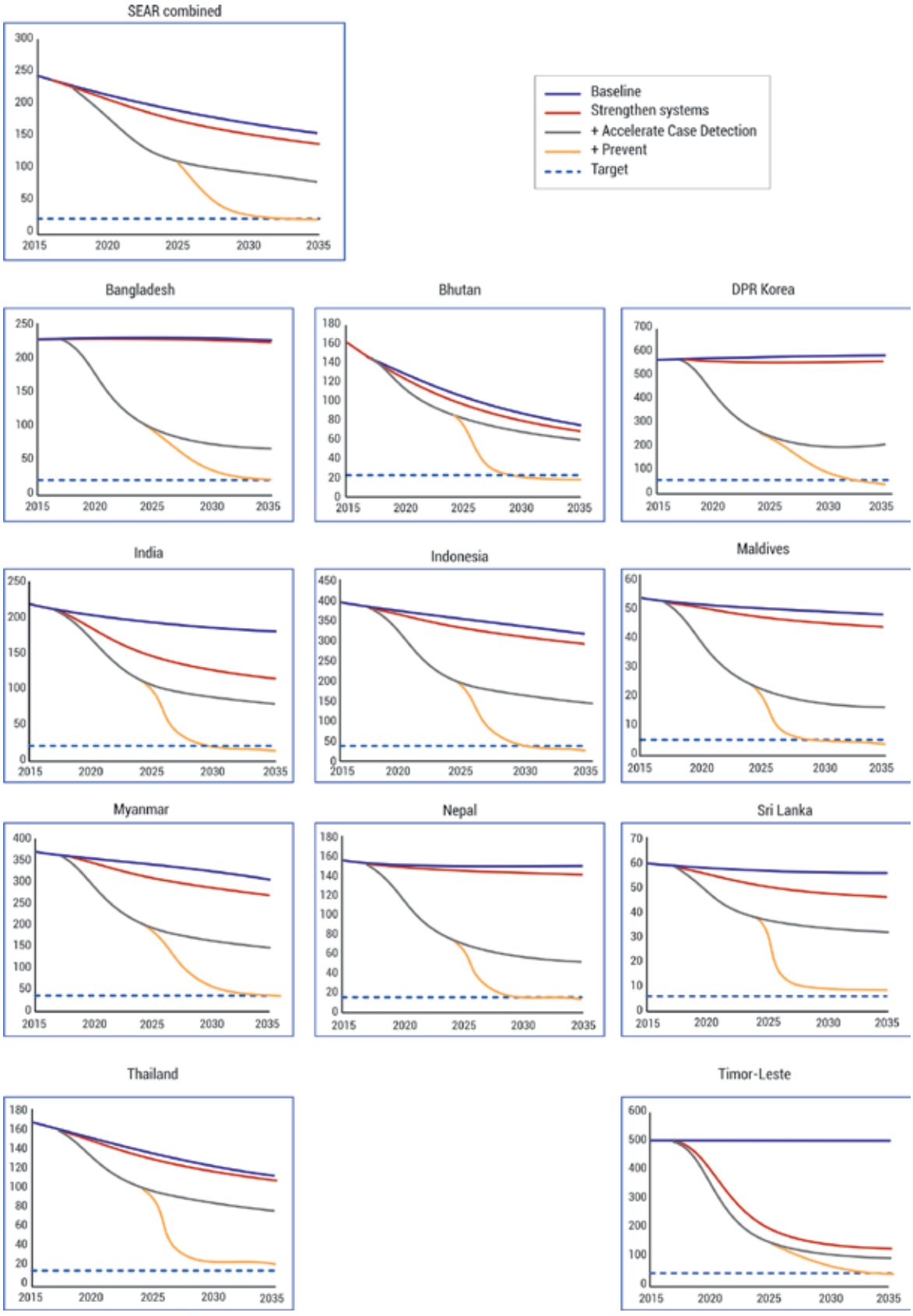
Through implementation of the DOTS strategy (1994–2005) and the Stop TB Strategy (2006–2015), Member States – especially those with a high burden of TB – established the basics required for providing high-quality TB diagnosis and treatment. These efforts contributed greatly to meeting the TB-related target of the Millennium Development Goals (MDGs) of halting and beginning to reverse the TB epidemic. Between 2000 and 2014, improvements in quality-assured diagnosis and treatment of TB contributed in the saving of 43 million lives worldwide. Although enhancing access to diagnosis and treatment remarkably improved outcomes in terms of reducing suffering and death, it had very little effect on achieving the desired impact in terms of declining the incidence rates and driving down the TB epidemic because the outreach of TB services still remains low leading to missing millions of patients needing treatment, patients not being diagnosed fast enough and services not being patient-centric. Moreover, TB is not only a biomedical and a public health problem but also a disease associated with poverty; TB will continue thriving as long as poverty persists.

The incidence rates of the TB disease and mortality vary considerably within the diverse group of countries that comprise this populous Region – as do the rates of MDR-RR TB and TB/HIV co-infection.

Progress towards meeting End TB goals for 2025 and 2030 is also highly varied – but, in almost every country, national efforts will have to be vastly stepped up to reach these important targets.

Ending TB is possible

Figure 4: The potential impact of different intervention combinations on the TB incidence rates (per 100 000 population) in SEA Region



Source: Modelling exercise (details available at Annexure)

Extraordinary, collective, parallel and urgent interventions are needed

Strengthening health-care services, accelerating case detection and preventing TB transmission are the key strategies under which proposed interventions have been modelled for different scenarios. The ideal package will need concurrent action on all, feeding into each other.

'Bending the Curve' in the Region implies bringing down TB incidence and mortality at an accelerated pace by fast-tracking high-impact interventions in parallel, through collective actions of governments, partners, communities and stakeholders.

Mission-mode investments in multiple areas are needed– in early diagnosis and treatment of all types of TB; in maximizing coverage; in patient support systems; in closing programme gaps; in human resources; in TB surveillance; in research; and in translating innovation into fast implementation.

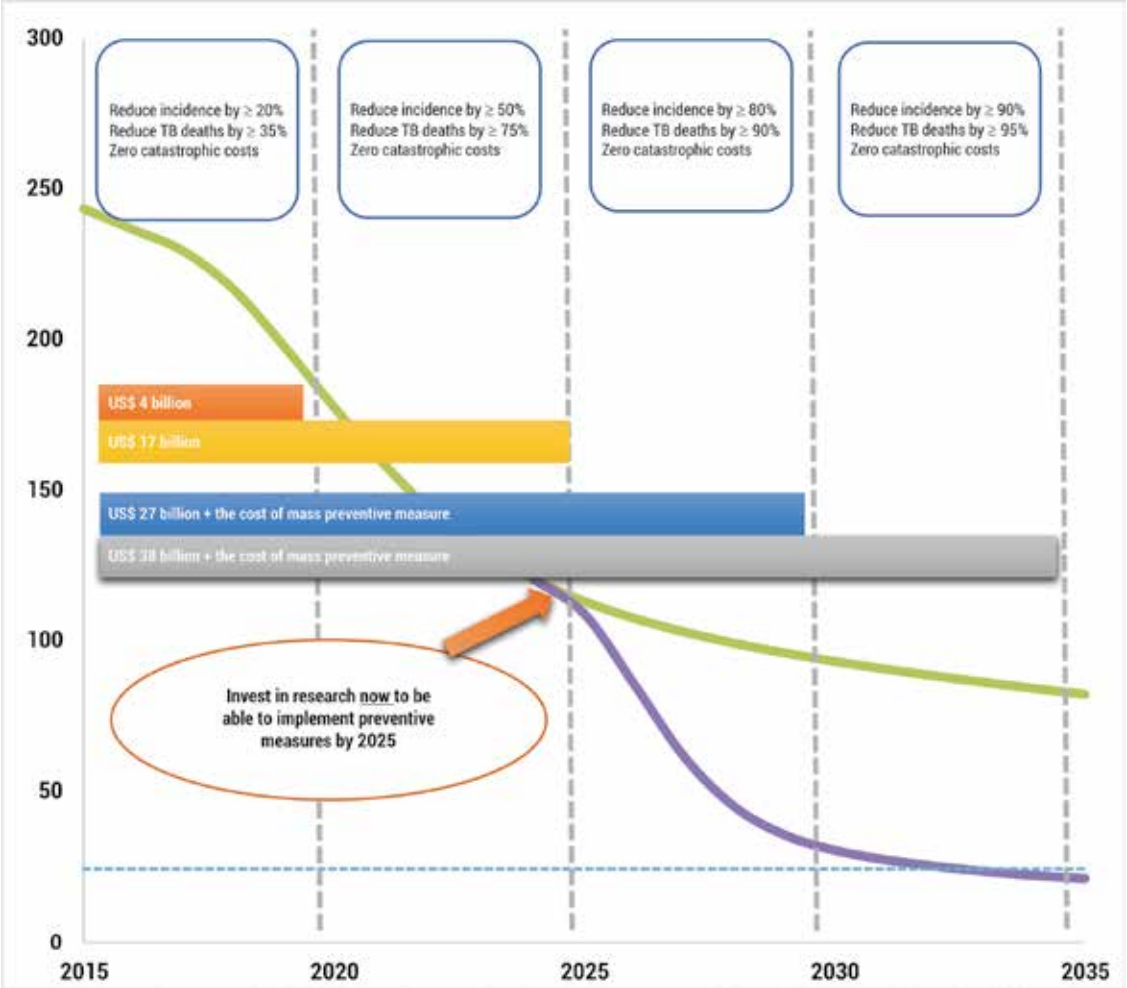
The message is clear:

a. There is a need to do things better – there are known interventions that will help improve programme performance..

b. There is a need to do more – operational gaps in implementation of existing, known strategies need to be filled.

c. There is a need to do new things – research is needed for innovation and for adopting new approaches.

Figure 5: Benchmarks and milestones for ending TB in SEAR



Interventions	Coverage levels			
Engaging non-NTP sector	48%	80%	80%	80%
Lab expansion	21%	35%	35%	35%
Public sector better diagnostics	48%	80%	80%	80%
Treatment initiation	92%	95%	95%	95%
Treatment completion	91%	95%	95%	95%
RR/MDR-TB proportion getting short regimen	48%	80%	80%	80%
Expected additional patients notified per year through accelerated case finding	1.6 million	900 000	225 000	150 000
Proportion of eligible persons receiving preventive therapy	10%	25%	>50%	>80%
	IPT (current criteria)		Mass preventive measure available from 2025 (biomarker guided eligibility)	

Source: Modelling exercise

Regional road map for ending TB

We need to do things better, we need to do more and we need to do new things.

The following interventions have been modelled successively adding each intervention in a combination strategy. All are assumed to be implemented with a steady (linear) scale-up, over 5 years starting from 2017 with the exception of the final intervention (mass preventive therapy), which is assumed to be scaled up over 5 years starting from 2025 (Figure 5).

Strengthen

- Private (or non-NTP) sector engagement covering 80% by 2025. The approach includes training and incentives for non-NTP providers, to follow standards of TB care
- Laboratory expansion, in order to improve access to diagnosis.
- Accelerated substitution (ultimately 80%) of smear by rapid diagnostic tests. Involves X-ray screening followed by confirmation.
- Proportion of TB diagnoses initiated on treatment increased from 88% to 95%
- Treatment completion increased from 85% to 95%
- The model also envisages that at least 80% of all patients needing second line treatment because of resistant bacillus will receive the shorter regimen

Accelerate

- Under the above strategies it is assumed that around 1.6 million patients will be notified by 2020. However this would decrease as the incidence starts falling.
- Contact investigations for every passively diagnosed TB case, to follow-up their extended contacts (colleagues, household, neighbours, etc) for active TB cases. As per the modelling exercise the programme should detect at least 1 new active case for every 2 patients notified
- Intensified case finding (ICF) would involve active screening of high risk cases or community based referrals from general population. Depending on local context this could mean HIV positive patients, other immunocompromised patients, elderly or pockets of population that are unreached but may have high transmission rates like slums. However, local epidemiology is also to be taken into consideration. ICF may also involve engaging community volunteers who screen their local communities for symptoms and refer those likely to have TB to appropriate centres.

Preventive therapy

- Current recommendations for Isoniazid Preventive Therapy (IPT) among high risk populations and contacts who do not have active TB needs to be followed. However IPT cannot be administered on mass scale in general population.
- At present, mass preventive interventions are purely hypothetical with assumed availability by 2025. This may include a diagnostic test that can distinguish high-risk latent infections from others, and a preventive therapy regimen that is feasible for mass administration or a vaccine that cuts the chain of transmission or another such prevention tool that can be applied on mass scale.

Commitment to end TB in the WHO South-East Asia Region

Figure 6: Key asks in the Delhi Call for Action to end TB

Delhi Call for Action to end TB in WHO South-East Asia Region

The goal of ending TB is not a wishful thinking.

In the recently concluded Ministerial Meeting in Delhi from 15–16 March 2017, all Member States of the Region signed the Call for Action for ending TB in the WHO South-East Asia Region. The key commitments in the Call for Action are as follows:

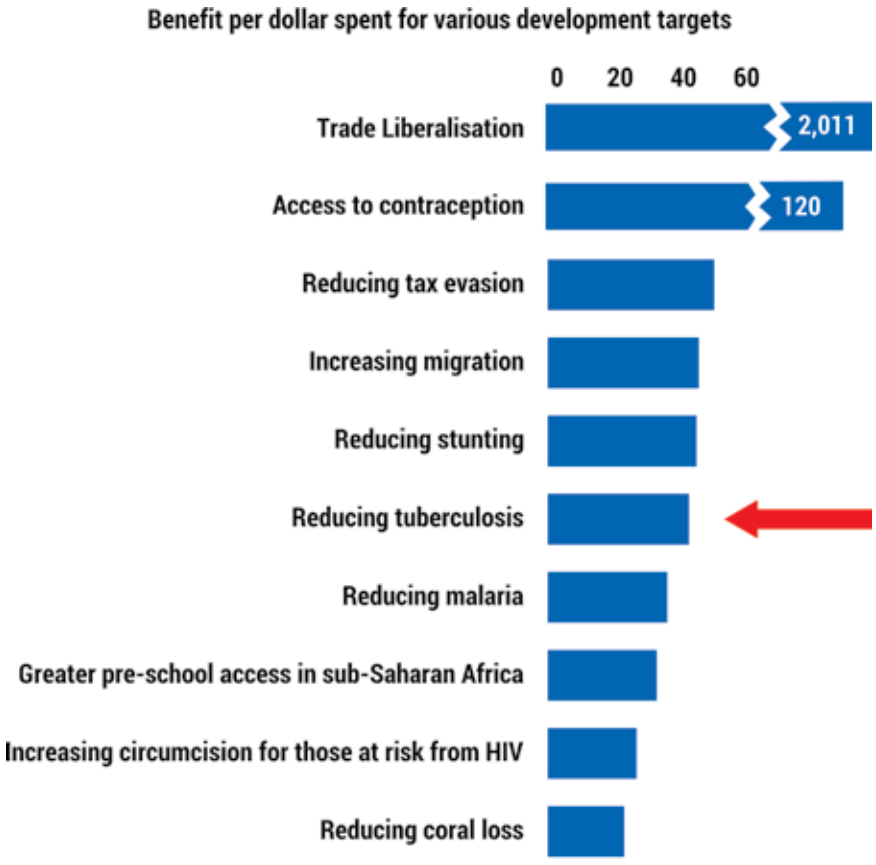
- LEAD implementation of the national TB responses in countries -- specifically the high-burden countries -- by an empowered national initiative that reports to the highest levels of government in Member States, and that includes a multisectoral response and is committed to translating policies into time-bound, result-oriented actions at multiple levels of administration, with ownership and access to real-time monitoring,
- INCREASE budgetary and human resource allocations by governments as well as by their global, domestic and other partners so as to ensure that national TB plans are evidence-informed, fully funded, rationally and effectively used, avoiding wastages,
- ENABLE, using innovative communications, the engagement and literacy of communities and individuals with TB and provide the best possible care to each and every person, including migrants, the aged and other high-risk populations, living with any form of TB, including drug- resistant TB and TB-HIV co-infections, presenting either to the public or the private sector, including general practitioners, while also expediting introduction and expansion of new tools of diagnosis, treatment and prevention as they become available,
- SUPPLEMENT medical care for TB with patient-centred, community-empowering, necessary social and financial protection in a holistic manner through collaborations across and beyond the health sector in every country of the Region,
- WORK jointly with the South-East Asia Regional Office of the World Health Organization and partners to further boost actions in countries, including forming regional research consortiums, mobilizing additional global resources and securing political commitment at the highest levels from countries through the Ministerial Meeting in Moscow, Russia, in November 2017, and at the UN General Assembly Session in 2018, thereby demonstrating regional commitment to end TB, and
- SET UP jointly with the South-East Asia Regional Office of the World Health Organization and partners a Regional Innovation to Implementation (I2I) fund to ensure accelerated sharing of knowledge, including the use of secondary data, intellectual resources and testing innovations to reach out and treat all cases.

The Regional Director of the WHO South-East Region has accorded a high priority to TB control in the Region, and this is now her eighth flagship area.

WHO and partners stand committed to support Member States in achieving this ambitious target of ending TB in the Region.

The resource challenge in meeting the targets

Figure 7: Investments in ending TB are cost-effective and yield many-fold returns



Source: Copenhagen Consensus Centre

Cost effectiveness of TB interventions

Potential incremental gains of ending TB by 2035

- ***More than 6.5 million lives saved***
- ***More than 40 million new cases averted***
- ***More than 140 million DALYs averted***

The economic case for investment in tuberculosis (TB) control is compelling. TB control has been part of an essential package of health services for most low- and middle-income countries (LMICs) for decades, based on the relatively high returns of TB control.

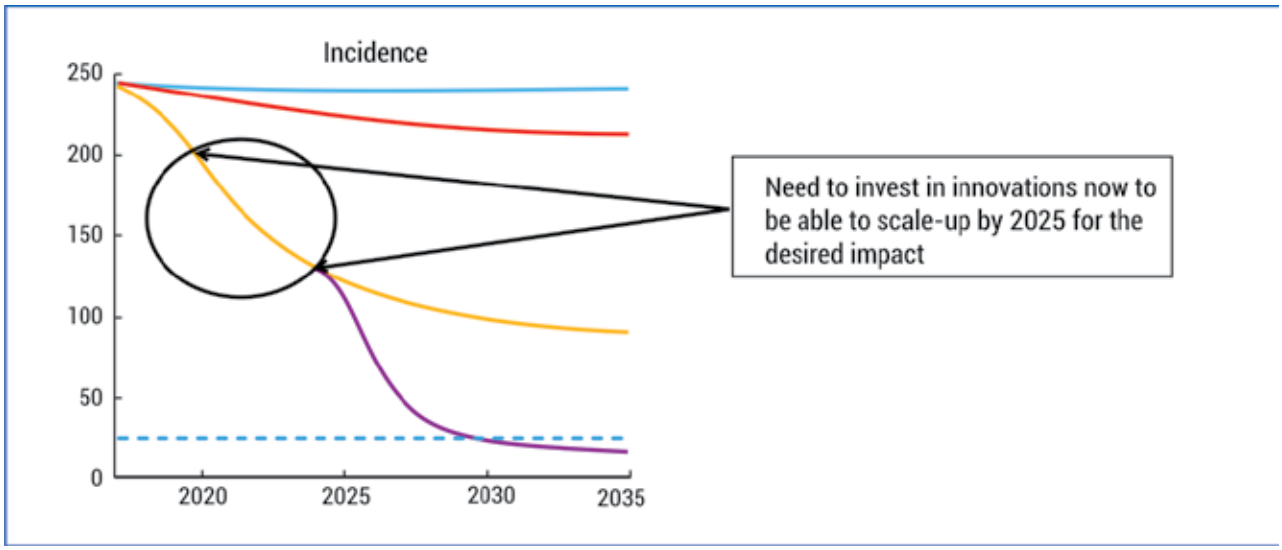
The economic case, put simply, is that TB treatment is low cost and highly effective, and on average may give an individual in the middle of their productive life about 20 additional years of life resulting in substantial economic and health return.[4] Moreover, the delivery of high-quality TB services can prevent the spread of the disease to others; slow the emergence of drug-resistant forms of the disease, a dangerous and costly form of TB; and disproportionately benefit the poor.

Most poverty-reduction measures are more expensive than cutting tariffs, but many are still well worth it. Providing contraception and other reproductive-health services to all who want them would cost US$ 3.6 billion a year, according to Mr Lomborg's researchers[5], yet generate annual benefits of US$ 432 billion – US$ 120 per dollar spent.

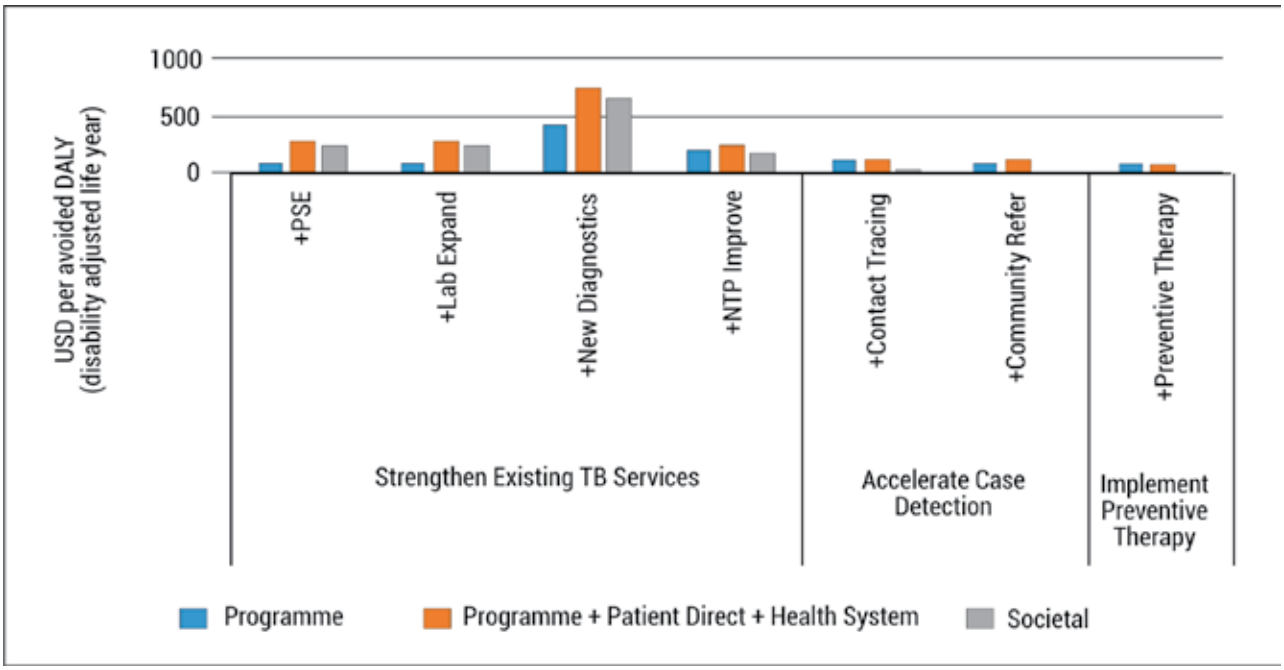
Increasing the nursery school enrolment rate in sub-Saharan Africa to 59% from its current 18% would generate benefits of US$ 33 per dollar spent. Reducing by 40% the number of children whose growth is stunted by malnutrition would be worth US$ 45 per dollar spent; reducing deaths from tuberculosis would generate a benefit of US$ 43 per dollar spent.[5]

Tuberculosis is the cornerstone of the global antimicrobial resistance (AMR) challenge: drug resistance is a major challenge today not only for TB but also for HIV and malaria. TB kills more people annually than any other infectious disease: 1.5 million die of TB every year, of whom 200 000 die of multidrug-resistant TB (MDR-TB). Analysis shows that of the 10 million total deaths that might be associated with drug resistance each year by 2050, about one fourth will come from drug-resistant strains of TB.[6] The report suggests that the global response to AMR is fundamentally incomplete if it does not directly address the particular issues related to TB.

Figure 8: The case for investing now



All interventions are cost-effective – less than Regional GNI per capita (USD 1900 per person)



Source: Modelling exercise

Investments are needed now, to avoid paying a heavy price later

Research and development takes time: need to start investment now to have the necessary tools by 2025.

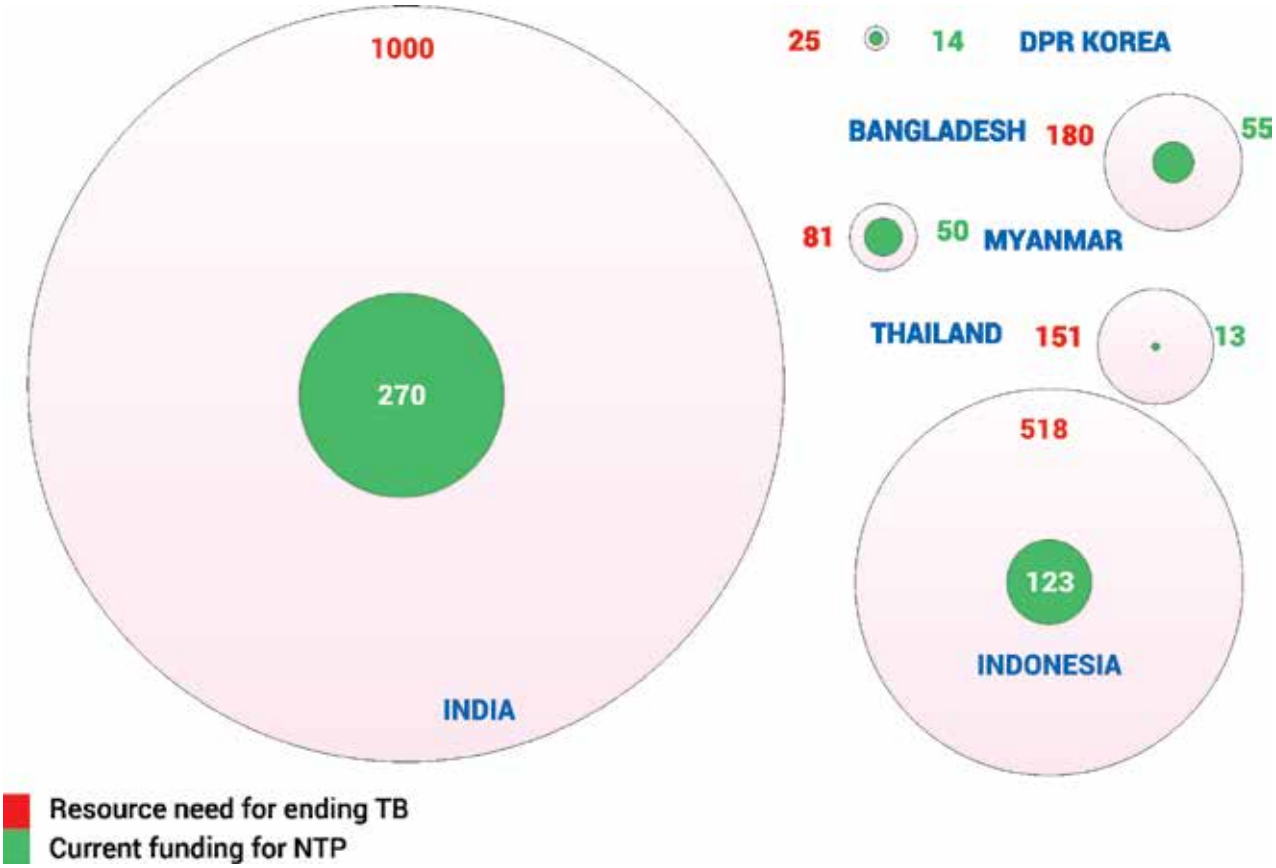
We need a paradigm shift in the scope, scale and reach of investments to end TB – with the highest political commitment; radically higher funding; united global, regional, national and community action; cross-sector partnerships; and interministerial collaboration on health, poverty, welfare, etc.

The interventions are cost effective – Comprehensive adoption of all interventions that build systems, engagement in accelerated case detection and preventive measures would require an annual average annual incremental expenditure of US$ 0.90 per person between 2017 and 2035 to achieve the global TB reduction targets.

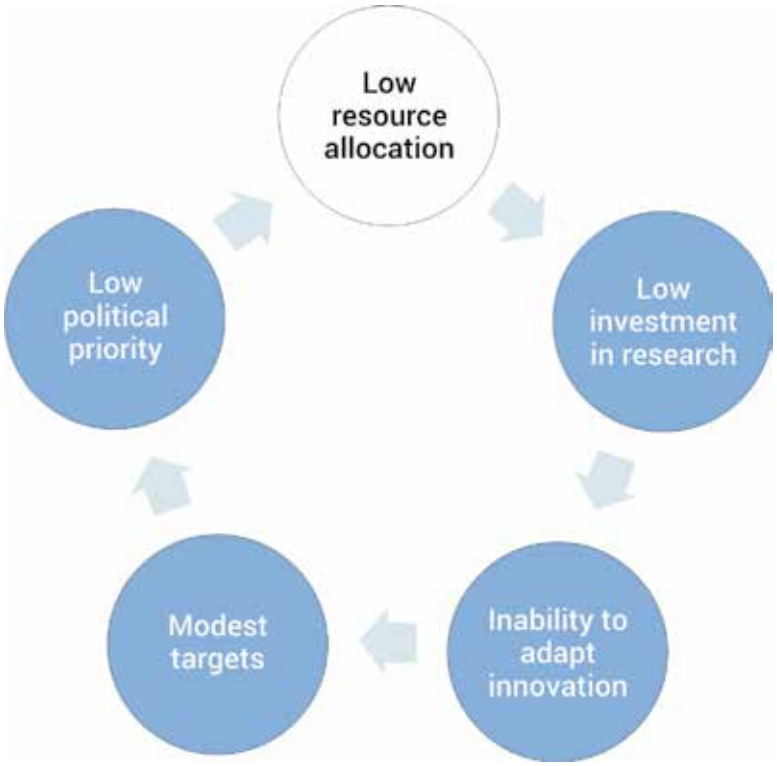
A total of US$ 26 billion is required additionally until 2035 to achieve the target in the Region

All South-East Asia Region	Total resource needs in US dollar millions
Baseline	11 450
Incremental for - Strengthen existing TB services	21 637
Interventions such as private sector engagement, laboratory expansion, newer diagnostics and quality treatment	
Incremental for - Accelerate case detection	37 839
Includes the above interventions and additionally contact tracing and targeted active case-finding through various means	

Figure 9: Resource gaps (in US$ million) per year in high burden countries to meet the End TB targets



Challenges with resource mobilisation



Plugging the financial resource gaps

Domestic financing is going to remain the most important source of finance for governments in this region, especially from the perspective of sustainability.

Among SEAR countries, India, Indonesia and Thailand have large unfunded gaps in their TB programme (Figure 9), which can possibly be filled in by domestic sources given their income status. Countries like Bangladesh, India and Indonesia would have to raise their allocations to the health sector in any case. While greater allocations to health may not necessarily translate into TB spending - given many other urgent priorities - it will go some way in meeting the resource needs for TB as well. Indonesia has been moving towards Universal Health Coverage (UHC) but still needs to allocate a greater share of its GDP to health and improve its accessibility issues to improve the UHC. Public health spending by DPR Korea has been much higher relative to other countries in the region, and the country has to find a way of raising resources for TB from within its domestic resource envelope for health.

There are many ways to explore additional domestic funding; an important channel will remain through taxes. Countries need to consider to what extent they can raise their tax revenues as a proportion of GDP; middle income countries and countries with fairly robust economic growth like India can certainly make additional efforts to raise their tax-GDP ratio so that the resource envelope can be expanded. Most of the SEAR countries have fairly low tax-GDP ratios that can certainly be raised if macroeconomic fundamentals are stable.

Strengthen financial protection and pre-pooling. Many countries in SEAR have been moving towards UHC to improve financial protection. This would continue to be an important tool of health financing and can help fund the components of the program like diagnostics and treatment. High direct and indirect costs of care hamper access and increase the risk of poor TB treatment outcomes[7]. WHO's End TB strategy also explicitly highlights the key role of UHC and social protection.

Donor funding is going to continue to be a key source in low and middle income countries. The Global Fund provides more than 65 percent of all international financing for TB, and has disbursed more than US$4.9 billion in TB programs in more than 100 countries since 2002.

For Bangladesh, DPR Korea and Myanmar among high burden countries, donor funding is going to remain critical. While Bangladesh and Myanmar have been able to secure significant external funding, DPR Korea has so far not been able to garner sufficient funds for TB programmes, domestic or international. DPR Korea needs to scale up MDR TB programmes and at present most of the financing has been insufficient for a rapid expansion of the programme[8].

International development agencies have to work in tandem with each other and with national governments to catalyse additional resources for countries that are in critical need of external funding for their TB programs.

Engagement of private sector in TB programme is important not only to raise funding but also to make the response more effective. Many of the SEAR countries are characterized by significant presence of the private sector, including for TB. It is, therefore, strategic to involve the private sector in partnerships with the public sector in activities consistent with country priorities, in joint public-private missions so that government's resources are augmented both financially as well as in non-monetary terms. This would include all the major stakeholders in the private sector – physicians, pharmacists, clinics and hospitals.

In some countries, the private sector is mandated to invest some minimum amount in socially relevant activities under the "Corporate Social Responsibility" mandate. This should be used innovatively for augmenting resources within countries[9].

Innovative financing: GAVI (global Vaccine Alliance) and GFATM (The Global Fund to Fight AIDS, Tuberculosis and Malaria) are examples of new agencies that came into being based on essentially innovative financing approaches to raise resources for important health goals.

Other innovative models for raising revenues include levy on air ticket sales (UNITAID) and financial transactions that have been used by a number of African countries[10], auctioning/sales of emission permits. The International Finance Facility for Immunization is also a way of raising funds through bonds[11]. Other innovations include schemes like Advance Market Commitments to provide incentives to develop new vaccines.

Development Impact Bonds (DIB): these are adapted from Social Impact Bonds (SIBs) that are being implemented in UK and USA. These are usually contract with public sector for an intervention that can improve social outcomes - "pay-for-success" projects. An investor is usually involved and the public sector passes on some of the savings to the investor. DIB are similar - the upfront funding can be from any source including private funders and donors and the remuneration can be by governments or other stakeholders.

However, there are also other models on innovative financing that can be used in the Region. Most of these are methods to leverage the private sector for raising additional resources but can also involve other donors and funding agencies and the government.

Results-based financing to improve efficiency of spending and reduce need for additional resources: in resource-constrained settings, it is critical to use the limited resources efficiently. There are examples of such mechanisms that can be applied in the region

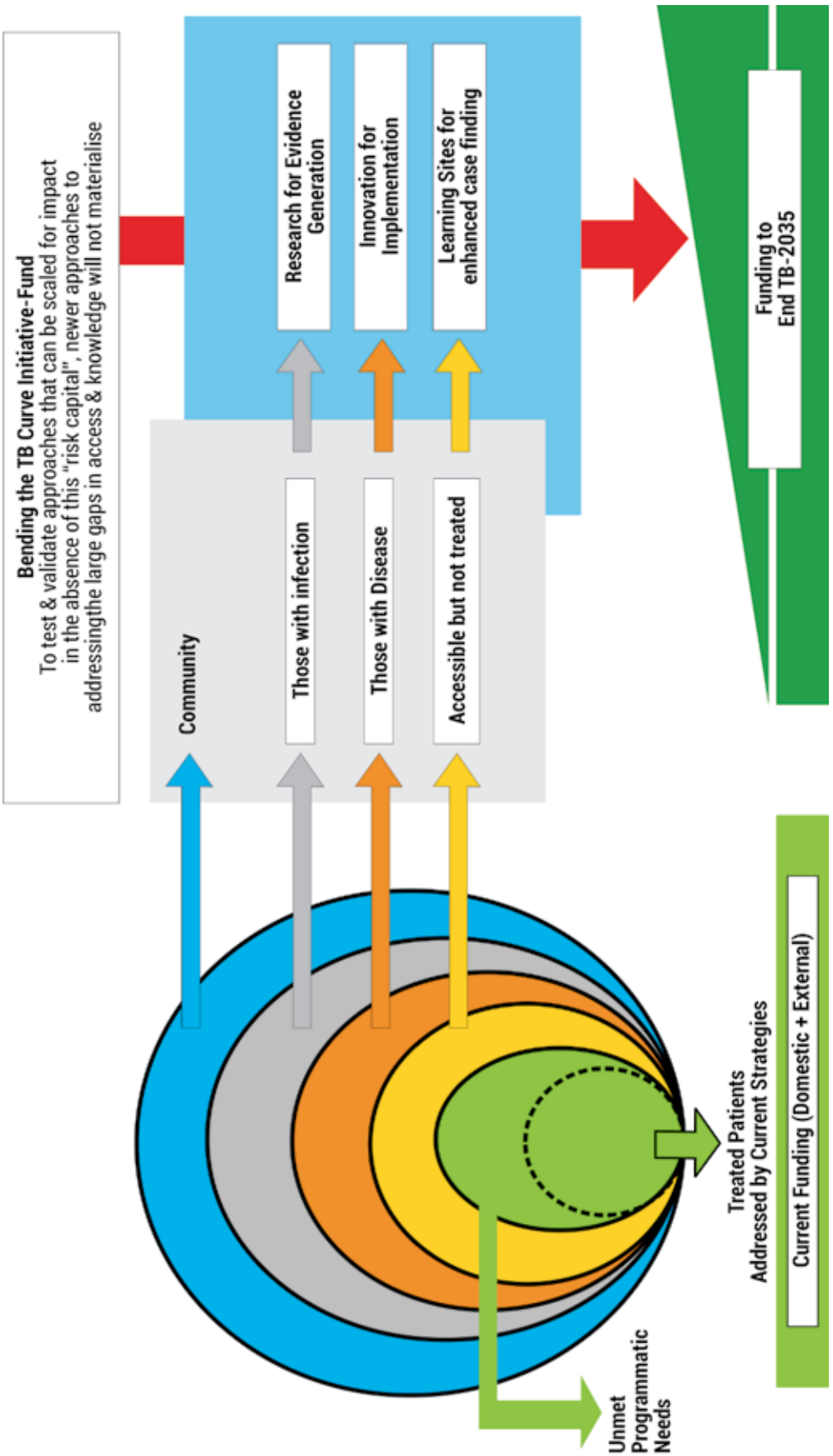
Result-based financing has worked well in many countries and mostly the examples are from the health sector. For example, health centre visits for preventive childhood care in Rwanda, a program in Argentina to reduce neo-natal mortality, a health and education program in Indonesia to improve outcomes, Madhya Pradesh Higher Education program[12] etc. International organizations like the World Bank have been significantly involved in such programs at country level.

WHO-SEARO could support Member States in plugging financial gaps by:

1. Advocacy for higher fund allocation through domestic source
2. Advocacy with international funding agencies for greater allocation for TB programmes in the Region, commensurate with high disease burden
3. Supporting Member States in mobilising resources through international agencies
4. Identifying innovative funding mechanisms suitable for country-specific needs
5. Establishing a fund to support innovation and translation of innovation to implementation (explained in greater details in next section)

Innovative financing mechanisms to support Member States

Figure 10: BENDING THE CURVE INITIATIVE - 'Innovation to Implementation' fund



‘Innovation to Implementation’ fund for achieving the End TB targets

As per the modelling calculations, the funding for TB programmes needs to be scaled up by at least 3.5 times for the Region as a whole. While stepped-up programme funding is an essential need, another equally essential need is to identify and incorporate high-impact interventions and approaches that can move national programmes to a comprehensive epidemic-control strategy. A comprehensive strategy would add vital interventions such as active case-finding, , patient-centric services (including the provision of socio-economic support to patients), targeting of local hotspots of transmission, and preventing future transmission by treating high-risk individuals and contacts of affected individuals. The End-TB milestones and targets can only be realistically brought within reach in the Region with a rapid move to comprehensive epidemic-control strategies.

The proposed concept of ‘Innovation to Implementation’ Fund is a response to this felt need and challenge (concept of fund provided in Figure 10). Currently, despite invaluable efforts of the Global Fund, the fiscal space to pilot and validate new interventions and approaches is limited and sometimes even non-existent in the Region. Ministries of health and finance are both understandably reluctant to invest in these without robust assessment of outcome and budgetary impacts. Consequently, the case for any new policy and programmatic intervention or approach must be made with persuasive cost-benefit evidence. Moreover, the evidence must show that this intervention or approach will work well in each one of the countries that are considering it; given the myriad differences between the nations in this Region, an innovation that is a breakthrough in one country may not show worthwhile results in others.

The Fund’s goal is to drive the development and subsequent programmatic adoption of high-impact, evidence-based interventions and approaches for comprehensive epidemic control, suited to the member States of the Region.

The Fund’s strategy is to seed innovation through support to small learning sites and then to rapidly evaluate and validate promising interventions and approaches by helping take them to scale.

The Fund’s functions could include:

- Support to learning sites to test and prove key missing elements of comprehensive strategies to end TB.
- Adoption of new tools and technologies including for diagnosis, vaccines, drugs, treatment modalities, infection control, ICT and others including site preparation for these.
- Learning sites for scaling up of interventions and approaches for accelerated case diagnosis.
- Technical support to facilitate integration of proven innovations into large-scale/area-specific and national programmes.
- Rapid documentation and dissemination of rigorous best practice, lessons learned and evaluation studies, so as to provide a regional knowledge-bank.

The Fund could be catalysed and steered by the WHO South-East Asia Regional Office as necessary. It would be guided by an inclusive, hands-on advisory board, drawn from civil society, committed legislators, bilateral and multilateral donors, foundations and ‘public-private’ partnerships, technical and scientific institutions and experts.

Genesis of the Delhi Call for Action

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Acknowledgement

Collaboration in Bending the Curve strategy development

World Health Organization
Regional Office for South-East Asia

PUBLIC HEALTH FOUNDATION OF INDIA

eSYS

Imperial College London

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- Rashmi Arora, ICMR, India
- Soumya Swaminathan, Secretary/DHR, India
- Sundari Mase, WHO India
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Annexure

Technical summary of modelling exercise

The overall model structure is shown in Fig.11. Here we present an overview of the model structure and rationale. See table 1 for a full list of the parameter inputs.

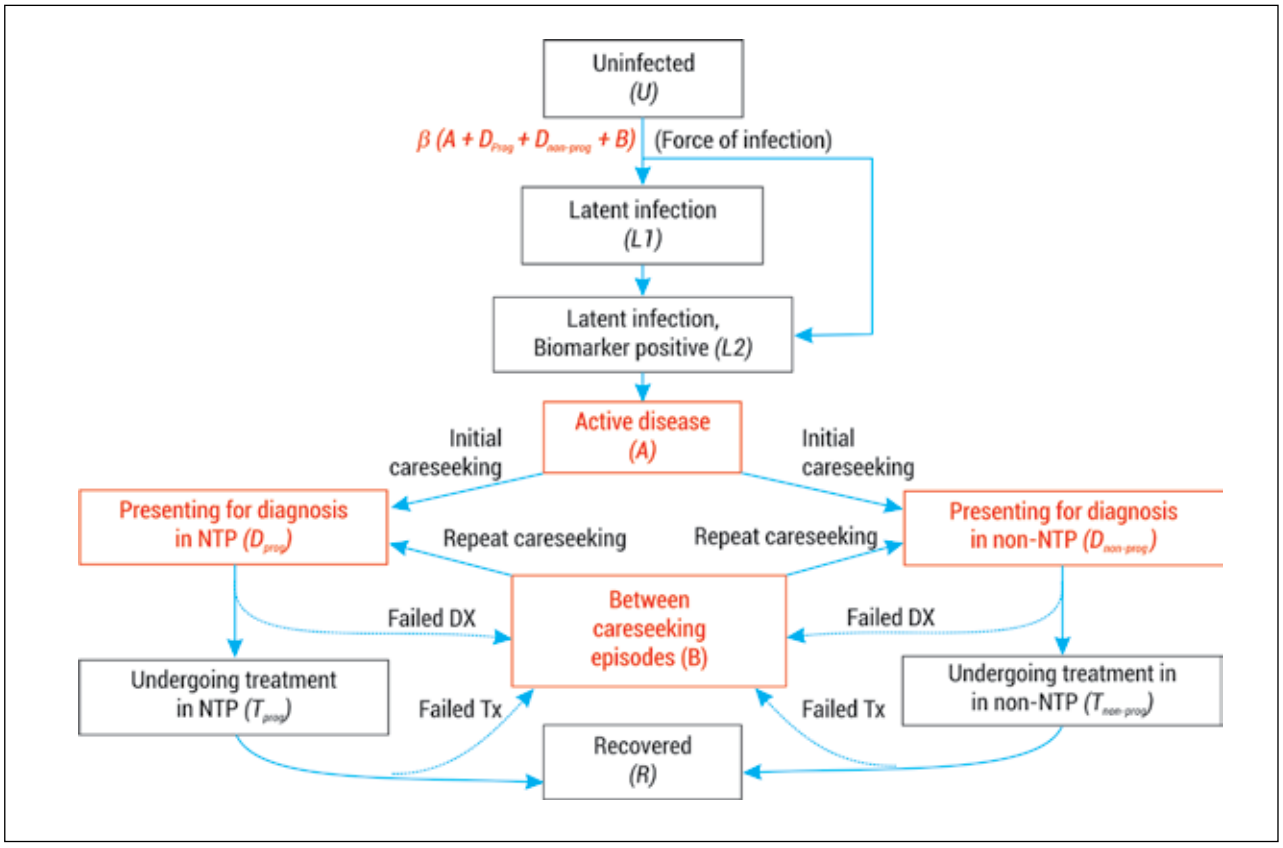

Figure 11: Overview of the model structure. Red boxes show states that are infectious, and thus contribute to the force-of-infection (see top). Arrows show population 'flows' between different compartments: the purpose of interventions is therefore to optimise these flows in such a way as to minimise the population in the red compartments.

The model divides the population into 'compartments', reflecting stages of infection, disease and diagnosis/treatment. Flows between these compartments are captured by a series of mathematical equations. The model explicitly captures the NTP and non-NTP sectors, and the respective standard of TB care in these sectors. In doing so, the model also captures the implications of diagnostic delays and treatment outcomes, for overall transmission. For simplicity, the model does not have age structure, and is nationally aggregated. However, it incorporates HIV/TB coinfection, as well as the generation and transmission of MDR-TB. Key structural elements are as follows:

Latent infection

Amongst people having latent TB infection, we distinguish those who will develop active TB disease within the next two years. It is assumed that these infections have an elevated expression of some biomarker that could be detected using a future, hypothetical biomarker test. Accordingly, the model distinguishes these infections as 'biomarker positive'.

Initial patient delay

It is assumed that, after patients develop symptoms, they undergo an initial delay before first seeking care (for example, as their symptoms develop in intensity). This delay is estimated, together with the infectiousness per undiagnosed case, to yield incidence and prevalence relevant to a specific country setting. Note that, because patients in this compartment have not yet visited a provider, they can only be reached through active case finding strategies. Additionally, this patient delay is distinguished from the 'diagnostic delay', the interval from first care seeking to ultimate diagnosis and treatment initiation. This latter delay is captured by the failures in the care cascade shown in Fig.11, which lead to a persisting population in the 'B' compartment.

NTP and non-NTP sectors

Upon seeking care, it is assumed that a proportion p of patients visit the NTP, while the remainder seek care in the non-NTP sector: the latter broadly including pharmacies, traditional healers, as well as physicians (private for profit and not-for-profit) who are not involved with NTP. The parameter p is chosen in such a way that simulated treatment initiations in the NTP agree with reported notifications (i.e. assuming that the non-NTP sector does not notify cases).

Under ideal conditions (perfectly efficient healthcare systems), TB patients would be immediately diagnosed upon visiting a provider, and then initiate and complete treatment appropriate to their drug sensitivity status.

Overall, therefore, the burden of cases in the B compartment is lowered by increasing the quality of diagnosis: this is achieved by non-NTP sector engagement (PSE) and further by lab expansion with increased use of rapid molecular tests. The burden in B is also reduced by minimising rates of loss from treatment.

Quantities governing the TB care cascade in the NTP and non-NTP sectors are shown in table 1.

Drug resistance

The transmission of both drug-sensitive (DS) and multidrug-resistant (MDR)-TB is modelled, treating these as two strains co-circulating in the population. The model captures the rate of primary acquisition of RR/MDR-TB from first-line treatment, as well as the transmission of MDR-TB. It is assumed that a proportion g of cases identified are subject to drug sensitivity testing. Those not identified as RR/MDR are assumed to undergo first-line treatment, and to remain infectious with resistant forms of TB during this time: upon failing first-line treatment, a certain proportion is switched to second-line therapy. As an intervention, the use of rapid molecular testing increases the proportion of MDR cases that are diagnosed as being drug-resistant TB.

HIV

The model structure shown in Fig.11 is replicated for TB patients coinfected with HIV. It is assumed that a proportion h of new TB cases are HIV co-infected, taking the value of h from WHO estimates. Individuals with HIV/TB infection have an elevated risk of developing active disease, with parameter values informed by the literature (see table 1). It is also assumed that HIV-positive patients undergoing ART have the same risk of developing active disease, as HIV-negative TB infections.

2. Model calibration

There are four free parameters, to be calibrated to each country setting: the mean annual infections per drug-susceptible TB case (β); the mean annual infections per multi-drug-resistant TB case (β_MDR); the mean, initial patient delay before first seeking care (d); the proportion of TB cases visiting an NTP provider at each care seeking attempt (p); and the proportion of TB diagnoses receiving a drug susceptibility test (δ).

The model calibrates these to each country setting, to the following data: estimated incidence (all forms of TB) in 2015; prevalence (all forms) in 2014; estimated proportion of TB infections that are MDR-TB in 2015; TB case notifications in 2015; and MDR-TB case notifications in 2015.

3. Implementing interventions

The following interventions are modelled, successively adding each intervention in a combination strategy. All are assumed to be implemented with a steady (linear) scale-up, over 5 years starting from 2017 with the exception of the final intervention (mass preventive therapy), which is assumed to be scaled up over 10 years starting from 2025.

Private/ non-NTP sector engagement

Training and incentives for non-NTP providers, to follow standards of TB care. In doing so, their probability of diagnosis per patient visit, and treatment initiation and completion rates amongst diagnosed TB patients, are all raised the level of the NTP. This is modelled as an increase in p from its calibrated value p_0 to $p_0+0.5\ (1-p_0)$.

Laboratory expansion

Expanding laboratory smear facilities, in order to improve access to NTP diagnosis. We assume conservatively that this measure results in a 25% increase in p, the proportion of patients accessing NTP services at each careseeking attempt.

Better diagnostics

Accelerated substitution (ultimately 80%) of smear by rapid diagnostic tests, for NTP and engaged non-NTP providers. Involves X-ray screening followed by confirmation, with a proportion (assumed around 20%) receiving rapid tests without screening..

NTP sector treatment

Proportion of TB diagnoses initiated on treatment increased from 88% to 95%, while treatment completion increased from 85% to 95% (default baseline values – may vary by country).

Contact tracing

For every passively diagnosed TB case, trace their extended contacts (colleagues, household, neighbours, etc) for active TB cases. Ongoing household studies in India suggest that 4-5% of household contacts of pulmonary TB cases also have active TB disease. If this yield is half as much in extended contacts, and if individuals have on average around 40 such contacts, then we estimate that this method could yield one additional TB case for every passively diagnosed case.

Intensified case finding

This as an additional flow from 'A' to 'DNTP' in the model, at a constant rate m. The most appropriate way to implement this case finding varies from country to country. We distinguish the 'Bangladesh model' where designated members of the community refer patients with TB symptoms to NTP facilities, and the 'India model', which involves active case-finding amongst risk-groups with elevated TB prevalence compared to the general population, such as slum dwellers and those suffering malnutrition. The model does not explicitly capture these risk groups..

Mass preventive therapy

All of the above interventions involve curative therapy, and may be feasible with currently available tools. However, we additionally consider the potential impact of preventive measures. Infection control measures would need to be deployed more broadly than, for example, in congregate settings, to impact transmission on a population level.

We model a potential future scenario: assuming that by 2025 there is a diagnostic test that can distinguish high-risk latent infections from others, and that there exists a preventive therapy regimen that - while not curative - is feasible for mass administration (being well-tolerated and having, for example, only a weekly regimen). We model this intervention as a constant rate, displacing individuals from the L2 to L1 compartment.

Finally, we note that model findings may be subject to substantial uncertainty. Some of this uncertainty arises from potential over- or under-estimates of TB burden (incidence, prevalence and MDR-TB), as well as from model assumptions in the absence of systematic evidence (e.g., as described above for case-finding interventions). The figure below shows results from a one-way sensitivity analysis, illustrating how quantitative model findings may change substantially, depending on assumed parameter values.

Such variation notwithstanding, the overall qualitative finding remains: that strengthening systems is critical for meeting the End TB goals, but true declines in TB incidence will require substantial acceleration in case-finding, and ultimately in population-level prevention.

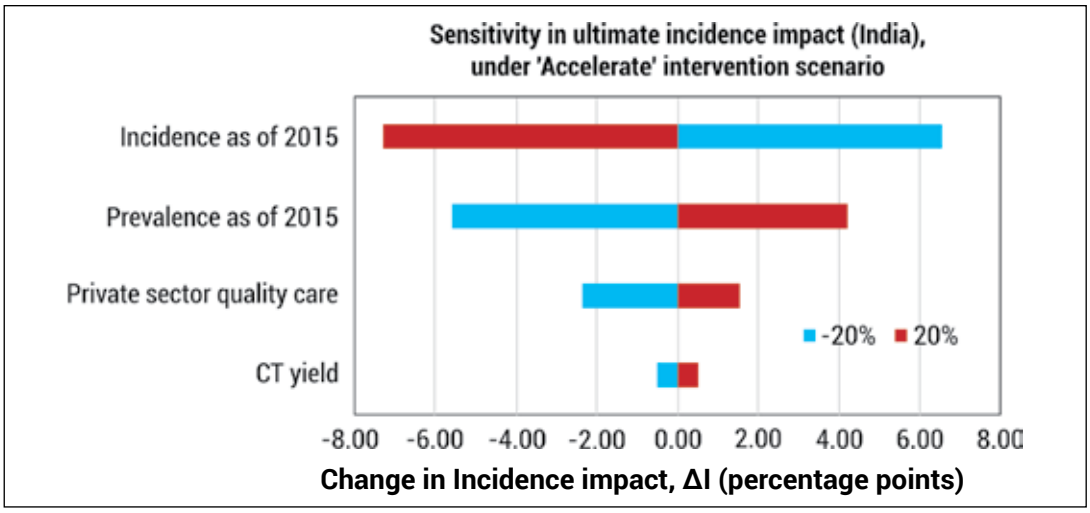

Figure 12. One-way sensitivity analysis of leading model inputs. Here, 'incidence impact' (ΔI) is the percent reduction in incidence in 2035, compared to that in 2015, taken under the 'accelerate' intervention scenario for illustration. The figure demonstrates the changes in impact that result, when changing the top four model inputs by +/-20%.

Parameter (refer individual country profiles)		Value	Source / Notes
Natural history parameters			
Hazard rate, untreated TB mortality		1/6	Tiemersma (PLoS One, 2011); corresponds to 50% mortality and 50% self-cure in an average of 3 years
Hazard rate, spontaneous recovery		1/6	
Proportion fast progressors	HIV –ve	0.14	Vynnycky & Fine (1997)
	HIV +ve	0.37	Sergeev (Sci Transl Med, 2012)
Hazard rate, breakdown to active disease	HIV –ve	0.001	Horsburgh (AJRCCM, 2010)
	HIV +ve	0.023	Horsburgh (AJRCCM, 2010)
Reduced susceptibility from prior infection, w		0.5	Assumption
Hazard rate, relapse		0.002	Driver (CID, 2001)
Quality of TB care			
Probability of diagnosis per visit to a provider	Public, $p^{(pu)}$	0.83	Subbaraman et al (PLoS Med, 2016)*
	Private, $p^{(pr)}$	0.7	Assumption
Proportion of TB diagnoses registered for treatment	Public, $q^{(pu)}$	0.88	Subbaraman et al (PLoS Med, 2016)*
	Private, $q^{(pr)}$	0.7	Assumption
Proportion completing treatment	Public, $c^{(pu)}$	0.85	Subbaraman et al (PLoS Med, 2016)*
	Private, $c^{(pr)}$	0.7	Assumption
First-line treatment duration, $\mathbf{t}_1$		2	Corresponds to a treatment duration of 6 months
Second-line treatment duration, $\mathbf{t}_2$		0.5	Corresponds to a treatment duration of 2 years
Hazard rate, followup careseeking		12	Assumption – corresponds to an average delay of 1 month between careseeking episodes (following failed diagnosis, or initial loss to followup)

Table 1: Summary of key baseline parameters used in the model. Certain parameter values, marked (*) were drawn from a recent systematic review for the public sector care cascade in India. These were amended for country settings where country-specific information was available (e.g. 99% treatment initiation rates in Bangladesh, where community groups are routinely involved in TB care).

5. Economic analysis

A two-stepped approach was undertaken. Firstly, unit costs for key TB diagnostic, treatment, and support interventions among World Health Organization Regional Office for South-East Asia (SEAR) countries of Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand and Timor-Leste have been estimated. Program-related unit costs include medicines, tests; human resources, a capital allowance for infrastructure and a support component to capture administration, and supervision.

Patient costs include direct and indirect costs. Direct costs include medical expenses related to consultation or facility admission; and non-medical expenses largely associated with travel. Indirect costs relate to the loss of income through an inability to work through ill-health, or attending health facilities. Unit cost data from each SEARO country have been used where available, and will be provided in a technical report. Key studies included: The Annex of Menzies et al. 2016, Lancet Glob Health 2016;4: e816–26, a review of Laurence YV, Griffiths UK, Vassall A. Costs to health services and the patient of treating tuberculosis: a systematic literature review. Pharmacoeconomics 2015; 33: 939–55, and Annexes for Stop TB 2016-202 Global Plan; and the global TB costing workbook supplied by Avenir Health.

Unit costs and projected occasions of diagnostic services and months of treatment from the epidemiological model were combined to estimate resource needs for passive (PSE, laboratory expansion, new diagnostics, NTP sector improvement) and active case finding (contract tracing, community referral and preventive therapy) based on the above unit costs. Increased program costs are estimated as a proportion of current public health spending in each country, while program, direct patient and indirect patient costs are combined to estimate total TB control and treatment costs. Total costs are expressed as a proportion of Gross National Income (GNI).

Secondly, a cost-effectiveness model was developed in Excel. Epidemiological model outputs were included over a 2017-2035 incremental cost projection, with all future costs being discounted at 3% rate. Results will be presented in 2017 USD, and adjusted using world economic growth deflators (www.worldbank.org). These incremental costs are related to projected reductions in burden of disease in the form of cost-effectiveness ratios. In this case cost-effectiveness ratios associated with different scenarios were estimated using incremental costs per DALY averted. A ratio of the cost of each life years lost to TB (disability adjusted) being avoided as a result an intervention being less than the GNI per person is deemed to be economically attractive.

World Health Organization

Regional Office for South-East Asia