

## Tuberculosis: Past, Present and Future

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### Abstract

#### Background

Tuberculosis (TB) is the second-most common cause of death from infectious disease (after those due to HIV/AIDS). Roughly one-third of the world's population has been infected with *M. tuberculosis*, with new infections occurring in about 1% of the population each year. People with active TB can infect 10-15 other people through close contact over the course of a year.

#### Materials and Methods

The current study is a review survey which was conducted to evaluate of current status of TB prevalence by studying WHO website, Centers for Disease Control and Prevention (CDC), United Nations Children's Fund (UNICEF) and United Nations (UN) websites.

#### Results

In 2014, 9.6 million people fell ill with TB and 1.5 million (1.1 million HIV-negative and 0.4 million HIV-positive) died from the disease. Over 95% of TB deaths occur in low- and middle-income countries, and it is among the top 5 causes of death for women aged 15 to 44. One million children (0-14 years) fell ill with TB, and 140 000 children died from the disease in 2014; also, about 80% of reported TB cases occurred in 22 countries. The 6 countries that stand out as having the largest number of incident cases in 2014 were: India, Indonesia, Nigeria, Pakistan, People's Republic of China and South Africa. The TB death rate dropped 47% between 1990 and 2015.

#### Conclusion

Despite the fact that nearly all patients can be cured, TB remains one of the world's biggest threats. Ending the TB epidemic by 2030 is among the health targets of the newly adopted Sustainable Development Goals.

**Key Words:** Children, HIV/AIDS, Prevalence, Tuberculosis.

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## 1-INTRODUCTION

### 1-1. Tuberculosis (TB)

Tuberculosis, or TB, is an infectious bacterial disease caused by *Mycobacterium tuberculosis*, which most commonly affects the lungs. It is transmitted from person to person via droplets from the throat and lungs of people with the active respiratory disease. In healthy people, infection with *Mycobacterium tuberculosis* often causes no symptoms, since the person's immune system acts to "wall off" the bacteria. The symptoms of active TB of the lung are coughing, sometimes with sputum or blood, chest pains, weakness, weight loss, fever and night sweats. Tuberculosis is treatable with a six-month course of antibiotics (1-3).

### 1-2. Who is most at risk?

Tuberculosis mostly affects adults in their most productive years. However, all age groups are at risk. Over 95% of cases and deaths are in developing countries. People who are infected with HIV are 20 to 30 times more likely to develop active TB (see TB and HIV section). The risk of active TB is also greater in persons suffering from other conditions that impair the immune system. One million children (0-14 years) fell ill with TB, and 140 000 children died from the disease in 2014. Tobacco use greatly increases the risk of TB disease and death. More than 20% of TB cases worldwide are attributable to smoking (4, 5).

### 1-3. Global impact of TB

TB occurs in every part of the world. In 2014, the largest number of new TB cases occurred in the South-East Asia and Western Pacific Regions, accounting for 58% of new cases globally. However, Africa carried the most severe burden, with 281 cases per 100 000 population in 2014 (compared with a global average of 133). In 2014, about 80% of reported TB cases occurred in 22 countries. The 6

countries that stand out as having the largest number of incident cases in 2014 were India, Indonesia, Nigeria, Pakistan, People's Republic of China and South Africa. Some countries are experiencing a major decline in cases, while in others the numbers are dropping very slowly. Brazil and China for example, are among the 22 countries with a sustained decline in TB cases over the past 20 years (1- 3).

### 1-4. Symptoms and diagnosis

Common symptoms of active lung TB are cough with sputum and blood at times, chest pains, weakness, weight loss, fever and night sweats. Many countries still rely on a long-used method called sputum smear microscopy to diagnose TB. Trained laboratory technicians look at sputum samples under a microscope to see if TB bacteria are present. With 3 such tests, diagnosis can be made within a day, but this test does not detect numerous cases of less infectious forms of TB. Diagnosing MDR-TB (see Multidrug-resistant TB section below) and HIV-associated TB can be more complex. A new 2 hour test that has proven highly effective in diagnosing TB and the presence of drug resistance is now being rolled-out in many countries. Tuberculosis is particularly difficult to diagnose in children (1, 5-10).

### 1-5. Treatment

TB is a treatable and curable disease. Active, drug-susceptible TB disease is treated with a standard 6 month course of 4 antimicrobial drugs that are provided with information, supervision and support to the patient by a health worker or trained volunteer. Without such support, treatment adherence can be difficult and the disease can spread. The vast majority of TB cases can be cured when medicines are provided and taken properly. Between 2000 and 2014, an estimated 43 million lives were saved through TB diagnosis and treatment (1, 8-11).

### 1-6. TB and HIV

At least one-third of people living with HIV worldwide in 2014 were infected with TB bacteria. People living with HIV are 20 to 30 times more likely to develop active TB disease than people without HIV. HIV and TB form a lethal combination, each speeding the other's progress. In 2014 about 0.4 million people died of HIV-associated TB. Approximately one third of deaths among HIV-positive people were due to TB in 2014. In 2014 there were an estimated 1.2 million new cases of TB amongst people who were HIV-positive, 74% of whom were living in Africa. WHO recommends a 12-component approach of collaborative TB-HIV activities, including actions for prevention and treatment of infection and disease, to reduce deaths (12-15).

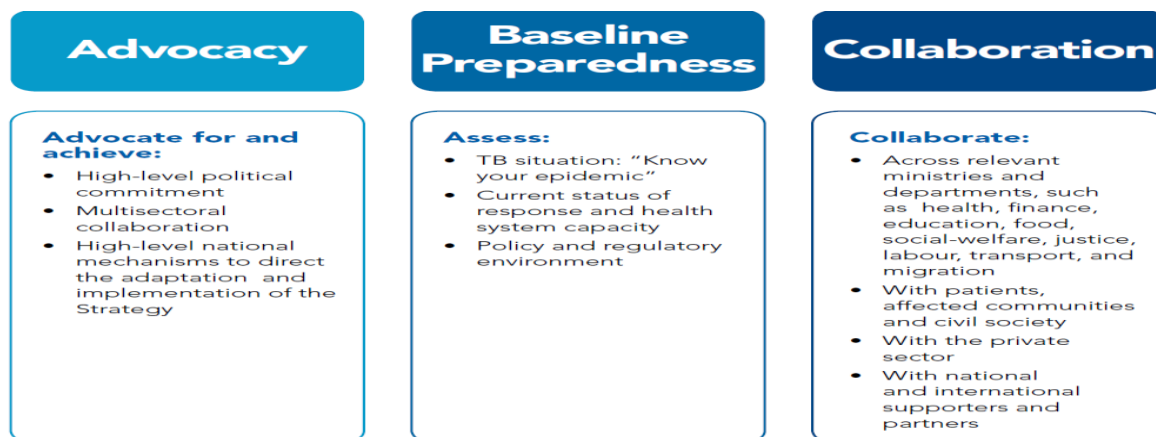
### 1-7. Multidrug-resistant TB

Standard anti-TB drugs have been used for decades, and resistance to the medicines is widespread. Disease strains that are resistant to a single anti-TB drug have been documented in every country surveyed. Multidrug-resistant tuberculosis (MDR-TB) is a form of TB caused by bacteria that do not respond to, at least, isoniazid and rifampicin, the 2 most powerful, first-line (or standard) anti-TB drugs. A primary cause of MDR-TB is inappropriate treatment. Inappropriate or incorrect use of anti-TB drugs, or use of poor quality medicines, can cause drug

resistance. Disease caused by resistant bacteria fails to respond to conventional, first-line treatment. MDR-TB is treatable and curable by using second-line drugs. However second-line treatment options are limited and recommended medicines may not be always available. The extensive chemotherapy required (up to 2 years of treatment) is more costly and can produce severe adverse drug reactions in patients. In some cases, more severe drug resistance can develop. Extensively drug-resistant TB, XDR-TB, is a form of multi-drug resistant tuberculosis that responds to even fewer available medicines, including the most effective second-line anti-TB drugs. About 480 000 people developed MDR-TB in the world in 2014. More than half of these cases were in India, the People's Republic of China and the Russian Federation. It is estimated that about 9.7% of MDR-TB cases had XDR-TB (1, 5, 13).

### 1-8. How can countries adapt the strategy?

To succeed, the strategy requires building on the gains made by current programs while moving beyond to a broader systems response. This includes elevated TB leadership, commitment and collaboration within diverse settings. To roll-out the Strategy, countries and all partners will need advocacy, baseline preparedness and collaboration (Figure.1) (1).



**Fig.1:** The programs adopted for succeed in the MDR-TB

## 2- MATERIALS AND METHODS

### 2-1. Literature Search

The following databases were searched for relevant papers and reports: MEDLINE, CINAHL, WHO website, Centers for Disease Control and Prevention (CDC), United Nations Children's Fund (UNICEF) and United Nations (UN) website, Embase, Cochrane Collection, Google Scholar, Pubmed and ISI Web of Knowledge. Key references from extracted papers were also hand-searched. These searches focused upon papers published between 1990 and 2015.

### 2-2. Search Terms

To evaluate the texts and websites, the singular or combination forms of the following keywords were used to search for the relevant literature: "Tuberculosis", "TB", "Children", "Mortality", "Prevalence" and "Worldwide".

## 3- RESULTS

### 3-1. Tuberculosis

- TB is a top killer worldwide, ranking alongside HIV/AIDS.
- TB places its heaviest burden on the world's most poor and vulnerable, aggravating existing inequalities.
- Due to TB, people face costs or suffer income loss equivalent on average to more than 50% of their income (1, 5, 13).

### 3-2. Burden

9.6 million people fell ill with TB in 2014; 1.5 million men, women and children died from TB in 2014;

1.2 million people living with HIV developed TB, with 0.4 million associated deaths in 2014;

480 000 people developed MDR-TB (multidrug-resistant TB) in 2014, with 190 000 associated deaths (1, 13).

### 3-3. Where are we today?

#### 3-3-1. Progress

43 million lives saved between 2000 and 2014 through effective TB diagnosis and treatment;

47% decline in TB mortality rate and 42% decline in TB prevalence rate since 1990; HIV-related TB deaths down by 32% in the last decade (1/3);

Fragile progress in MDR-TB Treatment for MDRTB has increased with almost all cases detected in 2014 started treatment (1, 3, 13, 15).

#### 3-3-2. Challenges

US\$ 1.4 billion funding gap per year for implementation of existing TB interventions. An additional gap of US\$ 1.3 billion exists for research.

3.6 million people with TB are missed by health systems every year and therefore may not get adequate care they need.

TB/HIV response needs acceleration Antiretroviral treatment, treatment of latent TB infection and other key interventions still need further scale-up.

MDR-TB remains a public health crisis only one in four MDR-TB cases detected and one in two cases cured (1, 13).

#### 3-4. Key facts

- ❖ Tuberculosis (TB) is a top infectious disease killer worldwide.
- ❖ In 2014, 9.6 million people fell ill with TB and 1.5 million died from the disease.
- ❖ Over 95% of TB deaths occur in low- and middle-income countries, and it is among the top 5 causes of death for women aged 15 to 44.
- ❖ In 2014, an estimated 1 million children became ill with TB and 140 000 children died of TB. TB is a leading killer of HIV-positive people: in 2015, 1 in 3 HIV deaths was due to TB.

- ❖ Globally in 2014, an estimated 480 000 people developed multidrug-resistant TB (MDR-TB).
- ❖ The Millennium Development Goal target of halting and reversing the TB epidemic by 2015 has been met globally. TB incidence has fallen by an average of 1.5% peryear since 2000 and is now 18% lower than the level of 2000.
- ❖ The TB death rate dropped 47% between 1990 and 2015.
- ❖ An estimated 43 million lives were saved through TB diagnosis and treatment between 2000 and 2014.
- ❖ Ending the TB epidemic by 2030 is among the health targets of the newly adopted Sustainable Development Goals (1, 13, 15).

### 3-5. How many TB cases and deaths are there?

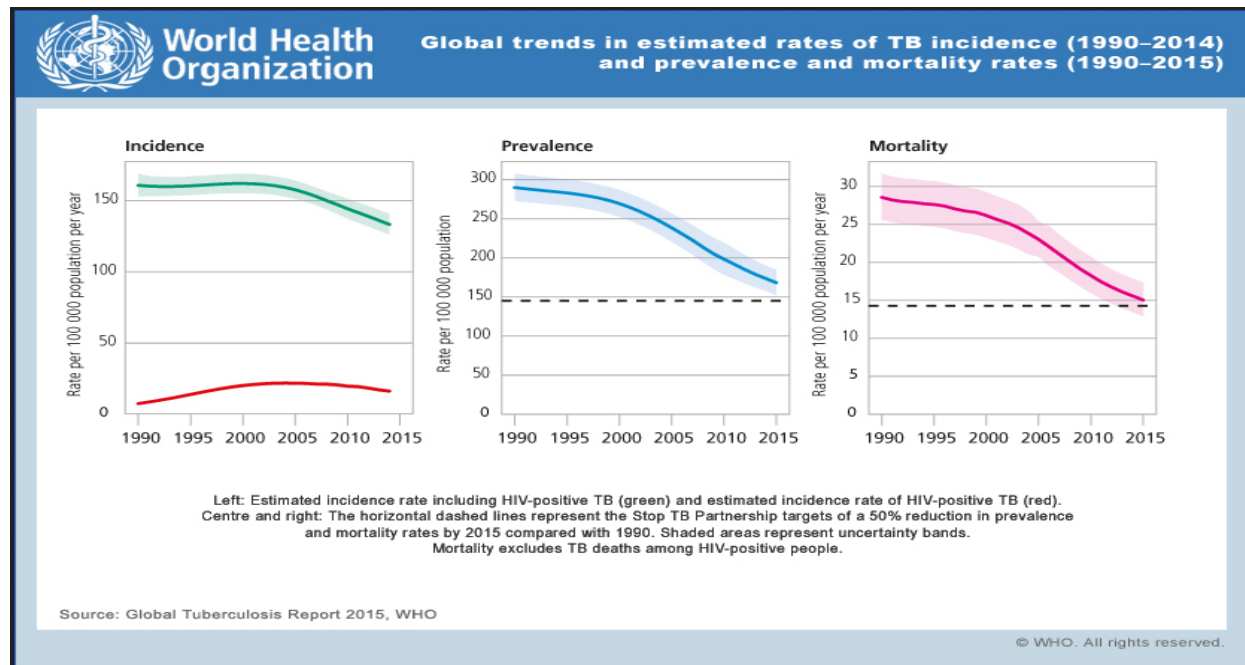
#### 3-5-1. Situation in 2014

Estimated: 9.6 million (range: 9.1–10 million) new TB cases.

Estimated: 1.1 million (range: 0.97–1.3 million) HIV-negative people died from TB and 0.39 million (range: 0.35–0.43 million) HIV-positive people died from TB. Notified: 6.1 million newly diagnosed TB cases. TB incidence has been falling globally for several years and fell at an average rate of about 1.5% per year between 2000 and 2014 (1, 5, 13, 15).

#### 3-5-2. Lives saved

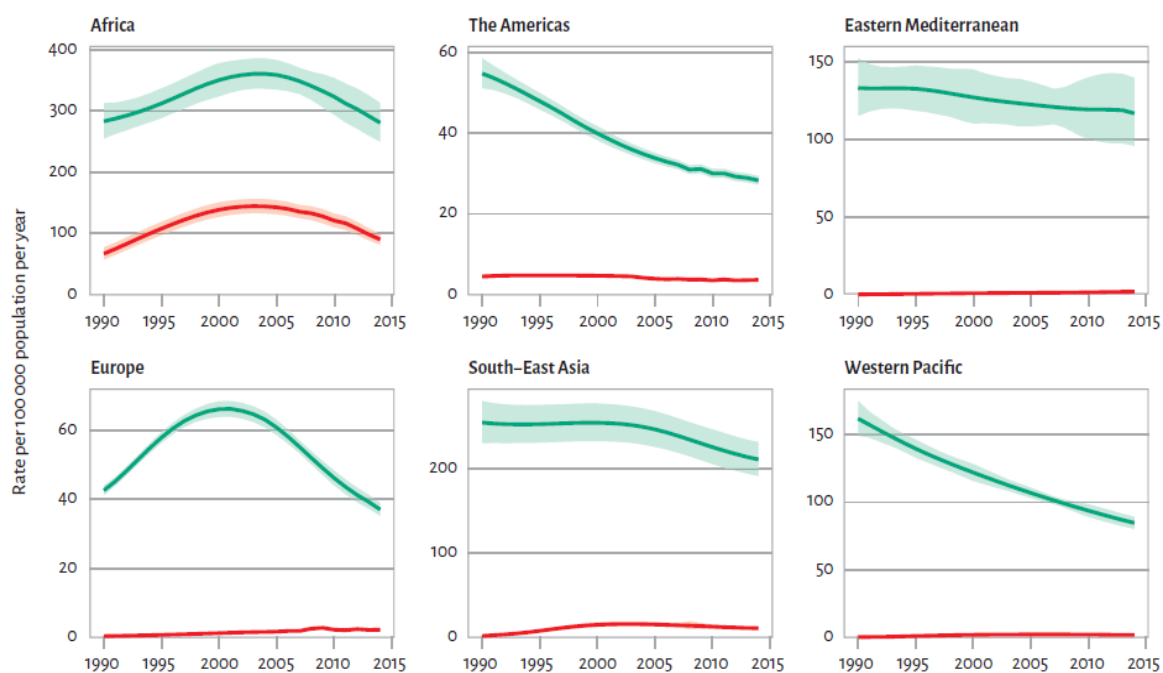
43 million people through effective diagnosis and treatment between 2000 and 2014. The TB mortality rate has fallen by an estimated 47% between 1990 and 2015 (Figur.2). The world and all of WHO’s six regions achieved the Millennium Development Goal target of halting and reversing TB incidence by 2015 (Figure.3)(1, 15, 17).



**Fig.2:** Global trends in estimated rates of TB incidence (1990-2014), and prevalence and mortality rates (1990–2015).

Left: Estimated incidence rate including HIV-positive TB (green) and estimated incidence rate of HIV-positive TB (red). Centre and right: The horizontal dashed lines represent the Stop TB Partnership targets of a 50% reduction in prevalence and mortality rates by 2015 compared with 1990. Shaded areas represent uncertainty bands. Mortality excludes TB deaths among HIV-positive people (17).

Prevalence of TB in the Worldwide



**Fig.3:** Estimated TB incidence rates by WHO region, 1990–2014. Estimated TB incidence rates (green) and estimated incidence rates of HIV-positive TB (red). Shaded areas represent uncertainty bands (17).

**3-6. Global strategy and targets for tuberculosis prevention, care and control after 2015**

From 2016, the goal is to end the global TB epidemic by implementing the End TB Strategy. The WHO End TB Strategy, adopted by the World Health Assembly in May 2014, is a blueprint for countries to end the TB epidemic by driving down TB deaths, incidence and eliminating catastrophic costs. It outlines global impact targets to reduce TB deaths by 90% and to

cut new cases by 80% between 2015 and 2030, and to ensure that no family is burdened with catastrophic costs due to TB. Ending the TB epidemic by 2030 is among the health targets of the newly adopted Sustainable Development Goals. WHO has gone one step further and set a 2035 target of 95% reduction in deaths and a 90% decline in TB incidence - similar to current levels in low TB incidence countries today (Figures 4, 5).

**Vision**  
A world free of TB. Zero deaths, disease and suffering due to TB.

**Goal**  
End the global tuberculosis epidemic.

**Indicators**

- 95% reduction by 2035 in number of **TB deaths** compared with 2015.
- 90% reduction by 2035 in **TB incidence rate** compared with 2015.
- Zero TB-affected families facing **catastrophic costs** due to TB by 2035.

**Fig.4:** The WHO End TB Strategy adapted by World Health Assembly in May 2014.

<b>VISION</b>	<b>A world free of tuberculosis</b> – zero deaths, disease and suffering due to tuberculosis			
<b>GOAL</b>	<b>End the global tuberculosis epidemic</b>			
<b>INDICATORS</b>	<b>MILESTONES</b>		<b>TARGETS</b>	
	<b>2020</b>	<b>2025</b>	<b>SDG 2030</b>	<b>END TB 2035</b>
Reduction in number of TB deaths compared with 2015 (%)	35%	75%	<b>90%</b>	<b>95%</b>
Reduction in TB incidence rate compared with 2015 (%)	20% (<85/100 000)	50% (<55/100 000)	<b>80%</b> <b>(&lt;20/100 000)</b>	<b>90%</b> <b>(&lt;10/100 000)</b>
TB-affected families facing catastrophic costs due to TB (%)	Zero	Zero	<b>Zero</b>	<b>Zero</b>

**Fig.5:** The United Nations Sustainable Development Goals (SDGs) include ending the TB epidemic by 2030 under Goal 3.

The Strategy outlines 3 strategic pillars that need to be put in place to effectively end the epidemic:

- ❖ **Pillar 1:** integrated patient-centred care and prevention
- ❖ **Pillar 2:** bold policies and supportive systems
- ❖ **Pillar 3:** intensified research and innovation.

The success of the Strategy will depend on countries respecting the following 4 key principles as they implement the interventions outlined in each pillar:

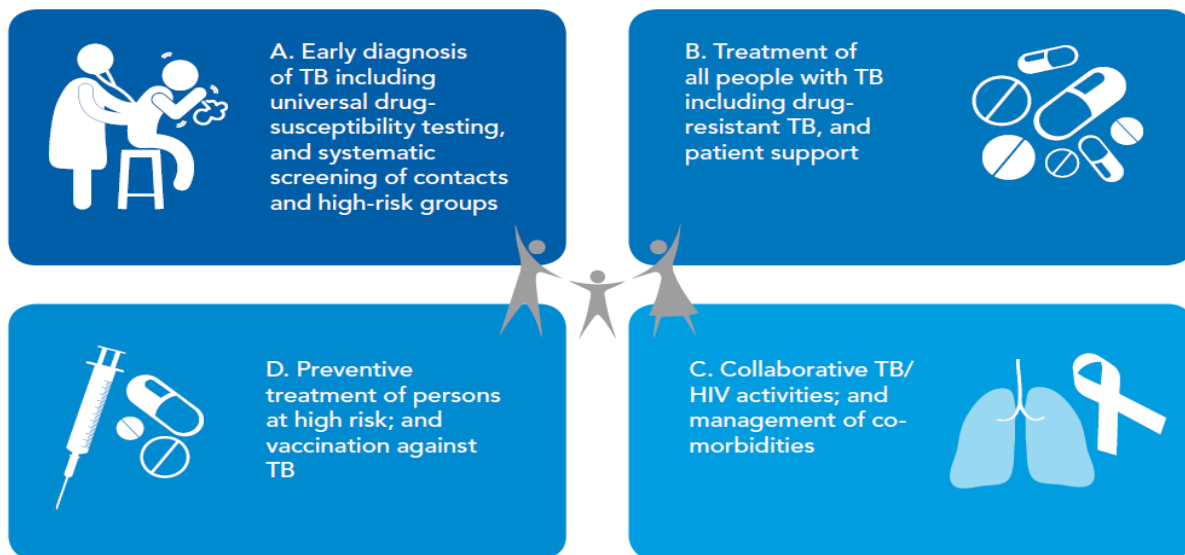
- government stewardship and accountability, with monitoring and evaluation;

- strong coalition with civil society organizations and communities;
- protection and promotion of human rights, ethics and equity;
- adaptation of the strategy and targets at country level, with global collaboration.

**3-6-1. PILLAR 1**

This pillar puts patients at the heart of service delivery. Focuses on early detection, treatment and prevention for all TB patients including children.

- Aims to ensure that all TB patients not only have equal, unhindered access to affordable services, but also engage in their care (Figure.6).



**Fig.6:** How pillar 1 work: Key components.

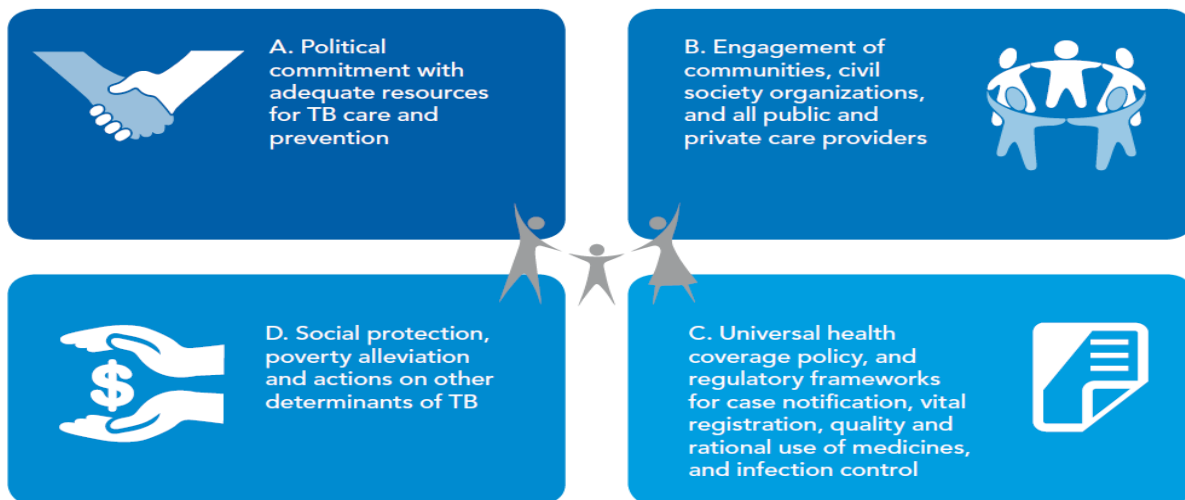
### 3-6-2. PILLAR 2

This pillar requires intense participation across government, communities and private stakeholders (Figure.7).

#### *Bold policies and supportive systems*

- Strengthens health and social sector policies and systems to prevent and end TB.

- Supports implementation of universal health coverage, social protection, and strengthened regulatory frameworks.
- Addresses the social determinants of TB and tackles TB among vulnerable groups such as the very poor, people living with HIV, migrants, refugees and prisoners.



**Fig.7:** How pillar 2 work: Key components.

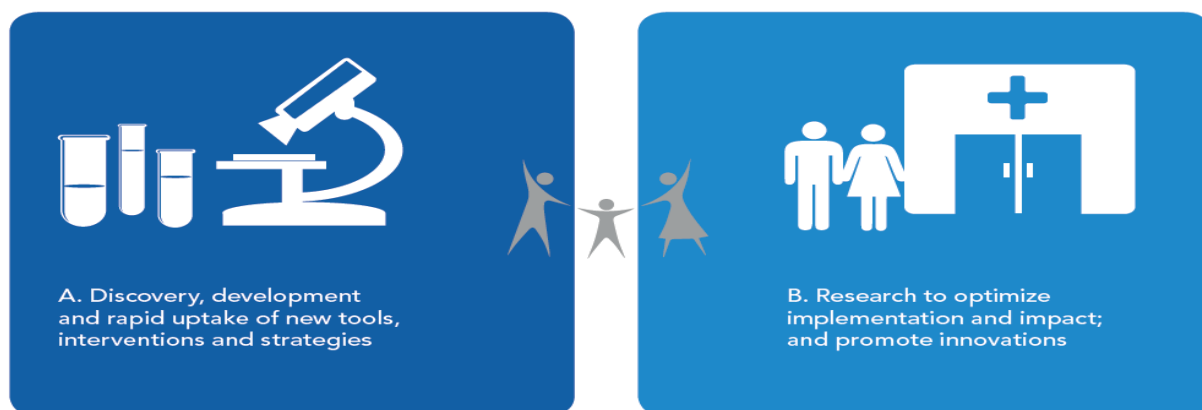
### 3-6-3. PILLAR 3

This pillar on research is critical to break the trajectory of the epidemic and reach the global targets (Figure.8).

#### *Intensified Research and Innovation*

- Aims to intensify research from the development of new tools to their adoption and effective rollout in countries.

- Pursues operational research for the design, implementation, and scaling-up of innovations.
- Calls for an urgent boost in research investments, so that new tools are developed, and made rapidly available and widely accessible in the next decade (1, 5, 16, 17).



**Fig.8:** How pillar 3 work: Key components.



### 3-7. Getting to the 2025 targets requires

Effective use of existing tools to combat TB, complemented by universal health coverage and social protection to:

- Push down global TB incidence rates from an annual decline of 2% in 2015 to 10% by 2025.
- Reduce the proportion of people with TB who die from the disease from 15% in 2015 to 5% by 2025 (1, 13, 16, 17).

### Moving forward to the 2035 targets

Requires the ensured availability of new tools from the research pipeline, in particular:

- Better diagnostics, including new point-of-care tests;
- Safer, easier and shorter treatment regimens;
- Safer and more effective treatment for latent TB infection;
- Effective pre- and post-exposure vaccines (Figure.9) (1).

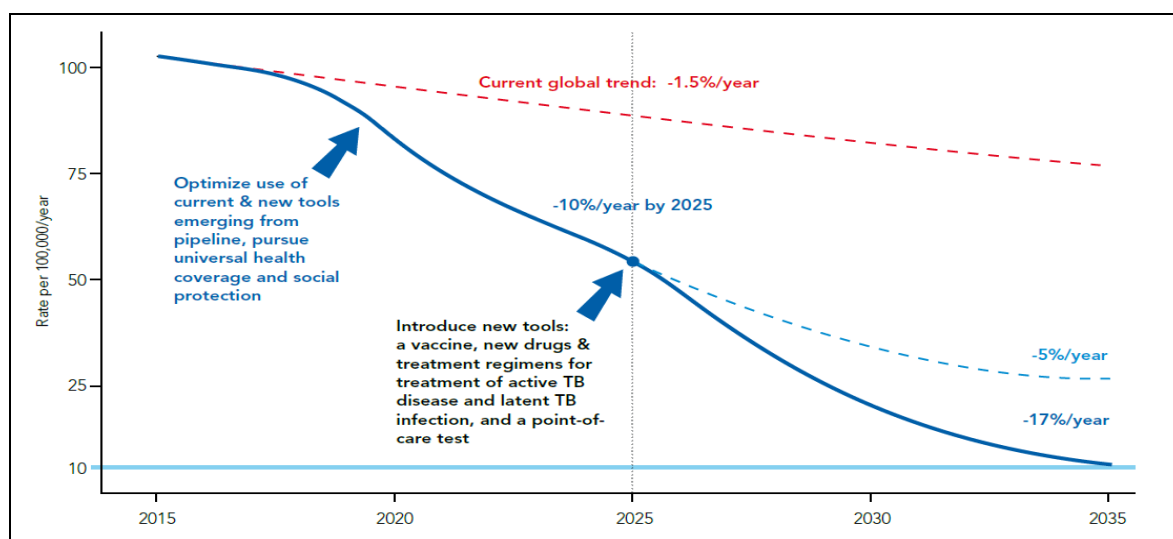


Fig.9: Desired decline in global TB incidence rates to reach the 2035 targets

### 3-8. Reaching the targets

To reach the targets set out in the End TB Strategy, the annual decline in global TB incidence rates must first accelerate from 2% per year in 2015 to 10% per year by 2025. Secondly, the proportion of people with TB who die from the disease (the case-fatality ratio) needs to decline from a projected 15% in 2015 to 6.5% by 2025. These declines in deaths and incidence by 2025 while ambitious are feasible with existing tools complemented by universal health coverage and social protection. To sustain progress beyond 2025 and achieve the SDG\* 2030 and End TB 2035 targets, additional tools must be available by 2025. In particular, a new vaccine that is effective pre- and post-exposure and a

safer and more effective treatment for latent TB infection are needed to reduce the number of new TB cases arising from the approximately 2 billion people worldwide who are infected with M. tuberculosis, as well as better diagnostics and safer and easier treatment including shorter drug regimens for TB disease. For new tools to be available by 2025, greatly enhanced and immediate investments in research and development are required. The figure below shows the projected acceleration of the decline in global TB incidence rates with optimization of current tools combined with progress towards universal health coverage and social protection from 2015, and the additional impact of new tools by 2025(Figure.10) (1, 13, 16, 17).

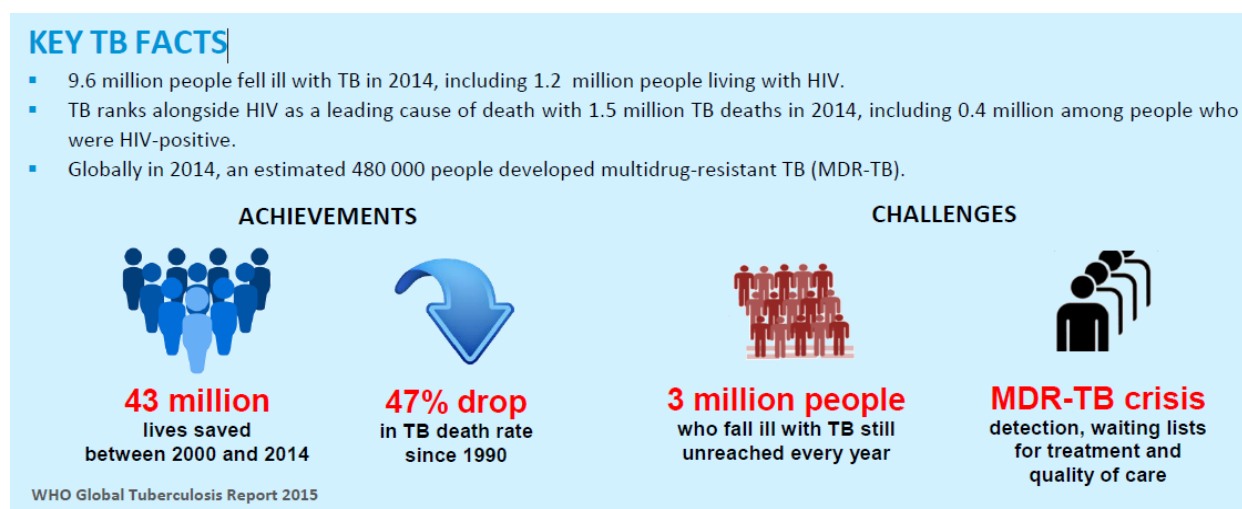


Fig. 10: Global strategy and targets for tuberculosis prevention, care and control after 2015.

### 3-9. Global TB strategy with ambitious targets accepted

The World Health Assembly, convened annually by WHO at the UN Palais des Nations in Geneva, passed a resolution in May 2014 approving with full support the new post-2015 Global TB Strategy with its ambitious targets. The strategy aims to end the global TB epidemic, with targets to reduce TB deaths by 95% and to cut new cases by 90% between 2015 and 2035, and to ensure that no family is burdened with catastrophic expenses due to TB. It sets interim milestones for 2020, 2025, and 2030. The resolution calls on governments to adapt and implement the strategy with high-level commitment and financing. It reinforces a focus within the strategy on serving populations highly vulnerable to infection and poor health care access, such as migrants. The strategy and resolution highlight the need to engage partners within the health sector and beyond, such as in the fields of social protection, labour, immigration and justice. The resolution requests the WHO Secretariat to help Member States adapt and operationalize the strategy, noting the importance of tackling the problem of multidrug-resistant TB and promoting collaboration across international borders. WHO is also asked to monitor implementation and evaluate

progress towards the milestones and the 2035 targets (1, 5, 16).

### 4- CONCLUSION

Tuberculosis (TB) is contagious and airborne. It ranks alongside HIV as a leading cause of death worldwide. 9.6 million people are estimated to have fallen ill with TB in 2014: 5.4 million men, 3.2 million women and 1.0 million children. An estimated 1.2 million people living with HIV developed TB in 2014. There have been major advances in prevention, diagnosis and treatment of TB: mortality has fallen 47% since 1990. Effective diagnosis and treatment of TB saved an estimated 43 million lives between 2000 and 2014. Despite these advances and despite the fact that nearly all cases can be cured, TB remains one of the world's biggest threats. In 2014, TB killed some 1.5 million people (1.1 million HIV-negative and 0.4 million HIV-positive). The toll comprised 890 000 men, 480 000 women and 140 000 children. One in 3 HIV deaths is due to TB.

- ❖ Ending the global TB epidemic is feasible with dramatic decline in TB deaths and cases, and elimination of economic and social burden of TB. Failure to do so will carry serious individual and global

public health consequences. Achievement of this goal by 2035 requires:

- ❖ Expanding the scope and reach of interventions for TB care and prevention, with a focus on high-impact, integrated and patient-centered approaches.
- ❖ Eliciting full benefits of health and development policies and systems, through engaging a much wider set of collaborators across government, communities and the private sector.
- ❖ Pursuing new scientific knowledge and innovations that can dramatically change TB prevention and care.

To ensure full impact, these actions must build on principles of government stewardship, engagement of civil society, human rights and equity, and adaptation to the unique context of diverse epidemics and settings (1, 13, 16-26).

**5- CONFLICT OF INTEREST:** None.

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