K4D | Knowledge, evidence and learning for development

Emerging issues in tuberculosis

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About the author:

Dr Peter MacPherson is a Wellcome Trust Clinical Research Fellow and Senior Lecturer at Liverpool School of Tropical Medicine, UK. He holds a PhD from LSTM, an MRes from University of Liverpool, an MPH from Harvard University, and did his undergraduate medical training at the University of Aberdeen.

Peter is based at the Malawi-Liverpool-Wellcome Trust Clinical Research Programme in Blantyre, Malawi, where he leads the Public Health Research Group. His research focuses on the epidemiology of the HIV and TB co-epidemics in sub-Saharan Africa, and on the development and evaluation of interventions to improve case detection and access to treatment. During his present Wellcome Fellowship, Peter is undertaking a number of randomised controlled trials of HIV/TB interventions, including a pragmatic randomised controlled trial of optimised HIV/TB screening using novel diagnostics and linkage to care among adults attending health centres with symptoms of tuberculosis (PROSPECT Study); an intensive TB/HIV household contact tracing intervention; and a male-partner-based index contact tracing study. During his Wellcome Clinical PhD, Peter did a cluster-randomised trial of a novel HIV self-testing and home initiation of treatment intervention among 17,000 adults in urban communities in Malawi.

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1. Key concepts

Tuberculosis (TB) is a bacterial infection that can cause disease in any part of the body, sometimes many years after initial infection. TB is transmitted between people when someone with active disease in their lungs or throat coughs and generates droplets containing *Mycobacterium tuberculosis*. There is a spectrum of infectiousness: people who produce larger amounts of TB bacteria in their sputum are more infectious, while people with TB in parts of their bodies other than the lungs are generally considered to be non-infectious.

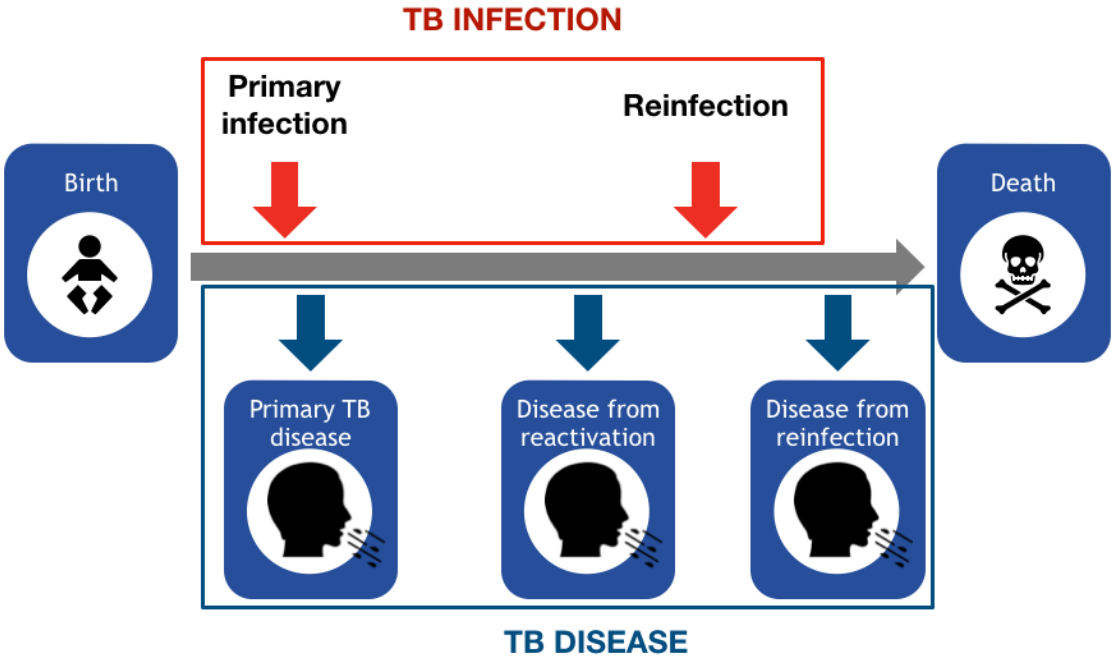
People who have prolonged close contact with infectious TB cases (such as household members) or those who have weakened immune systems (such as very young children and people living with HIV) are at the greatest risk of becoming infected with *Mycobacterium tuberculosis*. In countries with a high burden of TB, the age at which people most commonly become infected with TB is as a young child or in adolescence.

Typical symptoms of active TB include: cough, fever, night sweats, weight loss, coughing up blood, and loss of appetite. If TB disease occurs in a part of the body other than the lungs, there may be local symptoms (such as symptoms of meningitis or swollen lymph nodes in the neck).

TB infection (latent TB) refers to people who have been exposed to someone with infectious TB and have immunological evidence of infection (such as a positive tuberculin skin test) but don't have any symptoms or signs of active TB disease. People with latent TB infection are not infectious to others. Approximately 5-10% of people who are latently infected with TB will progress to develop active TB over the course of their lifetime. However, a number of factors increase the risk of progression from latent TB infection to disease. In general, 50% of people who go on to develop active TB will do so within the first two years of infection. People at the extremes of age (very young or very old) are at greater risk of developing active TB disease due to weakened immune systems. Additionally, people living with HIV infection have a substantially increased risk of TB disease compared to HIV-negative people; instead of having a 5-10% lifetime risk of TB, in some settings, an HIV-positive person's risk of developing active TB disease approaches 10% per year. Other conditions and medications that weaken the immune system, such as diabetes, malnutrition, alcoholism, treatment with immunosuppressant drugs, smoking, occupational exposure to silica dust (for example in miners), and air pollution also increase the risk of progression to TB disease.

2. Prevention, Diagnosis and Treatment

The TB life course



Vaccination against TB

The Bacillus Calmette-Guérin (BCG) vaccine has been used for nearly 100 years and provides moderate protection against infection and progression to TB disease among particular population groups. BCG provides protection against severe disseminated TB and TB meningitis when given to young children, and it can reduce the risk of development of pulmonary TB by about 60% when given to children living in northern latitudes. However, protection seems to be lower for children living in the tropics. The TB vaccine pipeline is limited, and we currently need a renewed focus on research, development, and translation.

Preventing TB

TB is the quintessential disease of poverty. Poor nutrition, unhealthy household and working conditions, and limited access to high quality health care are all strongly associated with increased risk of TB infection and disease.

Addressing the social determinants of TB is critical to improving TB care and prevention.

Priority interventions include:

- access to universal healthcare coverage;
- improved housing quality;

- improved and sustained infection control and quality of care within prisons, healthcare settings, and other congregate settings;
- adequate social protection systems to mitigate the catastrophic costs associated with TB disease.

Finding TB cases

With up to half of TB cases undiagnosed in some settings, efforts to find and treat people with TB need to be considerably enhanced. Until the introduction of the End-TB Strategy in 2015 (see below), the greatest emphasis was placed on finding individuals with sputum smear-positive pulmonary TB (microbiological evidence of TB in the lungs), with the rationale that these individuals were most infectious to others. In practice, this meant that TB case finding initiatives predominately focused on passive case detection—that is offering screening to people attending health facilities with symptoms of TB. However, it is increasingly recognised that passive case detection, while necessary, is not sufficient to close the TB case detection gap. This is because many people with TB symptoms find it difficult and expensive to access health centres and often delay seeking care until the disease is advanced. Additionally, focusing mostly on people with symptoms of pulmonary TB means that patients with other forms of TB may be less emphasised in national policies.

The End-TB Strategy promotes universal access to TB care and prevention. Due to the limitations of the passive case detection approach, recognition of the potential importance of active case finding for TB is rising. Active case finding involves first, systematically identifying populations at risk of TB and with poor access to care and second, offering universal screening and linkage to diagnosis and treatment services to these populations. Particular groups targeted for active case finding will depend on local epidemiology, priorities, and resources but may include: people living with HIV attending HIV care clinics; prisoners; healthcare workers; community members; migrants; and people attending health facilities for any reason.

Evidence for the effectiveness of active case finding approaches is still being established, but there is historical precedence: TB has been successfully controlled in many European and North American settings using active case finding approaches, in conjunction with improvements to living conditions.

Diagnosis of active TB

Diagnosis of active TB can be made by inspecting stained sputum under a light or fluorescence microscope for bacteria of the *Mycobacteria* species (**sputum smear microscopy**). However, this approach is resource intensive, requires a high and sustained degree of microscopy quality—often at primary care level—,poses an infection risk to health workers, and has suboptimal sensitivity (about 40% of cases of active TB will be missed by this approach).

Another diagnostic technique involves incubating a TB culture sputum within a culture bottle for 6-12 weeks. Newer automated culture systems (**the MGIT system**) give an automated signal once the growth of *Mycobacterium tuberculosis* is detected. Although the most accurate

diagnostic tool, TB culture is slow, expensive, requires advanced laboratory capacity, and poses infection risk to health workers, and therefore is not widely available in low resource settings.

A **chest x-ray** can also be used to look for the presence of typical signs of pulmonary TB disease. Chest x-rays may be used to screen large numbers of people rapidly (e.g. during active case finding interventions). However, this requires expensive x-ray equipment and trained radiographers and radiologists. Often, diseases other than TB (such as pneumonia) are mistaken for TB, meaning that an additional confirmatory test is usually required. Increasingly, computer-aided X-ray diagnosis—where image recognition software evaluates an x-ray and gives a probability of TB—is becoming available, although it has not yet been evaluated at scale.

The **GeneXpert MTB/Rif platform** is a relatively new TB diagnostic test that uses a molecular reaction within a completely encased cartridge to amplify TB proteins within a body fluid sample (sputum, stool, urine, etc.) to provide an automated TB diagnosis within 2 hours. Evidence shows that where GeneXpert is available, the time between presentation with TB symptoms and initiation of treatment is substantially reduced, although this has not translated into a reduction in case fatality. GeneXpert also allows for rapid identification of disease resistance to one of the key drugs to treat TB (rifampicin). Many countries have begun expanding availability of GeneXpert MTB/Rif through their primary and secondary health care systems. However, some current limitations include: the high unit cost per test (it is approximately 100 times more expensive than sputum smear microscopy); lower sensitivity for detecting TB among people living with HIV (although this may be improved in the anticipated second generation cartridge); and maintenance and sustainability issues.

The **lateral flow urinary lipoarabinomannan assay (LF-LAM)** is a point of care detection test for active TB that has been developed in recent years. People with active TB secrete in their urine a protein from the TB cell wall, which can be detected by the presence of a visual intensity reaction after the urine is incubated at room temperature for about 25 minutes on a test strip. The LF-LAM test can be done rapidly at the bedside, without laboratory infrastructure, and does not pose an infectious risk to health workers. Two randomised control trials have demonstrated that, among hospitalised patients with advanced HIV infection, the LF-LAM test has high diagnostic accuracy and is associated with reduced risk of death where implemented. Nevertheless, there remain some challenges with this test. Accuracy is currently poor for HIV-negative people and for people living with HIV who are not seriously ill. Additionally, some simplification of the test read strip is required to minimise misinterpretation errors. Hopefully, future generations of this test will address these issues.

Whole genome sequencing (WGS)—where the entire genetic code of TB organisms isolated from patients is described and compared to a reference set of genomes—has now been introduced routinely in England to guide clinical decision-making, earlier detection of resistance, and to support outbreak and epidemiological investigation. However, WGS requires sophisticated laboratory and bioinformatics infrastructure and currently requires that TB be cultured and DNA extracted before sequencing can be done. Additionally, the clinical and public health utility beyond research projects in low resource settings is uncertain. Nevertheless, the speed of advances in the sequencing field may mean that WGS rapidly appears on the horizon as a TB diagnostic tool.

Overall, the currently available diagnostics for active TB are suboptimal—particularly when compared to diagnostics for HIV where a simple finger-prick blood test is cheap, widely available, rapid, and highly accurate.

Evidence from a number of settings shows that the diagnostic and care-seeking pathways and prolonged treatment courses for TB are major contributors to patients experiencing catastrophic costs from TB.

Latent TB diagnosis and treatment

Currently the diagnosis of latent TB infection and prediction of which individuals will go on to develop active disease and require treatment is suboptimal. The tests available for the detection of latent TB rely on the body's immune response to exposure to *Mycobacterium tuberculosis.* One such test is the **tuberculin skin test (TST**), where TB proteins are injected within skin layers. The size of the immune reaction is read after 48-72 hours to determine the likelihood of infection being present and of that individual progressing to develop the disease. Other tests available include the **TSPOT test**, with requires that a venous blood sample be incubated with TB proteins in a laboratory. In the future, a blood test that uses a particular gene signal associated with risk of TB progression may become available. The test shows early promise, although larger studies are required.

Treatment of latent TB infection can reduce the risk of development of active TB disease, particularly for high risk individuals, such as children and people living with HIV. Currently, treatment regimens available include a 6-month course of isoniazid (known as isoniazid preventive therapy (IPT)), a 3-month course of rifapentine and isoniazid, and a 1-month course of isoniazid and rifapentine, which may be superior for people living with HIV.

Achieving high coverage of latent TB diagnosis, treatment, and adherence has been extremely challenging in most settings. Novel diagnostics, shortened and more effective treatment regimens, and operational research to improve outcomes are urgently required.

Antituberculosis treatment

Antituberculosis treatment is a combination of antibiotics that must be taken for at least 6 months to treat active TB disease. At a minimum, four different drugs are required to achieve high treatment success rates, and TB is usually curable if good levels of adherence to treatment are sustained throughout the 6-month treatment period. National TB programmes recommend a standardised 6-month treatment regimen of at least four antibiotics: rifampicin, isoniazid, pyrazinamide and ethambutol tablets. This is known as standard short course therapy as evidence from many years of trials, laboratory studies, and observational studies shows that this approach is likely to result in a successful treatment outcome for most people with TB. Standard short course TB treatment can usually be given to patients on an outpatient basis, provided they are able to take their medication with a high degree of reliability or have someone able to support them to do so.

Side effects are relatively common with antituberculosis treatment and may range from mild to life-threatening. Additionally, many of the antituberculosis drugs may interact with other medications (particularly oral contraceptives, antibiotics, and antiretroviral medications for treating HIV), meaning that treatment and dosing regimens may have to be modified.

Occasionally, the standard short course TB treatment may need to be adapted or prolonged. This is usually because there is evidence that the TB bacteria has developed resistance to the standard short course drugs, or because there is TB in a part of the body other than the lungs, such as TB meningitis or TB of the bone. In these cases, injectable drugs may be required for a long period, often necessitating prolonged inpatient hospital stays.

All TB treatment cases should be recorded in a standard TB treatment register that records the patient characteristics, site of TB disease in the body, the results of any investigations for TB and treatment outcomes (cured, completed treatment, failed treatment, died, transferred out, or lost to follow-up). TB treatment registers form the basis national and international TB surveillance systems.

Multi-and extensively-drug resistant TB (MDR-TB and XDR-TB)

MDR TB occurs when the TB organism is resistant to two of the drugs that comprise the standard short course treatment regimen (rifampicin and isoniazid). XDR TB occurs when the TB organism is resistant to rifampicin and isoniazid, as well as some of the second line drugs used to treat MDR-TB. MDR-TB and XDR-TB usually occur when a patient has had suboptimal treatment for active TB (either an inappropriate drug regimen or poor adherence), meaning that the TB bacteria evolves to develop resistance. However, in some places, such as in health care-associated outbreaks or in weak health systems in Eastern Europe, widespread MDR-TB prevalence of resistant disease among TB cases signifies that resistant organisms may be directly transmitted between people. MDR-TB and XDR-TB require prolonged courses of complicated and potentially toxic antibiotic treatments, often lasting up to 18-20 months, with a considerable amount of time spent in confinement as an inpatient receiving daily injections. Outcomes for people with MDR-TB and XDR-TB are poor, and mortality rates are high. Management of MDR-TB and XDR-TB is complex and expensive, and most countries in low resource settings have low capacity to respond to outbreaks of resistant infection, to rapidly diagnose resistant cases, or to support the management of people requiring treatment.

In recent years, the development of two new antituberculosis drugs—bedaquilline and delamanid, the first new TB drugs in nearly 50 years—and potential high-levels of treatment success obtained using combinations of these drugs with other TB drugs in a shortened 9-month regimen—has given hope that a more tolerable, outpatient treatment approach could be successful. This so-called “Bangladesh regimen” is currently been trialled in a multi-country study, and preliminary results show that this regimen can support patients to return to work earlier and reduce catastrophic household costs. Full results are awaited.

3. Epidemiology of TB

TB is now the leading infectious killer worldwide, and causes more deaths per year than HIV and malaria combined. An estimated one-quarter of the world’s population have latent TB, although rates are substantially higher in some settings, such as in sub-Saharan Africa.

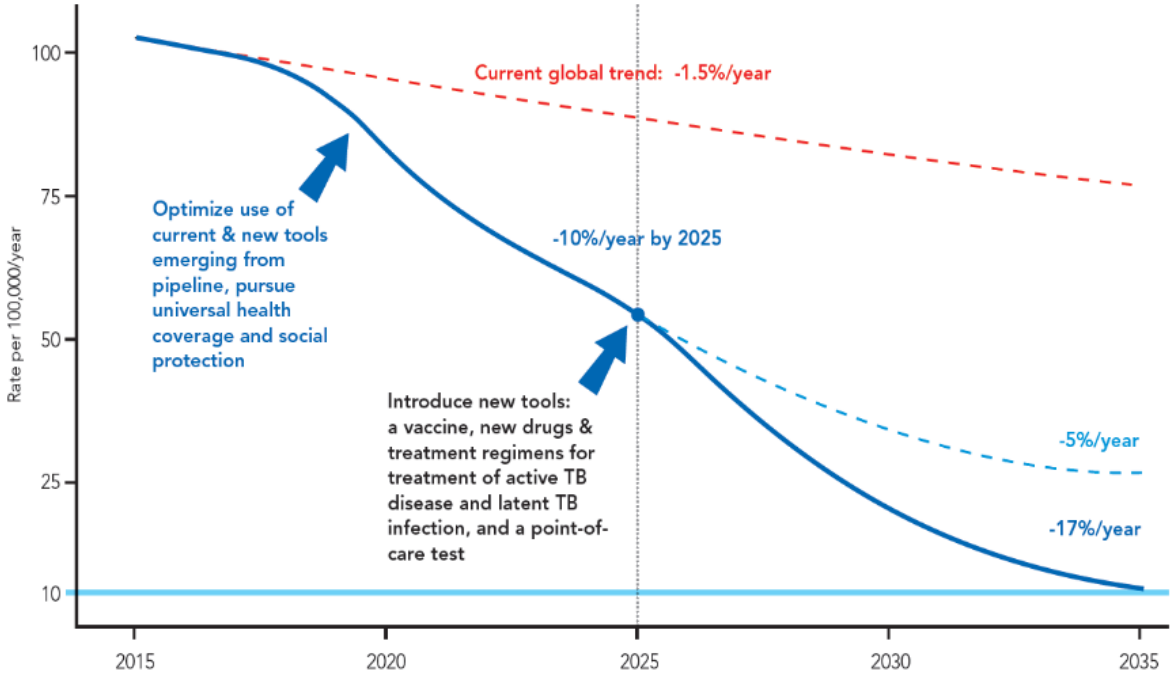
In 2016, 10.4 million new cases of TB occurred, and 1.8 million people died of TB. It is estimated that globally 39% of people with active TB disease went undetected by national treatment programmes. In Africa, this figure is higher, with nearly half of cases remaining undetected.

The estimated incidence of active TB disease per head of population is highest in the countries of sub-Saharan Africa, reflecting the effect of the HIV epidemic. TB incidence approaches as high as 2% per year in urban settings such as Cape Town. In terms of absolute numbers however, six countries (India, Indonesia, China, Nigeria, Pakistan and South Africa) amount for at least 60% of all new TB cases.

Of the 6.3 million new cases of TB registered by national TB programmes, 0.5 million had MDR-TB, and 0.5 million had HIV co-infection, with 82% of TB deaths among HIV-positive people occurring in sub-Saharan Africa.

The global incidence of TB has been slowly declining at an estimated rate of 1.5% per year, though there are considerable regional disparities. However, this overall decline is insufficient to meet global TB elimination goals, and intensified funding, research, development, and implementation of novel TB prevention and care approaches are required.

Estimated TB incidence under current and potential trends



4. The End TB Strategy and Sustainable Development Goals (SDGs)

The End TB strategy was adopted by the World Health Organisation (WHO) in 2015 and has an overall goal of ending the global TB epidemic.

Three specific targets have been developed:

- 95% reduction in TB deaths in 2035 compared to 2015 levels;
- 90% reduction in TB incidence in 2035 compared to 2015 levels;
- no households affected by catastrophic costs.

A number of End-TB milestone targets have been set for 2020 and for 2030.

VISION	**A world free of TB—zero deaths, disease and suffering due to TB**			
GOAL	**End the global TB epidemic**			
	MILESTONES		TARGETS	
INDICATORS	2020	2025	SGD 2030	END TB 2035
Percentage reduction in the absolute number of TB deaths (compared to 2015)	35%	75%	90%	95%
Percentage reduction in the TB incidence rate (compared to 2015)	20%	50%	80%	90%
Percentage of TB-affected households experiencing catastrophic costs due to TB (level in 2015 unknown)	0%	0%	0%	0%
PRINCIPALS	1. Government stewardship and accountability, with monitoring and evaluation. 2. Strong coalition with civil society organisations and communities 3. Protection and promotion of human rights, ethics and equity. 4. Adaptation of the strategy and targets at country level, with global collaboration.			
PILLARS AND COMPONENTS	**1. Integrated, patient-centred care and prevention** a. Early diagnosis of TB including universal drug-susceptibility testing and systematic screening of contacts and high-risk groups.			

	b. Treatment of all people with TB, including drug-resistant TB and patient support. c. Collaborative TB/HIV activities and management of comorbidities. d. Preventive treatment of persons at high risk and vaccination against TB. **2. Bold policies and supportive systems** a. Political commitment with adequate resources for TB care and prevention. b. Engagement of communities, civil society organizations, and public and private care providers. c. Universal health coverage policy and regulatory frameworks for case notation; vital registration; quality and rational use of medicines; and infection control. d. Social protection, poverty alleviation and actions on other determinants of TB. **3. Intensified research and innovation** a. Discovery, development, and rapid uptake of new tools, interventions, and strategies b. Research to optimize implementation and impact and promote innovations.

It is clear that the End TB Strategy closely aligns with the SDGs.

In particular, the following SDG targets are well-aligned with the End-TB strategy:

- SDG 3: Ensure healthy lives and promote well-being for all at all ages
- SDG 1: End poverty in all its forms everywhere
- SDG 2: End hunger, achieve food security and improved nutrition and promote sustainable agriculture
- SDG 5: Achieve gender equality and empower all women and girls
- SDG 7: Ensure access to affordable, reliable, sustainable and modern energy for all
- SDG 8: Promote inclusive and sustainable economic growth, employment and decent work for all
- SDG 10: Reduce inequality within and among countries
- SGD 11: Make cities and human settlements inclusive, safe, resilient and sustainable

Ending the TB epidemic will require substantial efforts beyond biomedical interventions. Expanding access to universal health care, strengthening social protection systems and committing to achieving the SDGs will need coordinated action at all levels of society.

With the experience gained from identifying and responding to the MDR-TB and XDR-TB epidemics, TB can be seen as a pathfinder case study for responding to the growing threat of antimicrobial resistance (AMR).

The Global Action Plan on AMR promotes:

- the need for an effective “one health” approach involving coordination among numerous international sectors and actors;
- improving awareness and understanding of antimicrobial resistance through effective communication, education and training;
- strengthening knowledge and evidence base through surveillance and research;
- reducing the incidence of infection through effective sanitation, hygiene and infection prevention measures;
- optimising the use of antimicrobial medicines in human and animal health;
- developing the economic case for sustainable investment that takes account of the needs of all countries and increasing investment in new medicines, diagnostic tools, vaccines and other interventions.

5. Catalysing partnership to action for TB

Funding for TB research, development and implementation has lagged considerably behind other major infectious diseases for decades. However, with the growing realisation that insufficient progress is currently being made on addressing the TB epidemics and the underlying determinants of TB, the global community has begun to mobilise.

In September 2018, a UN High Level Meeting of heads of states at the UN General Assembly will take place, focusing specifically on TB. This provides a unique opportunity for the global TB community, countries, regions, civil society and ministers to coalesce around a shared momentum to concentrate efforts to meeting the End TB targets and SDGs.

6. Questions to guide readings

1. Where you work, what populations and groups are under-served by TB diagnosis, care, and prevention services? How can these groups be more effectively reached?
2. Does your country's national TB plan emphasise TB prevention, social protection, universal health care access and elimination of catastrophic costs? If not, how can you influence key policymakers to raise awareness of these issues?
3. In your setting, what are the key knowledge gaps in TB that could be addressed by operational research studies? Do you know who to work with in the Ministry of Health and National TB Programme to foster a culture of research, innovation and development?
4. With the upcoming UN High Level Meeting on TB, what influence does your Ministry of Health have on setting an agenda towards accelerated action for ending the TB epidemic?
5. Can your Ministry of Health articulate the importance of health systems strengthening for the prevention of MDR-TB in line with the Global Action Plan on AMR?

7. Readings

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