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The impact of novel diagnostics on infectious disease epidemics

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Declaration

I declare that all the work presented in this thesis is my own. This work was conducted under the supervision of Professor Nimalan Arinaminpathy and Professor Timothy Hallett. Chapters 4 and 6 have been published (listed below). I would like to acknowledge the following collaborators: the Foundation for Innovative New Diagnostics for chapters 4 and 6, Johns Hopkins University for chapter 6, and the Clinton Health Access Initiative for chapter 5.

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Abstract

Diagnostic tests play a crucial role in the control and surveillance of infectious diseases, and to ensure effective clinical management. Novel diagnostic tests are traditionally evaluated in terms of their accuracy (sensitivity and specificity). Using mathematical models, I examine the impact of different novel diagnostic tests on the tuberculosis ("TB") and severe acute respiratory syndrome coronavirus 2 ("SARS-CoV-2") epidemics, and investigate how the context in which these tests are used may affect this impact.

In chapter 3, I evaluate the use of a hypothetical biomarker test that can detect individuals at imminent risk of progressing to active TB disease (incipient TB) and subsequent TB preventive treatment ("TPT") initiation in a high TB burden setting. I demonstrate that biomarker-led TPT can have a significant impact on TB incidence in a high TB burden setting; however, the cost of implementing such a strategy is likely to be prohibitive given the testing effort needed to identify those with incipient TB, even if testing is targeted to populations at high risk of TB.

Next, in chapter 4, I evaluate the use of urine-based tests for active TB disease, in a high TB and HIV burden setting. Although current urine-based tests for TB suffer from poor sensitivity, these tests are continuously improving, and are essential for TB diagnosis amongst patient subgroups who struggle to produce quality sputum and who are therefore missed by traditional methods of TB diagnosis. I demonstrate that although urine-based diagnostic tests reduce mortality amongst people living with HIV, population-level epidemiological impact is not seen unless the tests are deployed outside of HIV care and into routine TB care.

In chapter 5, I investigate the cost and epidemiological impact of expanding different TB public-private sector engagement services. My results reveal that services involving the use of Xpert, a highly accurate but costly test for diagnosing active TB disease are epidemiologically impactful, but costly, and thus have the highest cost per TB case or TB death averted than other services.

Finally, in chapter 6, I explore the context under when cheap but less accurate rapid antigen diagnostic tests ("Ag-RDTs") offer greater public health value than more accurate but costly nucleic acid amplification tests ("NAATs") that often have high turnaround times. My results highlight that Ag-RDTs-led strategies, despite their imperfect sensitivity and specificity, are more impactful at a lower cost than NAATs under different use-cases.

Overall, the context in which diagnostic tests are used is crucial in anticipating their impact. Factors, including but not limited to testing eligibility, levels of current testing and turnaround time, can affect

the potential epidemiological impact of a diagnostic test. Thus, future evaluation of diagnostic tests should move away from focussing exclusively on accuracy and move towards clearly defining different use-cases and investigating which factors other than accuracy, may affect the epidemiological impact of a diagnostic test.

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Abbreviations

Acronym	Definition
3HP	Weekly dose of rifapentine and isoniazid for 3 months
6H	Daily dose of isoniazid for 6 months
9H	Daily dose of isoniazid for 9 months
Ag-RDT	Rapid antigen diagnostic tests
AlereLAM	Alere Determine™ LAM Ag
ART	Antiretroviral therapy
ARTI	Annual risk of infection
BCG	Bacillus Calmette-Guerin vaccine
CDC	Centre for Disease Prevention and Control
CEA	Cost-effectiveness analysis
CFU	Colony forming units
CHAI	Clinton Health Access Initiative
CMEs	Continuing Medical Education
COVID-19	Novel coronavirus disease 2019
CrI	Credible intervals
DALY	Disability-adjusted life years
DOTS	Directly Observed Treatment, Short course
DR-TB	Drug-resistant TB
DS-TB	Drug-susceptible TB
EUA	Emergency use authorisation
FDA	U.S. Food and Drug Administration
FDC	Fixed-dose combination
FIND	Foundation for Innovative New Diagnostics
FujiLAM	Fujifilm SILVAMP TB LAM
GDP	Gross domestic product
HCW	Healthcare workers
HIC	High-income country
ICER	Incremental cost-effectiveness ratio
IGRA	Interferon-gamma release assay
IFN-γ	Interferon-gamma
IQR	Interquartile range
JEET	Joint Effort for Elimination of Tuberculosis
LAM	Lipoarabinomannan
LMIC	Low- and middle-income country
LTBI	Latent TB infection
MCMC	Markov chain Monte Carlo
MDR-TB	Multi-drug resistant TB
MTB	Mycobacterium tuberculosis
NAAT	Nucleic acid amplification test
NPV	Negative predictive value
NTEP	National TB Elimination Programme
NTP	National TB program
NTT	Number needed to treat
ODE	Ordinary differential equation
OOP	Out-of-pocket
PLHIV	People living with HIV
PPP	Public-private partnerships
PPSA	Patient-Provider Support Agencies
PPV	Positive predictive value
PRCC	Partial rank correlation coefficient
QALY	Quality-adjusted life years
QFT-GIT	QuantiFERON-TB Gold In-Tube
RNTCP	Revised National TB Control Programme
ROC	Receiving operating curve

RR-TB	Rifampicin-resistant TB
RSSY	Rashtriya Swasthya Suraksha Yojana scheme
RT-PCR	Real-time reverse-transcription polymerase chain reaction assay
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCT	Specimen collection and transportation
TB	Tuberculosis
TPP	Target product profile
TPT	TB preventive treatment
TST	Tuberculin skin test
WHO	World Health Organisation
XDR-TB	Extensively drug-resistant TB
Xpert	Xpert® MTB/RIF
YLD	Years lost due to disability
YLL	Years lost due to premature mortality

Chapter 1: Introduction

1.1. The importance of diagnostic tests

Diagnostic tests are used to detect the presence of a pathogen or evidence of a recent infection. Once a diagnosis has been made, an appropriate course of action can be taken by the clinician; this may include treatment commencement, surgery or contact tracing. Diagnostic tests are important for several reasons:

1) *Effective clinical management.* It is not always feasible to treat all patients suspected of having a disease due to the cost and risk of side effects from treatment; instead, diagnostic tests help the clinician rule-in or rule-out certain hypotheses. The earlier an infection is detected, the quicker the appropriate course of action can be pursued. This in turn, reduces the likelihood of the patient suffering from severe outcomes and increases the likelihood of treatment success (1–3). Timely detection and thus, early treatment initiation, may also reduce the time until recovery, and allow patients to return to work sooner, reducing societal costs.

2) *Appropriate disease control.* Detecting infectious individuals and their contacts is crucial for outbreak control to reduce onward transmission. Diagnostic tests can also be used for screening of the population to reduce transmission from asymptomatic individuals. Finally, another form of disease control is prevention; for example, detecting latent tuberculosis ("TB"), or detecting abnormal pre-cancerous cells in the cervix.

3) *Disease surveillance.* Surveillance is needed to prevent and control disease. It informs governments on the levels of circulating diseases, whether a change in policy is needed, and if the health system has sufficient capacity to respond. It also enables scientists to track trends and monitor what interventions are or are not working.

1.2. Thesis overview

The overarching aims of this thesis are to examine the impact that novel diagnostic tests may have on infectious disease epidemics, and to investigate how the context in which tests are used in is important in determining epidemiological impact. The focus will be on TB, which is the leading cause of death from an infectious disease. With the emergence of a novel coronavirus, severe acute respiratory syndrome coronavirus 2 ("SARS-CoV-2") at the end of 2019, I had the opportunity to apply the

concepts and approaches I learnt from modelling TB diagnostics to SARS-CoV-2 diagnostics. The purpose of each chapter is as follows:

- **Chapter 2:** A review of the literature which informed the subsequent chapters. I first provide an overview of diagnostic tests, followed by the epidemiology of TB and SARS-CoV-2, with a particular emphasis on diagnosis. I also review the differences between the South African and Indian healthcare setting, two settings with a high TB burden. Finally, I review common methodologies used to examine the potential impact of diagnostic tests.

- **Chapter 3:** Investigating the impact of detecting incipient TB on the TB epidemic in India. I develop a mathematical model of TB transmission that incorporates mixing between high-risk and low-risk populations. I further examine the cost-drivers of such an intervention, under what circumstances it may be considered cost-effective, and how results differ across different risk groups.

- **Chapter 4:** Investigating the impact of detecting active TB disease amongst people living with HIV with a urine-based test on the TB epidemic in South Africa. I develop a mathematical model of TB that incorporates HIV co-infection. I also differentiate between different patient sub-groups, in order to examine how test eligibility may impact results.

- **Chapter 5:** Investigating the impact and cost of private sector engagement in India on the TB epidemic. I develop a mathematical model of TB transmission incorporating drug resistance and differentiating between the public and private healthcare sector. I also develop a costing model to estimate the cost of scaling up these different engagement services.

- **Chapter 6:** Quantifying the trade-off between accurate but expensive and slow tests, with less accurate but cheaper and faster tests, for SARS-CoV-2. I develop a decision-tree to evaluate the impact of these tests under two use-cases (a community and hospital setting). I examine which variables are most influential in determining the value of these tests.

- **Chapter 7:** Discussing and concluding the findings of this thesis.

Chapter 2: Literature Review

2.1. The characteristics of diagnostic tests

2.1.1. Sensitivity and specificity

The performance of a test is determined by its sensitivity and its specificity. Sensitivity is a test's ability to classify an infected individual as a true positive, whereas specificity is a test's ability to classify a disease-free individual as a true negative (table 2.1). To determine the sensitivity and specificity of a new diagnostic test, the test is compared to the best currently available test, called a gold standard. If the best available test does not perform well, an alternative strategy is a composite reference standard, which involves combining several diagnostic tests (4). There is a trade-off between the sensitivity and specificity of a test, which will depend on the cut-off chosen for a positive diagnosis. Receiving operating curves ("ROC") compare the accuracy of different cut-off points, by plotting the rate of true positives (sensitivity) against the rate of false positives (1 – specificity) (fig 2.1). A line with gradient y=x indicates a test that performs no better than chance. The greater the area under the curve, the greater its accuracy.

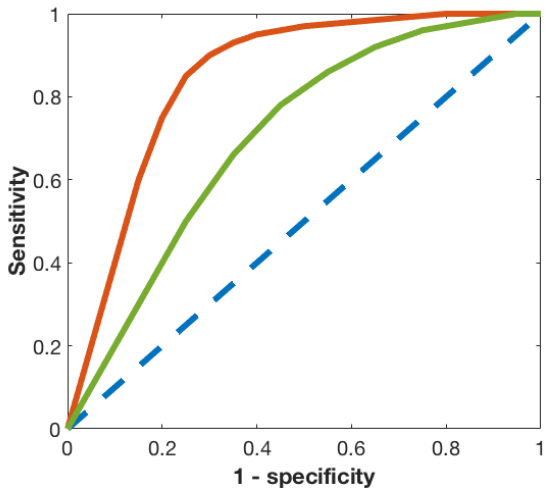

Figure 2.1. Example of a ROC curve. The blue-dashed line represents a test that performs no better than chance. Tests that perform better than chance lie to the left; the greater the area under the curve, the more accurate a test. In other words, the red-line represents a test that is more accurate than a test that is represented by the green-line; both in turn, are more accurate than a test represented by the blue-dashed line.

2.1.2. Positive and negative predictive values

The positive predictive value ("PPV") and the negative predictive value ("NPV") are calculated by combining the measures of sensitivity and specificity with disease prevalence. The PPV is defined as the proportion of those with a positive test that have the disease; NPV is defined as the proportion of

those with a negative test that do not have the disease (table 2.1). Increasing the prevalence of a disease increases the PPV and decreases the NPV.

New test result	**Disease status (according to the gold standard)**	
	Positive	Negative
Positive	True positive ("TP")	False positive ("FP")
Negative	False negative ("FN")	True negative ("TN")
	Sensitivity = TP / (TP + FN)	**Specificity** = TN / (TN + FP)
	PPV = TP / (TP + FP)	**NPV** = TN / (TN + FN)

Table 2.1. Calculating sensitivity, specificity, positive predictive value, and negative predictive value.

2.1.3. Target product profiles

The ideal characteristics of a diagnostic test, including sensitivity and specificity, are outlined in target product profiles ("TPP"). A TPP is a tool used to plan for the development of new products, listing the ideal characteristics a new product, whether a new drug, vaccine or test, should have, and the target population. TPPs are used by industry, but also by the World Health Organisation ("WHO") to help inform product developers, R&D and other agencies, what the priorities are and what products are urgently needed across a range of diseases.

What these ideal characteristics are is highly dependent on the setting the new test is aimed towards, and what the setting considers the most important outcome; for example, whether the aim of the test is to reduce transmission, reduce costs, or to guide clinical management. One important test characteristic is test accuracy, which is determined by sensitivity and specificity. Whether a test with high sensitivity but lower specificity is favoured, or vice versa, will depend on the setting, disease, and the relative magnitude of outcomes for true positives versus false negatives and true negatives versus false positives. For example, a test with high sensitivity may be favoured for a disease with high severity to reduce the chance of a misdiagnosis and for timely treatment initiation, whereas if the prevalence of a disease is low, a test with high specificity may be favoured to reduce the risk of false positives and unnecessary treatment. Other test characteristics that are often considered include cost, infrastructure requirements (including training requirements for healthcare workers and electricity requirements) and turnaround time. Again, the relative importance of these additional characteristics is highly setting-dependent. For example, a diagnostic test whose aim is to detect a disease in hard-to-reach areas that have little health infrastructure, would need to be suitable at the point-of-care, and should ideally meet the 'ASSURED' criteria: **A**ffordable, **S**ensitive, **S**pecific, **U**ser-friendly (minimum training required), **R**obust and rapid, **E**quipment-free, and **D**eliverable to the target population (5). On the other hand, in a setting concerned less about speed but more about accuracy,

for example for disease surveillance, then a highly sensitive and specific laboratory-based test is required.

2.2. Tuberculosis

2.2.1. Epidemiology

Tuberculosis ("TB"), caused by the bacterium *Mycobacterium tuberculosis* ("MTB"), is a leading cause of death, globally, from an infectious disease (6). In 2019, there were an estimated 8.9-11.0 million new cases and 1.20-1.50 million TB deaths (6). TB affects mainly low- and middle- income countries ("LMICs"), with just under half of incident cases in 2019 occurring in just five countries (India, Indonesia, China, the Philippines, and Pakistan) (6).

2.2.2. Natural history

TB is an airborne disease and is transmitted by aerosol droplets (7). According to current understanding of the natural history of TB, there are two main stages: latent infection ("LTBI") and active disease, both of which are described in further detail below. Traditionally, LTBI and active disease have been treated as two separate entities; however, increasing evidence suggests they should be considered to be at opposite ends of a spectrum, with individuals moving forward or backward along this spectrum depending on various factors, including immune status (8,9) (fig 2.2).

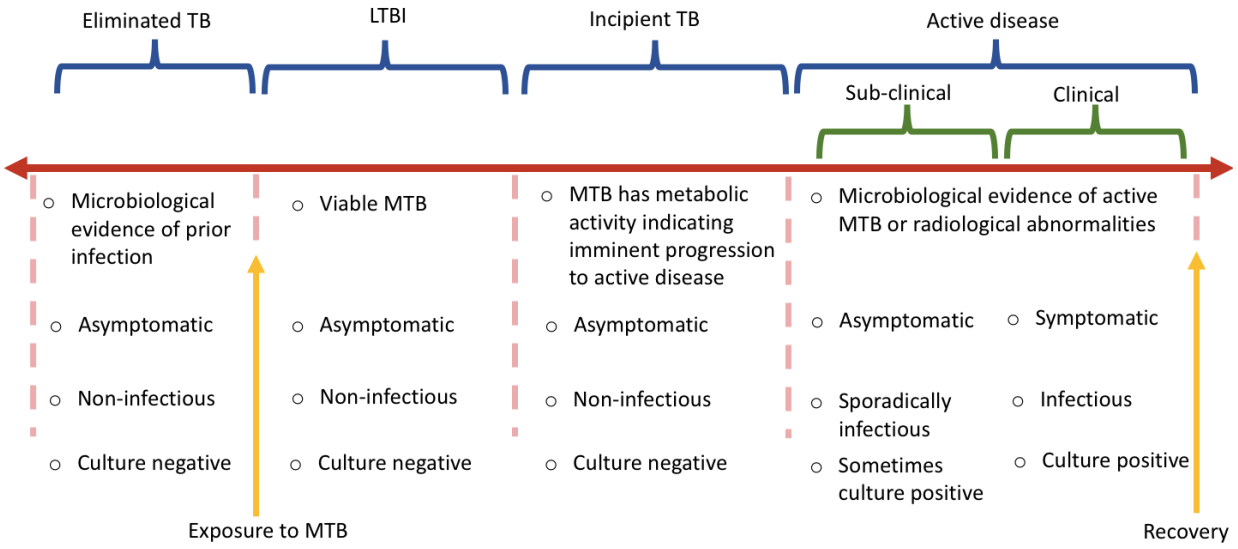

Figure 2.2. The different stages of TB infection and how they manifest. Adapted from Barry et al 2009 (9), Drains et al 2018 (10) and Pai et al 2016 (8). Note, not all individuals exposed to MTB will develop LTBI. Recovery may be due to TB treatment or self-cure.

2.2.2.1. Latent tuberculosis

Upon infection with MTB, the host's immune system is activated; in the majority, MTB replication is contained within granulomas containing macrophages, and T and B cells. If the immune system fails to eliminate the infection, a balance is achieved where MTB replication and dissemination is prevented, and immunopathology is limited (11); these individuals are described as having LTBI. LTBI individuals are asymptomatic, non-infectious and the only evidence of infection is an immune response when presented with MTB antigens (12). Traditionally, it was estimated that one third of the world population has LTBI (13); however, a more recent estimate suggests just under a quarter (14).

The risk of developing active TB disease changes over time and is age dependent. It is estimated that the risk of developing disease within the first five years of initial infection (fast progressors) is 4% if infected as a child (ages 0-10 years), increasing to 14% for those over the age of 20 years (15). LTBI can also progress to active disease many years after initial infection as endogenous reactivation or exogenous reinfection. Thus, the lifetime risk of developing active disease amongst those with LTBI is only 5-10% (6). There are several risk factors for disease progression, including but not limited to, recent TB infection (14), age (15), HIV co-infection (16,17), diabetes (18) and malnutrition (19,20). Risk factors are discussed in greater detail on page 22. Progression to active disease can be prevented by TB preventive treatment ("TPT") or vaccination; I discuss TPT in further detail on page 32.

2.2.2.2. Incipient tuberculosis

Between LTBI and active disease, there is a stage called incipient TB (21). Throughout, I follow the definition by Drain et al (10): individuals at this stage are at imminent risk of progressing to active disease in the absence of any intervention, but are asymptomatic and have no microbiological evidence of active disease. Using this definition, these individuals are unlikely to be infectious. It should be noted that across the literature, definitions for what comprises incipient TB differ. For example, the WHO defines it more broadly as "the prolonged asymptomatic phase of early disease during which pathology evolves, prior to clinical presentation as active disease"; this definition groups together incipient TB and subclinical TB,. I discuss in further detail the progress being made in detecting incipient TB in chapter 3.

2.2.2.3. Subclinical tuberculosis

Subclinical TB is defined as individuals with bacteriologically confirmed TB, but with no presentation of clinical symptoms. These individuals may contribute to onwards transmission (22–24). Until recently, the importance of subclinical TB has been largely overlooked. Recent studies that have analysed TB prevalence surveys found that around half of bacteriologically confirmed TB did not report symptoms (22,25). A modelling study suggests that subclinical TB may reduce the impact

of interventions (26). Many questions remain, such as how does the prevalence of subclinical TB vary across populations, and how much TB morbidity and mortality could be averted by targeting individuals with subclinical TB (10).

2.2.2.4. Active tuberculosis

An individual develops active disease when the balance between the immune system and MTB is disrupted, a process known as endogenous reactivation; MTB escapes from the granulomas and start replicating, leading to a pro-inflammatory response (11). Once an individual develops active disease, they are symptomatic and infectious. Typical symptoms include fever, night sweats, chest pain and coughing. However, symptoms will depend where the disease has established itself in the body (27).

Active TB disease presents itself in two ways: pulmonary and extrapulmonary. Pulmonary TB is when the disease affects the lungs, whereas extrapulmonary TB is when the disease affects other sites (for example, the lymph nodes). The majority of active disease cases are pulmonary, with only 16% of incident cases notified in 2019 being extrapulmonary (6). Extrapulmonary TB often goes undetected; a sputum sample is required for most current TB diagnostic tests, however patients with extrapulmonary TB are unlikely to have MTB in their sputum (because the MTB is present in organs other than the lungs). Further details on TB diagnostics are discussed on page 23.

2.2.2.5. Tuberculosis recurrence

TB can recur in two ways: exogenous reinfection or relapse. Exogenous reinfection is when an individual who has previously been infected with TB acquires a new infection, whereas an individual is said to have relapsed if they become reinfected with the original infection after successful treatment completion or self-cure. Prior infection is not completely protective against reinfection; a review estimated that prior infection confers 79% protection (28), although results differ substantially between studies (28–30). Risk factors for recurrent TB include HIV coinfection (31,32), being of an older age when experiencing a first episode of TB (33), and incomplete treatment (34,35).

The relative contribution of exogenous reinfection and relapse to TB recurrence is debated. It is generally believed that the risk of exogenous reinfection increases alongside the incidence of TB (15). Marx et al (36) carried out a longitudinal study in South Africa, and using DNA fingerprinting of MTB strains, found that relapse occurred predominantly in the first year after treatment completion, whilst exogenous reinfection dominated after the first year.

Studies from the pre-antibiotic and post-antibiotic era suggest that exogenous reinfection contributes more to transmission than endogenous reactivation (37). Pre-antibiotic era studies indicate that the

vast majority of active disease occurred within two years of infection (38,39); however, post-antibiotic era studies suggest that although isoniazid (an antibiotic that prevents LTBI from developing to active disease) reduced the likelihood of developing active disease in the first year, this difference was insignificant after the first year (40,41). Again, this supports the idea that most TB transmission is occurring in the first few years after infection (including exogenous reinfection), and not several years after infection due to endogenous reactivation. In lower TB burden countries, a greater proportion of cases are due to endogenous reactivation as a result of the low risk of transmission (37).

2.2.3. Risk factors for tuberculosis

Below, I discuss the main risk factors that increase an individual's risk of progression to active disease.

2.2.3.1. HIV

HIV is the strongest risk factor for the development of active disease, and increases the risk of reactivation between 15-22 times (42). This increased risk is due to the impairment of the host's cell-mediated immune response by HIV (16). TB is the leading cause of death in PLHIV, with one third of all deaths from AIDS due to TB (42,43). The risk of TB-related deaths is twice as high in PLHIV than amongst HIV negatives (44). Unfortunately, as PLHIV become increasingly immunosuppressed, they are more likely to develop extrapulmonary TB (45,46), making TB harder to detect. In 2018, 44% of TB-HIV coinfection did not access care (42). Autopsy studies highlight further the under-diagnosis of TB amongst PLHIV, which is often only revealed once the patient has died (47–51). The African region has the highest rate of TB-HIV coinfections, with HIV being a major driver of the TB epidemic; for example in South Africa, an estimated 59% of TB cases are coinfected with HIV (6). The WHO recommends routine HIV testing amongst all patients diagnosed with TB, and for PLHIV to be routinely screened for TB symptoms. PLHIV with LTBI should also be initiated onto TPT to prevent the development of active disease (42). The WHO further recommends antiretroviral therapy ("ART") initiation for all PLHIV coinfected with TB. A meta-analysis suggest that ART reduces the risk of developing TB by 65%, regardless of baseline CD4 cell count (52). Unfortunately, in 2019 only around 49% of PLHIV and TB were on ART (6).

2.2.3.2. Other risk factors

Other risk factors include age, diabetes, malnutrition, tobacco smoke and indoor air pollution. Comstock et al found that children under the age of four had the highest rates of TB disease with a second peak in older adolescents (53). Children have under-developed immune systems and are thus less able to control initial infection, whereas hormone modulation of the immune system may play a

role amongst adolescents (54). Overall, the risk of developing active TB disease amongst children follows the shape of a parabola: children under the age of 2 have the highest risk of developing active disease, with the risk decreasing as they grow older, but increasing again when they reach adolescence (55). There is inconclusive evidence about whether old age increases your risk of developing active disease (56).

It is estimated that diabetes increases the odds of an individual developing active disease by 2-4 times (18,57,58) through host immune function impairment (57). In addition, diabetes increases the risk of adverse TB treatment outcomes (59). Unfortunately, diabetes is becoming a global health problem, due to rising levels of obesity, with the biggest increase expected to occur in LMICs (60). There is concern that this increase in diabetes will counteract efforts achieved by TB control programmes (61). A randomised control trial, PROTID, is currently underway to generate evidence on the use of TPT amongst people with TB and diabetes (62).

In 2013, the WHO estimated that one quarter of all new TB cases was attributed to under-nutrition (63). Malnutrition impairs the host cell-mediated immune response, increasing susceptibility to TB infection, the risk of progression to active disease once infected (19,20) and the risk of drug toxicity (64,65). It is estimated that being underweight increases the risk of developing active disease by 2 to 3 times (17). Unfortunately, malnutrition increases an individual's susceptibility to infection, whilst infection increases an individual's risk of malnourishment for reasons including malabsorption of nutrients, loss of appetite and weight loss (66).

Tobacco smoke and indoor air pollution can alter the immunological response of the lung to MTB (67), as well as damaging the cilia in the airway (68). Meta-analyses have found evidence that smoking and air pollution increases the host susceptibility to TB infection, the risk of developing active TB disease and the risk of recurrent TB (69,70).

2.2.4. Diagnosing tuberculosis

2.2.4.1. Latent tuberculosis infection

Although high TB burden countries focus mainly on detecting and treating active disease, modelling studies suggest that if TB elimination is to be achieved, LTBIs need to be targeted (71–74). Nevertheless, it is estimated that only around 72% of patients intended to be screened for LTBI received a test, of which 93% received a test result (75).

The major limitation of diagnostic tests for LTBI is the lack of a gold standard for diagnosing LTBI; thus, the sensitivity and specificity of tests cannot be directly estimated. Instead, surrogates are used

to estimate the specificity and sensitivity of these tests. For example, patients with confirmed active TB disease are often used as surrogates to estimate the sensitivity of a LTBI diagnostic test, under the assumption that a LTBI test with 100% sensitivity would identify surrogates with confirmed active TB disease as having LTBI. On the other hand, healthy individuals with a low risk of disease are often used as surrogates to estimate the specificity of a LTBI diagnostic test, under the assumption that a test with 100% specificity would correctly identify these surrogates as not having LTBI disease. The disadvantage of using patients with active TB disease as surrogates is that these individuals tend to be immunosuppressed and thus, sensitivity may be underestimated in such studies (76). It is also complicated to compare studies that have used different types of surrogates, as well as comparing studies that evaluate tests in different epidemiological settings, with varying levels of TB incidence and risk factors.

Finally, current LTBI diagnostic tests measure the sensitisation of a patient's immune system to MTB. Therefore, they do not indicate whether a patient is still infected and cannot determine a patient's drug sensitivity status (77). Despite this, meta-analyses have shown that at-risk patients who test positive are still more likely to develop disease and benefit from TPT (78,79). Below, I discuss the main tests available (a summary is provided in table 2.2).

Tuberculin skin test

The tuberculin skin test ("TST"), also known as the Mantoux test, is the classical method to diagnose TB infection. When an individual is initially infected with TB, T-cells are sensitized; thus, when tuberculin from the TST is injected into the arm of an individual with LTBI, memory T cells are recruited to the injection site, typically 48-72 hours later. The memory T cells release lymphokines, resulting in the induration of the skin (80). The diameter of the induration is measured and interpreted according to different cut offs. In immunocompromised patients, such as those with HIV infection, the cut-off values are lowered, to reflect the host's decreased ability to produce an adequate immune response (81).

In terms of application, the TST is simple, easy to perform and suitable for rural settings that have limited laboratory infrastructure (82). However, the TST needs to be refrigerated and requires at least two healthcare visits, increasing the risk of lost to follow up (76). TST results are also subject to reader variability (83).

The specificity of TST is heterogeneous depending on the population examined, including whether or not a population has been vaccinated with the Bacillus Calmette-Guérin ("BCG") vaccine and exposure to environmental mycobacteria (84,85). The tuberculin used in the TST is a mixture of antigens, shared by MTB, *M. bovis BCG* and environmental mycobacteria; thus, the immune system

of an individual vaccinated with the BCG or who has been exposed to environmental mycobacteria may therefore present as a false positive during a TST (84). For example, a meta-analysis, that estimated pooled specificity exclusively from studies that had tested healthy individuals with low-risk of TB found non-BCG vaccinated populations had a pooled specificity of 97%, which decreased to 59% amongst vaccinated populations (86). However, the impact of BCG vaccination on TST is dependent on the age when the BCG was administered. Studies have shown that if the BCG is administered during infancy and it has been more than 10 years, the effect on TST is negligible (84). Finally, the specificity of the TST is reduced further by the booster phenomenon; the more TSTs a patient receives, a greater reaction to the test is seen, increasing the number of false positives (84,87,88).

TST sensitivity is dependent on the cut-off point chosen; by decreasing the cut-off points test sensitivity improves, but at the expense of specificity (89). A meta-analysis that estimated pooled sensitivity exclusively from studies that used active TB disease as a surrogate for LTBI and that used a cut-off of less than 10mm, estimated a sensitivity of 77% (85), whereas another meta-analysis that used a cut-off of less than 15mm, estimated a pooled sensitivity of 64% (90). TST has low sensitivity in immunocompromised patients (i.e., PLHIV). These patients tend to present an anergic response, increasing the risk of a false-negative result (85).

The NPV for TST is high; in other words, the chance an individual develops active TB disease is low if they are TST-negative. A meta-analysis estimated a pooled NPV of 99.4% (91). On the other hand, the PPV of TST is low, at around 1.5%, increasing to 2.4% amongst high-risk groups (91), suggesting that TST is poor at identifying individuals who are at high risk of developing active TB disease. Nevertheless, numerous studies have shown the benefit of TPT amongst individuals with a positive TST result (76,79).

Interferon-gamma release assays

Interferon-gamma release assay ("IGRAs") are *in vitro* blood tests measuring interferon-gamma ("IFN-γ") released by T cells in response to stimulation by MTB antigens. The two most common commercially available IGRAs are: QuantiFERON-TB Gold In-Tube ("QFT-GIT", Cellestis, Australia) and T.SPOT.TB (Oxford Immunotec, UK). A new version of QFT-GIT, QuantiFERON-TB Gold Plus ("QFT-Plus") was released in 2015. The broad difference between the two tests is in the way they detect IFN-γ: QFT detects the concentration of IFN-γ using an enzyme-linked immunosorbent assay (92), whereas T.SPOT.TB measures the number of IFN-γ releasing T cells using an enzyme-linked immunospot assay (93). Upon MTB infection, an individual's T cells are sensitised; thus, when the individual is stimulated with TB antigens from an IGRA, the T cells release

higher levels of IFN-γ than a non-infected individual (94). An individual is classified as infected with TB if the IFN-γ response is above the test cut-off. Like the TST, IGRAs cannot differentiate between LTBI and active disease (94).

In terms of application, IGRAs are advantageous as only a single healthcare visit is required. Furthermore, the interpretation of IGRA results are less subjective than TST (90,95,96). Nevertheless, IGRAs are more expensive than TST (90), and unlike TST, the tests involve taking blood samples, and require specialized equipment and trained personnel (90). Thus, in low-income settings with poor access to laboratory facilities, TST may be favoured. IGRAs suitable at the point-of-care are currently under development (97).

In terms of performance, IGRAs are more specific than TST, because the MTB antigens used are highly specific to MTB (98), reducing the risk of cross-reactivity. IGRAs may therefore be useful in individuals who have received the BCG vaccine after infancy (84,85,99) or amongst those that have received booster BCG vaccinations (100). In addition, serial testing can be performed without stimulating the booster phenomenon (99). Overall, a meta-analysis that estimated pooled specificity from studies exclusively using healthy individuals with low-risk of TB, estimated T.SPOT.TB to have a pooled specificity of 77% versus 57% for TST. In the same study, pooled specificity for QFT-GIT was similar to that of TST, at 71% and 70%, respectively (90). Another meta-analysis, again using healthy individuals with low-risk of TB as surrogates, estimated QFT-GIT to have a pooled specificity of 99% and 96%, amongst BCG-unvaccinated and BCG-vaccinated individuals (versus 97% and 59% for TST, respectively) (85).

Generally, studies have found IGRAs, especially T.SPOT.TB, to have higher sensitivity than TST. A meta-analysis that used active TB as a surrogate marker estimated the pooled sensitivity of T.SPOT.TB and QFT-GIT as 90% and 75%, respectively (versus 64% for TST) (90). QFT-Plus, is estimated to have even higher sensitivity for LTBI than QFT-GIT (101). There is conflicting evidence whether IGRAs have improved sensitivity amongst immunodeficient hosts compared to TST (94,102).

Like TST, it is estimated that IGRAs have high NPV. Meta-analyses estimate an NPV of over 99% (104,105). It is suggested that the ability of IGRAs to predict progression to active disease is only modest, although likely higher than the TST. A meta-analysis estimated the pooled PPV for IGRAs to be 2.7%, increasing to 6.8% amongst high-risk groups (compared to 1.5% and 2.4% for TST, respectively) (104). A more recent meta-analysis concluded similarly (105).

Overall, IGRAs may be useful in settings where post-infancy BCG-vaccination is common (85) and in high-income countries ("HICs") with a low burden of TB, due to their high specificity and logistical advantages. TSTs are still preferred in high TB burden LMICs (82).

C-Tb

A new generation of skin tests are under development, one of which is C-Tb (Statens Serum Institute, Denmark). The C-Tb combines the advantages of TST and IGRAs. It is a skin test, like TST, making it easier to use in the field, but uses two of the three antigens used in IGRAs, in order to have high specificity (106).

C-Tb requires 48 to 72 hours of incubation and a cold chain supply. Unlike TST which requires different cut-off points depending on the at-risk population, C-Tb has one universal cut-off, increasing its ease of use (107). Further studies are needed to determine the cost-effectiveness and acceptability of the test.

Phase III clinical trials found C-Tb to be safe (108) and suggest a specificity similar to QFT-GIT that is unaffected by BCG vaccination (109). Using active TB as a surrogate marker, sensitivity was estimated at 75% with similar results in HIV-positive and HIV-negative patients, although test sensitivity did decrease amongst HIV-positive patients with CD4 cell counts < 100 cells/mm^3 (110). It is unlikely that C-Tb will have a higher PPV than IGRAs for the development of active TB, considering that they are based on the same antigens (111).

Overall, the improved specificity of the C-Tb amongst BCG vaccinated individuals and ease of use in the field, may improve LTBI diagnosis in resource-limited settings, where IGRAs are too costly and problematic to use (112).

Test	Sensitivity	Specificity	PPV	NPV	Sample type	Infrastructure required	Relative cost
TST	64 – 77%	57 – 97%	1.5 – 2.4%	>99%	Skin	Primary care clinics, but requires refrigeration and trained healthcare workers	Medium
IGRAs	69 – 94%	71 – 99%	2.7 – 6.8%	>99%	Blood	Laboratory infrastructure and highly skilled healthcare workers needed	High
C-Tb	75%*	99%*	N/A	N/A	Skin	Primary care clinics, but requires refrigeration	Medium

Table 2.2. Summary of the main diagnostic tests for latent TB infection. Relative cost indicates how the cost of each test compares to each other. *Based on an individual study

2.2.4.2. Active tuberculosis

Due to the infectious nature of active TB disease, TB control efforts have traditionally focused on diagnosing and treating these individuals. Not only does detecting active TB disease in a timely manner reduce onward transmission, it also reduces the risk of severe clinical disease. Unlike LTBI diagnosis, a gold standard exists, making it easier to estimate the accuracy of new diagnostic tests. However, out of the 10 million new TB cases in 2019, only 7.1 million were diagnosed (6). In this section, I will explore the most common tests used to diagnose active TB disease (summarised in table 2.3).

Mycobacterial culture

Mycobacterial culture is considered to be the gold standard by the WHO for diagnosing active TB disease (113); however, it is rarely used in day-to-day diagnosis. It was previously used for in vitro phenotypic testing for drug resistance (114). Mycobacterial culture involves taking a sample from a patient with suspected TB and plating the sample on a solid or liquid medium in a laboratory. Due to the slow growing nature of mycobacteria, it typically takes 6-8 weeks, but can be as high as 12 (113). Specialised laboratory equipment and skilled laboratory workers are required due to the risk of laboratory-acquired TB when handling mycobacterial cultures (115). Thus, the per-test cost is high (116,117).

Sputum smear microscopy

Sputum smear microscopy has been the primary test used to diagnose active TB disease for over 100 years. A patient with suspected TB expectorates a sample of sputum; the sample is then prepared using an acid-fast stain procedure (a ‘smear’) and examined under a microscope. Typically, this

procedure is repeated twice. The number of acid-fast bacilli present in a smear indicates how infectious the patient is (46).

Depending on the result of a smear test, a patient can be diagnosed as either being smear positive or smear negative. Someone who is smear negative has clinical or radiological evidence of TB but has a negative result. Although smear negative infections are less infectious, they are responsible for around 13-20% of transmission (118–121). If smear-positives are indeed more infectious than smear-negatives, the main advantage of sputum smear microscopy is that it identifies the most infectious patients; in other words, patients that are more likely to transmit at higher rates (122). Furthermore, a study estimated that smear positive TB has TB-specific mortality rates 15 times higher than smear-negative TB (123). HIV coinfection increases the risk of smear negative results; Lawn et al found that between 1996 and 2004, as HIV prevalence was increasing, the rates of smear negative TB increased over 4-fold, whereas the rates of smear positive increased less than 2-fold (124).

The risk of healthcare workers ("HCWs") becoming infected whilst handling samples is lower than for mycobacterial cultures; thus, less training is required, and the test can be performed in primary-care clinics. Once initial equipment, such as microscopes, are purchased, sputum smear microscopy is inexpensive. It is also relatively quick to perform, typically requiring a few hours. Nevertheless, although it is easier to train HCWs to perform sputum smear microscopy than mycobacterial culture, skilled interpretation of the smears and a constant supply of reagents are needed (125).

Sputum smear microscopy relies on the patient expectorating sputum, ideally twice. Testing that is reliant on sputum is problematic amongst PLHIV, and patients with extrapulmonary or paucibacillary TB (i.e. children) (126,127). PLHIV are more likely to have extrapulmonary TB and struggle to produce sputum (128). Those with extrapulmonary TB in the absence of pulmonary involvement, have insufficient bacillary load in their sputum to be detectable by microscopy (129,130). Thus, some studies have reported sputum smear microscopy to have low sensitivity. One meta-analysis amongst PLHIV and HIV-negative individuals estimated the pooled sensitivity to be 64% (131), whereas a meta-analysis focussing exclusively on PLHIV calculated the pooled sensitivity to be 40% (132). It is estimated that sputum smear microscopy misses around 40-60% of TB cases (133). Overall, sputum smear microscopy has high specificity, at around 98% (131).

Xpert® MTB/RIF

Xpert® MTB/RIF ("Xpert"; Cepheid, USA) is a rapid molecular diagnostic test recommended by the WHO for use in adults and children (113). It is an automated real-time PCR assay using the GeneXpert platform and is typically performed on sputum. It can also detect rifampicin resistance. This ability to detect rifampicin resistance has led to a shift from phenotypic drug testing to genotypic

drug testing, allowing for quick identification (114). By the end of 2016, it was estimated, that 28 out of the 48 countries in the WHO's list of high burden countries have adopted the use of Xpert (113). Unfortunately, the roll-out has been impeded by several issues including poor policy adoption, insufficient comprehensive training amongst HCWs, lack of quality assurance, challenges in settings with unstable power supplies, poor equipment maintenance and weak supply chains (134–137).

In terms of logistics, an Xpert test is quick and provides results usually within two hours. If Xpert is placed in primary care clinics, a higher proportion of patients have a same-day diagnosis and same-day treatment initiation than sputum smear microscopy (133). This quick turnaround time, the time from sputum collection to a patient receiving test results, reduces lost-to-follow up, decreases delays in TB treatment initiation (138,139) and thus, can potentially improve patient outcome. Studies show that Xpert can be performed by minimally trained HCWs (133,139,140); however, many countries have placed Xpert in centralised laboratories which can increase turnaround time (141).

Logistical disadvantages include its higher cost compared to sputum smear microscopy; however, it has been suggested that the cost could be compensated by the test's faster turnover, and therefore, higher diagnostic yield (142). Pooled-sputum strategies are also being investigated to further reduce costs (143). Xpert also has high infrastructure requirements, requiring stable temperature, humidity and power supply; this is problematic in many high TB burden settings (134). These requirements have led to a relatively high failure rate, ranging between 5-17% depending on the setting (144,145). Finally, like sputum smear microscopy, a sputum sample is required.

In terms of performance, the main advantage of Xpert is that it can detect around 67% of TB cases that are missed by sputum smear microscopy, due to its higher sensitivity and lower threshold of detection (146). Overall pooled sensitivity is estimated to be around 89%; this increases to 98% amongst smear-positive, culture-positive patients (147). However, sensitivity suffers in sub-groups that find it more difficult to self-expectorate sputum; for example, a meta-analysis calculated a pooled sensitivity of 87% amongst pulmonary TB patients, but this decreased to 80% in extrapulmonary TB patients (148). Similarly, a meta-analysis estimated the pooled sensitivity to be around 79% in PLHIV (147,149). Specificity is consistently high at around 99% (147).

Despite the improved diagnostic performance of Xpert relative to sputum smear microscopy, the rates of TB treatment initiation, risk of mortality and treatment outcomes between the two diagnostic tests have stayed the same (133,138,150–153). One potential explanation is where Xpert tests are being carried out; if the machines are in laboratories or centralised health facilities instead of primary care clinics, the turnaround time is increased (150). This increases the risk of loss-to-follow up and onward transmission and fails to make use of the major advantage of Xpert – its speed. Unfortunately,

economic evaluations suggest that the unit cost of an Xpert test is greater at the point-of-care than at centralised healthcare facilities; the latter being able to test a higher volume of samples (140,154). Another explanation is high background rates of empirical treatment (where a patient initiates TB treatment based on clinical symptoms, despite a negative diagnostic test result). If a combination of smear microscopy and clinical judgement is relatively accurate, then the incremental benefit of Xpert is reduced (151,155,156). High rates of empirical treatment in cohorts tested with sputum smear microscopy will negate the improved diagnostic accuracy of Xpert. Thus, the incremental benefit of Xpert may be greater in countries with lower rates of empirical treatment (133).

Urine-lipoarabinomannan tests

To circumvent the issues surrounding sputum samples, there has been a drive to develop non-sputum-based diagnostic tests. A particular focus has been placed on urine; studies have found that over 90% of PLHIV can produce a urine sample, compared to 50% for sputum (157–159). Furthermore, urine collection is less invasive than sputum collection, and carries a lower infection risk. Using lateral-flow technology, a mycobacterial antigen, lipoarabinomannan ("LAM"), is detectable. LAM is a glycolipid component of the MTB cell wall (160), whose function includes inhibiting host macrophages and proinflammatory cytokines (161). Two lateral flow LAM tests exist: Alere Determine^{TM} LAM Ag ("AlereLAM"; Abbott, USA) and Fujifilm SILVAMP TB LAM ("FujiLAM"; Fujifilm, Japan). I discuss the logistical advantages and diagnostic performance of both tests in greater detail in Chapter 4.

Chest radiography

Although not recommended by the WHO as a diagnostic tool, chest radiography which identifies lung abnormalities, is frequently used, especially in the private sector in India (162) and for mass-screening efforts in Russia (163). Chest radiography is highly sensitive for pulmonary TB, ranging between 87-98% (162); however, it has poor specificity, ranging between 46-89%, as many lung abnormalities identified by the test are shared with other lung pathologies (162). In addition, chest radiography has significant inter-observer variation. Consequently, the WHO currently only recommends chest radiography in combination with bacteriological confirmation.

In terms of logistics, chest radiography has traditionally been challenging. Patients are exposed to radiation, and special equipment, power and highly skilled HCWs are needed, all of which limit access in rural and hard-to-reach areas (162). Nevertheless, advances in digital technologies has reduced the amount of radiation a patient is exposed to, and portable chest radiography and objective tools to interpret X-rays are under development (162,164).

Test	Sensitivity	Specificity	Sample type	Infrastructure required	Relative cost
Mycobacterial culture	100%	100%	Blood, sputum, urine	Specialised laboratory equipment; highly trained workers	High
Sputum smear microscopy	40-64%	97-99%	Sputum	Primary care clinics; skilled interpretation needed	Medium
Xpert MTB/RIF	46-89%	98-99%	Sputum	Ideally primary care clinics, but often found in centralised laboratories; high infrastructure requirement	High
Alere Determine LAM Ag	12-67%*	85-98%*	Urine	Primary care clinics; minimum training required; point-of-care	Low
Fujifilm SILVAMP TB LAM	36-84%* #	85-98%* #	Urine	Primary care clinics; minimum training required; point-of-care	Low
Chest X-ray	87-98%	46-89%	N/A	Primary care clinics, however some are now portable; skilled interpretation needed	Medium

Table 2.3. Summary of the main diagnostic tests for active TB disease. Relative cost indicates how the cost of each test compares to each other. * Amongst PLHIV with signs and symptoms of TB only; # Based on two studies only (165,166)

2.2.5. Treatment of tuberculosis

Below, I briefly discuss current treatment regimens for both LTBI and active TB disease, in addition to the emerging threat of antibiotic drug resistance.

2.2.5.1. Preventive treatment

The ability of TPT to prevent progression to active disease was first demonstrated in the 1950s and 1960s, when controlled isoniazid prophylaxis trials were carried out amongst children (167), contacts of people with known TB (168,169) and the community (170). The majority of the studies were carried out in the United States. More recently, a meta-analysis concluded that TPT reduces the risk of PLHIV developing active disease (79). A long-term trial found TPT reduces mortality in PLHIV, even amongst those on ART and those with high CD4 counts, concluding that TPT should be offered to all PLHIV (171).

In 2018, the United Nations held its first meeting on TB, and made a commitment to provide TPT to 30 million people globally between 2018 and 2022, in order to push towards TB elimination (172). In 2019, the number of individuals started on TPT increased to 4.1 million, a substantial increase from 1 million in 2015 (6). Nevertheless, around 70% of individuals are lost before TPT initiation, and only around 60% complete treatment (75).

Currently, around 60% of the high TB-HIV burden countries provide TPT to PLHIV initiating ART; however globally, TPT coverage is estimated to be around 50% (6). The reasons behind the slow scale-up of TPT amongst PLHIV include miscommunication between the TB and HIV programmes, supply chain issues and fear amongst HCWs that isoniazid uptake may increase drug resistance (173,174). Another issue is the low coverage of TPT amongst household contacts of diagnosed cases. The WHO currently recommends TPT amongst all household contacts of people with bacteriologically confirmed pulmonary TB (175). However, less than 20% of children under the age of 5 and less than 1% of those over the age of 5 that were household contacts of a positive TB case were initiated onto TPT (6,176).

There are currently 6 WHO-recommended TPT regimens (table 2.4). Traditionally, the standard course of TPT consists of a long course of daily isoniazid for either 6- ("6H") or 9- ("9H") months. A meta-analysis found that 6H had an efficacy of 69%, with the efficacy increasing to over 90% for 9H or longer (up to 12 months) regimens (177). Although effective at reducing the risk of active TB disease, patients have an increased risk of hepatotoxicity (178–180), and adherence is poor, in some cases less than 50%, due to the long duration of treatment (181). The protective effect of isoniazid TPT may wane (182), in some cases, immediately after treatment has stopped. This may be due to reactivation, if LTBI was inadequately treated, or due to reinfection (41).

TPT regimen	Prescription
6H	Daily dose of isoniazid for 6 months
9H	Daily dose of isoniazid for 9 months
3HP	Weekly dose of rifapentine and isoniazid for 3 months
3HR	Daily dose of rifampicin and isoniazid for 3 months
1HP	Daily dose of rifapentine and isoniazid for 1 month
4R	Daily dose of rifampicin for 4 months

Table 2.4. Summary of the WHO-recommended TB preventive treatment regimens.

Recently, the addition of rifamycins, a group of antibiotics that include rifampicin and rifapentine, have shorten the length of TPT regimens. Compared to long course isoniazid, studies suggest these regimens are non-inferior, improve patient adherence, have higher treatment completion rates and have fewer frequent adverse events (183–187). As the shorter regimens are relatively new, and thus costly, there has been an effort to reduce the cost of these regimens. Despite these efforts, less than 30% of high TB burden countries have started using 3HP; the remaining 70% exclusively recommend the use of 6H (6).

2.2.5.2. Active disease treatment

If the patient has drug-susceptible TB ("DS-TB"), active disease can be cured by a 6-month daily course of 4 antibiotics, commonly rifampicin, isoniazid, pyrazinamide and ethambutol ("2HRZE/4HR"). The first two months, referred to as the intensive phase, involves the patient taking all 4 antibiotics; the last 4 months, the continuation phase, involves the patient taking only 2 antibiotics, isoniazid and rifampicin (188). The same course of treatment is recommended for patients with extrapulmonary TB; although, those with a severe form of extrapulmonary TB may need to extend treatment to 9 months (189). Fixed dose combinations ("FDCs") were developed to reduce a patient's pill burden, to improve adherence and reduce the risk of drug resistance (190). However, a meta-analysis found that although FDCs simplify treatment for patients, it does not necessarily improve treatment outcome, nor compliance (191).

Globally, the treatment coverage for active TB disease was 71% in 2019; substantial progress has been made, considering that treatment coverage was only 59% in 2015. In 2019, treatment success rate was estimated at 85%, again varying substantially across countries and regions; amongst PLHIV, the rate of treatment success decreases to 76% due to PLHIV facing delays in diagnosis and treatment initiation (6).

The WHO estimated the median cost of treating DS-TB in 2019 was USD 860, with the cost decreasing in countries with a lower gross domestic product ("GDP") per capita (6).

2.2.5.3. Drug resistance

Different types of drug-resistance ("DR-TB") exist including rifampicin-resistant TB ("RR-TB"); multi-drug resistant TB ("MDR-TB") where individuals are resistant to rifampicin and isoniazid; MDR-TB with additional resistance to fluoroquinolones; and extensively drug-resistant TB ("XDR-TB") where individuals are resistant to rifampicin, isoniazid, fluoroquinolones and to at least one of the injectable second-line drugs.

Individuals develop DR-TB through treatment mismanagement (for example, if the supply of drugs is interrupted during the treatment or a wrong dosage is prescribed) or transmission from a patient with DR-TB. There is conflicting evidence on whether DR-TB transmits just as easily as DS-TB (192). However, a modelling analysis by Kendall et al suggests that the majority of MDR-TB stems from transmission instead of treatment-related acquisition of resistance (193). These results indicate that focussing exclusively on improving drug-susceptible treatment is unlikely to have a significant impact on reducing MDR-TB incidence.

RR- and MDR-TB patients are treated with second-line drugs. A meta-analysis suggests that the time to treatment initiation is extremely variable, and can take as long as 81 days from specimen collection (194). It is recommended that patients are given a combination of four drugs, three from Group A drugs (that includes fluoroquinolones) and one from Group B (clofazimine or cycloserine). XDR-TB patients have access to an even smaller pool of antibiotics and must take the drugs for around 18-20 months with a high risk of severe side effects (195).

Treatment success rate is poor for RR- and MDR-TB; in 2019, the treatment success rate was estimated to be 57%, with the remaining 43% having failed treatment (7%), died (15%), or were lost to follow up (21%). Overall, the WHO estimated treatment success for MDR-TB for the Southeast Asia and Africa regions in 2017 to be 52% and 64%, respectively; this rate decreases to 37% and 59% for XDR-TB, respectively (196).

The drugs for DR-TB are also costly. In 2019, the median cost of MDR-TB treatment was estimated at USD 5,659 per patient; like with DS-TB, the cost decreases with GDP per capita. The cost has also decreased year on year, partly due to decreasing the duration of hospitalisation and development of newer treatment regimens (6). As the burden of MDR-TB increases, the funding required for MDR-TB will increase to an estimated USD 5.7 billion in 2022 (6).

2.2.6. Policy

In 1995, the first major TB strategy, Directly Observed Treatment, Short course ("DOTS"), was launched by the WHO. The aim was to create a global systematic TB response through efforts such as directly observed TB treatment to increase treatment completion, as well as ensuring a continuous supply of medication (71). Raviglione et al (197) found that amongst countries that had adopted DOTS, treatment cure rates improved (76% compared to 42% in non-DOTS countries). Globally, it is estimated that case detection rates increased from 11% in 1995 to 45% in 2003 (198).

Although DOTS progressed TB control in the late 1990s and early 2000s, more action was needed to tackle issues such as DR-TB, the quality of TB care in the private sector and TB prevention. Consequently, additional strategies have been launched, including the Global Plan to Stop TB in 2006 and more recently, the End TB Strategy in 2015. The aims of the latter include reducing TB deaths and incidence by 95% and 90%, respectively, by 2035 compared to 2015. The first milestone was in 2020, where the aim was to reduce TB deaths and incidence by 35% and 20%, respectively (199). Although TB incidence is decreasing globally, this decrease was not enough to reach the first milestone, with only a 9% reduction in global incidence between 2015 and 2019 (6). Progress in

reducing TB mortality was even slower, with only a 14% reduction in TB mortality between 2015 and 2019, globally (6).

Although substantial progress has been made in the last decade, many barriers remain if the End TB Strategy aims are to be achieved. The Lancet Commission recommend five priority investments: (1) Ensure accurate rapid diagnostic tests and treatment are available to all those seeking care; (2) Reach high-risk populations and ensure they have access to treatment and care; (3) Increase investment in TB research, especially in developing new diagnostics, treatments and vaccines; (4) Increase investment in TB programmes; (5) Ensure countries are held accountable (200).

Unfortunately, the novel coronavirus disease 2019 ("COVID-19") pandemic at the end of 2019, caused by the severe acute respiratory syndrome coronavirus 2 ("SARS-CoV-2"), threatens to reverse this progress. The COVID-19 pandemic has placed countries under huge economic strain, and so TB budgets are likely to decrease (6). The lockdowns enforced by governments to control the spread of SARS-CoV-2 has led to prolonged household TB exposure, decreased TB case detection and has disrupted TB services (6,201). Multiple modelling studies have analysed the impact that disruption on TB services will have on TB incidence and mortality, concluding that TB levels could revert back to numbers seen in 2015 (202–204).

In the following section, I discuss in further detail two settings that I focus on in this thesis. These two settings are India, which has the world's highest absolute burden of TB, and South Africa, which has the world's highest rates of TB (6).

2.2.7. India

2.2.7.1. An overview of tuberculosis in India

Globally, India has the highest number of TB cases. Substantial progress has been made, and incidence has decreased from approximately 300 per 100,000 in 2000 to 193 per 100,000 in 2019 (6). Similarly, TB mortality amongst HIV-negatives has decreased from 60 per 100,000 in 2000 to 32 per 100,000 in 2019 (6). Factors that have fuelled the TB epidemic in India, include poverty, overcrowding, malnutrition, and high rates of tobacco smoking, all of which leave individuals more vulnerable to developing active disease (113,205). Although DR-TB and HIV/TB co-infection accounts for less than 5% and 4% of incident-TB cases in India, respectively (113), DR-TB is increasing, fuelled by the mismanagement of TB cases by the private healthcare sector. In India, the private healthcare sector plays a major role in healthcare provision due to an underfunded public sector (206–208).

2.2.7.2. Public healthcare sector

Healthcare offered by the government is, for the majority, cost-free and available to all citizens; however, there is heterogeneity between states (207,209) as healthcare expenditure is the responsibility of both the states and central government (210). This has led to a fragmented health sector (211) and vastly different public health spending per capita across states (212). Further heterogeneity lies between urban and rural areas; those living in urban areas tend to have greater access to public health facilities than those living in rural areas (207,211,213).

The Government of India, in the past couple of decades, has launched a variety of initiatives to improve the health of the population by increasing healthcare coverage and accessibility. Since 1962, India has had a National TB programme ("NTP"). In 1992, a study revealed that the NTP failed to meet many of its objectives due to a lack of funding. Many issues were raised, including drug shortages, lack of consensus surrounding treatment and incorrect diagnostic tools being used (clinical and radiological diagnosis were preferred over sputum smear microscopy) (214). Thus, to strengthen the NTP, the National TB Elimination Programme ("NTEP", formerly known as the Revised National TB Control Programme, "RNTCP") was developed and scaled-up from 1997. Its main target was to adopt DOTS, and for India to achieve 70% case detection and 85% cure rate. Since 2007, these targets have been achieved, and the rate of TB mortality has decreased (113). In 2012, TB was made a notifiable disease and the NTEP developed an online reporting platform, NIKSHAY, for public and private providers to notify TB cases. Despite this, notifications from the private sector remain low (215).

2.2.7.3. Private healthcare sector

In the past couple of decades, the private sector in India has grown rapidly (211,216). The private sector encompasses allopathic (degree and non-degree (217)) providers, chemists, and non-allopathic providers (ayuverdic and homeopathic practitioners). Reasons behind individuals seeking care in the private sector include: accessibility (209,211), flexible payment options (218–220), convenient opening times (211,221), shorter waiting times (209,221,222) and mistrust in government services (222).

It is estimated that around half of TB patients seek care and are treated in the private sector (223–225). However, it is difficult to get a precise number, for despite the Government of India making TB a notifiable disease, many private providers fail to notify for fear of losing their patients (226). A community survey found that 91% of private providers were aware that TB is a notifiable disease; however, 82% were unaware of the reporting system NIKSHAY (215). Drug sales data have provided an indication to the large extent to which patients are reliant on the private sector for TB treatment;

the study estimated that in 2014 between 1.19 and 5.34 million TB cases were treated in the private sector, more than twice the amount that was previously assumed (227).

The quality of care received in the private sector, varies hugely. A systematic review, assessing both public and private providers on their knowledge on the use of sputum smear microscopy and DS-TB, estimated that less than one half and one third had correct knowledge, respectively (228). A study in Chennai found that consulting an informal provider increased the delay from symptom onset to treatment initiation by 23 days (229). However, another study found that private providers were no worse than public providers in terms of diagnosis and treatment (230).

As a result of seeking care privately, many Indian households face catastrophic healthcare expenditure (231); defining catastrophic health expenditure as 10% of total household consumption or expenditure, it is estimated that around 17% of patients face catastrophic health expenditure (113). Out-of-pocket ("OOP") payments are one of the main causes of debt, and thus, poverty, in India (207,231).

2.2.7.4. Public-private sector partnerships

Since the early 2000s, the RNTCP has recognised the importance of engaging the private sector. Collaborations between the public sector and private providers are known as public-private mix or public-private partnerships ("PPP"). These projects include providing training for private laboratories, reaching out to private providers to encourage them to notify their TB patients, and encouraging private providers to refer their TB patients to the public sector for treatment (232,233).

However, uptake of PPP schemes has been low in many states (234). Reasons behind private providers refusing to sign up to PPP schemes, include concerns about a lack of return benefit for their engagement, lack of trust in the government, lack of flexibility and the viability of such schemes (235,236). Another reason for the slow uptake of PPP schemes is their affordability. However, three recent pilot programmes carried out across India found that these programmes were comparable in cost to what is already being spent in the public sector; these pilots provided monetary incentives to private providers and utilised private provider support agencies to train private providers (237).

Modelling studies have examined the impact private sector engagement may have on the TB epidemic. One study highlighted the fact that unless the private sector is engaged and is encouraged to increase their use of Xpert, a limited impact on the TB epidemic will be seen (238). Nevertheless, another study suggests that engaging the private sector will not be enough for India to reach TB

elimination, likely due to the large amount of transmission occurring before a patient first seeks care (239).

2.2.7.5. Cascade of care

In 2016, it was estimated that around 26% of TB patients in India were 'missing' (206). Care cascades can help identify at which stage these patients are being lost. Delays in diagnosing TB and initiating treatment increases the risk of onward TB transmission, increases the risk of morbidity and mortality, and incomplete and inappropriate treatment increases the risk of drug resistance.

A systematic review (224) of the Indian TB care cascade estimated the median duration of the total pathway (from onset of symptoms to treatment initiation) to be 52 days (interquartile range, ("IQR"): 47-62 days), when combining data from the public and private sector. Table 2.5 shows a breakdown of the delays that can occur throughout the cascade of care.

Type of delay	Definition	Delay (median, days)
Patient delay	From onset of symptoms to first consultation with a healthcare practitioner	18 (IQR: 14-27)
Diagnostic delay	From first consultation with a healthcare practitioner to receiving a TB diagnosis	31 (IQR: 25-25)
Treatment delay	From receiving a TB diagnosis to initiating TB treatment	3 (IQR: 2-4)

Table 2.5. Delays experienced from the onset of TB symptoms to initiating TB treatment. Data from Sreeramareddy et al (224), combining both the public and private sector.

It is estimated that a patient, on average, consults 2.7 providers before receiving a diagnosis (224). In 2013, out of the total number of incident TB cases, 68% of TB patients accessed TB tests (either in the public or private sector), 57% were diagnosed with TB, 50% initiated treatment, 43% completed treatment successfully, and 37% achieved one-year recurrence-free survival (240,241) (fig 2.3). Thus, the largest gaps in the Indian TB care cascade are individuals not accessing a TB test and receiving a TB diagnosis (241). Overall, the care cascade completion rate for all forms of TB is around 43%, and decreases to 7% amongst MDR-TB (241).

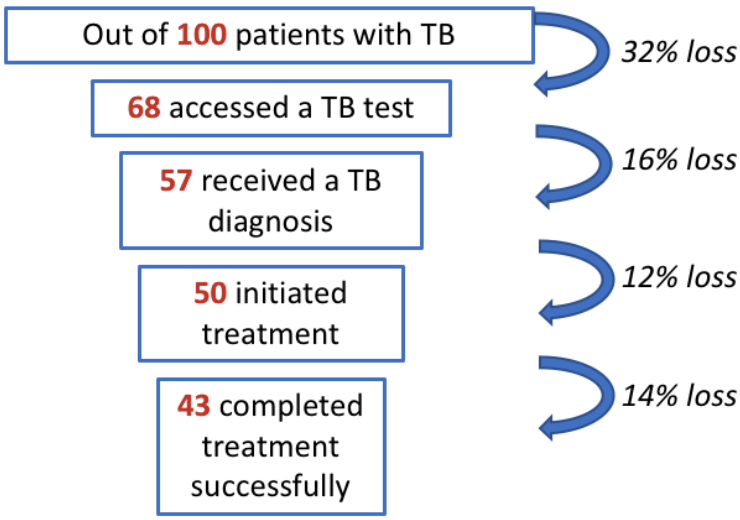

Figure 2.3. Tuberculosis care cascade losses in the public sector, India. Values were extracted from a meta-analysis by Subbaraman et al. (240).

2.2.8. South Africa

2.2.8.1. An overview of tuberculosis in South Africa

The TB epidemic in South Africa is driven by HIV; in 2018, it was estimated that around 59% of incident TB cases were co-infected with HIV (113). The government implemented the WHO's strategy of DOTS in 1994; however, as a consequence of the growing HIV epidemic, it had little impact on TB incidence (242). The growing TB and HIV epidemics were made worse by the weak health system and lack of coordination across the country. Globally, South Africa was amongst the slowest to expand ART for PLHIV, and it was not until 2003, ART became available at public services (242). As a result, adult life expectancy dropped from 63 years in 1990 to 54 years in 2003 (243).

As a result of the emergence of XDR-TB in 2005 (244), the government released the South African TB Strategic Plan in 2007. The aim was to make high quality diagnostic and treatment services accessible to all TB patients and ensure adequate funding (245). In 2009, the government released a further plan, aimed at reforming its health sector, with a particular focus on HIV and TB (246). The reforms saw large increases in the number of people tested for HIV and TB, improved ART coverage and an increase in the number of clinics offering DR-TB treatment. In 2011, the government recommended Xpert as the initial test for both TB and DR-TB; since then, Xpert has been widely implemented across South Africa. In 2014, the ratio of sputum smear microscopy tests to Xpert cartridges was 1.6, the lowest amongst high TB burden countries analysed (247). South Africa now has the largest number of people on ART worldwide (248). Since ART reduces the risk of developing

active TB disease amongst co-infected patients (52), the rollout of ART has contributed substantially to the decline of TB incidence and mortality in South Africa (249,250).

2.2.8.2. The South African healthcare system

The public sector is under-funded relative to the size of the population it treats; for example, in 2011, out of the 8.3% of GDP spent on health, only half was spent in the public sector, despite the sector treating over 84% of the population (251,252). The quality of care received in the private sector, like India, varies (252).

In 2015, the government introduced a new system of healthcare financing called the National Health Insurance. The aim of the new system was to provide access to 'appropriate, efficient and quality health services' to the entire population across 14 years, and remove OOP payments (251); in other words, providing universal healthcare coverage. PPPs were trialled for the National Health Insurance scheme. For example, private general practitioners were asked to provide public sector care; however, uptake was low due to poor compensation (253). Another example of a PPP is in HIV care; partnerships were created with private general practitioners to oversee the treatment of public sector patients, to reduce some of the burden on the public sector (254). Studies have found the partnerships to be successful, and that retention was high amongst the providers (255,256).

The majority of TB patients are treated in the public sector (257); it was estimated that 93% of TB tests and treatment were provided by the public sector in 2012 (258). All patients initiating TB treatment are noted in the electronic TB register. The majority of HIV and TB services are separated amongst primary healthcare clinics in South Africa. Most of the public TB services offer on-site HIV testing and referral for HIV care, whereas HIV services tend to refer presumptive TB patients for both screening and treatment (259).

2.2.8.3. Cascade of care

Due to the large number of public primary healthcare facilities, it is estimated that only 3-5% of TB patients are unable to access TB diagnostic tests (fig 2.4) (206,257). It is estimated that 14% of patients that seek a test, do not receive a diagnosis (fig 2.4) (257). In rural Eastern Cape Province, it is estimated that the median time from sputum collection to receiving a MDR-TB diagnosis was 27 days (IQR: 2-45 days), ranging from a day (IQR: 1-4 days) with Xpert to 45 days (IQR: 39-59 days) with a culture drug sensitivity test (260). Despite widescale implementation of Xpert, a nationwide retrospective cohort study analysing 2013 data found that although Xpert has reduced the treatment initiation delay and has improved case detection for DR-TB, the pre-treatment loss to follow-up gap has remained the same (261). Of the patients who receive a TB diagnosis, 15% do not initiate

treatment (fig 2.4) (257). This loss may be due to poor communication between patients and HCWs, and lack of counselling (262). A meta-analysis calculated the care cascade completion rate to be 53% and 22% for all forms of TB and MDR-TB, respectively (fig 2.4) (241,257). The largest gap in the South African care cascade is treatment completion; of the patients who initiated treatment in 2013, 24% did not achieve treatment success (fig 2.4) (257).

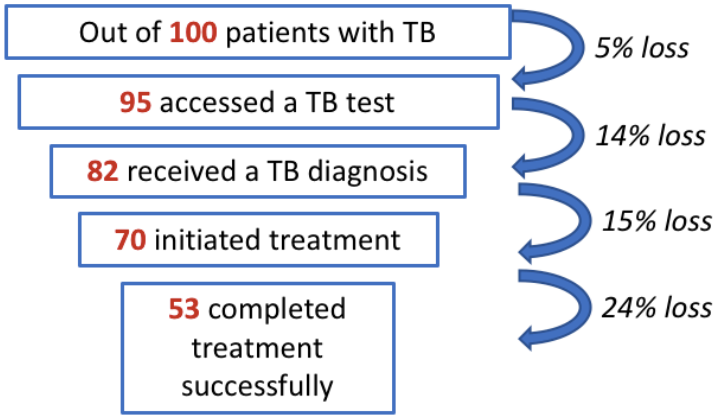

Figure 2.4. Tuberculosis care cascade losses in South Africa for all patients. Values were extracted from a meta-analysis by Naidoo et al. (257). Losses are an average of the private and public healthcare sector.

2.3. Coronavirus disease 2019

With the emergence of severe acute respiratory syndrome coronavirus 2 ("SARS-CoV-2") at the end of 2019, I had the opportunity to apply the concepts and approaches I learnt from modelling TB diagnostics to SARS-CoV-2 diagnostics. In this section, I provide a brief overview of the epidemiology of SARS-CoV-2, as well as the progress that has been made in diagnostics, treatment, and vaccines.

2.3.1. Epidemiology

The WHO was first notified of cases of SARS-CoV-2 in Wuhan City, China on 31st December 2019. It was quickly evident that the virus was spreading via human-to-human transmission (263). The majority of cases initially went undocumented, allowing for the rapid global spread of the virus (264–266). On the 20th January, Japan, Thailand and South Korea reported the first cases of COVID-19 outside of China (267). On the 11th March the WHO declared COVID-19 a pandemic (268). At this point, many countries had placed nationwide restrictions.

2.3.2. Natural history

SARS-CoV-2 is spread via respiratory droplets. Viral load peaks around the onset of symptoms and, for the majority, becomes undetectable within 2 weeks of symptom onset (269–272). Transmission may be possible up to 8 days after symptom onset (271,273).

Upon infection, SARS-CoV-2 targets cells in the respiratory tract (271). Dysregulation of the immune response, along with cytokine storms have been noted amongst severely ill hospitalised patients (274–276). The incubation period, the time from infection to symptom onset, ranges between 2 and 11 days, with a median of around 5 days (277–281). Although reinfection can occur (282,283), a study found that amongst 12,500 HCWs, those that had been infected, had a reduced risk of developing COVID-19 6-months after infection (284). Another study estimated that over 95% of subjects with prior infection had immunological memory even 8 months after infection (285).

Studies have reported varying rates of asymptomatic infection; it is difficult to ascertain the true prevalence of asymptomatic infections if patients are not followed up. For example, a study conducted in a nursing facility, found that 56% were asymptomatic when tested, of which 89% went on to develop symptoms (286). The true prevalence of asymptomatic infection may also be underestimated as asymptomatic cases may never seek diagnosis or care. One meta-analysis suggests that around 17% of cases are asymptomatic, whereas a modelling study estimated the proportion of asymptomatic cases in an outbreak in Vo', Italy, was as high as 42.5% (287). Transmission may occur via asymptomatic, pre-symptomatic and symptomatic patients (277,288,289); however, over half of transmission may be due to pre-symptomatic cases (272,290). A meta-analysis found the relative risk of transmission by asymptomatics was 42% lower than of symptomatic cases (291); another meta-analysis found that the transmission potential of pre-symptomatic cases was comparable to symptomatic cases, but lower in asymptomatic cases (292).

Amongst symptomatic patients, the majority develop symptoms 5 days after infection, with 97.5% developing symptoms within 11.5 days (278,293). The most common symptoms include fever, dry cough, fatigue, headaches and shortness of breath (281,293–296). As the pandemic progressed, olfactory and gustatory symptoms, such as loss of smell or taste, and diarrhoea also became apparent (297). Older individuals and those with comorbidities such as diabetes and cardiovascular disease are more likely to be hospitalised with respiratory distress and multiorgan failure, and require intensive care (294,298–300). The proportion of infected individuals requiring hospitalisation increases with age, ranging from less than 1% amongst those aged less than 20 years to 18% amongst those aged over 80 years (301,302).

2.3.3. Diagnosis of coronavirus disease 2019

At the start of the pandemic, diagnostics were vital in reducing the spread of COVID-19 due to the lack of vaccines and effective treatments. Diagnostic tests enable the differentiation between COVID-19 and other respiratory conditions, as well as the identification of asymptomatic infection. Table 2.6 provides a summary of the main diagnostic tests for COVID-19. I compare and discuss the different diagnostic tests for COVID-19 in greater detail in Chapter 6.

Many countries, including HICs, have faced challenges in scaling up diagnosis; these challenges include the need for rapid specimen collection and delivery, insufficient laboratory testing capacity, supply chain issues, and regulatory hurdles (303). Consequently, the majority of countries prioritised testing for specific sub-groups of the population, such as hospitalised patients presenting with COVID-19 symptoms (303). There is an urgent need for point-of-care diagnostic tests to ease the pressure from laboratories and reduce turnaround time. The Foundation for Innovative New Diagnostics ("FIND"), a non-profit whose aim is to accelerate the development, evaluation and delivery of diagnostic tests, are currently evaluating a range of diagnostic tests for COVID-19.

Test	Pooled sensitivity*	Pooled specificity	Sample type	Infrastructure required	Relative cost
Nucleic acid amplification tests	71-98%	99-100%	Generally, nasopharyngeal or oropharyngeal	Specialised laboratory equipment; highly trained workers	High
Serological tests	66-98%	96-99%	Blood	Depends on the type of test: ELISA- or chemiluminescent-based tests require specialised laboratory equipment; lateral flow tests are suitable at the point-of-care	Low
Rapid antigen diagnostic tests	56-98%	97-100%	Nasopharyngeal	Suitable at the point-of-care**	Low

Table 2.6. Summary of the main diagnostic tests for COVID-19. * Sensitivity varies hugely depending on sample type and at what time the sample was taken. For example, serological tests have a sensitivity close to zero, early on during the course of infection; **Suitable at the point-of-care, although the sensitivity and specificity of these tests at the point-of-care have not been tested.

2.3.4. Treatment of coronavirus disease 2019

The clinical management of hospitalised cases involves alleviating symptoms and supplemental oxygen. Many drugs to treat other diseases, ranging from antivirals to anti-inflammatory drugs, are being repurposed and tested in clinical trials.

Corticosteroids are anti-inflammatory drugs, that lower inflammation in the body and therefore reduce the risk of respiratory failure; however, they also inhibit the immune response and thus, reduce viral clearance. A clinical trial on dexamethasone, a corticosteroid, found that amongst patients on

mechanical ventilation, those receiving the drug had a significant lower risk of death than those receiving a placebo (rate ratio of 0.64); the risk of death was also lower amongst patients receiving oxygen but not mechanical ventilation (rate ratio of 0.82) (304). As a result, the WHO strongly recommends that corticosteroids be given for the treatment of patients with severe COVID-19 (305).

A wide range of antivirals are ongoing trials to determine their efficacy against SARS-CoV-2, including remdesivir and hydroxychloroquine. Remdesivir was initially developed for treating Ebola but was shown to be ineffective (306), whilst hydroxychloroquine is used to treat a wide range of diseases, including malaria. Both drugs were shown to have antiviral properties and were effective in controlling SARS-CoV-2 in vitro (307); however, clinical trials have not shown promising results for either drug (308–311).

2.3.5. Vaccines

Vaccines against COVID-19 are being developed at astonishing speed, of which several have received Emergency Use Listing by the WHO. These include the BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna), ChAdOx1 (AstraZeneca/University of Oxford) and Ad26.COV2.S (Janssen). BNT162b2 and mRNA-1273 are RNA vaccines, whereas ChAdOx1 and Ad26.COV2.S are recombinant vaccines. Trials have suggested that these vaccines have high efficacy, greater than 85%, against severe COVID-19 (312–315). Unfortunately, the trials were not geared to investigate whether the vaccines reduce transmission; trials are currently underway to assess this. At the time of writing, preliminary data suggests that the vaccines reduce transmission. One study from Israel suggests that individuals with SARS-CoV-2 infections that occurred after inoculation with the first dose of the BNT162 vaccine had reduced viral loads, suggesting these individuals were less infectious than non-vaccinated individuals (316). Another study conducted by Public Health England showed that the likelihood of household transmission from vaccinated individuals diagnosed with COVID-19 was reduced by 40-50% after one dose of the ChAdOx1 and BNT162b2 vaccines (317).

Vaccine uptake has been high amongst HICs and as a result, the number of hospitalisations has substantially decreased (318,319). Unfortunately, vaccine uptake remains low in LMICs. The WHO has launched COVAX, an initiative to provide COVID-19 vaccines for LMICs. Nevertheless, until vaccines become readily available to all countries, testing will remain a key part in the response against COVID-19.

2.4. Mathematical modelling of infectious diseases

2.4.1. What is mathematical modelling?

A mathematical model is a mathematical framework used to understand or make predictions about a system. In the field of infectious diseases, models are used to elucidate infectious disease dynamics, including pathogen evolution, intra- and inter-population spread and within-host dynamics. Understanding and predicting the spread of infectious diseases help inform decision making. However, it is important to keep in mind the limitations of models. Mathematical models rely heavily on data, and thus, are only as good as the quality of data. Thus, modelling is a balancing act between simplifying and adding complexity; too simple and the model does not represent reality closely enough, but too complex, and the amount of data needed and potential sources of error increase.

2.4.2. Types of mathematical models

A model can be either deterministic or stochastic. A deterministic model describes the average behaviour of a system, ignoring stochasticity that may occur at the individual level, whereas stochastic models incorporate stochasticity. Thus, in a deterministic model each parameter is assigned a fixed value that represents the average behaviour of the population, whereas in a stochastic model the parameters are assigned probability distributions (320). Stochastic models are often used to model outbreaks, where the number of infected individuals is low and thus, where stochastic variation becomes increasingly important (320). In this thesis, I exclusively use deterministic models. Deterministic and stochastic models can also be further sub-divided into dynamic and static models.

2.4.2.1. Dynamic models

Dynamic models are systems whose states change and interact over time. A commonly used dynamic model is a compartmental model. A compartmental model stratifies the population into compartments representing mutually exclusive states of health, relevant to the disease of interest. Fig 2.5 summarises common compartmental models. Most diseases have a more complex natural history and require more health states than the ones described in fig 2.5; for example, models can start incorporating care seeking behaviour or stratify by age structure. Model parameters describe the flow between compartments (table 2.7 defines the common parameters used for the different types of compartmental models described in fig 2.5). Therefore, the number of individuals entering or leaving a compartment within a given timeframe is dependent on per-capita rates and the number of individuals subjected to these rates. Ordinary differential equations (“ODEs”) are used to describe the rate of change of the population in the different health states over time.

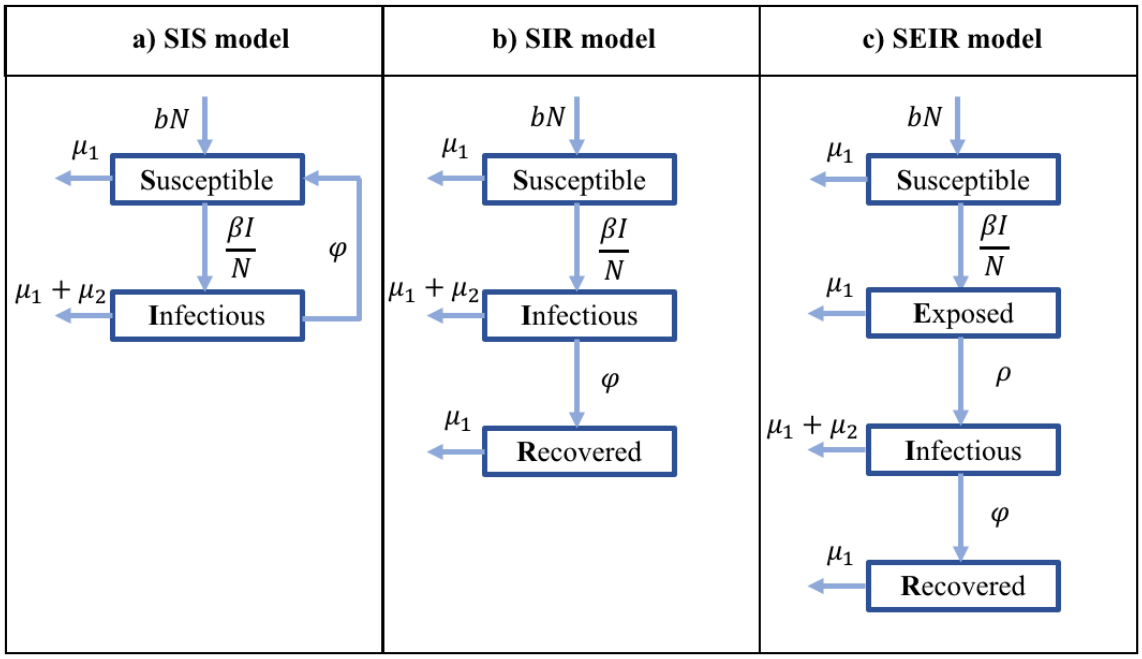

Figure 2.5. Basic examples of compartmental models of infectious diseases. Many models follow these core structures, but have additional compartments to represent additional disease states, care seeking behaviour, population structure and interventions. Note, that beta (β, the per capita rate of transmission) is determined by the rate of contact between individuals and the probability of transmission between an infectious individual and a susceptible individual. By multiplying the proportion of the population that is infectious (I/N), we get the force of infection ($\frac{\beta I}{N}$), in other words, the risk of an uninfected individual becoming infected. This assumes that the number of contacts depends on population size (frequency dependent transmission). Alternatively, density dependent transmission (βI) assumes individuals have a fixed number of contacts. The dependency of the force of infection on disease prevalence and the number of susceptibles means that transmission is a non-linear, dynamic process, with the individual risk of infection changing over time.

Symbol	Parameter definition
b	Birth rate
μ_1	Background death rate
μ_2	Disease-induced death rate
β	Rate of transmission
φ	Rate of recovery
$1/\rho$	Mean duration of latency

Table 2.7. Commonly used parameters in the mathematical modelling of infectious diseases. Note, parameters are per-capita rates in deterministic models (the average rate per person in a population), whereas in a stochastic model, the parameters are assigned a probability distribution.

2.4.2.2. Static models

Unlike dynamic models whose states change and interact, states in a static model do not. Although transmission dynamic models tend to be more appropriate when modelling infectious diseases, they are more complex and tend to require more data. Static models may be useful when modelling interventions that have no effect on the force of infection, for example modelling the impact of a drug

that reduces disease severity but not transmission (321). A common example of a static model is a decision tree.

A decision tree is a model consisting of branches used to represent a set of decisions and outcomes (i.e., cost or health status) for a patient or cohort. Each node represents either a choice (i.e. which diagnostic test should be used, or should treatment be initiated?), or a probability (i.e. probability of death) (322) (fig 2.6). Decision tree modelling is often used in health economics to compare the costs and effectiveness of competing interventions.

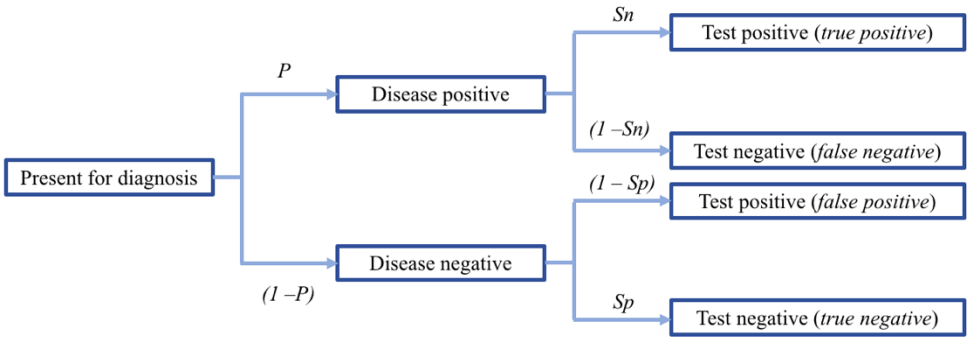

Figure 2.6. An example of a decision tree evaluating the use of a diagnostic test. From there, further states can be added to describe the outcome in terms of the cost and effects on health (i.e., recovery or death) of misdiagnosis and correct diagnosis. (P = probability of disease; Sn = test sensitivity; Sp = test specificity)

2.4.3. Uncertainty and sensitivity analysis

2.4.3.1. Uncertainty analysis

As models are simplifications of real-world systems, model outputs will always contain uncertainty. Although collecting more quality data can reduce this uncertainty, it is impossible to forecast with complete accuracy. Uncertainty can stem from incorrect assumptions made in terms of the model structure (model uncertainty), incorrect data or estimates used to inform model parameters (parameter uncertainty) and from the methodologies used. It is important to quantify the uncertainty of a model, in order to evaluate our confidence in model outputs.

Thus, uncertainty analysis aims to estimate the uncertainty surrounding model outputs and describe possible model outputs. This is often done by allocating probability distributions to model inputs (the probability that we will observe a particular range of values) to generate probability distributions of model outputs (323,324).

One statistical approach is Bayesian inference which provides insight into the posterior distribution over some unknown parameter within the model (323). The posterior distribution of a set of parameters can be defined using Bayes' theorem:

$$P(\theta|x) = \frac{P(x|\theta)P(\theta)}{P(x)}$$

Where $P(\theta|x)$ is the probability of the model parameters (θ) given the data (x), also known as the posterior distribution; $P(x|\theta)$ is the probability of the data given the model parameters, also known as the likelihood (information from the observed data about a set of parameters); $P(\theta)$ is the prior (prior belief about the model parameters before having seen the data); $P(x)$ is the probability that the data was generated by the model. The likelihood updates the prior, to form the posterior distribution. To calculate the denominator, $P(x)$, requires multidimensional integration over all possible parameter values, which quickly becomes intractable when a model has many parameters (325). To circumvent this issue, we can sample from:

$$P(\theta|x) \propto P(x|\theta)P(\theta)$$

where, the likelihood multiplied by the prior is proportional to the posterior distribution. If we sample enough times from the posterior distribution to form an approximate posterior distribution, it is possible to infer what this true posterior distribution looks like.

One common method used to sample from the posterior distribution is Markov chain Monte Carlo ("MCMC") sampling (325,326). Monte Carlo is a method used to estimate the properties of a distribution by examining random samples from the distribution; a Markov chain means that each random sample is used to generate the next sample, whilst trying to approximate independence between samples. Given a current sample θ_i, a new sample is proposed according to a proposal distribution; this new sample is then accepted or rejected depending on the acceptance-rejection algorithm. There are many types of MCMC algorithms including Metropolis Hasting, adaptive Metropolis and Gibbs sampling.

2.4.3.2. Sensitivity analysis

Sensitivity analysis examines how changes in model inputs (i.e., model parameters) impact model outputs. In other words, understanding how much each parameter is contributing to uncertainty and thus, which parameter is the model output most sensitive towards. The more sensitive a model output is towards model parameters, the higher the uncertainty of model outputs. In univariate sensitivity analysis, parameter values are changed one at a time to investigate the effect each parameter has on model outputs, whereas in multivariate sensitivity analysis, a combination of parameters are varied. Partial rank correlation coefficients ("PRCC") can be used to measure the correlation between each

parameter and relevant model outputs, to identify parameters that are most influential. In brief, PRCC is an efficient approach to global sensitivity analysis that quantifies the strength of association between any given parameter and model output, while simultaneously taking account of variation in all other parameters.

2.4.4. Tuberculosis models

The first mathematical model of TB was developed in the 1965 (327). Since then, models have been used to inform public health in a variety of ways, ranging from improving our understanding of the natural history of TB (15) to predicting the impact of current and novel technologies on the TB epidemic in a variety of settings (328). Below, I refer exclusively to deterministic compartmental models of TB transmission.

2.4.4.1. Tuberculosis model structure

It is important to understand the assumptions behind model structures and the data used to inform the models. Models are usually formulated according to the research question; for example, a model aimed at predicting a TB intervention in South Africa may want to incorporate HIV/TB co-infection. A typical TB model is shown in fig 2.7 and defined in table 2.8: susceptible individuals become infected with MTB, of which a proportion, known as fast progressors, progress quickly to active TB disease (the infectious state) and eventually recover, whereas the rest, known as slow progressors, progress to LTBI (latent state) and eventually go on to develop active TB disease and recover.

Ideally, different model structures would investigate the same question to identify variations in model outputs that are due to structural uncertainty. This has not often been done in the field of TB; only recently have two modelling studies incorporated this methodology (329,330). The first study assessed the feasibility of achieving the 2025 WHO TB targets in three high TB burden countries by using 11 independently developed models (330); the second investigated the cost-effectiveness of different TB control strategies using 9 independently developed models (329).

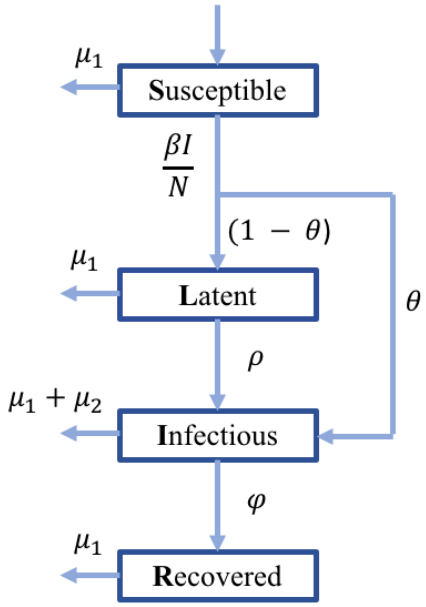

Figure 2.7. A typical tuberculosis model based on the SEIR structure. Note, here latent TB infection is equivalent to the "exposed" state. Additional compartments to reflect care seeking behaviour, diagnosis and treatment initiation can be added. Additional rates such as rate of relapse or differentiating between the rate of self-cure or rate of cure after treatment, are not shown.

Symbol	Parameter definition
$\boldsymbol{\mu_1}$	Background death rate
$\boldsymbol{\mu_2}$	TB-induced death rate
$\boldsymbol{\beta}$	Rate of transmission
$\boldsymbol{\theta}$	Proportion of cases undergoing fast progression
$\boldsymbol{\varphi}$	Rate of recovery
$1/\boldsymbol{\rho}$	Mean duration of latency

Table 2.8. Commonly used parameters in tuberculosis mathematical models.

Several reviews have summarised the TB modelling literature (331–333). A systematic review examined how models structured the progression from LTBI to active disease and the validity of these assumptions (332). Fig 2.8 shows the most common model structures used for modelling progression to active disease based on the 312 studies analysed in the review. The review concluded that a substantial number of the models were inconsistent with empirical evidence; for example, even though the model structure presented in fig 2.8 panel B is the second most common structure used amongst TB modellers, the authors found it to have a poor fit to empirical evidence, because it underestimates the short-term risk of progression to active disease whilst over-estimating the long-term risk of progression. The model structure presented in fig 2.8 panel A, although not the worst performer, was not great at predicting the risk of progression the years following infection. Similarly, another review that investigated the optimal way to incorporate latency dynamics in models found that panel A and B (fig 2.8) produced results that have a poor fit to the data in the first few months

after infection, and that models with two latency compartments replicated the data more accurately (333). This suggests that if the research question is focussed on the years directly following infection, fig 2.8 panel A and B may not be the best choice in terms of model structure.

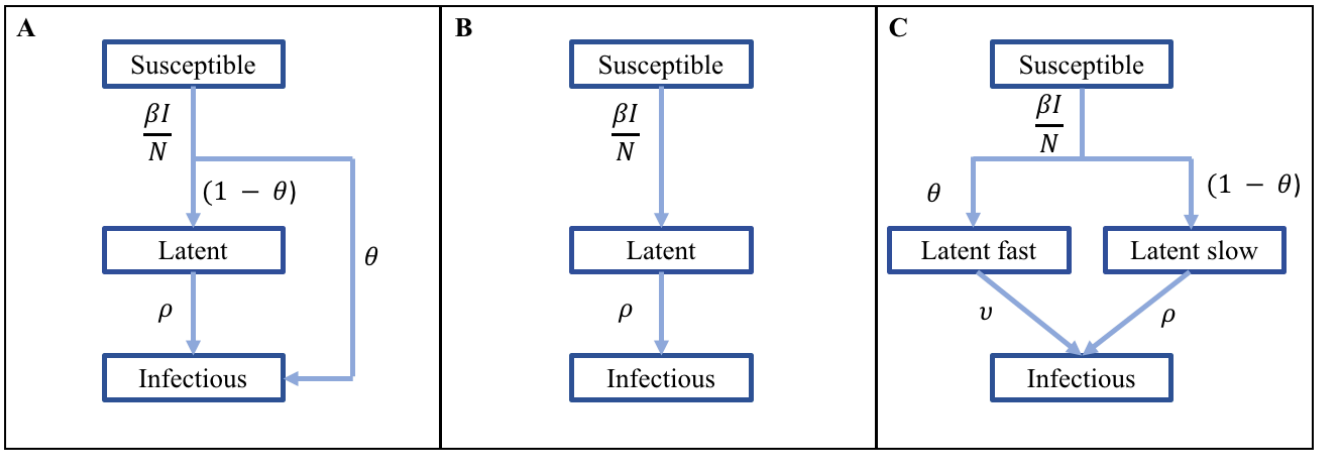

Figure 2.8. The three most common model structures to model the progression of disease. Adapted from Menzies et al (2018); 49% of modelling studies adopt panel A, 19% adopt panel B, and 11% adopt panel C (332).

Another review examined how models incorporated heterogenous infectiousness (331). The review concluded that many models did not incorporate this heterogeneity; amongst those that did incorporate heterogenous infectiousness, the majority were splitting the active disease compartment into two, to represent infectious smear positive individuals and less infectious smear negative individuals, or into pulmonary (more infectious) versus extrapulmonary TB (less infectious). However, the review did not investigate the impact of not incorporating heterogeneity into the model structure which is likely to be dependent on the research question.

Finally, a conceptual modelling study by Dowdy et al highlighted the importance of model structure and its effect on model outputs (26). In Dowdy's model, adding an extra health state to represent subclinical TB reduced the impact of various case-finding interventions, suggesting that models may overestimate or underestimate the impact of interventions based on their structure alone.

When modelling the impact of interventions, such as diagnostic tests, it is important to not only model the accuracy of such interventions, but also the setting. The impact a diagnostic test has on TB transmission depends on many factors including care seeking behaviour, access to the test, how much transmission occurs before seeking a test, whether HCWs perform the test correctly and whether HCWs have confidence in the test. These factors likely differ by setting, and likely varies over time throughout the course of infection (334). Thus, it is possible to have a perfectly sensitive and specific diagnostic test that has little impact on the local TB epidemic (335). A study found that the majority

of TB models that examine the impact of diagnostics tests are extremely homogenous; rate of TB transmission, rate of care seeking and the probability of successful diagnosis are all similar (334). The authors estimate that these assumptions overestimate the impact these tests may have on the TB epidemic and argue that ideally models should incorporate heterogenous rates to reflect different levels of transmission and care seeking over time. Nevertheless, this requires additional data that is not readily available; most diagnostic tests are evaluated under perfect conditions which does not accurately reflect how they perform under real life conditions in resource limited settings, and how TB transmission changes over time has not been well characterised. Overall, it is important to ensure the model structure and parameters reflect the setting of interest, otherwise the impact of an intervention may be under- or over-exaggerated; however, this added complexity needs to be balanced with data availability.

2.4.4.2. Tuberculosis model parameters

Many sources used to inform TB model parameters have come from trials conducted in the 1960s and 1970s, before chemoprophylaxis was widely available, and so the duration of TB infection without treatment could be monitored. Widely cited studies from the pre-chemoprophylaxis era include: Ferebee (1970), a review of chemoprophylaxis trials (40); Barnett et al (1971), a trial that followed TST positive cases in Saskatchewan, Canada (336); Comstock et al (1974), a BCG trial where the risk of developing TB amongst TST positive Puerto Rican children was investigated (53); Horwitz (1969), a trial that studied the risk of relapse in Denmark (337); and the Medical Research Council's trial on BCG and vole bacillus vaccines that looked at the progression to TB disease amongst adolescents and early adults in England and Wales (338). As the efficacy of TB treatment became evident, it became unethical to conduct such trials.

Values that were estimated in the pre-chemoprophylaxis era may no longer be applicable to the 21st century. For example, in 1985, using the data of studies from the pre-chemoprophylaxis era, Styblo formulated a "rule" that has, until the early 2000s, been used to inform TB studies. Styblo suggested that an incidence of 50 sputum smear positive TB cases per year per 100,000 generates an annual risk of infection ("ARTI") of 1% (339). The rule was widely used, as it allowed modellers to indirectly derive TB incidence from ARTI, the latter being a much easier measurement to make (340). However, as this rule was estimated from data in the pre-chemoprophylaxis era, the rule no longer holds, as the average duration of infectiousness and the average number of transmissions per year has changed due to treatment and improved living conditions (340).

Several commonly used parameters of TB models are hard to estimate, including the rate of endogenous reactivation and the proportion that undergo fast progression. It is impossible to measure

directly what proportion of incidence is as a result of these two phenomena (328). Instead, modelling studies such as Vynnycky & Fine (1997) and Sutherland et al (1982), and molecular epidemiological studies such as Horsburgh et al (2010) have estimated values for these rates and proportions (15,341,342). These papers are widely cited papers in TB modelling literature (343). However, both use datasets from low TB burden settings, the Netherlands, England and Wales, and the USA. To this date, no study has attempted the same analysis for high TB burden countries. Other parameters that are hard to measure include the rate of care seeking, as this rate is likely to vary hugely between and within countries and the rate of self-cure, which is based on studies conducted in the pre-chemoprophylaxis era (328,344). There is a need for a greater understanding of the natural history of TB, especially in high burden settings, and of heterogeneity in terms of geography and time, for both the natural history of TB and care seeking behaviour (328).

A review of TB mathematical models I conducted in 2016 found that modelling studies were significantly more likely to be cited as first-degree citations, followed by primary studies, reviews (fig 2.9) (343). The most cited modelling studies were Vynnycky & Fine (1997) and Dye et al (1998). This is supported by a more recent review (332). It is important for modellers to understand where the data informing their model originates from, to ensure the assumptions behind the data is appropriate to the research question of interest.

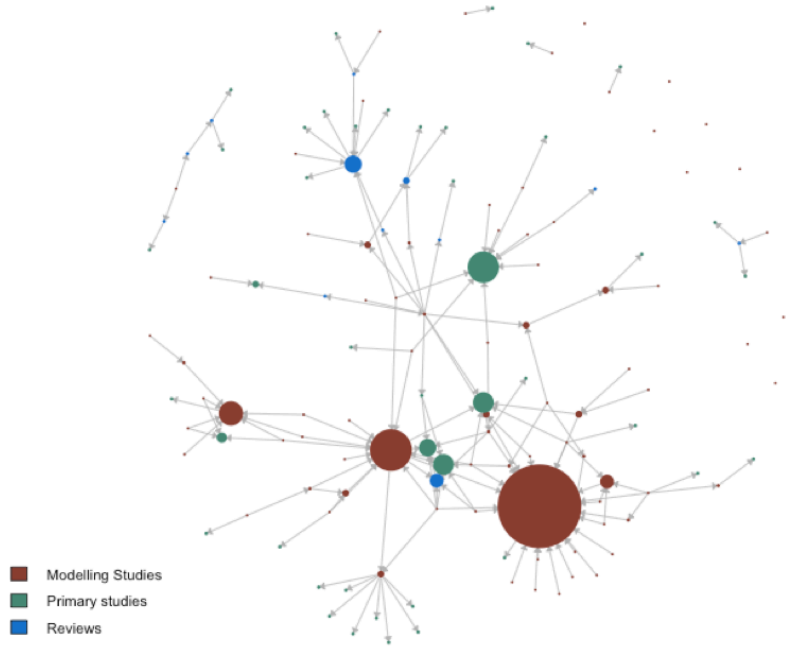

Figure 2.9. Network of citations. Focussing on the rate of endogenous reactivation, 82 modelling studies were selected after a literature search. First-degree citations were classified as a modelling study (red), primary study (green), or review (blue). Arrows point towards the cited study. Nodes are weighted according to the number of studies that have cited it, so that a larger node represents a more frequently cited study. Figure from unpublished work (343).

2.5. Economic evaluation

Health economics is the comparative analysis of alternative interventions in terms of their costs and health outcomes (345). As all healthcare sectors have finite resources, there is usually an opportunity cost to any intervention, where selecting one intervention prevents the roll out of another. Thus, there is a need to understand which interventions are most beneficial considering these constraints.

There are many types of economic analyses, including cost-effectiveness analysis ("CEA"), cost-benefit analysis and budget-impact analysis. CEA is commonly used, and below, I discuss its use in further detail.

2.5.1. Cost-effectiveness analyses

CEAs incorporate the benefits and costs of an intervention and compares it to alternative scenarios. Consequently, CEA provides a method for prioritizing the allocation of resources by informing policy makers on the interventions that minimises costs and maximises health outcomes.

A key measure in economic evaluation is the incremental cost-effectiveness ratio ("ICER"). An ICER represent the economic value of an intervention compared to its comparator:

$$ICER = \frac{\Delta\text{cost}}{\Delta\text{health}} = \frac{Cost_1 - Cost_2}{Health_1 - Health_2}$$

The denominator represents the difference in health outcomes between the two alternatives (described in further detail below), whereas the numerator represents the difference in cost. Ideally, an intervention is compared to the next-least expensive non-dominated alternative.

The costs and health outcomes between different alternative interventions can be visually represented by plotting a cost-effectiveness plane, with health outcomes plotted on the x-axis, and the incremental cost plotted on the y-axis (fig 2.10).

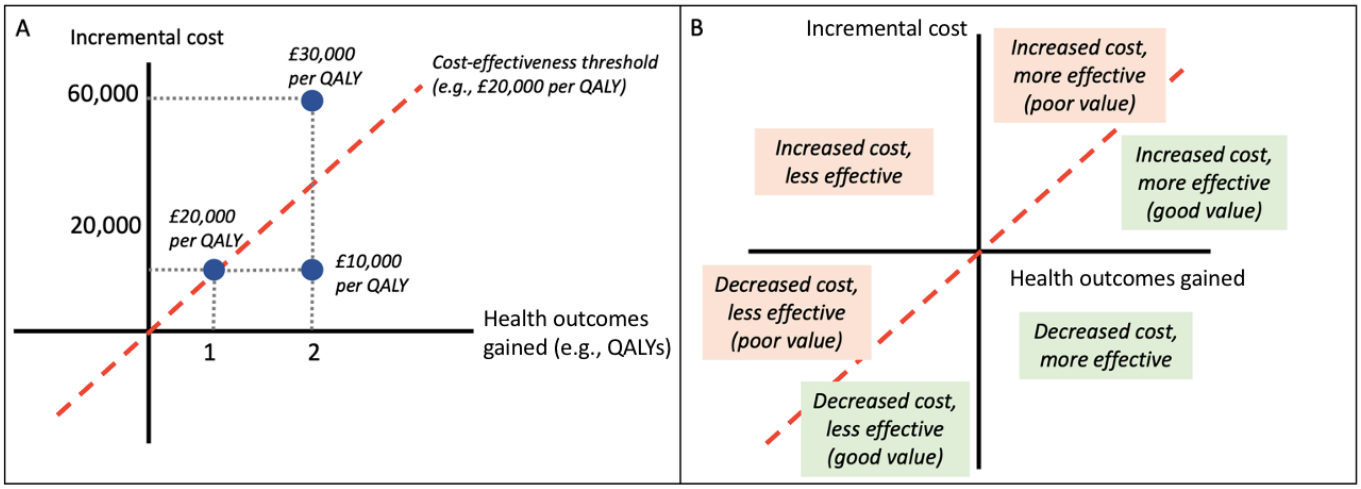

Fig. 2.10. Example of a cost-effectiveness plane. Here, the cost-effectiveness of an intervention is assessed given an objective of maximising health. Panel A shows the health outcomes gained and the incremental cost of adopting three new technologies (blue points) compared to an existing technology; the bottom two blue points are considered cost-effective assuming a cost-effectiveness threshold of £20,000 per QALY gained. Adapted from Glied & Smith (345). Panel B highlights what the different sections of a cost-effectiveness plane indicate; green boxes represent sections of the plane that are considered cost-effective, whereas red boxes represent sections of the plan that are considered not cost-effective.

A threshold is set to determine whether a specific cost per health outcome gained is considered cost-effective. If the ICER is less than the CEA threshold, then the intervention is considered cost-effective (345). There has been much debate about what an appropriate CEA threshold should be, in any given country (346). Traditionally, many studies have set the threshold as 1 to 3 times a country's GDP per capita. However, more recent evidence suggests that these thresholds may no longer be appropriate and are too high for many countries (346). Woods et al recalculated CEA thresholds for LMICs and estimated that the thresholds for such countries could be as low as 50% of their GDP per capita (347). In addition, classifying an intervention as cost-effective is not informative unless all other interventions are considered in that setting, to ensure that the money spent is maximising health outcomes (346). Finally, a cost-effective intervention does not necessarily mean it is affordable, especially if the disease has high prevalence (346).

Calculating health outcomes

Health outcomes gained from an intervention are typically measured by quality-adjusted life years ("QALYs") or disability-adjusted life years ("DALYs"). A QALY is a measure of the state of health of a person in which the length of life is adjusted to reflect the quality of life; one QALY is equivalent to living one year in perfect health. A DALY is a measure of the number of years lost due to ill health (348). So, the more QALYs gained, or the more DALYs averted, the more effective an intervention

is. DALYs for a wide range of diseases are published regularly in the Global Burden of Disease study, the first of which was in 1994 (349), and the most recent in 2020 (350).

A DALY is composed of the years of life lost due to premature mortality ("YLL") and the years lost due to disability ("YLD"),

$$DALY = YLL + YLD$$

YLL measures the reduction in life expectancy (one YLL represents the loss of one year of life), whereas YLD measures the number of years of good health lost due to the disease.

YLL is calculated by multiplying the number of cause-specific deaths by a loss function that states the years lost to death as a function of the age at which death occurs (global standard life expectancy):

$$YLL = no.of\ cause\ specific\ deaths\ \times global\ standard\ life\ expectancy\ at\ which\ death\ occurs$$

The global standard life expectancy at which death occurs is based on an aspirational projected reference life expectancy table (351). Thus, YLL puts greater weight on deaths that occur at a younger age. YLD is calculated by the following equation:

$$YLD = disease\ incidence\ \times\ disability\ weight\ \times\ duration\ of\ disease$$

YLD incorporates the number of new cases of a disease, a disability weight which factors in disease severity, and how long an average person lives with the disease before either cure or death.

Nevertheless, issues arise when using DALYs or QALYs. Measures, such as disability weight, are subjective. With regards to TB, there has been increasing interest in understanding the morbidity and mortality that occurs post-TB (352,353). Usually, most analyses only account for DALYs averted linked to TB disease, which assumes therefore, that the individual returns to full health once cured of TB. However, increasing evidence suggests that even after successful TB treatment, the risk of morbidity and mortality remains elevated (352–354). Not including morbidity post-TB may be underestimating the cost-effectiveness of certain TB interventions, such as TPT (354).

Calculating costs

The cost of an intervention depends on whether the analysis is being conducted from a societal perspective or from the perspective of the healthcare sector. If the analysis is being conducted from a societal perspective, costs including the loss of work productivity and the cost of transportation to the

hospital should be included. On the other hand, costs such as the cost of staff and supplies, are included if the healthcare sector's perspective is being considered.

Costing is a challenge in economic analysis. With regards to TB, there is a need to understand further the cost of a false positive and a false negative result, costs that are often underestimated. A false positive result will result in a disease-free individual initiating treatment, which incurs a cost due to the risk of side effects. It is also hard to estimate the cost of a false negative result (an untreated TB case), and whether or not the cost of onward transmission should be included (355). In terms of diagnostic tests, it can be challenging to estimate the cost of implementation, the cost of training HCWs to use the test and the cost of maintaining the tests. Thus, the cost of diagnostic tests is often underestimated (356).

Due to future uncertainty, it is common to discount both health outcomes and costs in future years; this is because, people generally value future costs and effects less than current costs and effects. A discount rate is defined as a rate that is used to convert future costs and health benefits into equivalent present values (345). In this way, interventions that incur costs now, but where we only see health gains in the future (i.e., human papillomavirus vaccination amongst young teenage girls to reduce incidence of cervical cancer later in life), will look less cost-effective under discounting compared to an intervention where health gains are seen immediately. However, choosing the appropriate discount rate, and whether to discount costs and effects by the same rate, can be challenging (357).

2.6. Thesis aims

The field of diagnostics for both TB and COVID-19 are seeing exciting new developments, thus there is a need to evaluate the impact these new diagnostics may have on their respective epidemics, and to understand why the context in which these new diagnostics are used in is important. Mathematical modelling and health economics are useful tools to do this. A lot of factors need to be considered whilst modelling the impact of diagnostic tests on TB: TB has a complex and long natural history, providing different opportunities to target diagnostic tests to; the different epidemiology of TB across countries; and varying healthcare systems which lead to different care cascades. Unlike the wealth of TB studies, COVID-19 is still in its infancy and is a rapidly changing field. The aims of this thesis are as follows:

1) What is the population-level impact of detecting incipient TB with a hypothetical biomarker test on the TB epidemic in India?
    a. What are the cost-drivers of such an intervention?
    b. Under what circumstances may the intervention be considered cost-effective?

c. How do results differ across different TB-risk groups?

2) What is the population-level impact of detecting active TB disease amongst PLHIV in South Africa with urine-based lateral flow assays?
    a. How much of an advantage does a novel lateral flow assay with improved sensitivity have over a pre-existing lateral flow assay?
    b. What is the impact of broadening testing eligibility on the TB epidemic?
    c. Do the results hold true for countries with a lower HIV burden?

3) What is the population-level impact of increasing private sector engagement on the TB epidemic in India?
    a. Which engagement activity (TB notifications, TB diagnostics or TB treatment) has the greatest impact on the TB epidemic?
    b. What are the costs of such activities, and which has the lowest ICER?
    c. How do results differ across cities that have different service provisions?

4) What is the trade-off between more accurate but more expensive and slower diagnostic tests, and less accurate but cheaper and faster diagnostic tests for SARS-CoV-2?
    a. Under what scenario can a less accurate test be beneficial?
    b. Do results differ by use-case?
    c. Which variables are most influential in determining the value of these tests?

Chapter 3: Results (i)

The potential value of biomarker-led preventive treatment in eliminating tuberculosis

TB prevention is essential for TB elimination, and as a result, approaches to identify individuals who would benefit from TB preventive treatment ("TPT"), such as those with incipient TB, are under development. Such a test will enable timely TPT initiation amongst individuals who are at imminent risk of progression to active TB. In this chapter, I develop a mathematical model of TB transmission in a slum and non-slum population of a major city in India. I investigate the potential impact biomarker-led TPT amongst cases of incipient TB may have on the TB epidemic, under two testing strategies, slum-only testing and whole-city testing (slum and non-slums alike). I also examine whether such strategies offer a cost-effective approach for TB control in high burden settings. I demonstrate that biomarker-led TPT can have an impact on TB incidence in an urban setting; however, the cost of implementing such a strategy is likely to be prohibitive, given the testing effort needed to identify those with incipient TB, even in a high-risk population. Despite the potential impact of such measures, results suggest that their cost-effectiveness would need to be carefully considered.

3.1. Introduction

High TB-burden countries traditionally focus on detecting and treating active TB disease (358). However, modelling studies suggest that unless the reservoir of latent TB infection ("LTBI") is targeted, TB-elimination targets will not be met, even if routine TB services are strengthened and accelerated (74,359–361). Nevertheless, the majority of individuals with LTBI do not benefit from TB preventive treatment ("TPT") due to the low risk of progression from LTBI to active disease (362). In addition, treating the approximate 2 billion people worldwide that are estimated to have LTBI would require costly efforts (363). Ideally, only those with the highest risk of disease progression would be treated.

Current tests for LTBI, tuberculin skin tests ("TST") and interferon gamma release assays ("IGRA"), have low positive predictive value ("PPV") for the development of active disease (approximately 2-3%). Assuming a 2-year cumulative TB incidence of 2% and TPT effectiveness of 50%, Petruccioli et al estimated that the number of patients needed to treat ("NTT") to prevent one case of TB is as high as 85 and 250 for IGRA and TST, respectively. According to the World Health Organisation ("WHO") target product profile ("TPP"), an optimal test would have a PPV of 16% and a NNT of 13, and should at least have a PPV of 6% and NNT of 40 (364). The WHO TPP further states that, ideally, the test should have a minimum sensitivity and specificity of 75% in detecting individuals at risk of developing active disease within two years (365).

As mentioned in chapter 2, certain epidemiological risk factors increase an individual's risk of progression to active disease by impairing the host's immune response. These risk factors include HIV, diabetes, age, malnutrition, tobacco smoke and indoor air pollution. Saunders et al developed and validated a risk score based on various risk factors to predict the risk of developing TB in adult contacts of patients with confirmed pulmonary TB in an intermediate-burden TB setting (366); however, these risk factors are likely to be setting-specific, and thus, the predictive power of the risk score is likely to also differ across settings (367). In addition, the risk score focusses on household transmission, and so there is a need for community transmission risk scores. Overall, these risk factors alone are unlikely to have strong predictive power. Consequently, there is a need for blood-based biomarkers that can identify individuals with the highest risk of progression to active disease.

Thus, in the last decade, studies have focussed on identifying biomarker signatures that offer prognostic value in identifying individuals at risk of developing active TB. This drive has led to the discovery of several gene signatures, ranging from signatures that can differentiate between active TB

and LTBI (368), those that can distinguish active TB from other diseases with similar clinical presentation (369,370) and those that indicate a successful treatment response (371).

One target is incipient TB, a stage between LTBI and active disease. Potential signatures of incipient TB have been identified. Zak et al identified a 16-gene signature with the ability to predict TB progression with a sensitivity and specificity of 54% and 83%, respectively, in the 12 months prior to active disease diagnosis amongst adolescents and adults in South Africa and the Gambia (372). Assuming a 2-year cumulative TB incidence of 2% and TPT effectiveness of 50%, it is estimated that the NNT to prevent one case of TB using the 16-gene signature is around 37 (364). This 16-gene signature was later reduced to an 11-gene signature, RISK11, with similar diagnostic accuracy (373). Using the RISK11 signature, the CORTIS trial examined the efficacy of a RISK11-guided TPT. Unfortunately, although the signature was able to distinguish between individuals who progressed to active TB disease and those who remained healthy, 3HP-based TPT amongst RISK11-positive individuals did not reduce incidence of TB over 15 months (374). However, the apparent lack of impact of 3HP amongst RISK11-positives may be due to the low number of TB cases in both RISK11-positive and -negative groups, and the high background risk of TB in the study setting (375). The performance of the signature was reduced further amongst people living with HIV ("PLHIV") (376). Mathematical modelling has examined the population-level impact of targeted TPT amongst HIV-negative RISK11-positive individuals versus IGRA-positive individuals in South Africa on TB incidence. Results suggest that although IGRA-targeted TPT would have a greater impact on TB incidence than RISK11-targeted TPT, it would result in a much higher NNT (around 1.7 times that of RISK11), suggesting that RISK11-targeting may allow for more efficient targeting of TPT (377).

A meta-analysis (378) on blood transcriptional signatures of incipient TB, tested 17 signatures in 4 different transcriptomic datasets to estimate their diagnostic performance. Sensitivities for the different signatures ranged between 24.7-39.9% in identifying individuals at risk of developing active TB disease within two years, increasing to 47.1-81.0% if the signatures were used to identify individuals at risk of developing active TB disease within three months. Specificity for the different signatures were consistently greater than 90%. Assuming a pre-test probability of 2%, the signatures had a PPV ranging between 7-9% if used to identify progression to active TB disease within 2 years and increased to 11-14% if used to identify progression within 3 months. Overall, the signatures only met the WHO TPP requirements if used to predict the short-term risk of active TB disease.

Several questions remain regarding the potential use of these signatures. These include whether or not the prognostic ability of these signatures can be improved for longer term predictions; whether these signatures can be used to prevent active TB disease through targeted TPT, including determining the efficacy of 3HP across different settings with varying levels of TB burden; finally, whether these

signatures have the same prognostic ability in the general population, considering that the majority of the signatures were discovered in populations with a higher lifetime risk of developing active TB than the general population. More studies are currently underway to answer these questions, including the C-TRIUMPH study in India (379).

With progress being made in detecting incipient TB and with the development of safer and shorter TPT regimens, such as 3HP, I modelled the epidemiological impact of biomarker-led TPT amongst cases of incipient TB in the example setting of Chennai, India. Globally, India has the largest burden of TB (358); Chennai is a populous city in India with around 20% of the population living in slums (380). In the latest National Strategic Plan 2017-2025, one of the priorities listed is the prevention of disease progression in high-risk groups, such as slums. Restricting interventions to high-risk individuals, should provide a more cost-effective solution. Thus, I developed a mathematical model of TB transmission differentiating between the slum and non-slum populations of Chennai. I considered two testing strategies: slum-only testing and whole-city testing (slum and non-slums alike). I further examined how the different testing strategies affect the cost-drivers and cost-effectiveness of the intervention. I deliberately undertook a simple costing approach, including not addressing the human resource requirements of such a strategy; instead, the aim of this approach was to gain relevant insights and is a basis for future, more complex, costing analyses. I aimed to answer the following questions:

- What is the population-level impact of detecting incipient TB on the TB epidemic in Indian high-risk and low-risk populations?
- Could such tools offer a cost-effective approach for TB control in high-burden settings?
- How do different testing strategies affect the impact and cost-efficiency of the intervention?

3.2. Methods

Here, I describe the model structure, data sources and interventions, with further details provided in appendix 1.

3.2.1. Model structure

I developed a deterministic, compartmental model of TB transmission amongst adults (>15 years old) in Chennai, India. The model structure is shown in fig 3.1. The model captures the background level of routine TB services in India, including the scale up of directly observed treatment (“DOTS”) under the Revised National TB Control Programme (“RNTCP”) between 1997 and 2007, and its

maintenance until the present day (381). I assumed a population size of 8.7 million (380) and an annual population growth rate of 2% (382).

Due to the importance of the private sector in the Indian healthcare system, where it is estimated that around half of patients initially seek care at a private provider (383–388), the model differentiates between seeking care in the public and private sector. Private providers are unregulated and often provide sub-standard level of care (228). Thus, I assumed that patients seeking care privately are less likely to be diagnosed correctly with TB and are more likely to default from treatment (table 3.1). I further assumed that mis-diagnosed TB cases continue seeking care once a month (table 3.1) and continue to pose a transmission risk.

I also captured the risk of cross-infection between slums and non-slums. It is estimated that around 20% of the population live in slums (380). Both settings are calibrated to different epidemiological data (see table 3.2) to reflect a concentrated TB setting in the slums, and a lower TB burden in the non-slums. To account for levels of mixing between the two populations, I modelled a cross group force of infection (table 3.1).

For simplicity, the model does not account for drug-resistant TB ("DR-TB"), pulmonary status or HIV/TB co-infection. DR-TB and HIV/TB co-infection accounts for less than 5% and 4% of incident-TB cases in India, respectively (358). Although DR-TB accounts for a disproportionate share of overall spending, I do not expect the omission of DR-TB from the model to substantially affect results, assuming that latent DR-TB will not be prevented from progressing by the treatment regimen used for incipient TB.

3.2.2. Data sources

Typically, incidence estimates are used to inform models; however, incidence data is often national estimates and do not necessarily reflect TB transmission in cities. Instead, the model was calibrated to the Annual Risk of TB Infection ("ARTI"), as the ARTI has been estimated in India at a sub-national level. The ARTI is the probability of acquiring a new TB infection or reinfection over a year. I used the ARTI from a study conducted in the slums and non-slum areas of Chennai city, where children were tested with TST, from which the prevalence and ARTI of TB was estimated. I also drew prevalence estimates from a prevalence survey in Chennai (389,390). To account for the fact that the ARTI and prevalence data are from specific settings, I incorporated uncertainty, to allow for differences across urban settings. TB mortality was taken from national WHO data (358). Table 3.2 summarises the data from these sources. These targets (table 3,2) were used to inform model parameters on the force of infection (β_S), the rate of initial care seeking for TB symptoms (δ_{1_s}) and

the rate of TB mortality (μ_1). I used Adaptive Bayesian Markov chain Monte Carlo ("MCMC") to calibrate the model (391). I modelled TB prevalence and ARTI from log-normal distributions, chosen to capture the uncertainty in these inputs. Next, I constructed the overall likelihood function of the data (x) based on a parameter set (θ), $P(x|\theta)$, as a product of the distributions over all the calibration targets (table 3.2) and multiplied this with uniform priors ($P(\theta)$; ranges specified in table 3.1). Thus, the posterior density is calculated by: $P(\theta|x) \propto P(x|\theta)P(\theta)$. By sampling from the posterior distribution using MCMC, I created an unbiased sample that approximates the posterior distribution. I refer to the uncertainty in model projections as the Bayesian credible intervals, using the 2.5th and 97.5th percentiles to reflect the lower and upper bound of an interval. Additional detail is provided in appendix 1.

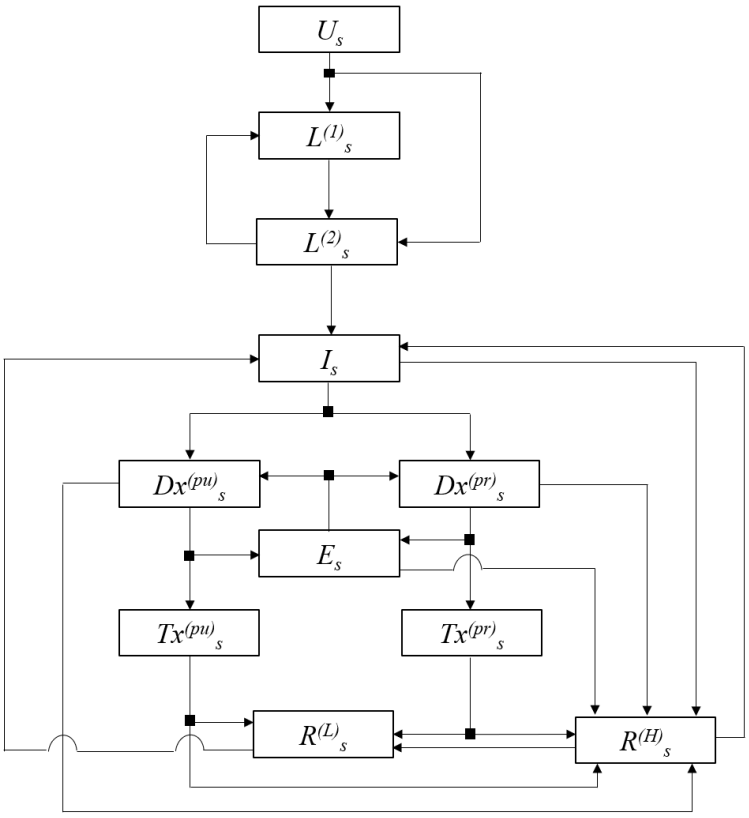

Figure 3.1. Schematic illustration of the model structure. Model compartments are as follows: uninfected with TB (U), latent infection ($L^{(1)}$), incipient TB ($L^{(2)}$), active TB disease (I), presented for care and awaiting diagnosis (Dx), on TB treatment (Tx), temporarily dropped out of the TB care cascade due to missed diagnosis or pre-treatment loss-to-follow-up (E), and recovered after self-cure with a high risk of relapse ($R^{(H)}$) or after treatment cure with a low risk of relapse ($R^{(L)}$). Dx and Tx are stratified by healthcare sector: private (pr) and public (pu) sector. All states are further sub-divided by location (s): slums and non-slums. I assume slums and non-slums population can infect each other, by assuming a cross group force of infection relative to the within group force of infection. See appendix 1 for further technical details, including model equations and calibration.

Parameter	Symbol	Value*		Source/Notes
TB natural history				
Mean rate of transmission per TB case	β_S	Non-slums	4.61 yr^{-1} [2.18-9.12]	Model estimate
		Slums	10.73 yr^{-1} [6.36-18.40]	
Cross group force of infection relative to the within group force of infection	ψ	0.30 [0.20-0.70]		Assumed
Proportion of TB infections undergoing rapid progression	θ	0.11 [0.09-0.15]		(15,392)
Per capita hazard rate of reactivation of latent TB infection to incipient TB	ρ_1	0.001 yr^{-1} [0.0003-0.0024]		(342,392)
Per capita hazard rate of developing active TB disease	ρ_2	1.00 yr^{-1} [0.50-4.00]		Assuming it takes 3 months to 2 years for the development of active disease from incipient TB (378).
Per-capita hazard rate of relapse	r_1	Following self-cure/treatment default	0.14 yr^{-1} [0.10-0.18]	(393,394)
	r_2	Following treatment cure, >2 years	0.002 yr^{-1} [0.001-0.003]	
Stabilisation of relapse risk following treatment	ς	0.5 yr^{-1} [0.4-0.6]		(393): most relapse occurs in the first two years after treatment
Per-capita hazard rate of spontaneous cure	φ	0.17 yr^{-1} [0.13-0.21]		(344)
Per-capita hazard rate of TB mortality	μ_1	0.14 [0.10 – 0.21]		Model estimate
Proportion reduction in susceptibility to reinfection due to previous infection	π	0.21 [0.15-0.25]		(395)
TB services				
Proportion of TB cases seeking care in the public sector	η	0.50 [0.40-0.60]		(228,384,396,397)
Per-capita hazard rate of initial care seeking for TB symptoms	δ_{1_s}	Non-slums	2.61 yr^{-1} [1.16-3.95]	Model estimate
		Slums	1.47 yr^{-1} [0.76-3.61]	
Per-capita hazard rate of repeat care seeking for TB symptoms (following missed diagnosis)	δ_2	12 yr^{-1} [6-26]		Assumption: corresponds to range of 2 weeks to 2 months

Proportion of TB cases diagnosed correctly, per care seeking attempt in routine TB services	ε_{Pu}	Public sector	0.84 [0.80-0.85]	(241,398)
	ε_{Pr}	Private sector	0.70 [0.50-0.75]	
TB treatment initiation delay	ϕ	52 yr^{-1}		Assumed: corresponds to a mean treatment delay of 1 week in routine TB care
Proportion of diagnosed TB cases successfully initiating treatment	ω	0.87 [0.80-0.90]		(241)
Per-capita hazard rate of first-line treatment completion	τ	2 yr^{-1}		Corresponds to a duration of 6 months
Proportion of TB cases that default from treatment	χ_{Pu}	Public sector	0.15 [0.13-0.17]	(6,241), assumed
	χ_{Pr}	Private sector	0.40 [0.30-0.50]	
Per-capita hazard rate of testing for incipient TB	κ_s	Non-slums	0-1.00	Varied from no testing, to testing 100% of the population per year
		Slums	0-1.00	
Preventive treatment efficacy	υ		0.90 [0.80-0.95]	(399)
Test for incipient TB sensitivity	p_{sn}	Current	0.30	(365,378)
		WHO	0.75	
Test for incipient TB specificity	p_{sp}	Current	0.94	(365,378), assumed
		WHO	0.94	
Demographics				
Per-capita hazard rate of background mortality	μ_2	0.015 yr^{-1}		World Bank estimates: corresponds to an average lifespan of 69 years
Proportion of the population living in slums	ϱ	0.20 [0.15-0.30]		(380)
Per-capita rate of population growth	σ	0.02 [0.01-0.025]		(382)
Costs				
Cost of 3HP per person	C_{TPT}	USD 15		(400)
Cost per active TB disease diagnosis (routine TB services)	C_D	USD 18.30		(401)
Cost of first line treatment for active TB disease per person per month	C_T	USD 23.70 per treatment-month		(401)
Cost of a future test for incipient TB per person	C_S	USD 10.86		Assumed to be similar in price to the cost of a TST test and two healthcare visits (402,403)

Table 3.1. List of model parameters and assumptions. For further technical details and model specification, see appendix 1. *Numbers in brackets represent sampling ranges; I assume all sampling ranges are uniformly distributed in the sampling process.

Indicator		Value	Source
TB prevalence	Non-slums	207 per 100,000 [190-212]	(389) The prevalence in slums and non-slums settings were estimated using the prevalence of culture-positive TB (259 per 100,000 (95% CI 217-299)) and the univariate odds ratio of culture-positive TB in slums versus non-slum settings (2.26 (95% CI 1.68-3.06)), whilst assuming the slums make up 20% of the population.
	Slums	468 per 100,000 [319-649]	
Annual risk of TB infection	Non-slums	1.5% [1.2-1.8]	(390)
	Slums	2.5% [2-3]	
TB mortality		33 per 100,000 [30-34]	(358)

Table 3.2. Calibration targets used to estimate model parameters

3.2.3. Intervention

I assumed that a test capable of identifying incipient TB is available. I defined incipient TB as individuals with LTBI who will progress to active disease within two years, without any intervention.

I modelled two different test performances:

1) *"Current performance"*: the test has similar diagnostic performance to the signatures reported in the meta-analysis by Gupta et al (378). I assumed a sensitivity of 30% and specificity of 94%.
2) *"WHO minimum performance"*: the test meets the WHO TPP performance requirements (365). I assumed a sensitivity of 75% and specificity of 94%. Note, the WHO TPP advises a minimum specificity of 75%; however, I assumed the test does not perform worse than the current performance reported in Gupta et al.

I modelled two testing strategies:

1) *"Whole-city testing"*: a certain proportion of the population of Chennai is tested for incipient TB (slums and non-slums) per year.
2) *"Slum-only testing"*: a certain proportion of the slum population is exclusively tested for incipient TB per year.

Table 3.3 summarises the different scenarios investigated.

Scenarios	Test performance	Testing strategy
1a	Current	Whole-city
1b	WHO minimum	Whole-city
2a	Current	Slum-only
2b	WHO minimum	Slum-only

Table 3.3. Scenarios modelled. I investigated a combination of test performances (current performance vs. WHO minimum performance) and testing strategies (whole-city vs. slum-only).

I defined false positives as individuals that have been incorrectly diagnosed as having incipient TB. I assumed that false positives can arise only from the early LTBI stage ($L^{(1)}$). However, it may be possible for false positives to arise from all individuals, except those with active TB disease or on TB treatment (U, $L^{(1)}$, $R^{(L)}$, $R^{(H)}$). Therefore, I conducted a sensitivity analysis on this assumption, with results presented in appendix 1.

Individuals diagnosed as having incipient TB (true- and false-positives) are initiated onto TPT, more specifically 3HP. I modelled a best-case scenario: I assumed all test positive individuals initiate TPT in both the public and private sector, and that all individuals adhere to treatment. Finally, I assumed each intervention scenario is initiated in 2020, and that the proportion of the target population accessing the test and TPT increased linearly across three years, until the whole target population was covered by 2023. I modelled the impact of the different intervention scenarios on TB incidence and mortality until 2035.

3.2.4. Economic evaluation

The purpose of the economic evaluation was to evaluate the cost-drivers and to determine the cost threshold a future test for incipient TB may need to meet to be considered cost-effective. I considered routine TB service costs as the comparator. I developed a simple cost model; I did not explicitly include the cost of human resources needed to run the intervention, a cost that is likely to be substantial, nor include discounting of future outcomes. Instead, the aim of this simplified costing analysis was as an informal analysis that serves as a lower bound for cost. I considered the TB programme cost perspective, ignoring costs to patients.

Cost drivers

I calculated the incremental spend between 2020 and 2035, which consisted of the cost of testing for incipient TB, the cost of TPT, and routine TB service costs (cost of diagnosing and treating active TB disease in the public sector) that are averted as a result of the intervention. To calculate the incremental spend, I assume an incipient TB test costs the equivalent to TST (table 3.4).

Cost-effectiveness analysis

I measured health impact using Disability Adjusted Life Years ("DALYs"). The incremental cost-effectiveness ratio ("ICER") can therefore be written as the ratio of incremental cost to incremental DALYs averted (equation 1, defined in table 3.4):

(1)

$$ICER = \frac{P_{TP} + P_{FP} + T - (A_0 - A_1)}{(D_0 - D_1)}$$

where P_{TP} and P_{FP} is the cost of TPT for true positives and false positives respectively, T is the total (population-level) cost of testing for incipient TB, $A_0 - A_1$ are the averted routine TB service costs and $D_0 - D_1$ are DALYs averted.

Although WHO suggests a cost-effectiveness threshold of 1- to 3-times the gross domestic product ("GDP") per capita, critics suggest these thresholds are too high and do not necessarily reflect the health opportunity cost. Wood et al estimated that for low- and middle- income countries, this threshold should in fact be between 1-51% of GDP per capita (404), whereas Ochalek et al developed a framework to generate country-specific thresholds that reflect health opportunity costs, and estimated India's to be between USD 264-363 (405). For simplicity, I assumed a cost-effectiveness threshold of 1- times India's GDP per capita (USD 2,104) (382), as per the WHO's recommendation. Considering this choice of threshold is optimistic compared to Wood et al and Ochalek et al, if results are not cost-effective under this choice threshold, this suggest they are robust to the choice of threshold. An intervention is considered cost-effective, if the ICER is less than the cost-effectiveness threshold, ϑ:

(2)

$$\vartheta \geq \frac{P_{TP} + P_{FP} + T - (A_0 - A_1)}{(D_0 - D_1)}$$

Equation 2 can be defined fully (equation 3) and rearranged to give the cost threshold a test for incipient TB will need to meet to be considered cost-effective (equation 4):

(3)

$$\vartheta \geq \frac{\kappa_s p_{sn} C_P \int_{2035}^{2020} L_s^{(2)} + \kappa_s (1 - p_{sp}) C_P \int_{2035}^{2020} L_s^{(1)} + \kappa_s C_T \int_{2035}^{2020} (U_s + L_s^{(1)} + L_s^{(2)} + R_s^{(L)} + R_s^{(H)}) - (A_0 - A_1)}{(D_0 - D_1)}$$

(4)

$$C_T \leq \frac{\vartheta (D_0 - D_1) - \kappa_s p_{sn} C_P \int_{2035}^{2020} L_s^{(2)} - \kappa_s (1 - p_{sp}) C_P \int_{2035}^{2020} L_s^{(1)} + (A_0 - A_1)}{\kappa_s \int_{2035}^{2020} (U_s + L_s^{(1)} + L_s^{(2)} + R_s^{(L)} + R_s^{(H)})}$$

The equation representing the threshold cost for an incipient TB test under the expanded false positive scenario is presented in appendix 1.

Notation	Definition
$\boldsymbol{D_0 - D_1}$	DALYs averted (0 = baseline, 1 = intervention) between 2020 and 2035. DALYs are calculated assuming the following: years of life lost due to premature mortality = 10, years lived with disability = 0.33 [0.22-0.45] (406,407)
$\boldsymbol{A_0 - A_1}$	Averted routine TB service costs (diagnosis and treating active disease) in the public sector as a result of the intervention between 2020 and 2035 (0 = baseline, 1 = intervention). I assume that for every true positive TB diagnosis, 9 non-TB cases that present to routine care with TB symptoms are tested, to account for the fact that amongst all patients presenting for care, there is a 10% prevalence of TB (240,408,409)
$\boldsymbol{\kappa_s p_{sn} C_P \int_{2035}^{2020} L_s^{(2)}}$	Total cost of treating true incipient TB cases with TPT between 2020 and 2035
$\boldsymbol{\kappa_s C_P (1 - p_{sp}) \int_{2035}^{2020} L_s^{(1)}}$	Total cost of treating false positives originating from $L_s^{(1)}$ only with TPT between 2020 and 2035
$\boldsymbol{\kappa_s \int_{2035}^{2020} (U_s + L_s^{(1)} + L_s^{(2)} + R_s^{(L)} + R_s^{(H)})}$	Number of individuals tested for incipient TB between 2020 and 2035
$\boldsymbol{\vartheta}$	Cost-effectiveness threshold. This was assumed to be USD 2,104 (1-times the GDP per capita of India) (410)
$\boldsymbol{\kappa_s}$	Rate of testing for incipient TB per person per year
$\boldsymbol{p_{sn}}$	Sensitivity of the test for incipient TB
$\boldsymbol{p_{sp}}$	Specificity of the test for incipient TB
$\boldsymbol{C_P}$	Cost of TPT per person
$\boldsymbol{C_T}$	Cost per test for incipient TB. Note, to calculate total incremental spend, I assumed the cost per test to be equivalent to the cost of a TST (USD 2-10; includes the cost of two healthcare visits) (411,412)
$\boldsymbol{\int_{2035}^{2020} L_s^{(2)}}$	Prevalence of $L_s^{(2)}$ (incipient TB) between 2020 and 2035
$\boldsymbol{\int_{2035}^{2020} (U_s + L_s^{(1)} + L_s^{(2)} + R_s^{(L)} + R_s^{(H)})}$	Prevalence of the population without active TB that are being screened for incipient TB between 2020 and 2035

Table 3.4. Economic evaluation notation.

3.3. Results

3.3.1. Model calibration

Fig 3.2 shows results of model calibration, displaying the model fit against each of the calibration targets listed in table 3.2. Fig 3.3 shows MCMC diagnostic checks, including the posterior density trace and autocorrelation plots for selected parameters.

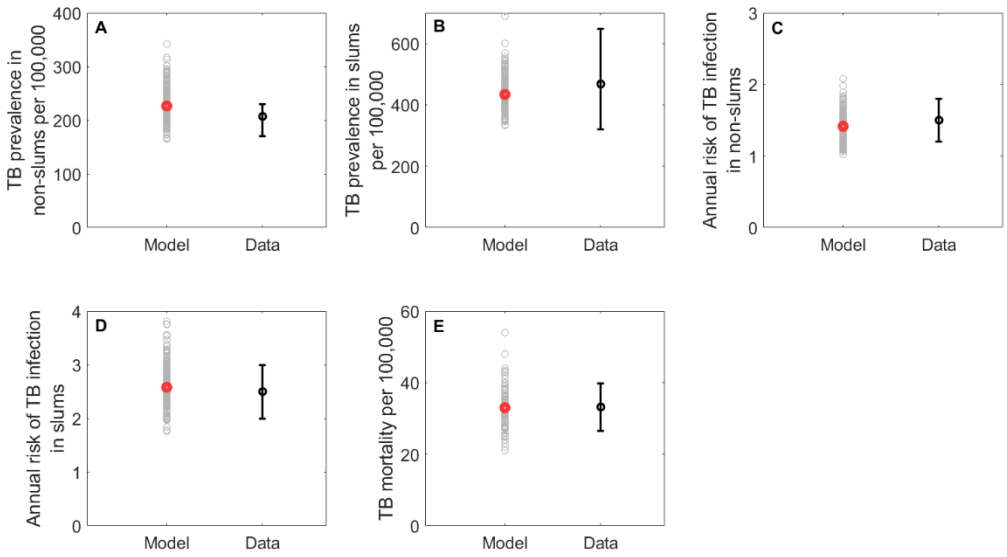

Figure 3.2. Model fits to data. Panel A – TB prevalence per 100,000 in non-slums, Chennai; B – TB prevalence per 100,000 in slums; C – ARTI in non-slums, Chennai; D – ARTI in slums, Chennai; E – TB deaths per 100,000, India. Grey - model runs; red - mean of model runs; black - data points are described in table 3.2**.**

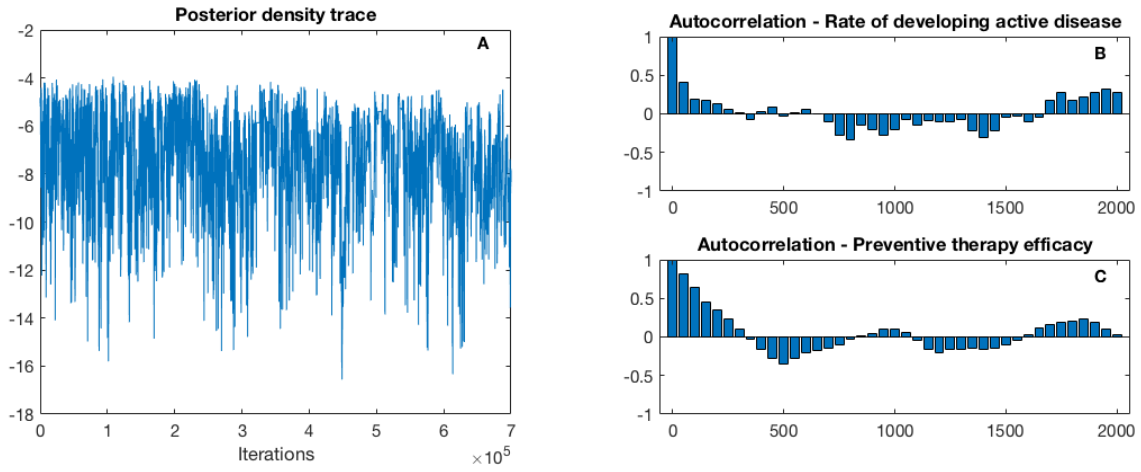

Figure 3.3. MCMC diagnostics. Panel A shows the posterior density trace, excluding the 'burn-in' period. Panel B and C show autocorrelation plots for two selected parameters (rate of developing active disease, and the efficacy of preventive therapy).

3.3.2. Epidemiological impact

For results discussed below, I assume 25% of the population is tested per year, unless otherwise stated.

Fig 3.4 and table 3.5 show model projections for the impact testing the population for incipient TB has on TB incidence and mortality. A test with current performance would avert 7% (95% Credible Intervals, CrI 3-15%; scenario 1a) and 4% (95% CrI 2-8%; scenario 2a) of cumulative TB incident cases under a whole-city and slum-only strategy, respectively. A similar impact is seen in terms of TB deaths, with 6% (95% CrI 3-13%; scenario 1a) and 4% (95% CrI 2-7%; scenario 2a) of cumulative TB deaths averted. If the sensitivity of the test increased to the WHO minimum performance requirements, the epidemiological impact would increase; for example, under a whole-city and slum-only strategy, the cumulative TB incident cases averted increased to 15% (95% CrI 7-30%; scenario 1b) and 10% (95% CrI 5-18%; scenario 2b), respectively.

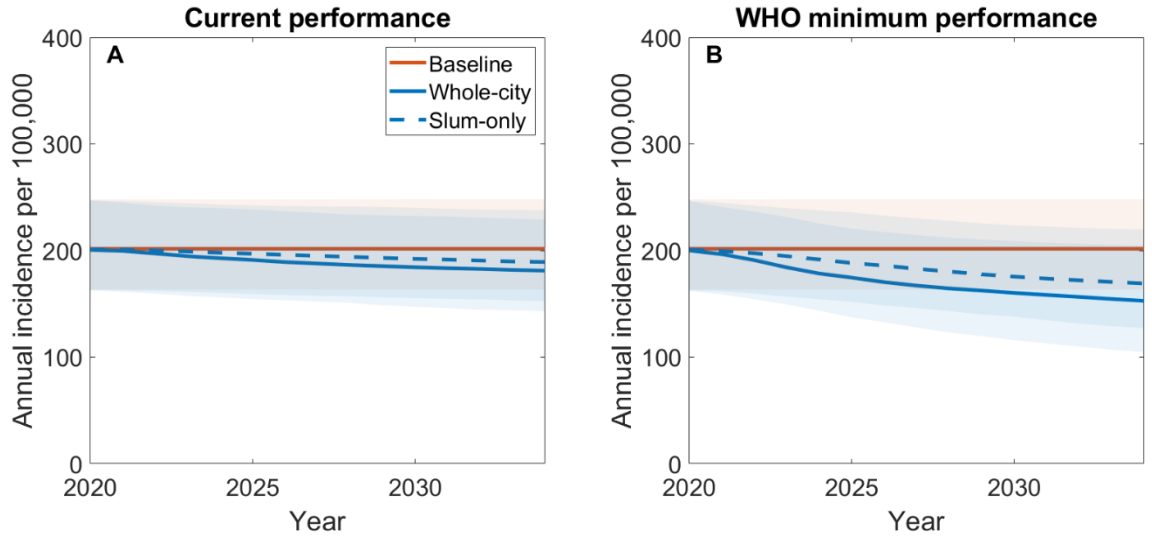

Figure 3.4. Model projections for annual overall TB incidence (slums and non-slums). I assumed 25% of the population is tested per year. Shown is a slum-only (blue dash line) and whole-city testing strategy (blue solid line). Panel A assumes the test has similar diagnostic performance to current data (sensitivity – 30%), whereas panel B assumes the test met the WHO minimum performance requirements (sensitivity – 75%). Baseline (red line) assumes current standard of TB care continued indefinitely. Shaded areas show Bayesian 95% credible intervals.

Testing strategy	Test performance	Cumulative incidence averted, 2020-2035	Cumulative TB deaths averted, 2020-2035
Whole-city	*Current performance*	18,000 (8,100-38,000)	2,900 (1,200-6,700)
	WHO minimum	40,000 (19,000-80,000)	6,500 (2,900-14,000)
Slum-only	*Current performance*	11,000 (5,300-22,000)	1,900 (730-3,900)
	WHO minimum	25,000 (13,000-48,000)	4,300 (1,800-8,500)

Table 3.5. Projected cumulative impact on TB cases and deaths averted relative to the status quo. I assumed 25% of the population is tested per year. Under the status quo I assumed the current standard of TB care in Chennai continued indefinitely. I assumed the test had similar diagnostic performance to current data (sensitivity – 30%) or the WHO minimum performance requirements (sensitivity – 75%). Brackets show Bayesian 95% credible intervals.

3.3.3. Cost drivers

Targeting testing towards individuals at higher risk of TB infection (slum-only testing) would detect more cases for a given cost, compared to whole-city testing (fig 3.5). Assuming the cost of an incipient TB test is equivalent to the cost of TST (between USD 2-10), under scenario 1a, 220 (95% CrI 101-475) active TB cases per 100,000 population would be averted, for an incremental cost of USD 5.2 million (95% CrI 5.1-5.4 million) per 100,000 population; under scenario 2a, 37% (95% CrI 24-62%) fewer cases were averted, but at 82% (95% CrI 75-88%) less cost (fig 3.5a). A test with improved performance (fig 3.5b) would avert more cases for a given cost. The cost of the intervention was driven by the cost of testing (fig 3.6). For example, under scenario 1a, the total cost of testing was 4 (95% CrI 3-6) and 31 (95% CrI 28-35) times larger than routine TB service and TPT costs, respectively. Targeted testing would reduce the cost of testing for incipient TB; testing was a cost driver if more than 5% of the population was tested per year with a test that had current performance

under a whole-city testing strategy and 36% per year under a slum-only strategy. The cost of TPT was consistently the smallest cost component.

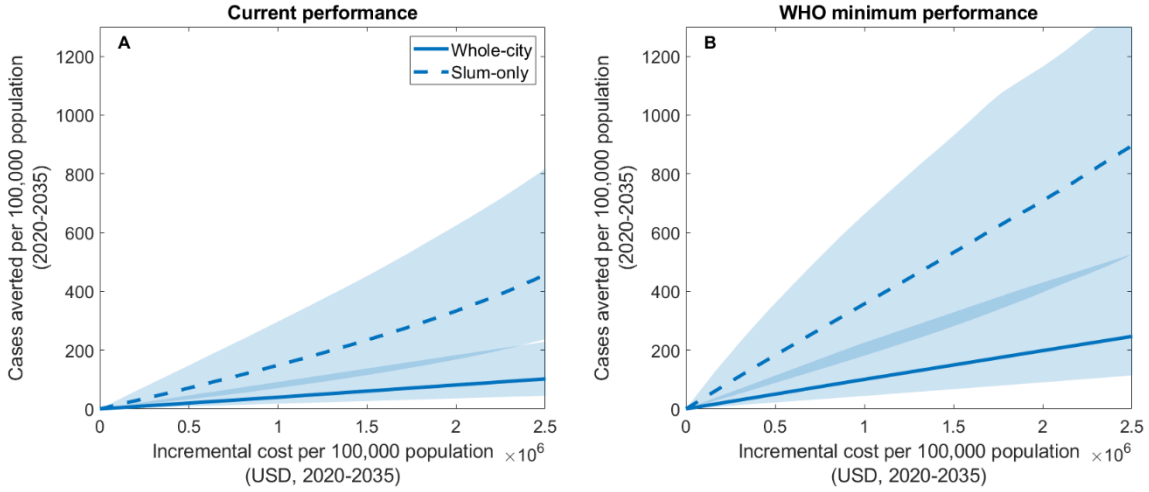

Figure 3.5. Incremental cost (USD) per case averted, per 100,000 between 2020 and 2035. Panel A assumes the test had similar diagnostic performance to current data (sensitivity – 30%), whereas panel B assumes the test met the WHO minimum performance requirements (sensitivity – 75%). I investigated two different testing strategies: a slum-only (dash line) and whole-city strategy (solid line). Shaded areas show Bayesian 95% credible intervals.

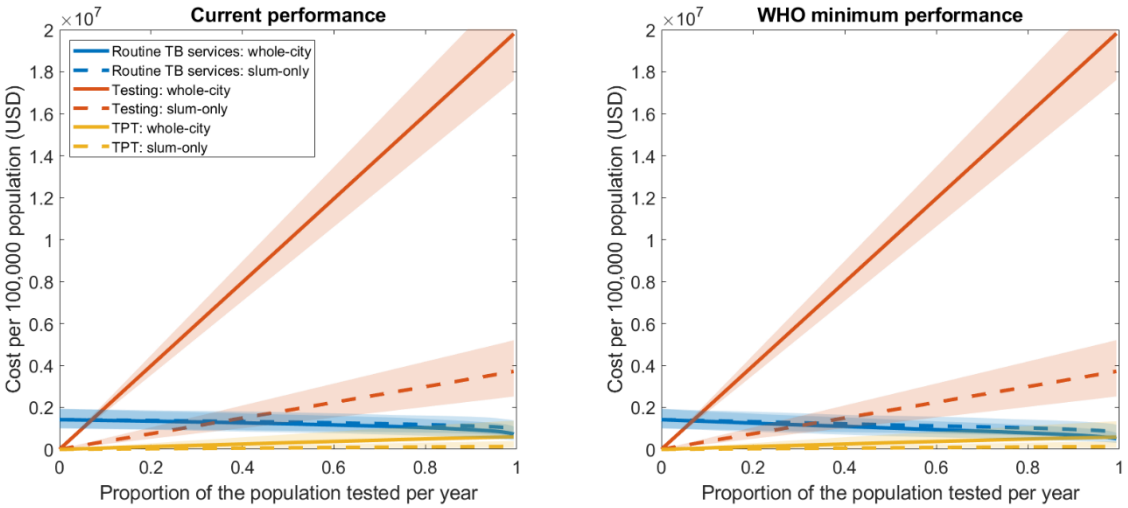

Figure 3.6. Cost drivers across increasing rates of testing for incipient TB between 2020 and 2035. I divided costs into the following components: cost of routine TB services (blue line), testing costs (cost of testing for incipient TB; red line), cost of TPT (yellow line). Panel A assumes the test had similar diagnostic performance to current data (sensitivity – 30%), whereas panel B assumes the test met the WHO minimum performance requirements (sensitivity – 75%). I investigated two different testing strategies: a slum-only (dash line) and whole-city strategy (solid line). Shaded areas show Bayesian 95% credible intervals.

3.3.4. Cost requirements

For fig 3.5 and 3.6, I assumed the cost of an incipient TB test to be equivalent to the cost of TST. Instead, fig 3.7 illustrates the cost an incipient TB test would need to meet to be considered cost-effective under a WHO cost-effectiveness threshold. These results suggest that the cost threshold the test would need to meet to be considered cost-effective is infeasibly stringent and would need to be in the order of 10^{-4} USD regardless of test performance, testing rate and testing strategy (fig 3.7). The need to test such large numbers, whilst not averting sufficient cases or deaths (averted routine TB service costs and DALYs), makes this intervention highly cost ineffective.

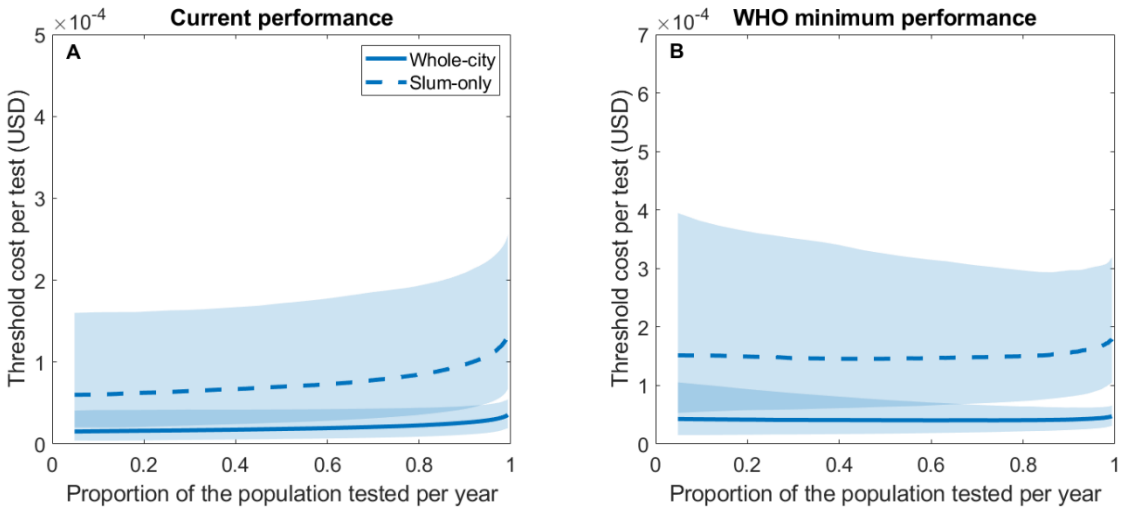

Figure 3.7. Cost requirements for future tests for incipient TB, across increasing testing. Threshold costs of a test was calculated according to a cost-effectiveness threshold of USD 2,104 (blue) (404). See table 3.4 and equation 1. Panel A assumes the test had similar diagnostic performance to current data (sensitivity – 30%), whereas panel B assumes the test met the WHO minimum performance requirements (sensitivity – 75%). I investigated two different testing strategies: a slum-only (dash line) and whole-city strategy (solid line). Shaded areas show Bayesian 95% credible intervals.

Table 3.6 illustrates the number of individuals that would need to be tested to identify one case of incipient TB and avert one case of active TB, assuming 25% of the population is tested per year between 2020 and 2035. Under scenario 1a, 287 (95% CrI 101-650) and 2,157 (95% CrI 1,002-4,717) individuals would need to be tested to identify one case of incipient TB and to avert one case of active TB, respectively. Under scenario 2a, these values decreased due to the higher prevalence of TB amongst slum-dwellers; 191 (95% CrI 64-445) and 643 (95% CrI 264-1,563) individuals would need to be tested to identify one case of incipient TB and to avert one case of active TB, respectively. As the test performance increases to meet the WHO minimum requirements, the number of individuals tested to avert one case of active TB would decrease to 966 (95% CrI 489-1,953) and 285 (95% CrI 125-656) under scenarios 1b and 2b, respectively, due to the higher test sensitivity.

	Testing strategy	Test performance	
		Current	*WHO minimum*
Number tested to detect one case of incipient TB	*Whole-city*	287 (101- 650)	123 (322 – 706)
	Slum-only	191 (64 – 445)	217 (80 – 480)
Number tested to avert one case of active TB	*Whole-city*	2,157 (1,002 – 4,717)	966 (489 – 1,953)
	Slum-only	643 (264 – 1,563)	285 (125 – 656)

Table 3.6. The number needed to be tested to detect one case of incipient TB and avert one case of active TB. I assume 25% of the population was screened per year between 2020 and 2035 under a whole-city or slum-only testing strategy, with a test that has current performance or WHO minimum performance. Brackets show 95% Bayesian credible intervals.

3.3.5. Sensitivity analyses

I examined the impact increasing the pool of individuals where false positives can arise from has on the cost-effectiveness of the intervention. Under the expanded false positive assumption, fewer cases would be averted for a given cost due to the extra cost of treating a larger number of false positives (fig A1.1); 220 (95% CrI 101-475) TB incident cases per 100,000 population were averted for an incremental cost of USD 5.5 million (95% CrI 5.3-5.6 million) per 100,000 population, USD 300,000 more than if false positives arise only from the early LTBI stage ($L^{(1)}$), under scenario 1a. The relative importance of TPT increased (fig A1.2); under a whole-city testing strategy and if more than 68% and 57% of the population were tested per year using a test with current performance and a test that meets the WHO minimum requirements, respectively, the cost of TPT would exceed routine TB service costs. The intervention was even less cost-effective due to the greater cost of treating the false positives (fig A1.3).

I also conducted a multivariate sensitivity to examine which model parameters (listed in table 3.2) model outputs were most sensitive towards (fig 3.8). Using cases averted as the model output, and focussing on scenario 1a, unsurprisingly, the model parameters that the model output was most sensitive towards were the efficacy of TPT, and the assumptions surrounding the rate of developing incipient TB and the duration of incipient TB.

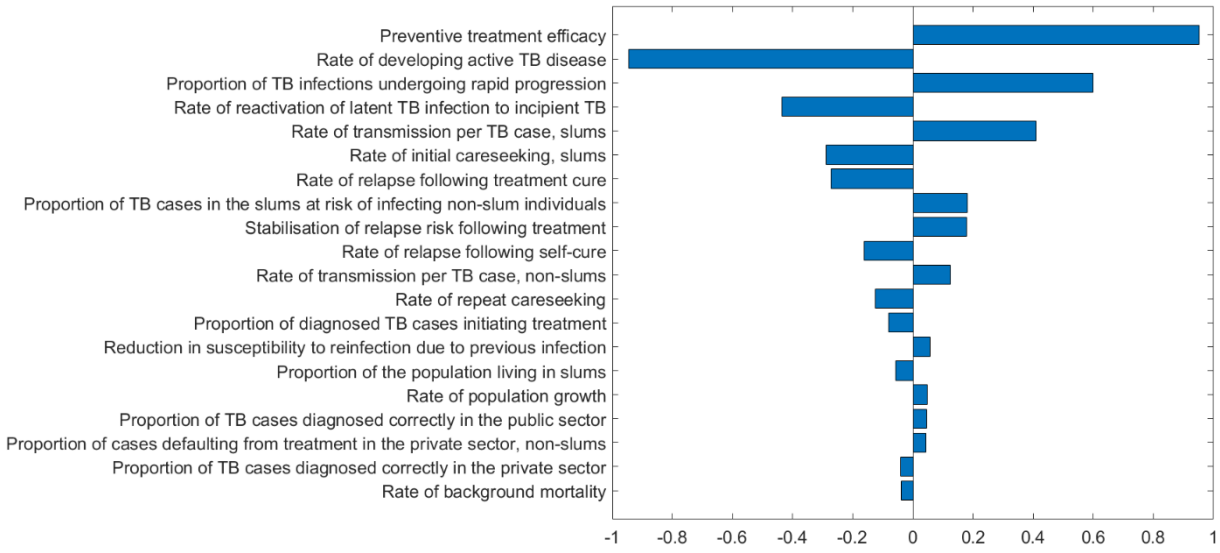

Figure 3.8. Multivariate sensitivity analysis of impact. Using scenario 1a (biomarker test with current performance and whole-city testing), and assuming that 25% of the population is tested per year, I used partial rank correlation coefficient ("PRCC") to examine the sensitivity between cases averted and the different parameters listed in table 3.1. Larger bars represent more sensitive parameters. Shown are the 20 most influential model parameters, in decreasing order of sensitivity from top to bottom.

3.4. Discussion

To reach TB elimination, countries will need to target the reservoir of LTBI. Novel biomarker signatures (378) offer an important opportunity to identify incipient TB, individuals with LTBI at imminent risk of developing active disease. In this work, I sought to examine the impact this new technology, coupled with TPT, may have on the TB epidemic in Chennai, a setting consistent with urban slums, and whether targeting testing towards individuals at high risk of TB infection may offer a more cost-effective approach. I observe that 10% (95% CrI 5-18%) of cumulative TB incident cases were averted under a slum-only strategy using a test meeting the WHO performance requirements, assuming a quarter of the population was tested per year, between 2020 and 2035. However, the intervention is likely to not be cost effective, considering that even under a targeted slum-only testing strategy using a test that meets the WHO minimum requirements, 285 (95% CrI 125-656) individuals would need to be tested to avert one case of active TB, pushing the threshold cost for such a test to be considered cost-effective, to well below USD 1.

Slum-dwellers are a high-risk population for developing active TB disease. By targeting areas with a higher risk of infection, more cases of TB or deaths can be averted for a given cost, compared to the general population; theoretically, in an area that has a higher risk of infection, the probability of finding an incipient TB case increases. Indeed, these results suggest that targeting slums does avert more cases for a given cost; however, the number of individuals that need to be tested to identify one

case of incipient TB is still not low enough, and DALYs averted high enough, to make the threshold cost of a test achievable, even amongst high-risk individuals. Therefore, there is a pressing need to understand, refine and combine measures of risk to improve the efficiency of incipient TB case finding; for example, by combining biomarker approaches with epidemiological risk factors. In other words, investigating what combination of risk factors may help focus future testing efforts to decrease the number of tests needed to detect one case of incipient TB; however, combining biomarker approaches with epidemiological risk factors may still not be enough to reduce the testing effort required and increase the cost-effectiveness of this intervention. As mentioned previously, risk-scores based on epidemiological risk factors are currently being developed to predict the risk of TB in adult contacts (366,413); however, questions remain on how the predictive power of these risk scores differ across different settings with different epidemiological risk factors and different burden of TB, and the amount by which predictive power can improve by combining the scores with biomarker approaches.

Expanding the pool of individuals where false positives can arise from, affects the cost-effectiveness and cost-drivers of the intervention. I compared two possibilities: false positives originating only from LTBI, or LTBI and all uninfected individuals. Potentially, uninfected individuals may produce similar host immune responses to the one the test detects due to a different infection (378). Expanding the pool of potential false positives, increased the total cost of TPT. Under this scenario, the cost of TPT exceeded routine TB service costs at high testing but only under the whole-city testing strategy; under the slum-only testing strategy, the cost of TPT remained the least dominant cost, regardless of test sensitivity or the proportion of the population tested. This suggests that if testing is targeted to the slums, the cost of TPT and the specificity of the test is less important, and only becomes increasingly significant at higher testing rates, under untargeted testing and if the pool of potential false positives increases. However, regardless of the false positive assumptions made in the model, the cost of testing remains dominant; thus, keeping the cost of the test low will have the largest impact in reducing the cost of the overall intervention. Although I assume that treating a falsely diagnosed LTBI with 3HP has no effect, treating LTBI with 3HP may in fact reduce the progression from LTBI to incipient TB, ultimately reducing TB incidence further. This suggests the model may be underestimating the impact of the intervention.

A couple of other mathematical modelling studies have also assessed the potential epidemiological impact incipient TB tests may have on TB. Sumner et al, using mathematical modelling, assessed the impact on TB incidence a test with similar diagnostic performance to the RISK11 signature may have amongst HIV-negatives in South Africa. They similarly concluded that although the impact on TB incidence is significant, the cost of such an intervention is likely to be high (377). An additional study by Arinaminpathy et al (74) investigated different strategies for TB elimination in Southeast Asia, one

of which was a biomarker test for incipient TB to guide TPT, alongside strengthening and accelerating routine TB services. They found that strengthening and accelerating routine TB services alone, was not enough to reach TB elimination; instead, a combination of the three strategies was needed. Although the results presented here support those presented in Arinaminpathy et al and Sumner et al, that incipient TB guided TPT may have an important epidemiological impact on the TB epidemic in a high burden setting, these results additionally suggest that the cost may be too prohibitive for implementation to be feasible in practice.

I have made several simplifications to the model. For the implementation of TPT, I have modelled a best-case scenario by assuming perfect adherence to TPT and that the intervention was rolled out in both the private and public sector simultaneously. If the use of 3HP for TPT is adopted in India, adherence to the regimen will likely be higher than 6-9H due to fewer side effects and shorter treatment duration (362); however, data suggests that around 5% of patients discontinue 3HP due to adverse events (414,415), and amongst homeless patients, as many as 20% stop treatment due to side effects, treatment refusal or lost to follow up (416). Furthermore, a meta-analysis found that across the LTBI care-cascade, the majority of losses occur during testing, before the start of treatment (75). I assumed that the intervention will be rolled out in both the public and private sector; in reality, the test is likely to be rolled out first in the public sector, followed by the private sector. Removing both these assumptions will make the intervention less effective and more costly per averted TB case. I also ignore the diagnosis of active TB from the intervention scenarios; testing for incipient TB may concomitantly detect cases of active TB disease, indicating the model may be underestimating the true impact of the intervention. In addition, I assume that test performance is independent to the risk of developing active disease; in other words, individuals with a false-negative test result for incipient TB are equally likely to develop active disease as true-positives. Finally, I use constant rates for the development of incipient TB and for the progression from incipient TB to active disease. This assumes that there is an exponential distribution of waiting times; for example, the majority of individuals will progress quickly to the next health state, whereas a minority will progress slowly. Thus, using a constant rate may underestimate the potential epidemiological impact of the intervention if certain individuals are progressing to active disease at a low rate. The exact duration of incipient TB is uncertain, however the majority of studies investigating potential biomarkers for incipient TB focussed on a maximum duration of 2 years before development of active disease (373). In reality, the duration of incipient TB is likely to be heterogenous. An alternative modelling strategy to a constant rate is using a fixed delay (for example, modelled using delay-differential equations), so that all individuals have incipient TB for the same duration.

Studies on South African gold miners, where there is a high risk of TB infection, have shown that the protective effect of TPT may be as little as 6-12 months (417,418). This suggests that if the risk of re-infection is continuously high, like in the slums, testing and treating individuals for incipient TB will need to be maintained. Similarly, the CORTIS trial found that treating incipient TB cases with 3HP did not reduce progression to active TB, and that this lack of impact may be due to the high background risk of reinfection (374). In my model, I assume that 3HP does prevent the progression from incipient TB to active TB, and I have not explicitly modelled the waning of protection after TPT completion; however, I assumed that individuals with incipient TB, upon treatment completion, revert to the early stage of LTBI, and have a chance of being re-infected. More research is needed to determine whether biomarker-led targeted TPT using 3HP can prevent active TB disease.

The results in this chapter suggest that even a "perfect" test would not be considered cost-effective. However, this work does not quantify the long-term benefits of TB elimination, suggesting that I might be under-estimating the cost-effectiveness of such an intervention and that cost-effectiveness analysis may not be the most appropriate tool to use under the circumstance of disease elimination. Furthermore, using current routine TB services as a comparator may also be inappropriate; instead, future work should assess the cost effectiveness of this intervention against other comparators, such as other forms of TPT using a different diagnostic test. As this economic evaluation does not consider alternative interventions to testing for incipient TB, this work does not identify the most cost-effective intervention for India to progress towards TB elimination. Instead, the aim of the analysis was to identify potential cost thresholds that future tests for incipient TB may need to meet. In this work, I have used an optimistic WHO-recommended cost-effectiveness threshold of one-time India's GDP per capita. This threshold is likely to be high and not reflect health opportunity cost, as discussed by Woods et al (404) and Ochalek et al (405). In addition, I have not discounted future outcomes, which will further reduce the cost-effectiveness of the intervention. However, considering that the intervention was not cost-effective even under an optimistic threshold and without discounting, suggests that the results are robust to the choice of threshold.

Finally, model outputs were highly sensitive towards the efficacy of 3HP and the rate of progression from incipient TB to active TB disease. If the efficacy of 3HP treatment increased, more TB cases were averted, whereas if the duration of incipient TB increased, fewer TB cases were averted. Current studies suggest that 3HP has a high efficacy, although more studies are needed across different populations. Generally, more research is needed on incipient TB; for example, whether or not active TB treatment could be an effective treatment against incipient TB cases that are only a few months away from developing active TB disease.

Future analyses should focus on a more comprehensive costing approach, to provide more precise costs for routine TB services and the intervention in question. Furthermore, it is of interest to examine the impact on results that imperfect adherence to TPT and imperfect rollout of the intervention across the private and public sector may have. More broadly, a greater understanding of measures of risk is needed, so that these potential biomarker tests can be targeted in a more cost-efficient manner.

3.5. Conclusion

With TB elimination on the agenda of high TB-burden countries, such as India, preventing LTBI from progressing to active TB disease is becoming increasingly crucial. Overall, this work suggests that even in a high TB burden country with targeted slum-only testing under optimal conditions, incipient TB case finding is not cost-effective and that biomarker-led TPT is likely to be prohibitively costly, due to the costly effort needed to detect and treat one case. Alternative targeted strategies will be needed. This work contributes to the growing body of evidence the impact that targeting TPT to specific sub-groups may have on TB epidemics in high-burden settings, and highlights where further research is needed in the field.

Chapter 4: Results (ii)

The potential impact of urine-lipoarabinomannan diagnostics on tuberculosis incidence and mortality: A modelling analysis

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C.M. Denkinger and S.G. Schumacher from the Foundations for Innovative New Diagnostics, and my supervisor, N. Arinaminpathy were involved in the conceptualisation of this work. I led the model development, analysis, and preparation of the manuscript. All authors were involved in reviewing and editing the manuscript.

Due to the limitations of sputum-based diagnostic tests, urine-based point-of-care tests offer new opportunities for TB diagnosis. As these tests continue to improve, it is important to anticipate their epidemiological impact. In this chapter, I develop a mathematical model that captures TB and HIV dynamics in South Africa. I investigate the impact of two urine lipoarabinomannan tests, distinguishing between current tests (accuracy consistent with Alere Determine^{TM} LAM Ag) and future tests (accuracy consistent with Fujifilm SILVAMP TB LAM), on TB incidence and mortality, across widening test eligibility. I demonstrate that although these tests could have an important effect in averting TB deaths amongst people living with HIV with advanced disease, these tests will need to be deployed more broadly than HIV care, and have sufficient diagnostic performance, to achieve population-level impact.

4.1. Introduction

In TB diagnosis, microbiological confirmation is typically conducted on sputum samples, using either traditional tools such as smear microscopy (419) or, more recently, rapid molecular tests such as Xpert (420,421). However, sputum-based tests have several limitations: Patients can find it difficult to provide good-quality sputum specimens with the required volume, particularly those living with advanced HIV disease (422). Additionally, sputum-based tests cannot detect extrapulmonary TB in the absence of pulmonary involvement. For these reasons, there has been increasing interest in new non-sputum-based diagnostic tools (423). In particular, urine-based tests aim to detect the lipoarabinomannan ("LAM") antigen, part of the outer cell wall of mycobacteria (159,165,422,424). It is less invasive to collect urine than sputum samples in clinical settings, with lower infection risk to healthcare workers ("HCW"). Moreover, urine-based tests can detect extrapulmonary TB (425). Below I discuss two urine LAM tests, Alere Determine^{TM} LAM Ag ("AlereLAM") and Fujifilm SILVAMP TB LAM ("FujiLAM").

Alere Determine^{TM} LAM Ag

AlereLAM is currently the only commercially available urine-based diagnostic for TB (424). It works by placing unprocessed urine of a suspected TB patient onto a test strip and incubating it for 25 minutes at room temperature. A visible band appears on the test strip at different intensities, which is compared by eye to the reference card supplied by the manufacturer (426). The advantages of AlereLAM are that it does not require a laboratory, technical equipment or electricity (427). It can be performed at the point-of-care: it is quick, cheap (around USD 3.50), simple to use and can be used by HCWs with minimum training (132,428). All these qualities could increase diagnostic yield due to high turnover (424).

Unfortunately, the sensitivity of AlereLAM is poor, especially amongst HIV-negative patients (429). Among people living with HIV ("PLHIV") with signs and symptoms of TB, pooled sensitivity was estimated to be 42% compared to a reference standard of either culture or nucleic acid amplification tests ("NAAT") (429). A common finding across many of the studies is the correlation of AlereLAM positivity with CD4 count (fig.4.1) (429). AlereLAM has higher sensitivity amongst patient sub-groups with lower CD4 counts (430–437). For example, Lawn et al. estimated AlereLAM sensitivity to be 67% at a CD4 count of <50 cells/μL, 52% at <100 cells/μL and 39% at <200 cells/μL amongst culture-confirmed patients (431). A meta-analysis has estimated the pooled specificity of AlereLAM to be 91% amongst culture-confirmed or NAAT-confirmed patients (429). A handful of studies have

found specificity to be consistent across all strata of CD4 counts (430–432,436), whereas others have reported decreasing specificity at lower CD4 counts (434,435).

There are several factors that may cause this wide variation in sensitivity and specificity across studies. Firstly, the sensitivity and specificity can change depending on the cut off used on the reference card; specificity increases with higher cut-offs, whereas sensitivity decreases (438,439). A second factor that can cause variation across studies is the reference standard used to compare AlereLAM performance. Studies are only reliable if the reference standard used has correctly identified the study participants as either being TB-positive or TB-negative. Unfortunately, correct identification can be challenging, especially amongst patients with extrapulmonary disease. For example, Lawn et al calculated the specificity of AlereLAM based on two different references, the first being a comprehensive reference standard (respiratory and non-respiratory samples), the second being only respiratory samples; specificity decreased from 99% to 90% depending if the comprehensive or the respiratory samples reference standards were used, respectively (440). Finally, how sick the study population is will lead to variation across different settings. As mentioned above, sensitivity improves amongst more severely ill patients. Thus, future studies should characterize their study population with markers such as CD4 cell count and body mass index, in order to improve comparability between studies (438).

Nevertheless, despite the wide variation in reported test performance, clinical trials show that AlereLAM may have a valuable impact in decreasing time to treatment initiation and averting TB deaths amongst hospitalised HIV patient populations (159,429). Firstly, it has the ability to detect individuals with the highest risk of mortality, and therefore, individuals who will benefit most from treatment (159,424,429,430,432,433,441–448). Gupta-Wright et al. estimated that AlereLAM test-positive individuals have a two-fold increased mortality risk (446), potentially due to the presence of LAM in the urine signifying a higher MTB load and thus, greater disease dissemination (427). Secondly, when AlereLAM is combined with existing diagnostic tools, the combined sensitivity is higher than when a one-stage diagnostic approach is used, although at a cost to specificity. For example, using AlereLAM in parallel to Xpert or sputum smear microscopy, the pooled sensitivity was 75% and 59% amongst PLHIV, a 13% and 19% increase over Xpert or sputum smear microscopy alone, respectively (132).

Weighing all this evidence, World Health Organisation (“WHO”) guidelines have restricted the use of AlereLAM in certain population sub-groups (table 4.1) (449). Uptake of AlereLAM in high HIV/TB burden countries remains low; a study that aimed to assess current usage of AlereLAM found that out of 24 countries, only 5 were currently using AlereLAM. The main barriers are the lack of budget

allocation for procuring the test, the lack of in-country pilot studies, and the test being suitable for only a small patient population (450).

Setting	To assist in the diagnosis of active TB in HIV-positive adults, adolescents, and children:	Strength of recommendation
Inpatients	with signs and symptoms of TB (pulmonary and/or extrapulmonary)	Strong
	with advanced HIV disease, or who are seriously ill (e.g., with respiratory rate of more than 30/minute, temperature of more than 39°C, etc.)	Strong
	irrespective of signs and symptoms of TB with a CD4 cell count of less than 200 cells/µl	Strong
Outpatients	with signs and symptoms of TB (pulmonary and/or extrapulmonary) or seriously ill	Conditional
	irrespective of signs and symptoms of TB with a CD4 cell count of less than 100 cells/µl	Conditional

Table 4.1. Summary of the WHO updated guidelines (2019) on the use of Alere Determine^{TM} LAM Ag.

Fujifilm SILVAMP TB LAM

FujiLAM was recently developed, with the aim of having higher sensitivity than AlereLAM. Like AlereLAM, it is a lateral-flow assay on an instrument-free platform, and is suitable for use at the point-of-care, with results available in less than an hour; however, it has an additional step that combines monoclonal antibodies that have a high affinity to LAM with an amplification step, improving the detection of LAM (165).

Preliminary results suggest FujiLAM has improved sensitivity to AlereLAM on biobanked samples from PLHIV, with comparable specificity. Using a composite reference standard (which includes clinical diagnosis), FujiLAM sensitivity was estimated to be 65%, compared to a sensitivity of 38% for AlereLAM, whereas specificity was 96% and 98% for FujiLAM and AlereLAM, respectively(165). When a microbiological reference standard was used instead, sensitivity increased to 70% and 42% for FujiLAM and AlereLAM, respectively, whereas specificity decreased to 91% and 95%, respectively (165). A similar pattern to AlereLAM is seen, where sensitivity increases with decreasing CD4 cell counts; for example, amongst patients with a CD4 cell count < 100 cells/µL, sensitivity was 81% compared to 53% with AlereLAM, whereas amongst patients with a CD4 cell count > 200 cells/µL, sensitivity decreased to 36% and 11% amongst FujiLAM and AlereLAM, respectively (fig.4.1) (165). Further analysis suggests that FujiLAM is better at reducing mortality in PLHIV, due to its improved sensitivity in PLHIV with higher CD4 cell counts, allowing for rapid testing in a greater proportion of patients (451).

Furthermore, a recent study in programmatic conditions demonstrated the potential for FujiLAM to identify TB amongst HIV-negative patients, showing a sensitivity of approximately 50% in this population (166), raising the possibility of deploying urine LAM tests outside HIV care. In the same study, a laboratory-based LAM assay demonstrated the potential sensitivity gains for future LAM tests; a research assay that uses the same antibodies as FujiLAM but that instead employs an electrochemiluminescence immunoassay platform, had a sensitivity of 67% amongst HIV-negative samples using a microbiological reference standard (166). Other developments, such as new techniques for concentrating the LAM antigen available in a sample (452), also highlight the potential for continued improvements in the performance of LAM tests.

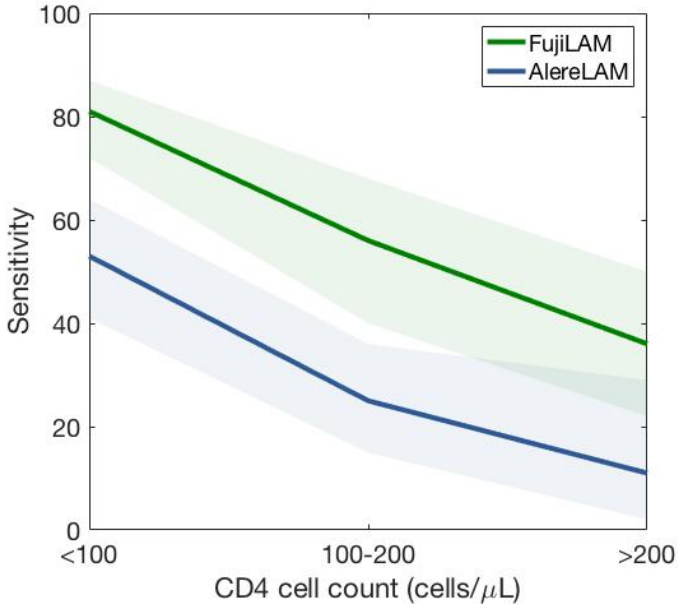

Figure 4.1. Sensitivity of AlereLAM and FujiLAM across different CD4 cell counts. Values were extracted from Broger et al. (165).

In this context, and as urine LAM tests continue to improve, it is important to anticipate their potential epidemiological impact, if deployed widely in future. Here, I examined this potential impact using a mathematical model of TB transmission, informed by the available evidence for the performance of AlereLAM and FujiLAM in different healthcare settings. I focused on South Africa, the country with the world's highest population rates of TB incidence, as well as the highest levels of HIV/TB coinfection. I modelled the potential TB incidence and mortality declines that would arise from the use of currently licensed LAM tests (consistent with AlereLAM) amongst those receiving HIV care, as well as a hypothetical scenario involving the use of potential future LAM tests in routine TB care, amongst HIV-negative patients. I aimed to answer the following questions:

- What is the population-level impact of detecting active TB disease amongst people living with HIV in South Africa with lateral flow assays?

- Will following existing urine LAM test eligibility criteria (table 4.1) lead to a substantial epidemiological impact?
- What is the epidemiological impact of broadening the eligibility criteria for urine LAM tests?

4.2. Methods

Here, I give an outline of the model structure, inputs, and intervention scenarios, with further technical details given in Appendix 2.

4.2.1. Model structure

I developed a deterministic compartmental model of TB transmission amongst adults (>15 years old) in South Africa, incorporating the role of HIV in driving TB dynamics. The overall model structure is illustrated schematically in fig 4.2. I did not aim to model the dynamics of HIV separately as I was interested in the effect of LAM tests on the TB epidemic, and not the HIV epidemic; thus, for the purpose of this analysis, I took the incidence of HIV, the proportion of PLHIV with and without TB, their CD4 cell counts, and the coverage of antiretroviral therapy ("ART") over time as given inputs for the model. Doing so captures the role of projected future ART coverage, and HIV trends, in the future trajectory of the TB epidemic in South Africa. I also developed a similar model parameterized to resemble the TB epidemic in Kenya, a country with a lower HIV burden.

Patients with extrapulmonary TB are often misdiagnosed if tested with sputum-based diagnostics (table 4.3). To capture the advantages of LAM testing for diagnosing TB amongst these patients, in the model, I distinguished extrapulmonary and pulmonary TB, while assuming that only the latter contribute to transmission. The sensitivity of LAM tests depends on the extent of HIV infection, and in particular the CD4 cell count (429). Accordingly, amongst those with HIV, I modelled 3 different CD4 cell count strata: those with a CD4 count > 200 cells/μl, those with a CD4 count between 100 and 200 cells/μl, and those with a CD4 count < 100 cells/μl. The model captures the rate at which those with HIV progress through declining CD4 counts, during the course of infection. I also incorporated HIV-associated hospitalisation, assuming CD4-dependent hazard rates of admission into hospital, and further assuming that upon admission, any ART-naïve patients are initiated on ART. I also captured the provision of HIV care in outpatient settings, assuming CD4-dependent rates of ART initiation in these settings. The model does not explicitly capture rifampicin-resistant or multi-drug-resistant TB, as these forms account only for 3%–4% of overall TB burden in South Africa.

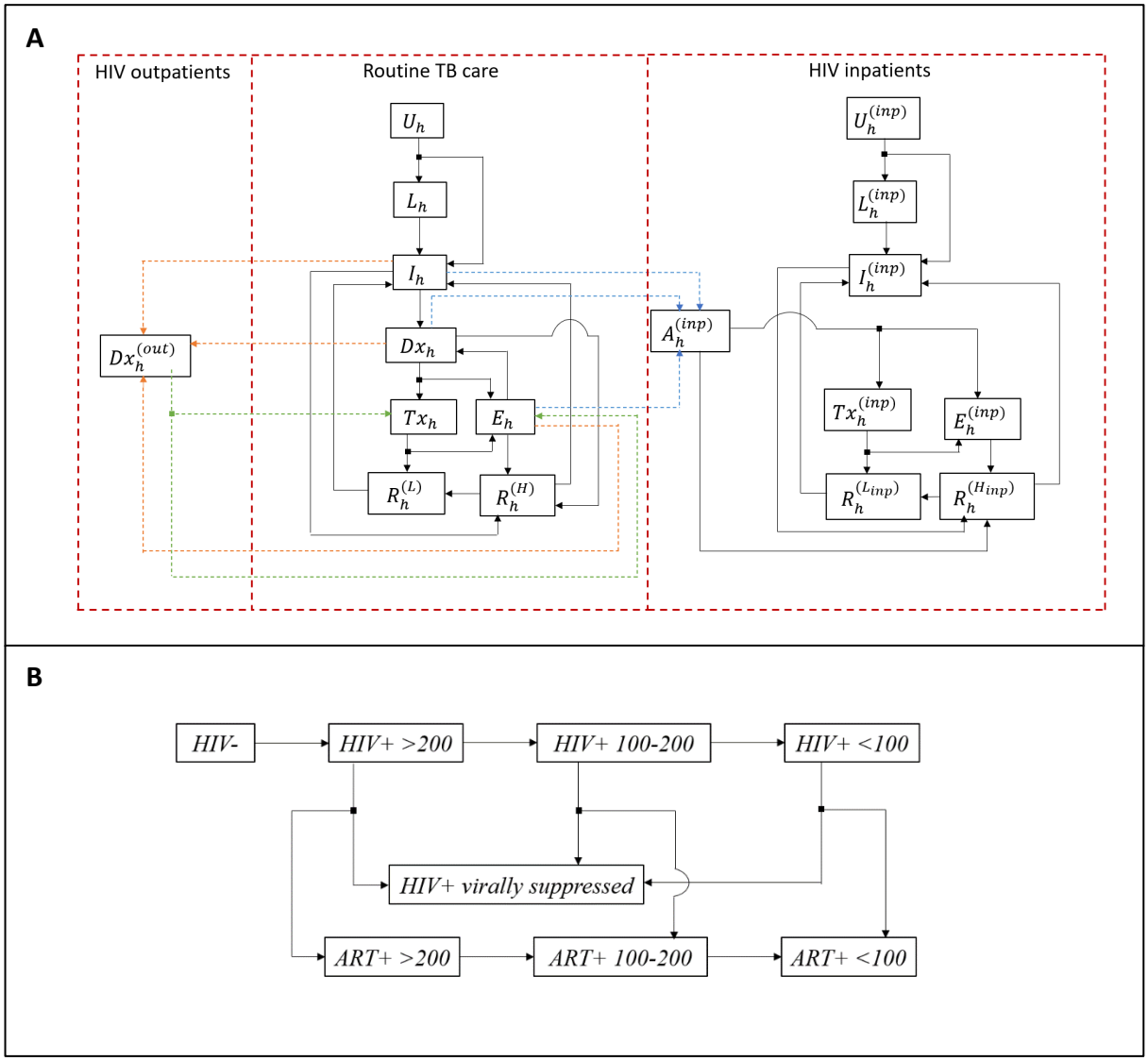

Figure 4.2. Schematic illustration of the model structure. (A) represents TB transmission dynamics in the general community (centre) and hospitalised PLHIV, represented by superscript 'inp' (right). Model compartments are as follows: uninfected with TB (*U*), latent infection (*L*), active TB disease (*I*), presented for care and awaiting diagnosis (*Dx*), on TB treatment (*Tx*), temporarily dropped out of the TB care cascade due to missed diagnosis or pre-treatment loss to follow-up (*E*), recovered from TB with a low or high risk of relapse ($R^{(H)}$ *and* $R^{(L)}$) and inpatient admissions (*A*). Each compartment is stratified further by HIV status, *h,* defined in table A2.2. (B) illustrates the transitions between the different HIV states, including ART state and CD4 count level (cells/μl). The following states are also further stratified into pulmonary TB and extrapulmonary TB: *I*, *Dx*, *Tx*, *E*, $R^{(H)}$, $R^{(L)}$, $Dx^{(out)}$, $I^{(inp)}$, $A^{(inp)}$, $Tx^{(inp)}$, $E^{(inp)}$, $R^{(L\_inp)}$, and $R^{(H\_inp)}$. Arrows represent transitions between states, at the per capita rates listed in table 4.3. Coloured-dash arrows in (A) illustrate movement of individuals with active TB disease into outpatient status (orange), out of outpatient status (green), and into inpatient status (blue). See Appendix 2 for further technical details, including model equations and calibration.

4.2.2. Data sources

I drew from WHO data for estimates of TB incidence and mortality in South Africa, along with reported notifications and treatment outcomes (113). For past HIV trends, I drew estimates from UNAIDS (453) for annual HIV incidence, the proportion of HIV cases being initiated on ART each year, and the proportion of those on ART being virally suppressed. For future projections, I drew from the Thembisa model (454), an HIV modelling framework that is the source of UNAIDs estimates (fig A2.2-2.3). Table 4.2 summarises the data for South Africa from these sources.

Indicator		Value (95% credible interval)	Source
TB epidemiology			
TB incidence, 2018		520 per 100,000 (373–691)	(113)
Mortality, 2018	HIV−	37 per 100,000 (35–39)	
	HIV+	73 per 100,000 (51–99)	
Notification rate, 2018		420 per 100,000 (358–438)	
HIV epidemiology and care			
HIV prevalence, 2017		7.5 million (6.9 million–8.0 million)	(453)
Proportion of TB cases coinfected with HIV		0.59 (0.55–0.65)	(113)
Proportion of PLHIV who have suppressed viral load		0.64 (0.58–0.68)	(453)
Of ART-naïve patients in the community, proportion by CD4 category	CD4 > 200	0.76 (0.61–0.91)	(455–457)
	CD4 100–200	0.12 (0.10–0.14)	
	CD4 < 100	0.12 (0.10–0.14)	
Of people initiating ART in outpatient settings, proportion by CD4 category	CD4 > 200	0.42 (0.33–0.49)	(444,458–462)
	CD4 100–200	0.26 (0.20–0.30)	
	CD4 < 100	0.32 (0.24–0.36)	
Of people initiating ART as inpatients, proportion by CD4 category	CD4 > 200	0.34 (0.27–0.41)	(165,445,463)
	CD4 100–200	0.25 (0.20–0.28)	
	CD4 < 100	0.41 (0.33–0.45)	
Overall number initiating ART, 2017		660,982	(453)
Percentage of HIV cases being hospitalised annually		5% (3.5%–6.5%)	(464)

Table 4.2. Calibration targets for South Africa used to estimate model parameters. CD4 counts are cells/μl.

I performed a literature search to identify the proportions of PLHIV in the 3 different CD4 strata described above, stratifying by 3 different population types, in line with WHO recommendations: (i) those initiating ART upon admission to hospital, (ii) those initiating ART as outpatients, and (iii) those who are not on ART. Fig 4.4 summarises the proportions thus extracted, and the sources of data used. This data informs model estimates for the timeliness of HIV treatment as follows: Early treatment yields a patient population with higher CD4 counts at the point of treatment initiation, and, conversely, late treatment is associated with a patient population having lower CD4 counts (table 4.2; fig 4.4). Therefore, by fitting the model to simultaneously capture CD4 progression and the distribution of CD4 counts at treatment initiation, I estimated the rate of treatment initiation at different CD4 counts, both in outpatient and inpatient settings (table 4.2; fig 4.4). I additionally collected data from the literature for other parameters: for example, for the proportion of HIV cases

that are hospitalised per year (464) and for the current standard of TB care amongst HIV inpatients (e.g., the proportion of hospital admissions receiving a TB test in routine practice) (159).

These targets (table 4.2) were used to inform model parameters including the force of infection (β), the infectiousness of TB in PLHIV relative to HIV-negatives (R_1), the rate of initial care seeking for TB symptoms (δ_{1_s}), the rate of TB mortality (μ_1), the rate of HIV acquisition (γ) and the rate of CD4 progression (ν). A full list of these parameters is shown in table 4.3. I used Adaptive Bayesian Markov chain Monte Carlo ("MCMC") to calibrate the model (391). I fitted beta and log-normal distributions to the calibration targets for all data that were proportions and for TB incidence, respectively. Next, I constructed the overall likelihood function of the data (x) based on parameter set (θ), $P(x|\theta)$, as a product of the distributions over all the calibration targets (table 4.3) and multiplied this with uniform priors ($P(\theta)$; ranges specified in table 3.1). Thus, the posterior density is calculated by: $P(\theta|x) \propto P(x|\theta)P(\theta)$. By sampling from the posterior distribution using MCMC, I created an unbiased sample that approximates the posterior distribution. I refer to the uncertainty in model projections as the Bayesian credible intervals, using the 2.5th and 97.5th percentiles to reflect the lower and upper bound of an interval. Additional detail is provided in appendix 2. I drew 5,000 samples from the posterior distribution. For any model projections based on these samples, I estimated uncertainty intervals using the 2.5th and 97.5th percentiles, referring to this estimate as the Bayesian credible interval ("CrI"). Further details on the model structure and calibration are given in Appendix 2.

Parameter	Symbol	Value*		Source/notes
TB natural history				
Mean rate of transmission per TB case	β	14.9 (11.4–18.6)		Model estimate
TB infectiousness in HIV+ (not virally suppressed) relative to HIV−	R_1	0.66 (0.60–0.80)		Model estimate
Proportion of TB infections undergoing rapid progression	θ_h	HIV− and virally suppressed	0.11 (0.09–0.15)	(15,16,392)
		HIV+, CD4 > 200	0.40 (0.33–0.51)	
		HIV+, CD4 100–200	0.80 (0.67–0.82)	
		HIV+, CD4 < 100	0.99 (0.90–1.00)	
Per capita hazard of reactivation of latent TB infection	ρ_h	HIV− and virally suppressed	0.001 years^{-1} (0.0003–0.0024)	(342,392,465)
		HIV+, CD4 > 200	0.005 years^{-1} (0.003–0.006)	
		HIV+, CD4 100–200	0.10 years^{-1} (0.085–0.150)	
		HIV+, CD4 < 100	0.20 years^{-1} (0.100–0.300)	
Per capita hazard rate of relapse	r_1	Following self-cure/treatment default	0.14 years^{-1} (0.10–0.18)	(34,35,394,466)
	r_2	Following treatment cure, >2 years	0.002 years^{-1} (0.001–0.003)	
Stabilisation of relapse risk following treatment	ς	0.5 years^{-1} (0.4–0.6)		(35): most relapse occurs in the first two years after treatment
Per capita hazard rate of spontaneous cure	φ_h	HIV− and virally suppressed	0.17 years^{-1} (0.13–0.21)	(344)
		HIV+	0 years^{-1}	
Per capita hazard rate of TB mortality (HIV-negative)	μ_1	0.29 years^{-1} (0.21–0.38)		Model estimate
	μ_4	Excess: inpatient	1 year^{-1} (0.5–2.0)	(159)
Proportion reduction in susceptibility to reinfection due to previous infection	π	0.21 [0.15-0.25]		(28)
Proportion of TB cases with pulmonary TB	α_h	HIV−	0.89 (0.80–0.90)	(113)
		HIV+	0.60 (0.50–0.70)	
HIV natural history				
Per capita hazard rate of HIV acquisition	γ	0.016 years^{-1} (0.013–0.021)		Model estimate, to match HIV incidence
Per capita hazard rate of CD4 progression, amongst those not virally suppressed	ν_1	>200 to 100–200	0.31 years^{-1} (0.26–0.37)	Model estimate
	ν_2	100–200 to <100	0.89 years^{-1} (0.88–0.90)	
Excess per capita hazard rate of TB+HIV+ mortality	μ_{3_h}	HIV+ and virally suppressed	0.01 years^{-1} (0.005–0.012)	(467–469)
		HIV+, CD4 > 200	0.03 years^{-1} (0.02–0.06)	
		HIV+, CD4 100–200	0.17 years^{-1} (0.13–0.21)	
		HIV+, CD4 < 100	0.60 years^{-1} (0.42–0.83)	
Routine TB services				

Per capita hazard rate of initial careseeking for TB symptoms	δ_1	HIV− and virally suppressed	2.5 years^{-1} (2.2–2.9)	Model estimate
Per capita hazard rate of repeat careseeking for TB symptoms (following missed diagnosis)	δ_2	HIV− and virally suppressed	12 years^{-1} (6–26)	Assumption: corresponds to range of 2 weeks to 2 months
Rate of careseeking amongst HIV+, relative to HIV−	R_2	1.5 (1.0–2.0)		Model estimate
Proportion of TB cases diagnosed correctly, per careseeking attempt in routine TB services	ε_R	HIV− pulmonary TB	0.73 (0.63–0.92)	Model estimate
	R_3	HIV+, relative to HIV−	0.31 (0.20–0.72)	
	R_4	Extrapulmonary, relative to pulmonary	0.21 (0.20–0.28)	
TB treatment initiation delay	ϕ_R	52 years^{-1} (24–100)		Assumed: corresponds to a mean treatment delay of 1 week in routine TB care
Proportion of diagnosed TB cases successfully initiating treatment	ω_R	0.88 (0.77–0.90)		(257,470)
Rate of first-line treatment completion	τ	2 years^{-1}		Corresponds to a duration of 6 months
Proportion cured after first-line treatment	χ_h	HIV−	0.82 (0.77–0.87)	(113,257)
		HIV+	0.80 (0.75–0.85)	
Proportion that can provide a sputum sample	ϑ_h^{sputum}	HIV−	0.90 (0.80–0.95)	(157–159,446)
		HIV+	0.50 (0.37–0.60)	
Proportion that can provide a urine sample	ϑ_h^{urine}	0.99 (0.97–1.00)		(165)
Proportion of Xpert-negative results that are clinically diagnosed	ι_h	HIV−	0.20 (0.16–0.24)	(257)
		HIV+	0.30 (0.24–0.36)	
HIV services				
Per capita rate of hospitalisation	h_h	HIV+, CD4 > 200	0.046 years^{-1} (0.032–0.063)	Model estimate
		HIV+, CD4 100–200	0.12 years^{-1} (0.08–0.14)	
		HIV+, CD4 < 100	0.23 years^{-1} (0.20–0.26)	
Per capita rate of ART initiation in outpatient settings amongst PLHIV	ϖ_h	HIV+, CD4 > 200	0.043 years^{-1} (0.020–0.085)	Model estimate
		HIV+, CD4 100–200	0.15 years^{-1} (0.09–0.27)	
		HIV+, CD4 < 100	0.28 years^{-1} (0.18–0.43)	
Proportion on ART that are virally suppressed	γ	0.88 (0.85–0.90)		(453)
Inpatients: Amongst admissions with TB, proportion having TB symptoms	s_I	0.95 (0.76–1.00)		(445)
Inpatients: Amongst admissions with TB, proportion receiving an Xpert test at baseline	ξ_I	1.00 (0.80–1.00)		Assuming proportion amongst inpatients is higher than amongst outpatients (see

				outpatient data below)
Inpatients: Proportion of diagnosed TB cases successfully initiating treatment	ω_I	1.00 (0.90–1.00)		(257,470)
Inpatients: Average duration of hospitalisation	ψ_h	HIV+, CD4 > 200	8 days (5–10)	(464)
		HIV+, CD4 100–200	9 days (6–11)	
		HIV+, CD4 < 100	10 days (7–13)	
Outpatients: Amongst those initiating ART, proportion having TB symptoms	s_O	0.82 (0.66–0.98)		(471)
Outpatients: Amongst those initiating ART, proportion of symptomatic patients currently receiving an Xpert test	ξ_O	0.80 (0.60–0.90)		(472)
Outpatients: Proportion of diagnosed TB cases successfully initiating treatment	ω_O	0.86 (0.70–0.92)		(257,470)
TB treatment initiation delay	ϕ	365 $years^{-1}$ (52–365)		Corresponds to a mean delay of 1 day
Demographics				
Per capita hazard rate of background mortality	μ_2	0.0156 $years^{-1}$		World Bank estimates: corresponds to an average lifespan of 65 years

Table 4.3. List of model parameters and assumptions. CD4 counts are cells/μl. *Numbers in brackets represent sampling ranges; I assume all sampling ranges are uniformly distributed in the sampling process.

4.2.3. Intervention scenarios

I distinguished 'current' and potential 'future' LAM tests. For the performance of the former, I drew from a systematic review of AlereLAM (429). For the latter, I took FujiLAM as an illustrative example, drawing from a recent study that estimated the performance of this test in HIV-negative patients (166). This same study highlighted the potential of future LAM tests to have improved performance compared to FujiLAM: the parameters for future LAM tests could therefore be interpreted as a lower bound for their performance (165) (table 4.4). I assumed that differences in test performance between inpatients and outpatients are driven primarily by variations in CD4 distributions between these populations, variations that are captured by the model. Accordingly, I concentrated on study findings stratified by CD4 status, rather than by inpatient or outpatient setting.

Test	Symbol	HIV−	HIV+				Source
			CD4 > 200	CD4 100–200	CD4 < 100	Virally suppressed	
Sputum Xpert	X_{sn}	89% (85-92)	79% (70–86)	79% (70–86)	79% (70–86)	79% (70–86)	(420)
Currently licensed LAM test	A_{sn}	—	12% (5–24)	26% (15–39)	57% (42–70)	42%[a] (32–52)	(165,429)
Future LAM test	F_{sn}	30% (20–50)	44% (30–59)	61% (44–73)	84% (71–91)	70%[a] (53–83)	(165,166)

Table 4.4. Test sensitivities. CD4 counts are cells/μl. Values in parentheses are 95% credible intervals. I assumed Xpert sensitivity to be independent of CD4 count amongst those with HIV. I assumed future LAM tests to be consistent with FujiLAM. [a]Sensitivities for patients with virally suppressed HIV infection were estimated by taking the 'overall' sensitivities of each test presented in the meta-analysis by Bjerrum et al. (429).

A test's epidemiological impact (i.e., on incidence and mortality) is driven by its sensitivity, or the proportion of true TB cases it can detect. A test's specificity, or the proportion of those without TB that it correctly diagnoses as negative, has no direct bearing on its epidemiological impact, and instead is more relevant for the number of unnecessary TB treatments incurred as a result of false-positive diagnosis (408). As the focus of the current work is on epidemiological impact, I concentrated on test sensitivity and not specificity. The model therefore does not address the adverse consequences of false-positive results, including additional costs and adverse treatment side effects.

I modelled the deployment of current and future LAM tests in 2 intervention scenarios reflecting the updated WHO guidelines (449) (table 4.1):

- In 'PLHIV inpatients only' (scenario i), LAM testing is conducted in PLHIV inpatients with signs and symptoms of TB and in all PLHIV with CD4 < 200 cells/μl, independent of symptoms.
- In 'PLHIV inpatients and outpatients' (scenario ii), LAM testing is conducted in PLHIV inpatients and outpatients prior to initiating ART treatment with signs and symptoms of TB, in all PLHIV inpatients with CD4 < 200 cells/μl, and in all PLHIV outpatients with CD4 <100 cells/μl, independent of symptoms.

Additionally, for future LAM tests alone, I modelled a hypothetical future scenario:

- 'Universal for all TB presumptive patients' (scenario iii), in which a future LAM test is deployed as part of routine TB diagnosis in patients presenting with symptoms of TB to a healthcare provider, regardless of HIV status.

The impact of scenario iii derives from the diagnosis of HIV-negative TB, and from the diagnosis of TB amongst those with undiagnosed HIV (and who may miss the opportunity for urine-based testing under current LAM testing guidelines). To assess which of these factors are most influential for

impact, I additionally simulated scenario iii under a hypothetical condition where FujiLAM has 0 sensitivity for TB in HIV-negative individuals. This artificial scenario is thus deliberately constructed so that the only incremental cases being diagnosed, relative to scenario ii, are those with HIV and not on ART.

I modelled each of these intervention scenarios, assuming them to be initiated in 2020; I assumed that the proportion of the target population accessing these tests increases linearly, until the whole population in South Africa is covered by 2023. I simulated the model forward to 2035, simulating incidence and mortality over this time.

I considered the impact of LAM testing with respect to 2 comparators:

- A 'status quo' comparator scenario, where the current standard of TB care continues indefinitely (where a proportion of patients presenting to care with signs and symptoms of TB are offered an Xpert test by a healthcare provider)
- An 'Xpert scale-up' comparator scenario, involving the scale-up of sputum-based Xpert across the country, to diagnose TB both amongst those receiving ART and in routine TB services. I assumed that all patients presumed to have TB based on symptoms receive Xpert testing by 2023 (in inpatient, outpatient, and routine care settings).

Consistent with diagnostic yields reported in the literature (table 4.3), I assumed that only 50% of patients with HIV (in both inpatient and outpatient settings) can provide a sputum sample for Xpert testing, while 99% of patients are able to provide a urine sample for LAM testing. I also considered clinical diagnosis that occurs after a negative Xpert test result. I assumed that 20% and 30% of patients with negative Xpert test results are clinically diagnosed and offered treatment amongst HIV-negative and HIV-positive patients, respectively (257). Using comparator and intervention scenarios, I projected estimates for the numbers of TB cases and deaths that would be averted under the intervention scenarios described above.

Finally, as a sensitivity analysis to examine the applicability of these results to other countries with a generalised HIV epidemic, I extended the model to capture epidemiological conditions consistent with Kenya, where an estimated 27% of TB is in HIV-coinfected patients, compared with 59% for South Africa (113). There is insufficient data from Kenya to calibrate all model parameters; I therefore sought only to capture gross epidemiological indicators consistent with Kenya (TB incidence, mortality, proportion of HIV coinfection, etc.), while assuming the same values as derived for South Africa for all parameters specific to CD4 counts (rates of ART initiation, hospitalisation,

etc.; see table A2.3 for further details). I then simulated the intervention scenarios described above, in this Kenya-like setting.

4.3. Results

4.3.1. Model calibration

Fig 4.3-4.4 shows results of model calibration, displaying the model fit against each of the calibration targets listed in table 4.2. Fig 4.5 show MCMC diagnostic checks, including the posterior density trace and autocorrelation plots for selected parameters. Model calibrations for Kenya are shown in Appendix 2 (fig A2.1).

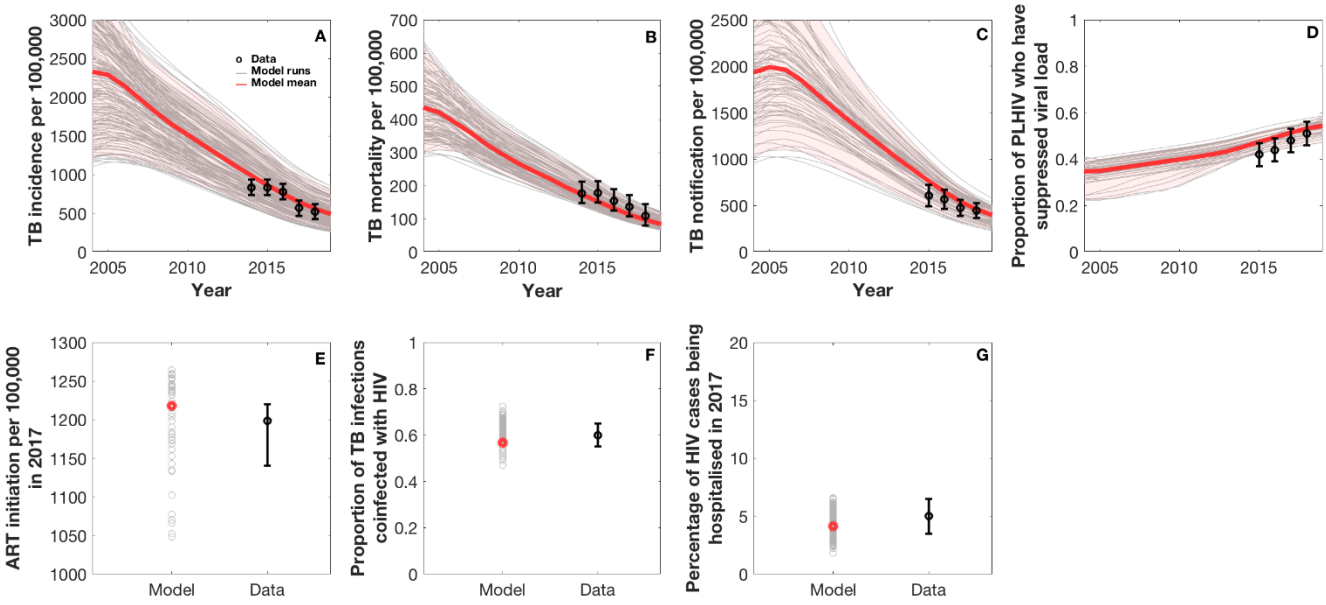

Figure 4.3. Model fits to data for South Africa.. (A) TB incidence; (B) TB mortality per 100,000; (C) TB notifications per 100,000; (D) proportion of PLHIV with suppressed viral loads; (E) ART initiations per 100,000; (F) proportion of TB cases coinfected with HIV; (G) percentage of HIV cases being hospitalised annually. Grey - model runs; red - mean of model runs; black - data points are described in table 4.2**.**

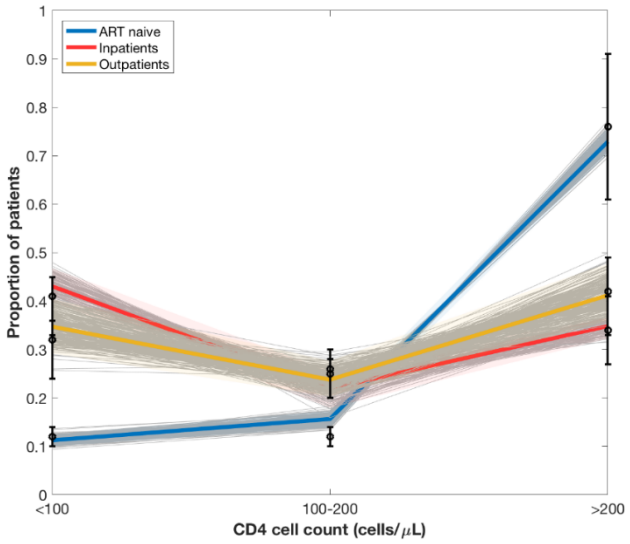

Figure 4.4. CD4 count distributions. Model fits to the data: mean model CD4 count distributions amongst ART-naïve PLHIV (blue), inpatients (red), and outpatients (yellow). Grey lines show the model runs, and black data points show the data, based on a literature search (table 4.2).

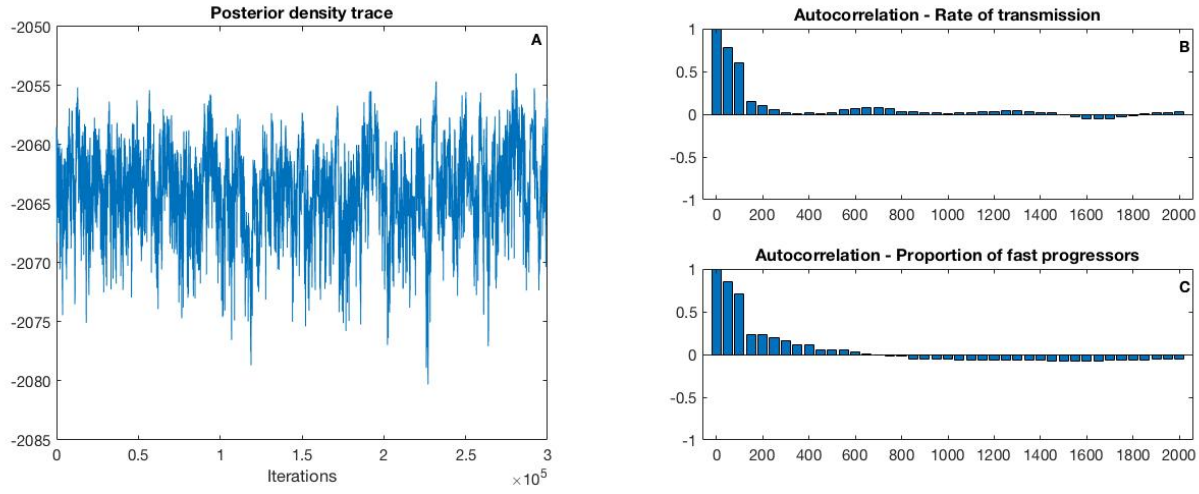

Figure 4.5. MCMC diagnostics. (A) shows the posterior density trace. (B) and (C) show autocorrelation function plots for 2 selected parameters (rate of transmission and proportion of fast progressors).

4.3.2. Epidemiological impact

The model projects that, under the status quo comparator between 2020 and 2035, there would be 2,700,000 (95% CrI 2,000,000–3,600,000) cumulative incident cases of TB in South Africa, and 420,000 (95% CrI 350,000–520,000) cumulative TB deaths.

Fig 4.6 and Fig 4.7 illustrate the potential impact of LAM tests relative to the status quo comparator, showing the TB cases and deaths averted each year, respectively. Table 4.5 summarises the cumulative impact in South Africa over the period 2020 to 2035, showing estimates for both cases

and deaths averted. Table 4.6 also summarises the cumulative impact, but under the Xpert scale-up comparator.

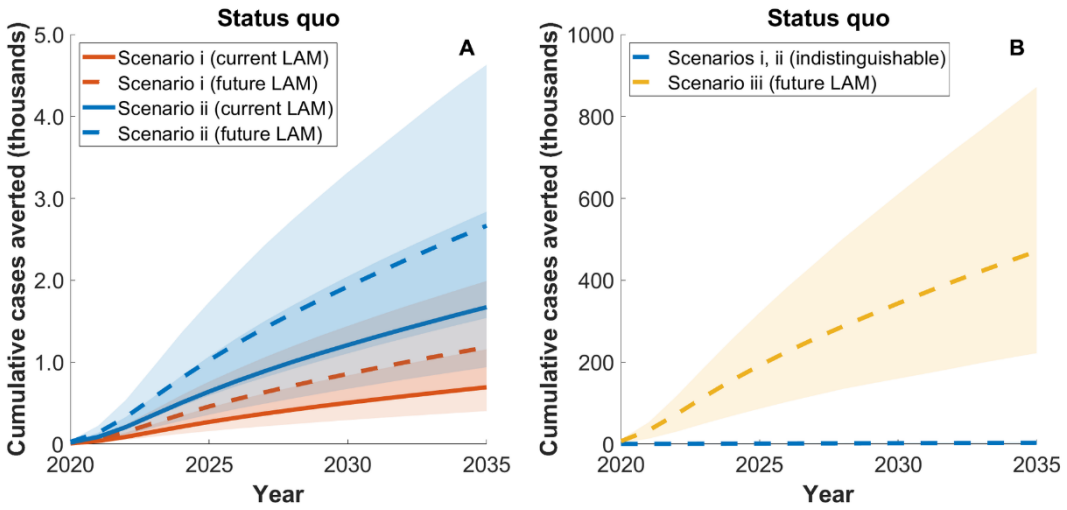

Figure 4.6. Model projections for impact of LAM tests in South Africa on TB incidence, relative to the status quo comparator. Under the status quo comparator, the current standard of TB care in South Africa is assumed to continue indefinitely. Shaded areas show Bayesian 95% credible intervals. Solid lines depict a currently licensed test, while dashed lines depict a future LAM test. Colours represent different implementation scenarios: inpatients only (red, scenario i), plus outpatients (blue, scenario ii) and plus routine TB care (yellow, scenario iii). (A) depicts scenarios i and ii only, while (B) additionally shows scenario iii (shown separately owing to the change in scale). Cumulative impacts over the period 2020–2035 are summarised in table 4.5.

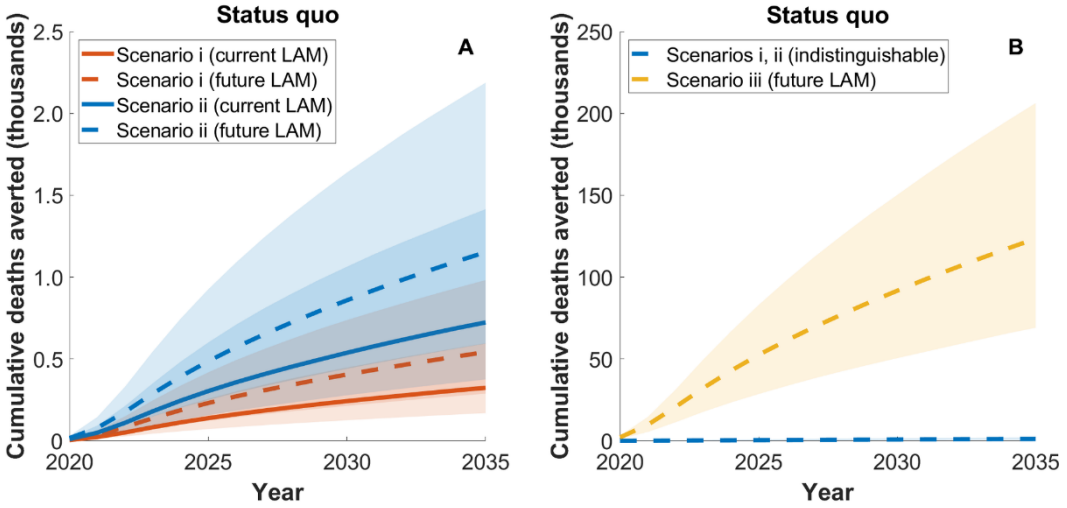

Figure 4.7. Model projections for impact of LAM test in South Africa on TB deaths, relative to the status quo comparator. Under the status quo comparator, the current standard of TB care in South Africa is assumed to continue indefinitely. Shaded areas show Bayesian 95% credible intervals. Solid lines depict a currently licensed test, while dashed lines depict a future LAM test. Colours represent different implementation scenarios: inpatients only (red, scenario i), plus outpatients (blue, scenario ii) and plus routine TB care (yellow, scenario iii). (A) depicts scenarios i and ii only, while (B) additionally shows scenario iii. Cumulative impacts over the period 2020–2035 are summarised in table 4.5.

Deployment level	LAM test	Cumulative incidence averted, 2020–2035		Cumulative TB deaths averted, 2020–2035		Cumulative TB deaths averted amongst inpatients, 2020–2035	
		Number	Percent	Number	Percent	Number	Percent
Inpatients (scenario i)	Currently licensed LAM	692 (402–1,156)	0.026 (0.014–0.043)	324 (170–596)	0.077 (0.045–0.125)	54 (33–86)	5.33 (4.18–6.29)
	Future LAM	1,181 (698–1,990)	0.045 (0.025–0.074)	543 (289–982)	0.129 (0.076–0.203)	90 (55–145)	8.75 (7.05–11.2)
Inpatients and outpatients (scenario ii)	Currently licensed LAM	1,670 (937–2,837)	0.063 (0.035–0.109)	724 (376–1,415)	0.173 (0.097–0.306)	58 (36–93)	5.73 (4.36–6.90)
	Future LAM	2,665 (1,539–4,631)	0.100 (0.056–0.175)	1,153 (594–2,188)	0.276 (0.156–0.486)	96 (58–155)	9.33 (7.43–12.1)
Inpatients, outpatients, and routine TB care (scenario iii)	Future LAM	470,590 (221,830–871,500)	17.7 (8.62–29.0)	123,520 (69,120–206,270)	29.6 (17.8–43.6)	402 (229–685)	39.7 (29.4–49.1)

Table 4.5. Projected cumulative impact relative to a status quo comparator, South Africa. Under the status quo comparator, I assume the current standard of TB care in South Africa to continue indefinitely. Values in parentheses are 95% credible intervals.

Deployment level	LAM test	Cumulative incidence averted, 2020–2035		Cumulative TB deaths averted, 2020–2035		Cumulative TB deaths averted amongst inpatients, 2020–2035	
		Number	Percent	Number	Percent	Number	Percent
Inpatients (scenario i)	Currently licensed LAM	171 (81–322)	0.0079 (0.0043–0.014)	153 (81–324)	0.050 (0.028–0.088)	34 (20–56)	4.68 (3.68–5.62)
	Future LAM	291 (136–546)	0.014 (0.0074–0.025)	256 (134–523)	0.083 (0.047–0.14)	56 (33–93)	7.69 (6.12–10.2)
Inpatients and outpatients (scenario ii)	Currently licensed LAM	395 (192–798)	0.019 (0.010–0.037)	330 (173–747)	0.108 (0.058–0.210)	36 (22–60)	4.99 (3.81–6.13)
	Future LAM	635 (293–1,327)	0.030 (0.016–0.060)	530 (271–1,143)	0.173 (0.094–0.329)	59 (35–98)	8.15 (6.41–10.8)
Inpatients, outpatients, and routine TB care (scenario iii)	Future LAM	119,670 (68,710–169,030)	5.68 (3.18–7.52)	50,174 (33,617–72,557)	16.4 (10.4–22.2)	204 (122–344)	28.7 (21.6–34.5)

Table 4.6. Projected cumulative impact relative to an Xpert scale-up comparator, South Africa. Under the Xpert scale-up comparator, I assume comprehensive expansion of access to sputum Xpert across South Africa, such that all individuals with symptoms suggestive of TB are tested with Xpert on their first presentation for care. Numbers in the table show the model-projected impact of LAM tests when deployed as an adjunct to Xpert, assuming (in all settings shown in the table) a simple diagnostic algorithm where TB is diagnosed if either a LAM test or Xpert is positive for TB. Values in parentheses are 95% credible intervals. As described in the main text, in the model, I also allow for clinical diagnosis amongst bacteriologically negative symptomatic patients.

Restricting the use of LAM tests to HIV care

These results (fig 4.6-4.7, table 4.5) illustrate that LAM tests could have a meaningful impact in saving lives amongst inpatients (scenario i); current and future LAM tests may avert, respectively, 54 (95% CrI 33–86) and 90 (95% CrI 55–145) TB deaths amongst inpatients, a 5.33% (95% CrI 4.18%–6.29%) and 8.75% (95% CrI 7.05%–11.2%) reduction of overall TB deaths in this population. At a population level, 324 (95% CrI 170–596) and 543 (95% CrI 289–982) TB deaths would be averted with current and future LAM tests, respectively, a limited impact (<1% of the country-level TB burden) that is clearly because of the small size of the population receiving the intervention.

When expanding LAM test deployment to outpatient settings (scenario ii), current and future LAM tests would avert, respectively, 724 (95% CrI 376–1,400) and 1,200 (95% CrI 594–2,200) TB deaths, roughly doubling the total deaths averted under scenario i. Notably, however, even with this widened eligibility, LAM tests continue to exert only a modest impact on the population-level TB epidemic, with <1% reductions in TB incidence and mortality (fig 4.6A and 4.7A; table 4.5).

Fig A2.4 illustrates the reason for the limited population-level impact under scenarios i and ii, even in a high-HIV-burden setting such as South Africa: it is due to the series of criteria that successively narrow the pool of eligible individuals to <5% of annual TB incidence.

Expanding the use of LAM tests to routine TB services

It is only when LAM tests are deployed in routine TB services (scenario iii) that true incidence-reducing impact emerges (fig 4.6B and 4.7B), with 470,000 (95% CrI 220,000–870,000) cumulative TB incident cases and 120,000 (95% CrI 69,000–210,000) TB deaths averted, respective reductions of 17.7% (95% CrI 8.62%–29.0%) and 29.6% (95% CrI 17.8%–43.6%).

Under the Xpert scale-up comparator, the incremental cases averted by a future LAM test in routine TB care (scenario iii) fall to 120,000 (95% CrI 69,000–170,000), a 5.68% (95% CrI 3.18%–7.52%) reduction from the 17.7% (95% Cri 8.62%–29.0%) achieved with the status quo comparator, owing to the improvements in diagnosis already achieved by Xpert scale-up. Under the same scenario, a future LAM test would avert 50,000 (95% CrI 34,000–73,000) TB deaths, a 16.4% (95% CrI 10.4%–22.2%) reduction. Overall, the effect of Xpert scale-up on the incremental impact of LAM tests is lower for deaths averted than for cases averted: this reflects the value of LAM tests in diagnosing extrapulmonary TB and TB in those with advanced disease, patients who would otherwise contribute more strongly to mortality than to transmission.

As noted above, the impact of scenario iii (fig 4.6B and 4.7B) could derive either from diagnosis of TB in HIV-negative individuals or from diagnosis of TB amongst those with HIV who have not yet been linked to care. To examine the roles of these 2 populations, I simulated a hypothetical scenario of a future LAM test being deployed in routine TB services, but with 0 sensitivity for TB in HIV-negative individuals. Under this hypothetical scenario the TB cases and deaths averted are, respectively, 12.1% (95% CrI 8.34%–17.6%) and 21.3% (95% CrI 15.2%–29.7%) in South Africa, hypothetical impacts that represent only marginal reductions of those reported in the bottom row of table 4.5. Overall, these findings illustrate that—when expanded from outpatients in HIV care to routine TB services—the key value of LAM tests would be in diagnosing TB amongst those with HIV who have not yet been initiated on ART.

4.3.3. The use of LAM tests in lower HIV-burden settings

Similar results are seen in a Kenya-like setting (table 4.7-4.8; fig 4.8). Relative to a status quo comparator, in scenarios i and ii, where LAM tests are deployed only amongst those receiving HIV care, the percentage decline in mortality amongst eligible groups is roughly half that in South Africa (table 4.7), owing to the smaller proportion of HIV cases having TB. As in South Africa, population-level declines in incidence and mortality would be <1% in these scenarios. However, when deployment of a future LAM test is expanded to routine TB services, 290,000 (95% CrI 190,000–470,000) cumulative TB incident cases and 58,000 (95% CrI 39,000–86,000) TB deaths are averted, a 19.8% (95% CrI 18.1%–22.7%) and 27.9% (95% CrI 25.7%–31.4%) reduction, respectively, in a Kenya-like setting (table 4.7), impacts that are comparable to those estimated for South Africa (table 4.5).

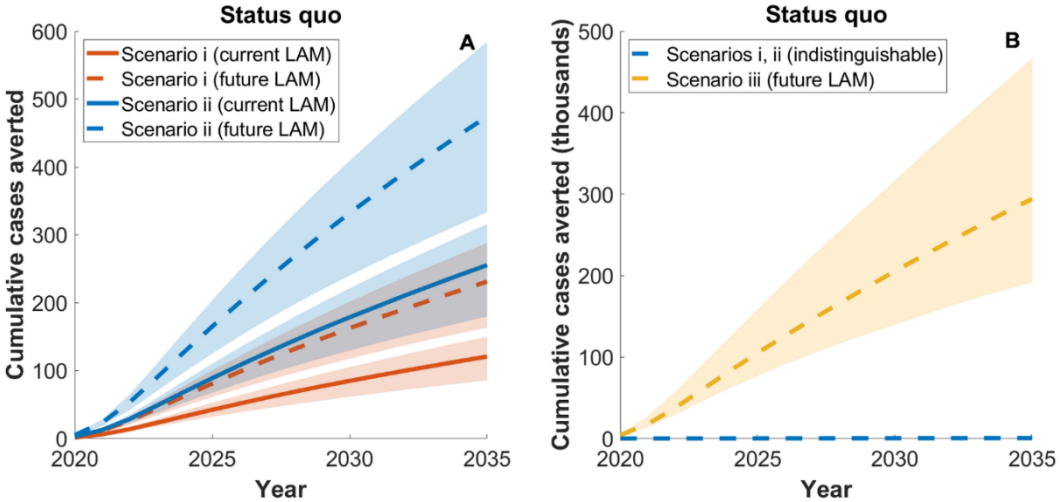

Figure 4.8. Model projections for impact of LAM tests in Kenya on TB incidence, relative to the status quo comparator. Under this comparator, the current standard of TB care in Kenya is assumed to continue indefinitely. Shaded areas show Bayesian 95% credible intervals. Solid lines depict a currently licensed test, while dashed lines depict a future LAM test. Colours represent different implementation scenarios: inpatients only (red, scenario i), plus outpatients (blue, scenario ii), and plus routine TB care (yellow, scenario iii). (A) depicts scenarios i and ii only, while (B) additionally shows scenario iii (shown separately owing to the change in scale). Cumulative impacts over the period 2020–2035 are summarised in table 4.7.

Deployment level	LAM test	Incidence averted between 2020 - 2035		TB deaths averted between 2020 – 2035		TB deaths averted amongst inpatients between 2020-2035	
		Number	Percent	Number	Percent	Number	Percent
Inpatients, scenario (i)	Currently licensed LAM test	121 (86-150)	0.008 (0.006-0.011)	49 (36-61)	0.023 (0.019-0.029)	14 (10-18)	3.00 (2.77-3.47)
	Future LAM test	231 (163-288)	0.015 (0.012-0.021)	94 (68-116)	0.044 (0.037-0.055)	26 (19-34)	5.71 (5.32-6.61)
Inpatients and Outpatients, scenario (ii)	Currently licensed LAM test	255 (180-316)	0.017 (0.013-0.024)	96 (70-119)	0.046 (0.038-0.057)	14 (10-18)	3.09 (2.85-3.59)
	Future LAM test	474 (333-584)	0.031 (0.024-0.044)	180 (130-223)	0.085 (0.072-0.105)	27 (20-35)	5.88 (5.47-6.81)
Inpatients, outpatients and routine TB care, scenario (iii)	Future LAM test	294,140 (191,930-466,480)	19.8 (18.1-22.7)	57,935 (38,818-86,317)	27.9 (25.7-31.4)	134 (98-204)	30.7 (28.8-33.9)

Table 4.7. Projected cumulative impact relative to a 'status quo' comparator, Kenya.
Under this comparator, we assume the current standard of TB care in Kenya to continue indefinitely.

Deployment level	LAM test	Incidence averted between 2020 - 2035		TB deaths averted between 2020 – 2035		TB deaths averted amongst inpatients between 2020-2035	
		Number	Percent	Number	Percent	Number	Percent
Inpatients, scenario (i)	Currently licensed LAM test	28 (20-36)	0.003 (0.002-0.004)	22 (16-27)	0.015 (0.013-0.019)	8 (6-10)	2.62 (2.41-3.05)
	Future LAM test	53 (37-69)	0.005 (0.004-0.007)	41 (31-51)	0.029 (0.024-0.036)	16 (12-19)	5.02 (4.64-5.83)
Inpatients and Outpatients, scenario (ii)	Currently licensed LAM test	55 (39-73)	0.005 (0.004-0.007)	40 (30-49)	0.028 (0.024-0.035)	8 (6-10)	2.69 (2.47-3.14)
	Future LAM test	103 (73-135)	0.009 (0.007-0.014)	74 (56-93)	0.053 (0.045-0.065)	16 (12-20)	5.14 (4.76-5.98)
Inpatients, outpatients and routine TB care, scenario (iii)	Future LAM test	38,492 (26,220-51,489)	3.51 (3.15-4.00)	13,495 (9,659-17,827)	9.63 (8.55-10.5)	51 (39-67)	17.0 (16.2-17.9)

Table 4.8. Projected cumulative impact relative to an 'Xpert scale-up' comparator, Kenya. Under this comparator we assume comprehensive expansion of access to sputum Xpert across Kenya, such that all individuals with symptoms suggestive of TB are tested with Xpert on their first presentation for care. Numbers in the table show model-projected impact of LAM tests when deployed as an adjunct to Xpert, assuming (in all settings shown in the table) a simple diagnostic algorithm where TB is diagnosed if either LAM tests or Xpert is positive for TB. As described in the main text, in the model we also allow for clinical diagnosis amongst bacteriologically negative symptomatics.

4.3.4. Multivariate sensitivity analysis

I conducted a multivariate sensitivity analysis to examine which model parameters (listed in table 4.3) model outputs were most sensitive towards. Using cases averted as the model output, and focusing on scenario iii, unsurprisingly, the model parameter that the model output was most sensitive towards was the rate of reactivation amongst HIV-negatives, a model parameter that directly effects the number of people who will develop active TB disease, suggesting that higher rates of reactivation decrease the number of cases averted.

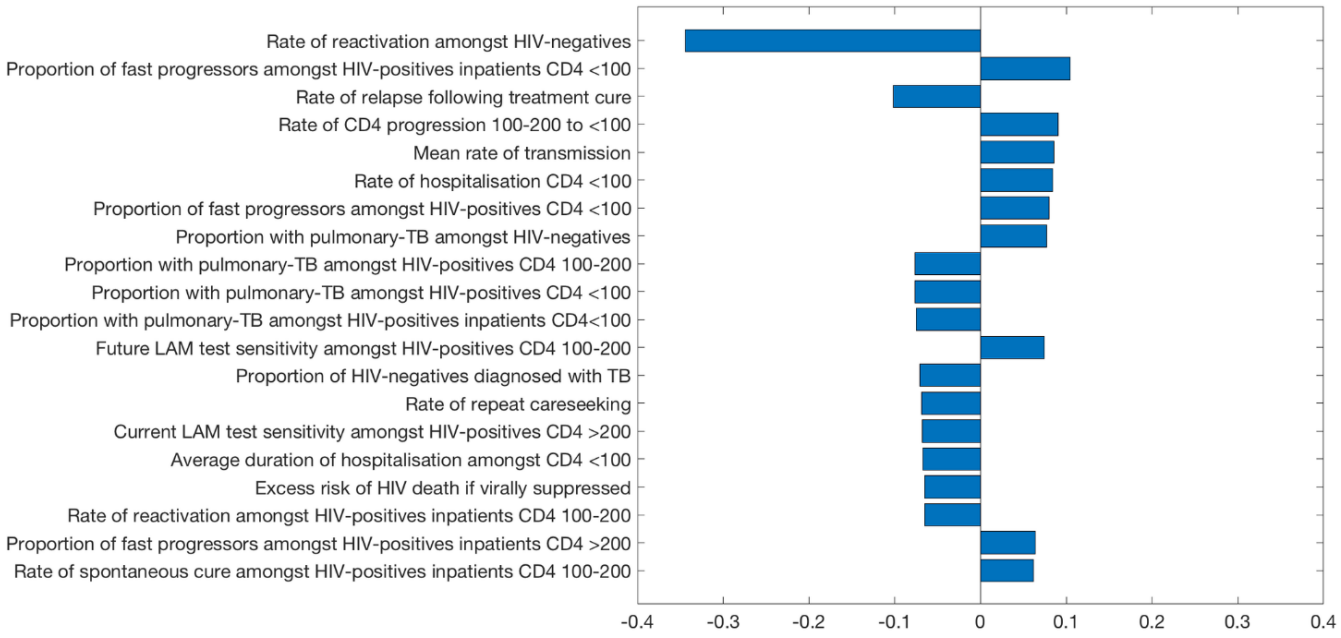

Figure 4.9. Multivariate sensitivity analysis of impact for South Africa. Using scenario iii (future LAM test deployment in routine TB care), I used partial rank correlation coefficient ("PRCC") to examine which parameter, listed in table 4.3, the output cases averted is most sensitive towards. Larger bars represent more sensitive parameters. Shown are the 20 most influential model parameters, in decreasing order of sensitivity from top to bottom.

4.4. Discussion

New non-sputum-based diagnostic technologies could raise new opportunities to accelerate current declines in TB incidence (200,473,474). In the current work, I have addressed one example of such technologies: lateral flow LAM assays, which offer the potential to diagnose TB through urine. Given that LAM tests perform best in PLHIV (429), it was reasonable to hypothesise that they would have a substantial epidemiological impact in settings such as South Africa, where the majority of TB cases are HIV coinfected. However, these results suggest a more nuanced message: For future LAM tests to achieve population-level reductions in TB burden, they would need to be offered more widely than amongst those receiving HIV care, and in routine TB care. Under this scenario, the patients who would benefit are not just HIV-negative cases, but also those with HIV who have not yet been engaged in HIV care. The latter population could arise from a variety of factors, including the rate of HIV diagnosis or gaps in linkage to ART initiation after a diagnosis has been made. In practice, the feasibility of such wide deployment of LAM tests will depend critically on the performance characteristics of the tests concerned.

Although I expect similar results to apply in other settings with a generalised HIV epidemic, this analysis does not address high-TB-burden countries where HIV is not a driving factor, such as India. The potential use of AlereLAM in such settings is an important area for further work. In these settings, I expect that the value of a future LAM test might be driven not by its ability to detect TB amongst those with HIV, but rather by its potential to be used more widely than current diagnostic tools needing laboratory capacity: for example, in primary care and in peripheral healthcare settings.

This work also does not address cost or cost-effectiveness, another important topic for future work. Recent analysis indicated that AlereLAM and FujiLAM would be cost-effective when deployed in inpatient settings in both Malawi and South Africa (475); future work, especially in the context of improved-performance tests, could benefit from incorporating a transmission framework. Relatedly, I have also not addressed the staffing and health system capacity that would be needed to facilitate the expansion of LAM testing in South Africa (476), nor the costs associated with undertaking CD4 cell count measurements. It should be noted that CD4 cell count measurement is increasingly being replaced by viral load monitoring. In addition, I have not addressed potential implementation challenges in the use of future LAM tests. For example, FujiLAM involves an additional step compared to AlereLAM; findings from ongoing trials will be valuable in determining whether this procedure reduces the performance of this technology to any appreciable extent.

Amongst additional model simplifications, I have not covered paediatric TB, an important and under-addressed part of TB burden. I have also taken a country-level perspective, despite wide subnational variation in TB/HIV burden within South Africa (477,478). For simplicity I have ignored drug resistance: despite the potential benefits of LAM tests, one notable limitation of these tests is that they cannot determine drug sensitivity. In the model calibration, I have captured temporal trends and projections in major features of the HIV epidemic in South Africa, such as HIV incidence and the proportion on ART; however, I have modelled other features as static, for example the percentage of HIV cases that are hospitalised. Further data on how this proportion has changed over time should allow the model to better capture these dynamics, potentially affecting my estimates for deaths averted amongst those being hospitalised. However, I have shown that this impact accounts for only a small proportion of overall TB burden in South Africa; I therefore do not expect these changes to affect the overall qualitative findings on the importance of widened eligibility for epidemiological impact. Finally, I assumed patients on ART do not default from treatment, which may underestimate the epidemiological impact of these interventions; individuals defaulting from ART tend to have a higher risk of mortality, and is where LAM tests may perform best.

Given the focus on epidemiological impact, the analysis of test performance is limited to test sensitivity. However, for any future LAM test that is intended for use in routine TB services, test specificity will be a critical performance characteristic, in order to minimise the number of unnecessary TB treatments incurred (408). Evidence suggests that both AlereLAM and FujiLAM may have reduced specificity at lower CD4 counts (165,449). Estimating this risk is an important area for future work: however, an important first step in this direction is to address the real uncertainties in quantifying specificity where the accuracy of the reference standard is unclear. An example of when a reference standard may be unclear includes the use of a sputum-based microbiological reference standard amongst patients with solely extrapulmonary TB and potentially also among patients with HIV, who are more likely to produce paucibacillary sputum (422,479). Although a LAM test may correctly diagnose such patients, this diagnosis would be deemed incorrect by a sputum-based microbiological reference standard. For future quantitative analysis, therefore, there is a need for more systematic estimates of specificity that take account of such shortcomings of any given reference standard. Combined use of microbiological and composite reference standards (i.e., including clinical diagnosis) may help in this regard.

4.5. Conclusion

While much of the existing literature on LAM tests addresses its diagnostic performance and implementation in defined clinical settings (159,165,166,429), this work complements this evidence basis by addressing the population level in countries with a high HIV and TB burden. To my knowledge, this is the first modelling study to examine the potential incidence and mortality impact that LAM tests may offer. In this study, I observe that even in a setting with high HIV burden, such as South Africa, future LAM tests will need to have sufficient performance to be offered more widely than HIV care, in order to have incidence-reducing impact. Future LAM tests will also need to have sufficient specificity to achieve this impact without incurring an undue burden of unnecessary TB treatment. Any emerging LAM technology meeting these criteria would be invaluable in accelerating current declines in TB burden. This work has helped inform recent WHO guidelines on the use of LAM tests (449).

Chapter 5: Results (iii)

The value and cost efficiency of private sector engagement

This chapter was conducted in collaboration with the Clinton Health Access Initiative (CHAI). CHAI implemented private sector engagement activities in various cities across India and have kindly provided me with costing data for these different activities. I led the development of the costing model in collaboration with CHAI. I also led the development of the TB transmission model and model analyses, under the supervision of N. Arinaminpathy.

The Joint Effort for Elimination of Tuberculosis ("JEET") is the largest private sector engagement initiative for TB in India. It is important to anticipate and understand how the different services offered by JEET should be expanded in the future. In this chapter, I develop a mathematical model of TB transmission in a typical urban Indian setting. I investigate the epidemiological impact of expanding four different PPSA services compared to a continuation of current levels of routine TB and JEET PPSA service coverage. I also develop a costing model for two cities with contrasting JEET coverage, Ahmedabad and Delhi, to examine which individual PPSA service and different combinations of PPSA services have the lowest incremental cost-effectiveness ratio ("ICER"). Under a limited budget, increasing the use of government supplied fixed-dose combination amongst private providers and increasing the proportion of active private providers should be prioritised, whereas services involving Xpert confirmatory testing, though impactful, have the highest ICER.

5.1. Introduction

Patients seeking care at private providers typically face long diagnostic delays and poor treatment outcomes, as private providers often use inaccurate diagnostic tests and do not usually offer treatment adherence support (480–482). Considering the dominance of the private sector in India, the government has recognised the importance of engaging private providers (483). The first public-private mix models focussed on improving the standard of TB care offered in the private sector and encouraging private providers to refer TB patients to the public sector (232). Unfortunately, these early public-private mix models had mixed impact on improving TB case notifications (232,234,484) and uptake was low amongst private providers (485). To improve the low uptake amongst private providers, interfacing agencies were developed to engage with private providers; these agencies subsidise and provide incentives to private providers if they follow the standard of care for the diagnosis and treatment of TB, as well as providing training and adherence support (237,486). Three pilot studies were launched in 2014 in two urban settings, Mumbai and Patna, and in a rural district, Mehsana (237,487). The pilot studies led to a substantial increase in TB notifications from providers (237). Retrospective analysis suggests that the cost per notified TB case from engaged private providers is comparable to public sector costs (237). A modelling study that examined the epidemiological impact of scaling up the pilot studies in Mumbai and Patna so that 75% of patient-provider interactions were captured, estimated that 21% and 16% of TB incidence could be averted, respectively, between 2018 and 2025 (239).

Building upon the success of the previous PPSA models, the Joint Effort for Elimination of Tuberculosis ("JEET") was launched by 3 partner organisations (the William J Clinton Foundation; Centre for Health, Research and Innovation; and Foundation for Innovative New Diagnostics) in 2018. It is the largest private sector engagement initiative for TB in India to date. Using patient-provider support agencies ("PPSAs"), the aim is to improve the quality of TB care in the private sector in an effective and sustainable manner. The main activities include increasing case notifications by engaging with private providers, improving the quality of TB diagnosis by providing free quality tests, and improving treatment outcomes by providing free fixed dose combination ("FDCs") and adherence support. JEET is currently running in more than 400 cities in over 17 states across India until 2021 (488). Although JEET has been operating across many major cities in India since 2018, uptake of their services, although good, could be improved. Thus, it is important to anticipate and understand which JEET PPSA services, in a given city, should be prioritised and expanded in the future.

5.2. Methods

In this work, I focus on Ahmedabad and Delhi, two urban settings where JEET is currently operating in and is looking to understand how best to expand PPSA service provisions. Ahmedabad is considered to have a high uptake of JEET PPSA services, whereas, Delhi is considered to have low uptake. To understand how best to expand the uptake of JEET service provisions in these two cities, the epidemiological impact and cost of expanding these services need to be considered. Here, I describe the model structure data sources, TB diagnosis and treatment amongst different healthcare providers, the interventions, and economic evaluation, with further details provided in appendix 3.

5.2.1. TB transmission model

Model structure

I developed a deterministic, compartmental model of TB transmission amongst adults (>15 years old) consistent with a typical urban setting in India. The model structure is shown in fig 5.1. The model captures the background level of routine TB services in India, including the scale up of the Revised National TB Control Programme ("RNTCP") between 1997 and 2007 (489), and the scale up of private sector engagement between 2017 and 2020 (483), and their maintenance until the present day. I assumed the population of each city is increasing annually by 2% (410). I also incorporated drug-resistant TB ("DR-TB"), including both rifampicin-resistant and multi-drug resistant TB, and calibrated the model so that 4% (3-5%) of incident TB case are DR-TB ((6), table 5.1 and table 5.2). For simplicity, I ignored HIV status, and distinction between pulmonary and extrapulmonary TB, although I conducted a sensitivity analysis on the latter.

I stratified the natural history of TB into the following distinct states: uninfected individuals who are susceptible to TB (U), latent TB infection (L), active TB disease (I) and recovered with either a low risk of relapse ($R^{(L)}$; individuals who have completed treatment) or a high risk of relapse ($R^{(H)}$; individuals who did not complete treatment or are self-curing). Upon infection, individuals either progress directly to active disease, also known as fast progressors, or progress to latent TB infection and have a low risk of developing active TB disease, also known as slow progressors (see table 5.1 for model parameters). An individual with active TB disease presents for diagnosis either in the public ($Dx^{(pu)}$) or private ($Dx^{(pr)}$) sector; an individual has a different probability of being correctly diagnosed with TB depending on the choice of healthcare provider (discussed in further detail below). A certain proportion of correctly diagnosed individuals will initiate TB treatment either in the public ($Tx^{(pu)}$) or private ($Tx^{(pr)}$) sector. Individuals with a missed TB diagnosis (E) will continue seeking care or recover with a high risk of relapse ($R^{(H)}$). I assumed that TB treatment in the public sector and private

sector have different rates of treatment completion, with individuals completing treatment recovering with a low risk of relapse ($R^{(L)}$), whereas those defaulting from treatment having a high risk of relapse ($R^{(H)}$).

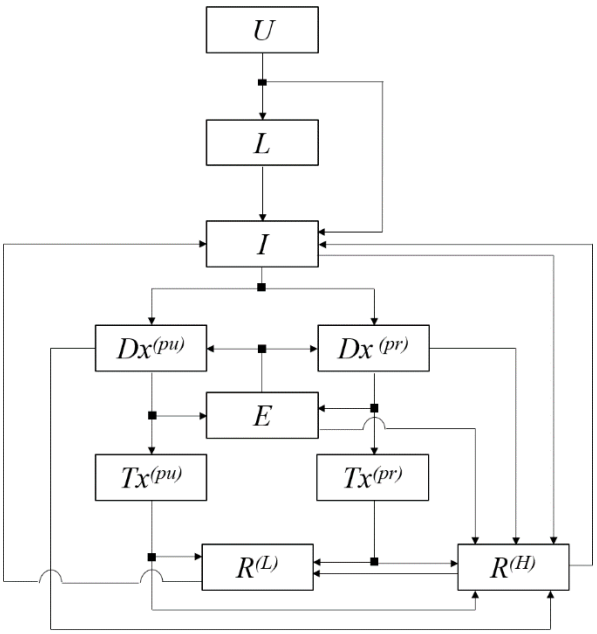

Figure 5.1. Schematic illustration of the TB transmission model structure. Model compartments are as follows: uninfected with TB (U), latent infection (L), active TB disease (I), presented for care and awaiting diagnosis (Dx), on TB treatment (Tx), temporarily dropped out of the TB care cascade due to missed diagnosis or pre-treatment loss-to-follow-up (E), and recovered with a low risk of relapse ($R^{(L)}$) or with a high risk of relapse ($R^{(H)}$). Dx and Tx are stratified by healthcare sector: private (pr) and public (pu) sector. The private sector is further subdivided into several types of providers as described in fig 5.4 and as described in section 5.2.2. Not shown for simplicity, is the acquisition and transmission of DR-TB. See appendix 3 for further technical details, including model equations and calibration.

For every true positive TB diagnosis, approximately nine uninfected individuals who present for diagnosis with symptoms of TB are also tested for TB (240,408,409,490–492). It is therefore important to count these extra TB diagnoses and the unnecessary false positive treatments. Thus, in addition to the TB symptomatic population described in fig 5.1, I separately simulated a non-TB symptomatic population (fig 5.2). From this population, the number of diagnoses and false positive treatments in both the public and private sector can be calculated. I calibrated the non-TB symptomatic model to give a 10% prevalence of TB amongst those presenting for care, in either the public or private sector (240,408,409).

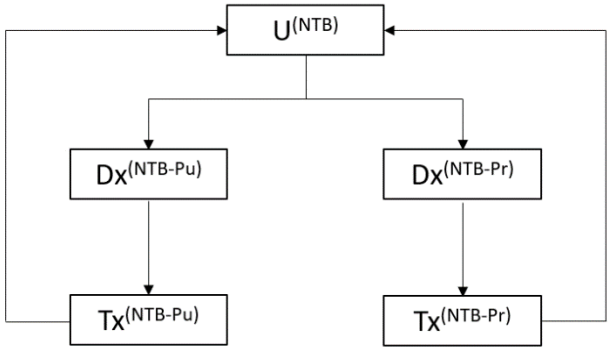

Figure 5.2. Schematic illustration of the non-infected TB-symptomatic model structure. Model compartments are as follows: uninfected with TB but TB symptomatic ($U^{(NTB)}$), presented for care and awaiting diagnosis in the public sector ($Dx^{(NTB\text{-}Pu)}$) or private sector ($Dx^{(NTB\text{-}Pr)}$), and TB treatment after a false-positive diagnosis in the public sector ($Tx^{(NTB\text{-}Pu)}$) or private sector ($Tx^{(NTB\text{-}Pr)}$). The private sector is further subdivided into several types of providers as described in fig 5.4 and as described in section 5.2.2. In order to maintain a constant population size amongst the non-infected TB-symptomatic population, I assume that upon treatment completion, individuals return to the uninfected TB-symptomatic state. The size of this population was determined so that amongst all patients presenting for care, there is a 10% prevalence of TB, in either the public or private sector (240,408,409).

Data sources

To reflect a typical urban setting in India (such as Ahmedabad and Delhi), I use the annual risk of TB infection ("ARTI") and the prevalence of TB. These data points have been estimated at a subnational level, whereas metrics such as incidence reflects national estimates; national estimates do not necessarily reflect TB epidemiology in urban settings. I assume an ARTI of 2% (1-3%), consistent with infection surveys in Chennai (390), a major city in India. I further assume a prevalence of 259 per 100,000, consistent with an urban prevalence survey of Chennai (389). I use 2019 national TB mortality data, estimated to be 32 (30-34) per 100,000 (6), to inform the rate of TB mortality. Table 5.2 summarises the data from these sources. These targets (table 5.2) were used to inform model parameters including the force of infection (β), the relative rate of transmission between DS-TB and DR-TB (d), the rate of initial care seeking for TB symptoms (δ_1) and the rate of TB mortality (μ_1). I used Adaptive Bayesian Markov chain Monte Carlo ("MCMC") to calibrate the model (391). I modelled TB prevalence and ARTI using log-normal distributions, and the proportion of TB that is DR using a beta distribution. Next, I constructed the overall likelihood function of the data (x) based on parameter set (θ), $P(x|\theta)$, as a product of the distributions over all the calibration targets (table 5.2) and multiplied this with uniform priors ($P(\theta)$; ranges specified in table 5.1). Thus, the posterior density is calculated by: $P(\theta|x) \propto P(x|\theta)P(\theta)$. By sampling from the posterior distribution using MCMC, I created an unbiased sample that approximates the posterior distribution. I refer to the uncertainty in model projections as the Bayesian credible intervals, using the 2.5th and 97.5th percentiles to reflect the lower and upper bound of an interval. I refer to the uncertainty in model

projections as the Bayesian credible intervals, using the 2.5th and 97.5th percentiles to reflect the lower and upper bound of an interval. Additional detail is provided in appendix 3.

Parameter	Symbol	Value*		Source/Notes
TB natural history				
Mean rate of transmission per TB case	β	10.42 yr^{-1} [7.28-17.24]		Model estimate
Relative rate of transmission between DS- and DR-TB	d	0.61 yr^{-1} [0.49-0.79]		Model estimate
Rate of MDR acquisition	m_a	Public sector/active providers that offer either adherence support of government supplied FDCs	0.01 [0.008-0.012]	(394)
	m_b	All private providers that are unengaged, inactive, or active that do not offer government supplied FDCs or adherence support	0.05 [0.04-0.06]	
Proportion of TB infections undergoing rapid progression	θ	0.11 [0.09-0.15]		(15,392)
Per capita hazard rate of progression to active disease from latency	ρ	0.001 yr^{-1} [0.0003-0.0024]		(342,392)
Per-capita hazard rate of relapse	r_1	Following self-cure/treatment default	0.14 yr^{-1} [0.10-0.18]	(393,394)
	r_2	Following treatment cure, >2 years	0.002 yr^{-1} [0.001-0.003]	
Stabilisation of relapse risk following treatment	ς	0.5 yr^{-1} [0.4-0.6]		(393): most relapse occurs in the first two years after treatment
Per-capita hazard rate of spontaneous cure	φ	0.17 yr^{-1} [0.13-0.21]		(344)
Per-capita hazard rate of TB mortality	μ_1	0.18 [0.13-0.25]		Model estimate
Proportion reduction in susceptibility to reinfection due to previous infection	π	0.21 [0.15-0.25]		(395)
TB services: diagnosis				
Proportion of TB cases seeking care in the public sector	η	0.50 [0.40-0.60]		(223,384,397,493)
Proportion of private providers that are engaged	e	Ahmedabad	0.50	Data provided by CHAI
		Delhi	0.73	
	$\propto$	Ahmedabad	0.39 [0.32-0.46]	

Heterogeneity index of the behaviour of engaged private providers		Delhi	0.32 [0.25-0.41]	Data provided by CHAI
Proportion of engaged private providers that are active	a	Ahmedabad	0.80	Data provided by CHAI
		Delhi	0.44	
Per-capita hazard rate of initial careseeking for TB symptoms	δ_1	1.38 yr^{-1} [0.88-2.38]		Model estimate
Per-capita hazard rate of repeat careseeking for TB symptoms (following missed diagnosis)	δ_2	12 yr^{-1} [6-26]		Assumption: corresponds to range of 2 weeks to 2 months
Proportion of TB cases diagnosed correctly, per careseeking attempt in routine public sector TB services	ε_{sn}	0.84 [0.80-0.85]		(240,398)
Specificity of diagnosis in routine public sector TB services	ε_{sp}	0.98 [0.97-0.99]		(240)
Xpert test sensitivity	x_{sn}	0.89 [0.85-0.92]		(147)
Xpert test specificity	x_{sp}	0.99 [0.98-1.00]		(147)
Proportion of active private providers that send samples for confirmatory Xpert testing 100% of the time	p_{Xpert1}	Ahmedabad	0.09	Data provided by CHAI
		Delhi	0.04	
Proportion of active private providers that never send samples for confirmatory Xpert testing	p_{Xpert0}	Ahmedabad	0.55	Data provided by CHAI
		Delhi	0.66	
Proportion of samples that are sent off for confirmatory Xpert testing amongst active private providers that occasionally send samples off for confirmatory Xpert testing	x_p	Ahmedabad	0.23	Data provided by CHAI
		Delhi	0.15	
Clinical diagnosis sensitivity (including chest X-ray)	c_{sn}	0.75 [0.65-0.80]		(398)

Clinical diagnosis specificity (including chest x-ray)	c_{sp}	0.85 [0.80-0.95]		(398)
Proportion of DR-TB cases receiving drug susceptibility testing at point of TB diagnosis	$\text{Þ}^{(pu)}$	Public sector	0.45 [0.40-0.50]	(6)
	$\text{Þ}^{(pr0)}$	Private sector (providers not using Xpert)	0	
	$\text{Þ}^{(pr1)}$	Private sector (providers using Xpert)	1.00	
TB services: treatment				
Proportion of diagnosed TB cases initiating TB treatment	ω	0.87 [0.85-0.90]		(240) Assumed that patients from active providers are referred to the public sector to initiate second line treatment.
Amongst DR-TB cases failing first-line treatment, the proportion successfully transferred to second-line treatment, public sector	p_{SL}	0.87 [0.85-0.92]		Assumption
TB treatment initiation delay	ϕ	52 yr^{-1}		Assumed: corresponds to a mean treatment delay of 1 week in routine TB care
Proportion of patients that agree to adherence support	p_{adh1}	0.92		Data provided by CHAI
Proportion of active providers that agree to adherence support	p_{adh2}	Ahmedabad	0.93	Data provided by CHAI
		Delhi	0.93	
Proportion of active providers that agree to government supplied FDCs	p_{fdc}	Ahmedabad	0.39	Data provided by CHAI
		Delhi	0.07	
Per-capita hazard rate of treatment completion	τ	First line	2 yr^{-1}	Corresponds to a duration of 6 months
	τ_{mdr}	Second line	0.5 yr^{-1}	Corresponds to a duration of 2 years
Proportion of TB cases that default from treatment	χ_{Pu}	First line, public sector	0.15 [0.13-0.17]	(6,241), data provided by CHAI
	$\chi_{\text{Pr\_Z}}$	First line, private sector: unengaged/inactive/active but no adherence support of government supplied FDCs offered	0.48 [0.45-0.55]	

	χ_{Pr_F}	First line, private sector: active (government supplied FDCs offered, no adherence support offered)	0.17 [0.16 -0.19]	
	χ_{Pr_A}	First line, private sector: active (no government supplied FDCs offered, adherence support offered)	0.21 [0.20-0.25]	
	χ_{Pr_AF}	First line, private sector: active (government supplied FDCs and adherence support offered)	0.15 [0.13-0.17]	
	χ_{mdr}	Second line	0.50 [0.45-0.60]	
Demographics				
Per-capita hazard rate of background mortality	μ_2	$0.015\ yr^{-1}$		World Bank estimates: corresponds to an average lifespan of 69 years
Per-capita rate of population growth	σ	0.02 [0.01-0.025]		(382)
Costs				
Cost per active TB disease diagnosis (passive case finding)	C_D	USD 18.30		(401)
Cost of first line treatment for active TB disease per person	C_T	USD 23.70 per treatment-month		(401)

Table 5.1. List of model parameters. *Numbers in brackets represent sampling ranges; I assume all sampling ranges are uniformly distributed in the sampling process.

Indicator	Value	Source
Annual risk of TB infection	2% [1-3]	(390)
TB prevalence	259 per 100,000 [217-299]	(389)
TB mortality	32 per 100,000 [30-34]	(6)
Percent of TB cases that are MDR	4% [3-5]	(6)

Table 5.2. Calibration targets used to estimate model parameters. I assumed the same prevalence, annual risk of TB infection, TB mortality and percent of TB cases that are MDR across Ahmedabad and Delhi.

5.2.2. TB diagnosis and treatment in India

Below, I describe the differences in TB diagnosis and treatment between the public and private sector. Specifically, I focus on the different types of private providers and how JEET improves TB diagnosis and treatment amongst these providers.

Public sector

Drawing from the literature, I estimated that half of patients seeking care for TB, seek care in the public sector (table 5.1) and that amongst those with drug-susceptible TB ("DS-TB"), 84% are correctly diagnosed as having TB (240,398) using a mix of sputum smear microscopy and Xpert testing (483). Amongst those correctly diagnosed as having TB, I assumed 87% initiate treatment (240), of which 85% complete treatment (240). Amongst individuals with DR-TB, 45% receive a drug-susceptibility test at the point of diagnosis (6), of which 87% initiate treatment and 50% complete treatment.

Private sector

The private sector in India is composed of different types of providers, ranging from qualified allopathic providers to non-allopathic providers (described in greater detail in Chapter 2). Consequently, the level of TB care received in the private sector differs widely. In each city, JEET maps and engages with private providers to improve TB notification, diagnosis and treatment outcomes.

Fig 5.3 summarises the different service provisions offered by JEET. In brief, field officers engage with private providers to encourage them to start or to continue notifying TB cases, to send sputum samples for confirmatory Xpert testing, to use government supplied FDCs and to offer adherence support. When a presumptive TB patient visits a private provider engaged by JEET, the patient is referred to a hub and sample collection centre where they are tested for TB free of charge. Hub agents at these centres are involved with the administration of TB notifications, in the collection of the samples, linking a patient with a treatment coordinator and keeping an inventory of FDC stocks. Specimen collection and transportation ("SCT") agents collect the samples from the centre and transports them to the laboratories where Xpert testing is performed. Test results are sent back to the hub centre and if positive, treatment coordinators will explain the importance of treatment adherence to the patient and monitor the patient until treatment completion. These activities can be summarised into 3 categories, discussed in further detail below: provider activation (engaging with a private provider), diagnostics (the use of Xpert) and treatment (the use of government supplied FDCs and adherence support).

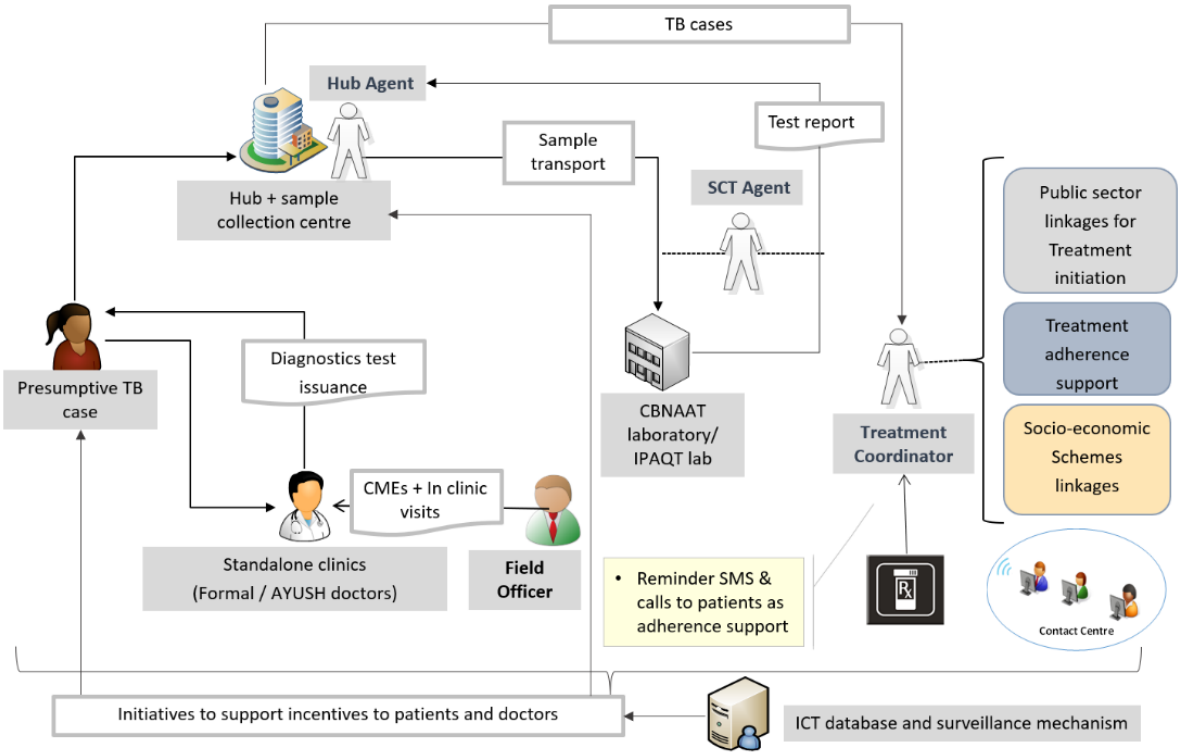

Figure 5.3. Summary of PPSA service provisions. Figure kindly provided by CHAI. A presumptive TB case (far left of diagram) seeks care at a private provider. Field officers frequently engage with private providers to encourage them to send the presumptive TB patient to a hub and sample collection centre (top left of diagram), where they can provide a sputum sample. The samples are then transported to a laboratory by SCT agents where Xpert (also known as CBNAAT) testing is performed (centre of diagram). Test results are then sent back to the hub where hub agents will then link a positive TB patient with a treatment coordinator and initiate the patient on TB treatment (FDCs, right of diagram)). Treatment coordinators ensure the patient adheres to their treatment by providing adherence support, including SMS and calls.

PPSA service provision 1: Provider activation

Private providers can be divided into 'engaged' and 'unengaged' private providers. Engaged private providers are providers that JEET have engaged with but are not yet necessarily notifying their TB cases. Unengaged private providers are providers who are yet to be engaged with by JEET. Engaged private providers can be further subdivided into active and inactive providers (fig 5.4). Active providers are providers that are engaged and are notifying TB cases, whereas, inactive providers, are engaged but not yet notifying. Table 5.4 highlights the proportion of engaged and active providers in Ahmedabad and Delhi. I define 'provider activation' as the conversion of a provider from an inactive state to an active state.

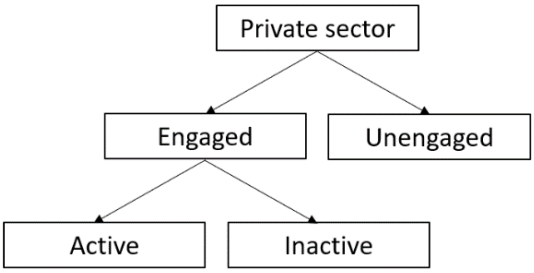

Figure 5.4. Private sector structure. Private providers are classified as either engaged or unengaged; engaged providers are those that are in contact with JEET, whereas unengaged providers are providers who are uninterested. Engaged providers can be further subdivided into active and inactive providers; active providers notify TB cases, whereas inactive providers do not.

City	Number of identified private providers	Number of engaged private providers	Number of active private providers
Ahmedabad	1899	952	762
Delhi	2780	2016	894

Table 5.3. Number of identified, engaged, and active private providers in 2019 in Ahmedabad and Delhi. I assume that all private providers have been identified.

As the transmission model follows the patient perspective of the careseeking journey, an important parameter relating to PPSA activities is the probability that a patient, when seeking care for their symptoms, visits a private provider amongst the categories listed above (active, inactive and unengaged). Furthermore, a small number of providers capture the majority of patients. Therefore, the probability that a patient visits an active provider is not necessarily the same as the proportion of providers that are active. If all the providers with the highest patient volume are already engaged, engaging the unengaged providers will have little incremental benefit. Thus, assuming homogenous behaviour will overestimate the impact of engaging more providers. I captured this heterogeneity in the model (fig 5.5, table 5.4) through a heterogeneity index (α), using data provided by CHAI from both Ahmedabad and Delhi:

$$n = p^{\alpha}$$

where p is the proportion of engaged providers responsible for n notifications. Thus, values of $\alpha < 1$ correspond with the situation where high-volume providers are preferentially engaged. For example, in Ahmedabad, 5%, 17%, and 41% of engaged providers (p = 0.05, 0.17 and 0.41) were responsible for 25%, 50% and 75% of notifications in 2019 (n = 0.25, 0.50, 0.75). This gives an average heterogeneity index of 0.39. Including this heterogenous behaviour in the model, assumes that provider recruitment works by engaging providers in decreasing order of patient volumes (i.e., the providers with the largest number of patients are engaged with first); this in fact closely reflects

reality, as JEET maps all the providers in a given city and engages first with providers who have the highest patient volumes. However, I assume that all providers, regardless of size, have similar behaviour with respect to other model parameters; in reality, larger providers may have different behaviour (i.e., be more responsive to engagement efforts) than smaller providers.

City	Heterogeneity index (α)
Ahmedabad	0.39 [0.32-0.46]
Delhi	0.32 [0.25-0.41]

Table 5.4. Heterogeneity index of private providers across Ahmedabad and Delhi. A heterogeneity index of 1 suggests that each provider sees the same number of patients (represented by the red line in fig 5.5). A smaller heterogeneity index indicates that a smaller number of providers are responsible for a larger number of patients.

Once providers are active, field officers continue to visit the providers to ensure they remain active; I refer to this activity as provider retention. Nevertheless, once active, there is an attrition rate from an active status to an inactive state. There are three main reasons behind this attrition: first of all, some providers may not have a sufficient load of TB patients every month and thus may notify infrequently depending on when they see a new TB patient; secondly, some providers, especially those that handle a smaller volume of TB patients, are seen less regularly by the field team and are therefore less likely to notify; and finally, some providers remain dissatisfied with the services offered by JEET, and therefore intentionally stop notifying patients until the field teams are able to improve their services. I capture this behaviour by weighting Xpert and FDC use by the number of months a provider was active for (discussed in further detail in the TB diagnosis and treatment sections).

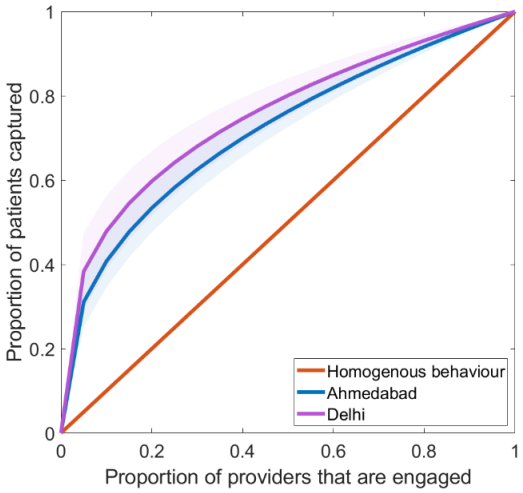

Figure 5.5. Heterogeneity in the behaviour of engaged private providers across Ahmedabad and Delhi. Homogenous behaviour (red line) assumes that private providers capture the same number of patients. Under this assumption, increasing the proportion of engaged providers, will linearly increase the proportion of patients captured. In reality, there are a few large private providers that capture most TB patients, and many smaller providers that capture few patients. The larger the area under the curve, the greater the heterogeneity. If the

providers that capture the most patients are already engaged by JEET, increasing the proportion of engaged providers further will have little incremental benefit. Therefore, assuming homogenous behaviour can overestimate the impact on TB epidemiology. Table 5.4 shows the heterogeneity index for each city.

PPSA service provision 2: TB diagnosis

Fig 5.6 shows a multimodal distribution for the uptake of Xpert amongst active private providers, including those who never use it; those who use it occasionally; and those for whom all notifications are Xpert confirmed. Most active providers do not confirm a TB notification with Xpert; in 2019, 55% and 66% of active providers in Ahmedabad and Delhi did not use Xpert confirmation. Providers who do not confirm a TB notification with Xpert instead test for TB themselves using a mix of chest x-ray and clinical judgement (240,480,483). Similarly, I assume that inactive and unengaged private providers do not use Xpert, and instead use a combination of chest x-ray and clinical judgement to diagnose TB. For the accuracy of diagnosis (test sensitivity and specificity), I drew from the literature for the performance of X-ray and clinical judgement in diagnosing TB ((147,398) (table 5.1).

Due to the shape of the distribution in fig 5.6, I divide active providers into 3 categories depending on their use of Xpert: providers that always confirm TB notifications with Xpert, providers that occasionally use Xpert, and providers that never use Xpert. I assume that providers that are classified as occasionally using Xpert use Xpert for at least 1% of their notifications but less than 100% of notifications. I calculate Xpert use amongst occasional Xpert users by finding the mean proportion of notifications that are Xpert confirmed, weighted by the number of months the providers were active for; weighted mean Xpert use was 22% and 15% in Ahmedabad and Delhi in 2019, respectively. Unweighted Xpert use (assumes that active providers were consistently active in 2019), was 34% and 25% in Ahmedabad and Delhi in 2019, respectively. Table 5.5 shows the number of active providers in each of these categories for Ahmedabad and Delhi in 2019. Once active providers become an Xpert user, field officers continue visits to encourage these providers to continue confirming TB notifications with Xpert.

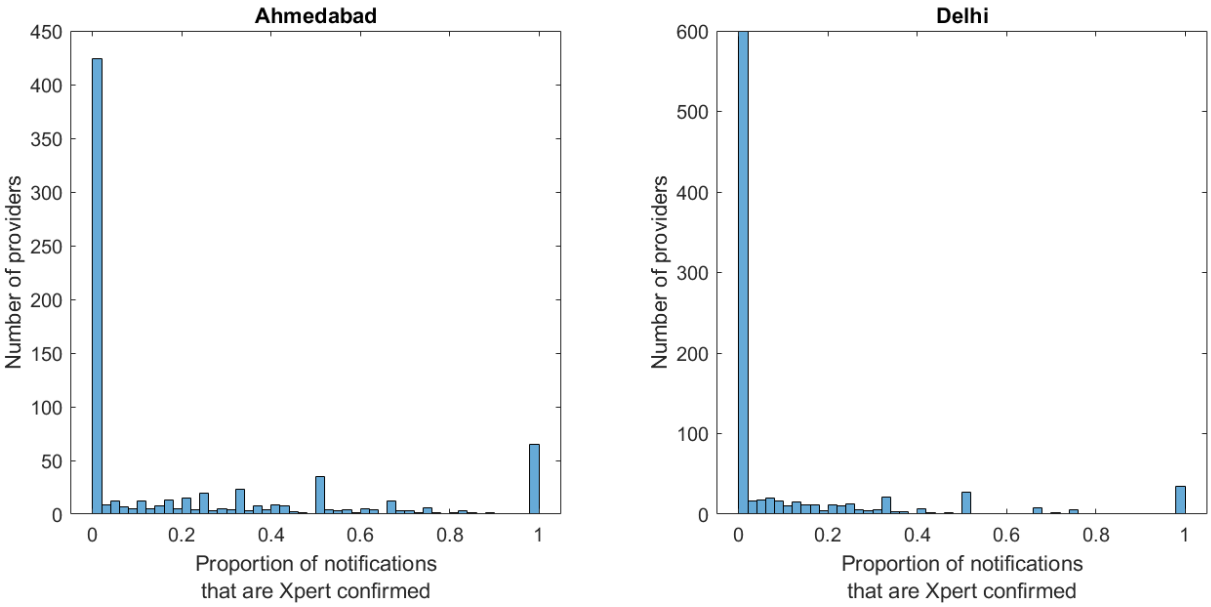

Figure 5.6. Xpert use amongst active private providers in Ahmedabad and Delhi in 2019. From this data, I classified active providers into thee categories: those that always use Xpert, those that use Xpert occasionally, and those that never use Xpert. To be classified as occasionally using Xpert, I assume that providers need to use Xpert for at least 1% of notifications and less than 100% of notifications.

	City	
	Ahmedabad	*Delhi*
Total no. of active providers	762	894
No. of active providers that always use Xpert	65	35
No. of active providers that occasionally use Xpert	278	265
No. of active providers that never use Xpert	419	594
Percent of notifications that are Xpert confirmed by occasional users, weighted	22%	15%
Percent of notifications that are Xpert confirmed by occasional users, unweighted	34%	25%

Table 5.5. Xpert use amongst active providers in Ahmedabad and Delhi in 2019. To be classified as occasionally using Xpert, I assume that providers use Xpert for at least 1% of notifications and less than 100% of notifications. The weighted percent of notifications that are Xpert confirmed takes into account the fact that active providers switch between an inactive and active state and is a product of the unweighted percent and the percent of months providers were active for.

PPSA service provision 3: TB treatment

JEET offer two different services for TB treatment via treatment coordinators: government supplied FDCs and adherence support. Government supplied FDCs are supplied for free to the patient by the government, whereas patients on adherence support receive regular text messages and calls to ensure treatment adherence (fig 5.3). Over 95% of active providers agree for JEET to offer adherence support to their TB patients, and similarly, 92% of patients agree to adherence support (table 5.6). The number of active providers that agree to government supplied FDCs in 2019 was much more variable across Ahmedabad and Delhi. Out of the 762 active providers in Ahmedabad, 529 agreed to use FDCs (69%), compared to only 242 out of the 894 active providers in Delhi (27%). However, although 69% and 27% of active providers in Ahmedabad and Delhi, respectively, agreed to government supplied

FDCs in 2019, only 39% and 7% of active providers were using them consistently, if FDC use was weighted by the number of months active providers were active for. The percent of active providers that consistently used government supplied FDCs increased to 45% and 10% in Ahmedabad and Delhi, respectively, if unweighted. Again, field officers visit these regularly to ensure providers are continuing to recommend government supplied FDCs and adherence support.

Based on the evidence discussed above, I consider 4 categories of active providers in the model: active providers that use government supplied FDCs and offer adherence support, those that use government supplied FDCs but do not offer adherence support, those that offer adherence support but do not use government supplied FDCs, and those that offer neither service. I drew from data provided by CHAI to inform treatment completion rates associated with each of these categories; active providers offering both services having the highest rate of treatment completion and those offering neither having the lowest rate (table 5.1). Finally, I assume that inactive and unengaged providers do not offer adherence support and thus patients seeking treatment from these providers have the poorest treatment completion rates.

All patients correctly diagnosed with DR-TB by a private provider are transferred to the public sector and initiated onto second line treatment.

	City	
	Ahmedabad	*Delhi*
Total no. of active providers	762	894
No. of active providers that offer adherence support	712	835
Percent of patients that agree to adherence support	92%	92%
No. of active providers that agree to government supplied FDCs	529	242
Percent of active providers that consistently use FDCs, unweighted	45%	10%
Percent of active providers that consistently use FDCs, weighted	39%	7%

Table 5.6. Number of active providers that offer government supplied FDCs and adherence support in Ahmedabad and Delhi in 2019. The weighted percent of active providers that consistently use FDCs considers the fact that active providers switch between an inactive and active state and is a product of the unweighted percent and the percent of months providers were active for.

5.2.3. Interventions

Fig 5.7 summarises the uptake of the various PPSA service provisions in 2019 across Ahmedabad and Delhi. I focus on the impact of increasing four of these provisions on the TB epidemic:

- *Intervention 1:* Increase the number of active providers. I refer to this as ‘provider activation’.
- *Intervention 2:* Increase Xpert use amongst occasional Xpert users
- *Intervention 3:* Encourage active providers that never use Xpert into occasionally using Xpert
- *Intervention 4:* Increase the use of government supplied FDCs amongst active providers.

Some providers will remain uninterested in taking up the interventions despite engagement efforts by field officers. After discussions with CHAI, we agreed on the following assumptions: 0% of inactive providers and 0% of occasional Xpert users are uninterested in notifying and increasing their Xpert use, respectively, whereas 42% of non-Xpert users are uninterested in using Xpert, and 35% of non-government supplied FDC users are uninterested in using government supplied FDCs. Thus, I considered two coverage levels: feasible maximum and theoretical maximum. The former accounts for the fact that some providers remain uninterested despite repeated engagement efforts (i.e., 42% of non-Xpert and 35% of non-FDC users remain resistant towards Xpert and FDCs, respectively), whereas the latter assumes that all providers take up the interventions. For further detail, see fig A3.1. For both cities, I examined the epidemiological impact increasing the four activities to their feasible and theoretical maximum has on the TB epidemic (fig A3.1), compared to an indefinite continuation of current levels of routine TB and PPSA services. I modelled existing PPSA activities from 2017 to current levels in 2020. I assumed the interventions are scaled up linearly between 2020 and 2021, and I run the model until 2035.

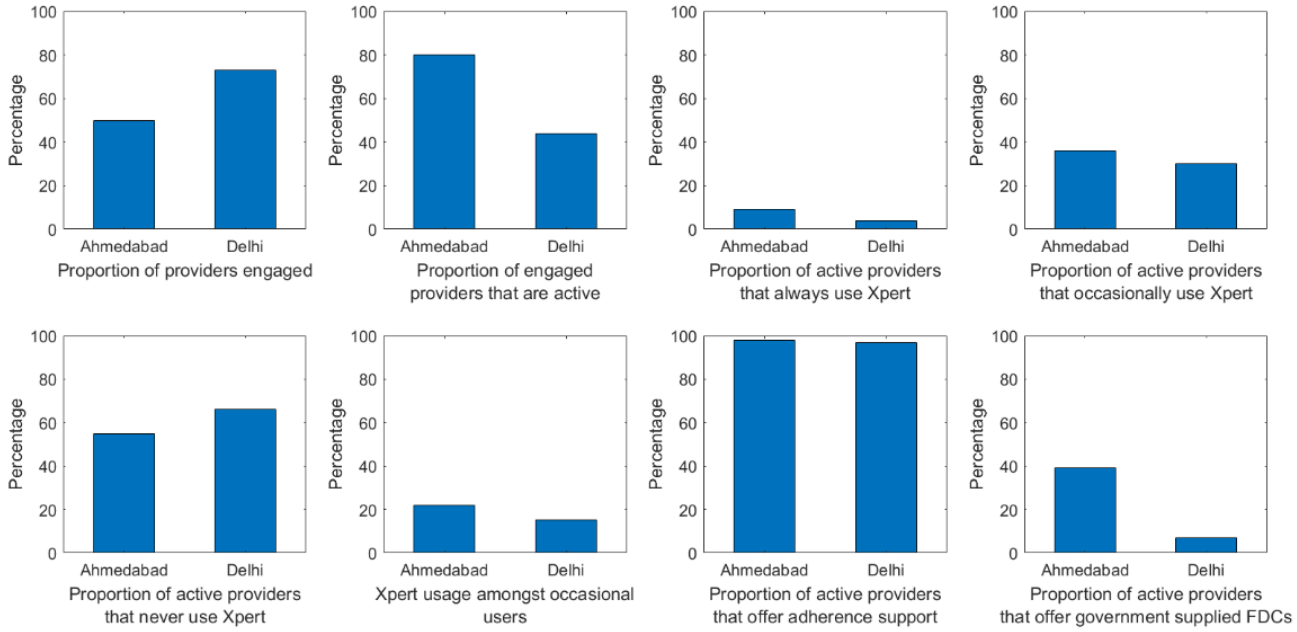

Figure 5.7. Summary of 2019 PPSA service provisions in Ahmedabad and Delhi in 2019

5.2.4. Economic evaluation

I actively collaborated with PPSA-implementing teams from CHAI who reconstructed spending data from 2019 for Ahmedabad and Delhi. Table 5.7 summarises the total cost in 2019 for the different activities involved in the service provisions offered by JEET. These activities include the salaries of field officer, treatment coordinators, hub agents, and SCT agents; the cost of continuing medical education ("CMEs"; seminars organised for providers to increase engagement); the cost of promotional materials which includes the cost of designing, printing and dissemination; sputum sample logistics which is the cost of transporting sputum samples to the laboratories, and includes the cost of procuring falcon tubes, carrier boxes, masks and hand sanitizer; the cost of Xpert tests, including the cost of test cartridges and manpower; and the cost of government supplied FDCs. I ignore any fixed costs (office expenditure and state programme management costs), as these costs remain unaffected by an increase in the coverage of the PPSA service provisions investigated in this work.

Cost item	**Total cost in 2019 (USD)**	
	Ahmedabad	Delhi
Field officer salary	31,433	55,936
Hub agent salary	113,808	281,373
SCT agent salary	2055	5287
Treatment coordinator salary	8569	13,445
CMEs	460	6095
Promotional material	10	10
Sputum sample logistics	2020	5090
Xpert tests	83,886	98,088
FDCs**	N/A	

Table 5.7. Total costs of PPSA activities in Ahmedabad and Delhi in 2019. I assume a conversion rate of USD 1 = 73 INR. *I assume a fix cost per FDC of 45 USD.

To estimate the cost of increasing the coverage of the different interventions, I categorised each cost item listed into table 5.7 into 6 different categories. These 6 different categories are provider activation, provider retention, diagnostic engagement, diagnostic logistics, treatment engagement and treatment logistics, and are described in greater detail in table 5.8. If a cost was associated with more than one category, the cost was subdivided across the relevant categories based on estimations from CHAI on the percentage of time spent on each category (table 5.9). For example, in Ahmedabad the total cost of field officers was split in the following way: 10% for provider activation, 42% for provider retention, 24% for Xpert engagement and 24% for FDC engagement.

Category	Description
Provider activation	Costs associated with the engagement of inactive providers to encourage them to become active and start notifying their TB cases
Provider retention	Costs associated with the engagement of active providers to encourage them to remain active and keep notifying their TB cases
Diagnostic engagement	Costs associated with encouraging active providers to start using Xpert, to increase their use of Xpert and maintain their use of Xpert
Diagnostic logistics	All other costs associated with Xpert testing that are not to do with engagement. Includes cost of transporting sputum samples, cost of staff and cost of the Xpert tests.
Treatment engagement	Costs associated with encouraging active providers to start using, increase or maintain their use of government supplied FDCs and adherence support.
Treatment logistics	Cost of government supplied FDCs and adherence support

Table 5.8. Costing categories. I categorise each cost item into one of the categories listed in this table to help identify the cost items that will increase as the coverage of the different interventions increase.

Ahmedabad						
Cost item	**Cost category**					
	Provider activation	Provider retention	Diagnostic engagement	Diagnostic logistics	Treatment engagement	Treatment logistics
Field officer	10%	42%	24%	-	24%	-
Hub agent	-	51%	-	24%	-	25%
SCT agent	-	-	-	100%	-	-
Treatment coordinator	-	-	-	-	-	100%
CMEs	-	40%	30%	-	30%	-
Promotional material	-	52%	29%	-	19%	-
Sputum sample logistics	-	-	-	100%	-	-
Xpert tests	-	-	-	100%	-	-
FDCs	-	-	-	-	-	100%
Delhi						
Cost item	**Cost category**					
	Provider activation	Provider retention	Diagnostic engagement	Diagnostic logistics	Treatment engagement	Treatment logistics
Field officer	13%	28%	32%	-	27%	-
Hub agent	-	74%	-	18%	-	8%
SCT agent	-	-	-	100%	-	-
Treatment coordinator	-	-	-	-	-	100%
CMEs	-	40%	30%	-	30%	-
Promotional material	-	52%	29%	-	19%	-
Sputum sample logistics	-	-	-	100%	-	-
Xpert tests	-	-	-	100%	-	-
FDCs	-	-	-	-	-	100%

Table 5.9. Costing split across PPSA activities for Ahmedabad and Delhi in 2019. The field officer split was determined by the percentage of calls that were made by a field officer for provider activation, provider retention, diagnostic engagement and treatment engagement; similarly, the hub agent split was determined by the proportion of time hub agents estimated they had spent on provider retention, diagnostic logistics and treatment logistics; the CMEs and promotional materials splits were determined by the amount of engagement that was aimed at provider retention, diagnostic engagement and treatment engagement, which was assumed constant across all cities. Each row adds up to 100%.

Next, to calculate the costs of the interventions, I calculated the per unit cost of each cost item. The units used are described in table 5.10 and 5.11 for Delhi and Ahmedabad, respectively. For example, to calculate the cost of field officers to retain one provider, I multiplied the total cost of field officers in 2019 (i.e., USD 31,433 in Ahmedabad), by the percentage of time spent by field officers on provider retention in 2019 (42%), divided by the number of active providers in 2019 (762 active providers); this averages to a field officer cost of USD17.77 to retain one provider per year.

PPSA activity: Provider activation					
Cost item	**Total cost**	**Category split**	**Unit description**	**No. of units**	**Cost per unit (USD)**
Field officer	55,936	13%	No. of visits in 2019 made to onboard an inactive provider	2984	2.50
PPSA activity: Provider retention					
Field officer	55,936	28%	No. of active providers in 2019	894	17.97
Hub agent	281,373	74%	No. of active providers in 2019	894	238.88
CMEs	6095	40%	No. of providers that attended CMEs in 2019	1469	1.70
Promotional material	10	52%	No. of active providers in 2019	894	0.006
PPSA activity: Diagnostic engagement					
Field officer	55,936	32%	No. of visits in 2019 made to active providers to increase Xpert usage	7219	2.54
			No. of active providers in 2019	894	20.54
CMEs	6095	30%	No. of providers that attended CMEs in 2019	1469	1.28
Promotional material	10	29%	No. of active providers in 2019	894	0.003
PPSA activity: Diagnostic logistics					
Hub agent	281,373	18%	No. of Xpert tests performed in 2019	4227	12.29
SCT agent	5287	100%	No. of Xpert tests performed in 2019	4227	1.28
Sputum sample logistics	5090	100%	No. of Xpert tests performed in 2019	4227	1.23
Xpert tests	98,088	100%	No. of Xpert tests performed in 2019	4227	23.80
PPSA activity: Treatment engagement					
Field officer	55,936	27%	No. of visits in 2019 made to active providers to use FDCs	5863	2.64
			No. of active providers in 2019	894	17.33
CMEs	6095	30%	No. of providers that attended CMEs in 2019	1469	1.28
Promotional material	10	19%	No. of active providers in 2019	894	0.002
PPSA activity: Treatment logistics					
Treatment coordinator	13,445	100%	No. of patient treatment months in 2019	108,915	0.13
Hub agent	281,373	8%	No. of FDC initiations in 2019	1480	13.65
FDCs	-	-	-	-	45

Table 5.10. Unit costs for Delhi.

PPSA activity: Provider activation					
Cost item	**Total cost**	**Category split**	**Unit description**	**No. of units**	**Cost per unit (USD)**
Field officer	31,433	10%	No. of visits in 2019 made to onboard an inactive provider	1548	2.08
PPSA activity: Provider retention					
Field officer	31,433	42%	No. of active providers in 2019	762	17.77
Hub agent	113,808	51%	No. of active providers in 2019	762	78.12
CMEs	460	40%	No. of providers that attended CMEs in 2019	51	3.70
Promotional material	10	52%	No. of active providers in 2019	762	0.007
PPSA activity: Diagnostic engagement					
Field officer	31,433	24%	No. of visits in 2019 made to active providers to increase Xpert usage	3572	2.17
			No. of active providers in 2019	762	10.15
CMEs	460	30%	No. of providers that attended CMEs in 2019	51	2.78
Promotional material	10	29%	No. of active providers in 2019	762	0.004
PPSA activity: Diagnostic logistics					
Hub agent	113,808	24%	No. of Xpert tests performed in 2019	3615	7.75
SCT agent	2055	100%	No. of Xpert tests performed in 2019	3615	0.58
Sputum sample logistics	2020	100%	No. of Xpert tests performed in 2019	3615	0.57
Xpert tests	83,886	100%	No. of Xpert tests performed in 2019	3615	23.80
PPSA activity: Treatment engagement					
Field officer	31,433	24%	No. of visits in 2019 made to active providers to use FDCs	3619	2.14
			No. of active providers in 2019	762	10.15
CMEs	460	30%	No. of providers that attended CMEs in 2019	51	2.78
Promotional material	10	19%	No. of active providers in 2019	762	0.003
PPSA activity: Treatment logistics					
Treatment coordinator	8569	100%	No. of patient treatment months in 2019	57,868	0.15
Hub agent	113,808	25%	No. of FDC initiations in 2019	3445	8.47
FDCs	-	-	-	-	45

Table 5.11. Unit costs for Ahmedabad

To increase the coverage of the intervention activities, I assumed a certain level of effort is needed to engage and convert the providers. This engagement is achieved through field officer visits. After discussions with CHAI, we agreed on the level of effort needed, and assumptions are presented in table 5.12. I also included the cost of visits that are wasted due to visiting uninterested providers.

PPSA activity	Effort needed
Provider activation	5 (4-7) visits needed to onboard an inactive provider
Increasing Xpert usage amongst occasional users	One visit increases a provider's Xpert use by 0.2%. Assumed the same across all cities.
Converting non-Xpert users to occasionally use Xpert	7 (5-8) visits needed to convert a non-Xpert user. Assumed the same across all cities
Converting non-FDC users to use FDC	6 (4-7) visits needed to convert a non-FDC user. Assumed the same across all cities.

Table 5.12. Engagement effort needed for each PPSA service provision in Ahmedabad and Delhi in 2019. As described in the text, values shown in these tables are essentially expert opinion, elicited through in-dept discussion with implementing teams from CHAI.

Finally, I also considered costs of routine TB services in the public sector, including the cost of diagnosis and the cost of treating DS- and DR-TB (table 5.1).

I calculated the incremental cost-effectiveness ratio ("ICER") by dividing the incremental cost of increasing the coverage of PPSA services by the number of TB cases averted between 2020 and 2035, relative to a baseline of indefinite continuation of current levels of routine TB and JEET PPSA services (i.e., comparing the interventions to a 'no intervention' status quo, whilst ignoring other interventions). Although, for optimal decision-making, an ICER should compare a strategy to the next-least expensive non-dominated strategy, the aim of this analysis was not to conduct a full cost-effectiveness analysis, but to estimate and compare the cost of scaling up the different PPSA services, and to calculate which service has the highest potential epidemiological impact for a given cost.

5.2.5. Sensitivity analyses

I conducted various sensitivity analyses to explore the impact of certain model assumptions on model results. Firstly, I considered an optimistic PPSA scale-up baseline that assumes active providers are consistently active, and so, Xpert and FDC use is not weighted by the number of months providers are active for. Thus, Xpert use under a current PPSA baseline increases from 22% to 34% and from 15% to 25% for Ahmedabad and Delhi, respectively; FDC use increases from 39% to 45% and from 7% to 10% for Ahmedabad and Delhi, respectively.

Under intervention 1, I assumed that newly active providers adopt the average behaviour of pre-existing active providers. A newly active provider suggests that they were unresponsive to previous engagement efforts, and thus may have worse behaviour than pre-existing active providers. I varied this assumption, by assuming that newly active providers have behaviour that is 25% and 50% worse than pre-existing active providers. For instance, using Ahmedabad as an example, 9% of pre-existing active providers use Xpert 100% of the time, and 36% use Xpert for on average 22% of TB diagnoses.

Assuming newly active providers have behaviour that is 25% and 50% worse, decreases the percentage of newly active providers that use Xpert 100% of the time decreases to 7% and 5% respectively; the percentage of newly active providers that use Xpert occasionally decreases to 27% and 18%, respectively, and Xpert use amongst these occasional users decreases to 17% and 11% from 22% and 15%, respectively.

I do not differentiate between extrapulmonary and pulmonary TB in the model; however, Xpert sensitivity is reduced amongst TB patients with extrapulmonary TB, thus high levels of extrapulmonary TB reduces the incremental benefit of Xpert testing. In certain Indian urban settings, CHAI field teams estimate as many as 50% of diagnosed TB cases are extrapulmonary TB. Thus, I reduced the proportion of TB patients presenting to care that are correctly diagnosed, assuming 50% of patients that present to care have extrapulmonary TB.

I also examined the impact varying maintenance costs by +/- 20% has on the ICER of the different interventions. I defined maintenance costs as costs that are associated with maintaining good behaviour amongst active providers (maintaining notifications, FDC use and Xpert use).
Finally, I conducted multivariate sensitivity analysis using partial rank correlation coefficient to assess which model parameters model outputs are most sensitive towards.

5.3. Results

5.3.1. Model calibration

Fig 5.8 shows results of model calibration, displaying the model fit against each of the calibration targets listed in table 5.2. Fig 5.9 shows MCMC diagnostic checks, including the posterior density trace and autocorrelation plots for selected parameters.

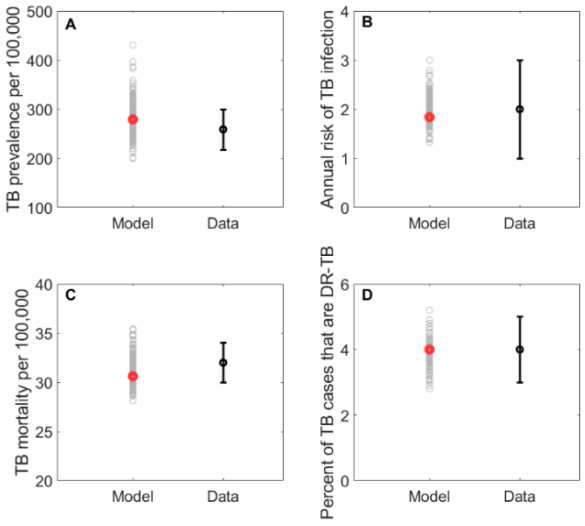

Figure 5.8. Model fits to data. Panel A – TB prevalence per 100,000 in a typical urban Indian setting. To calculate TB prevalence, I calculated the prevalence of TB amongst those with active TB disease and those on TB treatment; B – Annual risk of TB infection in a typical urban Indian setting; C – TB deaths per 100,000 in 2019, India; D – Percent of TB cases that are drug-resistant TB in 2019. Grey - model runs; red - mean of model runs; black - data points are described in table 5.2**.**

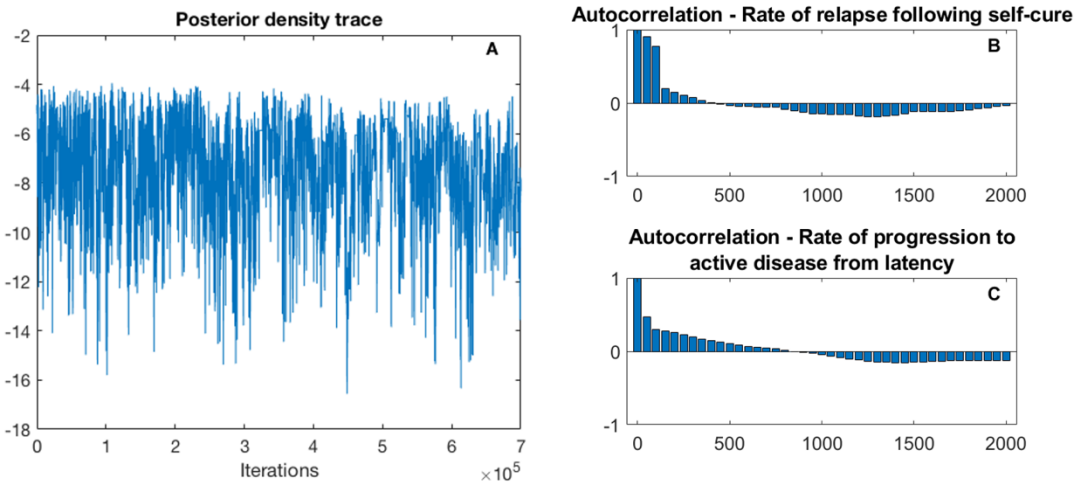

Figure 5.9. MCMC diagnostics. Panel A shows the posterior density trace, excluding the 'burn-in' period. Panel B and C show autocorrelation plots for two selected parameters (rate of relapse following self-cure and the rate of progression to active disease from latency).

5.3.2. Epidemiological impact

Fig 5.10-11 and table 5.13 show model projections for the impact on TB incidence between 2017 and 2035 in Ahmedabad and Delhi across varying PPSA coverage. Compared to a baseline where current routine TB services and PPSA coverage is maintained until 2035, increasing the four PPSA activities simultaneously to their feasible maximum coverage would avert 5.08% (95% CrI 4.44-6.23%) of cumulative TB cases, whereas increasing them to their theoretical maximum would avert 7.44% (95% CrI 6.15-9.21%) of cumulative TB cases between 2020 and 2035 in Ahmedabad. In Delhi, 5.41% (95% CrI 4.42-6.94%) and 6.72% (95% CrI 5.30-8.91%) of cumulative TB cases would be averted assuming a feasible and theoretical maximum coverage, respectively. A similar impact was seen on cumulative TB deaths averted. Focusing on DR-TB, a larger impact was seen on DR-TB cases and deaths averted as three of the four PPSA activities involved increasing the use of Xpert and thus increasing the likelihood of detecting rifampicin-resistance. For example, assuming PPSA activities are increased to their theoretical maximum coverage 13.94% (95% CrI 11.10-16.39%) and 34.63% (95% CrI 29.62-39.38%) of cumulative DR-TB cases and deaths would be averted between 2020 and 2035, respectively, compared to a baseline of current PPSA levels. This impact increased to 18.06% (95% CrI 14.97-21.91%) and 41.32% (95% CrI 35.18-46.78%) DR-TB cases and deaths averted in Delhi, respectively, due to the lower levels of Xpert at baseline in Delhi compared to Ahmedabad.

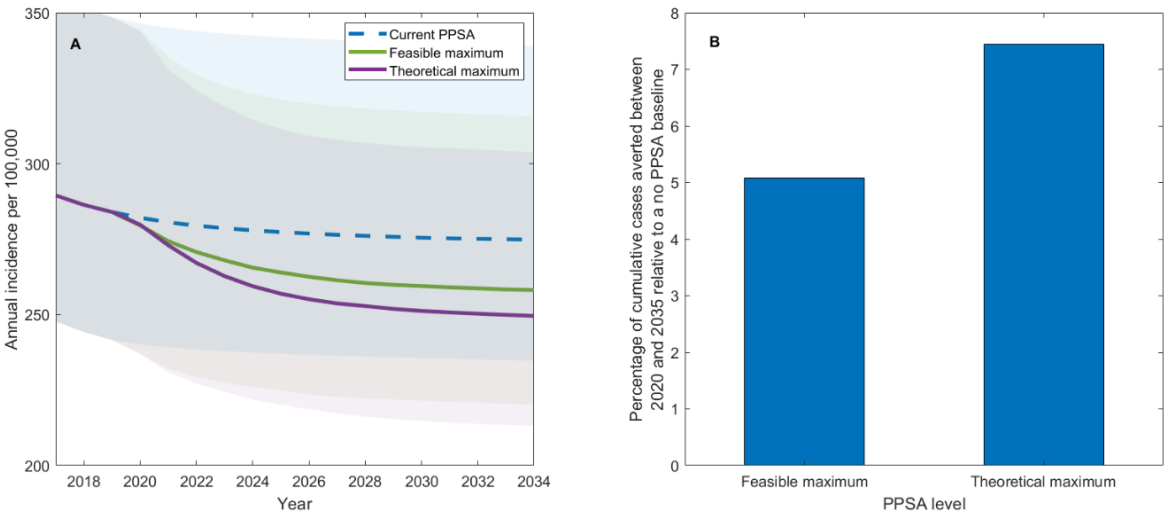

Figure 5.10. Model projections for the impact of increasing all PPSA service provisions to their feasible or theoretical maximum has on TB incidence in Ahmedabad between 2020 and 2035. Panel A shows the projected trajectory of TB incidence, assuming current PPSA scale up between 2017 and 2020, and its maintenance indefinitely (blue-dashed line), assuming that PPSA service provisions are increased to their feasible or theoretical maximum from 2020 to 2021 and maintained indefinitely (green and purple line, respectively). Shaded areas show 95% credible intervals. Panel B shows the percentage of cumulative cases averted between 2020 and 2035 by increasing PPSA to its feasible and theoretical maximum, compared to a baseline of current PPSA scale-up.

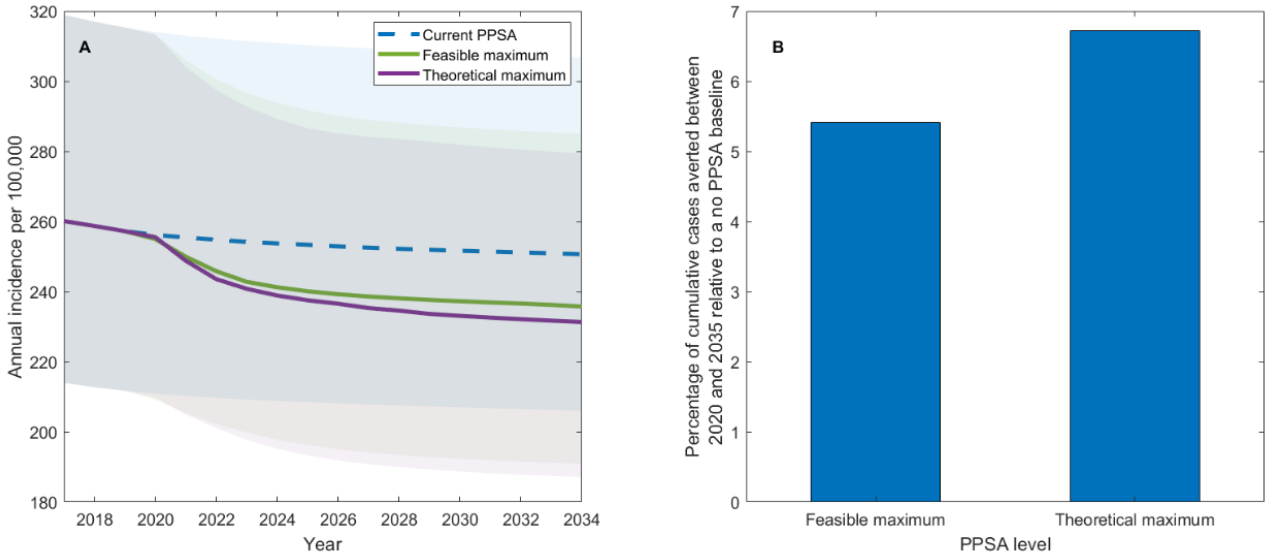

Figure 5.11. Model projections for the impact of increasing all PPSA service provisions to their feasible or theoretical maximum has on TB incidence in Delhi between 2020 and 2035. Panel A shows the projected trajectory of TB incidence, assuming current PPSA scale up between 2017 and 2020, and its maintenance indefinitely (blue-dashed line) and assuming that PPSA service provisions are increased to their feasible or theoretical maximum from 2020 to 2021 and maintained indefinitely (green and purple line, respectively). Shaded areas show 95% credible intervals. Panel B shows the percentage of cumulative cases averted between 2020 and 2035 by increasing PPSA to its feasible and theoretical maximum, compared to a baseline of current PPSA scale-up.

	Ahmedabad	Delhi
Feasible maximum		
% of cumulative TB cases averted, 2020-2035	5.08% (4.44-6.23)	5.41% (4.42-6.94)
% of cumulative TB deaths averted, 2020-2035	4.09% (2.84-5.76)	6.35% (4.88-8.18)
% of cumulative DR-TB cases averted, 2020-2035	8.03% (6.23-9.67)	13.96% (11.36-17.15)
% of cumulative DR-TB deaths averted, 2020-2035	20.72% (17.69-24.11)	32.13% (27.16-36.81)
Theoretical maximum		
% of cumulative TB cases averted, 2020-2035	7.44% (6.15-9.21)	6.72% (5.30-8.91)
% of cumulative TB deaths averted, 2020-2035	7.89% (5.65-10.63)	8.74% (6.75-11.26)
% of cumulative DR-TB cases averted, 2020-2035	13.94% (11.10-16.39)	18.06% (14.97-21.91)
% of cumulative DR-TB deaths averted, 2020-2035	34.63% (29.62-39.38)	41.32% (35.18-46.78)

Table 5.13. Projected epidemiological impact. Impact is measured as the cumulative impact on TB cases and deaths in Ahmedabad and Delhi between 2020 and 2035 relative to a baseline of current PPSA scale up.

5.3.3. Economic evaluation

I examined which combination of interventions had the lowest ICER assuming the interventions were scaled up to their feasible maximum. A full breakdown of the different cost components for each intervention is provided in fig A3.6. In Ahmedabad (fig 5.12, table A3.3), the individual intervention with the lowest ICER was increasing the proportion of active providers averting 3.00% (95% CrI 2.59-3.37%) of cumulative TB cases between 2020 and 2035 relative to a current PPSA baseline, for an incremental cost of USD 2.3 million (95% CrI 1.5 -3.7 million). On the other hand, in Delhi (fig

5.13, table A3.4), the individual intervention with the lowest ICER was increasing the proportion of FDC users, averting 1.13% (95% CrI 0.97-1.34%) of cumulative TB cases between 2020 and 2035 for an incremental cost of USD 4.5 million (95% CrI USD 3.3-5.9 million).

Next, I examined which intervention, in combination with the most cost-efficient individual intervention had the lowest ICER. In Ahmedabad, the intervention with the lowest ICER in combination with increasing the proportion of active providers, was increasing the proportion of FDC users; together, these two interventions averted 3.46% (95% CrI 2.96-3.91%) of cumulative TB cases between 2020 and 2035 relative to a current PPSA baseline at an incremental cost of USD 5.2 million (95% CrI 3.8 -8.2 million). On the other hand, in Delhi, the intervention with the lowest ICER in combination with increasing the proportion of FDC users, was increasing the proportion of occasional Xpert users, averting 3.80% (95% CrI 2.92-5.06%) of cumulative TB cases between 2020 and 2035 for an incremental cost of USD 31 million (95% CrI 22-47 million).

Out of the two remaining interventions, increasing the proportion of occasional Xpert users had the lowest ICER when combined with increasing the proportion of active providers and FDC users in Ahmedabad. A combination of the three interventions averted 3.67% (95% CrI 3.18-4.16%) of TB cumulative cases between 2020 and 2035 at an incremental cost of USD 7.2 million (95% CrI 5.7 million-10 million). In Delhi, this was increasing the proportion of active providers, with a combination of the three interventions averting 3.95% (95% CrI 3.05-5.22%) of TB cumulative cases between 2020 and 2035 at an incremental cost of USD 42 million (95% CrI USD 30-60 million).

Finally, combining all four interventions and assuming they were scaled up to their feasible maximum, 5.08% (95% CrI 4.44-6.23) of cumulative TB cases were averted between 2020 and 2035 compared to a current PPSA baseline for an incremental cost of USD 28 million (95% CrI 21 -41 million) in Ahmedabad. On the other hand, in Delhi, a combination of the four interventions averted 5.41% (95% CrI 4.42-6.94) of TB cumulative cases for an incremental cost of USD 157 million (95% CrI 101 -213 million).

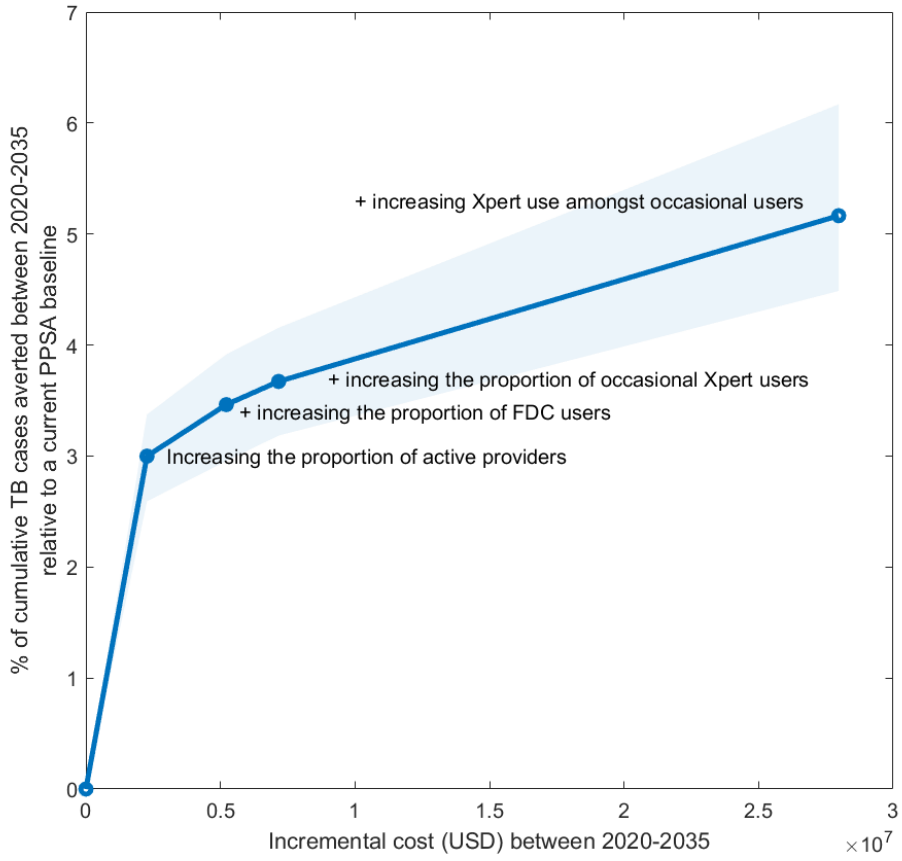

Figure 5.12. Cost-efficiency of PPSA service provisions in Ahmedabad. The first point on the graph represents the PPSA service provision (increasing the proportion of active providers) that had the lowest ICER on its own when scaled-up to its feasible maximum coverage; the second point represents which additional PPSA service provision (increasing the proportion of FDC users), in combination with the first point, had the lowest ICER; the third point represents, which additional PPSA service provision (increasing the proportion of occasional Xpert users) in addition to the first two services had the lowest ICER; and finally, the fourth point represents the incremental cost and epidemiological impact of increasing all four PPSA service provisions simultaneously to their feasible maximum. Shaded area shows the 95% credible interval. See table A4 for further details.

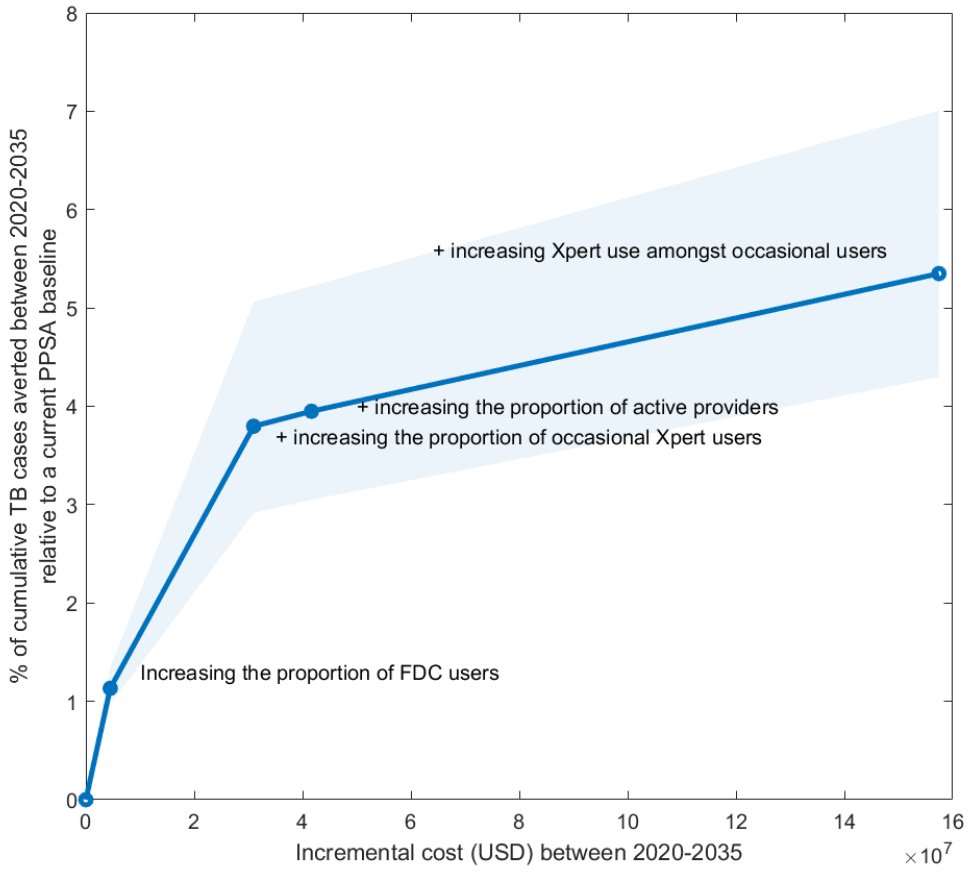

Figure 5.13. Cost-efficiency of PPSA service provisions in Delhi. The first point on the graph represents the PPSA service provision (increasing the proportion of FDC users) that had the lowest ICER on its own when scaled-up to its feasible maximum coverage; the second point represents which additional PPSA service provision (increasing the proportion of occasional Xpert users), in combination with the first point, had the lowest ICER; the third point represents, which additional PPSA service provision (increasing the proportion of active providers) in addition to the first two services, had the lowest ICER; and finally, the fourth point represents the incremental cost and epidemiological impact of increasing all four PPSA service provisions simultaneously to their feasible maximum. Shaded area shows the 95% credible interval. See table A5 for further details.

5.3.4. Sensitivity analysis

I conducted sensitivity analyses to analyse model assumptions. The first assumption I examined was whether active providers remain consistently active; in the main analysis I weighted Xpert and FDC use by the number of months active providers were active for. Unweighting Xpert and FDC use, which effectively assumes that active providers were constantly active, and assuming PPSA coverage was consistent with current coverage until 2035, averted 2.07% (95% CrI 1.68-2.51%) and 0.80% (95% CrI 0.53-1.07%) of cumulative TB cases relative to the weighted current coverage baseline in Ahmedabad and Delhi, respectively (fig A3.2 and fig A3.3, respectively). However, in terms of cost-efficiency, the combinations of the different PPSA activities that had the lowest ICER, presented in fig 5.12 and fig 5.13, remain unchanged.

The next model assumption I analysed was the proportion of TB patients with pulmonary TB versus extrapulmonary TB (fig A3.2 and fig A3.3). In the main analysis, I considered only pulmonary TB. Instead, assuming 50% of patients that present for TB care have pulmonary TB, 3.75% (95% CrI 2.49-4.90) of cumulative TB cases are averted between 2020 and 2035 relative to a current PPSA baseline in Ahmedabad, if all four interventions are increased to their feasible maximum coverage; this is a 1.33% decrease compared to when I assumed all patients have pulmonary TB (fig A3.2). In Delhi, a similar difference in impact was seen, with the percentage of cumulative TB cases averted falling to 4.28% (95% CrI 2.96-5.77%) from 5.41% (fig A3.3). Again, in terms of cost-efficiency, the combinations of the different PPSA activities that had the lowest ICER, presented in fig 5.12 and fig 5.13, remain unchanged.

Next, I conducted sensitivity analyses on assumptions that may affect the ICERs for each intervention. The first assumption I examined was the behaviour of newly active providers (table A3.3, table A3.4). In the main analysis, I assumed the behaviour of newly active providers was consistent with pre-existing active behaviour in terms of Xpert and FDC uptake. If the behaviour of newly active providers was 25% worse (in terms of Xpert and FDC user) than the behaviour of pre-existing active providers, the incremental cost of increasing the number of active providers to its feasible maximum decreases from USD 2.3 million (95% CrI USD 1.5 -3.8 million) to USD 2.2 million (95% CrI USD 1.4-3.7 million), and the percentage of cumulative TB cases averted between 2020 and 2035 decreased from 3.00% (95% CrI 2.59-3.37%) to 2.98% (95% CrI 2.58-3.35%) in Ahmedabad, due to the decrease in FDC and Xpert use, and adherence support offered. If behaviour of the newly active providers was 50% worse, then the incremental cost and percentage of cumulative TB cases averted between 2020 and 2035 decreased further to USD 2.1 million (95% CrI 1.3 -3.6 million) and 2.89% (95% CrI 2.48-3.24%), respectively. Despite the decrease in cases averted, and due to a decrease in incremental cost, increasing the proportion of active providers, regardless of their behaviour, was still the individual intervention with the lowest ICER in Ahmedabad.

Next, I examined how varying maintenance cost may affect the ICERs of the four interventions when scaled up individually (table A3.5 and table A3.6). For Ahmedabad, decreasing maintenance cost by 20% reduced the ICER of increasing the use of government supplied FDCs, making it the individual intervention with the lowest ICER (table A3.5). On the other hand, increasing the proportion of active providers remained the individual intervention with the lowest ICER if maintenance cost increased by 20%. For Delhi, increasing the proportion of FDC users remained the intervention with the lowest ICER regardless of a 20% increase or decrease in maintenance cost (table A3.6).
Finally, I conducted multivariate sensitivity analysis to examine which model parameter model outputs are most sensitive towards (fig A3.4 and fig A3.5). The model output, TB cases averted in

Ahmedabad, was influenced most strongly by the following three parameters: the rate of relapse following self-cure, the rate of stabilisation of the risk of relapse following treatment, and the rate of repeat care-seeking. For Delhi, the three most influential parameters were also the rate of relapse following self-cure and the rate of stabilisation of the risk of relapse following treatment, as well as the rate of progression to active disease from latency.

5.4. Discussion

To help India reach TB elimination, TB diagnosis and treatment in India's dominant private healthcare sector needs to improve. The largest private sector engagement initiative for TB in India to date, JEET, has focussed on encouraging private providers to notify their TB cases, to send TB sputum samples for confirmatory Xpert testing, to offer adherence support and to prescribe government supplied FDCs. In this work, I have addressed the question of how these different services provided by JEET should be expanded in the future and the potential epidemiological impact expanding these PPSA services further may have on the TB epidemic in Ahmedabad and Delhi, two cities with different coverage levels of PPSA services. I focussed on four interventions: increasing the proportion of active private providers, increasing the use of Xpert for confirmatory testing amongst active providers that are occasional users, converting non-Xpert users to start confirming TB test results with Xpert, and increasing the use of government supplied FDCs amongst active providers.

This work suggests that increasing all four interventions simultaneously to their maximum coverage can have a moderate impact on TB incidence, compared to maintaining pre-existing coverage of JEET and routine TB services; this impact is reduced if a feasible maximum coverage is considered, which considers the fact that some providers refuse certain PPSA services despite continued engagement efforts. Overall, the epidemiological impact between Ahmedabad and Delhi are very similar. A small increase in impact is seen in Delhi due to the lower coverage of PPSA services at baseline. A substantial impact is seen on DR-TB in terms of death and cases, due to the increase in the use of rapid molecular testing, which increases the probability of a correct diagnosis and appropriate treatment initiation.

These results are lower than those reported in another modelling study that examined the impact of increasing high-quality TB diagnosis and adherence support amongst private providers through private provider engagement in two Indian cities, Mumbai and Patna. The difference in results is likely because my interventions were compared to a baseline of current PPSA coverage, whereas the baseline of the other study assumed a baseline of no PPSA.

Levels of extra-pulmonary TB is influenced by factors such as HIV status, which is not covered in the model (130,494,495). Data provided by CHAI, suggest that certain cities in India, such as Delhi, have reported the percentage of TB cases that are extra-pulmonary, to be as high as 50%. Our results suggest that in settings with high levels of extra-pulmonary TB, the expected epidemiological impact of increasing PPSA services will be reduced, especially if the services focus heavily on increasing confirmatory testing with Xpert. In cities with high levels of extra-pulmonary TB, engaging with private providers and ensuring they follow the correct diagnostic protocol for diagnosing extra-pulmonary TB, will be paramount, in order to maximise the impact of private sector engagement on the TB epidemic. Nevertheless, the conclusion on which services should be prioritised in Delhi and Ahmedabad remain unchanged, regardless of the level of extra-pulmonary tuberculosis.

The epidemiological impact is likely to be reduced further if there is a high rate of attrition from an active to an inactive status amongst private providers. There are three main reasons behind this attrition: first of all, some providers may not have a sufficient load of TB patients every month and thus may notify infrequently depending on when they see a new TB patient; secondly, some providers, especially those that handle a smaller volume of TB patients, are seen less regularly by the field team and are therefore less likely to notify; and finally, some providers remain dissatisfied with the services offered by JEET, and therefore intentionally stop notifying patients until the field teams are able to improve their services. Understanding the reasons behind this behaviour will be important to ensure engagement efforts do not go to waste.

Ideally, all four interventions would be scaled up to their maximum coverage simultaneously; however, cost is likely to be a constraint. Analyses on the cost of scaling up the four interventions individually in Ahmedabad revealed that the intervention that averts the most cases of TB for a given cost was increasing the proportion of active providers. This held true even if the behaviour of newly active providers was worse than pre-existing active behaviours, in terms of diagnosis and treatment. The intervention with the largest ICER was increasing Xpert use amongst occasional users of Xpert; although this intervention averts a similar number of TB cases to increasing the proportion of active providers, it is the most expensive of the four interventions, due to the number of visits required to encourage providers to increase their use of Xpert for confirmatory testing.

On the other hand, in Delhi, the intervention with the smallest ICER was increasing the use of government supplied FDCs amongst active providers due to the low FDC coverage at baseline. Although increasing FDC use has the smallest epidemiological impact across the different interventions, it is highly cost efficient due to its low cost. Like Ahmedabad, the intervention with the highest ICER (least cost-efficient) was increasing Xpert use.

Overall, the interventions with the highest ICERs are those that involve Xpert. Although these interventions are epidemiologically impactful, they are extremely costly, due to the high cost of an Xpert test, the cost of testing symptomatic non-TB infected care-seekers and the cost of engaging with the active providers to increase their use of Xpert. Reducing the effort needed to convince private providers to increase Xpert use will be key in decreasing the cost. A recent study found that larger providers may be more willing to change their behaviour and adopt the use of Xpert compared to smaller providers; thus, targeting the larger providers may provide a more cost-efficient solution and help bring down the cost of increasing the use of Xpert amongst private providers (496).

A previous modelling study highlighted that unless the private sector is engaged and is encouraged to increase their uptake of Xpert, a limited impact on the TB epidemic will be seen (238). Although our results also show that increasing Xpert use has the largest epidemiological impact when compared to the other interventions, our results additionally highlight the fact that it is not the most cost-efficient; thus, under a limited budget, increasing Xpert use may not be the most appropriate intervention.

The limitations of this work can be divided into two categories: model limitations and economic limitations. A model simplification I have made is not explicitly differentiating between pulmonary and extrapulmonary TB in the model structure; however, to quantify the expected change in model outputs in areas with high levels of extrapulmonary TB, I conducted a sensitivity analysis around this model simplification. Another limitation is that the data sources used to inform the model are not specific to Ahmedabad and Delhi, and instead are based on Chennai, another large Indian city. Similarly, this analysis focusses purely on urban settings and not rural settings, that may have different careseeking pathways, different rates of TB infection and different provider behaviour (223,240). Thus, greater characterisation of these different settings is needed, to further refine the analysis.

In terms of economic limitations, the major limitation is that the costing data is from 2019, and thus, I am using retrospective programmatic data to inform the cost-efficiency of future interventions; future work could incorporate uncertainty intervals around each cost to reflect variation. In addition, the percentage of time spent by field staff on the different activities is subjective and was determined by questionnaires sent out to each field staff asking them to remember much time they had spent performing each activity. The number of visits needed to change the behaviour of a provider is also highly variable and were estimated by the CHAI field team using high level of assumptions; for instance, the number of visits until a provider changes their behaviour appears to be dependent on when a provider started notifying. Nevertheless, for simplicity, we assumed that all providers were responsive after the same number of visits. Another assumption I have made, is that the field team visits providers resistant to engagement efforts the same amount of time as non-resistant providers; in

reality, after a couple of visits, field officers know which providers are resistant, and thus, may choose instead to focus their efforts on non-resistant providers. Similarly, I do not consider the fact that once a provider has been visited by field staff a certain number of times, any subsequent visits are likely to be ineffective; for example, data from the field team suggests that approximately at the 50th visit by a field officer, a provider's Xpert use stops increasing. I have also assumed that the cost of field staff increases proportionally to the activity they are involved in and that costs increase linearly with coverage; in reality, there is a step-wise gradient, where, for example, a field officer can take on a certain number of new providers, before an additional field officer is needed. Thus, the cost of the different interventions may be over-estimated. In addition, unit costs may change with increasing coverage; unit costs may decrease at large volumes ('economies of scale') if the PPSA can negotiate for lower costs with high volumes, whereas unit costs could also increase due to 'hard to reach' providers (for example, there may be providers who are reluctant to engage and are therefore more costly to keep them on board). Finally, although at baseline I weighted FDC and Xpert use by the number of months providers were active for, I assume that under the different interventions, providers remain active; however, I do include the costs involved in maintaining this active behaviour.

Finally, a number of studies have shown Xpert to be cost-effective or at least cost-neutral in a variety of settings (497–499). I do not aim to assess whether these interventions would be cost-effective relative to a cost-effectiveness threshold. Similarly, for simplicity I ignore discounting of future outcomes as the aim of the analysis was to perform a simple economic analysis on the cost-efficiency of increasing the coverage of the different PPSA services compared to the status quo. Including discounting in the analysis is unlikely to affect the relative importance of the different interventions. Future work should include a full cost-effectiveness analysis (including discounting) to determine the cost-effectiveness of scaling up these interventions individually, and in combination, compared to alternative interventions for active TB disease.

5.5. Conclusion

In summary, increasing current PPSA services can have a modest impact on the TB epidemic in Indian urban settings and a significant impact on DR-TB. Under a limited budget, increasing the use of government supplied FDCs or increasing the proportion of active private providers should be prioritised. The services with the highest ICERs are those involving Xpert due to the high cost per test and engagement efforts needed.

Chapter 6: Results (iv)

Quantifying the potential value of antigen-detection rapid diagnostic tests for coronavirus disease 2019: a modelling analysis

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S.G. Schumacher and J.A. Sacks from the Foundations for Innovative New Diagnostics, D.W. Dowdy from the Johns Hopkins Bloomberg School of Public Health, and my supervisor, N. Arinaminpathy were involved in the conceptualisation of this work. I led the model development, analysis and preparation of the manuscript. All authors were involved in reviewing and editing the manuscript.

In this chapter, I shift the focus from TB to COVID-19. With the emergence of the severe acute respiratory syndrome coronavirus 2 ("SARS-CoV-2") at the end of 2019, the importance of diagnostic tests quickly became apparent due to the initial lack of effective treatment and vaccines. I had the opportunity to apply what I had learnt modelling novel TB diagnostic tests to COVID-19. Here, I aim to quantify the trade-offs between accessibility and performance of diagnostic tests for COVID-19. More specifically, comparing rapid antigen diagnostic tests ("Ag-RDTs") to nucleic acid amplification tests ("NAAT"), the former being more accessible but less accurate than the latter. I conduct decision analysis to evaluate the health system cost and health impact (deaths averted and infectious days isolated) of an Ag-RDT-led strategy, compared to a strategy based on NAAT and clinical judgment. I focus on two use cases for analysis: rapid identification of people with COVID-19 amongst patients admitted with respiratory symptoms in a 'hospital' setting; and early identification and isolation of people with mildly symptomatic COVID-19 in a 'community' setting. I demonstrate that despite their imperfect sensitivity and specificity, Ag-RDTs have the potential to be simultaneously more impactful and have a lower cost per death and infectious person-days averted, than NAAT. This work has led to the development of a user-friendly online tool (https://covid-ag-rdt.shinyapps.io/model/) that enables public health practitioners to examine model outputs for input parameter values relevant to their own settings.

6.1. Introduction

Virological testing is a critical part of the global response to severe acute respiratory syndrome coronavirus 2 ("SARS-CoV-2")(303,500,501). Early diagnosis allows infectious cases to be isolated in a timely manner, thus minimising opportunities for transmission. Amongst those at risk of severe outcomes of the disease, early diagnosis and initiation of appropriate therapy can substantially improve outcomes and avert mortality (277,304,502,503). Below I discuss the two main types of diagnostic tests, nucleic acid amplification tests ("NAAT") and rapid antigen diagnostic tests ("Ag-RDT").

Nucleic acid amplification tests

NAATs are molecular tests that detect and amplify a specific nucleic acid sequence. At the time of writing, 197 NAATs have received emergency use authorisation ("EUA") by the U.S. Food and Drug Administration ("FDA") to diagnose COVID-19 (504).

NAATs have been widely implemented in well-resourced settings since the outset of the pandemic (505). The most used NAAT for the diagnosis of SARS-CoV-2 infection is the real-time reverse-transcription polymerase chain reaction assay ("RT-PCR"). Swabs from the respiratory tract, nasopharyngeal and oropharyngeal, are taken from a presumptive SARS-Cov-2 infected patient. RNA samples are extracted from the swabs, and it is reverse transcribed into DNA; the DNA is then amplified using PCR with primers specific to the virus in question.

In terms of logistics, the advantage of PCR is that as soon as the virus has been sequenced, primers can be produced. However, these tests are challenging to implement at scale, particularly in resource-poor settings: they are costly and require good specimen transport systems, laboratory infrastructure, and highly trained technicians (506). Furthermore, depending on sample collection and transportation, and laboratory and staff capacity, turnaround times can be long; although the test takes between 4 to 6 hours, some countries, like South Africa, have seen turnaround times of as long as two weeks (506–508). In such cases a NAAT result adds little value to decisions around isolation or clinical management. In order to increase testing capacity and to make testing more readily available, many countries have developed testing "drive-throughs" and home testing, where patients take their own swabs and send them to the laboratories to get analysed (509).

RT-PCR is often used as the reference standard for the diagnosis of symptomatic SARS-CoV-2 infection. The diagnostic performance of new RT-PCR assays is usually determined in patients with symptoms consistent with COVID-19, repeated RT-PCR testing, and through the use of radiology

(510–512). A meta-analysis estimated a pooled sensitivity of 89% and a pooled specificity of 99% (513). However, the diagnostic performance of RT-PCR assays are often verified in ideal conditions with samples that have high viral loads (i.e. analytical sensitivity and specificity, and not clinical sensitivity and specificity) (510). Indeed, a systematic review estimated clinical sensitivity to be between 71-98% (514). False negative results are more likely the earlier patients are tested throughout the course of infection, as the viral load may be below the threshold of detection. One study estimated the probability of a false-negative result decreased from 100% four days before symptom onset to 67% one day before symptom onset, with the probability decreasing further following symptom onset, but rising again around a week after symptom onset (515). Similarly, a systematic review estimated that 89% of RT-PCR test results were positive between 0-4 days post-symptom onset, decreasing to 54% 10-14 days post-symptom onset (516). False negatives can also arise by incorrect sample collection, especially with home-testing kits (517). Finally, the method used to collect samples causes different sensitivity estimates (303). For example, one study estimated RT-PCR sensitivity to be 93% for bronchoalveolar lavage but as low as 32% for throat swabs (511). Swabs from the lower respiratory tract are more likely to test positive than swabs taken from the upper respiratory tract (513,516). False positive results may arise through incorrect testing procedures that lead to contamination (517). Unfortunately, the variation in diagnostic performance of RT-PCR tests depending on how, when and where a sample is collected, and in the preparation of the sample, impedes assessment of other novel diagnostic tests, when RT-PCR is used as a reference standard (303,512).

Since RT-PCR detects viral particles, patients may test positive for SARS-CoV-2 even several weeks post symptom onset (303,518); however, this does not indicate the patient is still infectious (519). The EU Centre for Disease Prevention and Control ("CDC") recommends that amongst hospitalised patients, at least two upper respiratory tract samples collected at more than 24 hours intervals should test negative for SARS-CoV-2 before viral clearance can be confirmed (520).

Rapid antigen diagnostic tests

Ag-RDTs detect SARS-CoV-2 proteins (antigens) to diagnose active infection. At the time of writing, a total of 8 Ag-RDTs have been given EUA by the FDA (504). The WHO have recently published target product profiles ("TPPs") for Ag-RDTs (521).

The majority of Ag-RDTs are lateral flow assays, which are easy, low-cost and rapid to use (< 30 minutes), making them suitable for the point-of-care. It should be noted that the majority of current Ag-RDTs recommend a nasopharyngeal specimen. Nasopharyngeal samples should ideally be performed by trained professionals to reduce sampling error (522).

Ag-RDTs detect patients that are the most infectious; however, they tend to suffer from lower sensitivity and may miss patients with lower viral loads early on or late during the infection (523). Initial evaluations of these tests reveal a handful have sensitivities and specificities comparable to RT-PCR. For example, the Abbott Panbio COVID-19 Ag Rapid Test Device had an overall sensitivity and specificity of 85.5% and 100%, respectively, relative to RT-PCR; sensitivity increased to 96.8% if the cycle threshold is greater than 25 (524). The test also performs better when patients are tested within a week of symptom onset; sensitivity decreased to around 75% if samples were taken over a week after symptom onset. Overall, a meta-analysis, that included studies using any type of reference standards (including RT-PCR and clinical diagnosis) found that Ag-RDTs had a pooled sensitivity of 56.2% and a pooled specificity of 99.5%; however, sensitivity varied hugely across tests, ranging from 0 to 94% (525). The tests have not been validated for use for home testing, which may reduce test sensitivity due to incorrect sampling.

To reduce errors with antigen tests, test results could be confirmed with RT-PCR. For example, in a high prevalence setting, a negative test may require confirmation with RT-PCR, whereas in a low prevalence setting, a positive test result may require confirmation (526).

The emergence of Ag-RDTs may help to address some of the challenges faced by NAAT. As RDTs are being procured by international donors for use in LMICs there is a need for guidance on how these tests should be used in these settings. I therefore sought to quantify these trade-offs between Ag-RDT-based testing and NAAT-based testing in the context of resource-limited settings. I aimed to answer the following questions:

- What is the trade-off between NAAT and Ag-RDT for SARS-CoV-2?
- Under what scenario can an Ag-RDT be beneficial?
- Do results differ by use-case?

6.2. Methods

6.2.1. Overview

The primary objective was to identify scenarios in which an Ag-RDT might offer greater individual and public health value at lower cost than reliance on NAAT, across a variety of resource-limited settings. To accomplish this, I first defined key use cases and plausible ranges for parameter values, in consultation with a group of experts deeply involved in their country's response to COVID-19 (table A4.2). To identify principles that might generalize across countries, these experts were drawn from a

range of different country settings; the ranges in parameter values also served to incorporate variation across these settings. (As described below, a key aim of the analysis was to analyse the most important sources of variation.) I then constructed decision trees that included both costs to the health system (e.g., treatment and management of hospitalised cases) and relevant health outcomes (deaths and infectious person-days averted). Finally, I simulated overall costs and outcomes under a wide array of parameter values and compared testing strategies using Ag-RDTs, those using NAAT where available. I also constructed a user-friendly online tool (https://covid-ag-rdt.shinyapps.io/model/) that enables public health practitioners to examine model outputs for input parameter values relevant to their own settings.

6.2.2. Model scenarios and structure

I denote an 'Ag-RDT-led strategy' as any testing strategy in which an Ag-RDT is the first diagnostic test performed (with the potential for follow-up NAAT confirmation). As an illustrative example, I focused on an Ag-RDT with sensitivity and specificity of 80% and 98% respectively, relative to NAAT, and costing 5 USD per test, consistent with recent WHO interim guidance and US FDA EUA antigen-detection tests (504,522). I compared the impact of using an Ag-RDT-led strategy to that of a 'NAAT-based strategy' in which NAAT was the only virological test performed, with reliance on clinical judgment where sufficiently rapid NAAT results were not available (see fig 6.1 for a summary of the diagnostic strategies modelled). To inform relevant use case scenarios, I consulted experts from India, South Africa, Nigeria, and Brazil to elicit expert opinion on the ways in which Ag-RDTs could offer value in their own country settings (see appendix 4 for further details). Based on this input, I selected two use case scenarios, as listed in table 6.1: (i) A 'hospital setting', where the test is used to support infection control and treatment decisions amongst patients being admitted to hospital with respiratory symptoms, and (ii) a 'community' setting, where the test is used in in decentralized community clinics to identify cases of COVID-19 who should self-isolate. Although Ag-RDTs could also be considered for use in identifying asymptomatic infections, both focal scenarios involved testing of only symptomatic individuals.

Use case scenario	Description	Assumed prevalence	Purpose of testing
Hospital setting	Testing amongst all patients being hospitalised with respiratory symptoms	25%	To identify patients with COVID-19 who should be housed in isolation wards (reducing infection risk in hospital). Amongst admissions with severe symptoms, to identify those with COVID-19 who might benefit from anti-inflammatory treatment (to reduce deaths)
Community setting	Decentralised, community-level facility available to all individuals with symptoms who want to be tested for COVID-19	5%	To identify COVID-19 amongst people with mild COVID-consistent symptoms. Positive test results would trigger isolation and contact tracing, to minimise opportunities for transmission.

Table 6.1. The use cases included in the present analysis. I performed sensitivity analysis on the assumed prevalence, varying the hospital setting prevalence between 10 - 30% and community setting prevalence between 1 - 10%. Results are presented in the supporting information.

For both use cases I constructed decision trees (fig 6.1) that represent the diagnostic use of the Ag-RDT, actions taken in response to the test results (or lack of results) and resulting outcomes. For simplicity and transparency, this model does not incorporate transmission dynamics but approximates epidemiological benefits based on the incremental change in the number of days that infectious individuals spend out of isolation; the magnitude of downstream impact would depend on factors, such as the rate of epidemic growth and the contact patterns of symptomatic versus pre- or asymptomatic cases, that are not specified in the model. The focus is therefore on the direct benefits that would accrue to patients receiving the test and, by extension, their immediate contacts (see right-hand column of table 6.1).

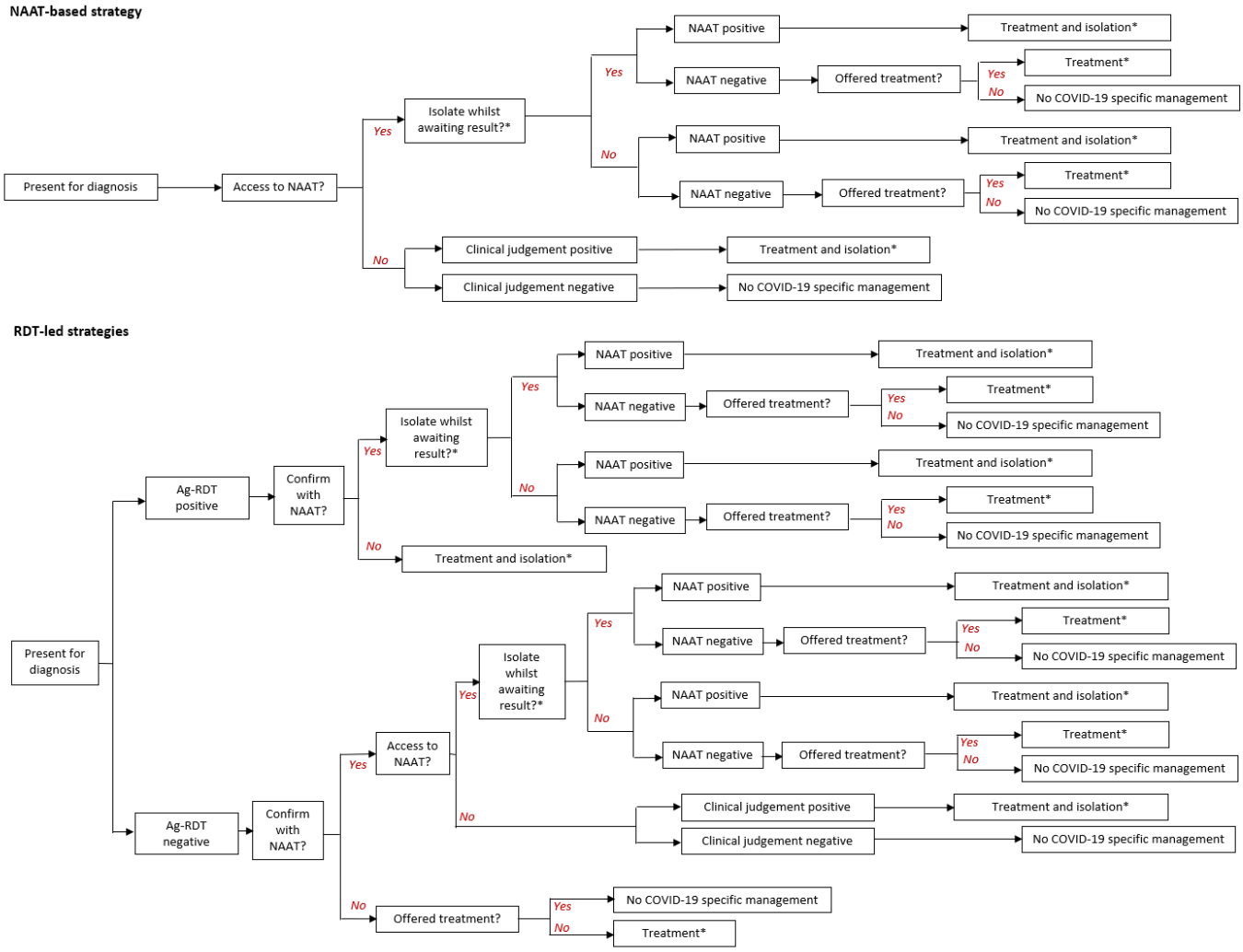

Figure 6.1. Schematic illustration of the decision tree approach. As described in the main text, the analysis focuses on the direct benefit to patients being tested in different settings. *In the hospital setting, I assumed that all patients were provided with supportive care (e.g., oxygen support) regardless of test results, as such care would be provided based on symptoms and not aetiology. However, I modelled the use of the test in guiding decisions about whom to isolate, and to treat with dexamethasone. Treatment did not apply to the community setting. Costs and deaths/infectious days averted were accumulated along each branch of the diagram as appropriate (for example, counting the costs of interim treatment and isolation along any branch labelled 'Yes' following 'Isolate whilst awaiting treatment?').

Model parameters, listed in table 6.2, represent the contextual factors to be examined (including plausible ranges for each), with the aim of identifying those factors that are most influential for the value of an Ag-RDT-led testing strategy relative to NAAT-based testing. The expert consultation highlighted that no standard guidance for whether or how Ag-RDTs should be used in conjunction with NAAT existed at the time (e.g., whether NAAT should be used to confirm an Ag-RDT negative result). Thus, I also defined and modelled three different options for the adjunctive use of NAAT in an Ag-RDT-led algorithm (an algorithm where the first test is an Ag-RDT):

(i) no confirmation of Ag-RDT results
(ii) NAAT confirmation of Ag-RDT negative results
(iii) NAAT confirmation of Ag-RDT positive results

Due to the lower sensitivity of Ag-RDT compared to NAAT, confirmation of Ag-RDT negative results with NAAT reduces the probability of false negatives, whereas confirmation of Ag-RDT positive results reduces the probability of false positives. The latter is especially important in settings with a low prevalence of COVID-19, where even small shortfalls in specificity can lead to substantial numbers of false positive diagnoses (527).

For the hospital setting, I assumed that all patients are isolated while awaiting NAAT results (whether in the NAAT-based strategy or while awaiting NAAT confirmation in an Ag-RDT-led strategy). I also present a sensitivity analysis of the alternative scenario where patients are not isolated while awaiting test results. By contrast, in the community setting I assumed that individuals are *not* isolated while awaiting any NAAT result, as this policy was considered infeasible due to the comparatively low prevalence of COVID-19 in this population, and the unnecessary expense and disruption this would entail to most tested individuals and their families.

Although NAAT specificity is near 100% for current or recent infection (528), not all NAAT-positive cases are necessarily infectious, given the potential to detect unviable viral genetic material after the infection has resolved (271,519,528) and for severe symptoms to develop near the end of the infectious period (302). By contrast, Ag-RDTs may detect only acute, but not recently cleared, infection (529,530). These distinctions have significance for the intended purpose of the test: where the purpose is to guide clinical decisions for treatment, knowing the aetiology of severe symptoms is important, regardless of viral antigenic load. On the other hand, where the purpose is early identification of infectious cases, detecting recently cleared infection can detract from the utility of a test. I captured these elements of both NAATs and Ag-RDTs by distinguishing ‘acute’ from ‘recent’ infection, and assuming that: (i) only acute infection is infectious; (ii) NAAT is able to detect both acute and recent infection with equal sensitivity, and (iii) an Ag-RDT is able to detect only acute infection (529). I accommodated wide uncertainty in the proportion of patients with acute infection in both the hospital and community settings; considering that viral load is highest just before symptom onset, and that the average COVID-19 patient is hospitalised 3 to 10 days after symptom onset (531), it is possible that a certain proportion of patients are no longer infectious by the time they are hospitalised. As discussed below, although these are useful simplifications for the purpose of the current analysis, these categorisations conceal potentially important complexities relating to temporal and between-individual variation in viral load, infectivity and detectability by a given test. In the present analysis, I incorporated a parameter for the proportion of those with COVID-19, amongst the

population being tested, that are still in the acute phase at the point of testing, allowing this parameter to occupy a wide range of values between 50% and 100%, acknowledging the existing uncertainty (table 6.2).

Parameter	Value		References
	Hospital setting	**Community setting**	
Epidemiology			
Prevalence of current or recent SARS-CoV-2 infection (%) *	25	5	Assumption
Proportion amongst those tested who are in acute phase	0.5– 1.00	0.5– 1.00	Assumption
Of those in acute phase, number of infectious days remaining (days)	5 – 15	5 – 15	(299)
Case fatality rate amongst hospitalised COVID-19 patients	0.20 – 0.30	N/A	(304)
Case fatality reduction amongst COVID-19 patients on dexamethasone (1 – risk ratio)	0.07 – 0.25	N/A	(304)
NAAT performance			
NAAT sensitivity (for current or recent SARS-CoV-2)	0.85 – 0.95	0.85 – 0.95	(271,513,514,516,517,519,528)
NAAT specificity	0.99 – 1	0.99 – 1	(271,517,519,528)
NAAT availability (proportion able to access NAAT test)	0.1 – 1	0.1 – 1	Assumption
Cost per NAAT test (USD)	20 – 70	20 – 70	
NAAT turnaround time (days)	1 – 10	5 – 15	(506), Expert consultation
Confirm Ag-RDT negative results with NAAT	Y/N	Y/N	
Confirm Ag-RDT positive results with NAAT **	Y/N	Y/N	
Isolate and initiate treatment (if indicated) whilst awaiting NAAT result	Y ***	N	
Ag-RDT performance (assumed fixed)			
Ag-RDT sensitivity for current infection, relative to NAAT (%, assumed only amongst acute cases)*	0.80	0.80	(504,532)
Ag-RDT specificity, relative to NAAT (%)*	0.98	0.98	(504,532)
Cost per Ag-RDT test (USD)	5	5	(532)
Clinical judgement and management			
Sensitivity of clinical judgment in absence of NAAT	0.45 – 0.99	0.45 – 0.99	(293,294,533,534)
Specificity of clinical judgment in absence of NAAT	0.20 – 0.70	0.20 – 0.50	(293,294,533,534)

Proportion of hospitalised patients with a negative COVID-19 test result (true and false negatives) that are initiated onto dexamethasone	0.05 – 0.15	N/A	Assumption
Duration of isolation (days)	10	10	(299)
Duration of dexamethasone treatment (days)	10	N/A	(304)
Cost of isolation per day (USD)	50 – 350	N/A	(535–537)
Cost of dexamethasone per day (USD)	0.13 - 3.5	N/A	(538)

Table 6.2. Contextual parameters and their uncertainty ranges. Ranges define limits on uniform distributions, chosen to capture plausible parameter ranges that may apply across a variety of low- and middle-income settings. As described in the main text, the main analysis is a systematic uncertainty analysis, structured to identify which of these uniform distributions is most influential for model outcomes. Footnotes: *I performed sensitivity analyses on these fixed parameters, with results presented in Appendix 4. I varied prevalence in the hospital setting between 10 - 30% and in the community setting between 1 - 10%. I varied Ag-RDT sensitivity and specificity between 75 – 95% and 98 – 100%, respectively, relative to NAAT. **I exclude any parameter draws involving NAAT confirmation of *both* Ag-RDT negative and Ag-RDT positive results. ***For patients with COVID-19 initiated on interim treatment while awaiting NAAT confirmation of an Ag-RDT result, but who subsequently receive an incorrect negative NAAT result, I assume that they do not receive any benefits of interim treatment.

6.2.3. Quantifying relative value

In the hospital setting, I assumed that the test would guide decisions about whom to isolate and whom to treat with dexamethasone (305), and moreover that all patients (regardless of test result) would receive supportive care such as oxygen support. I assumed a baseline of no COVID-19-specific intervention (i.e., supportive care, but with no NAAT or Ag-RDT testing strategy, nor treatment with dexamethasone). I assumed that hospitalised COVID-19 patients have a case fatality rate between 20-30% (304) without treatment, and that dexamethasone reduces this by 7-25% (table 6.2), consistent with recent study results for corticosteroid treatment of COVID-19 (304). I assume a 10-day treatment course of dexamethasone (304). I thus denoted ‘deaths averted’ as the reduction in deaths that would be achieved by a given testing strategy, relative to no intervention.

Similarly, as a simple proxy for the impact of a test on transmission in both hospital and community settings, I first assumed a uniform distribution for the number of infectious days remaining per patient amongst patients presenting with acute infection (table 6.2). I then recorded the number of patient-days of acute infection that were not spent in isolation, whether because of missed diagnosis or (in the case of NAAT) delayed diagnosis without isolation, while awaiting a test result. I denoted ‘infectious person-days averted’ as the reduction that would be achieved by a given testing strategy, relative to no-intervention baseline. For the community setting, I estimated the impact of a test only in terms of infectious person-days averted, as it is likely that most individuals receiving a test in a community setting suffer from mild COVID-19.

I also estimated the cost to the health system of the different interventions. For the hospital setting, I estimated the cost of testing, treatment, and isolation. For the community setting, I estimated only the cost of testing.

Using the model illustrated in fig 6.1, I estimated the impact (deaths or infectious person-days averted) and cost of each testing strategy. I stratified Ag-RDT-led strategies by the adjunctive role of NAAT in confirmation of a test result (i.e., whether to confirm Ag-RDT-negatives, Ag-RDT-positives, or not at all). For NAAT-based strategies, I assumed that only a proportion of eligible individuals receive a NAAT result (assuming a broad range of 10-100%), with the remainder managed through clinical judgment alone. For each use case, I sampled all parameters from the uncertainty ranges in table 6.2 using Latin Hypercube Sampling. For each sampled set of parameters, I calculated both incremental costs and the incremental primary outcome (deaths averted or infectious person-days that were isolated) under an Ag-RDT-led strategy or a NAAT-based strategy, relative to no intervention (that is, a scenario of no testing, nor clinical management of COVID-19). To quantify uncertainty, I calculated uncertainty intervals (UIs) as 2.5th and 97.5th percentiles over 10,000 samples and reported median values as point estimates.

To compare testing strategies, I first estimated the cost per death averted (in the hospital setting), and the cost per infectious person-day isolated (in both hospital and community settings) under NAAT-based and Ag-RDT-led strategies. However, I did not aim to determine whether or not an Ag-RDT would be cost-effective, given the uncertainties surrounding appropriate willingness-to-pay thresholds for emergency outbreak response (539). Instead, I compared the two strategies (Ag-RDT vs NAAT) using a simple approach of plotting their relative impact against their relative cost for each sampled set of parameters (see fig 6.2 for a schematic illustration of the approach). It is important to note that this approach is distinct from a conventional cost-effectiveness plane, as the axes are shown on a relative, rather than a nominal, scale. In the example of deaths, I denoted A_{RDT} as the deaths averted by Ag-RDT-led testing, relative to no intervention, and likewise for A_{NAT}. Similarly, I calculated the incremental cost C_{RDT} of an Ag-RDT-led strategy relative to no intervention, and likewise for C_{NAT}. I then plotted the relative impact (A_{RDT}/A_{NAT}) against the relative incremental cost (C_{RDT}/C_{NAT}).

I defined an Ag-RDT as being 'favourable' relative to NAAT, wherever its use resulted simultaneously in more deaths averted than NAAT (i.e. $A_{RDT} > A_{NAT}$), and a lower incurred cost per death averted than NAAT (i.e. $C_{RDT}/A_{RDT} < C_{NAT}/A_{NAT}$). I defined an Ag-RDT as being 'non-favourable' otherwise. I performed corresponding calculations for the outcome of infectious person-days successfully isolated. The focus in the following analysis is on identifying which circumstances would lead to an Ag-RDT being 'favourable' relative to NAAT.

Where simulation outputs were equivocal on the favourability of Ag-RDTs (i.e., straddling favourable and non-favourable regions), I evaluated the correlation between each parameter and relevant model outputs using partial rank correlation coefficient ("PRCC") to identify those parameters that were most influential on the proportion of a simulation falling in a favourable region. In particular, where simulation outputs straddled the vertical dashed line shown in fig 6.2, I evaluated correlations against the relative impact of Ag-RDT-led vs NAAT-based testing strategies. Where simulations straddled the diagonal line in the upper-right quadrant, I evaluated correlations against the relative cost-per-unit impact (i.e., per death averted or per infectious person-day isolated). Overall, in this way I sought to identify the contextual conditions under which an Ag-RDT-led strategy would, and would not, be favoured over NAAT.

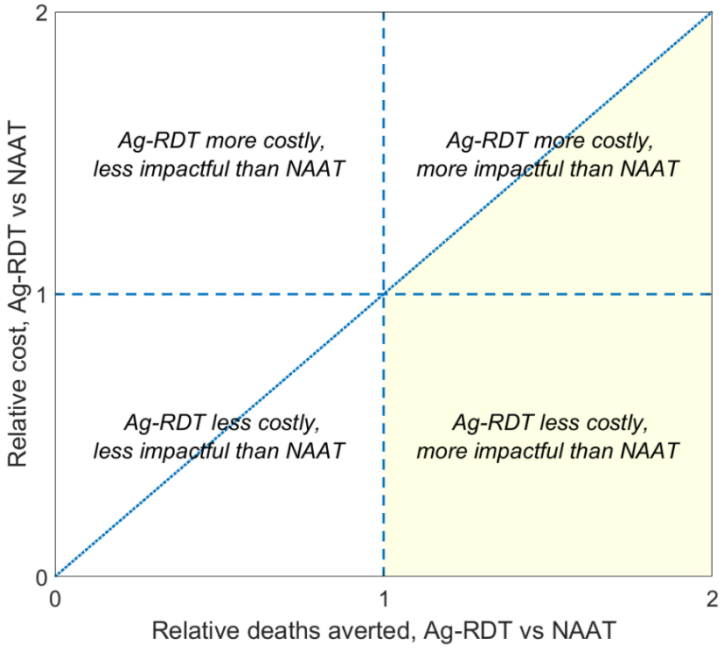

Figure 6.2 Schematic illustration for visualising the value of an Ag-RDT-led strategy, relative to a scenario involving NAAT and clinical judgement. Although the figure involves deaths averted, the same structure applies for averting infectious person-days. For a given set of parameters drawn from the parameter ranges shown in table 6.2, I simulated the cost and impact of a given Ag-RDT-led strategy, and of a NAAT-based testing strategy, both relative to a no-intervention scenario. This outcome was then represented in the figure by plotting the relative deaths averted by Ag-RDT vs NAAT (horizontal axis) against the relative cost of the two strategies (vertical axis). Thus, for example, in the lower right quadrant, an Ag-RDT-led strategy would cost less, but have more impact, than NAAT. The diagonal dashed line shows an important threshold: for points below this line, an Ag-RDT-led strategy would cost less per death averted than NAAT, and vice versa. Overall, therefore, the shaded area shows the region in which an Ag-RDT would simultaneously cost less per death averted, and avert more deaths overall, than NAAT. I denote this area as the 'favourable region' for an Ag-RDT, and elsewhere as 'non-favourable': in the current analysis I aim to identify the circumstances under which an Ag-RDT, of a given performance and cost, would occupy this region.

6.2.4. Additional sensitivity analysis

Finally, I analysed sensitivity to model assumptions not covered by the analyses above. As a focal model output for this sensitivity analysis, I chose the proportion of simulations that were favourable, under a given use case and a given scenario for the adjunctive use of Ag-RDT and NAAT. First, while the main analysis adopted fixed values for sensitivity and specificity of an Ag-RDT, sensitivity analyses examined how the proportion favourable would vary if Ag-RDT sensitivity ranged from 75 – 95% and if Ag-RDT specificity ranged from 98 – 100%. Second, I examined how the proportion favourable would vary if prevalence of COVID-19 ranged from 10-30% in the hospital setting and 1-10% in the community setting. Finally, for simplicity in the main analysis of the community setting, I assumed perfect adherence to isolation after a positive test result and no self-isolation amongst those testing negative. I relaxed these assumptions in the sensitivity analysis, and assumed that non-compliance with self-isolation reduced the infectious days averted by a proportion p, while those not required to isolate (i.e., those with false-negative test results, and those awaiting NAAT confirmation of an initial Ag-RDT result in the community) nevertheless self-isolated to a degree that reduced transmission by a factor q. I examined how the proportion favourable varied as either p or q ranged from 0 – 50%.

6.3. Results

As context to the primary analysis that follows, table 6.3 illustrates that both NAAT-based and Ag-RDT-based algorithms were more costly, but led to better health outcomes, than a scenario of no intervention. For example, a NAAT based algorithm in a hospital setting would cost USD 150,000 (95% uncertainty intervals (UI) 38,000 – 490,000) per death averted within the patient population, while an Ag-RDT-led algorithm, involving NAAT confirmation of Ag-RDT-negatives, would cost USD 140,000 (95% UI 36,000 – 440,000). Likewise, in a community setting, a NAAT based algorithm was estimated to cost USD 84 (95% UI 11 – 670) per infectious person-day isolated, versus USD 12 (95% UI 8 – 23) for an Ag-RDT-only algorithm (without NAAT confirmation).

Testing strategy		Hospital setting		Community setting
		Cost per death averted (USD)	Cost per infectious person-day isolated (USD)	Cost per infectious person-day isolated (USD)
NAAT-based		150,000 (38,000-490,000)	560 (150-1,600)	84 (11-670)
Ag-RDT-led	No Ag-RDT confirmation	53,000 (14,000-150,000)	160 (42-440)	12 (8-23)
	Confirm Ag-RDT -ve with NAAT	140,000 (36,000-440,000)	530 (140-1,500)	58 (17-190)
	Confirm Ag-RDT +ve with NAAT	54,000 (15,000-160,000)	150 (42-420)	51 (18-790)

Table 6.3. Summary of cost per death or infectious person-day averted of results presented in the main text. As explained in the Methods, impact and cost are estimated relative to a baseline of no testing, and no intervention. Numbers in brackets give 95% uncertainty intervals.

6.3.1. Hospital Setting

Fig 6.3 shows plots of relative incremental cost against relative impact in terms of deaths averted, comparing the Ag-RDT-led to the NAAT-based strategy in a hospital setting, with an assumed 25% prevalence of acute or recent COVID-19 amongst those being tested. For deaths averted, when an Ag-RDT was used in conjunction with NAAT to confirm Ag-RDT-negative results (red points), such a strategy had greater impact, and at lower cost per death averted, than a NAAT-based strategy ("favourable region") in 96% of all simulations. By contrast, Ag-RDT-led strategies that involved either no NAAT confirmation, or only confirmation of RDT-positive cases (respectively yellow and blue points), resulted in too many missed cases to exceed the impact of NAAT-based strategies in more than 92 and 96% of simulations, respectively. For settings in which NAAT was used to confirm Ag-RDT-negative results, fig 6.3B illustrates the relationship of each model parameter to the proportion of parameter samples that resulted in a "favourable" simulation. In particular, the availability of NAAT, sensitivity of clinical judgment amongst those unable to access NAAT, and proportion of cases tested during the acute phase were highly influential. Fig 6.3C shows the most influential parameters (NAAT availability and clinical judgment) in greater detail, with points in grey showing where an Ag-RDT was favourable. Broadly, the figure illustrates that an Ag-RDT would be favourable in settings of low NAAT availability and low sensitivity of clinical judgement: in indicative terms, as long as sensitivity of clinical judgement was <90%, and NAAT was available to <85% of patients, 99% of simulations were favourable.

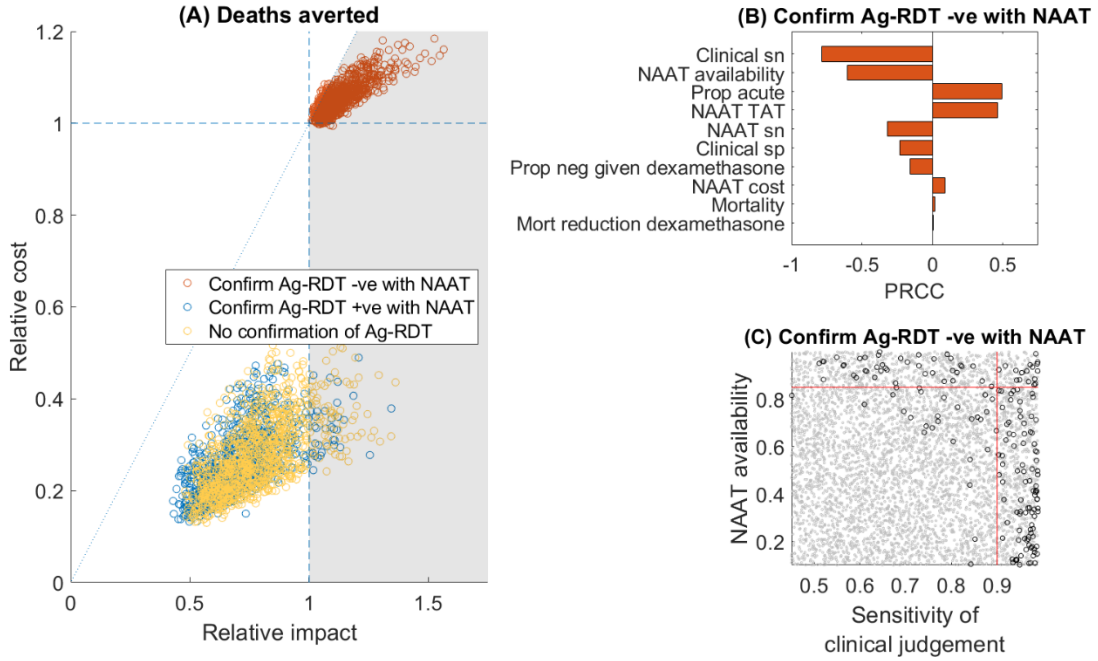

Figure 6.3. Relative value of Ag-RDT vs NAAT testing, for averting deaths in a hospital setting. (A) scatter plots for the relative impact of Ag-RDT vs NAAT (horizontal axis), vs the relative cost of the two strategies (vertical axis). Each dot represents a single simulation with parameter values drawn from the ranges in table 6.2. For a given set of parameters, I simulated the cost and impact of a given Ag-RDT-led strategy and of a NAAT-based testing strategy. This outcome was then represented by plotting the relative impact (deaths averted) of an Ag-RDT-led strategy vs. NAAT-based strategy against the relative cost. The grey-shaded area shows the region where an Ag-RDT-led strategy was 'favourable' over a NAAT-only strategy, meaning that it averted more deaths, and at a lower cost per death averted (see also fig 6.2). Colours of points indicate the adjunctive, confirmatory role of NAAT in an Ag-RDT-led strategy (see in-figure legend). Of the red points, 96% fell in the favourable region, whereas the majority of simulations for an Ag-RDT only (yellow) and NAAT confirmation of positive Ag-RDT results (blue) were unfavourable in 92% and 96% of simulations, respectively. (B) Sensitivity analysis on the red points in panel (A), to assess when these points fell above, or below, the diagonal dotted reference line. PRCC denotes 'partial rank correlation coefficient', against the cost per death averted. The longest bars indicate the most influential parameters; positive values indicate parameters that increased the favourability of the algorithm with increasingly positive values, and conversely for negative PRCCs. For example, when NAAT was used to confirm negative results, the favourability of an Ag-RDT-led strategy was improved in settings having lower clinical sensitivity and a higher proportion of acute infection. *Clinical sn* – sensitivity of clinical judgement; *prop acute* – proportion amongst those tested that are in the acute stage of infection; *NAAT TAT* – turnaround time of NAAT; *NAAT sn* – NAAT sensitivity; *Clinical sp* – specificity of clinical judgement; *Prop neg given dexamethasone* – proportion of hospitalised patients with a negative COVID-19 test result that are initiated onto dexamethasone; *Mort reduction dexamethasone* - Case fatality reduction amongst COVID-19 patients on dexamethasone. (C) The joint role of the two most influential parameters in panel (B). Grey and black points show parameter combinations where an Ag-RDT was favourable, and non-favourable, respectively, relative to NAAT. Red lines show 90% sensitivity of clinical judgment (vertical line), and 85% NAAT availability (horizontal line). In the lower left quadrant of these lines, an Ag-RDT was favourable over NAAT in 99% of simulations. In these results it is assumed that patients were placed in isolation and treated (where indicated) while awaiting a NAAT result: fig 6.5 shows results in the alternative scenario where they were not isolated, pending NAAT results.

Fig 6.4 shows similar results for the outcome of infectious person-days isolated in a hospital setting. Importantly, fig 6.4A illustrates the potential for the sole use of Ag-RDT (without NAAT confirmation) to offer higher impact, at lower cost, than a NAAT-based scenario (yellow points, 27%

of which were in the favourable region). Fig 6.4C shows a bivariate sensitivity analysis of the two most influential model parameters, demonstrating that an Ag-RDT-only strategy was likely to be favourable in terms of averting infection as long as the sensitivity of clinical judgement in the absence of NAAT was <80% and the availability of NAAT was <65%. Under these conditions, the proportion of simulations that were favourable was 66%.

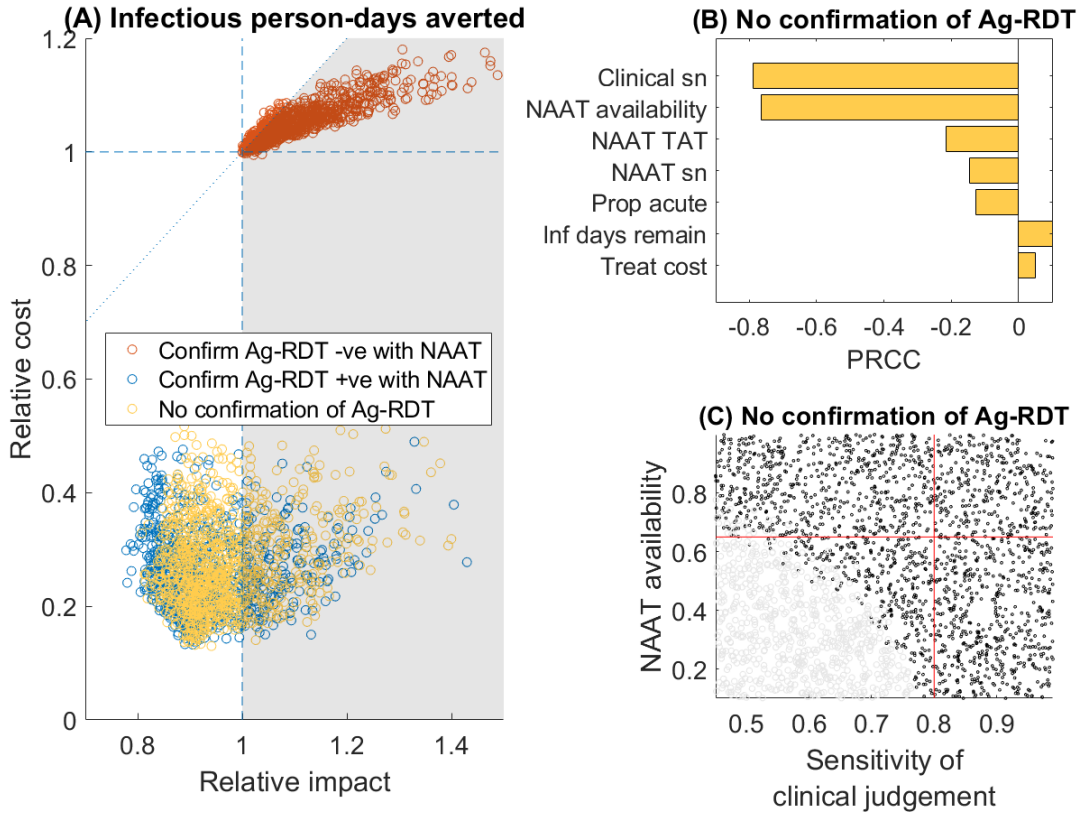

Figure 6.4. Relative value of Ag-RDT vs NAAT testing, for averting infections in a hospital setting. (A) scatter plots for the relative impact of Ag-RDT vs NAAT (horizontal axis), vs the relative cost of the two strategies (vertical axis). Of the yellow points (no NAAT confirmation of Ag-RDT results), 27% fell in the favourable region shaded in grey, 21% for NAAT confirmation of positive Ag-RDT results and 91% for NAAT confirmation of negative Ag-RDT results . Details as in fig 6.2 and fig 6.3. (B) Sensitivity analysis for model parameters on the yellow points in panel (A). The interpretation of PRCC is explained in further detail in the caption of fig 6.3. *Clinical sn* – sensitivity of clinical judgement; *NAAT TAT* – turnaround time of NAAT; *NAAT sn* – NAAT sensitivity; *prop acute* – proportion amongst those tested that are in the acute stage of infection; *Inf days remain* - Of those in acute phase, number of infectious days remaining; *Treat cost* – cost of treatment. Panel (C) concentrates on the two most influential parameters in this case, NAAT availability and sensitivity of clinical judgement. As in fig 6.3C, grey and black points show parameter regimes where an Ag-RDT was, respectively, favourable and unfavourable, relative to NAAT. Red lines show 80% sensitivity of clinical judgment (vertical line), and 65% NAAT availability (horizontal line). In the lower left quadrant of these lines, an Ag-RDT was favourable over NAAT in 66% of simulations. In these results it was assumed that patients were placed in isolation while awaiting a NAAT result: fig 6.6 shows results in the alternative scenario where they were not isolated.

These results assume that all patients were placed in isolation while awaiting NAAT results. Fig 6.5 and 6.6 show corresponding results when assuming no isolation pending NAAT results, illustrating that the results are essentially unchanged for deaths averted (fig 6.5). For infectious patient-days isolated, a practice of isolating patients pending NAAT results mitigated the drawbacks of multi-day NAAT turnaround times: a decision not to isolate pending results therefore reduced the impact of a NAAT-based strategy, thus making an Ag-RDT-only strategy more favourable in comparison. Fig 6.6 illustrates that, in such a scenario, 93% of simulations placed the Ag-RDT strategy in the favourable region.

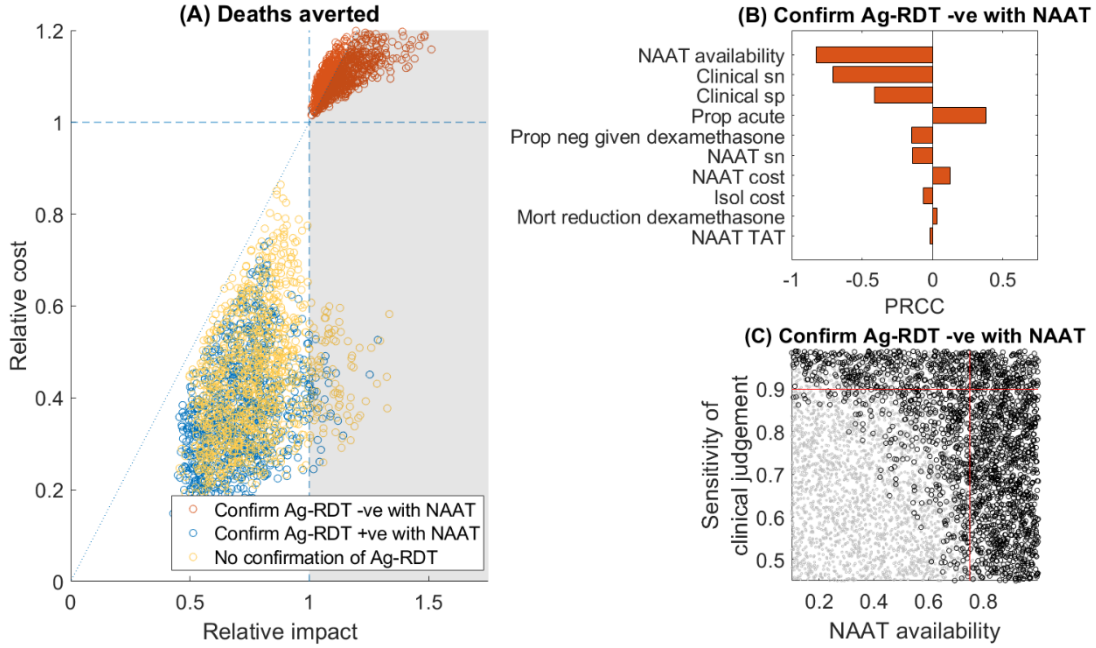

Figure 6.5. Relative value of Ag-RDT-led vs NAAT-based testing, for averting deaths in a hospital setting. The figure shows the same results as those presented in fig 6.3, but here assuming that all patients awaiting a NAAT result (whether as part of a NAAT-based strategy or for confirmation of Ag-RDT results) were *not* isolated during this time. Results illustrate qualitatively similar findings to those shown in the main text. In panel (A), in the scenario where Ag-RDT-negative results were confirmed using NAAT (red points), 57% of simulations placed the Ag-RDT-led strategy in the favourable region, below the diagonal dashed line, whereas only 7% and 5% of points under a Ag-RDT only strategy and NAAT confirmation of Ag-RDT-positive cases were favourable. Panels (B, C) show additional sensitivity analyses for these points in particular, as described in fig 6.3. *Clinical sn* – sensitivity of clinical judgement; *Clinical sp* – specificity of clinical judgement; *Prop acute* – proportion amongst those tested that are in the acute stage of infection; *Prop neg given dexamethasone* – proportion of hospitalised patients with a negative COVID-19 test result that are initiated onto dexamethasone; *NAAT sn* – NAAT sensitivity; *Isol cost* – Cost of isolation; *Mort reduction dexamethasone* - Case fatality reduction amongst COVID-19 patients on dexamethasone; *NAAT TAT* – turnaround time of NAAT. In (C), red lines show 75% NAAT availability (vertical line), and 90% sensitivity of clinical judgment (horizontal line). In the lower left quadrant of these lines, an Ag-RDT was favourable over NAAT in 85% of simulations.

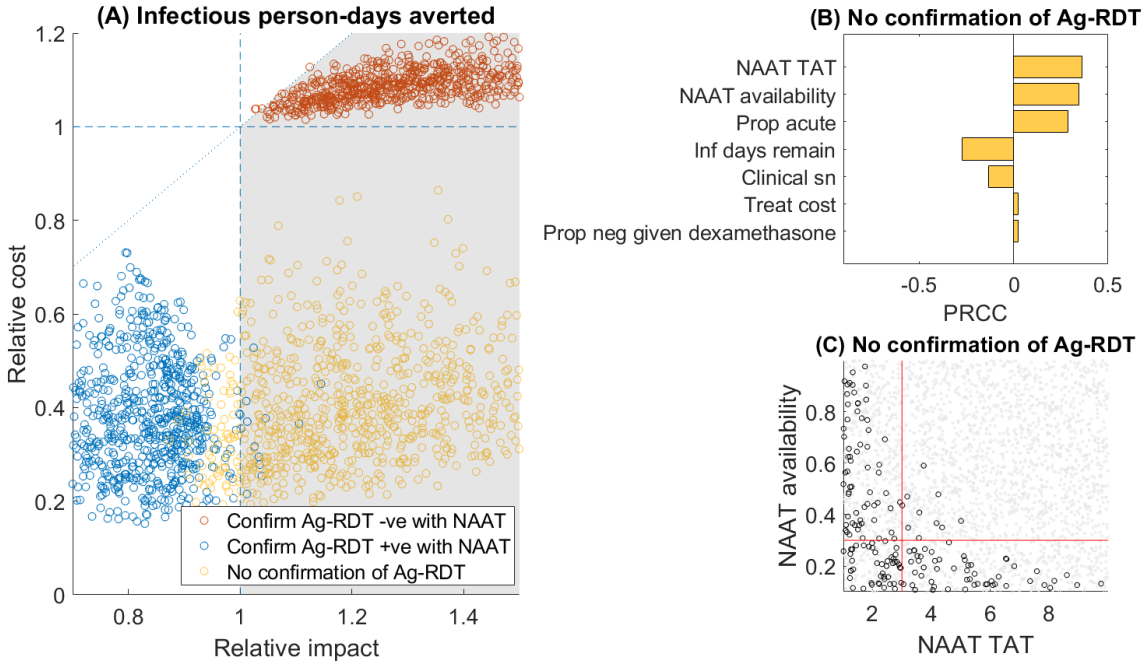

Figure 6.6. Relative value of Ag-RDT-led vs NAAT-based testing, for averting infections in a hospital setting. The figure shows the same results as those presented in fig 6.4, but here assuming all patients awaiting a NAAT result (whether as part of a NAAT-based strategy or for confirmation of Ag-RDT results) were not isolated during this time. In panel (A), in the scenario where there was no NAAT confirmation of Ag-RDT results (yellow points), 93% of simulations placed the Ag-RDT-led strategy in the favourable region, to the right of the vertical, dashed line. 99% and 4% of simulations were favourable under a NAAT confirmation of Ag-RDT negative and positive results, respectively. Panels (B, C) show additional sensitivity analyses for these points in particular, as described in fig 6.4. *NAAT TAT* – turnaround time of NAAT; *Prop acute* – proportion amongst those tested that are in the acute stage of infection; *Inf days remain* - Of those in acute phase, number of infectious days remaining; *Clinical sn* – sensitivity of clinical judgement; *Treat cost* – cost of treatment; *Prop neg given dexamethasone* – proportion of hospitalised patients with a negative COVID-19 test result that are initiated onto dexamethasone. In (C), red lines show a NAAT turnaround time of 3 days (vertical line), and a 30% NAAT availability (horizontal line). In the upper right quadrant of these lines, an Ag-RDT was favourable over NAAT in 69% of simulations.

6.3.2. Community Setting

Finally, fig 6.7 shows results for the community setting scenario. Key assumptions, compared to the hospital scenario, include: the sole priority is to avert infection, because mortality risk in the individuals being evaluated is low; lower prevalence of SARS-CoV-2 amongst those being tested (5%); and I assumed individuals are not placed in isolation while awaiting NAAT results, because of the infeasibility of doing so. Similarly to fig 6.4, confirming Ag-RDT-negative cases with NAAT was highly likely to avert more potential transmission than NAAT alone, and at lower cost per infectious day averted (red points, favourable in 80% of simulations). It was also possible for the sole use of Ag-RDT to be more impactful than NAAT while costing less (yellow points, favourable in 98% of simulations). Fig 6.7B illustrates the key drivers that increased the relative impact of Ag-RDT-only vs NAAT-based strategies. These were: a higher proportion of individuals that were still in their acute (infectious) phase while being tested; a higher availability of NAAT; a higher cost per NAAT test; and a longer NAAT turnaround time.

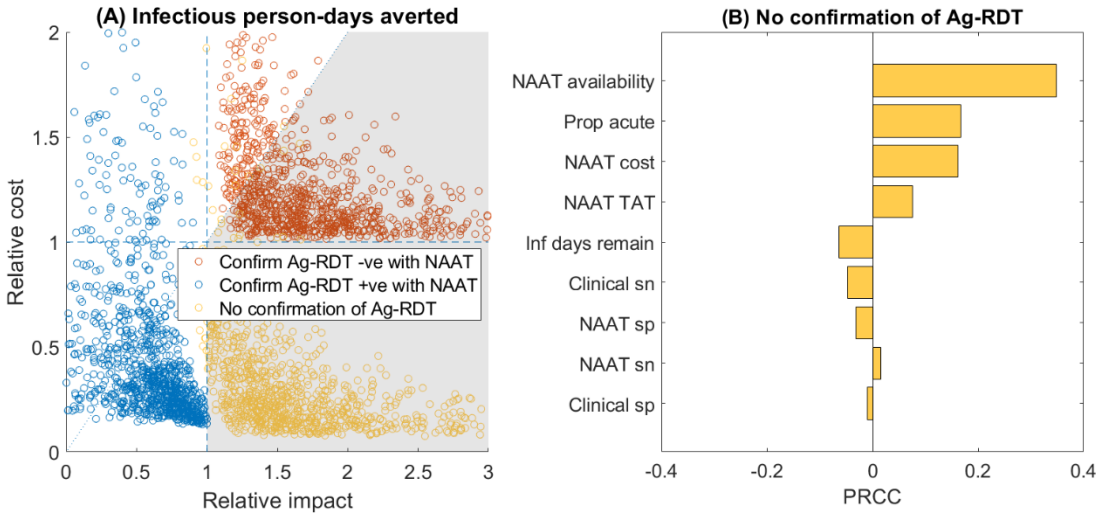

Figure 6.7. Relative value of Ag-RDT vs NAAT testing in a community setting. I assumed that in a community setting, the focus is on averting infection, and that any severe cases of respiratory disease are more likely to present in hospital settings (fig 6.4). Hence in this setting, I focused on infectious person-days averted; I also assumed that individuals awaiting NAAT results were not isolated during this time, owing to the infeasibility of doing so in this setting. (A) Scatter plot of the relative impact of Ag-RDT vs NAAT (horizontal axis) vs the relative cost of Ag-RDT vs NAAT (vertical axis). Dashed reference lines are as explained in fig 6.3, and in fig 6.2. Of the yellow points (no NAAT confirmation of Ag-RDT results), 98% fell in the favourable region shaded in grey; of the red points (confirm Ag-RDT negatives with a NAAT), 80% fell in the favourable region; of the blue points (confirm Ag-RDT positives with a NAAT) less than 1% of simulations were favourable. (B) Subgroup sensitivity analysis of the yellow points in panel (A). Interpretation of PRCC is as explained in fig 6.3 caption. *Prop acute* – proportion amongst those tested that are in the acute stage of infection; *NAAT TAT* – turnaround time of NAAT; *Inf days remain* - Of those in acute phase, number of infectious days remaining; *Clinical sn* – sensitivity of clinical judgement; *NAAT sp* – NAAT specificity; *NAAT sn* – NAAT sensitivity; *Clinical sp* – specificity of clinical judgement. Because the vast majority (98%) of simulations show Ag-RDT was favourable to NAAT in this scenario, I did not conduct additional bivariate sensitivity analyses.

6.3.3. Additional sensitivity analysis

Fig A4.1 – A4.3 show additional sensitivity analyses for both hospital and community settings, under alternative model assumptions. For example, the proportion of simulations being favourable for Ag-RDT remained stable with respect to alternative assumptions for the prevalence of COVID in the population being tested and under different algorithms, in both hospital and community settings (fig A4.1). Increasing Ag-RDT sensitivity increased the favourability of all three Ag-RDT algorithms in the hospital setting (fig A4.2A and A4.2B), but had only modest effect on the community setting (fig A4.2C). Increasing Ag-RDT specificity had similarly modest impact on an algorithm's favourability in all settings (fig A4.2D-F). Fig A4.3 shows analysis under alternative assumptions for self-isolating behaviour in the community setting. Diminishing compliance with requirements to self-isolate tended to reduce the favourability of an Ag-RDT-only strategy (i.e. with no NAAT confirmation), but had the opposite effect on the favourability of a strategy to confirm Ag-RDT-positives. In both cases, the proportion favourable varied by less than 10 percentage points over the parameter range examined here. Similar sensitivity was observed for model assumptions relating to voluntary self-isolation, when not required to do so (fig A4.3B).

6.4. Discussion

The emergence of Ag-RDTs for SARS-CoV-2 has raised important questions about trade-offs between accessibility and performance; to inform country-level decisions about the use of these tests, there is a need for more evidence on how to navigate such trade-offs. Recent models and commentaries have highlighted the potential utility of high-frequency, low-sensitivity testing of asymptomatic individuals (540), and the current analysis demonstrates that under certain circumstances, a less-sensitive but more-accessible test may be preferable for diagnosis of symptomatic COVID-19 as well. Rather than aiming to specify parameter values with precision, the approach instead embraces parameter uncertainty, by modelling a broad range of scenarios or contextual factors. This approach partly reflects the uncertainty in model parameters, but also their anticipated variability across different country settings and as local epidemics change over time. By structuring the approach in this fashion, I sought to identify the contextual factors that are most important in deciding the value of an Ag-RDT.

These results suggest that the value of an Ag-RDT-led strategy is strongly supported for evaluating symptomatic individuals in community settings, being highly likely to be simultaneously less costly and more impactful than relying on NAAT and clinical judgement (fig 6.7). In hospital settings, the favourability of Ag-RDT may be subject to certain qualifications. For example, in averting deaths, an Ag-RDT, supported by NAAT to confirm Ag-RDT-negative results, is likely to be favourable

(averting more deaths, at less cost per death averted) to NAAT and clinical judgment alone, in settings where NAAT is available for less than 85% of patients and sensitivity of clinical judgement (in the absence of NAAT) is less than 90% (fig 6.3). However, although confirmation of a negative Ag-RDT result with NAAT averts more deaths for a given cost than NAAT only, this algorithm is still more costly than a NAAT-only algorithm and may therefore raise challenges of affordability in settings with limited resources.

In the community setting, any reliance on NAAT-based testing would face substantial challenges in practice. For example, in most settings it is unlikely that individuals would be adequately isolated while awaiting NAAT results, given the large number of unnecessary isolations, and associated burden on patients and families, that such a strategy would incur. Moreover, it will also typically be infeasible to offer timely NAAT to all individuals with potential COVID-19 symptoms, given the attendant financial, human resource and supply constraints. In this setting, the analysis shows how an affordable, rapid test, even one with lower performance than NAAT, can achieve greater impact overall, and at lower cost, than a strategy that relies on NAAT instead.

Notably in both hospital and community scenarios, the key determining factors for the value of an Ag-RDT (namely, the availability of NAAT, sensitivity of clinical judgment, and proportion of cases tested during the acute phase) all relate to the ability of the existing system to detect cases of SARS-CoV-2. These findings highlight the potential value of implementation studies to gather data on these factors when making programmatic decisions for the introduction and implementation of new Ag-RDTs in any given setting. Overall, this work serves broadly to illustrate an analytical framework that could be readily adjusted to local realities in different settings. A simple, user-friendly web-based tool is available, to perform the simulations shown here, but also to allow these simulations to be extended to alternative, user-specified parameter ranges (https://covid-ag-rdt.shinyapps.io/model/).

Certain limitations of scope bear mention. The focus in this work is on identifying the circumstances in which an Ag-RDT might be most valuable, given a pre-specified performance profile. Recent guidance published by WHO addresses target product profiles for Ag-RDTs: that is, how a test should best be optimised in terms of accuracy, cost and ease-of-use, for specified use cases (521). For simplicity, the approach treats transmission-related impact of testing as being directly proportional to the number of days for which testing results in isolation of an infectious person, without considering variation between individuals or over time in the degree of infectivity or the strictness of isolation. Similarly, my assessment of mortality outcomes does not account for the potential of a test to indirectly reduce incidence and mortality by interrupting transmission. Further work using dynamic models of SARS-CoV-2 transmission would be valuable in addressing this gap. In addition, while the results are based on a broad sensitivity analysis, it should be noted that these same results may depend

on the range of parameters that I have assumed, and indeed these ranges may vary across different settings. The user-friendly tool allows users to adapt some of these ranges to specific settings. Amongst other limitations, I have adopted several simplifications, perhaps most importantly assuming a dichotomy between 'acute' and 'recent' infection and the detectability of each by NAAT or Ag-RDT. This assumption ignores potentially important complexities, including how infectivity varies over the clinical course; the stage in the clinical course at which individuals are likely to be tested; and the implications of changing viral/antigen/RNA load over the clinical course, for the ability of a given test to detect infection (269,271,272,541,542). Previous modelling studies have incorporated some combinations of these factors (501,540), but longitudinal data on all of these factors will be critical in refining these and other modelling approaches, to account fully for their potential interactions.

6.5. Conclusion

In summary, given the immediate importance of virological testing for the control of SARS-CoV-2, it is important for decisions about testing strategy to be guided by the available evidence. The results show how, in certain clinical conditions, the use of Ag-RDTs could achieve equal or greater impact, and at lower cost, than relying on NAAT alone. While the accuracy of diagnostic tools is important, other considerations are also critical: as control efforts increasingly shift from blanket lockdowns towards intensive testing and early identification, the speed, affordability, and ease-of-use of diagnostic tools are likely to play an increasingly key role in the response to SARS-CoV-2. The findings illustrate where such rapid and affordable tests are likely to improve outcomes in a more cost-efficient way than reliance on NAAT and clinical judgement alone. This work has also led to the development of a user-friendly online tool for use by public-health practitioners.

Chapter 7: Discussion

Diagnostic tests play a crucial role in the control and surveillance of infectious diseases, and to ensure effective clinical management. The aim of the thesis was to examine the potential impact that novel diagnostic tests may have on the TB and COVID-19 epidemics in settings with a high burden of disease. Traditionally diagnostic tests are evaluated on their accuracy (sensitivity and specificity). Instead, I paid particular attention to understanding the context in which diagnostic tests are used, and how this may affect their impact. I demonstrate that when evaluating diagnostic tests, it is important to move away from focussing only on their accuracy. Predicting the impact of these tests was made possible by mathematical models, a platform that allows for the integration of existing evidence and uncertainty analysis. In this section, I summarise the findings from each chapter and their implications, followed by future directions.

7.1. Summary of findings

Below, I summarise the main findings from each chapter. The aim of the thesis was to understand the impact that novel diagnostic tests may have on infectious disease epidemics (with a focus on TB), and to further understand how the context in which diagnostic tests are used may affect this impact. For each chapter, I developed a mathematical model unique to the diagnostic test in question.

In Chapter 3, I focussed on a hypothetical biomarker test that detects individuals who are at imminent risk of progressing to active TB disease within the next two years without intervention (i.e., incipient TB). As high-burden countries, such as India, start to look towards TB elimination, targeting TB stages prior to the development of active TB will become increasingly important. As incipient TB is asymptomatic, one method of detection is testing the entire population; however, frequent mass testing is likely to be costly. Thus, I assessed how the epidemiological impact and cost effectiveness of such a test may differ across populations with different levels of TB risk. I developed a mathematical model of TB transmission in a typical Indian slum (higher risk of TB) and non-slum (lower risk of TB). I found that such a test had important epidemiological impact across both settings, even with limited sensitivity. However, the intervention was costly, due to the large number of tests needed to identify a case of incipient TB, even in high-risk populations such as slums, and thus, was not cost effective. Although biomarker-led TB preventive treatment ("TPT") likely offers a more cost-effective approach than mass TPT (377,543) this work suggests that more refined measures of risk (including potential correlates such as nutrition status and other risk factors (366,413) are still needed to further reduce the cost per TB death or case averted.

In Chapter 4, I explored the potential epidemiological impact of urine-based diagnostic tests for active TB. People living with HIV ("PLHIV") are frequently misdiagnosed due to their inability to produce good quality sputum. Urine-based diagnostic tests can circumvent this issue, and therefore could improve diagnosis amongst PLHIV. Current urine-based tests suffer from poor accuracy amongst individuals with high CD4 cell counts, and consequently their use has been limited to PLHIV-inpatients and -outpatients with low CD4 cell counts. However, the performance of these tests is improving, and thus, it is important to anticipate the level of deployment needed to have population-level epidemiological impact. Thus, I developed a mathematical model of TB transmission in South Africa, a country with a high burden of both HIV and TB. I incorporated different patient subgroups (HIV-inpatients, HIV-outpatients, and routine TB care) so that different test eligibility criteria could be examined. I found that although urine-based diagnostic tests reduced mortality amongst PLHIV inpatients and outpatients, population-level epidemiological impact was not seen unless the tests were deployed outside HIV care and into routine TB care (including amongst HIV negatives), even in a

high-HIV burden setting. The results highlight that even if the coverage of Xpert, a high-performance test, is expanded, a urine-based test with poorer performance may still substantially reduce TB cases and deaths, especially in settings with a high HIV, extrapulmonary or paediatric TB burden, if deployed widely enough.

In Chapter 5, I investigated the potential epidemiological impact increasing various services offered by private sector engagement initiatives may have on the TB epidemic in a typical urban Indian setting. I further examined which service had the lowest incremental cost-effectiveness ratio ("ICER"). I developed a mathematical model of TB transmission, incorporating different types of private providers and drug-resistance. I also developed a costing model based on two cities with contrasting service coverage, Ahmedabad and Delhi. I demonstrated that increasing the various services can have a modest impact on TB cases and deaths, and a significant impact on drug-resistant TB. The interventions with the lowest ICERs were increasing the use of government supplied fixed dose combinations ("FDCs") and increasing the number of private providers that notify their TB, whereas interventions involving increasing the use of Xpert amongst the private providers were the least cost-efficient. These results imply that even though increasing the use of Xpert does have the largest impact on TB epidemiology, especially on drug-resistant ("DR-TB"), its cost is likely prohibitive especially under a limited budget.

Finally, in Chapter 6, I applied similar techniques used in the previous chapters to another respiratory pathogen, SARS-CoV-2. As SARS-CoV-2 spread globally in 2020, many countries were faced with insufficient laboratory capacity to perform nucleic acid amplification tests ("NAATs"), a reference standard for the diagnosis of COVID-19, resulting in high turnaround times. Meanwhile, rapid antigen diagnostic tests ("Ag-RDTs") were being developed; these tests are quick, cheap, and suitable at the point of care, but are less accurate. I explored the context under when Ag-RDTs could offer greater public health value than NAATs. I developed a different type of mathematical model, a decision tree, to evaluate the cost and health impact of different testing algorithms under a community and hospital setting. Unlike the TB models I created for the previous chapters, decision analysis does not consider transmission dynamics. I chose this model to represent clearly the actions taken by clinicians following a positive or negative test result. I approximated epidemiological impact by counting the incremental number of days infectious individuals spend out of isolation and the incremental number of deaths. The results demonstrate that in a hospital setting, an Ag-RDT-led strategy offered greater public health value if the accuracy of clinical judgement and the availability of NAAT was low, whereas an Ag-RDT-led strategy was favoured in a community setting, under a wide range of assumptions. These results suggest that despite their imperfect sensitivity and specificity, Ag-RDTs have the potential to be more impactful at a lower cost than NAATs under different use-cases.

7.2. Implications of findings

The implications of this work can be split into two categories: the direct implications on TB and COVID-19, and the broader implications on the use of diagnostic tests in general, and why context is important when examining their impact.

Overall, the results presented in this thesis suggest that novel diagnostic tests can have a modest impact on TB and COVID-19; however, the cost-effectiveness of these interventions needs to be carefully considered. Chapter 3 highlights the fact that targeting the TB stages prior to active TB disease to reach TB elimination is unlikely to be straightforward. Due to the number of people needed to test to detect one of these stages and initiate TPT, the cost of such an intervention is likely to be prohibitive and not cost-effective, especially in high TB burden countries. As high burden TB countries begin to look towards TB elimination, either more refined measures of risk are needed to reduce the number of people tested, or alternative interventions, such as vaccination, are urgently needed. Having more refined measures of risk in order to reduce the numbers needed to test to avert one case of active disease, will increase the cost-effectiveness of the intervention; however, if the measures of risk are too stringent, cases of incipient TB will inevitably be missed, and the overall epidemiological impact reduced (377). Future work should model and anticipate the epidemiological impact and cost-effectiveness of an intervention that combines biomarker-led TPT and risk-scores. In terms of vaccines, two types of vaccines are needed: one that prevents progression to disease to prevent LTBI from progression to active disease, and one that prevents infection in the first place. Two candidate vaccines are currently in phase 2b and phase 3 of trials, the former aiming to prevent TB infection and disease, and the latter to prevent TB disease (544,545).

Chapter 4 demonstrates the value of urine-based tests for TB diagnosis in high HIV-TB burden countries. Many countries have been hesitant to take up urine tests due to their low accuracy and lack of modelling studies examining their potential impact (450). Consequently, the use of these urine tests is restricted to HIV-inpatients and -outpatients with low CD4 cell counts (546). However, our results demonstrate that a population-level impact on TB incidence and mortality is only seen if the use of these tests are expanded into routine TB care; it is only at this broad deployment level that TB patients that are missed by Xpert, due to their inability at producing a good quality sputum sample, either due to being coinfected with HIV or having extrapulmonary TB, are being detected. Globally, around 16% of incident TB cases have extrapulmonary TB and 8% are co-infected with HIV (6). Urine-based TB tests present an opportunity to reduce the diagnosis gap amongst these population sub-groups. Overall, this work implies that future tests need to have wider eligibility; however, in order for this to happen, there are issues that need to be addressed, including not only test sensitivity, but specificity

too (i.e., the potential of false positives) and ease of implementation, both of which have been outside the scope of this work. Future work should also assess the potential impact of urine-based tests in different epidemiological settings (i.e., settings with low levels of HIV), different testing algorithms, and the cost-effectiveness of these tests compared to current diagnostic tests.

The results from chapter 5 imply that although increasing the use of Xpert amongst private providers has a moderate epidemiological impact, compared to other PPSA activities such as increasing FDC use and TB notification, it has the highest ICER (i.e., least cost-efficient). Although studies have shown Xpert to be cost-effective and epidemiologically impactful (140,498,499,547), our results suggest that under a limited budget, increasing Xpert use may not be the most appropriate course of action. This highlights the fact that increasing the use of an accurate test is not necessarily always the most cost-efficient option, and that interventions that are cheaper but have a lower epidemiological impact, such as increasing the use of FDCs, should not be ruled out. However, this work did not include a full cost-effectiveness analysis; for example, if down-stream benefits of averting DR-TB were included in the analysis, the ICER for the PPSA interventions involving Xpert may decrease. Additionally, depending on priorities, choosing the intervention with the largest impact (i.e., averts the most TB cases or deaths) regardless of the cost may be more appropriate than choosing an intervention that is the least costly but that has the smallest impact.

Similarly, chapter 6 highlights the fact that the use of an accurate test is not always the most cost-efficient option. Many countries have favoured the use of NAATs due to their higher accuracy, however our results demonstrate that Ag-RDTs can be more cost-efficient in certain use-cases. Like TB urine tests, these results highlight how tests with lower accuracy can play a critical role in certain use-cases. Indeed, countries have started using Ag-RDTs for mass testing, including regular testing of secondary school children in the UK (548). More real-world evidence is needed to assess the true impact of Ag-RDTs.

Although each chapter describes the potential impact diagnostic tests may have specifically on TB and COVID-19 epidemics, these results can be viewed more broadly. Novel diagnostic tests are traditionally assessed on their accuracy (sensitivity and specificity); due to the trade-off between sensitivity and specificity, defining what is an acceptable risk of a false positive or false negative result is challenging. However, this is further complicated by additional factors other than accuracy; there is also often a trade-off between accuracy and accessibility (549). Another study focussing on TB that used a simplified framework, demonstrated that the value of novel diagnostic tests is dependent not only on accuracy, but also on factors including patient care-seeking behaviour, health systems (i.e., linkage to treatment) and the natural history of TB (334). This is also highlighted in this work, with examples specific to TB and COVID-19. I show that the accuracy of a test is not always

indicative of its potential impact. Other factors such as turnaround time, cost, and sample requirements may also be influential depending on the context in which the tests are being used. I discuss these factors in more detail below.

Care-seeking pathway

The time taken for patients to seek care, where patients choose to seek care and at what stage of infection they seek care at, will affect the effectiveness of a novel diagnostic test (334). For example, if most transmission occurs before patients receive a test diagnosis, the impact of the diagnostic test on the epidemiology of the infectious disease in question will be limited (334). A modelling study examining the impact of increasing PPSA services in India found that the impact may be limited due to the patient delay of seeking care, allowing for high amounts of transmission (239). Another important factor is where in the healthcare system the tests are placed; results from chapter 4 suggest that introducing future urine tests not only into HIV care, but into routine TB care, to diagnose TB amongst patients with undiagnosed HIV can be beneficial.

Level of current testing

The coverage level and diagnostic performance of tests currently used in a setting may reduce the impact of a newly introduced test. For example, one theory why the rollout of Xpert has not led to an increase in TB treatment initiation in certain countries despite being more accurate than sputum smear microscopy, is due to high background rates of empirical treatment, reducing the incremental benefit of Xpert (155,156). The impact of current testing is seen in chapter 6, where the sensitivity of clinical judgement amongst patients unable to access NAAT was highly influential on the value of Ag-RDTs; a higher sensitivity of clinical judgement reduced the relative impact of Ag-RDTs under a hospital setting. Similarly, NAAT availability was also influential in determining the value of Ag-RDTs. Under a hospital setting, greater NAAT availability reduced the value of Ag-RDTs due to their superior accuracy assuming patients are isolated whilst awaiting test results, whereas under a community setting, greater NAAT availability increased the value of Ag-RDTs due to the longer turnaround times with NAAT. Similarly, the epidemiological impact of urine tests in South Africa is reduced if current Xpert coverage is increased so that all patients with symptoms suggestive of TB are tested with Xpert on their first presentation for care; nevertheless, even if Xpert coverage is increased to such levels, urine tests still offer additional benefit due to their reliance on urine instead of sputum, and thus, increasing TB diagnosis amongst population subgroups that struggle to produce good quality sputum. These results suggest that future urine tests have the potential to offer population level impact even alongside high levels of Xpert coverage.

Cost

The cost of a diagnostic test is often the focus of economic evaluations. A highly accurate but costly test is not always the most cost-effective nor cost-efficient option. For example, some studies suggest that the higher diagnostic yield of Xpert may compensate for its high cost (142), and that including Xpert in diagnostic algorithms is cost-effective or cost-neutral (155,498,499). However, the results in this thesis (chapters 5 and 6) clearly demonstrate that costly tests are not always the most cost-efficient option; even with a highly sensitive and specific test, a less accurate test may be more favourable if cheaper. Chapter 5 shows that although increasing Xpert use is epidemiologically impactful, due to the cost of Xpert testing and the cost of engaging with providers to use Xpert, increasing Xpert use was one of the least cost-efficient interventions; instead, less epidemiologically impactful but less costly interventions, such as increasing the use of government-supplied FDCs, were more cost-efficient. Similarly, chapter 6 demonstrates this for COVID-19, and how less accurate but cheaper Ag-RDTs are more cost-efficient than NAATs under various use-cases.

Another cost consideration is the cost of the program needed to implement a novel diagnostic test; these costs could include the cost of human resources, the cost of energy needed to power the test or the cost of transporting samples (550). This cost can often be much larger than the cost of the diagnostic itself. Costs further downstream, such as the cost of treating all patients that test positive as a result of the novel diagnostic, also need to be considered (551). Not including these additional costs may over-estimate the cost-effectiveness of an intervention. Finally, even if a test is considered cost-effective, it does not necessarily mean the test is affordable. The cost of implementation and what benchmark is considered affordable will be country-specific, so ideally economic evaluations are needed for different settings (549).

Turnaround time

A short turnaround time from the time a patient is tested to the time they receive the test result is crucial to reduce onwards transmission and loss to follow up. For example, Xpert tests placed at centralised laboratories often have longer turnaround times than those placed at the primary care level, increasing delays in TB treatment initiation and increasing loss to follow up (141); however, to complicate things further, economic evaluation suggests that the cost of Xpert is greater at the point of care than at centralised laboratories (140,154). Similarly, countries have faced long turnaround times with NAATs at the start of the COVID-19 pandemic. Results from chapter 6 demonstrate that Ag-RDTs are more cost efficient than NAATs under different testing algorithms and use-cases, with the length of the turnaround time being an influential parameter in determining this relative impact. Other studies have also reported the importance of turnaround time and test accessibility for COVID-19 diagnosis (540). Thus, when examining the impact of diagnostic tests, it is crucial to accurately define the use-case; for example, are patients isolated whilst awaiting test results, is the test suitable at the

point-of-care, and if not, how long does it take to get the sample from the clinic to the laboratory and back.

Nevertheless, even if a diagnostic test has a short turnaround time, it will have poor epidemiological impact if linkage to treatment is poor (549). Thus, modelling studies, when examining the potential impact of diagnostic tests, should incorporate this to reduce the risk of overestimating the epidemiological impact. Again, the rate of treatment initiation is likely to be setting specific.

Risk of disease

The population-level risk of disease will also impact the cost efficiency and effectiveness of a test. For example, if the risk of disease is low, a test with high specificity is crucial to reduce the risk of false positives and resulting treatment costs. This is demonstrated in chapter 3 – although a lot of emphasis has been placed on testing and treating patients with incipient TB as a more cost-efficient approach than mass latent TB infection testing, my results suggest that even under a slum-targeted testing strategy, testing for incipient TB is not cost-effective, due to the number of tests needed to detect a case of incipient TB. Thus, the risk of disease links into the cost of a test; testing a large number of people to detect or avert one case requires a cheap test. In the case of incipient TB, the cost per test needed for the intervention to be considered cost-effective in India, is not feasible.

Sample type

The type of sample a diagnostic test uses may also impact its overall performance. For example, to diagnose COVID-19, NAAT sensitivity decreases from 93% for bronchoalveolar lavage to 32% for a throat swab (511). Similarly, for TB, sputum collection from certain population sub-groups can be difficult, leading to these population subgroups being under- and mis-diagnosed. Furthermore, sputum collection for TB poses a risk of infection to the healthcare works, and thus, trained workers are required. Chapter 4 highlights how even if the coverage of Xpert, a highly accurate sputum-based test, is expanded, so that everyone presenting to care receives one, introducing urine-based tests can still avert a substantial number of cases due to the population sub-groups being missed by Xpert.

Overall, these results imply that a test that is less accurate than currently available tests should not automatically be written off; likewise, a more accurate test does not necessarily translate into a large epidemiological impact and is not necessarily cost-effective. Other factors including cost, ease of use, infrastructure and training requirements, and turnaround time all play an important role in make a less accurate test more epidemiologically impactful, or a more accurate test less impactful. Thus, defining the use-case is key, as the importance of these characteristics will differ depending on the use-case.

7.3. Limitations and future directions

One of the biggest challenges when constructing mathematical models is the availability of data. When available, parameter estimates should be made from systematic reviews or meta-analyses; unfortunately, such studies are not always available. Having more up to date data on incidence, prevalence and ARTI at subnational levels will help further our understanding on the heterogeneity of TB burden across India and other high TB burden countries and reduce the uncertainty around model projections. In India, this is further complicated by the dominant private healthcare sector, where, although TB is a notifiable disease, notifications from private providers remain low (215). Effort has been made to estimate the burden of TB in the private sector (227,240), however much uncertainty remains. It should also be noted that the TB modelling presented in this thesis was conducted prior to the COVID-19 pandemic. The pandemic has led to a resurgence in TB cases due to patients not accessing TB diagnostic and treatment services, thus updated data on the true burden of TB is needed. A modelling study estimates that in high burden settings, TB deaths over 5 years may increase by up to 20% (203). Future work should investigate how the COVID-19 pandemic has impacted the results presented in this thesis. Considering how many variables apart from test accuracy may impact the effectiveness of a diagnostic test (including patient behaviour, linkage to care and rates of current testing), and that these factors are likely to vary across settings, a huge amount of data is needed to construct models specific to each setting; results from one setting may not necessarily be generalisable. Future work should therefore aim to understand further how these different factors differ across settings. Finally, to provide greater weight and confidence to future model projections, future work should aim to validate the model against historical data, in order to see how well the model can retrospectively predict past TB epidemiological trends.

Another challenge with mathematical models is making assumptions about the natural history of pathogen in question and having sufficient data to support this. For example, the importance of additional stages within the natural history of TB, such as incipient and subclinical TB, are becoming increasingly apparent (26). How these stages are defined also vary; although incipient TB is defined as an infection that is at imminent risk of progressing to active disease (10), how this ‘imminent’ risk is defined, varies across studies. Similar issues arise with COVID-19, with questions remaining on the proportion of cases that present as either asymptomatic, presymptomatic or symptomatic.

An additional limitation is the availability of costing data. For chapter 5, I was fortunate to collaborate with CHAI who provided retrospective costing data for a variety of TB activities in different cities across India. Unfortunately, detailed costing is not always publicly available and is usually setting specific. For chapters 2 and 6, I had to rely on publicly available data that do not necessarily reflect

the true cost of the setting under examination; however, I took this uncertainty into consideration by widening the confidence intervals of each cost. In chapter 3, where I conducted a simple cost-effectiveness analysis on incipient TB testing, although the results suggest that the intervention is not cost effective, future work should consider conducting a full cost-effectiveness analysis that incorporates all health system costs involved with facilitating the expansion of mass testing and consider potential comparators. Furthermore, costing interventions involving diagnostic tests is complicated, considering all the upstream (i.e., patient behaviour) and downstream factors (i.e., linkage to treatment) that influence the epidemiological impact of a test (552).

Similarly, it is not always clear what cost-effectiveness threshold is appropriate. As mentioned in chapter 2, there has been much debate about what this threshold should be; traditionally, 1-3 times a country's GDP per capita has been used however recent data suggests these may be too high (347,405). In chapter 3, where I conduct a cost-effectiveness analysis, I assumed a threshold of 1 time the GDP per capita to represent an optimistic threshold, and to highlight the point that the intervention of incipient TB testing was not cost-effective, even under an optimistic threshold. Furthermore, all the costs examined in this thesis has focussed on the perspective of the health system, ignoring the costs incurred by patients. The costs incurred by patients as a result of an intervention will affect the uptake of an intervention, thus future analysis should consider examining the costs incurred by patients as a result of the different interventions examined in this thesis.

Cost-effectiveness analyses are further complicated when it comes to disease elimination. How we quantify the long-term downstream benefits of TB elimination remains uncertain. Unfortunately, ignoring these downstream long-term benefits may underestimate the cost-effectiveness of an intervention. This raises the question whether cost-effectiveness analysis is an appropriate tool to economically evaluate an intervention whose aim is to reach disease elimination.

7.4. Conclusion

In conclusion, novel diagnostic tests may have a significant impact on TB and COVID-19. More importantly, the context in which diagnostic tests are used is crucial in anticipating their impact. There is a clear need to move away from the vacuum of evaluating diagnostic tests purely on test accuracy. For example, diagnostic tests with poorer accuracy than pre-existing diagnostic tests may still be impactful under the right use-case if their characteristics, such as cost or turnaround time, differ from pre-existing tests. Thus, a novel diagnostic test with poor accuracy should not automatically be discarded; likewise, a test with high accuracy is not necessarily always the most appropriate or cost-effective solution. Future work should include data collection across different

settings, operational research, and implementation studies in order to help bridge the data gap so that full cost-effectiveness analyses of the tests examined in this thesis, specific to the use-case under investigation, can be performed.

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Appendix 1

The potential value of biomarker-led preventive treatment in eliminating tuberculosis: a modelling analysis

1. Materials and methods

Below, I describe the model, including its structure, governing equations and table of parameters. The model was designed in MATLAB.

1.1. Model structure

I modelled TB transmission amongst adults (>15 years old) in the slums and non-slums of Chennai, India. I modelled the fragmented healthcare system, by differentiating between the public and private sector (1–7). I calibrated the model to TB prevalence (slums and non-slums), annual risk of infection (slums and non-slums) and mortality (table 3.2). I ignore MDR-TB and pulmonary status.

I initially simulated the model to equilibrium after introducing TB into a disease-free population, without differentiating between the public and private sector. From 1997 to 2007 and its maintenance until the present day, I incorporated the RNTCP scale up and its impact on the TB epidemic (8). From 1997, I also incorporate population growth. I then simulate the model forward from the present day to 2035.

I considered two different scenarios where false positives that originate from testing for incipient TB may arise from: only from $L_s^{(1)}$, the second from U_s, $L_s^{(1)}$, $R_s^{(L)}$ and $R_s^{(H)}$. The threshold cost of a biomarker test for the latter scenario, is given by the following equation (for the former, see main text):

$$C_T \leq \frac{(\vartheta(D_0 - D_1)) - (\kappa_S p_{sn} C_P \int_{2035}^{2020} L_s^2) - (\kappa_S(1 - p_{sp}) C_P \int_{2035}^{2020} \sum[U_s + L_s^{(1)} + R_s^{(L)} + R_s^{(H)}] + (A_0 - A_1)}{\kappa_S \int_{2035}^{2020} \sum[U_s + L_s^{(1)} + L_s^{(2)} + R_s^{(L)} + R_s^{(H)}]} \quad (1)$$

1.2. Governing equations for the mathematical transmission model

The equations correspond to the model described in fig 3.1. State variables (capital letters) are as listed in Table A1.1, while model parameters (lower-case and Greek letters) are as listed in Table 3.1.

Model stage	Description
U_s	Uninfected
$L_s^{(1)}$	Latent infection
$L_s^{(2)}$	Incipient TB
I_s	Active TB
$Dx_s^{(pu)}$	Sought care, awaiting TB diagnosis, public sector
$Dx_s^{(pr)}$	Sought care, awaiting TB diagnosis, private sector
$Tx_s^{(pu)}$	Undergoing TB treatment, public sector
$Tx_s^{(pr)}$	Undergoing TB treatment, private sector
E_s	Between seeking care, after misdiagnosis or loss to follow up
$R_s^{(L)}$	Recovered, after treatment completion, low risk of relapse
$R_s^{(H)}$	Recovered, after self-cure, high risk of relapse
Subscript	**Description**
s	Location (0 = non-slums, 1 = slums)

Table A1.1. Model stages and subscript description

Uninfected

(2)

$$\frac{dU_s}{dt} = T - (\lambda_s + \mu_2)U_s$$

Latency

(3)

$$\frac{dL_s^{(1)}}{dt} = \pi\lambda_s(1-\theta)\sum[L_s^{(1)} + L_s^{(2)} + R_s^{(L)} + R_s^{(H)}] + \lambda_s\theta U_s + \kappa_s \upsilon p_{sn} L_s^{(2)} - (\rho_1 + \mu_2)L_s^{(1)}$$

Incipient TB

(4)

$$\frac{dL_s^{(2)}}{dt} = \pi\lambda_s\theta\sum[L_s^{(1)} + L_s^{(2)} + R_s^{(L)} + R_s^{(H)}] + \lambda_s\theta U_s + \rho_1 L_s^{(1)} - (\kappa_s \upsilon p_{sn} + \rho_2 + \mu_2)L_s^{(2)}$$

Active disease, pre-careseeking

(5)

$$\frac{dI_s}{dt} = \rho_2 L_s^{(2)} + r_1 R_s^{(L)} + r_2 R_s^{(H)} - (\varphi + \delta_{1\_s} + \mu_1 + \mu_2)I_s$$

Awaiting diagnosis, public sector

(6)

$$\frac{dDx_s^{(pu)}}{dt} = \eta\delta_{1\_s} I_s + \eta\delta_2 E_s - (\varphi + \phi + \mu_1 + \mu_2)Dx_s^{(pu)}$$

Awaiting diagnosis, private sector

(7)

$$\frac{dDx_s^{(pr)}}{dt} = (1-\eta)\delta_{1_s} I_s + (1-\eta)\delta_2 E_s - (\varphi + \phi + \mu_1 + \mu_2) Dx_s^{(pr)}$$

Treatment, public sector
(8)

$$\frac{dTx_s^{(pu)}}{dt} = \phi \varepsilon_{pu} \omega_{pu} Dx_s^{(pu)} - (\tau + \frac{\tau \chi_{pu}}{1-\chi_{pu}} + \mu_1) Tx_s^{(pu)}$$

Treatment, private sector
(9)

$$\frac{dTx_s^{(pr)}}{dt} = \phi \varepsilon_{pr} \omega_{pr} Dx_s^{(pr)} - (\tau + \frac{\tau \chi_{pr}}{1-\chi_{pr}} + \mu_1) Tx_s^{(pr)}$$

Missed diagnosis/initial loss to follow up
(10)

$$\frac{dE_s}{dt} = \phi(1-\omega_{pu}\varepsilon_{pu}) Dx_s^{(pu)} + \phi(1-\omega_{pr}\varepsilon_{pr}) Dx_s^{(pr)} - (\varphi + \delta_2 + \mu_1 + \mu_2) E_s$$

Post-treatment recovery
(11)

$$\frac{dR_s^{(L)}}{dt} = \varsigma R_s^{(H)} + \tau \sum [Tx_s^{(pu)} + Tx_s^{(pr)}] - (r_2 + \mu_1) R_s^{(L)}$$

Self-cure
(12)

$$\frac{dR_s^{(H)}}{dt} = \varphi \sum [Dx_s^{(pu)} + Dx_s^{(pr)} + E_s + I_s] + \frac{\tau \chi_{pu}}{1-\chi_{pu}} Tx_s^{(pu)} + \frac{\tau \chi_{pr}}{1-\chi_{pr}} Tx_s^{(pr)} - (r_1 + \mu_1) R_s^{(H)}$$

where term T represents births into the uninfected TB compartment. I assume it is equivalent to the number of deaths occurring in the model.

Force of infection

$$\lambda_s = \frac{\beta_s\left\{\Sigma\left[I_s + Dx_s^{(pu)} + Dx_s^{(pr)} + E_s\right]\right\} + \psi\beta_{s=1}\left\{\Sigma\left[I_{s=1} + Dx_{s=1}^{(pu)} + Dx_{s=1}^{(pu)} + E_s\right]\right\}}{N} \quad if\ s = 0 \tag{13}$$

$$\lambda_s = \frac{\psi\beta_{s=0}\left\{\Sigma\left[I_{s=0} + Dx_{s=0}^{(pu)} + Dx_{s=0}^{(pu)} + E_s\right]\right\} + \beta_s\left\{\Sigma\left[I_s + Dx_s^{(pu)} + Dx_s^{(pu)} + E_s\right]\right\}}{N} \quad if\ s = 1 \tag{14}$$

where N is the total population.

1.3. Model calibration

Through Adaptive Bayesian MCMC, I examined the uncertainty in data and model inputs (table 3.1 and table 3.2)(9). I was able to propagate this uncertainty into the model projections.

I define the posterior distribution as,

$$p(\theta|D) \propto L(D|\theta)\,.\pi(\theta) \tag{15}$$

where, θ is a vector of the data and model inputs subject to uncertainty, L is the likelihood of the data given θ, and π is the prior distribution. I assumed uniform distributions for the prior distributions. I defined the likelihood by fitting log-normal distributions to the calibration targets.

By sampling from the posterior distribution using MCMC, I created an unbiased sample that approximates the posterior distribution. A sample is randomly selected from $p(\theta|D)$, and depending on the proposal distribution, it is accepted or rejected. By using Adaptive Bayesian MCMC, the proposal distribution is updated continuously. Once the MCMC converged, I removed the burn-in period (10,000 iterations) and selected every 50th sample to reduce any autocorrelation. This provided 10,000 samples from the posterior distribution.

2. Supporting figures

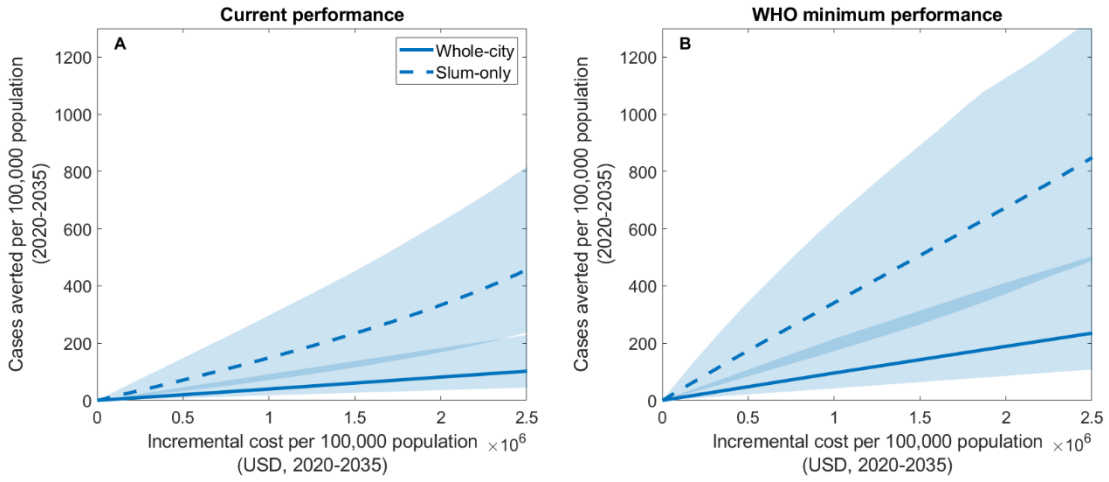

Figure A1.1. Incremental cost (USD) per case averted, under the expanded false positive scenario per 100,000 population between 2020 and 2035. Panel A assumes the test had similar diagnostic performance to current data (sensitivity – 30%), whereas panel B assumes the test met the WHO minimum performance requirements (sensitivity – 75%). I investigated two different testing strategies: a slum-only (dash line) and whole-city strategy (solid line). Shaded areas show Bayesian 95% credible intervals.

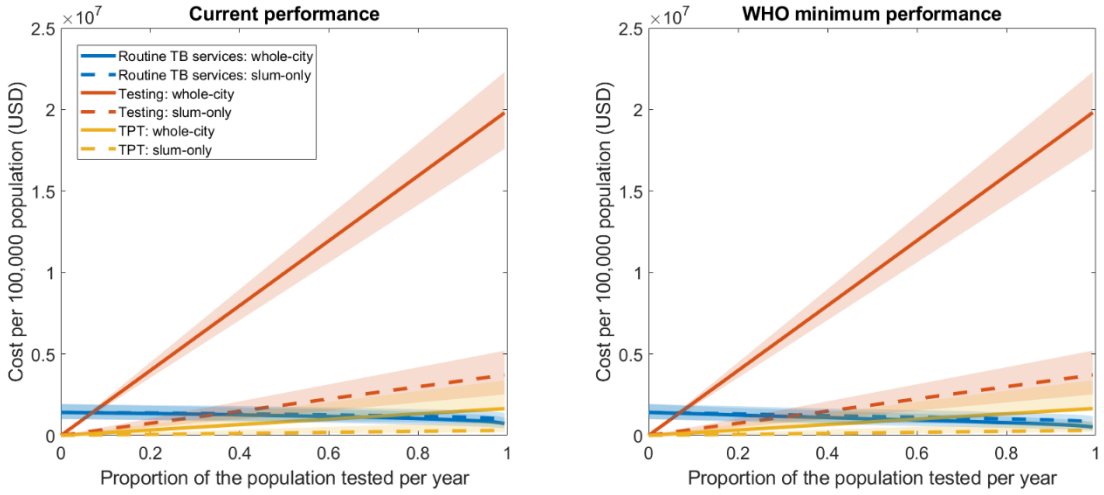

Figure A1.2. Cost drivers across increasing rates of testing for incipient TB between 2020 and 2035, under the expanded false positive scenario. I divided costs into the following components: cost of routine TB services (costs associated with active TB disease management; blue line), testing costs (cost of testing for incipient TB; red line), cost of preventive therapy (yellow line). Panel A assumes the test had similar diagnostic performance to current data (sensitivity – 30%), whereas panel B assumes the test met the WHO minimum performance requirements (sensitivity – 75%). I investigated two different testing strategies: a slum-only (dash line) and whole-city strategy (solid line). Shaded areas show Bayesian 95% credible intervals.

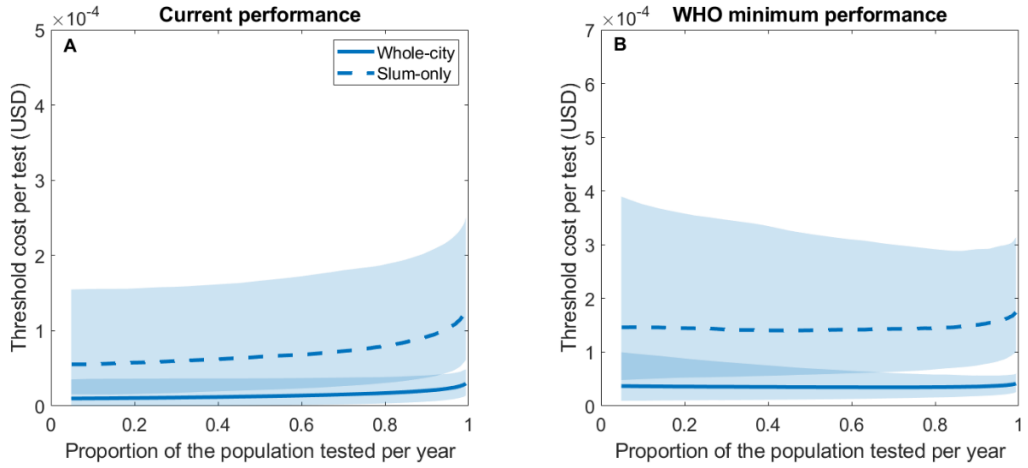

Figure A1.3 Cost requirements for future tests for incipient TB, under the expanded false positive scenario, across increasing testing rates. Threshold costs of a test per person was calculated according to a willingness-to-pay threshold of USD2,104. See table 3 and equation 1. Panel A assumes the test had similar diagnostic performance to current data (sensitivity – 30%), whereas panel B assumes the test met the WHO minimum performance requirements (sensitivity – 75%). I investigated two different testing strategies: a slum-only (dash line) and whole-city strategy (solid line). Shaded areas show Bayesian 95% credible intervals.

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Appendix 2

The potential impact of urine-lipoarabinomannan diagnostics on tuberculosis incidence and mortality: A modelling analysis

1. Materials and methods

Below, I describe the model, including its structure, governing equations, and parameters. The model was constructed in MATLAB.

1.1. Model structure

1.1.1. Overview

I modelled TB transmission amongst adults (>15 years old) in South Africa, incorporating the role of HIV in driving TB dynamics. I calibrated the model to TB incidence, mortality, and notification rates. I also used HIV incidence, the proportion of PLHIV with and without TB, their CD4 cell counts, ART coverage and percentage of HIV cases being hospitalised annually as inputs (table 4.2).

The model is stratified by pulmonary and extrapulmonary TB. Amongst those with HIV, the model is further stratified by CD4 count, using three categories: <100, 100 – 200, and >200, to align with the most recent WHO 2019 guidelines (table 4.2) for the use of LF-LAM (552). The model ignores drug resistance, as well as age structure in the population. However, it distinguishes different settings for TB and HIV care: routine TB services, those receiving HIV care in outpatient clinics, and those receiving HIV care as hospital inpatients.

1.1.2. Routine TB services

I assumed that those with active TB seek care at a certain per-capita rate, calibrated to epidemiological data (table 4.3), and allowing for different careseeking rates by HIV-negative and -positive status. I assumed that each visit to a healthcare provider results in TB diagnosis with a probability governed by a combination of test sensitivity and clinical diagnosis. Amongst those failing to be diagnosed, I assumed temporary dropout from the care cascade, to seek care again after a given per-capita rate (again, calibrated to epidemiological data).

South Africa has recently undergone an expansion in the use of molecular diagnostics such as Xpert, for sputum-based diagnosis in routine TB services (553). Under the introduction of LAM testing in routine TB services (scenario iii in the main text), I assumed that baseline levels of Xpert remain the same, but that LAM testing is used adjunctively, with a positive result on either test leading to a TB

diagnosis. To incorporate clinical diagnosis, I assumed that 20% and 30% of negative test results are clinically diagnosed and offered treatment, amongst HIV-negative and HIV-positive patients, respectively (554). The number of individuals initiating TB treatment, is defined by the following:

Baseline, status quo comparator: (1)

$$o_{R_h} = \varepsilon_R R_3 R_4 \phi_R \omega_R$$

Where the proportion of TB cases diagnosed correctly per careseeking attempt, o_{R_h}, is calibrated to TB notification rates.

Baseline, Xpert scale-up comparator: (2)

$$o_{R_h} = (1 - (1 - \varepsilon_R R_3 R_4)(1 - \vartheta_h^{sputum} X_{sn}))\phi_R \omega_R$$

Intervention, status quo comparator: (3)

$$o_{R_h} = (1 - (1 - \varepsilon_R R_3 R_4)(1 - \left(1 - \left(\varepsilon_R R_3 R_4 + \vartheta_h^{urine} F_{sn}\right)\right) \iota_h)(1 - \vartheta_h^{urine} F_{sn}))\phi_R \omega_R$$

Intervention, Xpert scale-up comparator: (4)

$$o_{R_h} = (1 - (1 - \varepsilon_R R_3 R_4)(1 - \left(1 - \left(\varepsilon_R R_3 R_4 + \vartheta_h^{urine} F_{sn}\right)\right) \iota_h)(1 - \vartheta_h^{urine} F_{sn})(1 - \vartheta_h^{sputum} X_{sn}))\phi_R \omega_R$$

1.1.3. HIV inpatients

The model captures the hospitalisation of PLHIV, at a CD4-dependent rate, reflecting data from South Africa on HIV-associated inpatient admissions (table 4.2, and fig A2.3). Upon admission, I assumed that of those with signs and symptoms of TB, a given proportion are offered an Xpert test at baseline. Under the introduction of LAM testing (scenarios i and ii in the main text), I assumed – consistent with current WHO guidelines (552) - that those with signs and symptoms of TB, and all those with CD4 cell count <200 cells/μl independent of symptoms, are offered a LAM test as an adjunctive test to Xpert, again allowing for clinical diagnosis amongst those with a negative test result.

Baseline, status quo comparator: (5)

$$o_{Ih} = \vartheta_h^{sputum} \xi_I X_{sn} s_I \omega_I \phi$$

Baseline, Xpert scale-up comparator: (6)

$$o_{Ih} = (1 - \left(1 - \vartheta_h^{sputum} \xi_I X_{sn}\right)\left(1 - \vartheta_h^{sputum} X_{sn}\right))s_I \omega_I \phi$$

Intervention, status quo comparator, currently licensed LAM test: (7)

$$o_{Ih} = (1 - (1 - \vartheta_h^{sputum}\xi_I X_{sn})(1 - ((1 - \vartheta_h^{sputum}\xi_I X_{sn} + \vartheta_h^{urine} A_{sn}))\iota_h))(1 - \vartheta_h^{urine} A_{sn}))s_I \omega_I \phi$$

Intervention, status quo comparator, future LAM test: (8)

$$o_{Ih} = (1 - (1 - \vartheta_h^{sputum}\xi_I X_{sn})(1 - ((1 - \vartheta_h^{sputum}\xi_I X_{sn} + \vartheta_h^{urine} F_{sn}))\iota_h))(1 - \vartheta_h^{urine} F_{sn}))s_I \omega_I \phi$$

Intervention, Xpert scale-up comparator, currently licensed LAM test: (9)

$$o_{Ih} = (1 - (1 - \vartheta_h^{sputum}\xi_I X_{sn})\left(1 - \left(\left(1 - (\vartheta_h^{sputum}\xi_I X_{sn} + \vartheta_h^{urine} A_{sn})\right)\iota_h\right)\right)(1 - \vartheta_h^{urine} A_{sn})(1 - \vartheta_h^{sputum} X_{sn}))s_I \omega_I \phi$$

Intervention, Xpert scale-up comparator, future LAM test: (10)

$$o_{Ih} = (1 - (1 - \vartheta_h^{sputum}\xi_I X_{sn})\left(1 - \left(\left(1 - (\vartheta_h^{sputum}\xi_I X_{sn} + \vartheta_h^{urine} F_{sn})\right)\iota_h\right)\right)(1 - \vartheta_h^{urine} F_{sn})(1 - \vartheta_h^{sputum} X_{sn}))s_I \omega_I \phi$$

1.1.4. HIV outpatients

The model also captures the provision of HIV care in outpatient settings, assuming CD4-dependent rates of ART initiation in these settings. These rates were calibrated to match data from South Africa for the distribution of CD4 counts amongst those initiating ART in outpatient facilities (table 4.2, and fig A2.3). Upon initiating HIV care, I assumed that of those with signs and symptoms of TB, a certain proportion are offered an Xpert test. As above, under the introduction of LAM testing (scenario ii in the main text), I assumed – consistent with current WHO guidelines (552) - that those with signs and symptoms of TB and those with a CD4 cell count <100 cells/μl independent of symptoms, are offered a LAM test as an adjunctive test to Xpert, again allowing for clinical diagnosis amongst those with a negative test result.

Baseline, status quo comparator: (11)

$$o_{Oh} = \vartheta_h^{sputum}\xi_O X_{sn} s_O \omega_O \phi$$

Baseline, Xpert scale-up comparator: (12)

$$o_{Oh} = (1 - (1 - \vartheta_h^{sputum}\xi_O X_{sn})(1 - \vartheta_h^{sputum} X_{sn}))s_O \omega_O \phi$$

Intervention, status quo comparator, currently licensed LAM test: (13)

$$o_{Oh} = (1 - (1 - \vartheta_h^{sputum}\xi_O X_{sn})\left(1 - \left(\left(1 - (\vartheta_h^{sputum}\xi_O X_{sn} + \vartheta_h^{urine}A_{sn})\right)\iota_h\right)\right)(1 - \vartheta_h^{urine}A_{sn}))s_O\omega_O\phi$$

Intervention, status quo comparator, future LAM test: (14)

$$o_{Oh} = (1 - (1 - \vartheta_h^{sputum}\xi_O X_{sn})\left(1 - \left(\left(1 - (\vartheta_h^{sputum}\xi_O X_{sn} + \vartheta_h^{urine}F_{sn})\right)\iota_h\right)\right)(1 - \vartheta_h^{urine}F_{sn}))s_O\omega_O\phi$$

Intervention, Xpert scale-up comparator, currently licensed LAM test: (15)

$$o_{Oh} = (1 - (1 - \vartheta_h^{sputum}\xi_O X_{sn})\left(1 - \left(\left(1 - (\vartheta_h^{sputum}\xi_O X_{sn} + \vartheta_h^{urine}A_{sn})\right)\iota_h\right)\right)(1 - \vartheta_h^{urine}A_{sn})(1 - \vartheta_h^{sputum}X_{sn}))s_O\omega_O\phi$$

Intervention, Xpert scale-up comparator, future LAM test: (16)

$$o_{Oh} = (1 - (1 - \vartheta_h^{sputum}\xi_O X_{sn})\left(1 - \left(\left(1 - (\vartheta_h^{sputum}\xi_O X_{sn} + \vartheta_h^{urine}F_{sn})\right)\iota_h\right)\right)(1 - \vartheta_h^{urine}F_{sn})(1 - \vartheta_h^{sputum}X_{sn}))s_O\omega_O\phi$$

1.2. Governing equations for the mathematical transmission model

The equations correspond to the model described in fig 4.1. State variables (capital letters) are as listed in table A2.1, while model parameters (lower-case and Greek letters) are as listed in table 4.3.

Model stage	**Description**
U_h	Uninfected
L_h	Latent infection
I_h	Active TB
Dx_h	Sought care, awaiting TB diagnosis
Tx_h	Undergoing TB treatment
E_h	Between seeking care, after misdiagnosis or loss to follow up
$R^{(L)}{}_h$	Recovered, after treatment completion, low risk of relapse
$R^{(H)}{}_h$	Recovered, after self-cure, high risk of relapse
A_h	Inpatient admission, awaiting TB diagnosis
Subscript	**Description**
h	HIV status (0 = HIV-, 1 = HIV+ >200, 2 = HIV+ 100-200, 3 = HIV+ <100 and 4 = ART+ virally suppressed), 5 = ART+ (not virally suppressed) >200, 6 = ART+ 100-200, 7 = HIV+ <100
Superscript	**Description**
inp	Inpatient (hospitalised HIV-positive patients)
out	Outpatient

Table A2.1. Model stages and subscript description

Uninfected (17)

$$\frac{dU_h}{dt} = \begin{cases} T + W_h^{(1)} - (\lambda + \mu_2)U_h & h = 0 \\ W_h^{(1)} + \psi_h U_h^{(inp)} - (\lambda + \upsilon_h + \mu_2 + \mu_{3_h})U_h & h > 0 \end{cases}$$

Latency (18)

$$\frac{dL_h}{dt} = \begin{cases} W_h^{(2)} + \pi\lambda(1-\theta_h)\sum\left[L_h + R_h^{(L)} + R_h^{(H)}\right] + \lambda(1-\theta_h)U_h - (\rho_h + \mu_2)L_h & h = 0 \\ W_h^{(2)} + \psi_h L_h^{(inp)} + \pi\lambda(1-\theta_h)\sum\left[L_h + R_h^{(L)} + R_h^{(H)}\right] + \lambda(1-\theta_h)U_h - (\rho_h + \upsilon_h + \mu_2 + \mu_{3_h})L_h & h > 0 \end{cases}$$

Active disease, pre-careseeking (19)

$$\frac{dI_h}{dt} = \begin{cases} W_h^{(3)} + \theta_h\lambda U_h + \pi\theta_h\lambda\sum\left[L_h + R_h^{(L)} + R_h^{(H)}\right] + \rho_h L_h + r_2 R_h^{(L)} + r_1 R_h^{(H)} \\ \qquad -(\delta_1 + \varphi_h + \mu_1 + \mu_2)I_h & h = 0 \\ W_h^{(3)} + \psi_h I_h^{(inp)} + \theta_h\lambda U_h + \pi\theta_h\lambda\sum\left[L_h + R_h^{(L)} + R_h^{(H)}\right] + \rho_h L_h + r_2 R_h^{(L)} + r_1 R_h^{(H)} \\ \qquad -(\delta_1 R_2 + \varphi_h + \varpi_h + \upsilon_h + \mu_1 + \mu_2 + \mu_{3_h})I_h & h > 0 \end{cases}$$

Awaiting diagnosis (20)

$$\frac{dDx_h}{dt} = \begin{cases} W_h^{(4)} + \delta_1 I_h + \delta_2 E_h - (\varphi_h + o_{R_h} + \mu_1 + \mu_2)Dx_h & h = 0 \\ W_h^{(4)} + \delta_1 R_2 I_h + \delta_2 R_2 E_h - (\varphi_h + o_{R_h} + \mu_1 + \mu_2 + \mu_{3\_h} + \varpi_h + \upsilon_h)Dx_h & h > 0 \end{cases}$$

Treatment (21)

$$\frac{dTx_h}{dt} = \begin{cases} W_h^{(5)} + o_{R_h}Dx_h - (\tau + \mu_2)Tx_h & h = 0 \\ W_h^{(5)} + \psi_h Tx_h^{(inp)} + o_{R_h}Dx_h + o_{O_h}Dx_h^{(out)} - (\tau + \upsilon_h + \mu_2 + \mu_{3_h})Tx_h & h > 0 \end{cases}$$

Missed diagnosis/initial loss to follow up (22)

$$\frac{dE_h}{dt} = \begin{cases} W_h^{(6)} + (1-o_{R_h})Dx_h + \tau(1-\chi_h)Tx_h - (\delta_2 + \varphi_h + \mu_1 + \mu_2)E_h & h = 0 \\ W_h^{(6)} + \psi_h E_h^{(inp)} + (1-o_{R_h})Dx_h + (1-o_{O_h})Dx_h^{(out)} + \tau(1-\chi_h)Tx_h & \\ \qquad -(\delta_2 + \varphi_h + \varpi_h + \upsilon_h + \mu_1 + \mu_2 + \mu_{3\_h})E_h & h > 0 \end{cases}$$

Post-treatment recovery (23)

$$\frac{dR_h^{(L)}}{dt} = \begin{cases} W_h^{(7)} + \tau\chi_h Tx_h + \varsigma R_h^{(H)} - (r_2 + \mu_2)R_h^{(L)} & h = 0 \\ W_h^{(7)} + \psi_h R_h^{(L_{inp})} + \tau\chi_h Tx_h + \varsigma R_h^{(H_{inp})} - \left(r_2 + \upsilon_h + \mu_2 + \mu_{3_h}\right)R_h^{(L)}(t) & h > 0 \end{cases}$$

Self-cure (24)

$$\frac{dR_h^{(H)}}{dt} = \begin{cases} W_h^{(8)} + \varphi_h \sum[E_h + Dx_h + I_h] - (\varsigma + r_1 + \mu_2)R_h^{(H)} & h = 0 \\ W_h^{(8)} + \psi_h R_h^{(H_{inp})} + \varphi_h \sum[E_h + Dx_h + I_h] - \left(\varsigma + r_1 + \upsilon_h + \mu_2 + \mu_{3_h}\right)R_h^{(H_{inp})} & h > 0 \end{cases}$$

Uninfected, inpatients (25)

$$\frac{dU_h^{(inp)}}{dt} = W_h^{(9)} + \upsilon_h U_h - (\lambda + \psi_h + \mu_2 + \mu_{3\_h})U_h^{(inp)} \qquad h > 4$$

Latency, inpatients (26)

$$\frac{dL_h^{(inp)}}{dt} = W_h^{(10)} + \upsilon_h L_h + \lambda(1-\theta_h)U_h^{(inp)} + \pi\lambda(1-\theta_h)\sum\left[L_h^{(inp)} + R_h^{(L_{inp})} + R_h^{(H_{inp})}\right] - (\psi_h + \rho_h + \mu_2 + \mu_{3_h})L_h^{(inp)} \qquad h > 4$$

Active disease, inpatients (27)

$$\frac{dI_h^{(inp)}}{dt} = W_h^{(11)} + \rho_h L_h^{(inp)} + \theta_h \lambda U_h^{(inp)} + r_1 R_h^{(H_{inp})} + r_2 R_h^{(L_{inp})} + \pi\theta_h\lambda\sum\left[L_h^{(inp)} + R_h^{(L_{inp})} + R_h^{(H_{inp})}\right] - (\varphi_h + \psi_h + \mu_1 + \mu_2 + \mu_{3_h} + \mu_4)I_h^{(inp)} \qquad h > 4$$

Hospital admissions awaiting diagnosis, inpatients (28)

$$\frac{dA_h^{(inp)}}{dt} = W_h^{(12)} + \upsilon_h \sum[I_h + Dx_h + E_h] - (o_{I_h} + \varphi_h + \mu_1 + \mu_2 + \mu_{3_h} + \mu_4)A_h^{(inp)} \qquad h > 4$$

TB treatment, inpatients (29)

$$\frac{dTx_h^{(inp)}}{dt} = W_h^{(13)} + \upsilon_h Tx_h + o_{I_h} A_h^{(inp)} - (\tau + \psi_h + \mu_2 + \mu_{3_h})Tx_h^{(inp)} \qquad h > 4$$

Missed diagnosis/initial loss to follow up, inpatients (30)

$$\frac{dE_h^{(inp)}}{dt} = W_h^{(14)} + (1 - o_{I_h})A_h^{(inp)} + \tau(1 - \chi_h)Tx_h^{(inp)}$$
$$-(\varphi_h + \psi_h + \mu_1 + \mu_2 + \mu_{3_h} + \mu_4)E_h^{(inp)} \qquad h > 4$$

Post-TB treatment recovery, inpatients (31)

$$\frac{dR_h^{(L_{inp})}}{dt} = W_h^{(15)} + \tau\chi_h Tx_h^{(inp)} + \upsilon_h R_h^{(L)} + \varsigma R_h^{(H_{inp})}$$
$$-[\psi_h + r_2 + \mu_2 + \mu_{3_h}]R_h^{(L_{inp})} \qquad h > 4$$

Self-cure, inpatients (32)

$$\frac{dR_h^{(H_{inp})}}{dt} = W_h^{(16)} + \upsilon_h R_h^{(H)} + \varphi_h \sum \left[A_h^{(inp)} + E_h^{(inp)} + I_h^{(inp)}\right]$$
$$-\left(\varsigma + r_1 + \psi_h + \mu_2 + \mu_{3_h}\right)R_h^{(H_{inp})} \qquad h > 4$$

Awaiting diagnosis at ART initiation, outpatients (33)

$$\frac{dDx_h^{(out)}}{dt} = W_h^{(17)} + \varpi_h \sum[I_h + Dx_h + E_h] - (\, o_{O_h} + \mu_1 + \mu_2 + \mu_{3_h})Dx_h^{(out)} \qquad h > 4$$

where term *T* represents births into the uninfected TB compartment. I assume it is equivalent to the number of deaths occurring in our model to ensure a constant population size.

Force of infection

$$\lambda = \frac{\mathrm{F}}{N} \tag{34}$$

where, (35)

$$\mathrm{F} = \beta\{\textstyle\sum_{h=0}[I + Dx + E]\} + \beta R_1\{\textstyle\sum_{h=1}^{4}[I + I^{(inp)} + Dx + Dx^{(out)} + E]\},$$

and N is the total population.

HIV-transitions

where terms in W_h^x represent transitions between HIV stages:

HIV state	Symbol
HIV-	h=0
HIV+ >200	h=1
HIV+ 100-200	h=2
HIV+ <100	h=3
ART+ virally suppressed	h=4
ART+ >200 (not virally suppressed)	h=5
ART+ 100-200 (not virally suppressed)	h=6
ART+ <100 (not virally suppressed)	h=7

Table A2.2. HIV transitions

I write X_h^z to denote HIV compartments. Super index *z* represents TB model stages described in the equations above (e.g. *z*=1 for the *uninfected stage*)

(36)

$$W_h^z = \begin{cases} -\gamma X_h^z & \text{if h} = 0 \\ \gamma X_0^z - \eta_1 X_h^z - \upsilon_h X_h^z - \varpi_h X_h^z & \text{if h} = 1 \\ \eta_1 X_1^z - \eta_2 X_h^z - \upsilon_h X_h^z - \varpi_h X_h^z & \text{if h} = 2 \\ \eta_2 X_2^z - \upsilon_h X_h^z - \varpi_h X_h^z & \text{if h} = 3 \\ \varpi_h \varrho X_1^z + \upsilon_h \varrho X_1^z + \varpi_h \varrho X_2^z + \upsilon_h \varrho X_2^z + \varpi_h \varrho X_3^z + \upsilon_h \varrho X_3^z & \text{if h} = 4 \\ \varpi_h (1-\varrho) X_1^z + \upsilon_h (1-\varrho) X_1^z - \eta_1 X_h^z & \text{if h} = 5 \\ \varpi_h (1-\varrho) X_2^z + \upsilon_h (1-\varrho) X_2^z + \eta_1 X_5^z - \eta_2 X_h^z & \text{if h} = 6 \\ \varpi_h (1-\varrho) X_3^z + \upsilon_h (1-\varrho) X_3^z + \eta_2 X_6^z & \text{if h} = 7 \end{cases}$$

1.3. Model calibration

I incorporated uncertainty in data and model inputs (table 4.2-4.3 and A2.3) using an Adaptive Bayesian MCMC from Haario et al (4).

Indicator		Value	Source
TB epidemiology			
TB incidence, 2018		292 per 100,000 [179-432]	(5)
Mortality, 2018	HIV-	38 per 100,000 [22-59]	
	HIV+	26 per 100,000 [16-38]	
Notification rate, 2018		189 per 100,000 [151-226]	
HIV epidemiology and care			
HIV prevalence, 2017		1.5 million [1.3-1.7]	(6)
Proportion of TB infections coinfected with HIV		0.27 [0.16-0.40]	(5)
Proportion of PLHIV who have suppressed viral load		0.68 [0.60-0.79]	(6)

Table A2.3. Calibration targets for Kenya used to estimate model parameters. Additional data (including CD4 categories by HIV status, and percentage of HIV cases being hospitalised annually) are the same as for South Africa (table 4.2).

I define the posterior distribution as,

$$p(\theta|D) \propto L(D|\theta)\,.\,\pi(\theta) \tag{37}$$

Where, θ is a vector of the data and model inputs subject to uncertainty, L is the likelihood of the data given θ (see below for its construction), and π is the prior distribution. I assumed uniform distributions (ranges shown in table 4.3) for the prior distributions. I defined the likelihood by fitting beta and log-normal distributions to the calibration targets (table 4.2) for all data that were proportions and for TB incidence, respectively. For example, the likelihood function for total TB incidence ($L_{Inc_{total}}$) can be written as:

$$L_{Inc_{total}}\big(Inc_{total}(\theta)\big) \tag{38}$$

Then, for a given set of parameters, θ, the overall likelihood, $p(\theta)$, was calculated as follows:

$$\log\big(p(\theta)\big) = \log\big(L_{Inc_{total}}\big(Inc_{total}(\theta)\big) + L_{x_2}\big(x_2(\theta)\big) + \cdots L_{x_z}(x_z(\theta))\big) \tag{39}$$

where $'x_2, x_3, \ldots'$represent successive data elements in table 2.

I sampled from the posterior distribution using MCMC, which should provide an unbiased sample that approximates the posterior distribution. A sample is randomly selected from $p(\theta|D)$, which is then accepted or rejected, depending on the proposal distribution. I did this using Adaptive MCMC, using the approach first proposed by Haario et al. In brief, I modelled the proposal distribution using a multivariate normal distribution, with mean zero and a given covariance matrix Σ. Standard MCMC approaches require that Σ be 'tuned' in order to sample efficiently from the posterior density, but in the present work, manual tuning is infeasible with the 122-dimensional parameter space being sampled from (table 4.3). Instead, the Haario algorithm approximates the covariance matrix empirically by computing the covariance of already-sampled parameters, during the execution of MCMC. I assumed uniform priors for all model parameters: if the width of the uniform distribution for parameter i is w_i, I initiated Σ simply as a diagonal matrix, with diagonal terms $\left(\frac{w_i}{50}\right)^2$. I found that no further 'tuning' was required. I removed the burn-in period (10,000 iterations) once the MCMC had converged and selected every 50th sample to reduce any autocorrelation. I ended up with 5000 samples from the posterior distribution. By incorporating uncertainty in data and model inputs, I was able to propagate this uncertainty into our model projections.

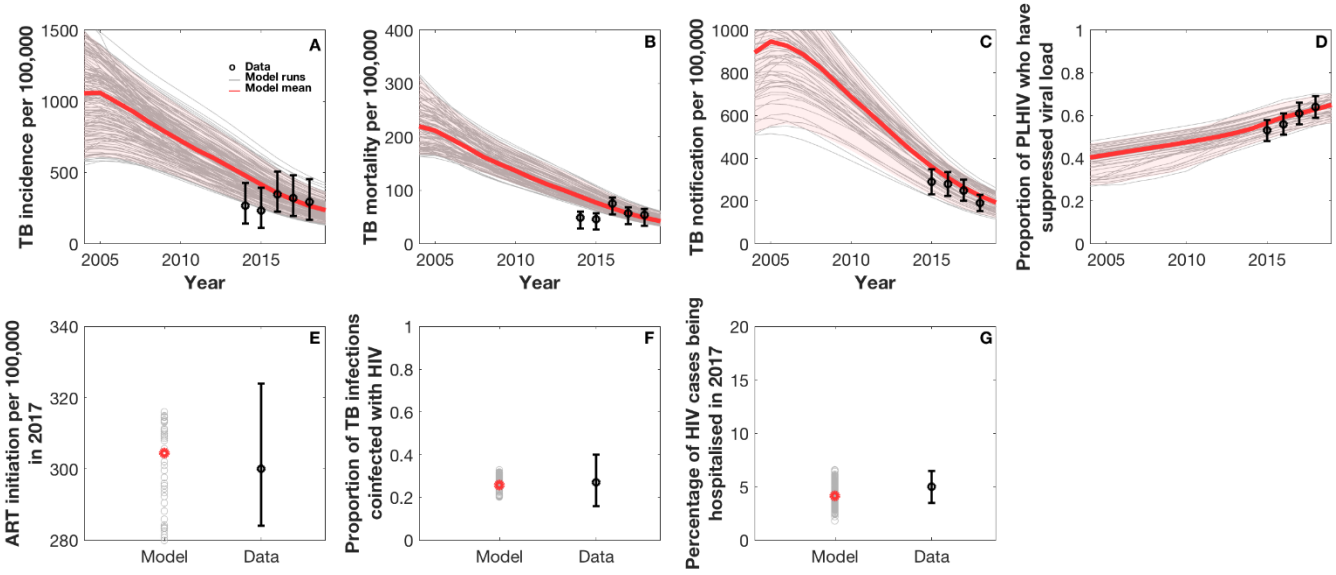

Figure A2.1. Model fits to data for Kenya. Data points are described in table A2.3 (A) TB incidence; (B) TB mortality per 100,000; (C) TB notifications per 100,000; (D) proportion of PLHIV with suppressed viral loads; (E) ART initiations per 100,000; (F) proportion of TB cases coinfected with HIV; (G) percentage of HIV cases being hospitalised annually.

2. Additional figures

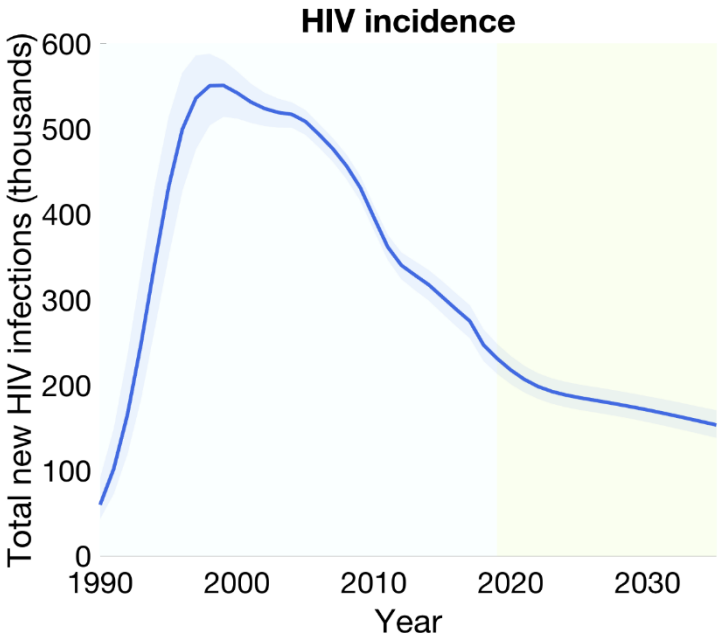

Figure A2.2. Total new HIV infections in South Africa. Past estimates (in blue shading) and future projections (in green shading).

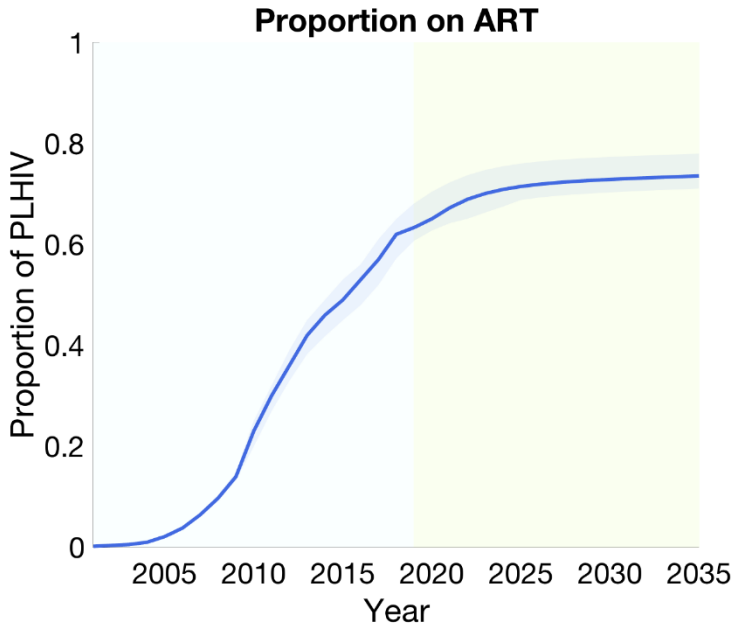

Figure A2.3. Proportion of PLHIV on ART in South Africa. Past estimates (in blue shading) and future projections (in green shading).

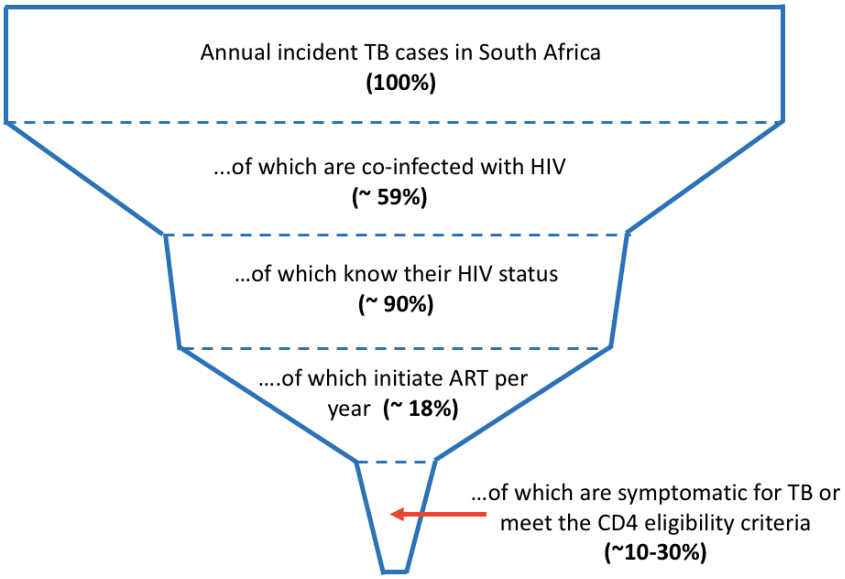

Figure A2.4. Cumulative effect of eligibility criteria. Flow diagram illustrating the effect of the most recent eligibility criteria in WHO recommendations for the use of LF-LAM on the size of the subset of TB incident cases who receive LAM testing. In South Africa, of patients with TB disease, around 59% are coinfected with HIV; of these, 90% are aware of their HIV status, of which, approximately 18% will initiate ART per year. Depending on the eligibility criteria, around 10%–30% of individuals who initiate ART will be eligible for LAM testing. For the purpose of this illustration, of the 7,700,000 who are HIV-positive, 2,900,000 were estimated not to be on ART in 2018. Approximately 90% of these (2,610,000) are aware of their HIV status. Model estimates suggest that approximately 480,000 initiated ART in 2018. Thus, we approximate that in 2018, 18% of individuals who were aware of their HIV infection, initiated ART (480,000/2,610,000).

3. Bibliography

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Appendix 3

The value and cost efficiency of private sector engagement

1. Materials and methods

Below, I describe the model, including its structure, governing equations and table of parameters. The model was designed in MATLAB.

1.1. Model structure

I modelled TB transmission amongst adults (>15 years old) in a typical urban setting in India. I modelled the fragmented healthcare system, by differentiating between the public and private sector (1–7). I further divide the private sector by engagement status, Xpert use and FDC use (see main text for more details). I calibrated the model to TB prevalence, annual risk of infection, and mortality (table 3.1.). I also modelled DR-TB, but ignore HIV status and the differentiation between pulmonary and extrapulmonary TB. The overall model structure is illustrated in Fig.5.1.
I initially simulated the model to equilibrium after introducing TB into a disease-free population, without differentiating between the public and private sector. From 1997 to 2007 and its maintenance until the present day, I incorporated the RNTCP scale up and its impact on the TB epidemic (8). From 1997, I also incorporate population growth. From 2017 to 2020, I simulate the scale up of PPSA services to current 2019 levels. I then simulate the model forward from 2020 to 2035.

1.2. Governing equations for the mathematical transmission model

The equations correspond to the model described in fig 5.1. State variables (capital letters) are as listed in table A3.1, while model parameters (lower-case and Greek letters) are as listed in table 5.1.

Model stage	Description
U	Uninfected
L	Latent infection
I_q	Active TB
$\boldsymbol{Dx_q^{(pu)}}$	Sought care, awaiting TB diagnosis, public sector
$\boldsymbol{Dx_q^{(pr)}}$	Sought care, awaiting TB diagnosis, private sector. This is split further depending on engagement status and Xpert use (table A3.2)
$\boldsymbol{Tx_q^{(FL:\,pu)}}$	Undergoing first line TB treatment, public sector
$\boldsymbol{Tx_q^{(FL:\,pr)}}$	Undergoing first line TB treatment, private sector. This is split further depending on FDC use and adherence support offered (table A3.2).
$\boldsymbol{Tx^{(SL)}}$	Undergoing second line TB treatment.
$\boldsymbol{E_q}$	Between seeking care, after misdiagnosis or loss to follow up
$R^{(L)}$	Recovered, after treatment completion, low risk of relapse
$R^{(H)}$	Recovered, after self-cure, high risk of relapse
Subscript	**Description**
q	Location (0 = DS-TB, 1 = DR-TB)

Table A3.1. Model stages and subscript description

Split	Description
Private sector diagnosis classification	
pr1	Unengaged private providers
pr2	Engaged, inactive private providers
pr3	Engaged, active private providers that send samples for confirmatory Xpert testing 100% of the time
pr4	Engaged, active private providers that send samples for confirmatory Xpert testing occasionally, Xpert
pr5	Engaged, active private providers that send samples for confirmatory Xpert testing occasionally, no Xpert
pr6	Engaged, active private providers that never send samples for confirmatory Xpert testing
Private sector first-line treatment classification	
PrZ1	Treatment offered by inactive and unengaged private providers
prAF	Engaged, active private providers that offer adherence support and government supplied FDCs (
prA	Engaged, active private providers that only offer adherence support
prF	Engaged, active private providers that only offer government supplied FDCs
prZ2	Engaged, active private providers that offer neither adherence support or government supplied FDCs

Table A3.2. Private sector classification

First, we have the states prior to a patient's visit to a provider:

Susceptible stage

$$\frac{dU}{dt} = T - (\lambda_q + \mu_2)U \quad (1)$$

where term T represents births into the uninfected TB compartment. I assume it is equivalent to the number of deaths occurring in the model.

Latency stage, slow progression

$$\frac{dL_q}{dt} = (1-\theta)\lambda_q U + \pi\lambda_q(1-\theta)\sum\left[L_q + R^{(H)} + R^{(L)}\right] - (\rho+\mu_2)L_q \quad (2)$$

Active disease, pre-careseeking

$$\frac{dI_q}{dt} = \theta\lambda_q U + \pi\lambda_q\theta\sum\left[L_q + R^{(H)} + R^{(L)}\right] + \rho L_q + r_1 R^{(H)} + r_2 R^{(L)} - (\varphi+\delta_1+\mu_1+\mu_2)I_q \quad (3)$$

where the subscript q denotes the TB strain.

$$q = \begin{cases} 0 & DS\,TB \\ 1 & DR\,TB \end{cases}$$

Upon presenting for care, I assume a proportion of patients visit the public sector (η) or the private sector ($1-\eta$). I divide the private sector further depending on whether private providers are engaged by JEET or not, and whether engaged providers are active or inactive. Finally, active providers are divided by their use of Xpert (table A3.2). The proportion of patients that visit each different type of provider can be written as:

Proportion of patients that visit public providers

$$v^{(pu)} = \eta \quad (4)$$

Proportion of patients that visit unengaged private providers

$$v^{(pr1)} = (1-\eta)(1-e^{\propto}) \quad (5)$$

Proportion of patients that visit engaged and inactive private providers

$$v^{(pr2)} = (1-\eta)e^{\propto}(1-a) \quad (6)$$

Proportion of patients that visit engaged and active providers that always use Xpert

$$v^{(pr3)} = (1-\eta)e^{\propto}ap_{Xpert1} \quad (7)$$

Proportion of patients that visit engaged and active providers that occasionally use Xpert, and receive an Xpert test

$$v^{(pr4)} = (1-\eta)e^{\propto}a(1-p_{Xpert1}-p_{Xpert0})x_p \quad (8)$$

Proportion of patients that visit engaged and active providers that occasionally use Xpert, and do not receive an Xpert test

$$v^{(pr5)} = (1-\eta)e^{\propto}a(1-p_{Xpert1}-p_{Xpert0})(1-x_p) \quad (9)$$

Proportion of patients that visit engaged and active providers that never use Xpert

$$v^{(pr6)} = (1-\eta)e^{\propto}ap_{Xpert0} \quad (10)$$

Private providers under the classification pr1, pr2, pr5 and pr6 rely on clinical diagnosis, whereas private providers under the classification pr3 and pr4 rely on Xpert testing. Thus, the following equations describe the different pathways for patients that seek care at the different providers described above:

Seeking care, awaiting TB diagnosis

$$\frac{dDx_q^{(pu)}}{dt} = v^{(pu)}\delta_1 I_q + v^{(pu)}\delta_2 E_q - (\varepsilon_{sn}\omega\phi(1-Þ_q^{(pu)}) + \left(\varepsilon_{sn}\omega\phi Þ_q^{(pu)}\right)_q + (1-\omega\varepsilon_{sn})\phi Þ_q^{(pu)} + \varphi + \mu_1 + \mu_2)Dx_q^{(pu)} \quad (11)$$

$$\frac{dDx_q^{(s)}}{dt} = v^{(s)}\delta_1 I_q + v^{(s)}\delta_2 E_q - (c_{sn}\omega\phi\left(1-Þ_q^{(pr0)}\right) + (c_{sn}\omega\phi Þ_q^{(pr0)})_q + (1-\omega c_{sn})\phi Þ_q^{(pr0)} + \varphi + \mu_1 + \mu_2)Dx_q^{(s)} \quad (12)$$

$$\frac{dDx_q^{(h)}}{dt} = v^{(h)}\delta_1 I_q + v^{(h)}\delta_2 E_q - (x_{sn}\omega\phi(1-Þ_q^{(pr1)}) + (x_{sn}\omega\phi Þ_q^{(pr1)})_q + (1-\omega x_{sn})\phi Þ_q^{(pr1)} + \varphi + \mu_1 + \mu_2)Dx_q^{(h)} \quad (13)$$

Where superscript (s) represents either pr1, pr2, pr5 or pr6 and superscript (h) represents either pr3 or pr4 (table A3.2)

Patients that are misdiagnosed will repeat the care-seeking process until they are diagnosed with TB, or they undergo self-cure and recover with a high risk of relapse:

Missed diagnosis

$$\frac{dE_q}{dt} = (1-\omega\varepsilon_{sn})\phi Dx_q^{(pu)} + (1-\omega c_{sn})\phi\sum\left[Dx_q^{(pr1)} + Dx_q^{(pr2)} + Dx_q^{(pr5)} + Dx_q^{(pr6)}\right] + (1-\omega x_{sn})\phi\sum\left[Dx_q^{(pr3)} + Dx_q^{(pr4)}\right] - (\varphi + \delta_2 + \mu_1 + \mu_2)E_q \quad \text{where q=0} \quad (14)$$

$$\frac{dE_q}{dt} = (1-\omega\varepsilon_{sn})\phi Þ_{pu} Dx_q^{(pu)} + (1-\omega c_{sn})\phi Þ_{pr0} \sum \left[Dx_q^{(pr1)} + Dx_q^{(pr2)} + Dx_q^{(pr5)} + Dx_q^{(pr6)}\right]$$
$$+(1-\omega x_{sn})\phi Þ_{pr1} \sum \left[Dx_q^{(pr3)} + Dx_q^{(pr4)}\right] + (\tau(1-p_{SL}) + \frac{\tau\chi_{pu}}{1-\chi_{pu}})Tx_q^{(FL:pu)}$$
$$+(\tau(1-p_{SL}) + \frac{\tau\chi_{\mathrm{PrZ}}}{1-\chi_{\mathrm{PrZ}}}) \sum [Tx_q^{(FL:prZ1)} + Tx_q^{(FL:prZ2)}] + (\tau(1-p_{SL}) + \frac{\tau\chi_{\mathrm{PrAF}}}{1-\chi_{\mathrm{PrAF}}})Tx_q^{(FL:prAF)}$$
$$+(\tau(1-p_{SL}) + \frac{\tau\chi_{\mathrm{PrA}}}{1-\chi_{\mathrm{PrA}}})Tx_q^{(FL:prA)}] + (\tau(1-p_{SL}) + \frac{\tau\chi_{\mathrm{PrF}}}{1-\chi_{\mathrm{PrF}}})Tx_q^{(FL:prF)} - (\varphi + \delta_2 + \mu_1 + \mu_2)E_q$$

where q=1 (15)

Treatment

I assume a patient initiates TB treatment at the same type of provider they were diagnosed by. For example, a patient diagnosed with TB by a public provider will also initiate TB treatment in the public sector (pu) and likewise, those diagnosed by unengaged or inactive private providers will also initiate TB treatment amongst unengaged or inactive private providers (prZ1). I split active private providers by the treatment services offered: government supplied FDCs and adherence support (prAF) adherence support only (prA), government supplied FDCs only (prF), or neither (prZ2) (table A3.2). The proportion of patients at active providers that receive the different treatment services offered is written as:

Proportion of patients at active providers that receive both adherence support and government supplied FDCs

$$v^{(prAF)} = p_{adh1}p_{adh2}p_{fdc} \quad (16)$$

Proportion of patients at active providers that receive only adherence support

$$v^{(prA)} = p_{adh1}p_{adh2}(1-p_{fdc}) \quad (17)$$

Proportion of patients at active providers that receive only government supplied FDCs

$$v^{(prF)} = (1-p_{adh1}p_{adh2})p_{fdc} \quad (18)$$

Proportion of patients at active providers that receive neither

$$v^{(prZ)} = (1-p_{adh1}p_{adh2})(1-p_{fdc}) \quad (19)$$

The rate of movement in and out of the different Tx compartments can be written as:

$$\frac{dTx_q^{(FL:y)}}{dt} = y_{sn}\phi\omega v^{(pr\_y)} Dx_q^{(y)} - (m_y + \tau + \frac{\tau\chi_y}{1-\chi_y} + \mu_2)Tx_q^{(FL:y)} \quad \text{where q = 0} \quad (20)$$

$$\frac{dTx_q^{(FL:\,y)}}{dt} = y_{sn}\phi\omega v^{(pr\_y)}\left(1-Þ_y\right)Dx_q^{(y)} + m_y Tx_{q=0}^{(FL:y)} - (\tau p_{SL} + (\tau(1-p_{SL}) + \frac{\tau\chi_y}{1-\chi_y}) + \mu_2)Tx_q^{(FL:y)} \quad \text{where q = 1} \quad (21)$$

$dTx_q^{(FL:\,y)}$ represents the different Tx compartments (pu, prZ1, prAF, prA, prF and prz2), defined in table A3.2). y_{sn} is the proportion of patients tested that are correctly diagnosed (in other words, the sensitivity of the test) and is dependent on where the patient is diagnosed: ε_{sn} when Dx^{pu} , c_{sn} when Dx^{pr1}, Dx^{pr2}, Dx^{pr5}, Dx^{pr6} and x_{sn} when Dx^{pr3}, Dx^{pr4}. ϕ is the treatment initiation delay (assumed to be 1 week across all providers) and ω is the proportion of diagnosed TB cases initiating TB treatment (assumed to be 0.87 across all providers) (9). $v^{(pr\_y)}$, described above, applies only to TB patients that are diagnosed by active private providers. $Þ_y$ is the proportion of MDR-TB cases receiving drug susceptibility testing at the point of TB diagnosis and is dependent on the amount of Xpert testing. I assume the proportion is 0.45, 1.00 and 0 in the public sector ($Þ^{(pu)}$), amongst private providers that always use Xpert, and amongst private providers that do not use Xpert, respectively (10). Thus, $1 - Þ_y$ represents TB patients with DR-TB that are not tested for drug resistance and are therefore mistakenly initiated onto first-line treatment. m_y is the rate of MDR acquisition and is assumed to be higher amongst all private providers (m_b) except active providers that offer government supplied FDCs and adherence support, than public sector providers (m_a) (11). τ is the rate of treatment completion for first line treatment and corresponds to a duration of 6 months. p_{SL} applies exclusively to TB patients with DR-TB and is defined as the proportion of DR-TB cases that fail first-line treatment and that are successfully transferred to second-line treatment. χ_y is the proportion of TB cases that default from first line treatment and is dependent on the treatment services offered by providers. I assume that the proportion of TB cases that default from treatment is 0.15 amongst both public sector providers (χ_{Pu}) and active private providers that offer both government supplied FDCs and adherence support (χ_{PrAF}); amongst active private providers that offer only government supplied FDCs (χ_{PrF}), the proportion is 0.17; this increases to 0.21 amongst active providers that offer only adherence support (χ_{PrA}); finally, this proportion is 0.48 amongst active providers that offer neither government supplied FDCs or adherence support, inactive and unengaged providers (χ_{PrZ}) (9,10).

The following equation represents the number of DR-TB patients receiving second-line treatment:

$$\frac{dTx_q^{(SL)}}{dt} = \varepsilon_{sn}\omega\phi Þ_{pu}Dx_q^{(pu)} + c_{sn}\omega\phi Þ_{pr0}\sum\left[Dx_q^{(pr1)} + Dx_q^{(pr2)} + Dx_q^{(pr5)} + Dx_q^{(pr6)}\right]$$
$$+x_{sn}\omega\phi Þ_{pr1}\sum\left[Dx_q^{(pr3)} + Dx_q^{(pr4)}\right]$$
$$+\tau p_{SL}\sum\left[Tx_q^{(FL:pu)} + Tx_q^{(FL:prZ1)} + Tx_q^{(FL:prZ2)} + Tx_q^{(FL:prAF)} + Tx_q^{(FL:prF)} + Tx_q^{(FL:prA)}\right]$$
$$-(\tau_{mdr} + \frac{\tau_{mdr}\chi_{\mathrm{mdr}}}{1-\chi_{\mathrm{mdr}}} + \mu_2)Tx_q^{(SL)} \quad (22)$$

TB patients that successfully complete TB treatment, recover with a low risk of relapse, and is written as:

Post-treatment recovery

$$\frac{dR^{(L)}}{dt} = \tau\sum\left[Tx_q^{(FL:pu)} + Tx_q^{(FL:prZ1)} + Tx_q^{(FL:prZ2)} + Tx_q^{(FL:prAF)} + Tx_q^{(FL:prF)} + Tx_q^{(FL:prA)}\right] +$$
$$\varsigma R^{(H)} - (r_2 + \mu_2)R^{(L)} \quad (23)$$

On the other hand, TB patients that either default from TB treatment or those that recover whilst still seeking care for TB, recover with a high risk of relapse, and is written as:

Post-self-cure recovery

$$\frac{dR^{(H)}}{dt} = \frac{\tau\chi_{pu}}{1-\chi_{pu}}Tx_q^{(FL:pu)} + \frac{\tau\chi_{PrZ}}{1-\chi_{PrZ}}\sum\left[Tx_q^{(FL:prZ1)} + Tx_q^{(FL:prZ2)}\right] + \frac{\tau\chi_{PrAF}}{1-\chi_{PrAF}}Tx_q^{(FL:prAF)} +$$
$$\frac{\tau\chi_{PrA}}{1-\chi_{PrA}}Tx_q^{(FL:prA)} + \frac{\tau\chi_{PrF}}{1-\chi_{PrF}}Tx_q^{(FL:prF)} + \varphi\sum[Dx_q^{(pu)} + Dx_q^{(pr1)} + Dx_q^{(pr3)} + Dx_q^{(pr4)} + Dx_q^{(pr5)} +$$
$$Dx_q^{(pr6)} + E_q + I_q] - (\varsigma + r_1 + \mu_2)R^{(H)} \quad (24)$$

The force of infection can be written as:

$$\lambda_q = \frac{\beta\left\{\Sigma\left[I_q + Dx_q^{pu} + Dx_q^{pr1:6} + E_q\right]\right\} + d_q\beta\left\{\Sigma\left[I_q + Dx_q^{pu} + Dx_q^{pr1:6} + E_q\right]\right\}}{N} \quad (25)$$

Non-TB symptomatic population

To count the number of false positive diagnoses that arise, I model a non-TB symptomatic population. I define non-TB symptomatic as patients that present to care with symptoms of TB, but that do not have TB. I assume this population to be independent of the TB population described above.

Non-TB symptomatics seeking care

$$\frac{dU^{(NTB)}}{dt} = y_{sp}\phi\omega Dx^{(NTB)} + \tau Tx^{(NTB)} - \delta_1 v^{(x)} U^{(NTB)} \quad (26)$$

where $v^{(x)}$ represents equation 4 to 10, depending on the type of provider a patient seeks care from, and where y_{sp} represents either the specificity of TB diagnosis in the public sector (ε_{sp}), specificity of Xpert (x_{sp}) or the specificity of clinical diagnosis (c_{sp}).

Awaiting diagnosis

$$\frac{dDx^{(NTB)}}{dt} = \delta_1 v^{(x)} U^{(NTB)} - \phi\omega Dx^{(NTB)} \quad (27)$$

Undergoing first-line TB treatment

$$\frac{dTx^{(NTB)}}{dt} = \left(1 - y_{sp}\right)\phi\omega Dx^{(NTB)} - \tau Tx^{(NTB)} \quad (28)$$

I assume the total population size of the non-TB symptomatic population remains constant. The size of this population was determined so that for every true positive TB diagnosis, approximately nine uninfected individuals who present for diagnosis with symptoms of TB are also tested for TB (9,12–16).

1.3. Model calibration

Through Adaptive Bayesian MCMC, I examined the uncertainty in data and model inputs (table 5.1 and table 5.2.)(17). I was able to propagate this uncertainty into the model projections.
I define the posterior distribution as,

$$p(\theta|D) \propto L(D|\theta)\,.\,\pi(\theta) \quad (29)$$

where, θ is a vector of the data and model inputs subject to uncertainty, *L* is the likelihood of the data given θ, and π is the prior distribution. I assumed uniform distributions for the prior distributions. I defined the likelihood by fitting log-normal distributions to the calibration targets.
By sampling from the posterior distribution using MCMC, I created an unbiased sample that approximates the posterior distribution. A sample is randomly selected from $p(\theta|D)$, and depending on the proposal distribution, it is accepted or rejected. By using Adaptive Bayesian MCMC, the proposal distribution is updated continuously. Once the MCMC converged, I removed the burn-in period (10,000 iterations) and selected every 50th sample to reduce any autocorrelation. This provided 10,000 samples from the posterior distribution.

2. Supporting figures

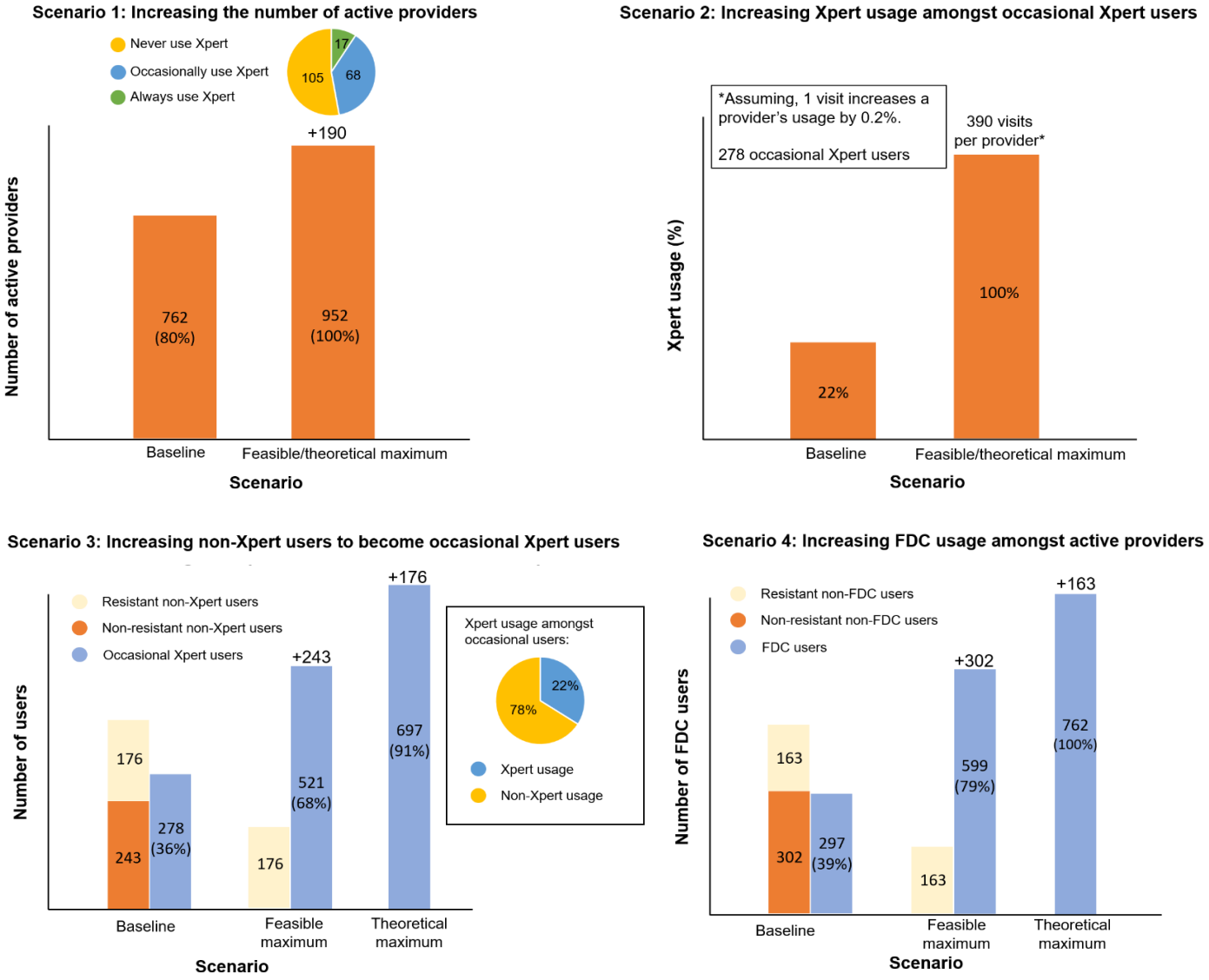

Fig A3.1. Feasible and theoretical maximums for each service provision, Ahmedabad. *Scenario 1:* I assume all inactive providers (190) are converted into active providers. I assume no inactive providers are resistant, thus the feasible and theoretical maximum scenarios are the same. Newly active providers are assumed to have the same behaviour as pre-existing active providers; in the case of Ahmedabad, 9% use Xpert 100% of the time, 36% use Xpert occasionally (with an average Xpert usage of 22%), 55% never use Xpert, 98% offer adherence support and 39% consistently use governmental FDCs. For example, of the 190 newly active providers, 17 providers use Xpert 100% of the time, 68 use Xpert occasionally, and 105 never use Xpert. *Scenario 2:* At baseline, occasional Xpert users use Xpert 22% of the time; this is increased to 100% under the feasible and theoretical maximum scenario. I assume no occasional users are resistant to increasing their Xpert usage. It is estimated that one visit by a field officer increases a provider's usage of Xpert by 0.2%. At baseline, Ahmedabad has 278 occasional Xpert users. *Scenario 3:* At baseline, there are 419 non-Xpert users and 278 occasional users. Of the 419 non-Xpert users, it is estimated that 42% are resistant to using Xpert; thus, only 243 non-Xpert users can be converted to become an occasional user. At the theoretical maximum, the percentage of active providers that use Xpert occasionally is 91%; the remaining 9% are providers that always use Xpert. *Scenario 4:* At baseline, there are 465 non-FDC users and 297 consistent FDC users. Of the 465, 35% are resistant to FDCs.

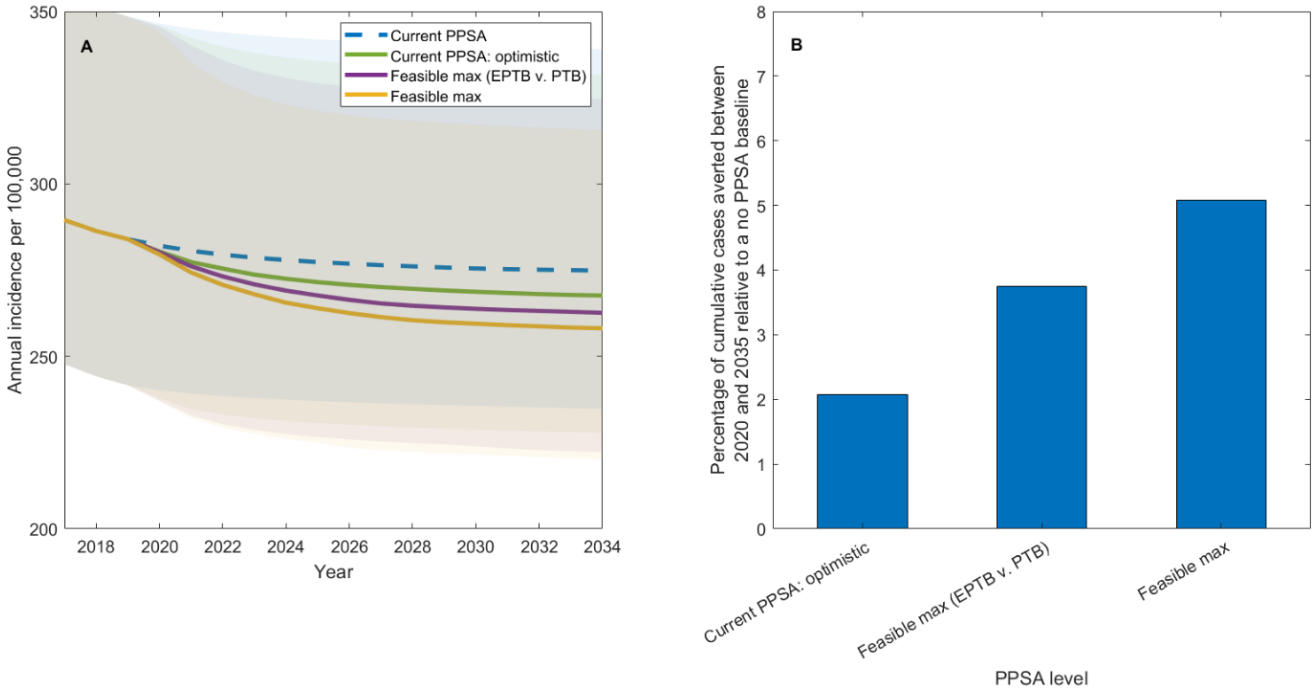

Fig A3.2. Sensitivity analysis on model projections for the impact of increasing all service provisions to their feasible maximum has on TB incidence in Ahmedabad between 2020 and 2035. Panel A shows the projected trajectory of TB incidence, assuming current PPSA scale up between 2017 and 2020 (blue dashed line) and its maintenance indefinitely; assuming current PPSA scale up between 2017 and 2020 whilst optimistically assuming that active providers are continuously active (Xpert use and FDC use is not weighted by the number of months active providers are active for) (green line); service provisions are increased to their feasible maximum from 2020 to 2021 and maintained indefinitely, but assuming that 50% of TB cases that present to care are extra-pulmonary TB (purple line); that service provisions are increased to their feasible maximum from 2020 to 2021 and maintained indefinitely, as presented in the main text (yellow line). Panel B shows the percentage of cumulative cases averted between 2020 and 2035 compared to a baseline of current PPSA scale up for each of the scenarios in panel A.

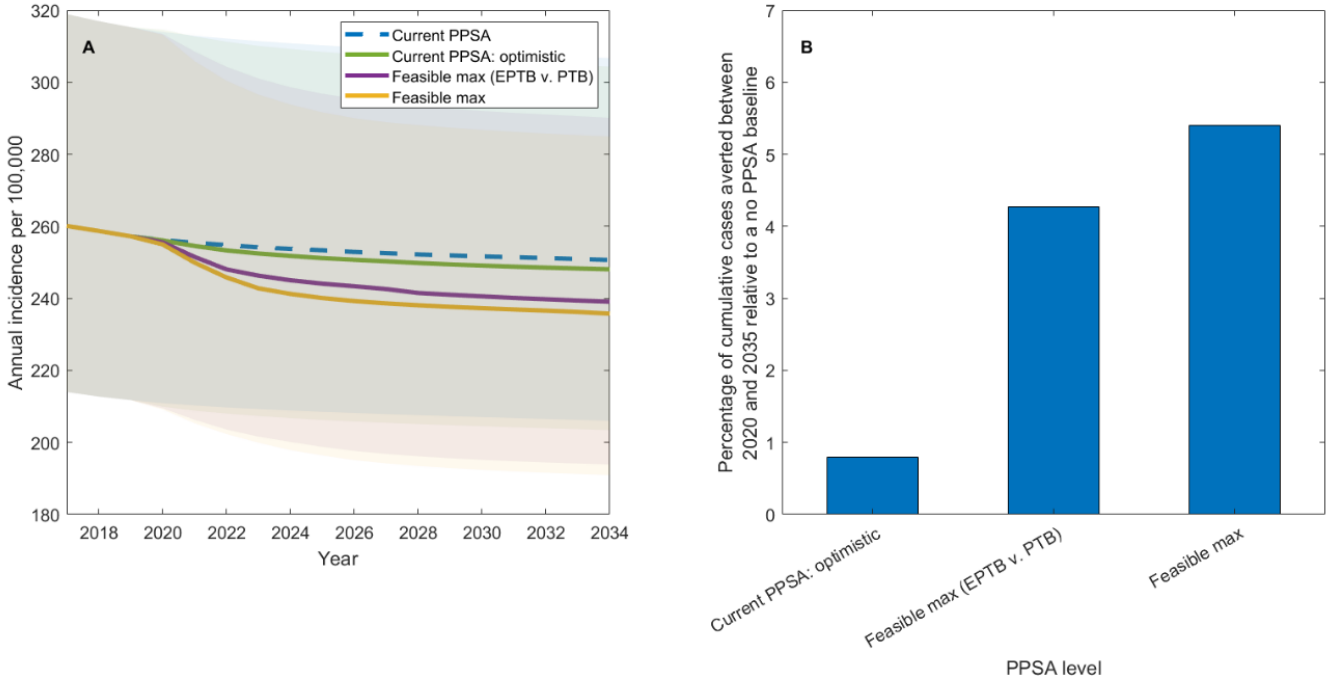

Fig A3.3. Sensitivity analysis on model projections for the impact increasing all service provisions to their feasible maximum has on TB incidence in Delhi between 2020 and 2035. Panel A shows the projected trajectory of TB incidence, assuming current PPSA scale up between 2017 and 2020 (blue dashed line) and its maintenance indefinitely; assuming current PPSA scale up between 2017 and 2020 whilst optimistically assuming that active providers are continuously active (Xpert use and FDC use is not weighted by the number of months active providers are active for) (green line); that service provisions are increased to their feasible maximum from 2020 to 2021 and maintained indefinitely, but assuming that 50% of TB cases that present to care are extra-pulmonary TB (purple line); that service provisions are increased to their feasible maximum from 2020 to 2021 and maintained indefinitely, as presented in the main text (yellow line). Panel B shows the percentage of cumulative cases averted between 2020 and 2035 compared to a baseline of current PPSA scale up for each of the scenarios in panel A.

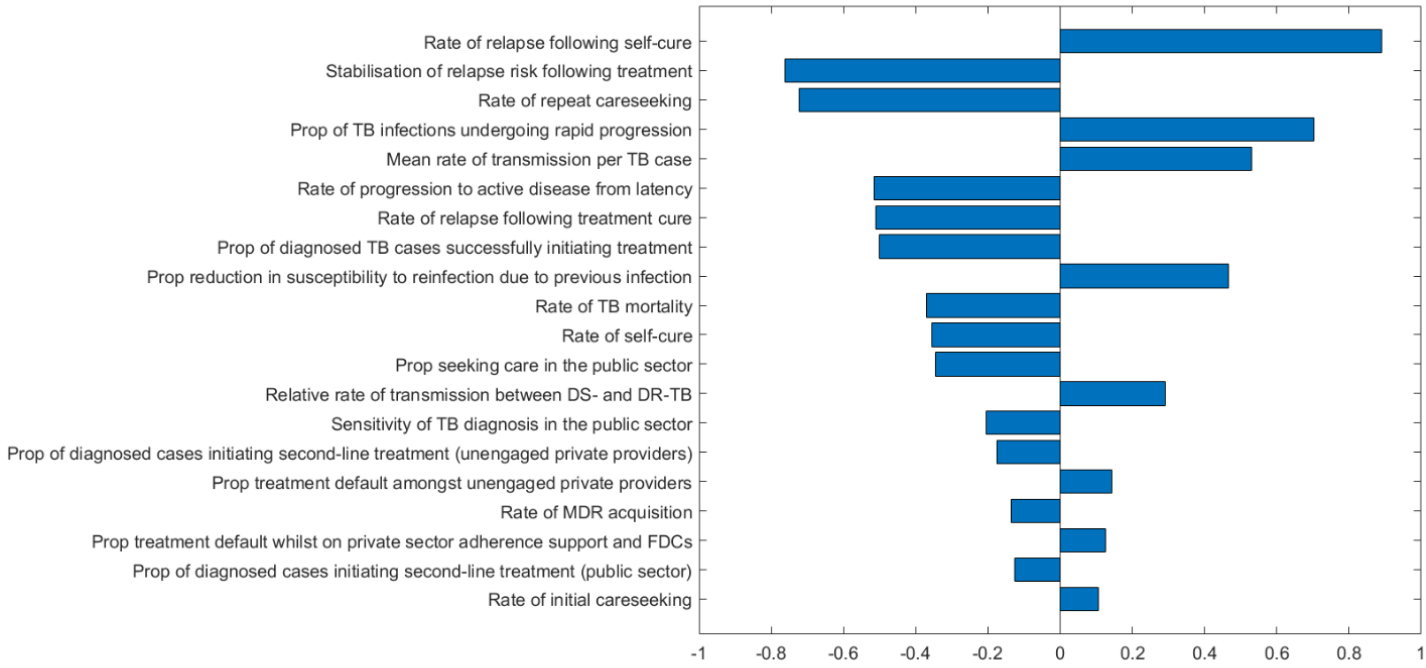

Fig A3.4. Multivariate sensitivity analysis of impact for Ahmedabad. I used partial rank correlation coefficient (PRCC) to examine which parameter listed in table 5.1 the output cases averted is most sensitive towards. Larger bars represent more sensitive parameters. Shown are the 20 most influential model parameters, in decreasing order of sensitivity from top to bottom.

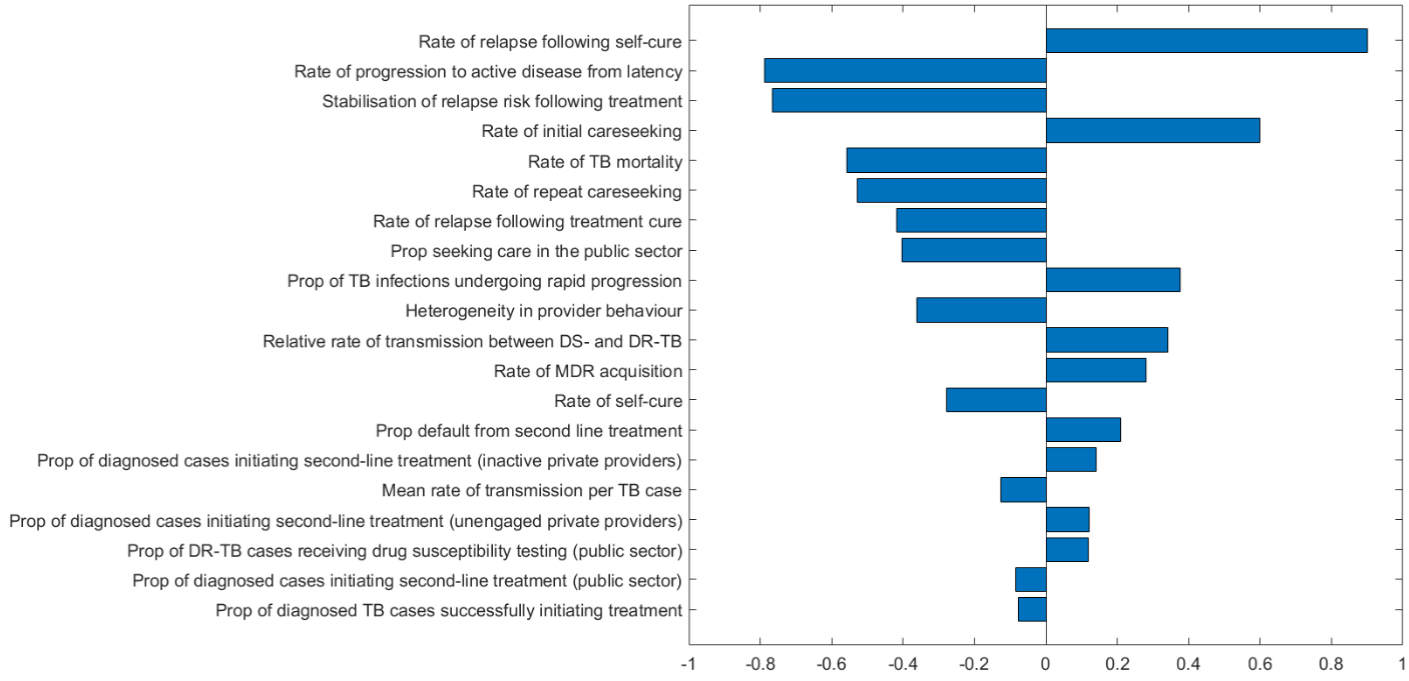

Fig A3.5. Multivariate sensitivity analysis of impact for Delhi. I used partial rank correlation coefficient (PRCC) to examine which parameter listed in table 5.1 the output cases averted is most sensitive towards. Larger bars represent more sensitive parameters. Shown are the 20 most influential model parameters, in decreasing order of sensitivity from top to bottom.

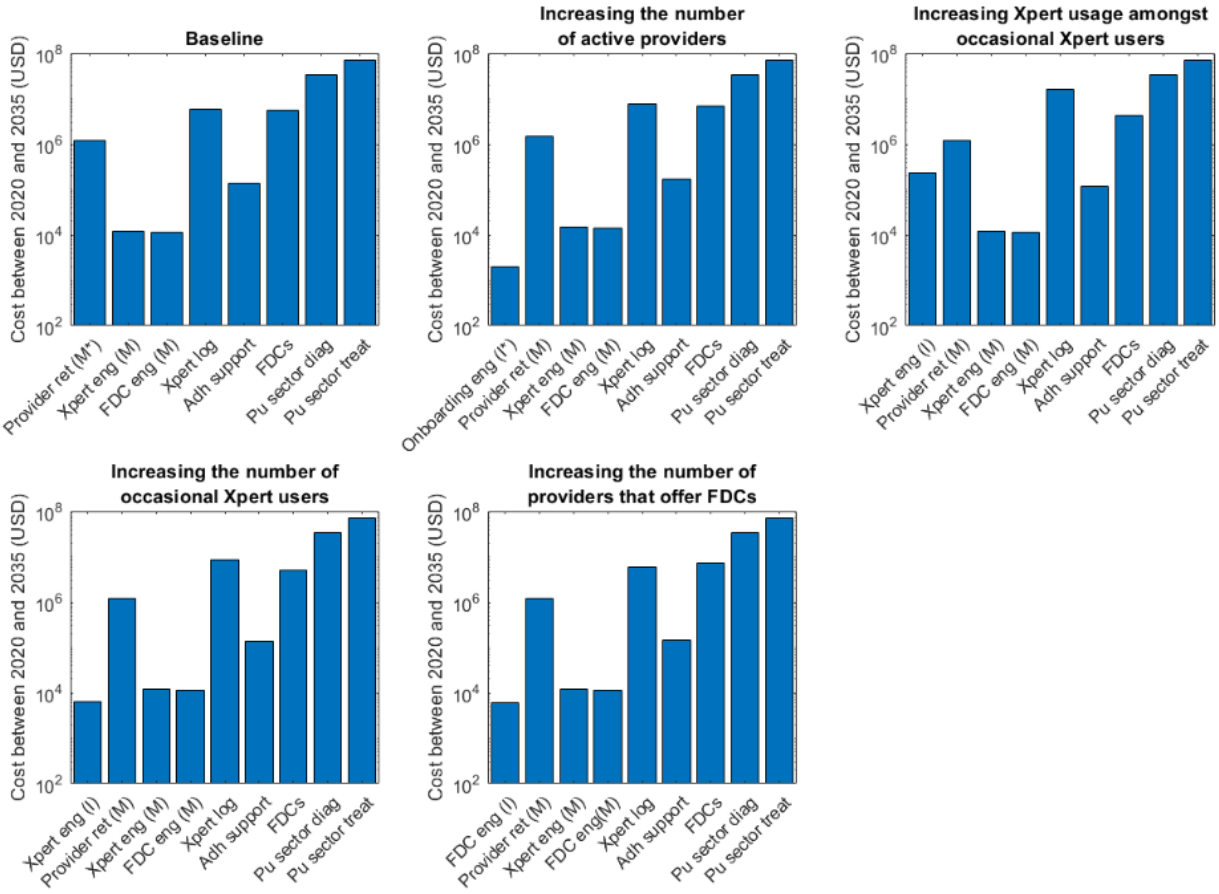

Fig A3.6. Breakdown of costs across each intervention between 2020 and 2035 for Ahmedabad. 'M' represents maintenance costs, and 'I' represents costs unique to each intervention. Provider ret – provider retention; Xpert eng – Xpert engagement; FDC eng – FDC engagement; Xpert log – Xpert logistics; Adh support – adherence support; Pu sector diag – public sector diagnosis; Pu sector treat – public sector treatment; onboarding eng – onboarding engagement.

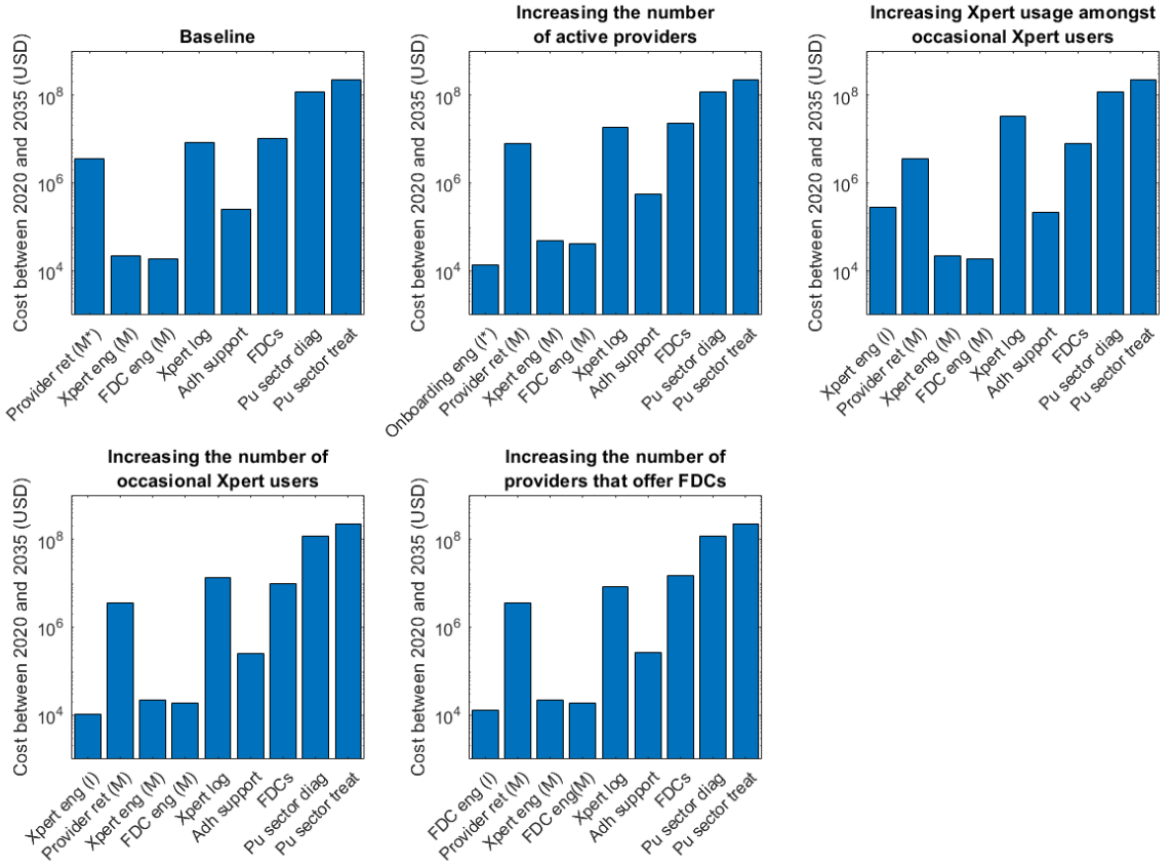

Fig A3.7. Breakdown of costs across each intervention between 2020 and 2035 for Delhi. 'M' represents maintenance costs, and 'I' represents costs unique to each intervention. Provider ret – provider retention; Xpert eng – Xpert engagement; FDC eng – FDC engagement; Xpert log – Xpert logistics; Adh support – adherence support; Pu sector diag – public sector diagnosis; Pu sector treat – public sector treatment; onboarding eng – onboarding engagement.

3. Supporting tables

Intervention	Incremental cost (2020-2035, USD)	Percentage of cumulative TB cases averted (2020-2035)	Cost-efficiency
Individual interventions			
Increasing the number of active providers (assuming newly active providers adopt average behaviour)	2,269,300 (1,477,000 – 3,723,000)	3.00% (2.59-3.37)	0.0032 (0.0019- 0.0050)
Increasing the number of active providers (assuming newly active providers' behaviour is 25% worse than average)	2,224,400 (1,435,200 – 3,672,300)	2.98% (2.58-3.35)	0.0032 (0.0019- 0.0051)
Increasing the number of active providers (assuming newly active providers' behaviour is 50% worse than average)	2,120,000 (1,339,000 – 3,555,300)	2.89% (2.48-3.24)	0.0033 (0.0019- 0.0053)
Increasing Xpert use amongst occasional users	9,005,000 (6,801,000 – 13,190,000)	2.83% (2.42-3.33)	0.0008 (0.0006- 0.0010)
Increasing the number of occasional Xpert users	2,211,700 (1,683,500 – 3,275,100)	2.32% (1.97-2.67)	0.0025 (0.0018- 0.0033)
Increasing the number of FDC users	1,787,700 (1,438,900 – 2,503,800)	2.53% (2.13-2.91)	0.0031 (0.0024- 0.0041)
Combination of the two most cost-efficient interventions: Increasing the number of active providers* + …			
+Increasing the number of occasional Xpert users	5,020,300 (3,590,000 – 7,512,900)	3.21% (2.84-3.61)	0.0015 (0.0010- 0.0022)
+ Increasing Xpert use amongst occasional users	13,427,000 (10,019,000 – 19,839,000)	3.81% (3.40-4.45)	0.0007 (0.0005- 0.0009)
+ Increasing the number of FDC users	5,217,100 (3,791,600 – 8,182,300)	3.46% (2.96-3.91)	0.0016 (0.0010- 0.0022)
Combination of the three most cost-efficient interventions: Increasing the number of active providers* + the number of FDC-users + …			
+Increasing the number of occasional Xpert users	7,163,000 (5,671,000 – 10,478,000)	3.67% (3.18-4.16)	0.0012 (0.0008- 0.0017)
+ Increasing Xpert use amongst occasional users	15,467,000 (11,921,000 – 22,411,000)	4.27% (3.81-4.87)	0.0007 (0.0005- 0.0009)
Combination of all interventions*			
+ Increasing Xpert use amongst occasional users	27,976,000 (21,331,000 – 40,913,000)	5.17% (4.49-6.17)	N/A

Table A3.3. Cost efficiency of service provisions in Ahmedabad. I also conduct a sensitivity analysis on the behaviour of newly active providers, and whether increasing the number of active providers remains the most cost-efficient individual intervention if the behaviour of newly active providers is assumed to be 25% and 50% worse than pre-existing active providers. Indeed, even if the behaviour of newly active providers is 50% worse, this intervention is still the most cost-efficient individual intervention when scaled up to its feasible maximum. *I assume that these newly active providers adopt average behaviour.

Intervention	Incremental cost (2020-2035, USD)	Percentage of cumulative TB cases averted (2020-2035)	Cost-efficiency
Individual interventions			
Increasing the number of active providers (assuming newly active providers adopt average behaviour)	20,760,000 (12,478,000 – 36,094,000)	3.06% (2.43-3.98)	0.0003 (0.0002- 0.0006)
Increasing Xpert use amongst occasional users	22,249,000 (13,546,000 – 30,724,000)	1.11% (0.97-1.27)	0.0001 (0.0001- 0.0002)
Increasing the number of occasional Xpert users	4,920,900 (2,985,500 – 6,819,600)	0.86% (0.73-1.03)	0.0004 (0.0003- 0.0006)
Increasing the number of FDC users	4,496,400 (3,283,400 – 5,866,200)	1.13% (0.97-1.34)	0.0006 (0.0004- 0.0007)
Combination of the two most cost-efficient interventions: Increasing the number of FDC-users + …			
+Increasing the number of active providers	30,981,000 (21,744,000-46,622,000)	3.80% (2.92-5.06)	0.00026 (0.00017- 0.0046)
+Increasing the number of occasional Xpert users	9,250,000 (6,796,000 – 12,272,000)	1.21% (1.05-1.41)	0.00028 (0.00021-0.00038)
+ Increasing Xpert use amongst occasional users	26,794,000 (17,716,000 – 36,310,000)	1.47% (1.29-1.72)	0.00012 (0.00008-0.00017)
Combination of the three most cost-efficient interventions: Increasing the number of FDC users + increasing the number of occasional Xpert users + …			
+ Increasing the number of active providers	41,648,000 (30,441,000 - 60,488,000)	3.95% (3.05-5.22)	0.00020 (0.00013 – 0.00033)
+ Increasing Xpert use amongst occasional users	60,238,000 (37,969,000 – 82,081,000)	1.96% (1.64-2.35)	0.00007 (0.00005 – 0.00010)
Combination of all interventions			
+ Increasing Xpert use amongst occasional users	157,450,000 (100,600,000 – 213,200,000)	5.35% (4.30-7.00)	N/A

Table A3.4. Cost efficiency of service provisions in Delhi. I also conduct a sensitivity analysis on the behaviour of newly active providers, and whether increasing the number of active providers remains the most cost-efficient individual intervention if the behaviour of newly active providers is assumed to be 25% and 50% worse than pre-existing active providers. Indeed, even if the behaviour of newly active providers is 50% worse, this intervention is still the most cost-efficient individual intervention when scaled up to its feasible maximum. *I assume that these newly active providers adopt average behaviour.

Intervention	Maintenance costs sensitivity analysis	Incremental cost (2020-2035, USD)	Percentage of cumulative TB cases averted (2020-2035)	Cost-efficiency
Increasing the number of active providers	*-20%:*	1,963,400 (1,170,200-3,416,300)	3.00% (2.59-3.37)	0.0037 (0.0021-0.0063)
	+20%	2,575,300 (1,782,200-4,028,200)		0.0028 (0.0017-0.0041)
Increasing the number of occasional Xpert users	*-20%:*	1,965,900 (1,440,400-3,030,200)	2.32% (1.97-2.67)	0.0028 (0.0020-0.0038)
	+20%	2,455,700 (1,930,200-3,520,000)		0.0023 (0.0017-0.0029)
Increasing Xpert use amongst occasional users	*-20%:*	8,743,000 (6,671,000-13,031,000)	2.83% (2.42-3.33)	0.0008 (0.0006-0.0010)
	+20%	9,232,000 (7,160,000-13,521,000)		0.0007 (0.0006-0.0009)
Increasing the number of FDC users	*-20%:*	1,541,800 (1,194,000-2,260,900)	2.53% (2.13-2.91)	0.0039 (0.0026-0.0050)
	+20%	2,031,600 (1,683,800-2,750,700)		0.0027 (0.0022-0.0036)

Table A3.5. Sensitivity analysis on the cost of maintenance in Ahmedabad. I explore whether increasing or decreasing maintenance cost by 20% effected the cost-efficiency order of individual service provisions. Maintenance costs include the cost of provider retention, the cost of Xpert engagement to maintain Xpert use, and the cost of FDC engagement to maintain FDC use. Generally, increasing the number of active providers remains the most cost-efficient individual intervention when increased to its feasible maximum; however, if the maintenance cost is decreased by 20%, then increasing the number of FDC users is the most cost-efficient.

Intervention	Maintenance costs sensitivity analysis	Incremental cost (2020-2035, USD)	Percentage of cumulative TB cases averted (2020-2035)	Cost-efficiency
Increasing the number of active providers	*-20%:*	19,145,000 (10,865,000 – 34,481,000)	3.06% (2.43-3.98)	0.0003 (0.0002-0.0007)
	+20%	22,375,000 (14,095,000 – 37,712,000)		0.0003 (0.0002 – 0.0006)
Increasing the number of occasional Xpert users	*-20%:*	4,205,900 (2,272,200 – 6,104,300)	0.86% (0.73-1.03)	0.0004 (0.0003-0.0008)
	+20%	5,638,400 (3,704,700 – 7,536,800)		0.0003 (0.0002-0.0005)
Increasing Xpert use amongst occasional users	*-20%:*	21,455,000 (12,823,000 – 29,889,000)	1.11% (0.97-1.27)	0.0001 (0.0001-0.0002)
	+20%	22,887,000 (14,255,000– 31,321,000)		0.0001 (0.0001-0.0002)
Increasing the number of FDC users	*-20%:*	3,782,600 (2,569,100 – 5,154,300)	1.13% (0.97-1.34)	0.0007 (0.0005-0.0009)
	+20%	5,215,100 (4,001,600 – 6,586,800)		0.0005 (0.0004-0.0006)

Table A3.6. Sensitivity analysis on the cost of maintenance in Delhi. I explore whether increasing or decreasing maintenance cost by 20% effected the cost-efficiency order of individual service provisions. Maintenance costs include the cost of provider retention, the cost of Xpert engagement to maintain Xpert use, and the cost of FDC engagement to maintain FDC use. Increasing the number of FDC users remains the most cost-efficient individual intervention when scaled up to its feasible maximum.

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Appendix 4

Quantifying the potential value of antigen-detection rapid diagnostic tests for coronavirus disease 2019: a modelling analysis

1. Model equations

Parameter	Notation
Epidemiology	
Prevalence of current or recent SARS-CoV-2 infection	P
Proportion amongst those tested who are in acute phase	p_{inf}
Of those in acute phase, number of infectious days remaining	D_{inf}
Case fatality rate amongst hospitalised COVID-19 patients	M
Case fatality reduction amongst COVID-19 patients on dexamethasone (1 – risk ratio)	M_{red}
NAAT performance	
NAAT sensitivity (for current or recent SARS-CoV-2)	N_{sn}
NAAT specificity	N_{sp}
NAAT availability (proportion able to access NAAT test)	p_{NAAT}
Cost per NAAT test	C_{NAAT}
NAAT turnaround time	D_{NAAT}
Isolate and initiate treatment (if indicated) whilst awaiting NAAT result*	I_{isol}
Ag-RDT performance	
Ag-RDT sensitivity for current infection, relative to NAAT	$R_{\text{inf }\_sn}$
Ag-RDT sensitivity for recent infection, relative to NAAT	$R_{\text{non\_inf }\_sn}$
Ag-RDT specificity, relative to NAAT	R_{sp}
Cost per Ag-RDT test	C_{RDT}
Confirmation of an Ag-RDT negative result with NAAT*	I_{neg}
Confirmation of an Ag-RDT positive result with NAAT*	I_{pos}
Clinical judgement and management	
Sensitivity of clinical judgement in absence of NAAT	J_{sn}
Specificity of clinical judgement in absence of NAAT	J_{sp}
Proportion of hospitalised patients with a negative COVID-19 test result (true and false negatives) that are initiated onto dexamethasone	p_{treat}
Duration of isolation	D_{isol}
Duration of treatment	D_{treat}
Cost of isolation per day	C_{isol}
Cost of treatment per day	C_{treat}

Table A4.1. Parameter notation. See table 6.2 in the main text for parameter values. *These variables are indicator variables (Yes = 1; No = 0); in other words, these variables switch components of the equations discussed below on and off depending on the algorithm selected.

For each algorithm, I calculated the costs, deaths averted, and infectious person-days averted. First, I calculated the probability of a positive diagnosis (true and false positives) and probability of a negative diagnosis (true and false negatives) for each algorithm. These probabilities were then multiplied by various parameters in order to calculate the various outputs.

1.1. Probability of a positive diagnosis

Below, are the probabilities of a positive diagnosis (D_{p_NAAT} and D_{p_RDT}) for each algorithm:

NAAT-based strategy

$$\boldsymbol{D_{p\_NAAT}} =$$

$$[P \times p_{NAAT} \times N_{sn}] + \quad \textit{1, True positive (NAAT)}$$
$$[P \times (1 - p_{NAAT}) \times J_{sn}] + \quad \textit{2, True positive (clinical judgement)}$$
$$[(1 - P) \times p_{NAAT} \times (1 - N_{sp})] + \quad \textit{3, False positive (NAAT)}$$
$$[(1 - P) \times (1 - p_{NAAT}) \times (1 - J_{sp})] \quad \textit{4, False positive (clinical judgement)}$$

Where P is the prevalence of current or recent SARS-CoV-2 infection; p_{NAT} is the proportion able to access a NAAT test; N_{sn} and $N_{sp}$is NAAT sensitivity and specificity, respectively; $J_{sn}$and J_{sp} is the sensitivity and specificity of clinical judgement in the absence of NAAT, respectively.

Ag-RDT-led strategy

There are three different Ag-RDT led strategies: (1) Ag-RDT only strategy, (2) Confirmation of an Ag-RDT negative result with a NAAT test, (3) Confirmation of an Ag-RDT positive result with a NAAT test. The overall probability of receiving a positive test result as a result of an Ag-RDT-led algorithm can be calculated by the following framework, with different components of the framework being zeroed by indicator variables (I_{neg} and I_{pos}) depending on which algorithm is selected:

Framework:

$$\boldsymbol{D_{p\_RDT}} = [D_{p\_RDT\_only} \times (1 - I_{neg} - I_{pos})] + [D_{p\_RDT\_neg} \times I_{neg}] + [D_{p\_RDT\_pos} \times I_{pos}]$$

The individual probabilities ($D_{p\_RDT\_only}$, $D_{p\_RDT\_neg}$ and $D_{p\_RDT\_pos}$) can be calculated by the following equations:

Ag-RDT only: ($D_{p\_RDT\_only}$)

$\boldsymbol{D_{p\_RDT\_only}} =$

$$\left[P \times p_{inf} \times R_{\text{inf }\_sn}\right] + \quad \textit{1, True positive, infectious}$$
$$[P \times (1 - p_{inf}) \times R_{\text{non\_inf }\_sn}] + \quad \textit{2, True positive, non- infectious}$$
$$[(1 - P) \times (1 - R_{sp})] \quad \textit{3, False positive}$$

Where P is the prevalence of current or recent SARS-CoV-2 infection; p_{inf} is the proportion amongst those tested who are in acute phase; $R_{\text{inf }\_sn}$, $R_{\text{non\_inf }\_sn}$ and $R_{sp}$is the Ag-RDT sensitivity for current infection, Ag-RDT sensitivity for recent infection, and Ag-RDT specificity, respectively, all relative to NAAT.

Confirmation of an Ag-RDT negative with a NAAT: ($D_{p\_RDT\_neg}$)

$\boldsymbol{D_{p\_RDT\_neg}} =$

$$[P \times p_{inf} \times R_{\text{inf }\_sn}] + \quad \textit{1, True positive (Ag-RDT), infectious}$$
$$[P \times (1 - p_{\text{inf}}) \times R_{\text{non\_inf }\_sn}] + \quad \textit{2, True positive (Ag-RDT), non-infectious}$$
$$[P \times p_{inf} \times (1 - R_{\text{inf }\_sn}) \times\ p_{NAAT} \times N_{sn}] + \quad \textit{3, True positive (NAAT), infectious}$$
$$[P \times (1 - p_{inf}) \times (1 - R_{\text{non\_inf }\_sn}) \times\ p_{NAAT} \times N_{sn}] + \quad \textit{4, True positive (NAAT), non-infectious}$$
$$[P \times p_{inf} \times (1 - R_{\text{inf }\_sn}) \times\ (1 - p_{NAAT}) \times J_{sn}] + \quad \textit{5, True positive (clinical judgement), infectious}$$
$$[P \times (1 - p_{inf}) \times (1 - R_{\text{non\_inf }\_sn}) \times\ (1 - p_{NAAT}) \times J_{sn}] + \quad \textit{6, True positive (C.J.), non-infectious}$$
$$[(1 - P) \times (1 - R_{\text{sp}})] + \quad \textit{7, False positive (Ag-RDT)}$$
$$[(1 - P) \times R_{\text{sp}} \times\ p_{NAAT} \times (1 - N_{sp})] + \quad \textit{8, False positive (NAAT)}$$
$$[(1 - P) \times R_{\text{sp}} \times\ (1 - p_{NAAT}) \times (1 - J_{sp})] \quad \textit{9, False positive (C.J.)}$$

Where P is the prevalence of current or recent SARS-CoV-2 infection; p_{inf} is the proportion amongst those tested who are in acute phase; $R_{\text{inf }\_sn}$, $R_{\text{non\_inf }\_sn}$ and $R_{sp}$is the Ag-RDT sensitivity for current infection, Ag-RDT sensitivity for recent infection, and Ag-RDT specificity, respectively, all relative to NAAT; p_{NAAT} is the proportion able to access a NAAT test; N_{sn} and $N_{sp}$is NAAT sensitivity and specificity, respectively; $J_{sn}$and J_{sp} is the sensitivity and specificity of clinical judgement in the absence of NAAT, respectively.

Confirmation of an Ag-RDT positive with a NAAT: $(D_{p\_RDT\_pos})$

$\boldsymbol{D_{p\_RDT\_pos}} =$

$[P \times p_{inf} \times R_{\text{inf }\_sn} \times N_{sn}] +$ *1, True positive, infectious*

$[P \times (1 - p_{inf}) \times R_{\text{non\_inf }\_sn} \times N_{sn}] +$ *2, True positive, non-infectious*

$[(1 - P) \times (1 - R_{\text{sp}}) \times (1 - N_{sp})]$ *3, False positive*

Where P is the prevalence of current or recent SARS-CoV-2 infection; p_{inf} is the proportion amongst those tested who are in acute phase; $R_{\text{inf }\_sn}$, $R_{\text{non\_inf }\_sn}$ and $R_{sp}$is the Ag-RDT sensitivity for current infection, Ag-RDT sensitivity for recent infection, and Ag-RDT specificity, respectively, all relative to NAAT; N_{sn} and $N_{sp}$is NAAT sensitivity and specificity, respectively.

1.2. Probability of a negative diagnosis

Below, are the probabilities of receiving a negative diagnosis (D_{n_NAAT} and D_{n_RDT}) for the different algorithms:

NAAT-based strategy

$\boldsymbol{D_{n\_NAAT}} =$

$[P \times p_{NAAT} \times (1 - N_{sn})] +$ *1, False negative (NAAT)*

$[P \times (1 - p_{NAAT}) \times (1 - J_{sn})] +$ *2, False negative (clinical judgement)*

$\left[(1 - P) \times (1 - p_{NAAT}) \times N_{sp}\right] +$ *3, True negative (NAAT)*

$[(1 - P) \times (1 - p_{NAAT}) \times J_{sp}]$ *4, True negative (clinical judgement)*

Where P is the prevalence of current or recent SARS-CoV-2 infection; p_{NAAT} is the proportion able to access a NAAT test; N_{sn} and $N_{sp}$is NAAT sensitivity and specificity, respectively; $J_{sn}$and J_{sp} is the sensitivity and specificity of clinical judgement in the absence of NAAT, respectively.

Ag-RDT-led strategy

As above, the probability of a negative test result due to an Ag-RDT-led algorithm can be calculated by the following framework, with different components of the framework being zeroed by indicator variables (I_{neg} and I_{pos}) depending on which algorithm is selected:

Framework:

$$\boldsymbol{D_{n\_RDT}} = [D_{n\_RDT\_only} \times (1 - I_{neg} - I_{pos})] + [D_{n\_RDT\_neg} \times I_{neg}] + [D_{n\_RDT\_pos} \times I_{pos}]$$

The individual probabilities ($D_{n\_RDT\_only}$, $D_{n\_RDT\_neg}$ and $D_{n\_RDT\_pos}$) can be calculated by the following equations:

Ag-RDT only: ($D_{n\_RDT\_only}$)

$$\boldsymbol{D_{n\_RDT\_only}} =$$

$$[P \times p_{inf} \times (1 - R_{\text{inf }\_sn})] + \quad \textit{1, False negative, infectious}$$
$$[P \times (1 - p_{inf}) \times (1 - R_{\text{non\_inf }\_sn})] + \quad \textit{2, False negative, non-infectious}$$
$$[(1 - P) \times R_{sp}] \quad \textit{3, True negative}$$

Where P is the prevalence of current or recent SARS-CoV-2 infection; p_{inf} is the proportion amongst those tested who are in acute phase; $R_{\text{inf }\_sn}$, $R_{\text{non\_inf }\_sn}$ and $R_{sp}$is the Ag-RDT sensitivity for current infection, Ag-RDT sensitivity for recent infection, and Ag-RDT specificity, respectively, all relative to NAAT.

Confirmation of an Ag-RDT negative with a NAAT: ($D_{n\_RDT\_neg}$)

$$\boldsymbol{D_{n\_RDT\_neg}} =$$

$$[P \times p_{inf} \times (1 - R_{\text{inf }\_sn}) \times p_{NAAT} \times (1 - N_{sn})] + \quad \textit{1, False negative (Ag-RDT \& NAAT), infectious}$$
$$[P \times (1 - p_{inf}) \times (1 - R_{\text{non\_inf }\_sn}) \times p_{NAAT} \times (1 - N_{sn})] + \quad \textit{2, False negative (Ag-RDT \& NAAT), non- inf}$$
$$[P \times p_{inf} \times (1 - R_{\text{inf }\_sn}) \times (1 - p_{NAAT}) \times (1 - J_{sn})] + \quad \textit{3, False negative (Ag-RDT \& C.J.), infectious}$$
$$[P \times (1 - p_{inf}) \times (1 - R_{\text{non\_inf }\_sn}) \times (1 - p_{NAAT}) \times (1 - J_{sn})] + \quad \textit{4, False negative (Ag-RDT \& C.J), non-inf}$$
$$\left[(1 - P) \times R_{sp} \times p_{NAAT} \times N_{sp}\right] + \quad \textit{5, True negative (Ag-RDT \& NAAT)}$$
$$[(1 - P) \times R_{sp} \times (1 - p_{NAAT}) \times J_{sp}] \quad \textit{6, True negative (Ag-RDT \& C.J)}$$

Where P is the prevalence of current or recent SARS-CoV-2 infection; p_{inf} is the proportion amongst those tested who are in acute phase; $R_{\text{inf }\_sn}$, $R_{\text{non\_inf }\_sn}$ and $R_{sp}$is the Ag-RDT sensitivity for current infection, Ag-RDT sensitivity for recent infection, and Ag-RDT specificity, respectively, all relative to NAAT; p_{NAAT} is the proportion able to access a NAAT test; N_{sn} and $N_{sp}$is NAAT sensitivity and specificity, respectively; $J_{sn}$and J_{sp} is the sensitivity and specificity of clinical judgement in the absence of NAAT, respectively.

Confirmation of an Ag-RDT positive with a NAAT: $(D_{n\_RDT\_pos})$

$\boldsymbol{D_{n\_RDT\_pos}} =$

$[P \times p_{inf} \times (1 - R_{\text{inf }\_sn})] +$ *1, False negative (missed by Ag-RDT), infectious*

$[P \times (1 - p_{inf}) \times (1 - R_{\text{non\_inf }\_sn})] +$ *2, False negative (Ag-RDT), non- infectious*

$\left[P \times p_{inf} \times R_{\text{inf }\_sn} \times (1 - N_{sn})\right] +$ *3, False negative (NAAT), infectious*

$[P \times (1 - p_{inf}) \times R_{\text{non\_inf }\_sn} \times (1 - N_{sn})] +$ *4, False negative (NAAT), non-infectious*

$\left[(1 - P) \times \left(1 - R_{sp}\right) \times N_{sp}\right] +$ *5, True negative (Ag-RDT & NAAT)*

$[(1 - P) \times R_{sp}]$ *6, True negative (Ag-RDT)*

Where P is the prevalence of current or recent SARS-CoV-2 infection; p_{inf} is the proportion amongst those tested who are in acute phase; $R_{\text{inf }\_sn}$, $R_{\text{non\_inf }\_sn}$ and $R_{sp}$is the Ag-RDT sensitivity for current infection, Ag-RDT sensitivity for recent infection, and Ag-RDT specificity, respectively, all relative to NAAT; N_{sn} and $N_{sp}$is NAAT sensitivity and specificity, respectively.

1.3. Probability of receiving a NAAT test

Here, I calculate the probability of receiving a NAAT test for each algorithm.

NAAT-based strategy

$\boldsymbol{N_{NAAT}} = p_{NAAT}$

Ag-RDT-led strategy

As above, the probability of receiving a NAAT test with an Ag-RDT-led algorithm can be calculated by the following framework, with different components of the framework being zeroed by indicator variables (I_{neg} and I_{pos}) depending on which algorithm is selected:

Framework:

$\boldsymbol{N_{RDT}} = [N_{RDT\_only} \times (1 - I_{neg} - I_{pos})] + [N_{RDT\_neg} \times I_{neg}] + [N_{RDT\_pos} \times I_{pos}]$

The individual probabilities ($(N_{RDT\_only}$, N_{RDT_neg} and $N_{RDT\_pos})$ can be calculated by the following equations:

Ag-RDT only: (N_{RDT_only})

$\boldsymbol{N_{RDT\_only}} = 0$

Confirmation of an Ag-RDT negative with a NAAT: (N_{RDT_neg})

$\boldsymbol{N_{RDT\_neg}} =$

$[P \times p_{inf} \times (1 - R_{\text{inf }\_sn}) \times p_{NAAT}] +$ *1, False negative (missed by Ag-RDT), infectious*

$[P \times (1 - p_{inf}) \times (1 - R_{\text{non\_inf }\_sn}) \times p_{NAAT}] +$ *2, False negative (Ag-RDT), non- infectious*

$[(1 - P) \times R_{\text{sp}} \times p_{NAAT}]$ *3, True negative (Ag-RDT)*

Where P is the prevalence of current or recent SARS-CoV-2 infection; p_{inf} is the proportion amongst those tested who are in acute phase; $R_{\text{inf }\_sn}$, $R_{\text{non\_inf }\_sn}$ and $R_{sp}$is the Ag-RDT sensitivity for current infection, Ag-RDT sensitivity for recent infection, and Ag-RDT specificity, respectively, all relative to NAAT; p_{NAAT} is the proportion able to access a NAAT test.

Confirmation of an Ag-RDT positive with a NAAT: (N_{RDT_pos})

$\boldsymbol{N_{RDT\_pos}} =$

$[P \times p_{inf} \times R_{\text{inf }\_sn}] +$ *1, True positive (detected by Ag-RDT), infectious*

$[P \times (1 - p_{inf}) \times R_{\text{non\_inf }\_sn}] +$ *2, True positive (Ag-RDT), non-infectious*

$[(1 - P) \times (1 - R_{\text{sp}})]$ *3, False positive (Ag-RDT)*

Where P is the prevalence of current or recent SARS-CoV-2 infection; p_{inf} is the proportion amongst those tested who are in acute phase; $R_{\text{inf }\_sn}$, $R_{\text{non\_inf }\_sn}$ and $R_{sp}$is the Ag-RDT sensitivity for current infection, Ag-RDT sensitivity for recent infection, and Ag-RDT specificity, respectively, all relative to NAAT.

1.4. Probability of receiving an Ag-RDT test

Here, I calculate the probability of receiving an Ag-RDT test for each algorithm.

NAAT-based strategy

$\boldsymbol{R_{NAAT}} = 0$

Ag-RDT-led strategy

As above, the probability of receiving an Ag-RDT test with an Ag-RDT-led algorithm can be calculated by the following framework, with different components of the framework being zeroed by indicator variables (I_{neg} and I_{pos}) depending on which algorithm is selected:

Framework:

$$\boldsymbol{R_{RDT}} = [R_{RDT\_only} \times (1 - I_{neg} - I_{pos})] + [R_{RDT\_neg} \times I_{neg}] + [R_{RDT\_pos} \times I_{pos}]$$

The individual probabilities (R_{RDT_only}, R_{RDT_neg} and R_{RDT_pos}) can be calculated by the following equations:

Ag-RDT only: (R_{RDT_only})

$$\boldsymbol{R_{RDT\_only}} = 1$$

Confirmation of an Ag-RDT negative with a NAAT: $\left(R_{RDT\_neg}\right)$

$$\boldsymbol{R_{RDT\_neg}} = 1$$

Confirmation of an Ag-RDT positive with a NAAT: (R_{RDT_pos})

$$\boldsymbol{R_{RDT\_pos}} = 1$$

1.5. Probability of death due to COVID-19

Using the probability of a true-positive test result and the probability of a false-negative test result, I calculated the probability of death due to COVID-19 for each algorithm. All the algorithms follow the same framework, listed below:

Framework for all algorithms:

$$probability\ of\ death =$$
$$[Probability\ of\ a\ true\ positive\ result\ \times M \times M_{red}] +$$
$$[Probability\ of\ a\ false\ negative\ result\ \times p_{treat} \times M \times M_{red}] +$$
$$[Probability\ of\ a\ false\ negative\ result\ \times (1 - p_{treat}) \times M]$$

Where M is the case fatality rate amongst hospitalised COVID-19 patients;
M_{red} is the case fatality reduction amongst COVID-19 patients on dexamethasone; p_{treat} is the proportion of hospitalised patients with a negative COVID-19 test result that are initiated onto dexamethasone.

1.6. Number of infectious days per person

Using the probability of a true-positive test result and the probability of a false-negative test result, I calculated the number of infectious days per person for each algorithm, as shown below. Note, whether individuals isolate whilst awaiting a NAAT result or not can be switched on and off by the indicator variable, $I_{isol.}$

NAAT-based strategy

$$Infectious\ days\ per\ person =$$

$$\left[Probability\ of\ a\ true\ positive\ (NAAT)\ \times p_{inf} \times \min\left(D_{inf}, D_{NAAT}\right) \times (1 - I_{isol})\right] +$$

$$\Big[Probability\ of\ a\ false\ negative\ (NAAT)\ \times p_{inf}$$

$$\times \Big(\left(\min\left(D_{inf}, D_{NAAT}\right) \times (1 - I_{isol})\right) + \max\left(D_{inf} - D_{NAAT}, 0\right)\Big)\Big] +$$

$$[Probability\ of\ a\ false\ negative\ (clinical\ judgement) \times p_{inf} \times D_{inf}]$$

Where p_{inf} is the proportion amongst those tested who are in acute phase; D_{inf} is the number of infectious days remaining amongst those in acute phase; D_{NAAT} is the NAAT turnaround time.

Ag-RDT only strategy

$$Infectious\ days\ per\ person = Probability\ of\ a\ false\ negative\ \times D_{inf}$$

Confirmation of an Ag-RDT negative with a NAAT

$$Infectious\ days\ per\ person =$$

$$\left[Probability\ of\ a\ true\ positive\ (NAAT)\ \times \min\left(D_{inf}, D_{NAAT}\right) \times (1 - I_{isol})\right] +$$

$$\Big[Probability\ of\ a\ false\ negative\ (NAAT)$$

$$\times \Big(\left(\min\left(D_{inf}, D_{NAAT}\right) \times (1 - I_{isol})\right) + \max\left(D_{inf} - D_{NAAT}, 0\right)\Big)\Big] +$$

$$[Probability\ of\ a\ false\ negative\ (clinical\ judgement) \times D_{inf}]$$

Where D_{inf} is the number of infectious days remaining amongst those in acute phase; D_{NAAT} is the NAAT turnaround time.

Confirmation of an Ag-RDT positive with a NAAT

$$Infectious\ days\ per\ person =$$
$$\left[Probability\ of\ a\ true\ positive\ (NAAT)\ \times \min\left(D_{inf}, D_{NAAT}\right) \times (1 - I_{isol})\right] +$$
$$\Big[Probability\ of\ a\ false\ negative\ (NAAT)$$
$$\times \left(\left(\min\left(D_{inf}, D_{NAAT}\right) \times (1 - I_{isol})\right) + \max\left(D_{inf} - D_{NAAT}, 0\right)\right)\Big] +$$
$$[Probability\ of\ a\ false\ negative\ (Ag\ RDT) \times D_{inf}]$$

Where D_{inf} is the number of infectious days remaining amongst those in acute phase; D_{NAAT} is the NAAT turnaround time.

1.7. Cost per person

Here, I calculate the cost per person. The total cost of an algorithm is as follows:

Framework for all algorithms:

$$Cost_{total} = Cost_{testing} + Cost_{isolation} + Cost_{treatment}$$

Below, I breakdown the costs of the different components (testing, isolation and treatment) for each algorithm. Note, whether individuals isolate whilst awaiting a NAAT result or not can be switched on and off by the indicator variable, $I_{isol.}$

NAAT-based strategy

Cost of testing

$$Cost_{NAAT\_testing} = N_{NAAT} \times C_{NAAT}$$

Where N_{NAAT} is the probability of receiving a NAAT test; C_{NAAT} is the cost per NAAT test.

Cost of isolation

$$Cost_{NAAT\_isolation} =$$

$$[p_{NAAT} \times I_{isol} \times D_{NAAT} \times C_{isol}] +$$
$$\left[\left(D_{p\_NAAT}(1) + D_{p\_NAAT}(3)\right) \times I_{isol} \times \max(D_{isol} - D_{NAAT}, 0) \times C_{isol}\right] +$$
$$[(D_{p\_NAAT}(1) + D_{p\_NAAT}(3)) \times (1 - I_{isol}) \times D_{isol} \times C_{isol}] +$$
$$[(D_{p\_NAAT}(2) + D_{p\_NAAT}(4)) \times D_{isol} \times C_{isol}]$$

Where p_{NAAT} is the proportion able to access a NAAT test; D_{NAAT} is the NAAT turnaround time; C_{isol} is the cost of isolation per person per day; $D_{p\_NAAT}(1)$ and $D_{p\_NAAT}(3)$ is the probability of a true-positive and a false-positive diagnosis when using a NAAT, respectively; $D_{p\_NAAT}(2)$ and $D_{p\_NAAT}(4)$ is the probability of a true-positive and a false-positive diagnosis under clinical judgement in the absence of NAAT, respectively; D_{isol} is the duration of isolation.

Cost of treatment

$$Cost_{NAAT\_treatment} =$$

$$\left[D_{p_{NAAT}} \times D_{treat} \times C_{treat}\right] + [D_{n_{NAAT}} \times p_{treat} \times D_{treat} \times C_{treat}]$$

Where D_{p_NAAT} and D_{n_NAAT} is the probability of a positive and a negative diagnosis under a NAAT strategy, respectively; D_{treat} is the duration of treatment; p_{treat} is the proportion of hospitalised patients with a negative COVID-19 test result that are initiated onto dexamethasone; C_{treat} is the cost of treatment per person per day.

Ag-RDT only

Cost of testing

$$Cost_{RDT\_testing} = C_{RDT}$$

Where C_{RDT} is the cost per Ag-RDT test.

Cost of isolation

$$Cost_{RDT\_isolation} = D_{p\_RDT\_only} \times D_{isol} \times C_{isol}$$

Where C_{isol} is the cost of isolation per person per day; $D_{p\_RDT\_only}$ is the probability of a positive diagnosis under an Ag-RDT only strategy; D_{isol} is the duration of isolation.

Cost of treatment

$$Cost_{RDT\_treatment} =$$

$$\left[D_{p_{RDTonly}} \times D_{treat} \times C_{treat}\right] + [D_{n_{RDTonly}} \times p_{treat} \times D_{treat} \times C_{treat}]$$

Where $D_{p_{RDTonly}}$ and $D_{n_{RDTonly}}$ is the probability of a positive and a negative diagnosis under an Ag-RDT only strategy, respectively; D_{treat} is the duration of treatment; p_{treat} is the proportion of hospitalised patients with a negative COVID-19 test result that are initiated onto dexamethasone; C_{treat} is the cost of treatment per person per day.

Confirmation of an Ag-RDT negative with a NAAT

Cost of testing

$$Cost_{RDT\_neg\_testing} = C_{RDT} + [N_{RDT\_neg} \times C_{NAAT}]$$

Where C_{RDT} is the cost per Ag-RDT test; C_{NAAT} is the cost per NAAT test; N_{RDT_neg} is the probability of receiving a NAAT test under a confirm Ag-RDT negative strategy.

Cost of isolation

$$\begin{aligned}
&Cost_{RDT_neg_isolation} = \\
&\big[\big(D_{p_RDT_neg}(1) + D_{p_RDT_neg}(2) + D_{p_RDT_neg}(7) + D_{p_RDT_neg}(5) + D_{p_RDT_neg}(6) \\
&\qquad + D_{p_RDT_neg}(9)\big) \times D_{isol} \times C_{isol}\big] + \\
&\big[N_{RDT_neg} \times I_{isol} \times D_{NAAT} \times C_{isol}\big] + \\
&\big[\big(D_{p_RDT_neg}(3) + D_{p_RDT_neg}(4) + D_{p_RDT_neg}(8)\big) \times I_{isol} \times \max(D_{isol} - D_{NAAT}, 0) \times C_{isol}\big] + \\
&[\big(D_{p_RDT_neg}(3) + D_{p_RDT_neg}(4) + D_{p_RDT_neg}(8)\big) \times (1 - I_{isol}) \times D_{isol} \times C_{isol}]
\end{aligned}$$

Where $D_{p\_RDT\_neg}(1)$ and $D_{p\_RDT\_neg}(2)$ is the probability of a true positive diagnosis when using an Ag-RDT amongst infectious and non-infectious cases, respectively; $D_{p\_RDT\_neg}(5)$ and $D_{p\_RDT\_neg}(6)$ is the probability of a true positive diagnosis when using clinical judgment in the absence of NAAT amongst infectious and non-infectious cases, respectively; $D_{p\_RDT\_neg}(7)$ and $D_{p\_RDT\_neg}(9)$ is the probability of a false positive diagnosis when using an Ag-RDT or under clinical judgement in the absence of NAAT, respectively; $D_{p\_RDT\_neg}(3)$ and $D_{p\_RDT\_neg}(4)$ is the probability of a true positive diagnosis when using NAAT amongst infectious and non-infectious cases, respectively; $D_{p_{RDT_{neg}}}(8)$ is the probability of a false positive diagnosis when using NAAT; N_{RDT_neg} is the probability of receiving a NAAT test; C_{isol} is the cost of isolation per person per day; D_{isol} is the duration of isolation; D_{NAAT} is the NAAT turnaround time.

Cost of treatment

$$Cost_{RDT\_neg\_treatment} =$$

$$\left[D_{p_{RDTneg}} \times D_{treat} \times C_{treat}\right] + [D_{n\_RDTneg} \times p_{treat} \times D_{treat} \times C_{treat}]$$

Where $D_{p_{RDTneg}}$ and D_{n_RDTneg} is the probability of a positive and a negative diagnosis under a confirm Ag-RDT negative strategy, respectively; D_{treat} is the duration of treatment; p_{treat} is the proportion of hospitalised patients with a negative COVID-19 test result that are initiated onto dexamethasone; C_{treat} is the cost of treatment per person per day.

Confirmation of an Ag-RDT positive with a NAAT

Cost of testing

$$Cost_{RDT\_pos\_testing} = C_{RDT} + [N_{RDT\_pos} \times C_{NAAT}]$$

Where C_{RDT} is the cost per Ag-RDT test; C_{NAAT} is the cost per NAAT test; N_{RDT_pos} is the probability of receiving a NAAT test under a confirm Ag-RDT positive strategy.

Cost of isolation

$$Cost_{RDT\_pos\_isolation} =$$
$$\left[N_{RDT\_pos} \times I_{isol} \times D_{NAAT} \times C_{isol}\right] +$$
$$\left[D_{p\_RDT\_pos} \times I_{isol} \times \max(D_{isol} - D_{NAAT}, 0) \times C_{isol}\right] +$$
$$[D_{p\_RDT\_pos} \times (1 - I_{isol}) \times D_{isol} \times C_{isol}]$$

Where $D_{p\_RDT\_pos}$ is the probability of a positive diagnosis; N_{RDT_pos} is the probability of receiving a NAAT test; C_{isol} is the cost of isolation per person per day; D_{isol} is the duration of isolation; D_{NAAT} is the NAAT turnaround time.

Cost of treatment

$$Cost_{RDT\_pos\_treatment} =$$
$$\left[D_{p_{RDTpos}} \times D_{treat} \times C_{treat}\right] + [D_{n\_RDTpos} \times p_{treat} \times D_{treat} \times C_{treat}]$$

Where $D_{p_{RDTpos}}$ and D_{n_RDTpos} is the probability of a positive and a negative diagnosis under a confirm Ag-RDT positive strategy, respectively; D_{treat} is the duration of treatment; p_{treat} is the proportion of hospitalised patients with a negative COVID-19 test result that are initiated onto dexamethasone; C_{treat} is the cost of treatment per person per day.

2. Expert consultation

To identify appropriate use cases for implementation of antigen-detection RDTs for SARS-CoV-2, I conducted a series of four expert consultations. For each consultation, I identified an in-country expert with knowledge of the landscape of diagnostic testing for infectious diseases and the country's response to the COVID-19 pandemic. I consulted experts in Brazil, India, Nigeria, and South Africa (experts listed in table A4.2 below) – countries with large populations, a breadth of income levels, broad geographic representation, and COVID-19 epidemics of substantial magnitude. Consultations were performed between July 2 and 7, 2020. Each consultation was structured as follows:

First, I provided background on the potential characteristics of an Ag-RDT: results within 30 minutes, more feasible to perform at point of care, performed on oropharyngeal/nasal/salivary specimens, and less sensitive than nucleic acid amplification tests. Second, I described the primary research objective: to estimate the benefits and harms of implementing Ag-RDTs in specific use cases. Third, I provided examples of paradigmatic use cases, in terms of eligible population and intended use of the Ag-RDT. Fourth, I asked in-country experts to identify at least two important use cases for their country's setting, asking that they define: (a) the eligible population; (b) the intended use/incremental benefit of Ag-RDT; (c) the status quo – how members of the population would be managed in the absence of an Ag-RDT; (d) how the status quo would change in the presence of an Ag-RDT (for both people testing positive and negative on Ag-RDT); (e) the most important outcomes/measures of value; and (f) the most important trade-offs to consider.

Each consultation lasted between 60 and 90 minutes, resulting in the following use cases being identified:

- Community-based testing of symptomatics, in decentralised clinics or in dedicated testing facilities in containment zones (India and South Africa)
- Testing of symptomatic individuals in health facilities and amongst those being admitted to hospital (India and South Africa)

- Testing of asymptomatic employees contacting high-risk populations such as long-term care facilities (South Africa)
- Testing of symptomatic outpatients (Brazil and Nigeria)
- Testing of asymptomatic employees in high-risk occupations such as healthcare workers (Brazil and Nigeria)

For the purpose of this analysis, I focused on the first two use cases listed above. However, the approach described in the study can also straightforwardly be extended to the other use cases listed here.

Name of expert	Country	Affiliation
Kiran Rade	India	Indian Council of Medical Research
Dhamari Naidoo	Nigeria	WHO Country Office
Francois Venter	South Africa	WITS Reproductive Health and HIV Institute
Amilcar Tanuri	Brazil	Federal University of Rio de Janeiro

Table A4.2. List of country experts consulted to identify appropriate use cases, for an Ag-RDT

3. Additional Figures

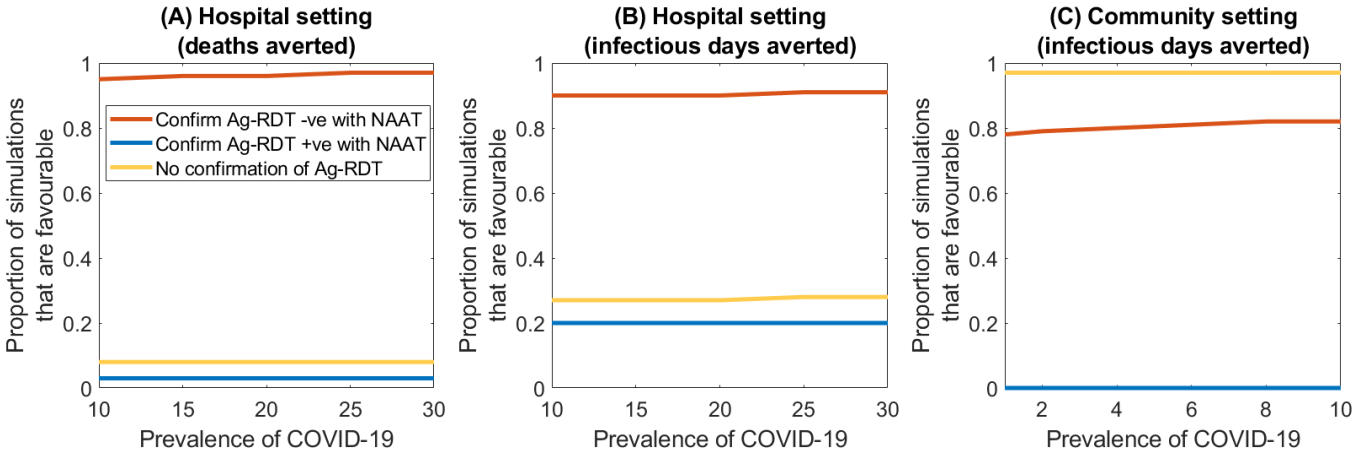

Figure A4.1. Sensitivity analysis to varying prevalence of COVID-19 amongst those being tested. As a focal model output, all figures show the proportion of simulations in which an Ag-RDT was favourable, with different algorithms labelled by the different line colours. Panels A and B show the impact of varying prevalence on deaths and infectious days averted, respectively, in a hospital setting. Panel C shows the impact on infectious days averted in a community setting. Similar to the analysis presented in the main text, I assumed that all individuals were isolated whilst waiting for a NAAT result in the hospital setting and that no one isolated whilst awaiting a test result in the community setting. Results illustrate that the proportion favourable remained stable to these alternative assumptions for prevalence.

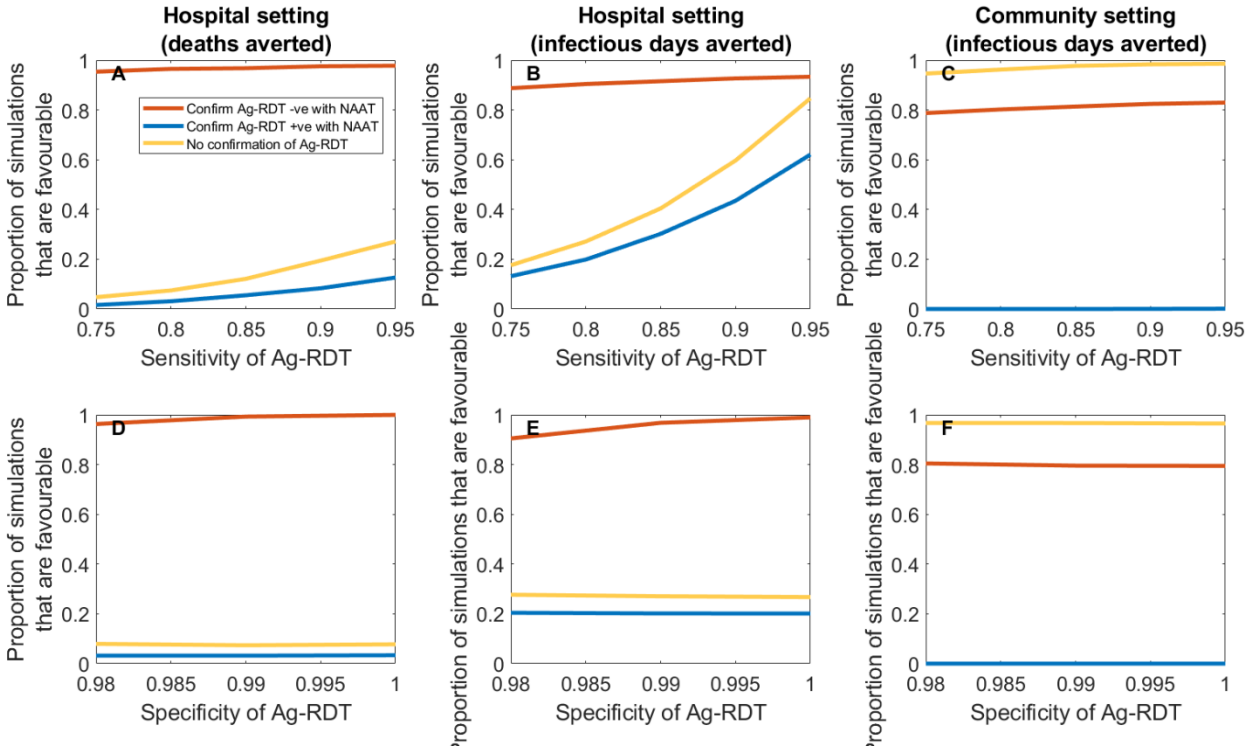

Figure A4.2. Sensitivity analysis to varying Ag-RDT sensitivity and specificity. As a focal model output, all figures show the proportion of simulations in which an Ag-RDT was favourable, with different algorithms labelled by the different line colours. Panels A-C show the sensitivity of Ag-RDT being varied between 75-95% across the hospital and community settings, assuming specificity remained fixed at 98%. Panels D-F show the specificity of Ag-RDT being varied between 98-100%, assuming sensitivity remained fixed at 80%. Similar to the analysis presented in the main text, I assumed that all individuals were isolated whilst waiting for a NAAT result in the hospital setting and that no one isolated whilst awaiting a test result in the community setting. Results illustrate that increasing Ag-RDT sensitivity increased the favourability of the "Ag-RDT only" and "confirm Ag-RDT negative" strategies (panel C). For example, the favourability of an algorithm that confirms an Ag-RDT negative result increased from 79% to 83% when sensitivity increased from 75% to 95%. Increasing sensitivity had little impact on the "confirm Ag-RDT positive" strategy; since the only costs incurred under this setting was the cost of a test, a NAAT-only strategy was often cheaper and averted more infectious days than the "confirm Ag-RDT positive" strategy (the cost of testing with an Ag-RDT and confirming a positive result with a NAAT test makes it costly, and by re-testing a positive result with a NAAT, the sensitivity of the algorithm was lower due to the imperfect sensitivity of NAAT). Similar to the hospital setting, specificity had little impact on an algorithm's favourability (panel F).

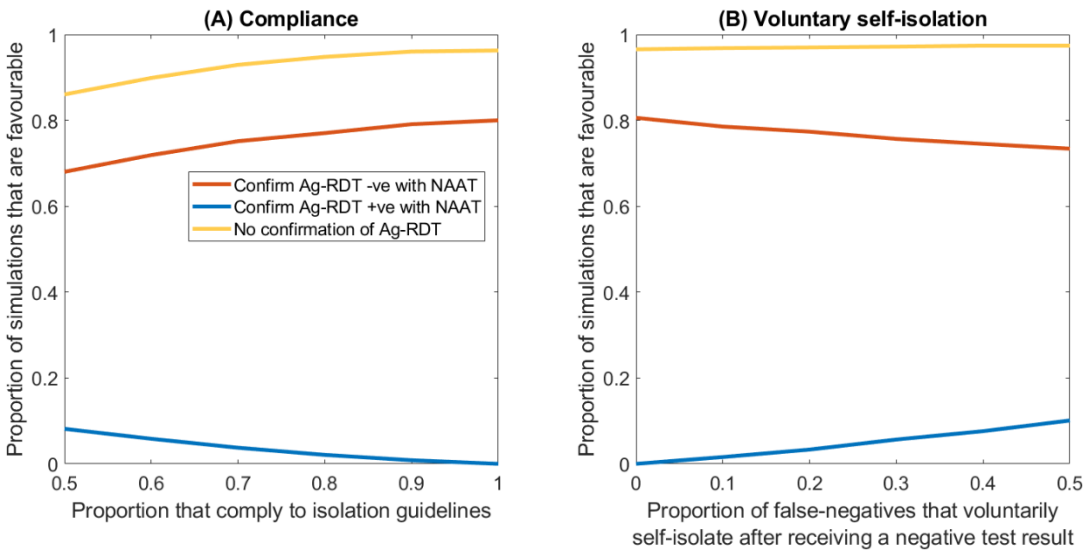

Figure A4.3. Sensitivity analysis to patient behaviour in relation to self-isolation, in the community setting. As a focal model output, all figures show the proportion of simulations in which an Ag-RDT was favourable, with different algorithms labelled by the different line colours. Panel A shows the impact of compliance amongst those required to self-isolate after a positive final test result. Panel B shows the impact of test-negative individuals voluntarily self-isolating. This sensitivity analysis was restricted to the community setting as it is likely that hospitals will enforce compliance to isolation guidelines. Results illustrate that increasing the proportion of compliance to isolation recommendations increased the favourability of both "Ag-RDT-only" and "confirm Ag-RDT negative" strategies, from 86% and 68% of simulations being favourable with 50% compliance to 98% and 80% with 100% compliance, respectively. The benefit of an Ag-RDT test in rapidly detecting COVID cases, and hence averting onward transmission, is reduced if these individuals did not isolate. However, the opposite was seen with the "confirm Ag-RDT positive" strategy, with the favourability of the algorithm decreasing from 8% to 0% if compliance doubled from 50% to 100%. Generally, this strategy detected fewer COVID cases than a NAAT-based strategy, due to the reduction in overall sensitivity caused by inclusion of NAAT confirmation; thus, increasing the proportion of individuals that did not comply had a greater effect on a NAAT-based strategy than the Ag-RDT strategy, hence increasing the latter's favourability. Similar results were seen for voluntary self-isolation (where false negatives voluntarily self-isolate).