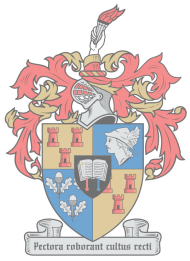
How can virtual implementation modelling inform the scale-up of new molecular diagnostic tools for tuberculosis?

RORY DUNBAR



Dissertation presented for the degree of Doctor of Philosophy in the Faculty of Medicine and Health Sciences at Stellenbosch University

Supervisor: Professor Nulda Beyers

Co-supervisor: Ivor Langley

Co-supervisor: Pren Naidoo

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DECLARATION

By submitting this dissertation electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by Stellenbosch University will not infringe any third-party rights and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

Date: 13 October 2017

This dissertation includes 2 original papers published in peer-reviewed journals, 1 accepted paper in a peer-reviewed journal and 1 unpublished paper. The development and writing of the papers (published and unpublished) were the principal responsibility of myself and, for each of the cases where this is not the case, a declaration is included in the dissertation indicating the nature and extent of the contribution of co-authors.

DECLARATION OF CONTRIBUTION BY CANDIDATE

With regards to the main empirical study (Policy Relevant Outcomes from Validating Evidence on ImpacT), the nature of my contribution was as follows: I conducted the overall data management, assisted with data analysis, reviewed the draft manuscripts and approved the final draft manuscripts for submission to peer-reviewed journals. These manuscripts are listed in the supplementary chapter at the end of the dissertation.

With regards to the dissertation, the nature of my contribution is as follows: I developed and validated the operational model as well as conducted the sensitivity analysis for the operational model. Once this operational model has been validated, I had numerous discussions with my supervisors to use the model to answer a series of questions important for the scale-up of new diagnostic tests for TB. Together we decided to compare various TB diagnostic algorithms as used in clinical practice to evaluate various scenarios, rather than to evaluate individual tests. I performed the overall data management and data analysis to answer all the questions posed necessary for all chapters. I wrote all chapters in this dissertation and for those chapters submitted to peer-reviewed journals, I wrote the manuscripts and submitted the final manuscripts for publication to the peer-reviewed journals.

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CONTENT

ABSTRACT

The aim of this dissertation was to develop an operational model to explain why the expected increase in the number of tuberculosis (TB) cases detected was not found in our empirical study, Policy Relevant Outcomes from Validating Evidence on ImpacT (PROVE IT), done in 142 health clinics in Cape Town after the roll-out of a new TB diagnostic test, Xpert MTB/RIF (Xpert). I then used the model to model the effect of interventions to improve the detection of TB and rifampicin resistant (RMP-R) TB. Strategies were modelled to reduce laboratory cost for detecting TB as well as the effect of introducing a more sensitive molecular diagnostic test, Xpert MTB/RIF Ultra (Ultra), as a replacement for Xpert on the number of TB and RMP-R TB cases detected.

I developed and validated an operational model using a discrete event simulation approach for the detection of TB and RMP-R TB in a smear/culture-based algorithm and an Xpert-based algorithm using data from published articles as well as from the step-wedge analysis of the Xpert-based TB diagnostic algorithm in Cape Town (PROVE IT). The model was adapted to incorporate a more sensitive molecular diagnostic test as a replacement test for Xpert in the Xpert-based algorithm. All comparisons between algorithms were conducted with identical population characteristics and adherence to diagnostic algorithms.

The empirical study found no increase in the number of TB cases detected (20.9% smear/culture-based and 17.7% with the Xpert-based algorithm) while the operational model, using identical population characteristics and adherence to diagnostic algorithms (adherence to algorithms as observed from the analysis of routine data in the empirical study), showed that there were more TB cases detected in the Xpert-based algorithm than in the smear/culture-based algorithm (an increase of 13.3%) (Chapter 2). The model indicated that a decrease in background TB prevalence and the extensive use of culture testing for smear-negative HIV-positive TB cases during the smear/culture-based algorithm contributed to not finding an increase in the number of TB cases detected in the empirical study.

When adherence to the diagnostic algorithms was modelled to be 100%, the model indicated a 95.4% increase in the number of RMP-R TB cases detected in the Xpert-based algorithm compared to the smear/culture-based algorithm, while the empirical

study showed only a 54% increase (Chapter 3). This difference is attributable to the differences in drug susceptibility test (DST) screening strategy between algorithms as well as poor adherence to diagnostic algorithms. In the smear/culture-based algorithm, only high MDR-TB risk cases are screened for RMP-R pre-treatment compared to all presumptive TB cases screened for RMP-R with the Xpert-based algorithm. The empirical study found that the proportion of TB cases with DST undertaken pre-treatment increased from 42.7% in the smear/culture-based algorithm to 78.9% in the Xpert-based algorithm.

The model indicated that for the Xpert-based algorithm compared to the smear-based algorithm (with 100% adherence to algorithms), the cost per TB case detected would increase by 114% with only a 5.5% increase in the number of TB cases detected (Chapter 3). Even though the model indicated a small increase in the number of TB cases detected, the real benefit of the Xpert-based algorithm is the 95.4% increase in RMP-R TB cases detected with only a 15.8% increase in the cost per RMP-R TB case detected (Chapter 3).

The model indicated that the best approach to improve the laboratory cost per TB case detected, would be a combined approach of increasing the TB prevalence among presumptive cases tested by using either a triage test or other pre-screening strategies, and a reduction in the price of Xpert cartridges (Chapter 4). With an increase in TB prevalence among presumptive cases tested to between 25.9% – 30.8% and the price of the Xpert cartridge reduced by 50%, the cost per TB case detected would range from US$50 to US$59, a level that is comparable with the cost per TB case detected in the smear/culture-based algorithm (US$48.77) found in the empirical laboratory costing study.

Finally, when modelling the use of the not-yet released Xpert MTB/RIF Ultra as a replacement for Xpert MTB/RIF (Chapter 5), the number of TB cases detected would increase by 3.4% and RMP-R TB cases detected by 3.5%. The number of false-positive TB cases detected with Ultra would however increase by 166.6%. We could not model the cost per TB case and cost per RMP-R TB case diagnosed with Ultra, as the price is not available yet. Ultra has small benefits over that of Xpert for both the number of TB and RMP-R TB cases detected and therefore the cost of introducing Ultra would be an important consideration in the decision to implement Ultra. The introduction of Ultra poses potential health system and patient related challenges due

to the high number of false-positive TB cases detected. Alternative strategies, such as alternative diagnostic algorithms, will have to be considered to find a balance between increased detection of TB cases and unnecessarily starting patients on TB treatment due to false positive results.

The strengths of the model used in this dissertation are that the model was developed and validated using detailed routine data and information collected with the empirical study on health and laboratory processes in a large number of clinics. The model made a direct comparison between the algorithms taking into account differences in population characteristics and adherence to algorithms. Generalisability of findings from the model and the use of the model for other settings may be limited as the model was validated against data from a well-resourced, urban setting, with good health and laboratory infrastructure and therefore may not reflect reality in other settings, such as rural areas.

The findings from the studies presented in this dissertation highlight the important role that an operation model can play in informing decision makers on the optimal use of a new diagnostic test in an operational setting, even after the rollout of the new test. Operational modelling can therefore be an effective tool to be used to assist the health department to optimise the way in which tests are currently used and could serve to inform decision makers about the implementation of new, more sensitive, diagnostic tests.

OPSOMMING

Die doel van hierdie verhandeling was om ’n bedryfsmodel te ontwikkel wat verklaar waarom ons empiriese studie PROVE IT (“Policy Relevant Outcomes from Validating Evidence on ImpacT”), wat ná die bekendstelling van ’n nuwe TB-diagnostiese toets, Xpert MTB/RIF (Xpert), by 142 gesondheidsklinieke in Kaapstad gedoen is, nié die verwagte toename in opgespoorde tuberkulose- (TB-)gevalle weerspieël het nie. Daarna het ek die model gebruik om die uitwerking te modelleer van intervensies ter verbetering van die opsporing van TB en rifampisienweerstandige (“RMP-R”) TB. Strategieë is gemodelleer om laboratoriumkoste vir TB-opsporing te verlaag en om te bepaal watter uitwerking die bekendstelling van ’n meer sensitiewe molekulêre diagnostiese toets, Xpert MTB/RIF Ultra (Ultra), as plaasvervanger vir Xpert op die getal opgespoorde TB- en RMP-R TB-gevalle sal hê.

Ek het ’n bedryfsmodel ontwikkel en valideer met behulp van ’n diskrete voorvalsimulasiebenadering vir die opsporing van TB en RMP-R TB in ’n smeer-/kwekingsgebaseerde algoritme en ’n Xpert-gebaseerde algoritme. Hiervoor is data uit gepubliseerde artikels sowel as die stapsgewyse analise van die Xpert-gebaseerde TB-diagnostiese algoritme in Kaapstad (PROVE IT) gebruik. Die model is aangepas om ’n meer sensitiewe molekulêre diagnostiese toets as plaasvervanger vir Xpert by die Xpert-gebaseerde algoritme in te sluit. Alle vergelykings tussen algoritmes is met identiese populasiekenmerke en nakoming van diagnostiese algoritmes uitgevoer.

Die empiriese studie het geen toename in die getal opgespoorde TB-gevalle gevind nie (20,9% smeer-/kwekingsgebaseerd en 17,7% met die Xpert-gebaseerde algoritme). Daarteenoor het die bedryfsmodel, wat gebruik gemaak het van identiese populasiekenmerke en nakoming van diagnostiese algoritmes (nakoming is waargeneem uit die ontleding van roetinedata in die empiriese studie), méér opgespoorde TB-gevalle in die Xpert-gebaseerde algoritme as in die smeer-/kwekingsgebaseerde algoritme gevind (’n toename van 13,3%) (hoofstuk 2). Die model het getoon dat ’n afname in TB-agtergrondprevalensie en die omvattende gebruik van kwekingstoetse vir smeernegatiewe MIV-positiewe TB-gevalle in die smeer-/kwekingsgebaseerde algoritme daartoe bygedra het dat die empiriese studie nie ’n toename in opgespoorde TB-gevalle weerspieël het nie.

Toe nakoming van die diagnostiese algoritmes op 100% gemodelleer is, het die model op ’n toename van 95,4% in die getal opgespoorde RMP-R TB-gevalle in die Xpert-gebaseerde algoritme vergeleke met die smeer-/kwekingsgebaseerde algoritme gedui, terwyl die empiriese studie ’n toename van slegs 54% getoon het (hoofstuk 3). Hierdie verskil kan toegeskryf word aan die verskillende middelvatbaarheidstoets-(“DST”-)siftingstrategieë vir die onderskeie algoritmes, sowel as swak nakoming van diagnostiese algoritmes. Met die smeer-/kwekingsgebaseerde algoritme word slegs gevalle met ’n hoë MDR-TB-risiko vir RMP-R-voorafbehandeling gesif; met die Xpert-gebaseerde algoritme, daarteenoor, word alle vermoedelike TB-gevalle vir RMP-R gesif. Die empiriese studie het bevind dat die persentasie TB-gevalle wat na aanleiding van DST voorafbehandel is, toegeneem het van 42,7% in die smeer-/kwekingsgebaseerde algoritme tot 78,9% in die Xpert-gebaseerde algoritme.

Die model het aan die lig gebring dat die koste per opgespoorde TB-geval vir die Xpert-gebaseerde algoritme vergeleke met die smeer-/kwekingsgebaseerde algoritme (met 100% nakoming van algoritmes) met 114% sal styg, met ’n toename van slegs 5,5% in die getal opgespoorde TB-gevalle (hoofstuk 3). Hoewel die model op ’n klein toename in opgespoorde TB-gevalle gedui het, is die werklike voordeel van die Xpert-gebaseerde algoritme die toename van 95,4% in opgespoorde RMP-R TB-gevalle, met ’n styging van slegs 15,8% in die koste per opgespoorde geval (hoofstuk 3).

Daarbenewens het die model getoon dat ’n gekombineerde benadering die beste sal wees om laboratoriumkoste per opgespoorde TB-geval te verbeter. So ’n gekombineerde benadering sal bestaan uit die verhoging van TB-prevalensie onder getoetste vermoedelike gevalle deur van hetsy ’n sorterings- (triage-)toets of ander voorafsiftingstrategieë gebruik te maak, sowel as ’n verlaging in die prys van Xpert-toetshouers (“cartridges”) (hoofstuk 4). Met ’n styging in TB-prevalensie onder getoetste vermoedelike gevalle tot tussen 25,9% en 30,8%, en ’n verlaging van 50% in die prys van die Xpert-toetshouer, sal die koste per opgespoorde TB-geval tussen VS$50 en VS$59 wees – wat soortgelyk is aan die koste per opgespoorde TB-geval in die smeer-/kwekingsgebaseerde algoritme (VS$48,77) wat die empiriese laboratoriumkostestudie bepaal het.

Laastens het die modellering van die gebruik van die tot nog toe nievrygestelde Xpert MTB/RIF Ultra as plaasvervanger vir Xpert MTB/RIF (hoofstuk 5) daarop gedui dat opgespoorde TB-gevalle met 3,4% en opgespoorde RMP-R TB-gevalle met 3,5% sal

toeneem. Die getal vals positiewe opgespoorde TB-gevalle met Ultra sal egter met 166,6% styg. Aangesien die pryse nog nie bekend is nie, kon ons nie die koste modelleer per TB- en RMP-R TB-geval wat met Ultra gediagnoseer word nie. Ultra bied betreklik klein voordele bo Xpert wat die getal opgespoorde TB- en RMP-R TB-gevalle betref, en daarom sal bekendstellingskoste ’n belangrike oorweging wees in die uiteindelike besluit om Ultra implementeer. Die bekendstelling van Ultra hou ook moontlike gesondheidsisteem- en pasiëntverwante uitdagings in weens die hoë getal vals positiewe opgespoorde TB-gevalle. Alternatiewe strategieë soos alternatiewe diagnostiese algoritmes sal oorweeg moet word om ’n balans te vind tussen beter opsporing van TB-gevalle en die onnodige aanvang van TB-behandeling vir pasiënte met vals positiewe resultate.

Die sterkpunte van die model wat in hierdie verhandeling gebruik is, is dat dit ontwikkel en gestaaf is met behulp van gedetailleerde roetinedata en inligting wat met die empiriese studie oor gesondheids- en laboratoriumprosesse in ’n groot getal klinieke ingesamel is. Die model het die algoritmes direk vergelyk, met inagneming van verskille in populasiekenmerke en nakoming aan algoritmes. Die veralgemeenbaarheid van bevindinge en toepassing in ander omgewings kan egter beperk wees omdat die model gestaaf is met behulp van data uit ’n hulpbronryke, stedelike omgewing met goeie gesondheids- en laboratoriuminfrastruktuur, en dus nie noodwendig die realiteit in ander omgewings soos landelike gebiede weerspieël nie.

Die bevindinge van die studies wat in hierdie verhandeling aangebied word, beklemtoon die belangrike rol wat ’n bedryfsmodel kan vervul om besluitnemers oor die optimale gebruik van ’n nuwe diagnostiese toets in ’n bedryfsomgewing in te lig, selfs ná die bekendstelling van die nuwe toets. Bedryfsmodellering kan dus ’n doeltreffende instrument wees vir die gesondheidsdepartement om die huidige gebruik van toetse te optimaliseer, en kan besluitnemers in die inwerkingstelling van nuwe, meer sensitiewe diagnostiese toetse bystaan.

ABBREVIATIONS

ART	Antiretroviral Treatment
DST	Drug Susceptibility Test
HIV	Human Immunodeficiency Virus
LED	Light emitting diode
LPA	Line Probe Assay
MDR-TB	Multidrug-resistant Tuberculosis
MGIT	Mycobacterial Growth Inhibitor Tube
MTB	Mycobacterium Tuberculosis
NHLS	National Health Laboratory Service
PHC	Primary Health Care
PROVE IT	Policy Relevant Outcomes from Validating Evidence on ImpacT
PTB	Pulmonary Tuberculosis
RMP-R	Rifampicin Resistant
TB	Tuberculosis
Ultra	Xpert® MTB/RIF Ultra
WHO	World Health Organisation
Xpert	Xpert® MTB/RIF

Chapter 1: Introduction

1.1 Tuberculosis in a global context

Tuberculosis (TB) remains a major cause of morbidity and mortality worldwide. Of the estimated 10.4 million incident TB cases (3.4 million bacteriologically confirmed) globally in 2015, 1.2 million were infected with the human immunodeficiency virus (HIV).[1] The Africa region accounted for 26% of global TB cases, 31% of whom are estimated to be HIV co-infected. The number of incident TB cases has been declining slowly with a 1.4% per year decline between 2000 to 2015.[1] However, a decline in TB incidence of between 4% and 5% per year by 2020 is required in order to achieve the goals set by World Health Organisation (WHO) in the End TB strategy.[1,2] In short, the End TB strategy set goals to achieve a 90% reduction in TB incidence rates by 2035 compared to that in 2015. The short-term goal for 2020 is a 20% reduction in TB incidence compared to that in 2015.[2,3] In 2015 there was a gap of 4.3 million between the estimated number of incident TB cases and the new TB cases notified to the WHO.[1]

The multidrug-resistant tuberculosis (MDR-TB), defined as resistance to rifampicin and isoniazid, crisis persists with a slower decrease in incidence than with TB overall and even an increase in some areas.[1] Of the 3.4 million bacteriologically confirmed TB cases notified globally in 2015, only 30% were reported to have had a drug susceptibility test (DST) for rifampicin and 132,120 rifampicin resistant (RMP-R) TB cases were detected. If all pulmonary TB (PTB) patients notified had a DST done, an estimated 340,000 RMP-R TB cases could have been detected. However, due to the lack of DST coverage only 40% of RMP-R TB cases (132,120) were detected and notified globally. In addition to the low DST coverage amongst cases already diagnosed with TB, there is a gap in diagnosing TB cases (see above) Of the total estimated 580,000 incident RMP-R TB cases globally[1], 240,000 were among undetected TB cases.

The gaps between the *estimated* number of cases and the cases *notified* for TB and RMP-R TB, reflect a combination of under-diagnosis of cases and under-reporting of detected TB and RMP-R TB. Factors contributing to under-diagnosis of TB and RMP-

R TB include amongst others poor access to health facilities, the failure to identify and test presumptive TB cases that do access health facilities and under-diagnosis due to the low sensitivity of the diagnostic test used. Sputum smear microscopy for acid-fast bacilli (smear microscopy) for instance is still widely used in many countries and due to its low sensitivity (particular in HIV-positive individuals) many TB case will remain undetected. The adherence to testing protocols, as stipulated in diagnostic algorithms, as well as the health characteristics (HIV-status, history of previous TB treatment) of an individual will affect the probability of successful TB detection. In addition, low availability of laboratory infrastructure for DST contributes to poor RMP-R TB case detection.

1.2 TB in South Africa

South Africa is one of the 22 high TB burden countries, with 454,000 (95% CI 294,000 - 649,000) incident TB cases in 2015 and an estimated TB incidence rate of 834 cases per 100,000 population .[1] The HIV epidemic is still a major driver of TB in South Africa. In 2015, 57% of TB cases were reported to be co-infected with HIV.[1] The overall estimated HIV prevalence in South Africa is 12.7%, which amounts to approximately 7,03 million people living with HIV in 2016.[4] Individuals who are HIV-positive are at higher risk of TB than HIV-negative individuals.[5]

TB incidence rates declined from a high of 977 per 100,000 in 2008 to 834 per 100,000 in 2015.[1] A study using a time series analysis of routine TB data found a similar decline in the incidence of microbiologically confirmed PTB cases from 848 per 100,000 in 2008 to 774 per 100,000 in 2012.[6] One of the reasons for the decline in TB incidence in South Africa could be attributed to the national increase in antiretroviral treatment (ART) uptake. The number of people on ART increased from 1.2 million in 2010 to 3.9 million in 2016.[7] A study conducted in one community in Cape Town reported a decline in TB prevalence amongst HIV-positive individuals from 9.2% in 2005 to 3.6% in 2008 after the rollout of ART, contributing to the overall decline from 3.0% to 1.6% in HIV-positive individuals while the TB prevalence in HIV-negative individuals was unchanged at 1.2% in 2005 and 1.0% in 2008.[8] Even if HIV-positive individuals are on ART, they are still at an higher risk of developing TB disease than HIV-negative individuals.[5]

1.3 Gaps in the number of estimated incident cases and the number notified to the WHO in South Africa

1.3.1 TB cases

In South Africa, the case detection gaps remain high with only 287,224 (63%) of the 454,000 (95% CI 294,000 – 649,000) estimated incident TB cases detected and notified in 2015 (Figure 2).[1]

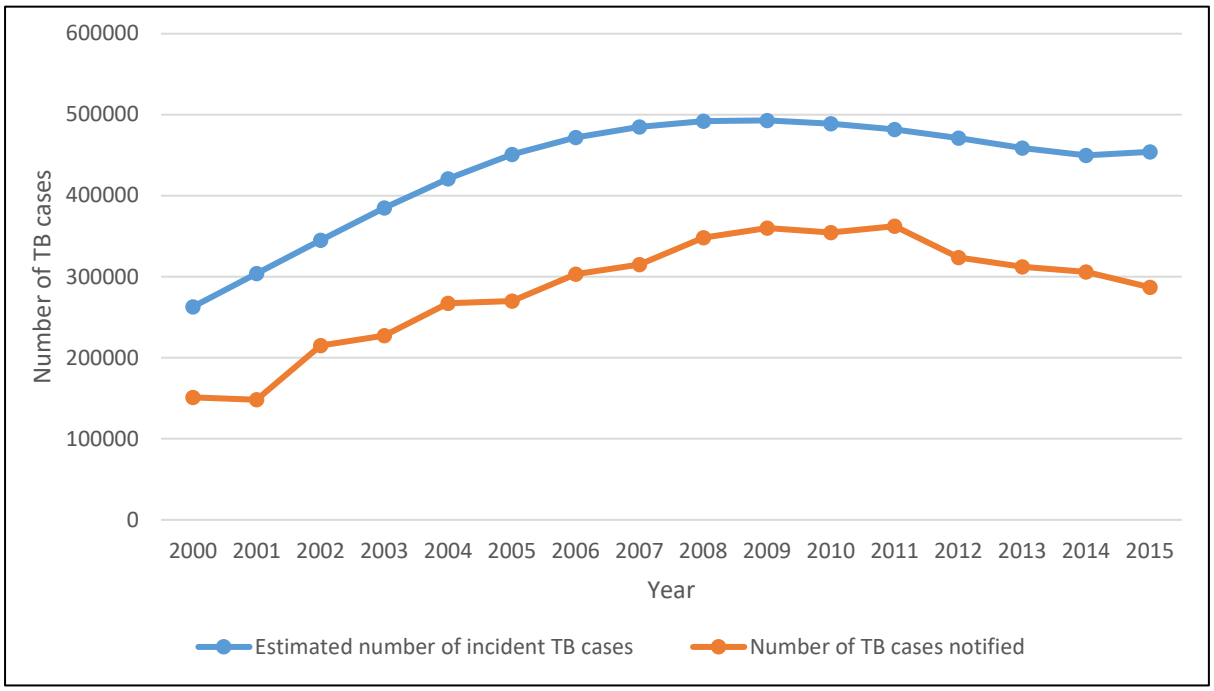

Figure 1: Number of estimated incident TB and number of TB cases notified to the WHO.[1] The graph shows WHO estimated number of incident TB cases and the number of TB cases notified to the WHO by the South African National TB Programme.

The estimated number of incident TB cases (Figure 1) could be an underestimation, as South Africa has never had a national TB prevalence survey (a national TB prevalence survey is planned for 2017). The number of incident TB cases are estimated from the number of TB cases notified to the WHO. The TB cases notified to the WHO does not reflect all the TB cases in South Africa due to (1) TB cases not accessing health services or who access health services but are not tested for TB, (2) TB cases tested for TB but TB was not detected due to test sensitivity, (3) successfully detected cases that do not initiate TB treatment and (4) TB cases that initiate treatment but are not recorded in the routine TB surveillance system (ETR.net).

A number of studies conducted in South Africa indicated that between 17% and 33% of detected TB cases were not recorded and reported to WHO.[9–11] In addition, other studies conducted in South Africa indicated that 15.5% to 34.7% of laboratory confirmed TB cases did not start TB treatment and were not recorded.[12–16]

Individuals who are HIV-positive have a higher risk of developing TB and often TB is difficult to detect in HIV-positive individuals. Therefore the WHO policy on collaborative TB/HIV activities to reduce the burden of TB and HIV recommended that routine HIV testing and counselling should be offered to all presumptive TB cases and not only to patients diagnosed with TB – testing algorithms take this into account and additional tests are performed for HIV-positive individuals.[17] In 2015, whilst 97% of TB cases on TB treatment in South Africa had a known HIV status, the proportion of presumptive TB cases that knew their HIV status during TB diagnostic screening was generally much lower and not well documented. A study conducted in India reported that only 44.6% of presumptive TB cases knew their HIV status.[18] Knowing the HIV status of a presumptive TB case influences the likelihood of successful TB detection. In South Africa, the TB diagnostic algorithm stipulates that all HIV-positive presumptive TB cases with a negative smear or Xpert result, receives a mycobacterial culture test (Figure 4 and 5).[19]

1.3.2 RMP-R TB cases

The WHO estimated that there were 20,000 (95% CI 13,000 – 27,000) RMP-R TB cases in South Africa in 2015.[1] However, only 12,527 RMP-R TB cases were reported to WHO illustrating the significant gaps in the detection and initiation of treatment of RMP-R TB cases. These gaps included the 454,000 estimated incident TB cases, of whom only 63% were notified and only 68% of these notified TB cases were tested for RMP resistance. Of those who tested positive for RMP resistance, only 63% started MDR TB treatment and were thus recorded and reported.

A drug resistance prevalence survey conducted in South Africa for the period 2012-2014, reported that 4.6% (95% CI 3.5% - 5.7%) of TB cases were resistant to RMP.[20] A nationwide retrospective cohort study in South Africa assessing second-line treatment initiation reported that in 2013, after full national rollout of Xpert, only 59%

of RMP-R TB cases received an initial Xpert test and 63% of RMP-R TB cases detected started treatment.[21]

Over the past decade, there has been an increase in the development of new TB diagnostic and drug susceptibility testing tools in an attempt to decrease the gaps in the overall number of estimated TB cases and RMP-R TB cases and those detected, recorded and ultimately notified to the WHO.[22–24]

1.4 TB and RMP-R diagnostic tests

1.4.1 Pre-molecular diagnostic tests

1.4.1.1 TB diagnosis

In most low and middle-income countries, the only TB diagnostic test available historically has been sputum smear microscopy with the availability of sputum culture in limited settings. The advantages of smear light microscopy are the simplicity in performing the test (no sophisticated technical expertise is required), low cost, high specificity in high TB endemic areas and ensuring that the most infectious TB cases can be identified. A major limitation of smear microscopy is low and variable sensitivity, particularly in HIV-positive individuals.[22–24] The sensitivity of conventional light microscopy is 53.8% on a single smear and 11.1% higher if a second smear is done.[25] With fluorescence microscopy the sensitivity increases by 10% and with chemical treatment and centrifugation the overall increase is 18% compared to unprocessed direct smear.[26,27] However, amongst HIV-positive cases the sensitivity of a single smear ranges from only 23% to 50%.[28–30]

The gold standard of TB diagnosis is sputum culture for mycobacteria which has the disadvantage of being a slow and expensive test, requiring sophisticated laboratory infrastructure and technical expertise.[31] A mycobacterial culture test on solid media takes up to 6 to 8 weeks, however, this delay has been reduced to between 8 and 16 days with the introduction of new Mycobacterial Growth Inhibitor Tube (MGIT) liquid culture methods.[32]

Due to the low sensitivity of smear microscopy, especially in HIV-positive cases, and the limited availability of adequate laboratory infrastructure to perform mycobacterial culture testing many TB cases are missed or their diagnosis is delayed.[33]

1.4.1.2 MDR-TB diagnosis

Phenotypic (culture-based) DSTs that were used historically can test for drug susceptibility for a wide spectrum of drugs: rifampicin, isoniazid, ethambutol, pyrazinamide, streptomycin, amikacin, kanamycin, capreomycin, ethionamide, ofloxacin, moxifloxacin.[19,34] The limitation of phenotypic DSTs is that they require a positive culture result first before testing for susceptibility can start, which takes a further 2 to 3 weeks.

1.4.2 Molecular (genotypic) diagnostic tests

In order to address the limitations of smear microscopy and culture, a number of more sensitive and rapid molecular diagnostic tests have become available.[22,23] The expectation was that these new molecular diagnostic tests would increase the number of cases detected and quicker diagnosis would facilitate early treatment initiation. Both of these factors could reduce the transmission of TB and ultimately the burden of TB. In addition, many of the new molecular diagnostic tests have the ability to test simultaneously for the presence of *Mycobacterium tuberculosis complex* (MTB) and drug resistance. Two of these new molecular tests have been implemented in South Africa: GenoType® MTBDRplus (Hain Lifescience, Nehren, Germany) Line Probe Assay (LPA)[35], endorsed by the WHO in 2008, and Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA)[36], endorsed by the WHO in 2010.

1.4.2.1 MTBDRplus Line Probe Assay

A key benefit of LPA is the simultaneous diagnosis of MTB and drug susceptibility testing for both rifampicin and isoniazid resistance. A meta-analysis of ten LPA studies has reported high sensitivity for rifampicin resistance of 98.1% (95% CI 95.9 to 99.1) and specificity of 98.7% (95% CI 97.3 to 99.4) with sensitivity for isoniazid resistance of 84.3% (95% CI 76.6 to 89.8) and specificity of 99.5% (95% CI 97.5 to 99.9).[37] A further benefit of LPA is the availability of a test result within 1 to 2 days with smear-positive specimens; however, delays has been reported for smear-negative

specimens as the test is undertaken on culture isolates.[37] A limitation of LPA is that it requires substantial technical skills and costly equipment, and is only suitable for use in large central laboratories.

1.4.2.2 Xpert® MTB/RIF

Xpert® MTB/RIF (Xpert) simultaneously detects MTB and RMP-R, however unlike LPA, Xpert does not detect isoniazid resistance. A Cochrane Review of fifteen studies with Xpert as the initial test replacing smear microscopy, reported a pooled sensitivity of 88% (95% CI 83 to 92) and specificity of 98% (95% CI 97 to 99) for detecting MTB, with a lower sensitivity for HIV-positive cases of 80% (95% CI 67 to 88).[38] For rifampicin resistance the sensitivity was 94% (95% CI 87 to 97) and specificity was 98% (95% CI 97 to 99). Key benefits of the Xpert test are that the equipment does not require a high level of technical skills and the equipment is suitable for placement in decentralised settings such as district and sub-district laboratories. The result from an Xpert test is available in less than 1 day (similar to smear microscopy and compared to 17 days for liquid culture and more than 30 days for solid culture).[36] Compared to other phenotypic DST methods with an average of 75 days, Xpert detects rifampicin resistance in less than 1 day.[36]

Xpert does come with some disadvantages such as; the shelf life of the cartridges is only 18 months, a very stable electricity supply is required for the Xpert instrument, the instrument needs to be recalibrated annually, adequate room temperature and very high cost of the cartridges.

1.5 TB diagnostic algorithms in South Africa

1.5.1 Smear/culture-based algorithm

Shortly after the WHO policy statement release, South Africa implemented LPA in 2008 as a replacement for conventional DST. From 2008 until 2011, South Africa used a smear/culture-based algorithm with LPA as one of the sequence of tests in the algorithm (Figure 2). The smear/culture-based algorithm had two distinctive arms that required different combinations of tests. The one arm addressed presumptive cases with no previous TB treatment or less than 4 weeks of TB treatment (low MDR-TB risk) and the second arm addressed presumptive TB cases with a history of previous TB

treatment, those from congregate settings or those in contact with an MDR-TB case (i.e. all those at high risk of MDR-TB). The smear/culture-based algorithm required that all presumptive TB cases submit two spot sputum specimens one hour apart and these were tested with fluorescence smear microscopy. In high MDR-TB risk presumptive cases, the second specimen underwent culture testing (BACTEC™ MGIT™ 960; BD, Spark, MD, USA). If the test was culture-positive, a LPA was undertaken. All new, smear-negative, HIV-positive individuals required a culture test.

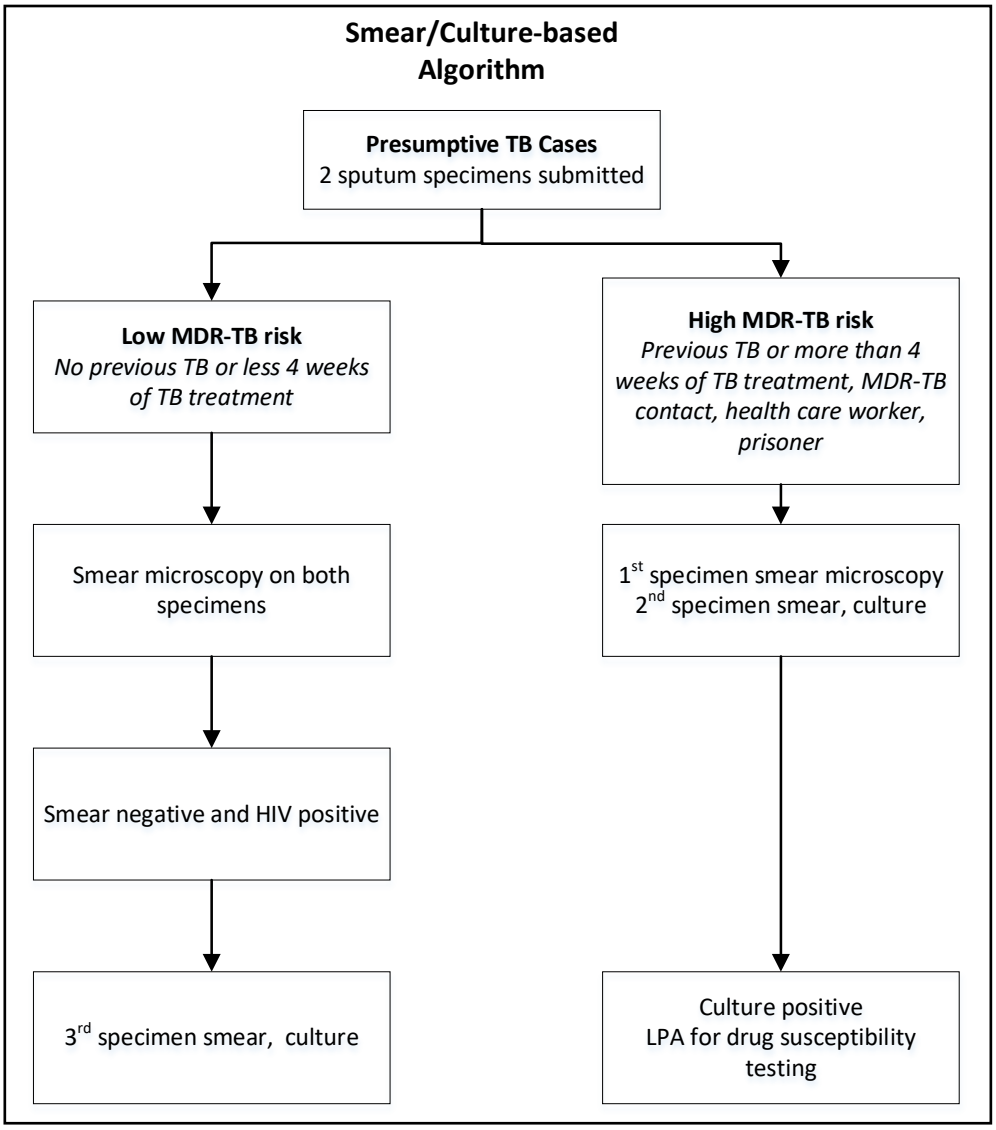

Figure 2: Smear/culture-based algorithm as stipulated by the South African National TB Programme[39]
With the smear/culture-based algorithm, all presumptive TB cases were required to submit two spot sputum specimens an hour apart to be tested with fluorescence smear microscopy. The second specimen underwent culture testing (BACTEC™ MGIT™ 960; BD, Spark, MD, USA) if the individual had a history of previous TB treatment, was from a congregate setting or had an MDR-TB contact. If culture-positive, a DST using GenoType® MTBDRplus LPA was undertaken. All new, smear-negative HIV-positive individuals required a culture test.
Abbreviations: TB - tuberculosis; HIV – human immunodeficiency virus; LPA - line-probe assay.

1.5.2 Xpert-based algorithm

As was the case with LPA, South Africa, was an early adopter of Xpert. After the WHO policy statement in 2010 recommending the use of Xpert as the initial test for all cases at high risk for MDR-TB or HIV-associated TB[36], South Africa introduced Xpert in 2011 as a replacement test for smear microscopy for all presumptive TB cases. The national scale-up was completed by 2013 in South Africa, with all facilities using the Xpert-based algorithm. With the Xpert-based algorithm, one spot specimen was collected and tested with Xpert and if TB was detected a second specimen was required and underwent smear. If the Xpert test detected rifampicin resistance, a culture and LPA was undertaken. If the Xpert test was negative and the individual was HIV-positive, the second specimen underwent culture and LPA. In the Western Cape, South Africa, the algorithm was slightly different with two spot specimens taken (Figure 3).

1.6 Challenges associated with implementing new diagnostic tests

There has been an increase in the number of new TB and RMP-R TB diagnostic tests since 2007.[23] Diagnostic tests, such as LPA and Xpert, were endorsed by the WHO based on limited data, largely based on the speed of diagnosing TB and RMP-R TB and improved test sensitivity.[24,36] There are many other new diagnostic tests currently under development and testing, for example the Xpert Ultra (Cepheid, Sunnyvale, CA, USA) cartridge, Genedrive MTB/RIF (Epistem Ltd, Manchester, M13 9XX, UK), Signature Mapping™ for Tuberculosis Detection Diagnostic System (Applied Visual Sciences Inc., Virginia, US) and loop-mediated isothermal amplification (Eiken Chemical Company Ltd, Tokyo, Japan).[40]

The endorsement by the WHO is an important step for the introduction of new diagnostic tests, however, numerous authors have suggested that the current process is not sufficient and that more evidence is needed to go beyond the accuracy (sensitivity and specificity) of a new proposed diagnostic test.[22,41,42] Further evidence is required that a new diagnostic test would work effectively in a routine operational setting with limited resources and in specific epidemiological settings.[43] The focus of policy recommendations issued by the WHO should be on the most cost-effective and efficient (more TB and RMP-TB cases detected with a shorter time to diagnosis) way of introducing and scaling up new diagnostic test within existing algorithms and varied

epidemiological settings. Policy recommendations are generally only based on demonstration studies, and recommendations with these specific focus areas mentioned above, are not possible at the time of endorsement due to the lack of data from implementation studies.

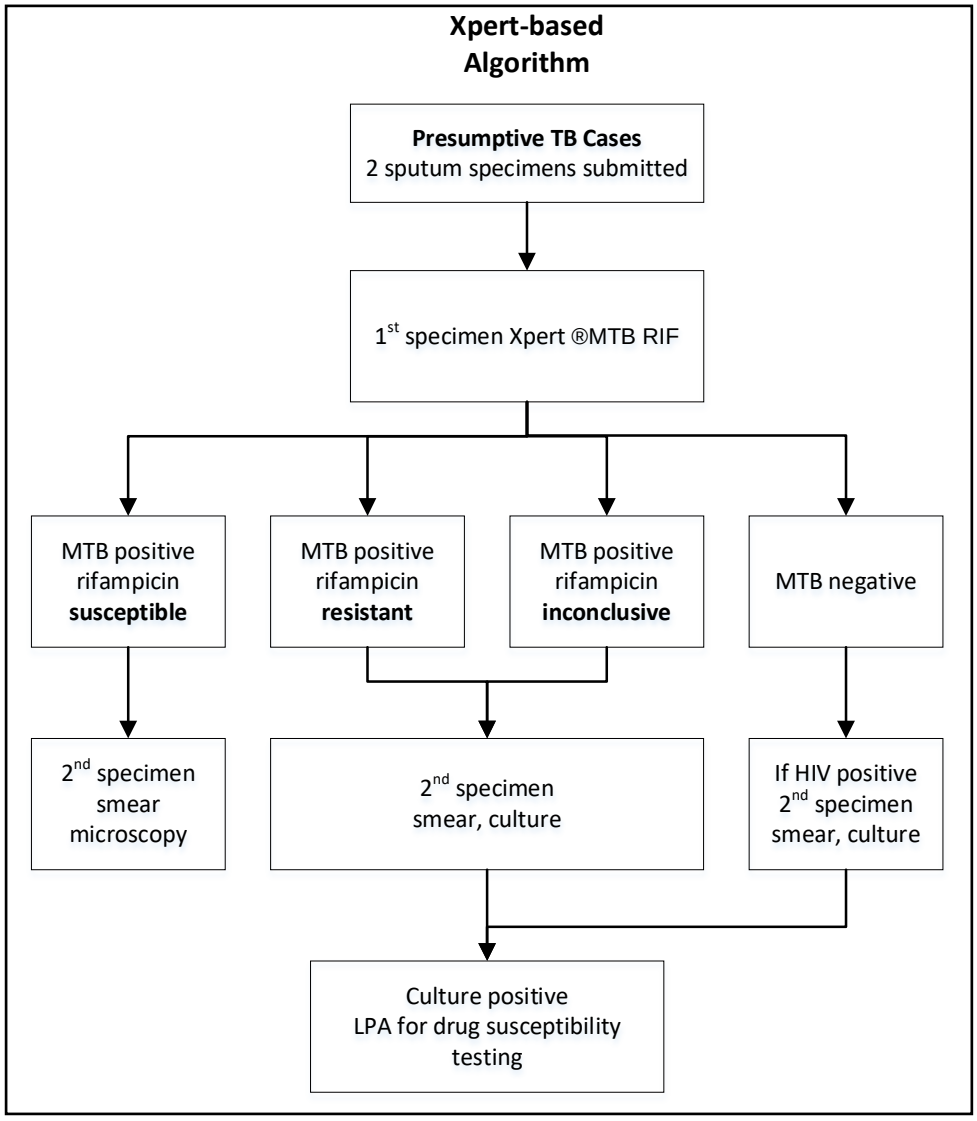

Figure 3: Xpert-based algorithm as stipulated by the South African National TB Programme and as implemented in Cape Town.[19] *With the Xpert-based algorithm, two spot specimens were collected and the first was tested with Xpert. If TB was detected and RMP-susceptible, the second specimen underwent smear and if RMP-R or RMP-inconclusive was detected, a culture and LPA test was undertaken. The second specimen underwent culture and LPA if the Xpert test was negative and the individual was HIV-positive.*
Abbreviations: TB - tuberculosis; HIV – human immunodeficiency virus; MTB – mycobacterium tuberculosis; RIF – rifampicin; LPA - line-probe assay.

These demonstration studies produce limited data with a focus on test accuracy under optimised programme conditions, operational aspects of the single test and some patient-related outcomes (for example diagnostic delay due to test turnaround times).[44] A further limitation of demonstration studies is that they are usually performed

at sites selected for their capacity to perform the studies (generally at moderate scale), therefore, these studies over-estimate effectiveness due to greater resource availability than would be available in routine operational settings.[22,45,46]

Due to the limitation of the WHO endorsement process for new diagnostic tests, it has been proposed that a three-stage process should be adopted in order to provide relevant evidence for the implementation of new TB diagnostic test.[22,23]

The first stage would be before policy recommendations are released and should include technical details to inform the policy. The questions asked during this stage should include whether the new diagnostic test has the technical requirements (sensitivity and specificity) and would be operationally capable (test turnaround time, time to diagnosis and treatment, and improved case detection for TB and/or RMP-R TB) to improve TB diagnosis. Studies to provide data for this stage would include controlled validation and demonstration studies.

The second stage would be before the new TB diagnostic test is scaled-up and should include evidence on the effectiveness of the test in terms of both cost and diagnosing more TB and RR-TB cases. During this stage it should be evaluated where best the new diagnostic test would fit taking existing diagnostic tests already used into consideration. It should be determined how and where the new test should be implemented in existing diagnostic algorithms and if specific populations (for example HIV-positive) would benefit based on the sensitivity and specificity of the new test as well as if drug resistance is tested for. Studies conducted to collect data during this stage should be done within routine programmatic conditions and at the level of the health system where the test would most likely be used (laboratory or point-of-care). These studies should be done in various countries representing various epidemiological populations (TB, RMP-R TB and HIV prevalence) and availability of health resources. Modelling during this stage could also be conducted to evaluate the effectiveness of the new test within various algorithms and populations with various epidemiological characteristics.

The third and final stage would be during and after scale-up of the new diagnostic test. This stage should evaluate if the new diagnostic test has been implemented optimally and identify and test interventions to inform the optimum use of the new test within

routine operational settings, in respect of both cases detected and the cost per case detected. Questions such as the level of adherence to the newly introduced diagnostic algorithm, and if the appropriate epidemiological population (HIV-positive, TB cases with a previously history of TB treatment) benefits from the new test should be evaluated. The long-term sustainability of cost to the health system should also be determined. Data to evaluate this final stage could be collected from routine recording and reporting systems. During this stage previously developed models could be improved, or new models developed, through further knowledge and data collected during this final stage of evaluation.[22,47]

1.7 Challenges in interpreting the implementation of new diagnostic tests

The decision by policy makers about which new test to implement in a diagnostic algorithm can be complicated. Decision makers require much more information than what is usually available on performance of a test in ideal conditions. They need to understand the operational and pragmatic impact of the introduction of a new diagnostic test within an already existing diagnostic algorithm. Decision makers need to take many factors into consideration including the best combination of diagnostic tests, the resources required, who should be tested and the TB epidemiology in the setting (prevalence of TB, HIV coinfection and drug resistance). These factors are often not known by decision makers and therefore, expensive and time consuming clinical trials are required to make decisions,[48] or decisions are made without all the necessary information.

Decision makers require evidence on what the best combination of tests are for their context and which test should be used for which patients as well as whether the new diagnostic test would replace an existing test or used in combination with existing tools. A further factor that could also make a decision to implement a new test more complex is if the population characteristics changes over time, for instance, if the TB prevalence declines over time. These changes in population characteristics could influence the long-term sustainability of using the new diagnostic test considering that many of the new diagnostic tests are much more expensive compared to those already used in countries. Two studies conducted in South Africa for example, reported the cost per Xpert test performed at US$25.90 and US$14.93 compared to the cost for smear at US$1.58 and US$3.40.[49,50]

1.8 Modelling and the use of modelling in TB

Models are simplified representations of complex real life scenarios, situations or processes. Modelling is useful in filling knowledge gaps when assessing the impact of interventions on a population-level or on a health system due to the lack of empirical evidence or in addition to empirical evidence. The information produced through modelling and the effects of potential interventions can also be used to plan future studies.[47,51]

The advantage of modelling is that interventions that would take months or years to have an impact on the health system, in real life, can be modelled in a few minutes or hours. Sensitivity analysis can be used to investigate how certain variables affects a single, independent variable and how much changes in those variables will change the independent variable, for example, the impact of various levels of TB prevalence amongst presumptive cases on the number of TB cases detected. Models can be used to model situations as they occur in real life rather than the idealised situation, for example, the lack of adherence to policy.

The data sources usually used to drive models are derived from published literature (i.e. meta-analysis, randomised control trials, cohort studies, global reports, unpublished literature, expert opinion, field data), and from assumptions. Therefore, models are only as good as the level of detail available to develop the logic of the model and the availability and accuracy of the data to drive the model.[47,52]

Models and the assumptions they are based on will not always stay relevant as systems, procedures and settings change over time.[47] Models should therefore be updated as more data becomes available or due to assumptions changing over time. The use of models by decision makers has been limited.[47,53] The development and validation of models usually takes time and models may therefore not be ready in time for decision makers to be informed by model results. Therefore, the balance between anticipating future policy questions and responding to current policy question is critical for models to be of any use in policy decisions.[47]

Two modelling approaches previously used in TB control are transmission (epidemiological) modelling and operational modelling.

1.8.1 Transmission modelling

Transmission modelling is a simplified means of describing the transmission of communicable disease, such as TB, through populations or individuals. These models are formulated through mathematical equations and generally divide the population under investigation within compartments based on disease status as represented in Figure 4. Transmission modelling can be used to predict the long-term impact of interventions on the community by projecting TB incidence, prevalence, and mortality.

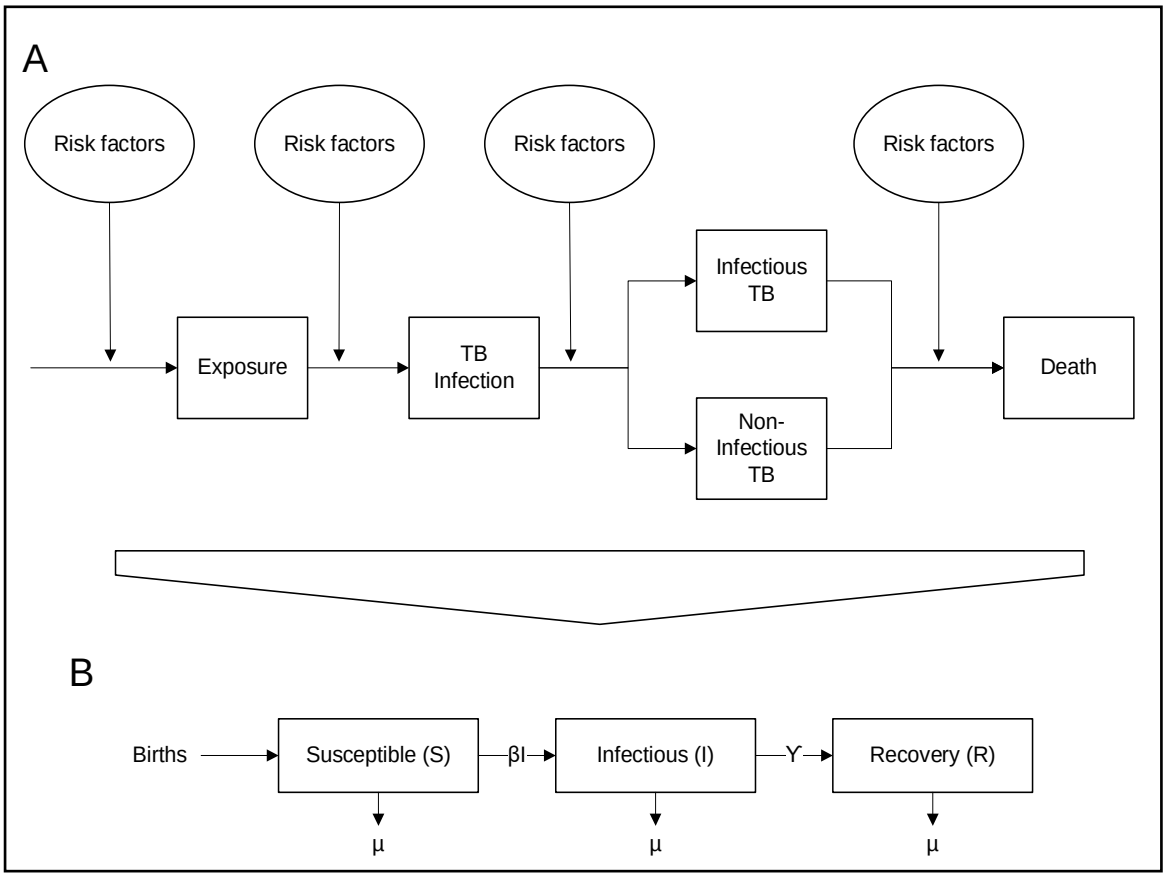

Figure 4: (A) A schematic representation of different disease states in TB epidemiology.

(B) Example of a simple transmission model representing different disease states. Differential equation involving variables S, I and R in respect of their rate of change in time t with an assumed death and birth rate μ using a fixed population N = S(t) + I(t) + R(t):

$S(t)' = \frac{dS}{dt} = \mu N - bSI - \mu S$, $I(t)' = \frac{dI}{dt} = bSI - rI - \mu I$, $R(t)' = \frac{dR}{dt} = rI - \mu R$

A TB transmission model was developed to evaluate the impact of different implementation strategies for scaling up the use of Xpert on TB incidence in India.[54] They developed a model of TB transmission, care-seeking behaviour, and diagnostic/treatment practices in India and explored the impact of six different Xpert rollout strategies. The model included the following six scenarios; (baseline scenario)

no improved diagnostic testing, (scenario 1) 40% of HIV-positive and high MDR-TB risk (had a history of previous TB treatment) presumptive TB cases presenting to the public sector had an Xpert, (scenario 2) the same as scenario 1 as well as an additional 20% of other presumptive TB cases presenting to the public sector had an Xpert, (scenario 3) the same as scenario 1 as well as an additional 20% of other presumptive TB cases presenting to private practitioners had an Xpert, (scenario 4) a combination of scenarios 2 and 3, (scenario 5) 20% of all presumptive TB cases in public or private sector had an Xpert, (scenario 6) 20% of presumptive TB cases diagnosed with TB in the public sector were referred for further diagnosis to the private sector with no Xpert available in either sector.

The model indicated that with the baseline scenario TB incidence would decrease annually by 2% over a 5 year period. The model indicated that the best strategy would be scenario 5 where 20% of all presumptive TB cases in public or private sector had an Xpert, with a 14.1% decrease in TB incidence. Results from the model suggest that the rollout of Xpert could substantially reduce the burden of tuberculosis due to current poor diagnosis of TB in India. The model also highlighted, that with the rollout of Xpert, the impact does not only rely on the sensitivity and specificity of the Xpert test but also on the behaviour of patients and providers, the level of access to new diagnostic tests and the availability of treatment following diagnosis.

The impact of using a new TB diagnostic test in the United Republic of Tanzania was projected with the use of a TB transmission model.[55] The model was calibrated using data from United Republic of Tanzania, including the epidemiology of tuberculosis and HIV infection. The influence of contextual factors and the impact of the introduction of a new more sensitive TB diagnostic on the projected TB epidemic was assessed. The model indicated that with the use of smear microscopy, the incidence of tuberculosis would decline by an average of 3.9% per year compared to a decline of 4.2% if a new more sensitive diagnostic test was added to the diagnostic algorithm. The decline in TB incidence however would be less if the algorithm with the new added diagnostic test is less sensitive than existing algorithm and if TB symptomatic individuals delayed accessing health services.

1.8.2 Operational modelling

Many operational models use a discrete event simulation (DES) approach where the system is first defined in terms of its most important elements, including the items or people processed through the system, resources, activities, rules and the process flow. The required outputs of the model are defined (e.g. productivity, costs, identification of bottlenecks, capacity and sensitivity to changes), along with the key input parameters to be investigated. Once the system is defined and appropriate parameter inputs are assigned (e.g. the number of items entering the system, the quantity of resources and the time for completing particular activities), then simulations can be run to assess the relative effect of different input assumptions on the modelled outputs.[56]

1.8.2.1 Operational models in commercial settings:

Operational models in industrial and commercial settings are widely used to plan and assess the performance and efficiency of processes.[57] A global company (Hayward Tyler) supplying mission-critical electric motors and pumps for the oils, gas, nuclear, industrial and chemical markets required a method of evaluating an ambitious plan to increase their business growth strategy and to visually communicate this strategy to employees, customers and investors.[58] The company undertook a business transformation project to focus on maximising efficiency, align capacity to demand and boosting profitability. The company developed a predictive model representing a “virtual factory” of the manufacturing operations, as the operations would evolve over a 5 – 10 year period. The model incorporated the factory production plant capacity and performance, factory layout, equipment requirements, shift patterns, and production demands. The model identified the requirements that will need to be considered, in the business growth strategy, in order to meet production and client demands as well as to maximise profitability.

1.8.2.2 Operational models in health settings:

Operational models have also increasingly been used to improve performance of the health sector. The use of operational models in health systems is common in high-income countries, but less so in middle- to low-income countries. A systematic review was done to evaluate the extent, quality and value of computer simulation modelling

in population health and health care delivery.[59] The review found that simulation modelling was used in varied health care related areas, including hospital scheduling and organization, communicable disease screening, costs of illness and economic evaluation. The authors concluded that simulation modelling is a powerful method to inform policy makers in the provision of health care.

A second review of the use of DES in modelling health-care systems found diverse objectives among these studies.[60] The review concluded that most of the reviewed studies reported on unit specific issues to find solutions to specific problems in individual units of health-care systems, such as staff-demand mismatch in accident and emergency departments, reducing waiting times in outpatient clinics, and better-utilising hospital beds.

1.8.2.3 Operational models in TB:

Operational modelling can be used to project the impact of interventions on health system costs and infrastructure, as well as patient access and outcomes. Operational modelling can therefore be used to evaluate how and where a new test should be implemented in existing diagnostic algorithms, as well as evaluate if specific populations (for example HIV-positive patients) benefit from the new test.

A further benefit of an operational model is that the effect or lack of effect after the introduction of a new test can be evaluated in order to explain findings from routine data and empirical studies. Operational models can help understand the health system impact in relation to the number of TB and RMP-R TB cases detected and the cost per case detected.

The key element that make up operational models are: entities - representing people or objects moving around a process (e.g. patients, specimens); attributes associated with entities (e.g. HIV status, previous history of TB treatment); queues representing waiting areas for entities (e.g. waiting rooms); activities where actions take place (e.g. sputum collection, return results); resources required to complete an activity (e.g. laboratory equipment and staff). Figure 5 is a simplified representation of such an operational model.

A study from United Republic of Tanzania used a discrete event simulation model with details on patient pathways to TB diagnosis integrated with a cost effectiveness analysis to enhance policy decisions on new diagnostics.[56] The study used data from two TB diagnostic centres to map patient pathways for all presumptive TB cases and individuals treated for TB as well as to map sputum sample pathways through the laboratory. The model was used to determine the impacts and cost of three alternative TB diagnostic algorithms compared to Ziehl Neelsen microscopy (baseline scenario). The alternative TB diagnostic algorithms were light emitting diode (LED) fluorescence microscopy (scenario 1), and two alternative algorithms using the molecular diagnostic test such as Xpert MTB/RIF with full rollout (scenario 2) and partial rollout (scenario 3) only testing HIV-positive cases and individuals with a history of previous TB treatment with the new molecular test. All comparisons are relative to the baseline scenario.

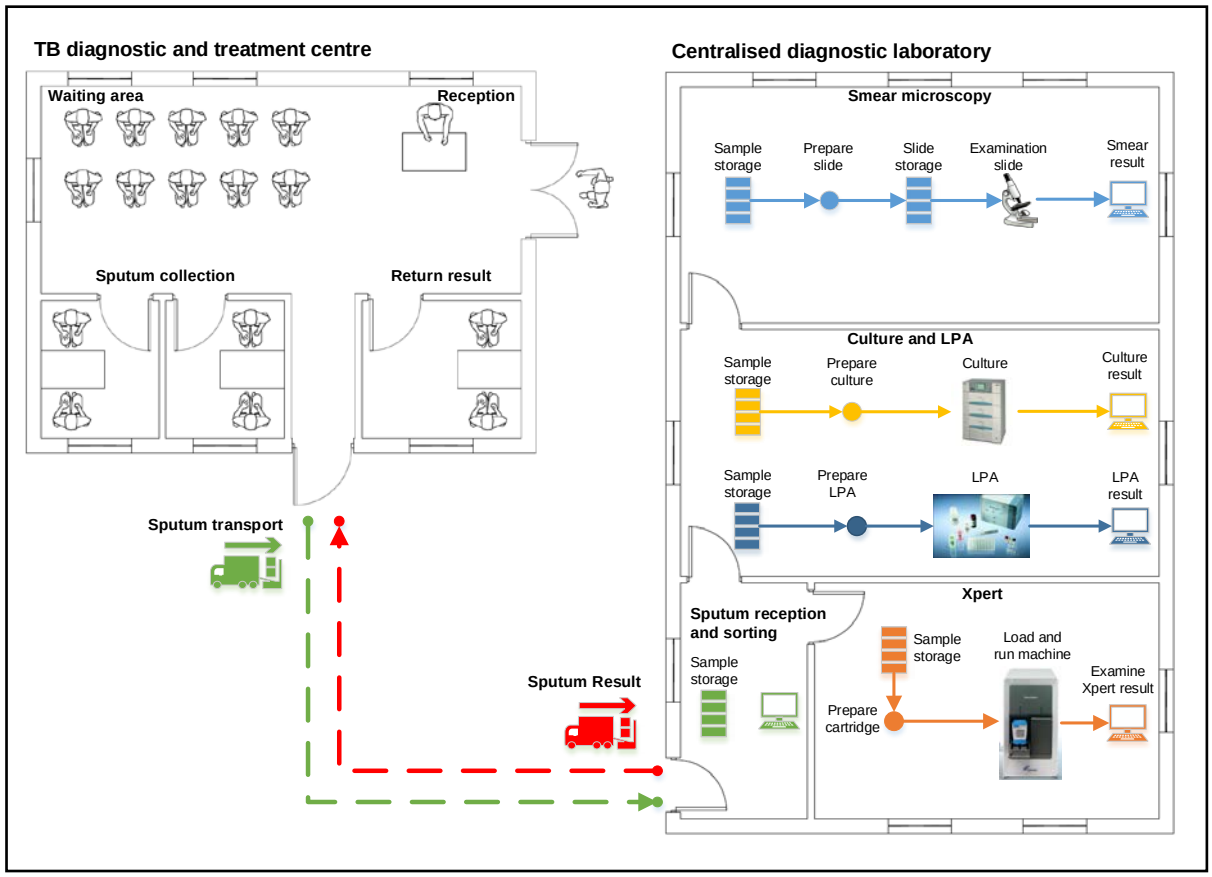

Figure 5: A simplified representation of an operational model. The operational mode incorporated specimen flow from specimen collection, through laboratory test procedures, to a result being provided to the patient.

The study found that operational modelling using DES could provide useful projections of the effects on the health system, running costs, and patient outcomes of alternative TB diagnostic strategies in the diagnostic centres of United Republic of Tanzania. The

model indicated that with the implementation of LED fluorescence microscopy the number of TB cases detected with a positive test result would increase per year from 562 (95% CI 545 – 578) to 670 (95% CI 648 – 691) with scenario 1, 1060 (95% CI 1041 – 1079) with scenario 2, and 898 (95% CI 882 – 915) with scenario 3. The number of false positive TB cases would decrease per year from 446 (95% CI 434 – 458) to 355 (95% CI 343 – 367) with scenario 1, 53 (95% CI 48 – 57) with scenario 2, and 188 (95% CI 178 – 197) with scenario 3.

1.9 Modelling and the impact of Xpert in South Africa

An initial modelling study conducted using a *transmission model*, before the rollout of Xpert in South Africa, estimated the impact of rolling out Xpert on TB-associated morbidity and mortality, in five countries of southern Africa, including South Africa, over a 10 year period.[61] This model, in the absence of pre-existing data, had to make use of assumptions including the prevalence of TB amongst presumptive cases and the time it would take for a diagnosis to be completed. The model compared two diagnostic algorithms, with the first algorithm (smear/culture-based) comprising of smear microscopy for all presumptive TB cases and culture testing for all smear-negative presumptive TB cases with a history of previous TB and the second algorithm (Xpert-based) using Xpert on all presumptive TB cases who are HIV-positive or do not know their HIV status.

The model indicated that over a 10 year period, the average number of TB cases correctly detected (true positive) with the smear/culture-based algorithm would be 151,000 (95% CI 100,000 – 215,000) and 175,000 (95% CI 120,000 – 245,000) with the Xpert-based algorithm. The average diagnostic cost per presumptive TB case diagnosed would be US$31 (95% CI 25 – 38) with the smear/culture-based algorithm and US$45 (95% CI 40 – 50) with the Xpert-based algorithm. The average cost per true positive TB cases diagnosed would be US$181 (95% CI 117 – 287) with the smear/culture-based algorithm and US$211 (95% CI 136 – 334) with the Xpert-based algorithm.

The model estimated a large population level impact over a 10 year period for all five countries with the rollout of Xpert as a result of more TB cases detected and a reduction in the time to initiating TB treatment. The model indicated a decline in TB

prevalence of 186 (95% CI 86 – 350) per 100,000 population, TB incidence by 35 (95% CI 13 – 79) per 100,000 population and annual TB mortality by 50 (95% CI 23–89) per 100,000 population.

A *population-level decision model* estimated the impact and cost of scaling up Xpert in South Africa.[62] The model indicated that with full scale up of Xpert the number of TB cases detected would increase by 30%-37% per year and the number of MDR-TB cases by 69%-71%. The cost per presumptive TB case tested would increase by between 53%-57% and the cost per TB case detected would increase 15%-17%.

After the rollout of Xpert in South Africa, a number of studies were conducted to evaluate the implementation of Xpert in South Africa which. A prospective cluster-randomised trial of Xpert compared to smear microscopy and culture conducted in a primary health care clinic in Cape Town, South Africa, showed an increase in the proportion of bacteriologically confirmed TB cases initiating TB treatment within 3 months. The study reported that amongst presumptive TB cases, the yield of bacteriologically confirmed TB was 17% (167/1,003) with smear/culture and 26% (257/982) with Xpert (risk ratio 1.57, 95% CI 1.32–1.87, p = 0.001). Of these bacteriologically confirmed TB cases the proportion who initiated TB treatment within 3 months was 23% (229/1,003) with smear/culture and 28% (277/982) with Xpert (risk ratio 1.24, 95% CI 1.06–1.44, p = 0.013).[63]

The XTEND (Xpert for TB—Evaluating a New Diagnostic) trial was a pragmatic two arm cluster-randomised trial with the primary outcome to determine if mortality at 6 months from enrolment differed between a smear/culture and an Xpert-based algorithm.[64] The trial found no difference in 6-month mortality with Xpert (3.9% with Xpert compare to 5% with the smear/culture-based algorithm (adjusted risk ratio 1.10, 95% CI 0.75 to 1.62).

As part of the XTEND trial, a cross-sectional exit study was done to evaluate whether the likelihood of a health care worker requesting a sputum from individuals with TB symptoms who have already accessed a clinic, changed with the rollout of Xpert in South Africa.[65] The study found that there was no significant difference between algorithms in the likelihood that a health care worker requesting a sputum for TB investigation, 26% in the Xpert and 19.8% in the smear/culture-based algorithm

(adjusted prevalence ratio 1.31, 95% CI 0.78 to 2.20). When restricted to all participants attending the clinic specifically due to TB symptoms the difference was 49.1% with Xpert and 29.9% in the smear/culture-based algorithm adjusted prevalence ratio 1.38 (95% CI 0.88 to 2.16). As part of the same trial, an evaluation was done to determine the adherence to TB diagnostic algorithm after an initial sputum smear or Xpert-negative test for HIV-positive individuals.[66] Adherence was higher in the smear/culture-based algorithm (32%) than in the Xpert-based algorithm (14%) (adjusted risk ratio 0.34, 95% CI 0.17 to 0.65).

The PROVE IT (Policy Relevant Outcomes from Validating Evidence on ImpacT) study, done in Cape Town by the Desmond Tutu TB Centre, Stellenbosch University, evaluated the impact of the Xpert-based diagnostic algorithm within a routine operational setting in Cape Town.

1.9.1 Three important findings from the Prove IT study are outlined below.

1.9.1.1 TB yield

A stepped-wedge analysis of TB yield (the proportion of presumptive cases diagnosed with TB) was undertaken in five sub-districts as facilities transitioned from using a smear/culture-based algorithm to an Xpert based algorithm over 7 time periods between 2010 and 2013.[67] The study found a decline in TB yield over time from 23.6% (1911/8083) at T1 to 17.4% (1422/8126) at T7. This was possibly attributable to a declining TB prevalence. The decrease in yield was not attributable to an increase in case-finding as the proportion of the population tested did not increase over the seven time periods evaluated (the proportion of the population tested was 0.95%, 0.93%, 0.85%, 0.84%. 0.80%, 0.84%, 0.89%). When the time-effect was taken into consideration, there was no difference in TB yield - TB yield was 19.3% in the Xpert-based algorithm compared to 19.1% in the smear/culture-based algorithm with a risk difference of 0.3% (p=0.796). Factors that may well have contributed to the yield parity between algorithms included inconsistent implementation of the Xpert-based algorithm and the frequent use of culture tests in the smear/culture-based algorithm.

1.9.1.2 RMP-R TB yield

TB cases included in the stepped-wedge study of TB yield in five sub-districts over seven one-month time periods, before, during and after the introduction of the Xpert-based algorithm as described above, were analysed to assess the proportion of RMP-R TB cases identified pre-treatment and during the course of 1st line TB treatment.[68]

The study found that the Xpert-based algorithm was more effective in identifying RMP-R TB cases than the smear/culture-based algorithm. Pre-treatment, there was a higher probability of having DST undertaken (RR=1.82, p<0.001) and of being diagnosed with RMP-R TB (RR=1.42, p<0.001) in the Xpert-based algorithm than in the smear/culture-based algorithm. During the course of 1st-line TB treatment, there was no significant differences between algorithms in either the proportion of TB cases with DST undertaken (RR=1.02, p=0.848) or with RMP-R TB diagnosed (RR=1.12, p=0.678). Overall 8.5% of TB cases were detected with RMP-R TB in the Xpert-based algorithm compared to 6% in the smear/culture-based algorithm.

This difference was attributable to simultaneous screening for MTB and RMP-R in the Xpert-based algorithm. The study suggests that this is important and that the previous strategy of only screening those at high risk of RMP-R TB pre-treatment may have resulted in missed cases. The proportion screened and identified with RMP-R TB during the course of 1st line treatment was not higher in the smear/culture-based algorithm, suggesting that cases missed pre-treatment were not tested and diagnosed during the course of 1st line treatment.

1.9.1.3 Laboratory costs

Laboratory costs at the central National Health Laboratory were compared in the smear/culture-based algorithm (2011) and the Xpert-based algorithm (2013). The study used an ingredients-based costing approach based on the cost per unit and quantities utilised for buildings, equipment, consumables, staff and overheads.[69] The allocation of costs was based on reviews of standard operating procedures and laboratory records as well as direct observation and timing of the test procedures.

The study found a 43% increase in overall PTB laboratory costs from $440,967 in the smear/culture-based algorithm to $632,262 in the Xpert-based algorithm during 3-

month periods in 2011 and 2013 (all costs were expressed in 2013 terms). The cost per TB case diagnosed increased by 157%, from $48.77 in the smear/culture-based algorithm to $125.32 in the Xpert-based algorithm. The mean total cost per RMP-R TB case diagnosed (cost for TB diagnosis plus marginal cost for RMP-R diagnosis) was similar at $190.14 in the smear/culture-based algorithm compared to $183.86 in the Xpert-based algorithm with 95 and 107 cases diagnosed in respective algorithms. The additional total diagnostic costs translated to a cost of $6,274 per additional RMP-TB case diagnosed in the Xpert-based algorithm compared to the smear/culture-based algorithm. The difference in TB prevalence between the two time periods and differences in adherence to the algorithms may have contributed to the increased cost per TB case diagnosed in the Xpert-based algorithm.

All three of these observational studies had limitations. It was difficult to control for confounding due to for example the differences in background TB prevalence over time and differences in health system performance (e.g. clinicians adherence to TB diagnostic algorithms). Adherence to TB diagnostic algorithm is difficult to assess using routine laboratory data. Clinical staff requesting diagnostic tests may not always follow diagnostic algorithms as stipulated by policy, therefore, tests may sometimes be requested other than what is stipulated in the diagnostic algorithm (reflex testing) which may also include unnecessary repeat tests. These inconsistencies in adherence to diagnostic algorithm made it difficult to compare the performance of the smear/culture and Xpert-based algorithms. It was also difficult to address bias due to the non-random allocation of sites to different study arms.

As part of the PROVE IT study of new TB diagnostics in South Africa, we developed an *operational model* using a discrete event simulation approach for the existing smear/culture-based algorithm and the newly introduced Xpert-based algorithm in Cape Town. The model was developed, validated and calibrated using data collected in PROVE IT, from the studies described above.

1.10 Aim

The overall aim of this dissertation was to develop and validate an operational model for the diagnosis of TB and RMP-R TB in Cape Town, that could be used to (1) explain why the expected increase in the number of TB cases detected (TB yield) was not

found, (2) model the effect of interventions to improve the detection of TB and RMP-R TB in terms of the number of TB and RMP-TB cases detected, (3) model the impact of variable model inputs on laboratory cost for TB and RMP-TB detected, (4) model strategies to reduce laboratory cost for TB diagnosis and (5) model the effect of introducing a more sensitive molecular diagnostic test (for example Xpert Ultra) as a replacement for Xpert on the number of TB and RMP-R TB cases detected.

1.11 Layout of this dissertation

In chapter 2 (Operation modelling: The mechanisms influencing TB diagnostic yield in an Xpert based diagnostic algorithm), I address why the expected increase in the number of TB cases detected (TB yield) was not found in the PROVE IT empirical study.

In this study, I used an operational model to compare the diagnostic yield in the smear/culture and Xpert-based algorithms and to investigate the mechanisms influencing TB yield in Cape Town. This allowed us to better understand why we did not find the expected increase in TB diagnostic yield in the PROVE IT empirical study.[67] Detail regarding model development and validation as well as sensitivity analysis can be found in the supplement for chapter 2.

In chapter 3 (Improving rifampicin resistant tuberculosis diagnosis with Xpert® MTB/RIF: modelling interventions and costs), I model interventions to improve the diagnosis of RMP-R TB in terms of the number of RMP-TB cases detected and cost.

In this study, I used an operational model to compare the number and proportion of RMP-R TB cases identified, and the cost per RMP-R TB case identified between a smear/culture and an Xpert-based algorithm. Since adherence to the Xpert-based algorithm in South Africa has been sub-optimal, I also evaluated the effect of increased adherence to the algorithm and increased HIV testing amongst presumptive TB cases on the number and proportion of RMP-R TB cases identified.

In chapter 4 (High laboratory cost predicted per tuberculosis case diagnosed with increased case finding without a triage strategy), I model strategies to reduce the cost per TB case detected.

In this study, I used the operational model to simulate the effect of increased case finding and triage strategies on laboratory costs per TB case detected and per additional TB case detected in the Xpert-based compared to the smear/culture-based algorithm. I also assessed the effect on laboratory costs if the Xpert cartridge price was reduced.

In chapter 5 (Modelling the impact of Xpert® MTB/RIF Ultra as a replacement test for Xpert® MTB/RIF), I model the effect of introducing a more sensitive molecular diagnostic test (for example Xpert Ultra) on the number of TB and RMP-TB cases detected.

In this study, I adapted the operational model to compare the detection of TB and RMP-TB cases between an Xpert-based algorithm, as currently implemented in Cape Town, South Africa, and the newly develop Xpert MTB/RIF Ultra (not yet implemented).

1.12 Ethics approval and permissions

Stellenbosch University's Health Research Ethics Committee (IRB0005239) (N10/09/308) and The International Union Against Tuberculosis and Lung Disease's (59/10) Ethics Advisory Group approved the study. The City Health Directorate, Western Cape Health Department and National Health Laboratory Service granted permission to use routine health data.

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Chapter 2: Operation modelling: The mechanisms influencing TB diagnostic yield in an Xpert based diagnostic algorithm

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Summary: In this chapter, I address why the expected increase in the number of TB cases detected was not found in our empirical study (PROVE IT). I developed and validated an operational model using routine data from the empirical study representing TB diagnostic algorithms as implemented in Cape Town. I used the model to compare the number of TB cases detected in a smear/culture-based and an Xpert-based algorithm using identical input parameters (population characteristics and adherence to diagnostic algorithms) for both algorithms.

The model indicated that, with identical population characteristics and adherence to diagnostic algorithms, there was an increase in the number of TB cases detected with the Xpert-based compared to the smear/culture-based algorithm. The model indicated that a decrease in TB prevalence during the rollout of Xpert as well as different levels in adherence to the diagnostic algorithms were some of the reasons that the empirical study did not find an increase in TB yield. Furthermore, in our setting, the high efficiency of the central laboratory as well as extensive use of culture testing for smear-negative cases in the smear/culture-based algorithm limited the observed benefit of the rollout of the Xpert-based algorithm.

My contributions: In this chapter, I did the development, validation and sensitivity analysis of the model. I conducted the overall data management and data analysis for this chapter as well as conceived, designed and performed the experiments of running the different scenarios in the model. I wrote the manuscript and submitted the final manuscript for publication to the peer-reviewed journal.

Co-author contribution: Pren Naidoo, Ivor Langley and Nulda Beyers contributed with conceiving and designing experiments. The co-authors reviewed the draft manuscript and approved the final draft manuscript for submission.

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Operational modelling: the mechanisms influencing TB diagnostic yield in an Xpert® MTB/RIF-based algorithm

R. Dunbar,* P. Naidoo,* N. Beyers,* I. Langley†

***Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, South Africa; †Centre for Applied Health Research and Delivery, Liverpool School of Tropical Medicine, Liverpool, UK**

SUMMARY

SETTING: Cape Town, South Africa.

OBJECTIVE: To compare the diagnostic yield for smear/culture and Xpert® MTB/RIF algorithms and to investigate the mechanisms influencing tuberculosis (TB) yield.

METHOD: We developed and validated an operational model of the TB diagnostic process, first with the smear/culture algorithm and then with the Xpert algorithm. We modelled scenarios by varying TB prevalence, adherence to diagnostic algorithms and human immunodeficiency virus (HIV) status. This enabled direct comparisons of diagnostic yield in the two algorithms to be made.

RESULTS: Routine data showed that diagnostic yield had decreased over the period of the Xpert algorithm roll-out compared to the yield when the smear/culture algorithm was in place. However, modelling yield under identical conditions indicated a 13.3% increase in diagnostic yield from the Xpert algorithm compared to smear/culture. The model demonstrated that the extensive use of culture in the smear/culture algorithm and the decline in TB prevalence are the main factors contributing to not finding an increase in diagnostic yield in the routine data.

CONCLUSION: We demonstrate the benefits of an operational model to determine the effect of scale-up of a new diagnostic algorithm, and recommend that policy makers use operational modelling to make appropriate decisions before new diagnostic algorithms are scaled up.

KEY WORDS: TB diagnostic yield; modelling; simulation; TB diagnosis

TUBERCULOSIS (TB) remains a major cause of morbidity and mortality worldwide. Of the global estimated 10.4 million incident TB cases in 2015, 1.2 million were infected with the human immunodeficiency virus (HIV).[1] The Africa region accounted for 26% of global TB cases, 31% of whom are estimated to be HIV–co-infected. The main contributing factor driving the TB epidemic is ongoing transmission due to undiagnosed TB cases, diagnosed cases not initiating treatment[2–4] and diagnostic and treatment initiation delays.[5,6]

Increased investment in recent years has resulted in a number of new, more sensitive and rapid diagnostic tests for TB, with the expectation that this would lead to an increase in the number of cases diagnosed and earlier diagnosis and initiation of treatment, thus reducing transmission and, ultimately, the burden of disease. One of these tests, the Xpert® MTB/RIF assay (Cepheid, Sunnyvale, CA, USA), was endorsed by the World Health Organization (WHO) and recommended as the initial diagnostic test for those with suspected multidrug-resistant TB (MDR-TB) or HIV-associated pulmonary TB (PTB).[7] South Africa replaced smear microscopy with Xpert as the first test in the diagnostic algorithm for all presumptive PTB cases in 2011.[8]

The decision by policy makers about which new test to implement in a diagnostic algorithm can be complicated, and factors to be considered include the best combination of diagnostic tests, the resources required, who should be tested and the TB epidemiology in the setting (prevalence of TB, HIV co-infection and drug resistance). Often many of these factors are not known, and expensive and time-consuming clinical trials are required to make informed decisions,[9] or decisions are made without all the necessary information.

The variable results reported from studies evaluating the implementation of Xpert highlight the complexity in deciding if and how a new diagnostic test should be implemented within a diagnostic algorithm. For example, a population-level decision model estimated that full Xpert coverage would identify

Correspondence to: Rory Dunbar, Desmond Tutu TB Centre Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, P O Box 241, Francie van Zyl Avenue, Tygerberg 7505, South Africa. e-mail: rdun@sun.ac.za

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30% more TB cases (with yield increasing from 15% to 19%) in South Africa in 2013 compared to smear and culture.[10] A prospective cluster-randomised trial of Xpert compared to smear microscopy and culture conducted in a primary care clinic in Cape Town, South Africa, showed an increase in TB yield from 17% with smear and culture to 26% with Xpert.[11] A study conducted in North Ethiopia among household contacts of TB index cases showed an increase of 64.3% in TB detection between smear microscopy (12.8%) and Xpert (35.9%).[12] However, other studies in South Africa and Zimbabwe have not found increases in TB yield.[13,14] Xpert is expensive to implement and use, and the health system and patient impacts and benefits under routine operational conditions are still uncertain.

Modelling as a framework to help with decision making is an attractive and viable option to guide policy makers in implementing new diagnostic tests and algorithms. Operational modelling could identify gaps within a health system and options for addressing these.[15] Projections of the impact of interventions on patient access and outcomes and health system costs and infrastructure could help guide policy makers on which new diagnostic tests and algorithms should be implemented.

As part of an evaluation of new TB diagnostics in South Africa (Policy Relevant Outcomes from Validating Evidence on ImpacT, PROVE IT), we developed an operational model using a discrete event simulation approach for the previous smear/culture-based TB diagnostic algorithm and the newly introduced Xpert-based algorithm in Cape Town and validated the model outputs by comparing these with routine TB programme data.[16]

We used the operational model to investigate the mechanisms influencing TB yield in our setting and to better understand why we did not find the expected increase in TB diagnostic yield in our own empirical study.[16] We used simulated model scenarios, including a decrease in TB prevalence, varying adherence to protocol in diagnostic algorithms and knowledge of HIV status to make direct comparisons of the proportion of presumptive cases diagnosed as TB (TB yield), missed cases (false-negatives) and unnecessarily treated cases (false-positives) in the smear/culture and Xpert-based algorithms.

METHODS

Setting

The model was developed (Appendix Tables A.1 and A.2* and Figures 1 and 2) and validated (Appendix Table A.3) using routine National Health Laboratory Service (NHLS) data collected for the period from 2010 to 2013 over seven time points (T1 to T7) in Cape Town,[16] one of the larger cities in South Africa, with a population of 3.7 million in 2011 (national census 2011) and 28 658 TB cases reported; 47% of TB cases tested were co-infected with HIV (source: routine TB programme data, Cape Town Health Directorate).

Municipal and provincial health authorities provided TB diagnostic services at 142 primary health care (PHC) facilities. Sputum samples collected for TB testing at PHC facilities were couriered to the central NHLS on a daily basis for testing, and results were returned via courier and fax.

Two diagnostic algorithms (Appendix Figure A.1) were used in the study period. A smear/culture-based TB algorithm was used before August 2011, with all presumptive cases required to submit two spot sputum samples taken at least 1 h apart. Both sputum samples were examined using fluorescence microscopy after being chemically treated, centrifuged and stained. Among previously treated presumptive cases, the second sample was cultured using BACTEC™ MGIT™ 960 (BD, Sparks, MD, USA) and tested for drug susceptibility using the GenoType® MTBDR*plus* (Hain LifeScience, Nehren, Germany) line-probe assay (LPA). For new presumptive cases who were smear-negative and HIV-infected, a third sample was required for culture.

An Xpert-based algorithm was phased in from August 2011 to February 2013, with Xpert replacing smear microscopy for all presumptive cases. The first of two sputum samples submitted was tested using Xpert. If TB was detected, smear microscopy was performed on the second sample. In HIV-infected cases with negative Xpert results, the second sample underwent culture and LPA. All definitions for terms used throughout the article are given in Table 1.

Model development

The Witness package, a discrete event and continuous process simulator,[17] was used to develop a comprehensive model to represent the diagnosis of PTB in Cape Town. The model incorporated TB diagnostic algorithms (Appendix Figure A.1) as well as patient pathways and sample flow (Appendix Figure A.2) from specimen collection through laboratory test procedures to a result being provided to the patient and treatment initiation.

Table 2 summarises the model validation, and a detailed account of model development (Appendix Tables A.1 and A.2), more details about validation (Appendix Table A.3) as well as model sensitivity analysis, are available in the online Appendix.

Simulated scenarios: comparing the smear/culture and Xpert-based algorithms

To determine why the expected increase in TB yield was not observed in our setting with the roll-out of the

* The appendix is available in the online version of this article, at http://www.ingentaconnect.com/content/iuatld/ijtld/2017/00000021/00000004/art00006

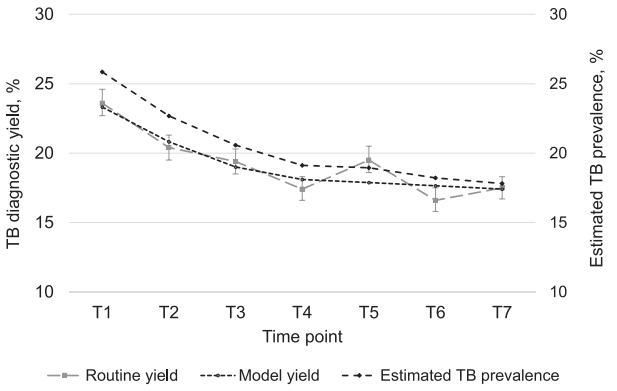

Figure 1 Model output comparing observed yield and model yield for all presumptive cases.

Xpert-based algorithm, we modelled both algorithms with identical input parameters to eliminate any differences in population characteristics (TB prevalence, HIV status, history of previous anti-tuberculosis treatment) during the time the smear/culture-based algorithm was in use and during the Xpert roll-out. We used estimated prevalence data from the most recent time point (T7) and an average of population parameters (proportion of previously treated cases and HIV status) over the seven time points. We ran the model for a period of 3 years for each simulation.

In the base-case scenario (Scenario A), we set levels of adherence to testing protocols in both algorithms at 85%, and assumed that 50% of presumptive cases knew their HIV status. Various other scenarios were modelled (Table 3) and, unless otherwise specified, the baseline parameters for Scenario A were maintained for all the following scenarios. In Scenario B, the estimated TB prevalence among presumptive TB cases was increased by 10%. In Scenario C, we increased the number of cultures for smear-negative and Xpert-negative presumptive TB cases to that found in routine practice: smear/culture-based algorithm: new HIV-negative 30% and HIV-positive 92%, previously treated HIV-negative 10% and HIV-positive 95%; Xpert-based algorithm: new HIV-negative 5% and HIV-positive 92%, previously treated HIV-negative 10% and HIV-positive 95%.

In Scenario D, we assessed the effect of an increase in known HIV status (from 50% to 85%) on outputs. In Scenario E, we tested the effect of 100% adherence to testing protocols in each algorithm, with 50% of presumptive TB cases' HIV status known. With Scenario F, we increased both HIV status known and adherence to testing protocols to 100%. With Scenario G, the use of culture was removed from both algorithms, as in most settings culture is not used as extensively as in Cape Town or is not used at all as part of the diagnostic algorithm. In Scenario H, we lowered the test sensitivity of smear microscopy by 10%. Scenario input parameters are summarised in Appendix Tables A.4 and A.5. For each scenario, we compared TB yield between the algorithms for all TB cases, and also assessed the proportion of missed cases (false-negative or TB not detected but TB present) and cases treated unnecessarily (false-positive or TB detected but no TB present). We undertook

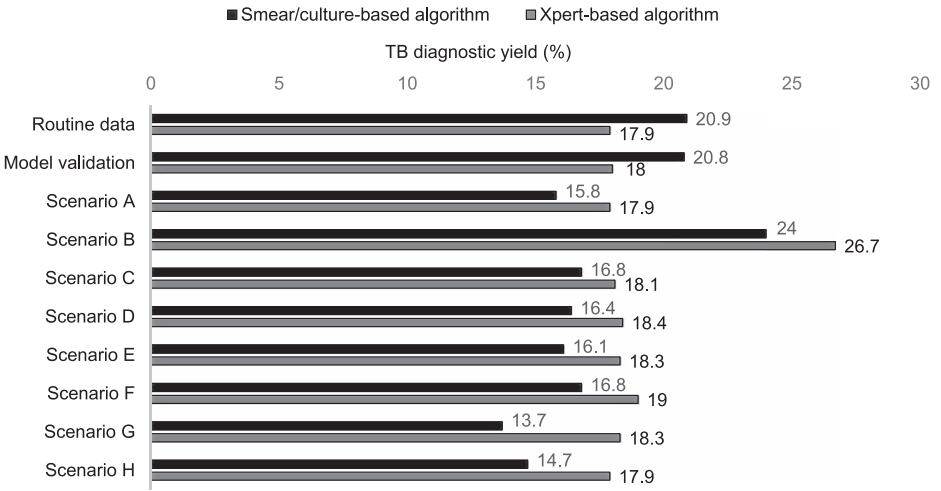

Figure 2 Model outputs from the scenarios comparing TB diagnostic yield (%) between algorithms and sensitivity of input parameters. Diagnostic yield from routine data. Model with routine data as input parameters. Scenario A: 85% adherence to algorithm and 50% of presumptive cases know their HIV status; Scenario B: increase estimated TB prevalence among presumptive cases by 10%; Scenario C: increase additional culture for smear or Xpert-negative presumptive cases per routine practice; Scenario D: increased proportion (85%) of presumptive cases know their HIV status; Scenario E: adherence (100%) to algorithms; Scenario F: increased proportion (100%) of presumptive cases know their HIV status and adherence (100%) to algorithms; Scenario G: remove culture as part of the sequence of tests required in each diagnostic algorithm; Scenario H: lower the sensitivity of smear microscopy by 10%. TB = tuberculosis.

Table 1 Definitions used throughout the study

Presumptive case	Defined as an individual with pre-treatment sputum samples submitted for diagnostic purposes
TB prevalence among presumptive cases	The proportion of true TB cases among presumptive cases. For model purposes, this is defined as culture-positive cases
TB case	An individual with one or more smears positive and/or culture positive for *M. tuberculosis* and/or *M. tuberculosis* detected on Xpert (includes true-positive cases and false-positive cases)
New presumptive cases	An individual with no previous anti-tuberculosis treatment or <4 weeks of previous anti-tuberculosis treatment
Previously treated presumptive cases	An individual with >4 weeks of previous anti-tuberculosis treatment
TB testing protocol	The sequence of tests required in each diagnostic algorithm
TB diagnostic yield	The number of TB cases diagnosed (based on the full TB testing protocol performed) expressed as a proportion of presumptive cases tested TB diagnostic yield = (True positive + false positive)/Presumptive cases
False-positive	The proportion of individuals with culture-negative TB who are incorrectly diagnosed with TB
False-negative	The proportion of individuals with culture-positive TB in whom a TB diagnosis is missed
True-positive	The proportion of individuals with culture-positive TB who are diagnosed with TB

TB = tuberculosis.

the analysis for new and previously treated TB cases, and for HIV-positive and HIV-negative TB cases (Appendix Table A.6–A.13).

Analysis

All patient and laboratory test information was written to a Microsoft SQL Server database (Microsoft, Redmond, WA, USA). Model outputs were aggregated by month over a 3-year period to produce means and 95% confidence intervals (CIs) for diagnostic yield and proportions that were false-negative and false-positive. We used the *t*-test to determine differences in means between observed and modelled outputs for the model validation and between algorithms for simulated scenarios. Differences are expressed as absolute values. All analyses were undertaken using STATA version 14 (StataCorp, College Station, TX, USA).

Ethics statement

The study was approved by the Health Research Ethics Committee at Stellenbosch University, Tygerberg, South Africa (IRB0005239) (N10/09/308) and the Ethics Advisory Group at the International Union

Table 2 Model validation comparing TB yield from routine data and model outputs (%)

	T1	T2	T3	T4	T5	T6	T7	Weighted mean ± SD	Mean difference % (95%CI)	*P* value
All presumptive cases										
Smear/culture-based algorithm										
Routine data	23.6	20.4	18.0	18.8	20.6	NA*	NA*	20.9 ± 2.1	0.1 (−3.0 to 3.3)	
Model outputs	23.4	20.8	18.7	17.3	17.4	NA*	NA*	20.8 ± 2.2		0.928
Xpert-based algorithm										
Routine data	NA*	NA*	21.2	16.9	19.3	16.6	17.5	17.9 ± 1.5	−0.1 (−1.8 to 1.6)	
Model outputs	NA*	NA*	19.5	18.5	18.1	17.7	17.4	18.0 ± 0.6		0.874
Overall										
Routine data	23.6	20.4	19.4	17.4	19.5	16.6	17.5	19.2 ± 2.2	0.0 (−2.4 to 2.5)	
Model outputs	23.4	20.8	19.1	18.1	17.9	17.7	17.4	19.2 ± 2.0		0.988
New presumptive cases										
Smear/culture-based algorithm										
Routine data	23.2	20.9	17.0	16.8	19.7	NA*	NA*	20.4 ± 2.5	0.8 (−2.6 to 4.3)	
Model outputs	22.1	19.8	17.6	16.3	16.0	NA*	NA*	19.6 ± 2.1		0.581
Xpert-based algorithm										
Routine data	NA*	NA*	21.7	15.7	18.7	15.8	16.2	17.1 ± 1.9	0.0 (−2.1 to 2.0)	
Model outputs	NA*	NA*	18.3	17.5	17.0	16.7	16.8	17.1 ± 0.5		0.975
Overall										
Routine data	23.2	20.9	18.8	16.1	18.9	15.8	16.2	18.5 ± 2.5	0.4 (−2.3 to 3.0)	
Model outputs	22.1	19.8	17.9	17.1	16.9	16.7	16.8	18.1 ± 1.9		0.764
Previously treated presumptive cases										
Smear/culture-based algorithm										
Routine data	26.6	23.1	21.6	25.3	23.5	NA*	NA*	24.4 ± 1.9	0.2 (−2.7 to 3.1)	
Model outputs	26.5	24.1	22.1	20.3	21.3	NA*	NA*	24.2 ± 2.1		0.897
Xpert-based algorithm										
Routine data	NA*	NA*	23.6	21.7	22.6	19.8	24.2	22.1 ± 1.7	0.9 (−0.9 to 2.9)	
Model outputs	NA*	NA*	23.2	21.4	21.1	20.9	20.2	21.2 ± 0.9		0.276
Overall										
Routine data	26.6	23.1	22.5	22.8	22.7	19.8	24.2	23.2 ± 2.0	0.7 (−1.7 to 3.1)	
Model outputs	26.5	24.1	22.6	21.1	21.2	20.9	20.2	22.4 ± 2.1		0.535

*The smear/culture-based algorithm was not in use in the TB programme during T6 and T7; and the Xpert-based algorithm was not in use during T1 and T2.
TB = tuberculosis; SD = standard deviation; CI = confidence interval; NA = not applicable.

Table 3 Model outputs from the scenarios comparing TB diagnostic yield (%) between algorithms and sensitivity of input parameters

	Smear/culture-based algorithm			Xpert-based algorithm			Change in yield between algorithms (relative % difference)
Routine and modelled data across all time periods (i.e., smear/culture T1–T5 and Xpert T3–T7)							
Diagnostic yield from routine data		20.9			17.9		−3.0 (−14.4)
Model with routine data as input parameters		20.8			18.0		−2.8 (−13.5)
Modelled scenarios: all input parameters identical between algorithms	True TB	Not TB	Yield	True TB	Not TB	Yield	
Scenario A: 85% adherence to algorithm and 50% of presumptive cases know their HIV status*							
TB detected	15.0	0.8	15.8	16.3	1.6	17.9	2.1 (13.3)
TB not detected	3.3	80.9		2.1	80.0		
Scenario B: increase estimated TB prevalence among presumptive cases by 10%							
TB detected	23.3	0.7	24.0	25.3	1.5	26.7	2.7 (11.3)
TB not detected	5.1	70.9		3.1	70.2		
Scenario C: increase additional culture testing for smear or Xpert-negative presumptive cases to that found in routine practice†							
TB detected	16.0	0.8	16.8	16.4	1.7	18.1	1.3 (7.7)
TB not detected	2.3	80.9		1.9	80.0		
Scenario D: increased proportion (85%) of presumptive cases know their HIV status							
TB detected	15.6	0.8	16.4	16.7	1.7	18.4	2.0 (12.2)
TB not detected	2.6	81.0		1.5	80.0		
Scenario E: 100% adherence to algorithms; 50% know their HIV status							
TB detected	15.3	0.8	16.1	16.5	1.8	18.3	2.2 (13.7)
TB not detected	3.0	80.9		1.8	79.9		
Scenario F: 100% adherence to algorithms; 100% know their HIV status							
TB detected	16.1	0.7	16.8	17.1	1.9	19.0	2.2 (13.1)
TB not detected	2.1	81.1		1.1	79.9		
Scenario G: remove culture as part of the sequence of tests required in each diagnostic algorithm							
TB detected	12.9	0.8	13.7	16.5	1.8	18.3	4.6 (33.6)
TB not detected	5.4	80.9		1.8	80.0		
Scenario H: lower the sensitivity of smear microscopy by 10%							
TB detected	13.9	0.8	14.7	16.3	1.6	17.9	3.2 (21.8)
TB not detected	4.4	80.9		2.1	80.0		

* In Scenario A, 85% of cases in each algorithm received the initial tests as required and 85% of smear- or Xpert-negative cases who were HIV-infected underwent culture; 50% of presumptive cases knew their HIV status. The same values for TB prevalence (18.8%), proportions of HIV−, HIV+ (status known and undiagnosed), new and previously treated cases were used in each algorithm. All scenario changes are in relation to Scenario A. Yield = TB detected (true TB + not TB).
† In Scenario C, culture in smear/culture-based algorithm increased new HIV− (0–30%), HIV+ (85–92%), previously treated HIV− (0–10%) HIV+ (85–95%); Xpert-based algorithm: new HIV− (0–5%), HIV+ (85–92%), previously treated HIV− (0–10%), HIV+ (85–95%).
TB = tuberculosis; HIV = human immunodeficiency virus; − = negative; + = positive.

Against Tuberculosis and Lung Disease, Paris, France (59/10). A waiver for informed consent was granted for use of routine data. The City Health Directorate, Western Cape Health Department, Cape Town, and the National Health Laboratory Services, Pretoria, South Africa, granted permission to use routine health data.

RESULTS

Model validation

The mean differences between observed yield from routine data and model outputs over the seven time points is shown in Figure 1 and Table 2. The TB yield from the model closely approximated that from routine data for both diagnostic algorithms. The mean model yield was 0.1% ($P = 0.928$) lower than observed values in the smear/culture-based algorithm and 0.1% ($P = 0.874$) higher in the Xpert-based algorithm overall (Figure 1; Table 2).

Simulated scenarios: comparing the smear/culture and Xpert-based algorithms

Figure 2 and Table 3 summarise the model outputs from the scenarios comparing the TB diagnostic yield from the smear/culture and Xpert-based algorithms. In Scenario A (detail in Appendix Table A.6), with 85% adherence to the diagnostic algorithms and where 50% of presumptive cases knew their HIV status, the overall TB diagnostic yield was 15.8% in the smear/culture-based algorithm compared to 17.9% in the Xpert-based algorithm (relative difference 13.3%), with respectively 3.3% and 2.1% of presumptive cases having a missed TB diagnosis. A lower proportion of cases were falsely diagnosed with TB in the smear/culture-based algorithm (0.8%) than in the Xpert-based algorithm (1.6%).

When the estimated TB prevalence among presumptive cases was increased by 10% (absolute) (Scenario B) (Appendix Table A.7), the yield was 24.0% and 26.7% in the respective algorithms. The relative increase in yield between algorithms was 11.3%. The proportion of missed cases was respectively 5.1% and 3.1%.

When Scenario A was adjusted so that the proportions of smear-negative and Xpert-negative cases who received a culture test were set to reflect the values found in routine practice (Scenario C), the

overall yield was 16.8% in the smear/culture-based algorithm compared to 18.1% in the Xpert-based algorithm, a relative increase of 7.7%. The proportion of missed cases was 2.3% and 1.9% in the respective algorithms (Appendix Table A.8). In comparison to Scenario A, the relative increase in TB yield was 6.3% in the smear/culture-based algorithm and 1.1% in the Xpert-based algorithm in Scenario C.

If HIV testing among presumptive TB cases was increased and 85% knew their HIV status (Scenario D) (Appendix Table A.9), the overall yield was 16.4% in the smear/culture-based algorithm compared to 18.4% in the Xpert-based algorithm (relative difference 12.2%), with 2.6% and 1.5% missed cases in the respective algorithms. In comparison to Scenario A, an increase in HIV testing resulted in a relative increase of 3.8% and 2.8% in TB yield in the respective algorithms.

If adherence to the testing protocol in each algorithm was increased to 100% but only 50% of presumptive TB cases knew their HIV status (Scenario E) (Appendix Table A.10), the TB yield was 16.1% in the smear/culture-based compared to 18.3% in the Xpert-based algorithm, with a relative increase of 10.9%. The proportion of missed cases was respectively 3.0% and 1.8%. In comparison to Scenario A, the relative increase in TB yield was 1.9% in the smear/culture-based algorithm compared to 2.2% in the Xpert-based algorithm.

If adherence to the testing protocol in each algorithm was increased to 100% and 100% of presumptive TB cases knew their HIV status (Scenario F) (Appendix Table A.11), the TB yield was 16.8% in the smear/culture-based compared to 19.0% in the Xpert-based algorithm, with a relative increase of 13.1% between algorithms. The proportion of missed cases was respectively 2.1% and 1.1%. In comparison to Scenario A, the relative increase in TB yield was 6.3% in the smear/culture-based algorithm compared to 6.1% in the Xpert-based algorithm.

Removing culture as part of the testing protocol from both algorithms (Scenario G) (Appendix Table A.12) resulted in a TB yield of 13.7% and 18.3% in the respective algorithms. The relative increase in yield between algorithms was 33.6%. The proportion of missed cases was 5.4% in the smear/culture algorithm compared to 1.8% in the Xpert algorithm.

If we assume the sensitivity of smear microscopy to be 10% lower than that estimated in our model (Scenario H) (Appendix Table A.13), the yield in the smear/culture algorithm would be 14.7% (missed cases 4.4%), with a relative increase in yield with the Xpert algorithm of 21.8%.

DISCUSSION

A strength of this study was the availability of detailed routine data and information collected on health and laboratory processes, which allowed us to develop a precise operational model to assess the impact of different diagnostic algorithms in Cape Town. The model input parameters were mostly based on these detailed routine data, and only a few assumptions were made. We assumed that prevalence among presumptive cases was higher among HIV-positive presumptive cases than among HIV-negative cases,[18,19] and among previously treated than among new cases;[20] we assumed a decrease in TB prevalence among presumptive cases over time based on the empiric yield data, which showed a decrease in yield over time despite similar proportions of the population being tested.[16] The latter assumption is supported by national data that showed a decrease in the number of laboratory-confirmed cases since 2011 (nationally and across the Western Cape Province).[21]

The availability of routine TB NHLS data collected through the PROVE IT study allowed us to validate the model by comparing TB yield observed in routine practice to model outputs using input parameters from seven different time points during the period when PHC facilities changed from the smear/culture algorithm to the Xpert algorithm. This comparison built confidence in the outputs from the model and confirmed that the outputs were credible. Overall model outputs closely resembled the TB yield observed in Cape Town over the seven time points, with a mean difference of 0.1% ($P = 0.951$) between routine data and the model outputs.

A direct comparison of TB yield in the Xpert and smear/culture-based algorithms in routine practice is difficult due to the variability in the population characteristic at each time point and different levels of adherence to testing protocols. When the Xpert-based algorithm was newly introduced, it took staff a period of time to adapt their clinical practice and become familiar with the new protocols. The global stock-out of the Xpert test during the study period also played a role in the extent to which testing protocols were followed. The operational model allows a direct comparison between the two algorithms with identical population characteristics and adherence to testing protocols. To understand the mechanisms and the extent to which they influenced TB yield in our setting, we used the validated model to compare various scenarios.

In Scenario A, with 85% adherence to algorithm and 50% of presumptive cases knowing their HIV status, the yield in the Xpert-based algorithm was higher than in the smear/culture-based algorithm, with a relative increase of 13.3%. Although the TB diagnostic yield was higher in the Xpert-based algorithm, the increase was lower than the predicted

increase with full roll-out of Xpert in South Africa[10] and reported by other studies.[11,12]

Scenarios B and C provide insights into the findings on TB yield from our empirical study. The TB yield in the smear/culture-based algorithm in Scenario B, where TB prevalence was 10% higher than in Scenario A, was 25% higher than in the Xpert-based algorithm in Scenario A, demonstrating the impact of a decline in prevalence among presumptive TB cases on TB yield. This helps explain findings from the empirical study that reported yields of 20.9% in the smear/culture-based and 17.9% in the Xpert-based algorithm.[16] It is likely that the change in prevalence in our setting during the study period was lower than the 10% value tested in the model.

Our model showed the impact of additional culture testing on reducing the difference in TB yield between algorithms. When the proportions of smear- and Xpert-negative cases who received culture tests were increased to reflect those found in routine practice (Scenario C), the relative increase in yield between the smear/culture and Xpert-based algorithms was reduced to 7.7%. This was attributable to a higher proportion of smear-negative than Xpert-negative cases undergoing culture. A cluster-randomised study in four other provinces also found that culture was more likely to be undertaken for smear-negative (32%) than Xpert-negative (14%) HIV-infected cases.[22] It was proposed that a greater belief in the efficacy of the Xpert test contributed to this.

Scenarios D to F provide insights into the potential benefits of interventions that strengthen the health system. Increasing the proportion of presumptive cases who knew their HIV status from 50% to 85% had a small influence on TB yield: the yield increased by 3.8% in the smear/culture-based algorithm, and by 2.8% in the Xpert-based algorithm in relative terms from Scenario A. It is interesting to note the modest benefits, considering the effort required to increase HIV testing of presumptive cases to this extent.

In Scenario E for the Xpert-based algorithm, increasing adherence to the algorithm to 100%, but with only 50% of presumptive TB cases knowing their HIV status, produced a 2.2% relative increase in yield compared to Scenario A. Increasing adherence to 100% and with 100% knowing their HIV status resulted in a relative increase in yield of only 6.1% in the Xpert-based algorithm in Scenario F compared to Scenario A. In addition to this disappointingly small benefit, 100% adherence is not realistic in routine practice due to the failure to request the correct test (due to new or locum staff who are unfamiliar with Xpert and costs concerns, for example), the availability of the Xpert test due to maintenance on Xpert machines or stock-outs and clinical decisions overriding the use of the testing algorithm. It is important to note that we started on a baseline of 85% adherence to the algorithms and with 50% knowing their HIV status; the increases in yield would be greater if these baseline values were lower. In a future study, we will model the effect of a more sensitive test than Xpert to assess the extent to which this can increase TB diagnostic yield.

We compared two scenarios that are pertinent to other settings. In Scenario G, where culture was removed from the algorithms, there was a 33.6% relative difference in TB yield between the smear/culture and the Xpert-based algorithm. The diagnostic benefits of Xpert are thus likely to be greater in areas that do not use or have very limited use of culture. The performance of smear microscopy in our central laboratory may also be much higher than reported by peripheral microscopy units. This is possibly due to greater proficiency and technical aspects in the central laboratory. It has been shown that an increase in yield for smear microscopy could be achieved by chemical treatment, centrifugation and fluorescence microscopy,[23–25] as used in our laboratory. If we did not have these benefits and smear microscopy sensitivity was 10% lower, the relative increase in TB yield in the Xpert-based algorithm would have been 21.8% compared to that in the smear/culture-based algorithm.

Limitations

We did not have data on TB prevalence for presumptive cases. This was estimated with a range of values tested in the model. The model was validated against data from Cape Town, a well-resourced urban setting where there is extensive use of culture in both algorithms. This may limit the generalisability of the findings to other settings.

As complete data are rarely available for any modelling study, assumptions are required for some input parameters. A model is also, by definition, a simplification of real-life processes. In this study, our model was validated by running the model with input parameters based on routine data for seven individual time points and comparing the output from the model against corresponding routine data (Figure 1; Table 2). Cost implications, treatment delay and rifampicin resistance were not addressed in the current study and will be reported in future studies.

CONCLUSION

We have developed and validated an operational model that can be used to directly compare the TB diagnostic yield between different algorithms, i.e., a smear/culture-based and an Xpert-based algorithm. Our model accounted for the variability found in routine practice and made it possible to eliminate the effect of a difference in population characteristics and adherence to testing protocols within algorithms on the TB diagnostic yield.

We were able to show that extensive use of culture in the smear/culture-based algorithm and decline in TB prevalence are the main factors likely to have contributed to our not finding an increased TB yield in the Xpert-based algorithm in our empiric study. The Xpert-based algorithm is likely to yield greater diagnostic benefits in areas without culture or with less sensitive TB microscopy.

We have demonstrated the benefits of using an operational model to determine the effect of scaling up a new diagnostic algorithm and investigate the mechanistic reasons that influence the yield of a new TB diagnostic algorithm. We would therefore recommend that policy makers use operational modelling to make appropriate decisions before new diagnostic algorithms are scaled up. The model could provide evidence as to how the greatest benefits could be obtained by using a new diagnostic test within a TB diagnostic algorithm and in a specific setting.

Acknowledgements

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Conflicts of interest: none declared.

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APPENDIX

Modelling as a framework to help with decision making is an attractive and viable option to guide policy makers in implementing new diagnostic tools and diagnostic algorithms. Two modelling approaches previously used in tuberculosis (TB) control are transmission (epidemiological) modelling and operational modelling.[1] Transmission modelling can be used to predict the long-term impact of interventions on the community by projecting TB incidence, prevalence and mortality. Operational modelling, on the other hand, can be used to project the impact of interventions on health system costs and infrastructure, as well as patient access and outcomes. Operational modelling can also be useful in identifying gaps within a health system and to identify ways to address the gaps within the health system.[2] An operational model is a simplified representation of complex real-life processes. The data sources usually used to drive operational models are derived from published literature (i.e., meta-analyses, randomised control trials, cohort studies, global reports, unpublished literature, expert opinion, field data), and from assumptions. Models are therefore only as good as the level of detail available to develop the logic of the model and the availability and accuracy of the data to drive the model.[3]

In industrial and commercial settings, operational models are widely used to plan and assess the performance and efficiency of processes.[4] Operational models have also increasingly been used to improve performance of the health sector.[5,6] The use of operational models in health systems is common in high-income countries, but not in middle- to low-income countries at this stage. Many operational models use a discrete event simulation approach, where the system modelled is first defined in terms of its most important elements, including the items or people processed through the facility, resources, activities, rules and the process flow. The required outputs of the model are defined (e.g., productivity, costs, identification of bottlenecks, capacity and sensitivity to changes), along with the key input parameters to be investigated. Once the system is defined and appropriate parameter inputs are assigned (e.g., the number of items entering the system, the quantity of resources and the time for completing particular activities), then simulations can be run to assess the relative effect of different input assumptions on the modelled outputs.[7]

Model development

The Witness package, a discrete event and continuous process simulator,[8] was used to develop a comprehensive model to represent the diagnosis of pulmonary TB (PTB) in Cape Town, South Africa. The model incorporated the TB diagnostic algorithms (Figure A.1), as well as patient pathways and sample flow (Figure A.2) from specimen collection, through laboratory test procedures, to a result being provided to the patient and treatment initiation.

The main elements in the model (Table A.1) were entities (representing patients, sputum samples), activities (representing patient reception, sputum collection from the patient, sample transport, sample registration at the laboratory, sample preparation and test procedures, review and return of results to primary health care [PHC] facilities), queues (representing delays before each activity, e.g., patient waiting in reception prior to clinical evaluation and sputum collection, batching and other processes in

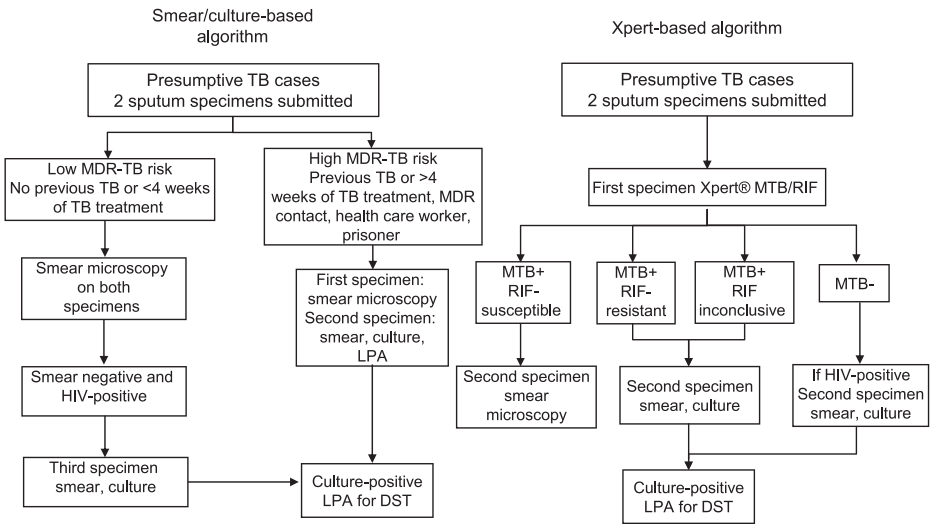

Figure A.1 TB diagnostic algorithms. The simplified sequence of diagnostic tests in each algorithm and the action taken based on test results is shown. TB = tuberculosis; MDR-TB = multidrug-resistant TB; LPA = line-probe assay; MTB = *Mycobacterium tuberculosis*; RIF = rifampicin; HIV = human immunodeficiency virus; DST = drug susceptibility testing.

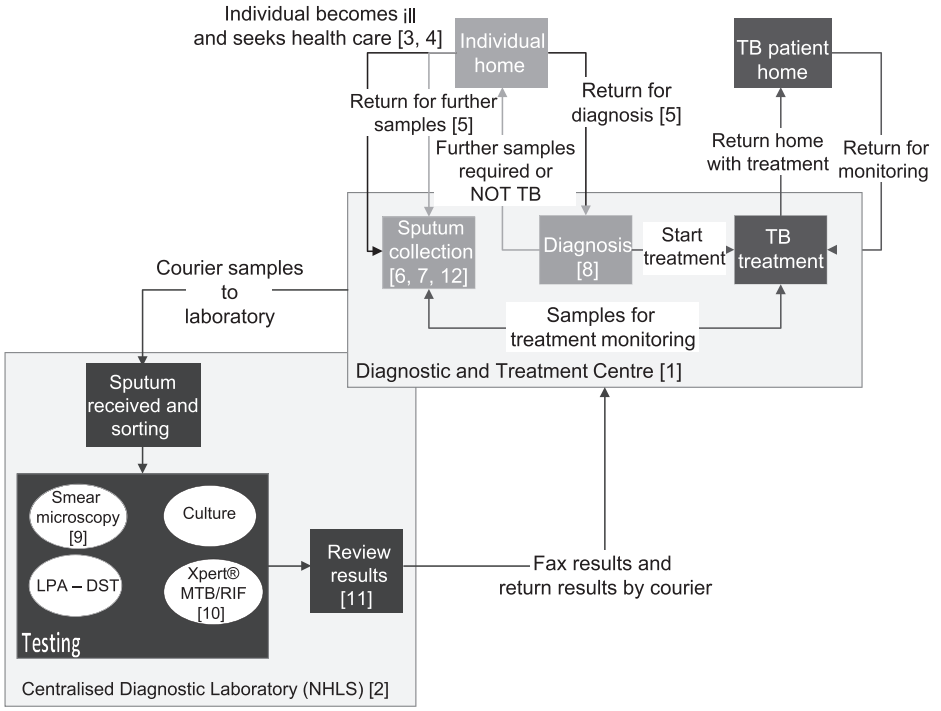

Figure A.2 A representation of the diagnostic pathway for the diagnosis of TB in Cape Town, South Africa.* * See Table A.2. TB = tuberculosis; LPA = lineprobe assay; DST = drug susceptibility testing; NHLS = National Health Laboratory Services.

the laboratory) and resources (representing health facility and laboratory staff and equipment).

The model structure follows the patient and sample pathways (Figure A.2), with the flow of entities between activities and queues dictated by rules, which are dependent on attributes for entities (patient or sample).

Input parameters

A detailed list of the input parameters, including processing times, patient and sample data as well as test sensitivity and specificity, is shown in Table A.2.

Input data sources

Health system and laboratory processes were mapped in three ways: through key informant interviews, through the review of standard operating procedures and through detailed observation and timing of clinic and laboratory processes, all undertaken as part of the PROVE IT study.

Characteristics of presumptive cases were derived from electronic laboratory TB test data received from the National Health Laboratory Services (NHLS) Data Warehouse. Data included demographic information, treatment history (new or previously treated cases) human immunodeficiency virus (HIV) status (HIV-negative, HIV-positive, status unknown), test type (smear, culture or Xpert® MTB/RIF), test results and date when sputum was collected, tested and results available.

As there were no unique identifiers in the NHLS data to link results belonging to an individual, matching was performed on personal identifying information (first name, family name, date of birth and facility folder number). After record matching, all personal identifying information was removed. These data were used to assess adherence to testing protocols in each algorithm and to calculate diagnostic yield (the proportion of presumptive cases diagnosed as TB).

Data on the sensitivity and specificity of tests were obtained from systematic reviews and published literature.[9–11] We did not have data on the proportion of true TB cases among presumptive cases (TB prevalence), and we tested a range of prevalence values, assuming that prevalence was lower among HIV-negative than among HIV-positive,[12,13] and among new than among previously treated presumptive cases[14]; the outputs in comparison to observed TB yield values from routine data were then assessed (see below).[15]

Model outputs

The output from the model indicated the proportion of cases diagnosed as TB (TB yield, i.e., true-positive and false-positive cases) and the proportion of cases missed (false-negative) using the diagnostic algorithm in different scenarios.

Model calibration and validation

To have confidence in the model and the outputs produced, the model was verified and validated.[16]

Table A.1 The key elements used in the model developed for this study

Model element type	Representation of
Entities	Patients, presumptive cases reporting to a TB diagnostic centre (clinic) for TB diagnosis
	Sputum sample
Attributes	Number of sputum samples required
	Number of sputum samples collected
	Previous history of anti-tuberculosis treatment (new, previous TB)
	HIV status (HIV−, HIV+, HIV+ with status not known)
	Test result
Activities	Clinic
	Reception
	TB room
	Sputum collection
	Patient return home
	Courier, transport of samples from clinic to central laboratory
	Laboratory
	Sample sorting/reception
	Smear
	Preparation
	Microscopy
	Review result
	Fax result
	Culture
	Preparation
	MGIT
	ZN smear
	Fax result
	Xpert
	Preparation
	Xpert test
	Review results
	Fax result
Queues	Clinic
	Waiting room at reception
	Waiting for sputum collection
	Patient
	Wait for result or provide further sputum samples
	Laboratory
	Sample waiting for preparation
	Sample waiting for testing/batching
	Microscopy
	Culture
	Xpert
	Result waiting for review
	Result waiting to be faxed

TB = tuberculosis; HIV = human immunodeficiency virus; − = negative; + = positive; MGIT = Mycobacteria Growth Indicator Tube; ZN = Ziehl-Neelsen.

Model verification to ensure that the coding and logic of the model and its execution were correct was performed through incremental model building and carefully scrutinising the structure and logic of the model at each stage. The distribution of input parameters was assessed against outputs to make sure that the model assigned patient categories correctly.

The model was validated using input parameters from routine data and by comparing TB yield from model outputs to routine data.[15] As part of the PROVE IT Study, NHLS data from presumptive cases had previously been collected and analysed to compare TB yield in the smear/culture-based algorithm to that in the Xpert-based algorithm over seven time periods (T1–T7), during which the PHC changed from the former algorithm to the latter.[15] The model used probability distributions derived from this analysis to assign patients to categories: diagnostic algorithm used, HIV status (known HIV-positive, undiagnosed HIV and HIV-negative) and treatment history (new or previously treated).

Data on HIV status were only available for time points T6 and T7 (50% knew their HIV status), and similar proportions were assumed for T1–T5. The extent to which testing protocols was followed in each diagnostic algorithm was derived from these data. As we did not have data on TB prevalence among presumptive cases, a range of values were tested. We made the assumption that prevalence among presumptive cases was higher among HIV-positive presumptive cases than among HIV-negative cases,[12,13] and among previously treated than among new cases.[14] We

Table A.2 Main input parameters for operational model*

Input parameter	Description	Values		Source
Processing times				
TB diagnostic and treatment facility processing times	Duration of activities within the diagnostic centre for reception, sputum collection and returning results	Not defined for current model		
Laboratory process times Duration of and batching process for microscopy, culture and drug susceptibility testing. Preparation and processing times for Xpert	Sample collection times by courier	First sputum delivery: between 2 and 3 pm		Interviews with NHLS staff, review of SOPs and direct observations of laboratory procedures
	Sample sorting time	25 min in batches of 96		
	Xpert preparation time	50 min in batches of 16		
	Xpert test time	1 h 50 min		
	Smear preparation time	2 h for 96 samples		
	Microscopy reading	1 h per batch of 96		
	Culture preparation	2 h per batch of 750		
	Culture test time	5–36 days		
Patient data				
Number of new patients seeking diagnosis Number and arrival rate of individuals seeking diagnosis	Number of presumptive cases per day	Uniform distribution: Minimum = 11 Maximum = 690 Mean = 55		NHLS data warehouse and sampled from a uniform distribution
Arrival time of patients[4]	The time during the day that the patient arrives at the diagnostic centre	5 days: Monday to Friday 8 am to 5 pm Working 540 min per day		Sampled from user-defined distribution starting at the opening time of the health facility with all patients arriving by closing time.
Return probability[5]	The probability that an individual returns to the diagnostic centre for the next stage of the diagnostic process	Not defined for current model		Published literature[18,19]
HIV status of presumptive cases[6]	Proportion of presumptive cases who are identified as HIV+	New presumptive cases = 18% Previous history of TB = 35%		Estimated from NHLS Data Warehouse data for 2013
History of previous TB treatment for presumptive cases[7]	Proportion of presumptive cases with previous TB treatment	Average over all observed time points = 24% (breakdown by time point in Table A.3)		Estimated from NHLS Data Warehouse data and stepped wedge analysis[15]; 90% of presumptive cases with missing previous TB treatment status were assumed to be new cases
Proportion of presumptive cases with diagnostic test performed[8] Average over all observed time points (breakdown by time point in Table A.3)	Smear/culture algorithm:	New cases	Previous history of TB	Estimated from NHLS Data Warehouse data and stepped wedge analysis[15]
	Two smears	84%	82%	
	Smear-negative with culture	36%	85%	
	Xpert algorithm:			
	Xpert	77%	65%	
	Xpert-negative with culture	18%	41%	
Diagnostic test accuracy				
Accuracy of smear microscopy[9]	Sensitivity and specificity of LED fluorescence microscopy	Two sputum samples HIV−: sensitivity 75%, specificity 99% HIV+: sensitivity 65%, specificity 99%		Published literature[9,10]
Accuracy of Xpert[10]	Sensitivity and specificity of Xpert in identifying TB from sputum samples	HIV−: sensitivity 89%, specificity 98% HIV+: sensitivity 80%, specificity 98%		Published literature[11]
Proportion of tests by test type that give no result[11]	Level of retesting required for smear, culture or Xpert	2%		Estimated from NHLS Data Warehouse data and stepped wedge analysis[15]

Table A.2 *(continued)*

Input parameter	Description	Values	Source
Number of sputum tests required per patient with suspected TB[12]	The number of sputum samples required for each diagnostic algorithm	Two sputum samples	South African National TB Guidelines[20]

* See Figure A.2.
TB = tuberculosis; NHLS = National Health Laboratory Services; SOPs = standard operating procedures; HIV = human immunodeficiency virus; + = positive; LED = light-emitting diode; − = negative.

assumed a decrease in TB prevalence among presumptive cases based on the routine yield data, which showed a decrease in yield over time despite a similar proportion of the population being tested.[15] This is supported by national data that show a reduction in the number of laboratory-confirmed cases since 2011 (nationally and across the Western Cape Province).[17] A summary of the population characteristics used for model validation by time period is provided in Table A.3.

The availability of TB test data collected through the PROVE IT study allowed us to validate the model by comparing TB yield observed in routine practice to model outputs using the input parameters from seven different time points during the period when PHC facilities changed from the smear/culture algorithm to

Table A.3 Population characteristics used for model validation by time period (%)

	T1*	T2*	T3*	T4*	T5*	T6*	T7*
History of previous anti-tuberculosis treatment							
Proportion of previously treated cases	29	24	24	25	25	24	19
HIV status							
New presumptive cases							
HIV-positive	36	36	36	36	36	36	36
HIV-negative	64	64	64	64	64	64	64
Previously treated presumptive cases							
HIV-positive	53	53	53	53	53	53	53
HIV-negative	47	47	47	47	47	47	47
Proportion who know their HIV status							
Estimated TB prevalence among presumptive cases							
New presumptive cases							
HIV-positive	26	23	21	19	19	18	17.8
HIV-negative	25	22	19	18	17.8	17	17
Previously treated presumptive cases							
HIV-positive	27	24	23	21.5	21.5	21	20.8
HIV-negative	26	23	22	20	19.8	19.8	19.5
Proportion of presumptive cases tested using algorithm							
Smear/culture-based	100	100	57	30	19	0	0
Xpert-based	0	0	43	70	81	100	100
Adherence to smear/culture-based algorithm							
New presumptive cases with two smears	85	85	85	85	85	—	—
Previously treated presumptive cases with culture	88	91	90	92	75	—	—
Adherence to Xpert-based algorithm							
All presumptive cases with Xpert test done	—	—	57	67	63	75	80
Proportion of patients who were smear or Xpert-negative with culture							
Smear/culture-based algorithm							
New presumptive cases							
HIV-positive	92	92	92	92	92	92	92
HIV-negative	30	30	30	30	30	30	30
Previously treated presumptive cases							
HIV-positive	95	95	95	95	95	95	95
HIV-negative	10	10	10	10	10	10	10
Xpert-based algorithm							
New presumptive cases							
HIV-positive	92	92	92	92	92	92	92
HIV-negative	2	2	2	2	2	2	2
Previously treated presumptive cases							
HIV-positive	95	95	95	95	95	95	95
HIV-negative	10	10	10	10	10	10	10

*T1–T7 reflect the time points evaluated as part of a non-randomised stepped-wedge evaluation of TB yield with a transition from a smear/culture to an Xpert-based algorithm in Cape Town.[15] At T1 and T2, all facilities used the smear/culture-based algorithm; this decreased to 65% of facilities at T3, 38% at T4 and 23% at T5. At T6 and T7, all facilities used the Xpert-based algorithm: T1, November 2010; T2, May 2011; T3, November 2011; T4, May 2012; T5, November 2012, T6, May 2013; T7, November 2013. Values are derived from routine data.[15]
HIV = human immunodeficiency virus; TB = tuberculosis.

Table A.4 Input parameters used in base-case (Scenario A) comparing the smear/culture and Xpert-based algorithms (%)*

History of previous anti-tuberculosis treatment	25
HIV status	
New presumptive cases	
HIV-positive	36
HIV-negative	64
Previously treated presumptive cases	
HIV-positive	53
HIV-negative	47
Proportion who know their HIV status	50
Estimated TB prevalence among presumptive cases	
New presumptive cases	
HIV-positive	17.8
HIV-negative	17
Previously treated presumptive cases	
HIV-positive	20.8
HIV-negative	19.5
Adherence to smear/culture-based algorithm	
New presumptive cases with two smears	85
Previously treated presumptive cases with culture	85
Adherence to Xpert-based algorithm	
All presumptive cases with Xpert test done	85
Proportion smear or Xpert-negative with culture testing	
Smear/culture-based algorithm	
New presumptive cases	
HIV-positive	85
HIV-negative	0
Previously treated presumptive cases	
HIV-positive	85
HIV-negative	0
Xpert-based algorithm	
New presumptive cases	
HIV-positive	85
HIV-negative	0
Previously treated presumptive cases	
HIV-positive	85
HIV-negative	0

* Input parameters used in all scenarios except where specific parameters are changed for a scenario (Table A.6).
HIV = human immunodeficiency virus; TB = tuberculosis.

the Xpert algorithm. This comparison built confidence in the outputs from the model, and confirmed that the outputs were credible. Overall model outputs closely resembled TB yield observed in Cape Town over the seven time points, with a mean difference of 0.0% ($P = 0.988$) between the routine data and the model outputs (Table 2).

Model sensitivity analysis

We selected five parameters to test the sensitivity of our results to uncertainty in the parameter values. The parameters evaluated were the estimated TB prevalence among presumptive cases, the proportion of presumptive cases with previous anti-tuberculosis treatment, the test sensitivity of smear microscopy and Xpert, the proportion of adherence to testing algorithms and the extent of use of culture. These parameters were selected because they have a direct impact on the probability of being correctly tested with TB, and therefore an impact on the primary outputs, i.e., diagnosed as TB (TB yield), missed cases (false-negative) and unnecessarily treated cases (false-positive).

This analysis is summarised in Tables A.14 and A.15 as well as in Figures A.3 and A.4. The analysis shows that TB diagnostic yield is sensitive to TB prevalence among presumptive cases and, to a lesser extent, to test sensitivity and previous history of TB. The proportion of HIV-positive cases among presumptive cases had more of an effect on the Xpert-based algorithm, with a decrease in yield as the proportion of HIV-positive cases increased.

Table A.5 Input parameters used in other simulated scenarios comparing the smear/culture and Xpert-based algorithms (%)

	Smear/culture-based algorithm		Xpert-based algorithm	
Scenario B: increase estimated TB prevalence among presumptive cases by 10%				
	Scenario A	Scenario B	Scenario A	Scenario B
New presumptive cases				
HIV-negative	17	27	17	27
HIV-positive	17.8	27.8	17.8	27.8
Previously treated presumptive cases				
HIV-negative	19.5	29.5	19.5	29.5
HIV-positive	20.8	30.8	20.8	30.8
Scenario C: increase additional culture testing for smear or Xpert-negative presumptive cases				
	Scenario A	Scenario C	Scenario A	Scenario C
New presumptive cases				
HIV-negative	0	30	0	5
HIV-positive	85	92	85	92
Previously treated presumptive cases				
HIV-negative	0	10	0	10
HIV-positive	85	95	85	95
Scenario D: increased proportion of presumptive cases know their HIV status				
	Scenario A	Scenario D	Scenario A	Scenario D
Proportion of presumptive cases	50%	85%	50%	85%
Scenario E: adherence to algorithms				
	Scenario A (85%)	Scenario E (100%)	Scenario A (85%)	Scenario E (100%)
New presumptive cases				
HIV-negative	2 smear	2 smear	Xpert test	Xpert test
HIV-positive	2 smear	2 smear	Xpert test	Xpert test

Table A.5 *(continued)*

	Smear/culture-based algorithm		Xpert-based algorithm	
Previously treated presumptive cases				
HIV-negative	Culture test	Culture test	Xpert test	Xpert test
HIV-positive	Culture test	Culture test	Xpert test	Xpert test
As part of follow-up testing if smear or Xpert is negative				
New presumptive cases				
HIV-negative	0	0	0	0
HIV-positive	85	100	85	100
Previously treated presumptive cases				
HIV-negative	0	0	0	0
HIV-positive	85	100	85	100
Scenario F: increased proportion of presumptive cases know their HIV status (100%) and adherence to algorithm (100%)				
	Scenario A	Scenario F	Scenario A	Scenario F
Proportion of presumptive cases	50%	100%	50%	100%
	Scenario A (85%)	Scenario F (100%)	Scenario A (85%)	Scenario F (100%)
New presumptive cases				
HIV-negative	2 smear	2 smear	Xpert test	Xpert test
HIV-positive	2 smear	2 smear	Xpert test	Xpert test
Previously treated presumptive cases				
HIV-negative	Culture test	Culture test	Xpert test	Xpert test
HIV-positive	Culture test	Culture test	Xpert test	Xpert test
As part of follow-up testing if smear or Xpert is negative				
New presumptive cases				
HIV-negative	0	0	0	0
HIV-positive	85	100	85	100
Previously treated presumptive cases				
HIV-negative	0	0	0	0
HIV-positive	85	100	85	100
Scenario G: remove culture test as part of the sequence of tests required in each diagnostic algorithm				
	Scenario A	Scenario G	Scenario A	Scenario G
New presumptive cases				
HIV-negative	0	0	0	0
HIV-positive	0	0	0	0
Previously treated presumptive cases				
HIV-negative	85	0	0	0
HIV-positive	85	0	0	0
As part of follow-up testing if smear or Xpert test is negative				
New presumptive cases				
HIV-negative	0	0	0	0
HIV-positive	85	0	85	0
Previously treated presumptive cases				
HIV-negative	0	0	0	0
HIV-positive	85	0	85	0
Scenario H: lower test sensitivity of smear microscopy by 10%				
	Scenario A	Scenario H		
HIV-negative	75	65		
HIV-positive	65	55		

TB = tuberculosis; HIV = human immunodeficiency virus.

Table A.6 Scenario A: comparison of smear/culture and Xpert-based algorithm model outputs (with 85% adherence to algorithms)*

	Smear/culture-based algorithm			Xpert-based algorithm			Change in yield between algorithms % difference *P* value		
	HIV−	HIV+	Overall	HIV−	HIV+	Overall	HIV−	HIV+	Overall
All presumptive cases									
Yield†	14.8	17.3	15.8	17.1	19.2	17.9	2.3 ($P < 0.001$)	1.9 ($P < 0.001$)	2.1 ($P < 0.001$)
FP†	0.9	1.0	0.9	1.9	2.2	2.0	1	1.2	1.1
FN†	20.7	14.4	18.0	12.6	9.5	11.3	8.1	4.9	6.7
New presumptive cases									
Yield†	13.6	15.2	14.2	16.5	17.9	17.0	2.9 ($P < 0.001$)	2.7 ($P < 0.001$)	2.8 ($P < 0.001$)
FP†	0.9	0.9	0.9	2.0	2.1	2.0	1.1	1.2	1.1
FN†	25.3	21.3	23.8	13.4	11.5	12.7	11.9	9.8	11.1
Previously treated presumptive cases									
Yield†	19.5	21.5	20.6	19.1	21.7	20.5	0.4 ($P = 0.476$)	0.2 ($P = 0.644$)	0.0 ($P = 0.894$)
FP†	0.9	1.0	0.9	1.8	2.3	2.1	0.9	1.3	1.2
FN†	3.9	2.2	3.0	9.5	6.1	7.6	5.6	3.9	4.6

* In Scenario A, 85% of cases in each algorithm received the initial tests as required and 85% of smear- or Xpert-negative cases who were HIV-infected underwent culture; 50% of presumptive cases knew their HIV status. The same values for TB prevalence, proportions of HIV–, HIV+ (status known and undiagnosed), and new and previously treated cases were used in each algorithm.
† TB diagnostic yield (yield) = (TP + FP)/presumptive cases; TP = correctly diagnosed with TB/culture-positive TB cases; FP = incorrectly diagnosed with TB/culture-negative TB cases; FN = incorrectly NOT diagnosed with TB (missed)/culture-positive TB cases.
HIV = human immunodeficiency virus; − = negative; + = positive; FP = false-positive; FN = false-negative; TB = tuberculosis; TP = true-positive.

Table A.7 Scenario B: increase in estimated TB prevalence among presumptive cases by 10%*

	Smear/culture-based algorithm % (95%CI)			Xpert-based algorithm % (95%CI)			Change in yield between algorithms % difference *P* value		
	HIV−	HIV+	Overall	HIV−	HIV+	Overall	HIV−	HIV+	Overall
All presumptive cases									
Yield†	22.7	26.0	24.0	25.7	28.1	26.7	3.0 ($P < 0.001$)	2.1($P < 0.001$)	2.7 ($P < 0.001$)
FP†	1.0	1.0	1.0	1.9	2.2	2.0	0.9	1.2	1
FN†	20.5	13.9	17.8	12.1	9.6	11.0	8.4	4.3	6.8
New presumptive cases									
Yield†	21.1	23.4	21.9	25.1	26.6	25.6	4.0 ($P < 0.001$)	3.2 ($P < 0.001$)	3.7 ($P < 0.001$)
FP†	1.0	1.1	1.0	2.0	2.2	2.0	1	1.1	1
FN†	25.0	20.3	23.3	12.9	11.7	12.5	12.1	8.6	10.8
Previously treated presumptive cases									
Yield†	29.2	31.4	30.4	28.3	31.2	29.9	0.9 ($P = 0.125$)	0.2 ($P = 0.771$)	0.1 ($P = 0.212$)
FP†	0.9	0.9	0.9	1.8	2.2	2.0	0.9	1.3	1.1
FN†	3.6	2.4	3.0	8.8	5.8	7.1	5.2	3.4	4.1

* In Scenario B, the estimated TB prevalence among presumptive case was increased by 10; 50% of presumptive cases knew their HIV status. The same values for proportions of HIV–, HIV+ (status known and undiagnosed), and new and previously treated cases were used in each algorithm.
† TB diagnostic yield (yield) = (TP + FP)/presumptive cases; TP = correctly diagnosed with TB/culture-positive TB cases; FP = incorrectly diagnosed with TB/culture-negative TB cases; FN = incorrectly NOT diagnosed with TB (missed)/culture-positive TB cases.
TB = tuberculosis; CI = confidence interval; HIV = human immunodeficiency virus; − = negative; + = positive; FP = false-positive; FN = false-negative; TP = true-positive.

Table A.8 Scenario C: increased proportion of smear- or Xpert-negative presumptive cases with additional culture*

	Smear/culture-based algorithm % (95%CI)			Xpert-based algorithm % (95%CI)			Change in yield between algorithms % difference *P* value		
	HIV−	HIV+	Overall	HIV−	HIV+	Overall	HIV−	HIV+	Overall
All presumptive cases									
Yield†	15.9	18.2	16.8	17.2	19.3	18.1	1.3 ($P < 0.001$)	1.2 ($P < 0.001$)	1.3 ($P < 0.001$)
FP†	0.9	1.0	0.9	2.0	2.2	2.1	1.1	1.2	1.2
FN†	14.5	9.8	12.5	11.9	8.8	10.6	2.6	1	1.9
New presumptive cases									
Yield†	15.0	16.4	15.5	16.7	18.1	17.2	1.7 ($P < 0.001$)	1.6 ($P < 0.001$)	1.7 ($P < 0.001$)
FP†	0.9	0.9	0.9	2.0	2.1	2.0	1.1	1.2	1.1
FN†	17.5	14.5	16.4	12.7	10.8	12.0	4.8	3.7	4.4
Previously treated presumptive cases									
Yield†	19.6	21.6	20.7	19.4	21.9	20.7	0.2 ($P = 0.632$)	0.3 ($P = 0.543$)	0.0 ($P = 0.895$)
FP†	0.9	1.0	0.9	1.9	2.4	2.1	1	1.4	1.2
FN†	3.5	1.6	2.4	8.7	5.2	6.8	5.2	3.6	4.4

* In Scenario C, 85% of cases in each algorithm underwent the initial tests as required; 50% of presumptive cases knew their HIV status. Additional culture was based on values found in routine practice for each patient category (smear/culture algorithm by 14.3%, Xpert algorithm by 8%). The same values for TB prevalence, proportions of HIV–, HIV+ (status known and undiagnosed), and new and previously treated cases were used in each algorithm.
† TB diagnostic yield (yield) = (TP + FP)/presumptive cases; TP = correctly diagnosed with TB/culture-positive TB cases; FP = incorrectly diagnosed with TB/culture-negative TB cases; FN = incorrectly NOT diagnosed with TB (missed)/culture-positive TB cases.
CI = confidence interval; HIV = human immunodeficiency virus; − = negative; + = positive; FP = false-positive; FN = false-negative; TB = tuberculosis; TP = true-positive.

Table A.9 Scenario D: increased proportion (85%) of presumptive cases who know their HIV status*

	Smear/culture-based algorithm			Xpert-based algorithm			Change in yield between algorithms % difference *P* value		
	HIV−	HIV+	Overall	HIV−	HIV+	Overall	HIV−	HIV+	Overall
All presumptive cases									
Yield†	14.8	18.7	16.4	17.1	20.5	18.4	2.3 ($P < 0.001$)	1.8 ($P < 0.001$)	2.1 ($P < 0.001$)
FP†	0.9	0.9	0.9	1.9	2.4	2.1	1	1.5	1.2
FN†	20.7	5.9	14.4	12.6	2.7	8.4	8.1	3.2	6
New presumptive cases									
Yield†	13.6	17.1	14.9	16.5	19.2	17.5	2.9 ($P < 0.001$)	2.2 ($P < 0.001$)	2.6 ($P < 0.001$)
FP†	0.9	0.9	0.9	2.0	2.4	2.1	1.1	1.5	1.2
FN†	25.3	8.9	19.3	13.4	3.4	9.7	11.9	5.5	9.6
Previously treated presumptive cases									
Yield†	19.5	22.0	20.8	19.1	23.0	21.2	0.4 ($P = 0.476$)	1.0 ($P = 0.043$)	0.0 ($P = 0.297$)
FP†	0.9	0.9	0.9	1.8	2.4	2.1	0.9	1.5	1.2
FN†	3.9	0.7	2.1	9.5	1.5	5.1	5.6	0.8	3

*Scenario D, 85% of cases in each algorithm underwent the initial tests as required and 85% of smear- or Xpert-negative cases that were HIV-infected underwent culture; 85% of presumptive cases knew their HIV status. The same values for TB prevalence, proportions of HIV–, HIV+ (status known and undiagnosed), and new and previously treated cases were used in each algorithm.
†TB diagnostic yield (yield) = (TP + FP)/presumptive cases; TP = correctly diagnosed with TB/culture-positive TB cases; FP = incorrectly diagnosed with TB/culture-negative TB cases; FN = incorrectly NOT diagnosed with TB (missed)/culture-positive TB cases.
HIV = human immunodeficiency virus; − = negative; + = positive; FP = false-positive; FN = false-negative; TB = tuberculosis; TP = true-positive.

Table A.10 Scenario E: increased adherence to smear/culture and Xpert algorithm to 100%*

	Smear/culture-based algorithm % (95%CI)			Xpert-based algorithm % (95%CI)			Change in yield between algorithms % difference *P* value		
	HIV−	HIV+	Overall	HIV−	HIV+	Overall	HIV−	HIV+	Overall
All presumptive cases									
Yield†	14.9	17.7	16.1	17.5	19.5	18.3	2.5 ($P < 0.001$)	1.8 ($P < 0.001$)	2.2 ($P < 0.001$)
FP†	0.9	1.0	0.9	2.1	2.4	2.2	1.2	1.4	1.3
FN†	19.8	12.1	16.5	10.9	9.0	10.1	8.9	3.1	6.4
New presumptive cases									
Yield†	13.6	15.6	14.4	17.1	18.4	17.6	3.5 ($P < 0.001$)	2.7 ($P < 0.001$)	3.2 ($P < 0.001$)
FP†	0.9	0.9	0.9	2.1	2.4	2.2	1.2	1.5	1.3
FN†	25.3	19.0	22.9	11.0	10.5	10.8	14.3	8.5	12.1
Previously treated presumptive cases									
Yield†	20.3	21.9	21.2	19.0	21.8	20.5	1.3 ($P = 0.013$)	0.2 ($P = 0.744$)	0.7 ($P = 0.057$)
FP†	0.9	1.0	0.9	1.9	2.5	2.2	1	1.5	1.3
FN†	0.0	0.0	0.0	10.6	6.2	8.2	10.6	6.2	8.2

*In Scenario E, adherence to the full range of tests required in each algorithm was set at 100% from 85%; 50% of presumptive cases knew their HIV status. The same values for TB prevalence, proportions of HIV–, HIV+ (status known and undiagnosed), and new and previously treated cases were used in each algorithm.
†TB diagnostic yield (yield) = (TP + FP)/presumptive cases; TP = correctly diagnosed with TB/culture-positive TB cases; FP = incorrectly diagnosed with TB/culture-negative TB cases; FN = incorrectly NOT diagnosed with TB (missed)/culture-positive TB cases.
CI = confidence interval; HIV = human immunodeficiency virus; − = negative; + = positive; FP = false-positive; FN = false-negative; TB = tuberculosis; TP = true-positive.

Table A.11 Scenario F: increased proportion of presumptive cases who know their HIV status to 100% and adherence to algorithms to 100%*

	Smear/culture-based algorithm % (95%CI)			Xpert-based algorithm % (95%CI)			Change in yield between algorithms % difference *P* value		
	HIV−	HIV+	Overall	HIV−	HIV+	Overall	HIV−	HIV+	Overall
All presumptive cases									
Yield†	14.9	19.7	16.8	17.5	21.2	19.0	2.5 ($P < 0.001$)	1.5 ($P < 0.001$)	2.1 ($P < 0.001$)
FP†	0.9	0.8	0.9	2.1	2.7	2.3	1.2	1.9	1.4
FN†	19.8	0.0	11.5	10.9	0.0	6.3	8.9	0	5.2
New presumptive cases									
Yield†	13.6	18.5	15.4	17.1	20.1	18.2	3.5 ($P < 0.001$)	1.5 ($P < 0.001$)	2.8 ($P < 0.001$)
FP†	0.9	0.9	0.9	2.1	2.8	2.3	1.2	1.9	1.4
FN†	25.3	0.0	16.0	11.0	0.0	7.0	14.3	0	9
Previously treated presumptive cases									
Yield†	20.3	22.0	21.2	19.0	23.5	21.4	1.3 ($P = 0.013$)	1.5 ($P = 0.004$)	0.2 ($P = 0.623$)
FP†	0.9	0.8	0.8	1.9	2.6	2.3	1	1.8	1.5
FN†	0.0	0.0	0.0	10.6	0.0	4.7	10.6	0	4.7

*In Scenario F, increase in the percentage of presumptive cases who knew their HIV status from 50% to 100% and adherence to the full range of tests required in each algorithm to 100% from 85%. The same values for TB prevalence, proportions of HIV–, HIV+ (status known and undiagnosed), and new and previously treated cases were used in each algorithm.
†TB diagnostic yield (yield) = (TP + FP)/presumptive cases; TP = correctly diagnosed with TB/culture-positive TB cases; FP = incorrectly diagnosed with TB/culture-negative TB cases; FN = incorrectly NOT diagnosed with TB (missed)/culture-positive TB cases.
CI = confidence interval; HIV = human immunodeficiency virus; − = negative; + = positive; FP = false-positive; FN = false-negative; TB = tuberculosis; TP = true-positive.

Table A.12 Scenario G: remove culture test as part of the sequence of tests required in smear/culture and Xpert algorithms*

	Smear/culture-based algorithm % (95%CI)			Xpert-based algorithm % (95%CI)			Change in yield between algorithms % difference *P* value		
	HIV−	HIV+	Overall	HIV−	HIV+	Overall	HIV−	HIV+	Overall
All presumptive cases									
Yield†	14.0	13.3	13.7	17.5	19.5	18.3	3.5 ($P < 0.001$)	6.2 ($P < 0.001$)	4.6 ($P < 0.001$)
FP†	0.9	1.0	0.9	2.1	2.4	2.2	1.2	1.4	1.3
FN†	25.3	35.2	29.4	10.9	9.0	10.1	14.4	26.2	19.3
New presumptive cases									
Yield†	13.6	12.5	13.2	17.1	18.4	17.5	3.5 ($P < 0.001$)	5.9 ($P < 0.001$)	4.3 ($P < 0.001$)
FP†	0.9	0.9	0.9	2.1	2.4	2.2	1.2	1.5	1.3
FN†	25.3	36.1	29.3	11.0	20.3	10.5	14.3	15.8	18.8
Previously treated presumptive cases									
Yield†	15.4	14.8	15.1	19.0	21.8	20.5	3.6 ($P < 0.001$)	6.9 ($P < 0.001$)	5.4 ($P < 0.001$)
FP†	0.9	1.0	0.9	1.9	2.5	2.2	1	1.5	1.3
FN†	25.2	33.6	29.9	10.6	6.2	8.2	14.6	27.4	21.7

*In Scenario G, culture testing was removed as part of the sequence of tests required in each algorithm; 50% of presumptive cases knew their HIV status. The same values for TB prevalence, proportions of HIV–, HIV+ (status known and undiagnosed), and new and previously treated cases were used in each algorithm.
†TB diagnostic yield (yield) = (TP + FP)/presumptive cases; TP = correctly diagnosed with TB/culture-positive TB cases; FP = incorrectly diagnosed with TB/culture-negative TB cases; FN = incorrectly NOT diagnosed with TB (missed)/culture-positive TB cases.
CI = confidence interval; HIV = human immunodeficiency virus; − = negative; + = positive; FP = false-positive; FN = false-negative; TB = tuberculosis; TP = true-positive.

Table A.13 Scenario H: lower test sensitivity of smear microscopy by 10% in smear/culture algorithm*

	Smear/culture-based algorithm % (95%CI)			Xpert-based algorithm % (95%CI)			Change in yield between algorithms % difference *P* value		
	HIV−	HIV+	Overall	HIV−	HIV+	Overall	HIV−	HIV+	Overall
All presumptive cases									
Yield†	13.4	16.6	14.7	17.1	19.1	17.9	3.6 ($P < 0.001$)	2.6 ($P < 0.001$)	3.2 ($P < 0.001$)
FP†	1.0	1.0	1.0	1.9	2.2	2.0	0.9	1.2	1
FN†	28.6	18.0	24.1	12.6	9.5	11.3	16	8.5	12.8
New presumptive cases									
Yield†	12.0	14.2	12.8	16.5	17.9	17.0	4.6 ($P < 0.001$)	3.7 ($P < 0.001$)	4.2 ($P < 0.001$)
FP†	1.0	1.1	1.0	2.0	2.1	2.0	1	1	1
FN†	35.1	26.8	32.0	13.4	11.5	12.7	21.7	15.3	19.3
Previously treated presumptive cases									
Yield†	19.2	21.4	20.4	19.1	21.7	20.5	0.1 ($P = 0.881$)	0.3 ($P = 0.493$)	0.1 ($P = 0.681$)
FP†	0.9	0.9	0.9	1.8	2.3	2.1	0.9	1.4	1.2
FN†	5.4	2.7	3.9	9.5	6.1	7.6	4.1	3.4	3.7

* In Scenario H, the test sensitivity of smear microscopy was reduced by 10%. The Xpert algorithm is set as per Scenario A; 50% of presumptive cases knew their HIV status. The same values for TB prevalence, proportions of HIV–, HIV+ (status known and undiagnosed), and new and previously treated cases were used in each algorithm.
† TB diagnostic yield (yield) = (TP + FP)/presumptive cases; TP = correctly diagnosed with TB/culture-positive TB cases; FP = incorrectly diagnosed with TB/culture-negative TB cases; FN = incorrectly NOT diagnosed with TB (missed)/culture-positive TB cases.
CI = confidence interval; HIV = human immunodeficiency virus; − = negative; + = positive; FP = false-positive; FN = false-negative; TB = tuberculosis; TP = true-positive.

Table A.14 Summary of input and output parameters for model sensitivity analysis*

	Base value	High value	Low value
Estimated TB prevalence among presumptive cases			
Input	18.9	28.9	8.9
Output			
Smear/culture-based algorithm			
Yield	15.8	24.0	7.6
FP	0.9	1.0	1.0
FN	17.6	17.4	16.9
Xpert-based algorithm			
Yield	17.5	26.1	8.7
FP	1.9	1.9	1.9
FN	12.5	12.5	12.4
Proportion of presumptive cases with previous anti-tuberculosis treatment			
Input	25	50	15
Output			
Smear/culture-based algorithm			
Yield	15.8	17.3	15.2
FP	0.9	1.0	1.0
FN	17.6	11.7	19.3

Table A.14 *(continued)*

	Base value	High value	Low value
Xpert-based algorithm			
Yield	17.5	18.2	17.0
FP	1.9	2.0	1.9
FN	12.5	11.1	13.1
Test sensitivity of smear microscopy and Xpert			
Input			
Smear microscopy (two samples)			
HIV-negative	75	85	65
HIV-positive	65	75	55
Xpert			
HIV-negative	89	94	81
HIV-positive	80	88	67
Output			
Smear/culture-based algorithm			
Yield	15.8	17.0	14.7
FP	0.9	1.0	1.0
FN	17.6	11.4	23.6
Xpert-based algorithm			
Yield	17.5	18.1	16.5
FP	1.9	1.9	1.9
FN	12.5	9.3	17.9

* TB diagnostic yield (yield) = (TP + FP)/presumptive cases; TP = correctly diagnosed with TB/culture-positive TB cases; FP = incorrectly diagnosed with TB/culture-negative TB cases; FN = incorrectly NOT diagnosed with TB (missed)/culture-positive TB cases.
TB = tuberculosis; FP = false-positive; FN = false-negative; HIV = human immunodeficiency virus; TP = true-positive.

Table A.15 Proportion of culture as part of the sequence of tests required in each diagnostic algorithm and 100% adherence to algorithms*

	Smear/culture-based algorithm		Xpert-based algorithm	
	Base	0% culture	Base	0% culture
Use of culture				
Input				
As part of the initial sequence of tests				
New presumptive cases				
HIV-negative	0	0	0	0
HIV-positive	0	0	0	0
Previously treated presumptive cases				
HIV-negative	85	0	0	0
HIV-positive	85	0	0	0
As part of follow-up testing if smear or Xpert test is negative				
New presumptive cases				
HIV-negative	0	0	0	0
HIV-positive	85	0	85	0
Previously treated presumptive cases				
HIV-negative	0	0	0	0
HIV-positive	85	0	85	0
Output				
Yield	15.8	13.7	17.5	17.2
FP	0.9	0.9	1.9	2.0
FN	17.6	29.4	12.5	14.7
Adherence to algorithms				
Input				
As part of the initial sequence of tests				
	85% adherence	100% adherence	85% adherence	100% adherence
New presumptive cases				
HIV-negative	2 smears	2 smears	Xpert test	Xpert test
HIV-positive	2 smears	2 smears	Xpert test	Xpert test
Previously treated presumptive cases				
HIV-negative	Culture test	Culture test	Xpert test	Xpert test
HIV-positive	Culture test	Culture test	Xpert test	Xpert test
As part of followup testing if smear or Xpert test is negative				
	Base	0% culture	Base	0% culture
New presumptive cases				
HIV-negative	0	0	0	0
HIV-positive	85	100	85	100
Previously treated presumptive cases				
HIV-negative	0	0	0	0
HIV-positive	85	100	85	100
Output				
	85% adherence	100% adherence	85% adherence	100% adherence
Yield	15.8	16.1	17.5	18.3
FP	0.9	0.9	1.9	2.2
FN	17.6	16.5	12.5	10.1

* TB diagnostic yield (yield) = (TP + FP)/presumptive cases; TP = correctly diagnosed with TB/culture-positive TB cases; FP = incorrectly diagnosed with TB/culture-negative TB cases; FN = incorrectly NOT diagnosed with TB (missed)/culture-positive TB cases.
HIV = human immunodeficiency virus; FP = false-positive; FN = false-negative; TB = tuberculosis; TP = true-positive.

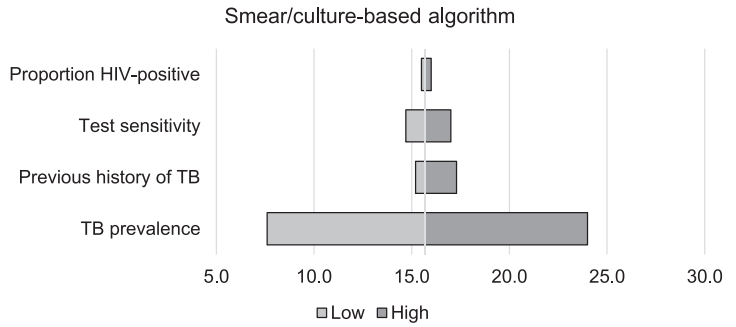

Figure A.3 Oneway sensitivity analysis with results on the effect of change in input parameters on TB diagnostic yield for the smear/culturebased algorithm. HIV = human immunodeficiency virus; TB = tuberculosis.

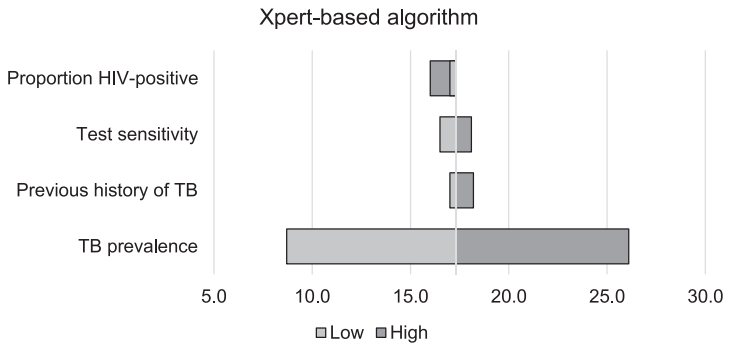

Figure A.4 One-way sensitivity analysis with results on the effect of change in input parameters on TB diagnostic yield for the Xpert-based algorithm. HIV = human immunodeficiency virus; TB = tuberculosis.

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RESUME

CONTEXTE : Le Cap, Afrique du Sud.

OBJECTIF : Comparer le rendement diagnostique des algorithmes de frottis/culture et d'Xpert® MTB/RIF et étudier les mécanismes influençant le rendement de la tuberculose (TB).

MÉTHODE : Nous avons élaboré et validé un modèle opérationnel du processus de diagnostic de la TB, d'abord avec l'algorithme de frottis/culture et ensuite avec l'algorithme de l'Xpert. Nous avons modélisé les scénarios en variant la prévalence de la TB, l'adhésion aux algorithmes de diagnostic et le statut du virus de l'immunodéficience humaine. Ceci a permis de faire des comparaisons directes du rendement diagnostique dans les deux algorithmes.

RÉSULTATS : Les données de routine ont montré que le rendement diagnostique avait diminué pendant la période de lancement de l'algorithme Xpert par rapport à la période où l'algorithme frottis/culture était en place. Cependant, le rendement de la modélisation dans des conditions identiques a mis en évidence une augmentation de 13,3% du rendement diagnostique de l'algorithme Xpert comparé au frottis/culture. Le modèle a démontré que l'utilisation extensive de la culture dans l'algorithme frottis/culture et le déclin de la prévalence de la TB étaient les principaux facteurs contribuant à ne pas trouver d'augmentation du rendement diagnostique dans les données de routine.

CONCLUSION : Nous avons démontré les bénéfices d'un modèle opérationnel afin de déterminer l'effet de l'expansion d'un nouvel algorithme de diagnostic et de recommander que les décideurs politiques utilisent la modélisation opérationnelle pour prendre des décisions appropriées avant que de nouveaux algorithmes de diagnostic ne soient étendus.

RESUMEN

MARCO DE REFERENCIA: La Ciudad del Cabo en Suráfrica.

OBJETIVO: Comparar el desempeño de un algoritmo diagnóstico basado en la baciloscopia y el cultivo y un algoritmo con la prueba Xpert® MTB/RIF e investigar los mecanismos que influyen en su eficacia.

MÉTODOS: Se creó un modelo operativo del proceso diagnóstico de la tuberculosis (TB) y se evaluó inicialmente con el algoritmo de la baciloscopia y el cultivo y luego con el algoritmo que incluía la prueba Xpert. Se simularon modelos con diferentes hipótesis de prevalencia de TB, adhesión a los algoritmos y situación frente a la infección por el virus de la inmunodeficiencia humana. Estos modelos permitieron una comparación directa del rendimiento diagnóstico de ambos algoritmos.

RESULTADOS: Los datos de la práctica corriente pusieron de manifiesto que el rendimiento diagnóstico disminuyó durante el período de despliegue del algoritmo con la prueba Xpert en comparación con el rendimiento que se lograba cuando se aplicaba el algoritmo de la baciloscopia y el cultivo. Sin embargo, al utilizar la modelización en idénticas condiciones, se obtuvo un aumento de 13,3% del rendimiento diagnóstico del algoritmo con la prueba Xpert en comparación con el algoritmo de la baciloscopia y el cultivo. La modelización reveló que un uso extenso del cultivo en el algoritmo de la baciloscopia y el cultivo y la disminución de la prevalencia de TB fueron los principales factores que explicaban el hecho de no haber logrado un mejor rendimiento diagnóstico en los datos de la práctica corriente con la prueba Xpert.

CONCLUSIÓN: En el presente estudio se demuestra la utilidad de un modelo operativo diseñado con el propósito de determinar el efecto de la ampliación de escala de un nuevo algoritmo diagnóstico y se recomienda que las instancias normativas apliquen la modelización operativa a fin de adoptar las decisiones apropiadas, antes de ampliar la escala de nuevos algoritmos diagnósticos.

Chapter 3: Improving rifampicin resistant tuberculosis diagnosis with Xpert® MTB/RIF: modelling interventions and costs

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Summary: In this chapter, I model interventions to improve the diagnosis of RMP-R TB in terms of the number of RMP-R TB cases diagnosed and cost. I developed and validated an operational model using routine data from the empirical study representing TB and RMP-R TB diagnostic algorithms as implemented in Cape Town. I modelled the RMP-R TB cases detected and missed in the smear/culture and Xpert-based algorithms using identical input parameters (population characteristics and 100% adherence to diagnostic algorithms) for both algorithms. I then modelled interventions in the Xpert-based algorithm by varying adherence to the Xpert-based algorithm and varying the proportion who know their HIV status during TB diagnosis.

The model indicated a small increase in the number of TB cases detected (5.1%) with the real benefit of the Xpert-based algorithm the 102.6% increase in the number of RMP-R TB cases detected with only a 7.4% increase in the cost per RMP-R TB case detected between the smear/culture and Xpert-based algorithm. When adherence to the Xpert-based algorithm was increased from 50% to 100%, the number of RMP-R TB cases detected increased by 63.4%. Increasing the proportion who know their HIV status in the Xpert-based algorithm from 60% to 100% resulted in only a 4.6% increase in RMP-R TB cases detected. The Xpert-based algorithm is efficient in detecting RMP-R TB as the increase in costs is offset by the increase in the number of cases detected. Adherence to the Xpert-based algorithm is important to ensure all presumptive TB cases receive the benefit of simultaneous TB and RMP-R testing.

My contributions: In this chapter, I did the development and validation of the model. I conducted the overall data management and data analysis as well as conceived, designed and performed the experiments of running the different scenarios in the model. I wrote the manuscript and submitted the final manuscript for publication to the peer-reviewed journal.

Co-author contribution: Pren Naidoo, Ivor Langley and Nulda Beyers contributed with conceiving and designing experiments. The co-authors reviewed the draft manuscript and approved the final draft manuscript for submission.

Improving rifampicin resistant tuberculosis diagnosis with Xpert® MTB/RIF: modelling interventions and costs

Authors:

Rory Dunbar[1], Pren Naidoo[1], Nulda Beyers[1], Ivor Langley[2]

Affiliations:

[1]Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, South Africa
[2]Centre for Applied Heath Research and Delivery, Liverpool School of Tropical Medicine, Liverpool, United Kingdom

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Correspondence address:
Rory Dunbar: rdun@sun.ac.za

Conflicts of interest
The authors declare that they have no financial or non-financial conflicts of interests.

Setting

Cape Town, South Africa

Objective

To model RMP-R diagnosis and laboratory costs in smear/culture and Xpert-based algorithms and the effect of varying adherence and HIV testing in the Xpert-based algorithm.

Methods

We used a validated operational model (100,000 population) and published laboratory cost data. We estimated the number and cost of RMP-R TB cases identified between a smear/culture and Xpert-based algorithm. We modelled varying adherence and different levels of known HIV-status to the Xpert-based algorithm.

Results

RMP-R TB cases identified increased from 603 with smear/culture to 1,178 with the Xpert-based algorithm (100% adherence - 60% knew their HIV status). The overall laboratory cost increased from U$1,073,858 to U$2,430,050 and the cost per RMP-TB case identified increased from U$1,781 to U$2,063 in respective algorithms.

When adherence to the Xpert-based algorithm was increased from 50% to 100% (60% knew their HIV-status), the number of RMP-R TB cases identified increased from 721 to 1,178.

Conclusion

The Xpert-based algorithm is efficient in identifying RMP-R TB as the increase in costs is offset by the increase in the number of cases identified. Adherence to the Xpert-based algorithm is important to ensure all presumptive TB cases receive the benefit of simultaneous TB and RMP-R testing.

3.1 Introduction

Globally the multidrug-resistant tuberculosis (MDR-TB) crisis is continuing. The burden of MDR-TB is decreasing more slowly than the overall burden of tuberculosis (TB) and in some countries the MDR-TB burden is on the increase.[1] The World Health Organisation (WHO) collectively defines cases of MDR-TB (defined as resistance to rifampicin and isoniazid) and rifampicin-resistant (RMP-R) TB as MDR/RMP-R TB with the recommendation to start all these cases on a second-line MDR-TB regimen.[1]

The gaps between the estimated number of incident MDR/RMP-R TB cases, the number diagnosed and the number notified are still of major concern. Globally there were 3.4 million bacteriologically confirmed TB cases notified in 2015 of which only 30% were reported to have had a drug susceptibility test (DST) for rifampicin. In 2015, 132,120 cases of MDR/RMP-R TB were detected and notified globally which amounts to only 40% of the estimated 340,000 MDR/RMP-R TB cases that could have been detected had DST been provided to all pulmonary TB patients notified in 2015.[1]

In South Africa, there were a total of 294,603 TB cases notified in 2015 of whom 196,783 (66.8%) were tested for RMP resistance. Of the 19,613 MDR/RMP-R TB cases diagnosed only 12,527 were reported to have started treatment.[1]

The WHO endorsed the use of Xpert® MTB/RIF (Xpert) (Cepheid, Sunnyvale, CA, USA) in 2010[2] after which South Africa implemented Xpert in 2011 as a replacement test for smear microscopy for all presumptive TB cases. The introduction of the more sensitive Xpert test[2,3] offered improved TB case detection with the added benefit of simultaneous screening for RMP-R. The Xpert test makes it possible for a RMP-R TB result to be available in the laboratory within a few hours rather than in 2 to 6 weeks as would be the case with culture-based testing.[4] However, studies have reported variable adherence to the Xpert-based algorithm. A nationwide retrospective cohort study in South Africa assessing second-line treatment initiation reported that in 2013, after full national rollout of Xpert, only 59% of RMP-R TB cases received an initial Xpert test and 63% of RMP-R TB cases diagnosed started treatment.[5]

The PROVE IT (Policy Relevant Outcomes from Validating Evidence on ImpacT) Study evaluating the impact of Xpert in Cape Town, South Africa, compared the proportion of RMP-R TB cases diagnosed pre-treatment in the smear/culture-based and Xpert-based algorithms.[6] This study found that the proportion of TB cases with DST undertaken pre-treatment increased from 42.7% in the smear/culture-based algorithm to 78.9% in the Xpert-based algorithm. The proportion of TB cases with RMP-R diagnosed was 5.5% and 7.7% respectively - a 33.3% increase in RMP-R TB cases. A laboratory costing study in PROVE IT, reported a 42% increase in overall TB diagnostic costs and a 157% increase in the cost per TB case diagnosed with the transition from a smear/culture to the Xpert-based algorithm with a similar cost per MDR/RMP-R TB case diagnosed of US$190.14 and US$183.86 respectively.[7] Underlying differences in the populations tested (prevalence of TB, HIV coinfection and drug resistance, TB cases with a previously history of TB treatment) and adherence to the algorithms may have contributed to these findings and was a limitation in both studies.

This study used an operational model to compare the number and proportion of RMP-R TB cases identified, and the cost per RMP-R TB case identified between a smear/culture and an Xpert-based algorithm. Since adherence to the Xpert-based algorithm in South Africa has been sub-optimal, we evaluated the effect of increased adherence to the algorithm and increased HIV testing amongst presumptive TB cases (which influences the ability to diagnose Xpert-negative TB cases) on the number and proportion of RMP-R TB cases identified.

3.2 Methods

3.2.1 Definitions

Presumptive case: *We defined a presumptive TB case in the model as an individual who had pre-treatment sputum specimens collected for TB diagnostic purposes.*
TB case: *We defined a TB case in the model as an individual with culture positive TB, irrespective of how the individual was ultimately identified (i.e. tested positive by either sputum smear microscopy or culture or Xpert). False positive TB cases (true negative TB cases in the population as defined by culture, with a positive test result by either sputum smear microscopy or Xpert) identified in the model were excluded.*

RMP-R TB case: *We defined a RMP-R TB case in the model as a TB case with rifampicin resistance. False positive RMP-R TB cases (true negative RMP-R TB cases in the population as defined by culture and conventional DST, with a positive test* by either LPA or Xpert) *were excluded.*

Adherence to algorithm: *We defined adherence to an algorithm as the proportion of presumptive TB cases that received the full sequence of test as stipulated by the diagnostic algorithm (Figure 1).*[8]

3.2.2 Setting and timeframe

The study is set in Cape Town, one of the large cities in South Africa, with a population of 3.7 million in 2011 (National Census 2011). MDR/RMP-R case notification among TB cases increased from 3.6% (1,020/28,644) in 2011 to 4.4% (1,134/25,846) in 2013 (Routine TB Programme Data, Cape Town Health Directorate, April 2016).

In Cape Town, free TB diagnostic services are provided at 142 primary health care (PHC) facilities in eight health sub-districts. All TB diagnostic tests are performed at a central laboratory, National Health Laboratory Services (NHLS), with all sputum specimens collected for TB testing at PHC facilities couriered to NHLS on a daily basis for testing and results returned to facilities via courier and fax.

Up until August 2011 a smear/culture-based algorithm was in place in Cape Town and from August 2011 an Xpert-based algorithm was introduced with Xpert replacing smear microscopy as a 1st-line test (Figure 1). The rollout of the Xpert-based algorithm was completed by February 2013 (with 5 Xpert GX XVI modules placed at the laboratory[7]).

3.2.3 Model development

We developed and validated an operational model using routine National Health Laboratory data collected for the period 2010 to 2013 in Cape Town, including the period when Xpert was rolled out.[9] The Witness package[10], a discrete event and continuous process simulator, was used to develop a comprehensive model to represent the diagnosis of pulmonary TB and RMP-R TB in Cape Town. The model incorporated the TB diagnostic algorithms (Figure 1) and specimen flow from

specimen collection, through laboratory test procedures, to a test result being available at the laboratory. The model was developed for both the previous smear/culture-based and current Xpert-based algorithms as stipulated by the South African National TB programme.[8]

Further details regarding model development, validation as well as model sensitivity analysis was previously published.[9]

3.2.4 Model inputs

As part of the PROVE IT (Policy Relevant Outcomes from Validating Evidence on ImpacT) Study conducted in Cape Town, routine TB and MDR/RMP-R TB treatment data as well as NHLS data from presumptive TB cases had previously been collected and analysed to compare TB yield[11] and RMP-R TB yield[6] in the smear/culture and the Xpert-based algorithms. Input parameters for the model used probability distributions derived from these analyses (Table 2). We used identical input parameters to model the number and proportion of RMP-R TB cases identified amongst 100,000 presumptive TB cases screened in the smear/culture and Xpert-based algorithms.

Laboratory cost data per test in each algorithm were obtained from a costing evaluation undertaken at the high throughput central laboratory (NHLS) in Cape Town (Table 1).[7] Costs were calculated for sputum smear microscopy, culture, line probe assay (LPA) and Xpert and used to estimate total TB diagnostic costs in each algorithm (all expressed in 2013 values).

In the Xpert-based algorithm, we modelled scenarios with varying levels of adherence to the algorithm (at increments of 10% from 50% to 100%) and varying the proportion of presumptive TB cases that knew their HIV status (at 60%, 80% and 100%) since routine NHLS data showed that 50% of presumptive TB cases knew their HIV status in 2013.[9,11]

3.2.5 Model outputs and analysis

We firstly modelled the RMP-R TB cases identified and missed in the smear/culture and Xpert-based algorithms. We report the RMP-R cases identified as a number and

as a percentage of TB cases identified among the 100,000 presumptive TB cases evaluated.

The overall laboratory TB diagnostic costs per algorithm were calculated using model outputs on the number of tests undertaken and cost per test from the costing study (Table 1).[7] We calculated the cost per RMP-R TB case identified in both algorithms by dividing the total TB diagnostic costs by the number of RMP-R TB cases identified. We calculated the cost per additional RMP-R TB case identified in the Xpert-based algorithm by dividing the difference in total diagnostic costs by the difference in the number of RMP-R TB cases identified between the algorithms.

In order to evaluate the effect of varying adherence levels to the Xpert-based algorithm and varying proportion of HIV testing in the Xpert-based algorithm we compared the number and proportion of RMP-R TB cases identified and missed in each scenario.

3.3 Ethics statement

The Health Research Ethics Committee at Stellenbosch University (IRB0005239) (N10/09/308) and Ethics Advisory Group at The International Union Against Tuberculosis and Lung Disease (59/10) approved the study. The City of Cape Town Health Directorate, Western Cape Health Department and National Health Laboratory Service granted permission to use routine health data.

3.4 Results

3.4.1 Model outputs for the smear/culture and Xpert-based algorithms at 100% adherence to algorithms

3.4.1.1 RMP-R TB cases identified

The model indicated that if 60% of presumptive cases knew their HIV status, 603 RMP-R cases (3.9% of 15,475 TB cases) were identified in the smear/culture compared to 1,178 RMP-R cases (7.2% of 16,332 TB cases) identified in the Xpert-based algorithm.

When 100% of presumptive cases knew their HIV status, 608 RMP-R cases (3.8% of 16,144 TB cases) were identified in the smear/culture compared to 1,232 RMP-R cases (7.3% of 16,968 TB cases) in the Xpert-based algorithm (Table 3).

3.4.1.2 RMP-R TB cases missed

In the scenario where 60% of presumptive cases knew their HIV status, a total of 795 (56.9%) RMP-R cases were missed in the smear/culture-based algorithm: 231 (16.5%) had a false negative TB test, 13 (0.9%) had a false negative RMP-R result and 551 (39.4%) had no DST done pre-treatment. In the Xpert-based algorithm a total of 220 (15.7%) RMP-R cases were missed: 144 (10.3%) had a false negative TB test, 76 (5.4%) had a false negative RMP-R result and all presumptive cases were screened for RMP resistance pre-treatment (Table 3).

When 100% of presumptive cases knew their HIV status, a total of 790 (56.5%) RMP-R cases were missed in the smear/culture-based algorithm: 226 (16.2%) had a false negative TB test, 13 (0.9%) had a false negative RMP-R result and 551 (39.4%) had no DST done pre-treatment. In the Xpert-based algorithm a total of 166 (11.9%) RMP-R cases were missed: 88 (6.3%) had a false negative TB test, 78 (5.6%) had a false negative RMP-R result and all presumptive cases were screened for RMP resistance pre-treatment (Table 3).

3.4.1.3 Laboratory costs

In the scenario where 60% of presumptive TB cases knew their HIV status the overall laboratory TB diagnostic cost was U$1,073,858 in the smear/culture and U$2,430,050 in the Xpert-based algorithm. The cost per RMP-R TB case identified was U$1,781 in the smear/culture compared to U$2,063 in the Xpert-based algorithm. If 100% of presumptive TB cases knew their HIV status the overall laboratory TB diagnostic costs were U$1,240,777 and U$2,700,384 respectively and the costs per RMP-R TB case identified were U$2,041 and U$2,192 respectively.

The cost per additional RMP-R TB cases identified in the Xpert compared to smear/culture-based algorithm was US$2,359 and US$2,339 in scenarios when 60% and 100% respectively knew their HIV status (Table 3).

3.4.2 Model outputs for an Xpert-based algorithm with varying adherence to the algorithm

3.4.2.1 RMP-R TB cases identified

In scenarios where 60% of presumptive cases knew their HIV status and with 50% adherence to the algorithm, 721 RMP-R cases (4.7% of 15,398 TB cases) were identified, increasing to 1,178 (7.2% of 16,332 TB cases) RMP-R cases identified with 100% adherence to the algorithm.

In scenarios where 100% of presumptive cases knew their HIV status and with 50% adherence to the algorithm, 742 RMP-R cases (4.7% of 15,892 TB cases) were identified, increasing to 1,232 (7.3% of 16,968 TB cases) RMP-R cases with 100% adherence to the algorithm (Table 4, Figure 2 and 3).

3.4.2.2 RMP-R TB cases missed

In a scenario when 60% of presumptive cases knew their HIV status and with 50% adherence in the Xpert-based algorithm, 677 (48.4%) RMP-R cases were missed: 240 (17.2%) had a false negative TB test, 40 (2.9%) had a false negative RMP-R result and 397 (28.4%) had no DST done pre-treatment. When adherence increased to 100%, 220 (15.7%) RMP-R cases were missed: 144 (10.3%) had a false negative TB test, 76 (5.4%) had a false negative RMP-R result and all cases had a DST done pre-treatment (Table 4, Figures 3).

3.4.3 Model outputs for an Xpert-based algorithm with varying proportion of presumptive cases that knew their HIV status

3.4.3.1 RMP-R TB cases identified

In scenarios where we set adherence to the algorithm at 50% and varied the proportion of presumptive cases who knew their HIV status, 721 RMP-R cases (4.7% of 15,398 TB cases) were identified when 60% of presumptive TB cases knew their HIV-status increasing to 742 RMP-R cases (4.7% of 15,892 TB cases) when 100% knew their HIV status.

When we set adherence at 100% 1,178 RMP-R cases (7.2% of 16,332 TB cases) were identified when 60% knew their HIV status increasing to 1,232 RMP-R cases (7.3% of 16,968 TB cases) when 100% knew their HIV status (Table 4, Figures 2 and 3).

3.4.3.2 RMP-R TB cases missed

In a scenario when 60% of presumptive cases knew their HIV status and with 50% adherence in the Xpert-based algorithm, 677 (48.4%) RMP-R cases were missed: 240 (17.2%) had a false negative TB test, 40 (2.9%) a false negative RMP-R result and 397 (28.4%) had no DST done pre-treatment. When 100% knew their HIV status 656 (46.9%) RMP-R cases were missed: 217 (15.5%) had a false negative TB test, 42 (3.0%) had a false negative RMP-R result and 397 (28.4%) were not screened for RMP-R pre-treatment (Table 4, Figures 3).

3.5 Discussion

In many countries, including South Africa, DST was historically limited to presumptive TB cases with a history of previous TB treatment as these cases have a higher risk than new cases of developing MDR-TB.[12–14] Therefore, in the smear/culture-based algorithm DST was limited to those with a history of previous TB treatment, MDR-TB contacts or those in congregate settings. It was assumed that the small number of new TB case with MDR-TB missed pre-treatment would start 1st-line TB treatment and would eventually be diagnosed with MDR-TB when 1st-line treatment failed. In contrast, with the Xpert-based algorithm all presumptive TB cases receive an Xpert test and are simultaneously screened for RMP-R.

The PROVE IT Study which used a non-randomised stepped-wedge design to compare TB yield between the smear/culture and Xpert-based algorithms found no difference in TB yield between algorithms[11]. Possible factors contributing to this finding included the following: (1) a decline in TB prevalence over time; (2) higher than expected use of culture in the smear/culture-based algorithm; (3) limited use of culture for HIV-infected Xpert-negative cases; (4) and poor adherence to the Xpert-based algorithm. Despite this, the PROVE IT study found a 54% increase in the number of RMP-R TB cases diagnosed pre-treatment (from 269 to 415)[6], which may be an underestimate of the benefit of the Xpert-based algorithm on RMP-R TB

diagnosis. The model allowed us to address these issues and enabled comparison of the two algorithms with similar adherence and identical population characteristics.

The model showed small differences in the number of TB cases identified (Table 3) between the smear/culture and Xpert-based algorithms (a 5.5% and 5.1% increase in TB yield when 60% and 100% of presumptive cases respectively knew their HIV status). The real benefit of the Xpert-based algorithm was the 95.4% and 102.6% increase in the number of RMP-R TB cases identified when 60% and 100% of presumptive cases respectively knew their HIV status. The overall laboratory costs between algorithms increased by 126.3% and 117.6% when 60% and 100% of presumptive cases respectively knew their HIV status. These costs were off-set by the increase in the number of RMP-R TB cases identified, resulting only in a 15.8% and 7.4% increase respectively in the cost per RMP-R TB case identified in the Xpert-based algorithm.

In the Xpert-based algorithm, cases not tested by Xpert were tested by the previous smear/culture-based algorithm. When adherence to the Xpert-based algorithm was increased from 50% to 100%, the number of RMP-R TB cases identified increased by 63.4% if 60% of presumptive TB cases knew their HIV-status (Table 4). This illustrates the importance of simultaneous screening for TB and RMP-R, as occurs with adherence to the Xpert-based algorithm.

Increasing the proportion of presumptive TB cases who knew their HIV status had very little effect on the number of RMP-R TB cases identified in the Xpert-based algorithm. When the proportion was increased from 60% to 100%, the number of RMP-R TB identified increased by 2.9% and 4.6% at 50% and 100% adherence respectively. However, HIV-testing of presumptive TB cases does have other clinical importance, for example access to antiretroviral therapy.

3.5.1 Strengths and limitations

The strengths of the current study are that we used a validated model, based on real data on testing and diagnosis, to estimate the number and cost per RMP-R TB cases identified in the smear/culture and Xpert-based algorithms. Our study provides a better estimate of these as the PROVE IT laboratory costing and RMP-R TB yield

studies included false-positive TB and RMP-R TB cases and the population tested in the Xpert and smear/culture eras may have had different characteristics.[6,7,11]

The model was validated against data from Cape Town, a well-resourced urban setting where there was extensive use of culture. This may limit the generalisability of our findings to other settings.

3.6 Conclusion

The model showed a substantial increase in the number of RMP-R TB cases identified with a transition from a smear/culture to an Xpert-based algorithm even though the increase in the number of TB cases identified was small. The Xpert-based algorithm was relatively efficient in diagnosing RMP-R TB cases as the overall increase in laboratory costs was offset by the increased number of RMP-R TB cases identified. Our model highlights the importance of adherence to the Xpert-based algorithm in order to ensure that all presumptive TB cases receive an Xpert test and are simultaneously tested for TB and RMP-R.

The value of this operational model is that future new diagnostic tests and their use in a TB diagnostic algorithm, within an operational setting, can be evaluated.

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Authors contributions: RD, PN, NB, and IL designed the study. RD conducted the modelling and data analysis and wrote the first draft of the Article. All authors reviewed.

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Table 1: Test costs for sputum smear microscopy, culture, line probe assay and Xpert in the smear/culture and Xpert-based algorithms (Reprinted with permission of the International Union Against Tuberculosis and Lung Disease. Copyright © The Union)*[7]

	Smear microscopy (Bleach treated) US$	Smear microscopy & culture US$	Culture confirmation US$	MTBDRplus line-probe assay US$	Xpert US$
Smear/culture-based algorithm					
Building space	0.02	0.14	0.05	0.15	-
Equipment	0.11	0.72	0.02	0.17	-
Consumables	0.36	3.87	0.84	12.67	-
Staff	0.55	2.21	0.57	1.34	-
Overheads[#]	1.80	1.80	0.00	1.80	-
Cost per test	2.85	8.75	1.49	16.12	-
Xpert-based algorithm					
Building space	0.02	0.14	0.05	0.15	0.06
Equipment	0.13	0.74	0.02	0.18	0.40
Consumables	0.36	3.87	0.84	12.67	14.62
Staff	0.55	2.21	0.57	1.34	1.32
Overheads[#]	2.64	2.64	0.00	2.64	2.64
Cost per test	3.70	9.62	1.49	16.98	19.03

**Test costs are for the central National Health Laboratory only. All costs are expressed in 2013 CPI-adjusted values. Overhead costs included costs for buildings, equipment, consumables and staff involved in specimen sorting and registration, results processing, procurement, stores, training, supervision and management. Specimen transport, electricity, water, sanitation, municipal and biohazardous waste disposal, cleaning and janitorial services, security services and telephone and Internet costs were also included. In each scenario tested, we determined the number of tests performed per algorithm, applied the above costs and calculated the cost per TB and RMP-R TB case identified.*

Table 2: Input parameters used for the smear/culture and Xpert-based algorithms

			Input values (%)	
			New presumptive cases	Previously treated presumptive cases
			75	25
HIV status		HIV-positive	36	54
		HIV-negative	64	46
Best estimated TB prevalence amongst presumptive cases			18	21
Estimated proportion of RMP-R cases amongst TB cases			6	12
Accuracy of fluorescence light-emitting diode (LED) smear microscopy[15,16] (1 specimen)	Sensitivity	HIV-positive	55	
		HIV-negative	60	
	Specificity	HIV-positive	99	
		HIV-negative	99	
Accuracy of fluorescence light-emitting diode (LED) smear microscopy[15,16] (2 specimens)	Sensitivity	HIV-positive	65	
		HIV-negative	75	
	Specificity	HIV-positive	99	
		HIV-negative	99	
Accuracy of Xpert MTB/RIF for TB[17]	Sensitivity	HIV-positive	80	
		HIV-negative	89	
	Specificity	HIV-positive	98	
		HIV-negative	98	
Accuracy of GenoType® MTBDRplus LPA for RMP-R TB[18]	Sensitivity	HIV-positive	98	
	Specificity	HIV-positive	98	
Accuracy of Xpert MTB/RIF for RMP-R TB[17]	Sensitivity	HIV-positive	94	
	Specificity	HIV-positive	98	

NHLS data from presumptive cases had been analysed previously as part of the PROVE IT (Policy Relevant Outcomes from Validating Evidence on ImpacT) study. Input parameters derived from these analyses were used as probability distributions for the model.[6,9,11] Test sensitivity and specificity is provided relative to culture and phenotypic culture-based DST.

Table 3: The number and percentage of TB and RMP-R TB cases identified in a smear/culture compared to an Xpert-based algorithm and laboratory diagnostic cost for both algorithms

	Smear/Culture-based algorithm n (%)			Xpert-based algorithm n (%)			Relative % difference in Xpert compared to smear/culture-based algorithm		
	% knew their HIV status*			% knew their HIV status*			% knew their HIV status*		
	60	80	100	60	80	100	60	80	100
TB cases identified	15,475 (15.5)	15,810 (15.8)	16,144 (16.1)	16,332 (16.3)	16,670 (16.7)	16,968 (17.0)	5.5	5.4	5.1
RMP-R TB cases identified	603 (3.9)	607 (3.8)	608 (3.8)	1,178 (7.2)	1,201 (7.2)	1,232 (7.3)	95.4	97.9	102.6
RMP-R TB cases missed and the reasons why they were missed (% of total RMP-R TB cases)									
False negative TB test	231 (16.5)	227 (16.2)	226 (16.2)	144 (10.3)	120 (8.6)	88 (6.3)			
False negative RMP-R result	13 (0.9)	13 (0.9)	13 (0.9)	76 (5.4)	77 (5.5)	78 (5.6)			
No DST done	551 (39.4)	551 (39.4)	551 (39.4)	0	0	0			
Laboratory diagnostic cost									
Total TB diagnostic costs	1,073,858	1,159,092	1,240,777	2,430,050	2,567,444	2,700,384	126.3	121.5	117.6
Cost per RMP-R TB case identified	1,781	1,910	2,041	2,063	2,138	2,192	15.8	12.0	7.4
Cost per additional RMP-R TB case identified				2,359	2,371	2,339			

Amongst the population of 100,000 presumptive TB cases there were 18,155 true TB cases and 1,398 true RMP-R TB cases. Adherence to algorithms at 100%. All costs are expressed in 2013 CPI-adjusted values and in US$.

* Proportion of presumptive TB cases that knew their HIV status.

Table 4: The number and percentage of TB and RMP-R TB cases identified in an Xpert-based algorithm with varying adherence to the algorithm and proportion that knew their HIV status

	Adherence to the Xpert-based algorithm					
	50%	60%	70%	80%	90%	100%
TB cases identified						
60% knew their HIV status	15,398 (15.4)	15,610 (15.6)	15,926 (15.9)	16,116 (16.1)	16,243 (16.2)	16,332 (16.3)
80% knew their HIV status	15,659 (15.7)	15,916 (15.9)	16,226 (16.2)	16,415 (16.4)	16,568 (16.6)	16,670 (16.7)
100% knew their HIV status	15,892 (15.9)	16,213 (16.2)	16,531 (16.5)	16,719 (16.7)	16,869 (16.9)	16,968 (17.0)
RMP-R TB cases identified						
60% knew their HIV status	721 (4.7)	855 (5.5)	963 (6.0)	1,034 (6.4)	1,122 (6.9)	1,178 (7.2)
80% knew their HIV status	730 (4.7)	869 (5.5)	979 (6.0)	1,051 (6.4)	1,146 (6.9)	1,201 (7.2)
100% knew their HIV status	742 (4.7)	884 (5.5)	996 (6.0)	1,074 (6.4)	1,166 (6.9)	1,232 (7.3)
RMP-R TB cases missed and the reasons why they were missed (% of total RMP-R TB cases)						
False negative TB test						
60% knew their HIV status	240 (17.2)	184 (13.2)	174 (12.4)	165 (11.8)	138 (9.9)	144 (10.3)
80% knew their HIV status	228 (16.3)	172 (12.3)	159 (11.4)	146 (10.4)	116 (8.3)	120 (8.6)
100% knew their HIV status	217 (15.5)	156 (11.2)	141 (10.1)	122 (8.7)	97 (6.9)	88 (6.3)
False negative RMP-R result						
60% knew their HIV status	40 (2.9)	52 (3.7)	59 (4.2)	65 (4.6)	76 (5.4)	76 (5.4)
80% knew their HIV status	43 (3.1)	50 (3.6)	58 (4.1)	67 (4.8)	74 (5.3)	77 (5.5)
100% knew their HIV status	42 (3.0)	51 (3.6)	59 (4.2)	68 (4.9)	73 (5.2)	78 (5.6)
No DST done						
60% knew their HIV status	397 (28.4)	307 (22.0)	202 (14.4)	134 (9.6)	62 (4.4)	0
80% knew their HIV status	397 (28.4)	307 (22.0)	202 (14.4)	134 (9.6)	62 (4.4)	0
100% knew their HIV status	397 (28.4)	307 (22.0)	202 (14.4)	134 (9.6)	62 (4.4)	0

Amongst the population of 100,000 presumptive TB cases there were 18,155 true TB cases and 1,398 true RMP-R TB cases.

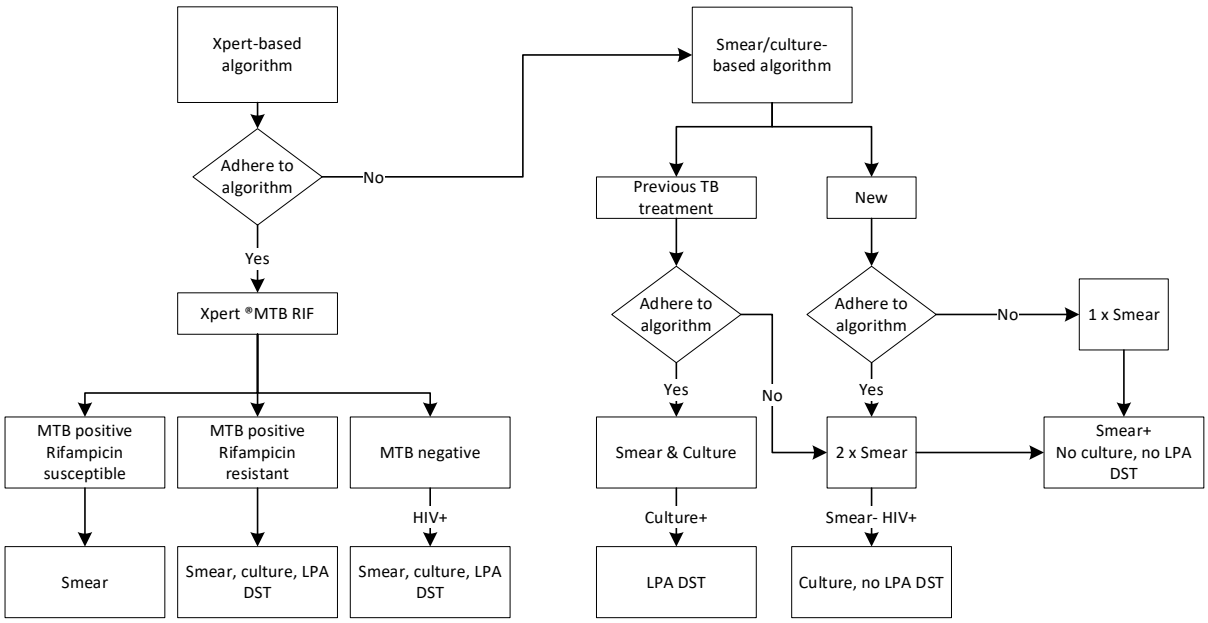

Figure 1: TB diagnostic algorithms as stipulated by the South African National TB program.[8] The simplified sequence of diagnostic tests in each algorithm and the action taken based on test results are shown.
With the Xpert-based algorithm, two spot specimens were collected and the first was tested with Xpert. If TB was detected, the second specimen underwent smear and if RMP-R was detected, a culture and LPA test was undertaken. The second specimen underwent culture and LPA if the Xpert test was negative and the individual was HIV-infected.
With the smear/culture-based algorithm, all presumptive TB cases were required to submit two spot sputum specimens an hour apart to be tested with fluorescence smear microscopy. The second specimen underwent culture testing (BACTEC™ MGIT™ 960; BD, Spark, MD, USA) if the individual had a history of previous TB treatment, was from a congregate setting or had an MDR-TB contact. If culture-positive, a DST using GenoType® MTBDRplus LPA was undertaken. All new, smear-negative HIV-infected individuals required a culture test to diagnose paucibacillary TB, however a DST was not required pre-treatment.
In both algorithms, new and previously treated cases in which first line TB treatment regimens failed had specimens submitted for culture and LPA during the course of treatment.
Abbreviations: TB - tuberculosis; HIV – human immunodeficiency virus; MTB – mycobacterium tuberculosis; RIF – rifampicin; DST - drug susceptibility test; LPA - line-probe assay.

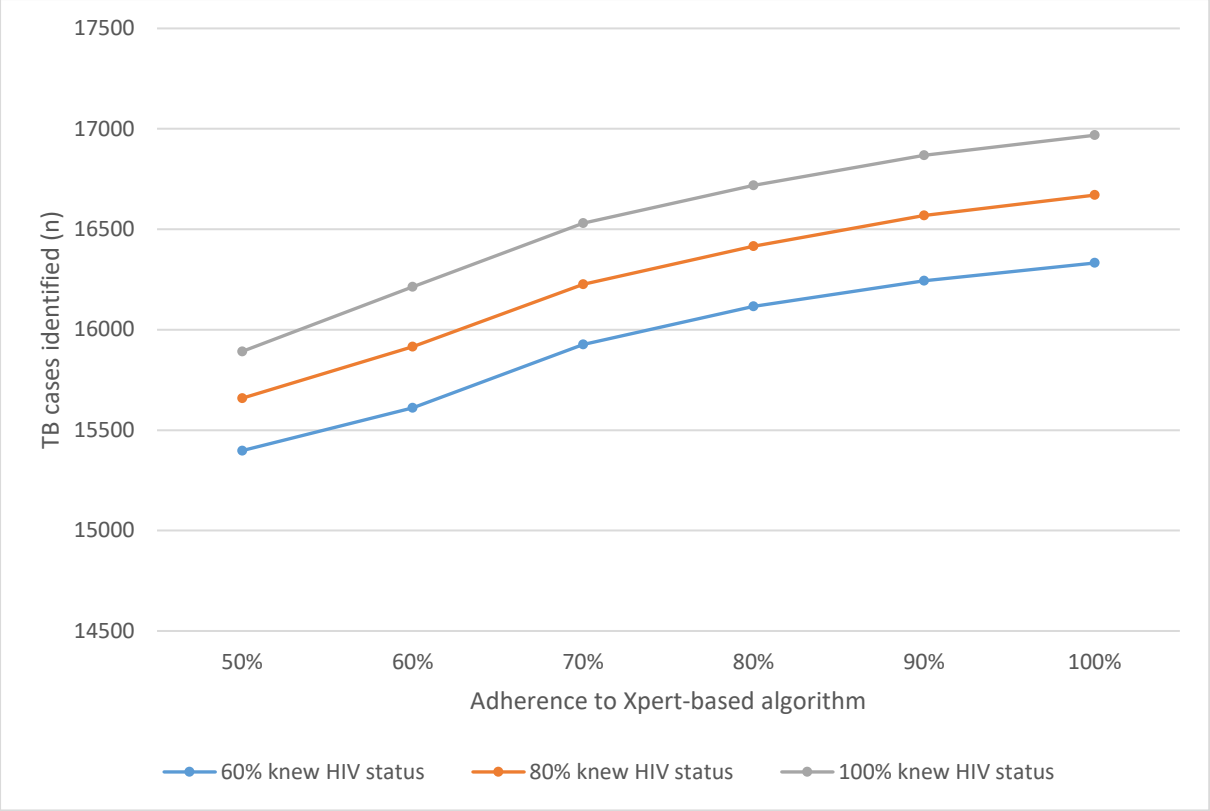

Figure 2: The number of TB cases identified in an Xpert-based algorithm with varying adherence to the algorithm and proportion that knew their HIV status. TB = tuberculosis; HIV = human immunodeficiency virus.

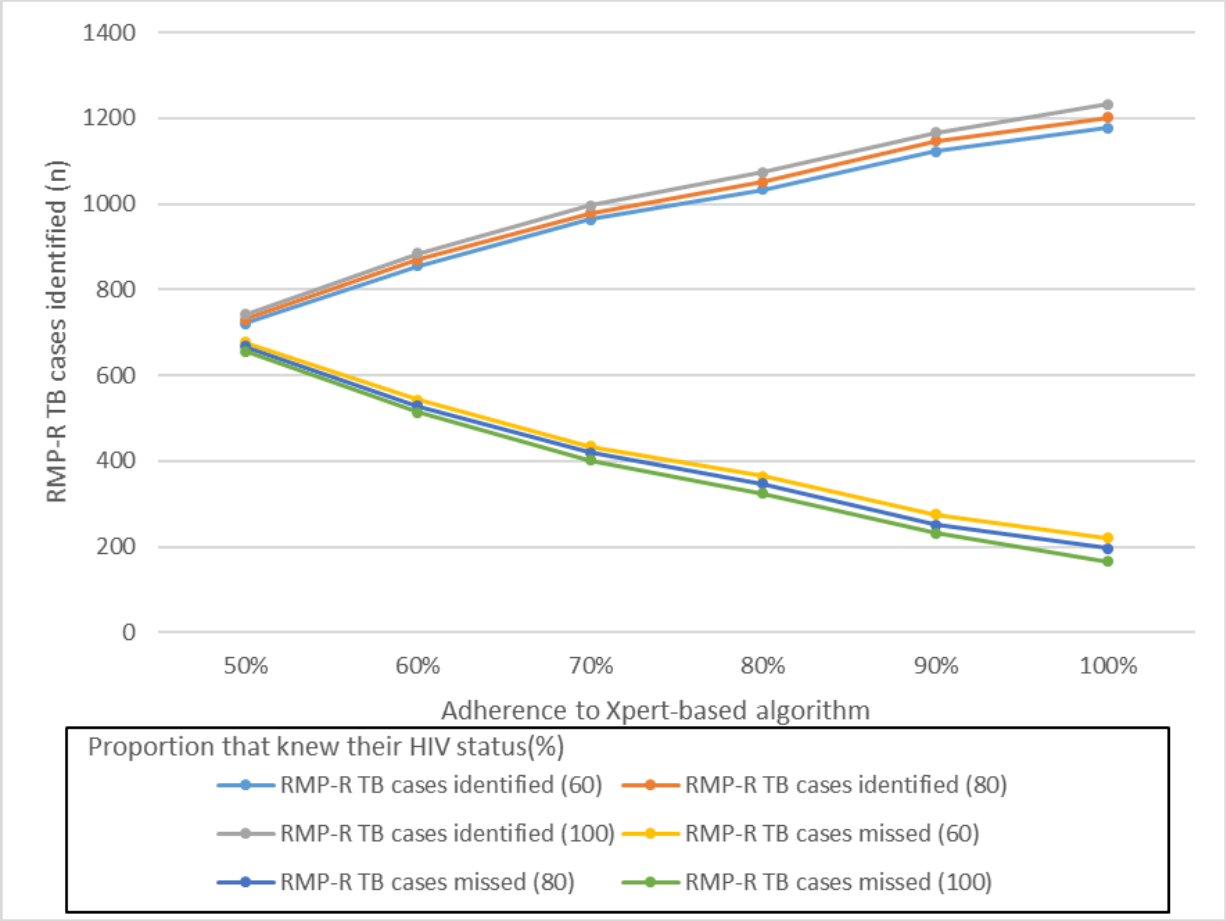

Figure 3: Number of RMP-R TB cases identified and missed in an Xpert-based algorithm with varying adherence to the algorithm and proportion that knew their HIV status. RMP-R TB = rifampicin resistant tuberculosis; HIV = human immunodeficiency virus

Chapter 4: High laboratory cost predicted per tuberculosis case diagnosed with increased case finding without a triage strategy

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Summary: In this chapter, I model strategies to reduce the cost per TB case detected. I use a validated operational model representing TB diagnosis in Cape Town for both the smear/culture and Xpert-based algorithms and published laboratory cost data. I modelled the effect of varying the prevalence of TB among presumptive cases; decreased (as would occur if case-finding was scaled-up) and increased (as would occur if a triage screening test was used). I also reduced the price per Xpert cartridge by 10%, 25% and 50% and assessed the effect on cost per TB case detected.

The model indicated that with a TB prevalence among presumptive cases of 18.3% (best estimate from empirical analysis) the cost per TB case detected increased by 142% between the smear/culture and Xpert-based algorithm with only an 8.7% increase in TB cases detected. If the TB prevalence among presumptive cases was 10.6% and with a 50% reduction in the price of Xpert cartridges, the cost per TB case detected is still high, at US$142. With a further increase (relative to the estimated 18.3%) in TB prevalence among presumptive cases tested to between 25.9% – 30.8% and the price of the Xpert cartridge reduced by 50%, the cost per TB case detected would range from US$50 to US$59 (comparable to the US$48.77 found in routine practice with smear/culture). Unless triage strategies are identified, the cost per TB case detected with increased case-finding will not be sustainable, even if Xpert cartridge prices are reduced.

My contributions: In this chapter, I conducted the overall data management and data analysis as well as conceived, designed and performed the experiments of running the different scenarios in the model. I wrote the manuscript and submitted the final manuscript for publication to the peer-reviewed journal.

Co-author contribution: Pren Naidoo, Ivor Langley and Nulda Beyers contributed with conceiving and designing experiments. The co-authors reviewed the draft manuscript and approved the final draft manuscript for submission.

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High laboratory cost predicted per tuberculosis case diagnosed with increased case finding without a triage strategy

R. Dunbar,* P. Naidoo,* N. Beyers,* I. Langley†

*Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, South Africa; †Centre for Applied Heath Research and Delivery, Liverpool School of Tropical Medicine, Liverpool, UK

SUMMARY

SETTING: Cape Town, South Africa.

OBJECTIVE: To model the effects of increased case finding and triage strategies on laboratory costs per tuberculosis (TB) case diagnosed.

METHODS: We used a validated operational model and published laboratory cost data. We modelled the effect of varying the proportion with TB among presumptive cases and Xpert cartridge price reductions on cost per TB case and per additional TB case diagnosed in the Xpert-based vs. smear/culture-based algorithms.

RESULTS: In our current scenario (18.3% with TB among presumptive cases), the proportion of cases diagnosed increased by 8.7% (16.7% vs. 15.0%), and the cost per case diagnosed increased by 142% (US$121 vs. US$50). The cost per additional case diagnosed was US$986. This would increase to US$1619 if the proportion with TB among presumptive cases was 10.6%. At 25.9–30.8% of TB prevalence among presumptive cases and a 50% reduction in Xpert cartridge price, the cost per TB case diagnosed would range from US$50 to US$59 (comparable to the US$48.77 found in routine practice with smear/culture).

CONCLUSION: The operational model illustrates the effect of increased case finding on laboratory costs per TB case diagnosed. Unless triage strategies are identified, the approach will not be sustainable, even if Xpert cartridge prices are reduced.

KEY WORDS: TB diagnostic; diagnostic cost; operational modelling; simulation

DESPITE A 22% REDUCTION in the number of deaths in the last 15 years, tuberculosis (TB) remained one of the top 10 causes of death worldwide in 2015. Although the global TB incidence rate declined by 1.4% per year in this period, 10.4 million incident cases were reported globally in 2015.[1] There are still major gaps in TB case finding and diagnosis, with the World Health Organization (WHO) estimating that one third of incident TB cases are either missed through current TB screening and diagnostic efforts or are not notified.[2]

As part of the End TB Strategy, three people-centred targets were introduced, which consist of reaching 90% of all people who need anti-tuberculosis treatment, including 90% of people in key populations and achieving at least 90% treatment success rates. The strategy recommends that countries set an operational target of reaching at least 90% of people in key populations through improved access to services, systematic screening, where required, and new case-finding methods, and of providing all people in need with effective and affordable treatment.[1,3]

The South African Department of Health plans to substantially scale up case-finding efforts based on the End TB Strategy. This has cost implications, as the cost per presumptive TB case tested and diagnosed with TB is higher with Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA), which was introduced in 2013, than with the previous smear/culture-based algorithm. Two studies in South Africa reported a cost per Xpert test performed of US$25.90 (in 2010 $US)[4] and US$14.93 (in 2012 $US) compared with respectively US$1.58 and US$3.40 for smear.[5] A study conducted in Cape Town, South Africa, found that the cost per TB case diagnosed increased by 157%, from US$48.77 in the previous smear/culture-based algorithm to US$125.32 in the newly introduced Xpert-based algorithm.[6] A study conducted in India, evaluating the costs of various pulmonary TB diagnostic strategies, found that the strategy with Xpert as the first-line test had the highest cost per TB case diagnosed.[7]

Correspondence to: Rory Dunbar, Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Francie Van Zijl Dr, Tygerberg Hospital, Cape Town 7505, South Africa. e-mail: rdun@sun.ac.za

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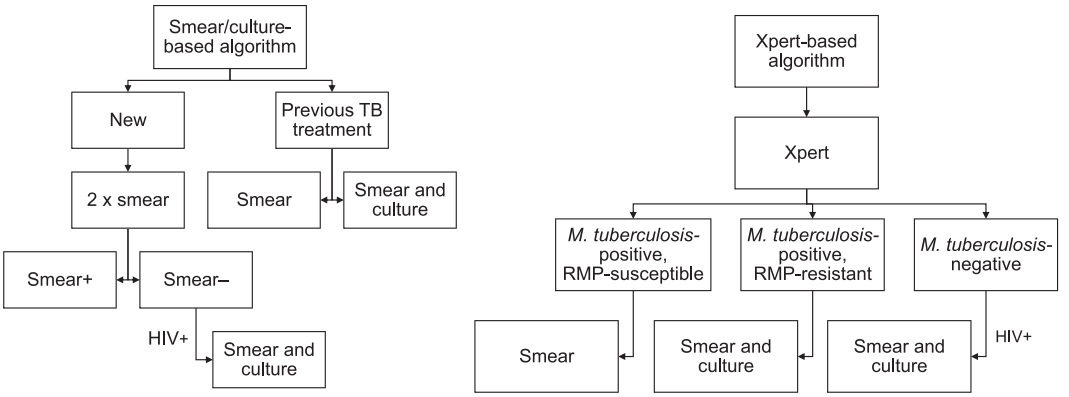

Figure 1 TB diagnostic algorithms. Diagnostic algorithms as stipulated by the South African National TB programme.[11] The simplified sequence of diagnostic tests in each algorithm and the action taken based on test results is shown. TB = tuberculosis; + = positive; − = negative; HIV = human immunodeficiency virus; RMP = rifampicin.

The scale-up of case-finding efforts and the introduction of alternative case-finding strategies, such as improved sensitivity and specificity of pre-screening strategies[8] or a triage-screening test,[9,10] will have an effect on the proportion of TB prevalence among presumptive cases. As case-finding efforts are scaled up and more people are screened for TB, the proportion with TB among those tested is likely to decline, and the cost per TB case diagnosed will consequently increase. There is little evidence at present on what the proportion of TB among presumptive cases should be to optimise the cost of diagnosing a case of TB.

The aim of the present study was to use an operational model to simulate the effect of a decrease (scale-up of case finding) and an increase (triage screening test) in the proportion of TB cases among presumptive cases tested on laboratory cost 1) per TB case diagnosed and 2) per additional TB case diagnosed in the Xpert-based compared with the smear/culture-based algorithm. We also assessed the effect on laboratory costs if the Xpert cartridge price was reduced.

METHODS

Setting

The operational model was developed for the TB diagnostic algorithms implemented in Cape Town, one of the largest cities in South Africa, with a population of 3 740 025 in 2011 (National Census 2011). In 2011, 28 644 TB cases were reported (case notification rate 752 per 100 000 population), and among the 97% of cases tested for human immunodeficiency virus (HIV), 47% of TB cases were co-infected with HIV (Source: Routine TB Programme Data, Cape Town Health Directorate, Cape Town, South Africa, April 2016).

Municipal and provincial health authorities provided TB diagnostic services at 142 primary health care (PHC) facilities. All sputum samples collected for TB testing at PHC facilities were couriered to the central National Health Laboratory Services (NHLS) on a daily basis for testing, and results were returned to the facilities via courier and fax.

A smear/culture-based algorithm (Figure 1) was used in all facilities until August 2011; all presumptive cases were required to submit two spot sputum samples 1 h apart. Previously treated presumptive cases as well as new smear-negative cases co-infected with HIV underwent culture using BACTEC™ MGIT™ 960 (BD, Sparks, MD, USA).

Between August 2011 and February 2013, an Xpert-based algorithm (Figure 1) was phased in, with Xpert replacing smear microscopy for all presumptive cases; after February 2013, all facilities used the Xpert-based algorithm. The first of two sputum samples submitted was tested using Xpert. In HIV-infected cases who were Xpert-negative, the second sample underwent culture.

Definitions

Presumptive case: for this model, presumptive cases were those who accessed the PHC facilities and had sputum samples collected for TB testing.

TB case: a TB case was defined in the model as an individual with culture-positive TB, irrespective of how the individual was ultimately diagnosed (i.e., test positive on sputum smear microscopy, culture or Xpert). False-positive cases were thus excluded.

Model development

A comprehensive operational model representing TB diagnosis in Cape Town PHC facilities has been developed using the Witness package (Lanner, Redditch, UK), a discrete event and continuous process simulator.[12] The model was validated for both the historic smear/culture and newly introduced Xpert-based algorithm using routine programmatic data,[13] and the findings were published.[14] The model incorporated patient pathways and sample flow from specimen collection and laboratory test procedures to

Table 1 Test costs for sputum smear microscopy, culture and Xpert® MTB/RIF by algorithm.* (Reprinted with permission of the International Union Against Tuberculosis and Lung Disease. Copyright © The Union)[6]

	Smear microscopy (bleach-treated) US$	Smear microscopy and culture US$	Culture confirmation US$	Xpert US$
Smear/culture-based algorithm				
Building space	0.02	0.14	0.05	—
Equipment	0.11	0.72	0.02	—
Consumables	0.36	3.87	0.84	—
Staff	0.55	2.21	0.57	—
Overheads†	1.80	1.80	0.00	—
Cost per test	2.85	8.75	1.49	—
Xpert-based algorithm				
Building space	0.02	0.14	0.05	0.06
Equipment	0.13	0.74	0.02	0.40
Consumables	0.36	3.87	0.84	14.62
Staff	0.55	2.21	0.57	1.32
Overheads†	2.64	2.64	0.00	2.64
Cost per test	3.70	9.62	1.49	19.03

* Test costs are for the central National Health Laboratory only. All costs are expressed in 2013 CPI-adjusted values.
† Includes costs for buildings, equipment, consumables and the staff involved in specimen sorting and registration, results processing, procurement, stores, training, supervision and management. Specimen transport, electricity, water, sanitation, municipal and biohazardous waste disposal, cleaning and janitorial services, security services and telephone and internet costs were also included. In each scenario tested, we determined the number of tests performed per algorithm, applied the above costs and calculated the cost per tuberculosis case diagnosed.
CPI = Consumer Price Index.

a result being provided to the patient and treatment being initiated at the PHC facility.

Laboratory cost data

Laboratory cost data per test in each algorithm were obtained from a costing evaluation undertaken at the high-throughput central laboratory (NHLS) in Cape Town.[6] An ingredients-based costing approach was used, with test cost based on building cost per m^2, equipment, consumables, staff and overheads (Table 1).[6] Costs were calculated only for sputum smear microscopy, culture and Xpert, and were used to estimate diagnostic costs in each algorithm as appropriate. The cost of drug susceptibility testing was not considered in the current model.

Model inputs

For direct comparisons of cost per TB case diagnosed between algorithms, we modelled both algorithms with identical input parameters for the proportion with TB among the presumptive cases being tested, HIV status, history of previous anti-tuberculosis treatment and adherence to testing protocols.[14] The model input parameters used for both the smear/culture and Xpert-based algorithms are summarised in Table 2.

Simulated scenarios

We modelled scenarios in which we reduced and increased the proportion with TB among presumptive cases being tested. From our previous analysis, the most likely estimate for the proportion with TB among presumptive cases tested was 18.3%, which we selected as our starting point.[14] We varied the proportion to a low of 3.0% (scenarios 6–11) and a high of 30.8% (scenarios 1–5). We also assessed the effect on cost per TB case diagnosed if the price per Xpert cartridge was reduced by 10%, 25% and 50%.

Table 2 Input parameters used comparing the smear/culture and Xpert® MTB/RIF based algorithms

	Input values %
History of previous anti-tuberculosis treatment	25
HIV status*	
New presumptive cases	
HIV-positive	36
HIV-negative	64
Previously treated presumptive cases	
HIV-positive	53
HIV-negative	47
Proportion knowing their HIV status	50
Best estimated proportion of TB cases among presumptive cases	18.3†
Adherence to a smear/culture-based algorithm	
New presumptive cases with 2 smears	85
Previously treated presumptive cases with culture	85
Adherence to the Xpert-based algorithm	
All presumptive cases with the Xpert test performed	85
Proportion smear or Xpert-negative with culture	
Smear/culture-based algorithm	
New presumptive cases	
HIV-positive	85
HIV-negative	0
Previously treated presumptive cases	
HIV-positive	85
HIV-negative	0
Xpert-based algorithm	
New presumptive cases	
HIV-positive	85
HIV-negative	0
Previously treated presumptive cases	
HIV-positive	85
HIV-negative	0
Accuracy of smear microscopy[15,16]	
Sensitivity	
HIV-positive	65
HIV-negative	75
Specificity	
HIV-positive	99
HIV-negative	99
Accuracy of Xpert[17]	
Sensitivity	
HIV-positive	80
HIV-negative	89
Specificity	
HIV-positive	98
HIV-negative	98

* Data on HIV status were only recorded for 2013, and showed that 50% of presumptive cases knew their HIV status; similar proportions were assumed for the model.[12–14]
† Best estimated proportion of TB cases among presumptive cases.[12–14] As part of the PROVE IT Study, NHLS data from presumptive cases had previously been collected and analysed to compare TB yield in the smear/culture-based algorithm to that in the Xpert-based algorithm. Input parameters for the model used probability distributions derived from this analysis.
HIV = human immunodeficiency virus; TB = tuberculosis; PROVE IT = Policy Relevant Outcomes from Validating Evidence on ImpacT evaluation; NHLS = National Health Laboratory Services.

Model outputs and analysis

Outputs from the model on the number of tests performed per algorithm and the number of TB cases diagnosed under different scenarios and cost per test from our costing study[6] were summarised in Microsoft Excel™ (Microsoft Corp, Redmond, WA). They were used to calculate overall diagnostic costs per algorithm, cost per TB case diagnosed and cost per additional TB case diagnosed in the Xpert-based algorithm compared with that in the smear/culture-based algorithm. We used the validated model to predict the costs per TB case diagnosed under various conditions.

Ethics statement

The Health Research Ethics Committee at Stellenbosch University, Tygerberg, South Africa (IRB0005239) (N10/09/308) and the Ethics Advisory Group of the International Union Against Tuberculosis and Lung Disease, Paris, France (59/10) approved the study protocol. The City of Cape Town Health Directorate, the Western Cape Health Department and NHLS granted permission to use routine health data.

RESULTS

At our published best estimate of 18.3%[13,14] TB prevalence among presumptive cases, the proportion diagnosed with TB increased from 15.0% in the smear/culture-based algorithm to 16.3% in the Xpert-based algorithm, a relative increase of 8.7%. The cost per TB case diagnosed increased from US$50 in the smear/culture-based algorithm to US$121 in the Xpert-based algorithm, a relative increase in cost of 142% (Table 3, Figure 2). The cost per additional TB case diagnosed in the Xpert-based algorithm compared with that in the smear/culture-based algorithm was US$986 (Table 3, Figure 3).

The effect of varying the proportion with TB among presumptive cases tested

When the proportion with TB among presumptive cases tested was lowered to 3.0% (scenario 11) or increased to 30.8% (scenario 1) in the model, the proportion of TB cases diagnosed ranged from 2.5% to 25.3% in the smear/culture-based algorithm and from 2.7% to 27.4% in the Xpert-based algorithm.

The cost per TB case diagnosed ranged from US$299 to US$30 in the smear/culture algorithm and from US$727 to US$73 in the Xpert-based algorithm (Table 3, Figure 2). At the lowest proportion of TB among presumptive cases tested (3.0%; scenario 11), the cost per additional TB case diagnosed was US$9245, and at the highest TB proportion (30.8%; scenario 1), the cost per additional TB case diagnosed was US$603 in the Xpert-based algorithm compared to the smear/culture-based algorithm (Table 3, Figure 3).

The effect of Xpert cartridge price

At the current best-estimated proportion of 18.3% with TB among presumptive cases tested, the cost per TB case diagnosed would be respectively US$114, US$102 and US$83 in the Xpert-based algorithm if the price of the Xpert cartridge was reduced by 10%, 25% and 50% (Table 4, Figure 2). The cost per additional TB case diagnosed in the Xpert-based algorithm compared with that in the smear/culture algorithm would be US$886, US$737 and US$489 at these respective reductions in cartridge price (Table 4, Figure 3).

The effect of varying both TB prevalence among presumptive cases and the Xpert cartridge price

At 3.0% (scenario 11) TB prevalence among presumptive cases, the cost per TB case diagnosed in the Xpert-based algorithm was respectively US$682, US$613 and US$499 if the price of the Xpert cartridge was reduced by 10%, 25% and 50%. At 30.8% (scenario 1) TB prevalence among presumptive cases (scenario 1), the cost per TB case diagnosed was respectively US$68, US$61 and US$50 if the price of the Xpert cartridge was reduced by 10%, 25% and 50% (Table 4, Figure 2).

The cost per additional TB case diagnosed in the Xpert-based algorithm compared with that in the smear/culture algorithm was respectively US$8290, US$6857 and US$4470 at 3.0% (scenario 11) of presumptive cases tested having TB and if the price of the Xpert cartridge was reduced by 10%, 25% and 50%. At 30.8% (scenario 1) TB prevalence among presumptive cases, the cost per additional TB case diagnosed in the Xpert-based algorithm compared with that in the smear/culture algorithm was respectively US$543, US$454 and US$304 if the price of the Xpert cartridge was reduced by 10%, 25% and 50% (Table 4, Figure 3).

DISCUSSION

It was hoped that with the roll-out of Xpert as a replacement for smear microscopy the proportion of TB cases diagnosed would increase due to the higher test sensitivity of Xpert.[17–19] A population-level decision model study estimated that with full Xpert coverage, the total TB diagnostic cost for South Africa would increase annually by 53–57%/year, with the increase in cost offset by a 30–37% increase in TB cases diagnosed.[20]

The results from our operational model and laboratory and cost data collected for 142 PHC facilities show, however, that at the current best estimate of 18.3% TB prevalence among presumptive cases, there was a 142% relative increase in cost per

Table 3 Cost per TB case diagnosed in the smear/culture and Xpert-based algorithms and the cost per additional TB case diagnosed as the proportion of TB among presumptive cases tested varies ($n = 100\,000$)*

	Proportion with TB among presumptive cases † %	Smear/culture-based algorithm		Xpert-based algorithm		Changes with the Xpert-based algorithm		Cost per additional TB case diagnosed ‡ $\left(\frac{d-b}{c-a}\right)$
		TB cases diagnosed (a) *n* (%)	Total laboratory cost (cost per TB case diagnosed) (b) *n* (%)	TB cases diagnosed (c) *n* (%)	Total laboratory cost (cost per TB case diagnosed)	TB cases diagnosed % ($c - a$)	Cost per TB case diagnosed ($d - b$)	
Scenario 1	30.8	25 315 (25.3)	750 903 (30)	27 362 (27.4)	1 984 981 (73)	2.0	42.88	603
Scenario 2	28.4	23 335 (23.3)	751 703 (32)	25 245 (25.2)	1 981 627 (78)	1.9	46.28	644
Scenario 3	25.9	21 334 (21.3)	752 504 (35)	23 104 (23.1)	1 978 708 (86)	1.8	50.37	693
Scenario 4	23.3	19 157 (19.2)	753 144 (39)	20 748 (20.7)	1 974 388 (95)	1.6	55.85	768
Scenario 5	20.8	17 059 (17.1)	754 001 (44)	18 474 (18.5)	1 970 809 (107)	1.4	62.48	860
Best estimate§	18.3	15 024 (15.0)	755 034 (50)	16 254 (16.3)	1 967 340 (121)	1.2	70.78	986
Scenario 6	15.8	12 993 (13.0)	756 041 (58)	14 019 (14.0)	1 963 148 (140)	1.0	81.85	1 177
Scenario 7	13.2	10 813 (10.8)	756 365 (70)	11 685 (11.7)	1 958 961 (168)	0.9	97.70	1 379
Scenario 8	10.6	8 721 (8.7)	757 687 (87)	9 461 (9.5)	1 955 514 (207)	0.7	119.81	1 619
Scenario 9	8.0	6 658 (6.7)	758 825 (114)	7 173 (7.2)	1 951 139 (272)	0.5	158.04	2 315
Scenario 10	5.5	4 595 (4.6)	759 585 (165)	4 882 (4.9)	1 947 306 (399)	0.3	233.57	4 138
Scenario 11	3.0	2 544 (2.5)	760 312 (299)	2 672 (2.7)	1 943 670 (727)	0.1	428.56	9 245

* All costs are expressed in 2013 CPI-adjusted values and in US$.
† Proportion of TB cases diagnosed among presumptive cases tested.
‡ Cost per additional TB case diagnosed in the Xpert-based algorithm compared to in the smear/culture-based algorithm.
§ Best estimate of proportion of TB cases among presumptive cases based on the proportion of TB cases diagnosed from 2013 routine data.[13,14]
TB = tuberculosis; CPI = Consumer Price Index.

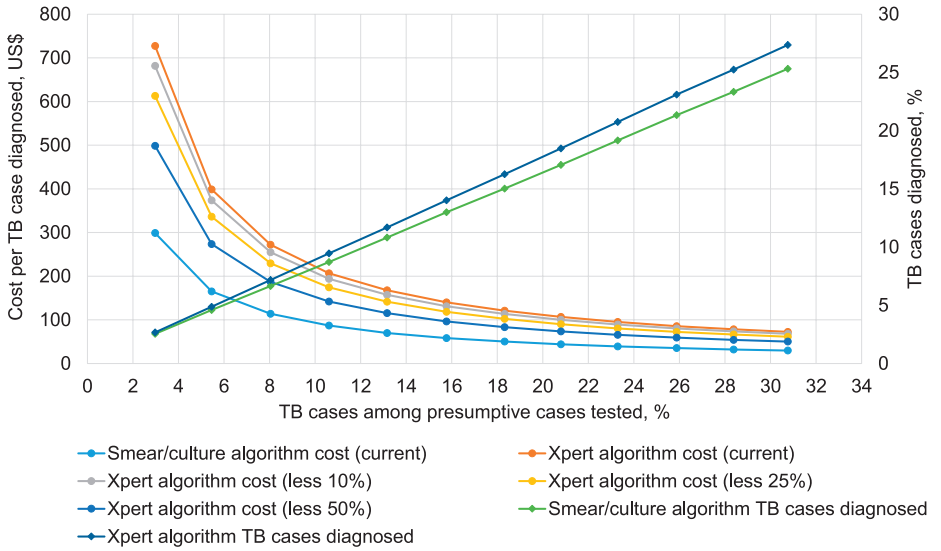

Figure 2 Diagnostic yield and cost per TB case diagnosed as proportion of TB among presumptive cases is varied and Xpert costs are reduced. All costs per TB case diagnosed are expressed in 2013 CPI-adjusted values. 'Current' costs are at levels reported from the laboratory cost study.[6] Xpert cartridge prices were reduced by 10%, 25% and 50%. The primary *y*-axis shows current costs in each algorithm and the cost per TB case diagnosed as the proportion with TB among presumptive cases tested is increased at different Xpert cartridge prices (with reductions of 10%, 25% and 50%). The secondary *y*-axis shows the proportion of TB cases diagnosed as the proportion with TB among presumptive cases tested is increased in the smear/culture and the Xpert-based algorithms. TB = tuberculosis; CPI = Consumer Price Index. This image can be viewed online in colour at http://www.ingentaconnect.com/content/iuatld/ijtld/2017/00000021/00000009/art00014

TB case diagnosed in the Xpert-based algorithm compared with that in the smear/culture-based algorithm, with a relative increase in the number of TB cases diagnosed of only 8.7%. The increase in the cost per TB case diagnosed was slightly lower in our study than the 157% reported in a study conducted in Cape Town using routine laboratory data. The Cape Town study, however, reported a temporal decline in TB diagnostic yield from 20.4% to 16.6% for the period 2010–2013, due to a possible decline in TB

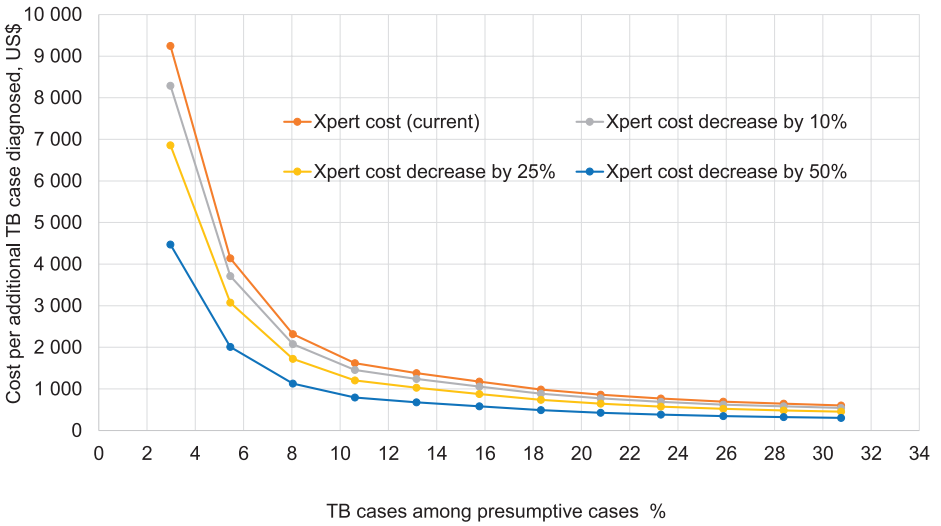

Figure 3 Cost per additional TB case diagnosed in the Xpert-based algorithm compared to the smear/culture-based algorithm as proportion with TB among presumptive cases tested is varied and Xpert prices are reduced. All costs per TB case diagnosed are expressed in 2013 CPI-adjusted values. 'Current' cost is reported from the laboratory cost study.[6] Xpert cartridge prices were reduced by 10%, 25% and 50%. TB = tuberculosis; CPI = Consumer Price Index. This image can be viewed online in colour at http://www.ingentaconnect.com/content/iuatld/ijtld/2017/00000021/00000009/art00014

Table 4 Cost per TB case diagnosed and cost per additional TB case diagnosed in the Xpert-based algorithm with a reduction in Xpert cartridge price and with varying proportions of presumptive cases tested having TB

	TB cases among presumptive cases %	Xpert-based algorithm cost per TB case diagnosed US$*			Cost per additional TB case diagnosed US$*†		
		Reduction in Xpert cartridge price					
		10%	25%	50%	10%	25%	50%
Scenario 1	30.8	68	61	50	543	454	304
Scenario 2	28.4	74	66	54	580	484	324
Scenario 3	25.9	80	72	59	624	520	347
Scenario 4	23.3	89	80	66	691	576	383
Scenario 5	20.8	100	90	74	774	644	428
Best estimate‡	18.3	114	102	83	886	737	489
Scenario 6	15.8	131	118	96	1057	879	581
Scenario 7	13.2	157	141	115	1239	1029	678
Scenario 8	10.6	194	174	142	1453	1206	793
Scenario 9	8.0	255	229	187	2078	1722	1128
Scenario 10	5.5	374	336	274	3712	3074	2009
Scenario 11	3.0	682	613	499	8290	6857	4470

* All costs are expressed in 2013 CPI-adjusted values.
† Cost per additional TB case diagnosed in the Xpert-based algorithm compared to in the smear/culture-based algorithm.
‡ Best current estimate of proportion with TB among presumptive cases tested.[13,14]
TB = tuberculosis; CPI = Consumer Price Index.

prevalence attributed to the rapid scale-up of antiretroviral treatment, and costs were partially influenced by this.[13] An advantage of our model is that we were able to compare outputs when input parameters between algorithms were similar.

The cost per TB case diagnosed is directly influenced by the proportion of TB prevalence among presumptive cases. As case-finding efforts are scaled up and the number of individuals tested for TB increases, the proportion with TB among those tested will decrease, and therefore the cost per TB case diagnosed will increase. This increase in cost has serious implications for South Africa's efforts to increase case finding, and alternative strategies would need to be considered to reduce costs.

One approach to reduce the cost per TB case diagnosed would be to increase the proportion with TB among the presumptive cases being tested. This could be accomplished by implementing an improved triage or testing strategy.[9] A study using a decision analytical model showed that with a hypothetical triage test with sensitivity equivalent to that of the Xpert test, 75% specificity and cost of US$5 per test would reduce the total diagnostic cost by 39% in South Africa.[21] No triage test is currently available, and this has been identified as one of the priorities in the development of new diagnostics for TB.[22] It has been shown that pre-screening with smear microscopy could reduce the cost per TB case diagnosed by more than 20%.[8]

A further approach to reduce the cost would be a reduction in the price of the Xpert cartridge. Our model shows that with a 50% reduction in the price of Xpert cartridges and with the proportion with TB among presumptive cases tested at 3%, the cost per TB case diagnosed would be US$499, which is extremely high. At a more realistic proportion of 10.6% TB prevalence among presumptive cases and a 50% reduction in the price of Xpert cartridges, the cost per TB case diagnosed is still high, at US$142.

The best approach to improve affordability would therefore be a combination of increasing the proportion with TB among presumptive cases tested using either a triage test or other pre-screening strategies, and a reduction in the price of Xpert cartridges. Our model shows that if the proportion with TB among presumptive cases tested was 25.9–30.8% and the price of the Xpert cartridge reduced by 50%, the cost per TB case diagnosed would range from US$50 to US$59, a level that is comparable with the cost per TB case diagnosed in the smear/culture-based algorithm (US$48.77) found in a laboratory costing study.[6]

Strengths and limitations

The strengths of the current study are that we used a validated model, based on real data on testing and diagnosis, to estimate the cost per TB case diagnosed in the smear/culture and Xpert-based algorithms. Our study provides a better estimate of the cost per TB case diagnosed. The previous laboratory costing study included false-positive cases in the cost calculation. Our model suggests that the proportion of false-positive cases is lower in the Xpert-based than in the smear/culture-based algorithm.[14]

The model was validated using routine programmatic data from Cape Town, a well-resourced urban setting where culture is extensively used. This may limit the generalisation of findings to other settings. We did not consider the costs for diagnosis of multidrug-resistant TB and the added benefit of the

Xpert test in identifying rifampicin resistance at screening; this will be reported in a future study. The impact of new TB diagnostic algorithms on patient costs is extremely important and was not considered in this study; however, patient costs from the broader PROVE-IT (Policy Relevant Outcomes from Validating Evidence on ImpacT) study have been published.[23]

Recommendations

We recommend that alternative, more cost-effective, strategies be implemented in settings where the proportion with TB among presumptive cases tested is low or declining over time, as would occur with increased case-finding efforts. Recommended strategies would include better pre-screening or a triage screening test to increase the proportion with TB among presumptive cases tested with Xpert. Substantial further reductions in the price of Xpert cartridges are also recommended to make using Xpert affordable in low-resource settings. Further operational research is required to determine the most effective triage strategies to make Xpert more sustainable and affordable.

CONCLUSION

An analysis of routine laboratory data has shown that, in our setting, the introduction of Xpert as a replacement test for smear microscopy has resulted in a much higher cost per TB case diagnosed.[6] The high cost is not offset by a substantially higher number of TB cases diagnosed despite the increased sensitivity of the Xpert test.[13]

The operational model illustrates the effect of increased case-finding efforts on laboratory costs per TB case diagnosed. It is clear that unless alternative triage strategies are identified, the approach will not be sustainable, even if Xpert cartridge prices are reduced. Additional studies are required to assess the cost-effectiveness of alternative strategies and their impact on TB transmission.

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RESUME

CONTEXTE : Le Cap, Afrique du Sud.
OBJECTIF : Modéliser les effets de stratégies accrues de recherche des cas et de triage sur les coûts de laboratoire par cas de tuberculose (TB) diagnostiqué.
MÉTHODES : Nous avons utilisé une modèle opérationnel validé et publié les données de coût de laboratoire. Nous avons modélisé l'effet de la variation de la proportion de patients avec TB parmi les cas présumés et des réductions de prix des cartouches d'Xpert sur le coût par cas de TB et par cas supplémentaire de TB diagnostiqué dans les algorithmes basés sur l'Xpert par rapport à ceux basés sur le frottis/la culture.
RÉSULTATS : Dans notre scénario actuel (18,3% atteints de TB parmi les cas présumés), la proportion de cas diagnostiqués a augmenté de 8,7% (16,7% contre 15,0%) et le coût par cas diagnostiqué a augmenté de 142% (121 $US contre 50 $US). Le coût par cas supplémentaire diagnostiqué a été de 986 $US. Ceci augmenterait à 1619 $US si la proportion de patients avec TB parmi les cas présumés était de 10,6%. Avec entre 25,9% et 30,8% de patients avec TB parmi les cas présumés et avec 50% de réduction du prix des cartouches d'Xpert, le coût par cas de TB diagnostiqué se situerait entre 50 $US et 59 $US (comparable aux 48,77 $US trouvés en pratique de routine avec frottis/culture).
CONCLUSION : Le modèle opérationnel illustre l'effet de l'augmentation de la recherche des cas sur les coûts de laboratoire par cas de TB diagnostiqué. A moins d'identifier des stratégies de triage, l'approche ne sera pas pérennisable, même si le prix des cartouches d'Xpert est réduit.

RESUMEN

MARCO DE REFERENCIA: Ciudad del Cabo en Suráfrica.
OBJETIVO: Modelizar los efectos que ejercen las estrategias de aumento de la búsqueda de casos y de preselección de los pacientes, en los costos de laboratorio por cada caso de tuberculosis (TB) diagnosticado.
MÉTODOS: Se aplicó un modelo operativo validado y datos publicados sobre los costos de laboratorio. Se llevó a cabo una modelización del efecto de la modificación en la proporción de casos de TB diagnosticados en las personas con presunción clínica de la enfermedad y de la disminución del precio del cartucho utilizado en la prueba Xpert, en los costos por caso de TB y por caso adicional de TB diagnosticados con los algoritmos fundados en la prueba Xpert en comparación con los algoritmos basados en la baciloscopia y el cultivo.
RESULTADOS: En la hipótesis adoptada (18,3% casos de TB en las personas con presunción clínica), la proporción de casos diagnosticados aumentó un 8,7% (16,7% contra 15,0%) y el costo por caso diagnosticado aumentó un 142% (121 USD contra 50 USD). El costo por caso adicional diagnosticado fue 986 USD. El costo aumentaría a 1619 USD cuando la proporción de casos con TB es 10,6%. Si la proporción es de 25,9% a 30,8% de casos de TB en las personas con presunción clínica, con una reducción de 50% del precio del cartucho Xpert, el costo por caso de TB diagnosticado oscilaría entre 50 USD y 59 USD (equivalente al costo observado de 48,77 USD en la práctica corriente con la baciloscopia y el cultivo).
CONCLUSIÓN: El presente modelo operativo explica el efecto de un aumento de la búsqueda de casos sobre los costos de laboratorio por caso de TB diagnosticado. A menos que se definan estrategias de preselección de los pacientes la estrategia no es sostenible, incluso cuando se considera una disminución del precio del cartucho de la prueba Xpert.

Chapter 5: Modelling the impact of Xpert® MTB/RIF Ultra as a replacement test for Xpert® MTB/RIF

Unpublished. Plan to submit November 2017.

Summary: In this chapter, I model the effect of introducing a more sensitive molecular diagnostic test, Xpert MTB/RIF Ultra (Ultra), on the number of TB and RMP-R TB cases detected. I used an operational model representing the diagnosis of pulmonary TB and RMP-R TB in Cape Town for the Xpert MTB/RIF (Xpert) based algorithm. I modelled scenarios comparing the effect of TB and RMP-R TB detection if Ultra replaced Xpert. All scenarios used identical population characteristics and 100% adherence to the diagnostic algorithms to compare the Xpert-based and Ultra-based algorithms. I also modelled scenarios with 60% and 100% of presumptive TB cases knowing their HIV status.

The model indicated a 3.4% (60% know their HIV status) and 0.9% (100% know their HIV status) increase in the number of TB cases detected between the Xpert-based and Ultra-based algorithm. However, the number of false positive TB cases detected would increase by 167%. The model indicated a 3.5% (60% know their HIV status) and 0.8% (100% know their HIV status) increase in the number of RMP-R TB cases detected. In our model for Cape Town, Ultra has small benefits over that of Xpert for both the number of TB and RMP-R TB cases detected and therefore the cost of introducing Ultra would be an important consideration in the decision to implement Ultra. In settings with high proportions of presumptive TB cases with a history of previous TB treatment, the introduction of Ultra poses potential health system and patient related challenges.

My contributions: In this chapter, I adapted the previously developed and validated operational model to compare the Xpert-based algorithm with the Ultra-based algorithm. I conducted the overall data management and data analysis for this chapter as well as conceived, designed and performed the experiments of running the different scenarios in the model. I also wrote this chapter.

Co-author contribution: Pren Naidoo, Ivor Langley and Nulda Beyers contributed with conceiving and designing experiments. The co-authors reviewed the draft chapter and approved the final draft chapter published in this dissertation.

Modelling the impact of Xpert® MTB/RIF Ultra as a replacement test for Xpert® MTB/RIF

5.1 Introduction

Although tuberculosis (TB) is a curable disease, it remains a global health challenge. In 2015, the World health Organisation (WHO) estimated that there were 10.4 million incident TB cases globally; 1.2 million (11%) were human immunodeficiency virus (HIV) co-infected cases. There were 1.4 million estimated TB deaths among HIV-negative TB cases in 2015, and an additional 0.4 million deaths amongst HIV-positive TB cases.[1]

Some of the key drivers of the TB epidemic are HIV (HIV-positive individuals at a 20 to 37-fold increased risk of developing TB[2]) and under-diagnosis or late diagnosis of TB and rifampicin resistant (RMP-R) TB, which results in deaths amongst TB cases[3,4] and transmission to other individuals.[5]

Of the 3.4 million bacteriologically confirmed TB cases notified globally in 2015, only 30% were reported to have had a drug susceptibility test (DST) for rifampicin.[1] If all pulmonary TB patients notified in 2015 had a DST done, an estimated 340,000 RMP-R TB cases could have been identified. Due to poor DST coverage only 132,120 RMP-R TB cases were detected and notified globally.

In 2010, the WHO endorsed the use of Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) (Xpert) and recommended its use as the initial diagnostic test in individuals presumed to have RMP-R TB or HIV co-infected TB cases[6] and expanded the recommendation in 2014 to include all presumptive TB cases.[7] Xpert simultaneously detects *Mycobacterium tuberculosis* (MTB) and rifampicin resistance on a single specimen. Xpert was rolled out in over 120 countries by 2016, with varied implementation strategies followed by different countries.[8]

A Cochrane Review reported that Xpert, as an initial test replacing smear microscopy, had a pooled sensitivity of 89% (95% CI 83% to 92%) and specificity of 98% (95% CI 97% to 99%) for detecting MTB and sensitivity was 94% (95% CI 87% to 97%) and specificity was 98% (95% CI 97% to 99%) for RMP-R.[9] In HIV-positive individuals, Xpert has a sensitivity for detecting MTB of 80% (95% CI 67% to 88%). This lower

sensitivity in HIV-positive individuals is a serious limitation, especially in settings such as South Africa where the HIV prevalence is high (18.9 [16.6 - 21.0] of the adult population (aged 15 to 49) were estimated to be HIV-positive in 2016).[10]

In order to address some of the limitations of Xpert (low sensitivity for detecting MTB especially in HIV-positive and imperfect detection of RMP-R TB) a new test, Xpert MTB/RIF Ultra (Ultra), has been developed.[11] A prospective multicentre (10 sites across 8 countries) diagnostic accuracy study was conducted to assess performance in geographically diverse, high-burden settings.[12] The study compared the performance of Ultra for detection of MTB and RMP-R in adults suspected of having pulmonary TB against the performance of Xpert, with culture and phenotypic drug susceptibility as the reference standard. Ultra had a higher sensitivity, in particular among smear-negative culture-positive specimens from HIV-positive individuals, and lower specificity for detecting MTB (Table 1).

If Ultra was to replace Xpert for the diagnosis of TB, the higher sensitivity will potentially result in more true cases of TB being diagnosed, while the lower specificity will potentially result in more false positive cases being diagnosed. The decision of whether or not to implement a new test with higher sensitivity and lower specificity will be dependent on the setting in which Ultra is implemented (for example, HIV prevalence, previous history of TB treatment and TB prevalence).

The aim of this study was to use an operational model to compare the detection of TB and RMP-R TB cases between the current Xpert-based algorithm and a potential new Ultra-based algorithm.

5.2 Methods

5.2.1 Definitions used in the model

Presumptive case: *A presumptive TB case is an individual who had pre-treatment sputum specimen collected for TB diagnostic purposes.*

TB case: *A TB case is an individual with culture positive TB, irrespective of how the individual was ultimately identified (i.e. tested positive by either sputum smear microscopy or culture or Xpert or Ultra).*

True positive: *A presumptive case with culture positive TB that is correctly detected with TB by the test in use.*

False positive: *A presumptive case without TB (culture negative) that is incorrectly detected with TB by the test in use.*

False negative: *A presumptive case with culture positive TB in whom TB is not detected*

RMP-R TB case: *A RMP-R TB case is a TB case with true rifampicin resistance.*

Adherence to algorithms: *We defined adherence to an algorithm as the proportion of presumptive TB cases that received the full sequence of tests as stipulated by the diagnostic algorithm (Figure 1).*[13]

TB yield: *The proportion of the presumptive TB cases correctly diagnosed with TB (i.e. includes only true positive cases).*

5.2.2 Setting and timeframe

The study uses data from Cape Town, one of the largest cities in South Africa, with a population of 3.7 million in 2011 (National Census 2011). In Cape Town, free TB diagnostic services are provided at 142 primary health care (PHC) facilities in eight health sub-districts. All TB diagnostic tests are performed at a central National Health Laboratory Service (NHLS), with all sputum specimens collected for TB testing at PHC facilities couriered to NHLS on a daily basis for testing and results returned to facilities via courier and fax. Results can also be accessed electronically.

South Africa was an early adopter of Xpert and shortly after the WHO policy statement in 2010[6], South Africa introduced Xpert as a replacement test for smear microscopy for all presumptive TB cases. The rollout of Xpert started in Cape Town in August 2011, with full rollout completed in February 2013. The implementation of the Xpert-based algorithm was slightly different in Cape Town compared to the rest of South Africa, with two spot specimen required in Cape Town compared to one spot specimen in the rest of South Africa.

This study used the Xpert-based algorithm as implemented in Cape Town. With the Xpert-based algorithm, the first specimen collected was tested with Xpert and if TB was detected the second specimen underwent fluorescence light-emitting diode (LED) smear microscopy for acid-fast bacilli. If Xpert detected RMP-R, a culture and GenoType® MTBDRplus (Hain LifeScience GmbH, Nehren, Germany) line-probe assay (LPA) test was undertaken. If Xpert was negative and the individual was HIV-positive, the second specimen underwent culture and LPA.

5.2.3 Model development

We used an operational model previously developed and validated using routine National Health Laboratory Service (NHLS) data collected for the period 2010 to 2013 in Cape Town for the detection of TB and RMP-R TB.[14–16] The operational model was developed using the Witness package[17], a discrete event and continuous process simulator and incorporated specimen flow from specimen collection, through laboratory test procedures, to a result being provided to the patient. The original operational model was developed to compare the previously used smear/culture-based algorithm and currently used Xpert-based algorithm, as stipulated by the South African National TB programme and as implemented in Cape Town.[13] For the current study, we used the Xpert-based algorithm in the model to compare Xpert to Ultra and replaced Xpert for Ultra in the new Ultra-based algorithm (Figure 1).

5.2.4 Model inputs

Routine TB treatment and NHLS data for all presumptive TB cases had previously been collected and analysed as part of the PROVE IT (Policy Relevant Outcomes from Validating Evidence on ImpacT) study. The PROVE IT study included a comparison of TB yield[16] and RMP-R TB[14] yield between the previously used smear/culture-based algorithm and the newly introduced Xpert-based algorithm. For the current study, we used probability distributions derived from the PROVE IT analyses as input parameters for the model (Table 2).

Test sensitivities and specificities were obtained from published literature, including findings reported from a multicentre non-inferiority diagnostic accuracy study comparing Ultra to Xpert.[12,18,19] The sensitivity and specificity for detecting TB with Xpert or Ultra was defined in the model relative to culture positive TB cases in the

model. The sensitivity and specificity for detecting RMP resistance with Xpert or Ultra was defined, in the model, relative to culture positive TB cases with RMP resistance (true RMP-R TB cases).

5.2.5 Model scenarios

We modelled scenarios comparing the TB and RMP-R TB yield among 100,000 presumptive TB cases in the Xpert and Ultra-based algorithms. We used identical population characteristics and adherence to algorithms as inputs in each algorithm. All scenarios were modelled with a 100% adherence to the diagnostic algorithms and with either 60% or 100% of presumptive TB cases knowing their HIV status.

5.2.6 Model outputs and analysis

We used the modelled scenarios to identify the number and percentage of TB and RMP-R TB cases detected by either the Xpert-based or Ultra-based algorithm.

We report the number of true TB cases detected as a percentage of the 100,000 presumptive TB cases (TB yield) based on the full testing protocol defined in each algorithm (Figure 1). We also report the number and percentage of presumptive TB cases with false positive and false negative TB test results.

The number and percentage of RMP-R TB cases (RMP-R yield) correctly detected, the number of false negative and false positive RMP-R TB cases detected by either the Xpert-based or Ultra-based algorithm are reported as a percentage of true TB cases in the model.

5.3 Ethics statement

The Health Research Ethics Committee at Stellenbosch University (IRB0005239) (N10/09/308) and Ethics Advisory Group at The International Union Against Tuberculosis and Lung Disease (59/10) approved the study. The City of Cape Town Health Directorate, Western Cape Health Department and National Health Laboratory Service granted permission to use the routine health data in the validation of the model.

5.4 Results

5.4.1 TB cases detected

Model outputs comparing TB cases detected in the Xpert-based and Ultra-based algorithms for 100,000 presumptive TB cases are summarised in table 3. In the scenario where 60% of presumptive cases know their HIV status, the model identified 16,248 (16.2%) true TB cases in the Xpert-based algorithm and 16,797 (16.8%) in the Ultra-based algorithm, a 3.4% difference in the number of cases identified. If 100% of presumptive cases know their HIV status, the model identified 17,012 (17.0%) in the Xpert-based algorithm and 17,160 (17.2%) in the Ultra-based algorithm, a 0.9% difference the number of cases identified.

In a scenario where 60% of presumptive cases know their HIV status, there were 1,907 (1.9%) false negative tests (missed TB cases) in the Xpert-based algorithm compared to 1,358 (1.4%) in the Ultra-based algorithm, a 28.8% reduction in the number of TB cases missed. When 100% of presumptive cases know their HIV status, there were 1,143 (1.1%) false negative tests in the Xpert-based algorithm and 995 (1.0%) in the Ultra-based algorithm, a 12.9% reduction in the number of TB cases missed.

In a scenario where 100% of presumptive cases know their HIV status, the model identified 1,576 (1.6%) false positive TB cases in the Xpert-based algorithm and 4,201 (4.2%) in the Ultra-based algorithm, an increase of 166.6%.

5.4.2 RMP-R TB cases detected

The model outputs for detecting RMP-R TB cases are summarised in Table 4. In a scenario where 60% of presumptive cases know their HIV status, the model indicated that 1,186 (6.5%) TB cases would be detected with RMP-R in the Xpert-based algorithm compared to 1,228 (6.8%) in the Ultra-based algorithm, an increase of 3.5% in the number of RMP-R TB cases detected.

When 100% of presumptive cases know their HIV status, the number of TB cases detected with RMP-R would be 1,263 (7.0%) in the Xpert-based algorithm and 1,253 (6.9%) in the Ultra-based algorithm, a decrease of 0.8%.

In a scenario when 60% of presumptive cases know their HIV status, 212 (1.2%) RMP-R TB cases would be missed in the Xpert-based algorithm and 170 (0.9%) in the Ultra-based algorithm, a decrease of 19.8%. In this scenario, the number of missed RMP-R TB cases in the model comprise of 164 (77.4%) with an initial negative TB result and 48 (22.6%) with a false negative RMP-R TB result in the Xpert-based algorithm compared to 104 (61.2%) with an initial negative TB result and 66 (38.8%) with a false negative RMP-R TB result in the Ultra-based algorithm.

In the scenario when 100% of presumptive cases know their HIV status, 135 (0.7%) RMP-R TB cases would be missed in the Xpert-based algorithm and 145 (0.8%) in the Ultra-based algorithm. In this scenario, the number of missed RMP-R TB cases in the model comprise of 87 (64.4%) with an initial negative TB result and 48 (35.6%) with a false negative RMP-R TB result in the Xpert-based algorithm compared to 79 (54.5%) with an initial negative TB result and 66 (45.5%) with a false negative RMP-R TB result in the Ultra-based algorithm.

5.5 Discussion

Increased efforts to address the ongoing TB and RMP-R TB diagnostic challenges have resulted in the development of new molecular tests. Xpert MTB/RIF, one of these new tests, was endorsed by the WHO in 2010[6,7]. South Africa adopted Xpert early and started implementing an Xpert-based algorithm in 2011. Even though Xpert has improved sensitivity and specificity compared to smear microscopy, Xpert still has some limitations, including lower sensitively among HIV-positive individuals. Previous studies have also reported concerns regarding false positive Xpert results, especially amongst those with a history of previous TB treatment.[6,20,21] In order to address some of these limitation, Ultra was developed. However, even though Ultra has a higher sensitively for the detection of TB than Xpert, specificity is lower.[11]

We used a previously developed and validated operational model to assess the potential impact of introducing Ultra as a replacement for Xpert in the current Xpert-based algorithm.

The model indicated that if Ultra replaced Xpert and when 60% of presumptive TB cases know their HIV status, there would be only a small (3.4%) increase in the number of TB cases detected. This is slightly less than the modelled 4.7% increase in

the number of TB cases detected in the Xpert-based algorithm if the proportion of presumptive TB cases who know their HIV status increased from 60% to 100%. When 100% of presumptive cases know their HIV-status in both the Xpert and the Ultra algorithms, the difference in TB yield between algorithms was low at 0.9%.

However, despite the relatively small increase in the number of TB cases detected by Ultra, the model indicated that when 100% of presumptive TB cases know their HIV status, the number with a false positive test result would increase massively by 167% with the Ultra-based algorithm. This is due to the lower specificity of Ultra compared to that of Xpert, especially for those with a history of previous TB treatment. Previous studies have already highlighted the concern of false positive test results with Xpert.[6,20,21] The model indicated that this will be an even bigger problem if Ultra was implemented, especially in settings such as Cape Town where a high proportion (24%)[16] of presumptive TB cases have a history of previous TB treatment.[22] This presents a challenge for the health system: although more true TB cases are likely to be identified and treated with Ultra, the number of unnecessarily treated individuals is also likely to increase. It will be necessary for policy makers to consider the trade-off between high sensitivity and low specificity and whether identifying more cases is more important than unnecessarily treating people who do not have TB.

While the number of TB cases missed decreased by 28.8% with the Ultra-based compared to the Xpert-based algorithm when 60% of presumptive TB cases know their HIV status, this decrease was only 12.9% when 100% of presumptive TB cases know their HIV status. This is due to more Xpert-negative HIV-positive cases receiving a culture test, which reduces the benefits gained from Ultra's higher sensitivity.

The model indicated a small benefit for the detection of RMP-R TB cases. There was only a 6.5% increase in detecting RMP-R TB cases in the Ultra-based algorithm. This increase in RMP-R TB cases is due to more TB cases detected with Ultra. The number of RMP-R TB cases missed decreased by 24.8% with the Ultra-based algorithm. This decrease is due to the higher specificity of Ultra in detecting TB cases resulting in fewer false negative TB results and therefore fever RMP-R TB cases missed. Both Xpert and Ultra only produce a RMP-R result if the test in positive for TB.

These model outputs were based on population characteristics and the diagnostic algorithm in Cape Town where we have a high TB incidence, a high HIV prevalence and a high proportion of previously treated presumptive TB cases. Different results might be obtained under different epidemiological conditions and it is possible that these results will be different, with lower false positive tests in areas with lower TB incidence and lower proportions of retreatment cases. The WHO reported that in low TB burden settings, false positive results were not a major concern.[11]

5.5.1 Strengths and limitation

The strengths of the current study are that we used a previously developed, validated and published operational model, based on operational data on testing and diagnosis, to estimate the number of TB and RMP-R TB cases identified in an Xpert-based algorithms and extrapolated this to the Ultra-based algorithm. The model compared the two algorithms using identical population characteristics and adherence to algorithms. We compared the algorithms taking the full sequence of tests in each algorithm into consideration (as they would be used in routine practice), and not only the performance of the individual Xpert or Ultra tests.

The Xpert model was validated against data from Cape Town, a well-resourced urban setting with a well functioning centralised laboratory and the availability of culture testing. This may limit the generalisability of our findings to other settings. We did not consider alternative diagnostic algorithms to that of the currently used Xpert-based algorithm in Cape Town. For the current comparison, we assumed Ultra would be introduced as a direct replacement for Xpert (Figure 1). We did not consider cost to the health system, cost to the patient, time to treatment initiation and initial loss to follow-up for TB or RMP-R TB. This will be included in future analyses and publications.

5.6 Conclusion

Our model suggests that Ultra will have small benefits over that of Xpert for both the number of TB and RMP-R TB cases detected in our setting and therefore the cost of introducing Ultra would be an important consideration in the decision to implement Ultra. This benefit is reduced as more presumptive TB cases know their HIV status,

as more HIV-positive presumptive TB cases with initial negative Xpert would go on to have a culture test and if culture-positive a LPA.

The implementation of Ultra would however result in an almost 3-fold increase in the number of false positive TB cases identified. In certain settings, especially those with high proportions of previously treated TB cases, the introduction of Ultra poses serious challenges: would health services be willing to treat 2,625 individuals unnecessarily, in order to identify 549 more TB cases?

Alternative strategies, such as alternative diagnostic algorithms, will have to be considered to find a balance between increased detection of TB cases and unnecessarily starting patients on TB treatment due to false positive results. Further operational research is required to evaluate the full effect of introducing Ultra in different settings with different population characteristics and existing or new diagnostic algorithms.

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Table 1: Reported sensitivity and specificity of Xpert MTB/RIF and Xpert TB/RIF Ultra for detecting mycobacterium tuberculosis and rifampicin resistant from a multicentre study.[12]

	MTB Sensitivity (95% CI)		
	Pooled*	HIV-	HIV+
Xpert	82.9% (78.8% – 86.4%)	89.3% (83.1% - 93.7%)	75.5% (65.8% - 83.6%)
Ultra	87.8% (84.8% - 90.9%)	90.6% (84.7% - 94.8%)	87.8% (79.6% - 93.5%)
	MTB Specificity (95% CI)		
	Pooled*	No history of TB treatment	History of previous TB treatment
Xpert	98.0% (96.8% - 98.8%)	98.4% (97.0% - 99.2%)	96.9% (93.7% - 98.7%)
Ultra	94.8% (93.0% - 96.2%)	95.9% (94.1% - 97.4%)	91.5% (87.1% - 94.8%)
	RMP sensitivity (95% CI)	RMP specificity (95% CI)	
Xpert	95.5% (90.9% - 98.2%)	97.9% (95.7% - 99.1%)	
Ultra	94.8% (90.1% - 97.7%)	98.2% (96.1% - 99.3%)	

Xpert and Ultra sensitivities and specificities were extracted from findings reported from a multicentre non-inferiority diagnostic accuracy study conducted by FIND (Campus Biotech, Geneva, Switzerland).[12]

** Pooled estimate include patient with unknown HIV status.*

MTB = mycobacterium tuberculosis; CI = confidence interval; HIV = Human Immunodeficiency Virus; RMP = rifampicin.

Table 2: Input parameters used for the Xpert-based and Ultra-based algorithms

			Input values (%)	
			New presumptive cases	Previously treated presumptive cases
			75	25
HIV status		HIV-positive	36	54
		HIV-negative	64	46
Best estimated TB prevalence amongst presumptive cases			18	21
Estimated proportion of RMP-R cases amongst TB cases			6	12
Accuracy of fluorescence light-emitting diode smear microscopy[18,19] (1 specimen)	Sensitivity	HIV-positive	55	
		HIV-negative	60	
	Specificity	HIV-positive	99	
		HIV-negative	99	
Accuracy of fluorescence light-emitting diode smear microscopy[18,19] (2 specimens)	Sensitivity	HIV-positive	65	
		HIV-negative	75	
	Specificity	HIV-positive	99	
		HIV-negative	99	
Accuracy of Xpert MTB/RIF for TB[12]	Sensitivity	HIV-positive	75.5	
		HIV-negative	89.3	
	Specificity		98.4	96.9
Accuracy of Ultra MTB/RIF for TB[12]	Sensitivity	HIV-positive	87.8	
		HIV-negative	90.6	
	Specificity	HIV-positive	95.9	91.5
		HIV-negative		
Accuracy of GenoType® MTBDRplus LPA for RMP-R TB[18,19]	Sensitivity	HIV-positive	98	
	Specificity	HIV-positive	98	
Accuracy of Xpert MTB/RIF for RMP-R TB[12]	Sensitivity		95.5	
	Specificity		97.9	
Accuracy of Ultra MTB/RIF for RMP-R TB[12]	Sensitivity		94.8	
	Specificity		98.2	

HIV = Human Immunodeficiency Virus; TB = tuberculosis; RMP-R = rifampicin resistant; LPA = line probe assay.

Table 3: Model output comparing the detection of TB in the Xpert-based and Ultra-based algorithms and the influence of increased HIV testing among 100,000 presumptive cases

		Xpert-based algorithm n (%)	Ultra-based algorithm n (%)	Difference in number of cases between algorithms (% difference)
60% of presumptive cases know their HIV status	TB cases identified	16,248 (16.2)	16,797 (16.8)	549 (3.4)
	False positive TB test	1,576 (1.6)	4,201 (4.2)	2625 (166.6)
	False negative TB test	1,907 (1.9)	1,358 (1.4)	-549 (-28.8)
100% of presumptive cases know their HIV status	TB cases identified	17,012 (17.0)	17,160 (17.2)	148 (0.9)
	False positive TB test	1,576 (1.6)	4,201 (4.2)	2625 (166.6)
	False negative TB test	1,143 (1.1)	995 (1.0)	-148 (-12.9)

Amongst the 100,000 presumptive TB cases, there were 18,155 true TB cases. Adherence to algorithms was set at 100% for all scenarios.
HIV = Human Immunodeficiency Virus; TB = tuberculosis.

Table 4: Model output comparing the detection of rifampicin resistant tuberculosis between the Xpert-based and Ultra-based algorithms

		Xpert-based algorithm n (%)	Ultra-based algorithm n (%)	Difference in number of cases between algorithms (% difference)
60% of presumptive cases know their HIV status	RMP-R TB cases identified	1,186 (6.5)	1,228 (6.8)	42 (3.5)
	False positive RMP-R result	326 (1.8)	301 (1.7)	-25 (-7.7)
	RMP-TB cases missed	212 (1.2)	170 (0.9)	-42 (-19.8)
	Reasons for RMP-R TB cases missed (% of total RMP-R TB cases missed)			
	False negative TB test	164 (77.4)	104 (61.2)	-60 (-36.6)
	False negative RMP-R result	48 (22.6)	66 (38.8)	18 (37.5)
100% of presumptive cases know their HIV status	RMP-R TB cases identified	1,263 (7.0)	1,253 (6.9)	-10 (-0.8)
	False positive RMP-R result	342 (1.9)	310 (1.7)	-41 (-12.0)
	RMP-TB cases missed	135 (0.7)	145 (0.8)	10 (7.4)
	Reasons for RMP-R TB cases missed (% of total RMP-R TB cases missed)			
	False negative TB test	87 (64.4)	79 (54.5)	-8 (-9.2)
	False negative RMP-R result	48 (35.6)	66 (45.5)	18 (37.5)

Amongst the 18,155 true TB cases there were 1,398 true RMP-R TB cases. Adherence to algorithms at 100%. RMP as a proportion of TB cases in model (18,155). RMP-R TB cases detected, false-positive RMP-R and RMP-R TB cases are reported as a percentage of true TB cases in the model (18,155).

HIV = Human Immunodeficiency Virus; TB = tuberculosis; RMP-R = rifampicin resistant.

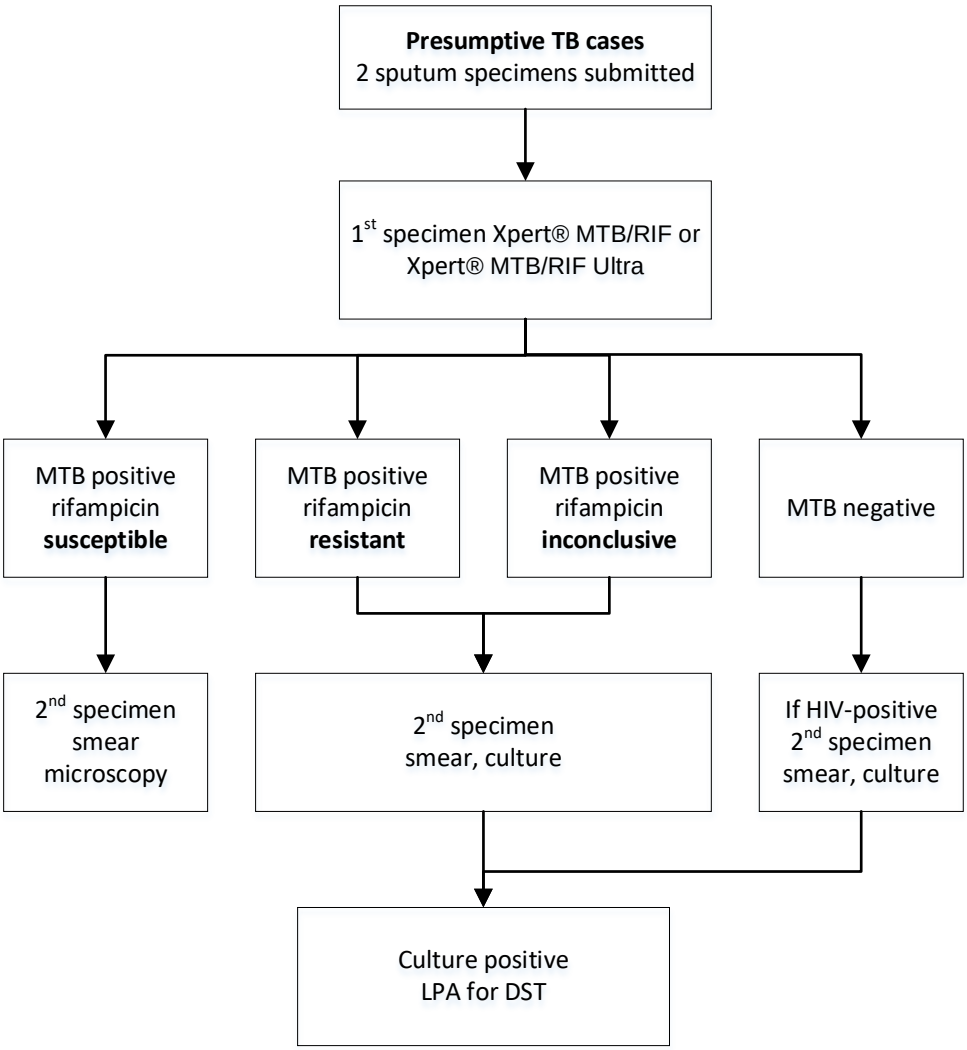

Figure 1: The Xpert-based diagnostic algorithm as implemented in Cape Town.[13] *In the Xpert-based algorithm, two spot specimens were collected and the first was tested with Xpert. If TB was detected, the second specimen underwent smear microscopy. If RMP-R was detected, a culture (BACTEC™ MGIT™ 960; BD, Spark, MD, USA) and LPA (GenoType® MTBDRplus line-probe assay) test was undertaken. The second specimen underwent culture and LPA if the Xpert test was negative and the individual was HIV-positive.*
In the model, we assume that Ultra will replace Xpert without further changes to the existing algorithm.
Abbreviations: TB - tuberculosis; HIV – human immunodeficiency virus; MTB – mycobacterium tuberculosis; RIF – rifampicin; DST - drug susceptibility test; LPA - line-probe assay.

Chapter 6: Discussion

Tuberculosis (TB) and rifampicin resistant (RMP-R) TB are major concerns globally. In 2015, TB was still one of the top 10 causes of death worldwide and the World Health Organisation (WHO) estimated that one third of incident TB cases as well as many RMP-R TB cases were missed, partly due to ineffective diagnosis[1], including the use of insensitive tests such as smear microscopy[2–4], the low availability of culture and drug susceptibility test (DST) infrastructure and delays experienced with the use of culture and conventional DST, which on solid media takes 4-6 weeks to provide a TB result and an additional 2-3 weeks to provide a RMP-R result.[5] Undiagnosed TB and RMP-R TB cases, diagnostic and treatment delays[6,7] and treatment non-initiation among diagnosed cases[8–10] (which is partly influenced by diagnostic delays) all contribute to the ongoing transmission of TB and RMP-R TB.

These challenges have led to increased investment in the development and rollout of new, more sensitive and rapid molecular diagnostic tests for TB and RMP-R TB, with the expectation that these tests would lead to an increase in the number of cases detected and earlier diagnosis and initiation of treatment, thus reducing transmission and, ultimately, the burden of disease. Some of these new diagnostic tests such as line probe assay (LPA) and Xpert MTB/RIF (Xpert), have already been rolled out, or are in the process of being rolled out, in many countries.[11] There are also many other new diagnostic tests currently under development and testing, for example the Xpert TB/RIF Ultra (Cepheid, Sunnyvale, CA, USA) cartridge, Genedrive MTB/RIF (Epistem Ltd, Manchester, M13 9XX, UK), Signature Mapping™ for Tuberculosis Detection Diagnostic System (Applied Visual Sciences Inc., Virginia, US) and loop-mediated isothermal amplification (Eiken Chemical Company Ltd, Tokyo, Japan).[12]

It is essential that during and after the rollout of a new diagnostic test, studies are conducted to evaluate the impact of the new diagnostic test and to identify and test interventions to inform the optimal use of the new test within routine operational settings.[2]

The PROVE IT (Policy Relevant Outcomes from Validating Evidence on ImpacT) study evaluated the impact of the rollout of an Xpert-based algorithm within a routine

operational setting in Cape Town. A limitation of this observational study was that several confounding factors were likely to have contributed to the differences found between the smear/culture and Xpert-based algorithms, making interpretation of the impact of Xpert difficult. These included differences in population characteristics, for example due to a decline in TB prevalence over time, and differences in adherence to the algorithms (including differences in the proportion of human immunodeficiency virus (HIV) positive smear- and Xpert-negative cases with culture tests). Since HIV data was not available consistently, the study could not fully assess the interaction of HIV as a co-variable.

I developed an operation model that could account for these differences in population characteristics and adherence to diagnostic algorithms and to fill gaps in data that were not available through routine data alone. With the model, it was possible to directly compare model outputs for the smear/culture and Xpert-based algorithms whilst allowing us to account for differences in population characteristics and adherence to diagnostic algorithms.

6.1 The overall aim of this dissertation

The overall aim of this dissertation was to use an operational model to compare the proportion of TB and RMP-R TB cases detected (yield), the costs, the model inputs influencing these and the potential impact of health system strengthening interventions in the smear/culture and Xpert-based algorithms. I developed and validated an operational model for the diagnosis of TB and RMP-R TB in Cape Town using data collected during the PROVE IT study. I used the outputs from the model to: (1) explain why the expected increase in TB yield was not found in our empirical study (2) model the effect of interventions on the number of TB and RMP-R TB cases detected (3) model the impact of varying inputs on laboratory cost for TB and RMP-R TB detected (4) model strategies to reduce laboratory cost for TB diagnosis (5) model the effect of introducing a new more sensitive diagnostic test as a replacement for Xpert.

This chapter sets out to synthesise the findings from the operational model used in this dissertation and to provide an overview of using an operational model to assess the mechanisms that influence the diagnosis of TB and RMP-R TB in an Xpert-based algorithm. I discuss the use of an operational model to assess interventions to improve

TB and RMP-R TB diagnosis and the impact on laboratory cost. The rollout of a new more sensitive diagnostic test (Xpert Ultra) as a replacement for Xpert is discussed. I address the strengths and limitations of this research and discuss what it contributes to the evidence base on operational modelling and the use of these models in rolling out new TB diagnostic tests in routine operational settings.

6.2 Modelling TB yield in the smear/culture and Xpert-based algorithms

The empirical study from PROVE IT reported a decrease in TB yield from 20.9% with the smear/culture-based algorithm compared to 17.7% in the Xpert-based algorithm. The decrease in TB yield was attributed to a decrease in TB prevalence. Differences in adherence to the diagnostic algorithms may also have contributed. In order to account for these differences, we modelled a scenario where the population characteristics and adherence to testing protocols were identical in both algorithms (Chapter 2).[13]

In a scenario with identical population characteristics and adherence to testing protocols, the TB yield was 15.8% in the smear/culture-based algorithm compared to 17.9% in the Xpert-based algorithm, an increase of 13.3%. This increase is well below the 30%-37% estimated by a population-level decision model in South Africa[14]. However, the increase is close to that reported from a prospective cluster-randomised trial conducted in a primary care clinic in Cape Town which reported an increase in TB yield from 17% with a smear/culture-based algorithm to 26% with an Xpert-based algorithm.[15]

Both TB prevalence and the extent to which culture testing is undertaken for HIV-positive smear- or Xpert-negative presumptive TB cases are important variables influencing TB yield.

6.2.1 How did TB prevalence affect TB yield?

In order to evaluate the effect of TB prevalence on TB yield, I modelled a scenario with a 10% increase in TB prevalence amongst presumptive cases to 28.8% from the baseline of 18.8% (Chapter 2).[13] When I compared TB yield in the smear/culture-based algorithm at this increased TB prevalence (28.8%) compared to TB yield in the

Xpert-based algorithm at the baseline TB prevalence (18.8%) as calculated from routine data, the model indicated a 30% decrease in TB yield, from 23.3% in the smear/culture-based algorithm to 16.3% in the Xpert-based algorithm.

Even though the TB prevalence amongst presumptive case in the empirical study is unlikely to have declined by as much as 10% (absolute), this partly helps to explain findings from the empirical study and why TB yield did not increase with the rollout the Xpert-based algorithm.[16]

6.2.2 How did culture testing affect TB yield?

According to the diagnostic algorithms, HIV-positive presumptive TB cases with a smear- or Xpert-negative result require a culture test. Routine laboratory data for the empirical study had incomplete HIV data for presumptive TB cases. It was therefore not possible to assess adherence to the algorithm for HIV-positive TB cases who required a culture test after an initial smear-negative or Xpert-negative test result.[16] I addressed this limitation in data by modelling a scenario to show the impact of additional culture testing on reducing the difference in TB yield between algorithms (Chapter 2).[13]

When I increased the proportion of smear-negative and Xpert-negative cases who received culture tests in the model to similar levels to that found in routine practice in our setting, the difference in TB yield between algorithms was reduced to 7.7%. This was attributable to a higher proportion of smear-negative cases in the smear/culture-based algorithm undergoing culture testing compared to Xpert-negative cases undergoing culture testing in the Xpert-based algorithm.

A cluster-randomised trial in four provinces in South Africa also found that culture was more likely to be undertaken for smear-negative (32%) than Xpert-negative (14%) HIV-positive cases.[17] The authors suggested that a greater belief in the efficacy of Xpert may have contributed to fewer culture tests being undertaken on HIV-positive, Xpert-negative presumptive TB cases.

6.3 Modelling RMP-R TB yield in the smear/culture and Xpert-based algorithms

The difference in levels of adherence to DST screening between algorithms in the empirical PROVE IT study made interpretation of the impact of RMP-R TB diagnosis with the rollout of the Xpert-based algorithm difficult. The empirical study found that among presumptive cases diagnosed with TB, 5.5% were identified as RMP-R TB cases in the smear/culture-based algorithm compared to 7.7% in the Xpert-based algorithm, an increase of 54%.[18] The empirical study reported that only 42.7% of presumptive cases (new cases = 31.6%; previous history of TB treatment = 68.1%) diagnosed with TB had a DST done in the smear/culture-based algorithm compared to 78.9% in the Xpert-based algorithm.[18]

I modelled a scenario to compare RMP-R TB yield between algorithms with 100% adherence to algorithms, where 60% of presumptive TB cases know their HIV status in both algorithms and with identical population characteristics (TB prevalence among presumptive TB case = 18.1%, RMP-R prevalence = 7.7%, HIV-positive = 40%, history of previous TB treatment = 25%) (Chapter 3). Among the presumptive cases diagnosed with TB the model identified 3.9% with RMP-R TB in the smear/culture-based algorithm compared to 7.2% in the Xpert-based algorithm, an increase of 95.4%. This difference is attributable to the differences in DST screening strategy between these algorithms. In the smear/culture-based algorithm, only high MDR-TB risk cases are screened for RMP-R at pre-treatment compared to all presumptive TB cases with Xpert-based algorithm.

In a model scenario with 100% adherence to algorithms and where 100% of presumptive TB cases know their HIV status, 56.5% RMP-R TB cases were missed in the smear/culture-based algorithm compared to 11.9% in the Xpert-based algorithm. In the smear/culture-based algorithm 39.4% of RMP-R TB cased were missed due to no DST done compared to all cases having a DST in the Xpert-based algorithm where testing for RMP-R and TB are done simultaneously.

6.4 How can modelling inform the focus of health system strengthening interventions?

I modelled scenarios to provide insights into the potential benefits of interventions that could strengthen the health system after full rollout of the Xpert-based algorithm. These modelled interventions included increasing adherence to the Xpert-based algorithm and increasing HIV testing amongst presumptive TB cases.

6.4.1 Adherence to diagnostic algorithms

6.4.1.1 Effect on TB yield

During the study period, adherence to the Xpert-based algorithm was sub-optimal due to the failure to request the Xpert test by staff that were unfamiliar with the algorithm, due to costs concerns and to clinical decisions overriding the use of the testing algorithm. At times the Xpert test may not have been available due to maintenance on Xpert machines or cartridge stock-outs.

Increasing adherence to the Xpert-based algorithm in the model from 50% to 100% (when 60% of presumptive cases know their HIV status) would increase TB yield by only 6.1% from 15.4% to 16.3% (Chapter 3). This is a small benefit considering that 100% adherence is not a realistic goal in routine practice.

6.4.1.2 Effect on RMP-R TB yield

When adherence to the Xpert-based algorithm was increased from 50% to 100% (with 60% of presumptive cases know their HIV status), the number of RMP-R TB cases detected increased by 63.4% (Chapter 3). The number of RMP-R cases missed decreased from 48.4% to 15.7%. In the modelled scenario with 50% adherence to the Xpert-based algorithm, RMP-R TB cases were missed for the following reasons: 17.2% had a false negative TB test, 2.9% had a false negative RMP-R result and 28.4% had no DST done pre-treatment.

In the modelled scenario with 100% adherence to the Xpert-based algorithm, when all cases had a DST done pre-treatment, the reasons for RMP-R cases missed were as follows: 10.3% had a false negative TB test and 5.4% had a false negative RMP-R.

This illustrates the importance of simultaneous screening for TB and RMP-R, as occurs with adherence to the Xpert-based algorithm.

6.4.2 Increased HIV testing among presumptive TB cases

6.4.2.1 Effect on TB yield

Increasing the proportion of presumptive cases who know their HIV status from 60% to 100% in the model increased TB yield from 15.4% to 15.9%, an increase in TB yield of 3.2% (Chapter 3). This is a modest increase in TB yield, considering the effort required to increase HIV testing so that all presumptive TB cases have an HIV test. Increasing HIV testing does however have other important clinical benefits, for example in enabling access to antiretroviral therapy.

6.4.2.2 Effect on RMP-R TB yield

Increasing the proportion of presumptive TB cases who know their HIV status had very little effect on the number of RMP-R TB cases detected in the Xpert-based algorithm (Chapter 3). When the proportion was increased from 60% to 100%, the number of RMP-R TB cases detected increased by 2.9% (with 50% adherence to the algorithm) and by 4.6% (with 100% adherence to the algorithm).

6.5 The influence of context on the impact of a new diagnostic test

The expected impact of implementing a new diagnostic test will vary depending on the epidemiology of the setting where the new test is implemented.[19] Similarly, the existing diagnostic tests and algorithms already in place as well as where the new diagnostic test is placed within exiting algorithms will affect the observed impact of the new diagnostic test. If the new test is rolled out in a setting where TB cases are already being detected with tests with a high sensitivity (e.g. through the use of high-quality diagnostics such as culture as is the case in Cape Town), the new tool will have a much lower impact than if it is deployed in a setting where TB cases are frequently missed due to low sensitivity as occurs in settings that use only smear microscopy.

6.5.1 Epidemiology of settings

In order to determine the effect of a difference in TB epidemiology on TB yield, we modelled the effect of different TB prevalence levels amongst presumptive cases on TB yield (Chapter 2). In a scenario where the TB prevalence amongst presumptive cases was 10% lower in the smear/culture-based algorithm (18.8%) than in the Xpert-based algorithm (28.8%), the TB yield increased from 15.8% in the smear/culture-based algorithm to 26.7% in the Xpert-based algorithm, an increase of 69%. If we model a scenario with a 10% increase in TB prevalence amongst presumptive cases (from 18.8% to 28.8%) in the Xpert-based algorithm the TB yield increased from 17.9% to 26.7%, an increase of 49.2%.

6.5.2 New diagnostic test in relation to existing diagnostic tests and algorithms

In a scenario where culture testing was removed from the algorithms (85% adherence to algorithms and 50% of presumptive case know their HIV status), there was a 33.6% increase in TB yield between the smear/culture and the Xpert-based algorithm (Chapter 2). The diagnostic benefits of Xpert are thus likely to be greater in areas that do not use or have very limited use of culture.

The performance of smear microscopy in our central laboratory in Cape Town may also be much higher than in settings where smear microscopy is done at point-of-care. This is possibly due to greater proficiency and technical aspects (centrifugation, chemical treatment, fluorescence microscopy) at the central laboratory. In a modelled scenario (85% adherence to algorithms and 50% of presumptive case know their HIV status) where the sensitivity of smear microscopy was 10% lower (70% to 60%), as assumed would be the cases if smear microscopy was done at point-of-care, the TB yield increased from 14.7% in the smear/culture-based algorithm to 17.9% in the Xpert-based algorithm, an increase of 21.8% (Chapter 2).

6.6 Cost implications with the rollout of the Xpert-based algorithm

The empirical costing study undertaken in PROVE IT showed that the laboratory cost per pulmonary TB case detected increase by 157%, from $48.77 in the smear/culture-based algorithm to $125.32 in the Xpert-based algorithm.[20] The cost per RMP-R TB

case detected (cost of TB diagnosis plus cost of RMP-R diagnosis) was similar at US$190.14 in the smear/culture-based algorithm and US$183.86 in the Xpert-based algorithm. A direct comparison in laboratory cost between the two algorithms was difficult to make due to the decline in TB prevalence over the study period, differences in adherence to the diagnostic algorithms, and possibly some wasteful testing due to unnecessary repeat tests requested.

We modelled a scenario to directly compare laboratory costs between algorithms. We modelled both algorithms with identical input parameters for TB prevalence among the presumptive cases tested (18.1%), HIV status (60% knew their HIV status and 40% were HIV-positive), history of previous tuberculosis treatment (25%) and adherence to diagnostic algorithms (100%) (Chapter 3).[21] The model indicated that the cost per TB case detected would increase by 114% for the Xpert-based algorithm compared to the smear-based algorithm, with only a 5.5% increase in the number of TB cases detected.

The model indicated that even though the increase in the number of TB cases detected was small, the most important benefit of the Xpert-based algorithm was the 95.4% increase in the number of RMP-R TB cases detected with only a 15.8% increase in the cost per RMP-R TB (Chapter 3). The cost per additional RMP-R TB case detected in the Xpert-based algorithm compared to the smear/culture-based algorithm was U$2,359. These high costs should be weighed against potential cost savings that may be realised through reducing TB and RMP-R TB transmission.

Numerous studies have indicated that the use of Xpert has come at a much higher cost than tests previously used for TB diagnosis. Two studies in South Africa reported a cost per Xpert test performed of US$25.90 (in 2010 US$)[22] and US$14.93 (in 2012 US$) compared with respectively US$1.58 and US$3.40 for smear.[23] A study conducted in India, evaluating the costs of various pulmonary TB diagnostic strategies, found that the strategy with Xpert as the first-line test had the highest cost per TB case detected.[24] These high diagnostic costs to the health system in developing countries are not likely to be sustainable in the long term, and alternative strategies need to be sought.

6.7 Efforts to decrease the cost per TB case detected in the Xpert-based algorithm as case-finding is scaled-up

The South African Department of Health plans to substantially scale-up case-finding efforts to meet the End TB Strategy goals. As part of the End TB Strategy, three people-centred targets were introduced which consist of reaching 90% of all people who need anti-tuberculosis treatment, including 90% of people in key populations and achieving at least 90% treatment success rates. The strategy recommends that countries set an operational target of reaching at least 90% of people in key populations through improved access to services, systematic screening where required, new case-finding methods, and providing all people in need with effective and affordable treatment.[1,25]

The cost per TB case detected is directly influenced by the TB prevalence among presumptive cases tested for TB. As case-finding efforts are scaled-up and the number of individuals tested for TB increases, the proportion with TB among those tested will decrease, and therefore the cost per TB case detected will increase. This increase in cost has serious implications for South Africa's efforts to increase case-finding, and alternative strategies would need to be considered to reduce costs while still finding cases.

Other than reducing the price of the Xpert cartridge, a further approach to reduce the cost per TB case detected would be to increase TB prevalence (the proportion of people who have TB) among the presumptive cases tested. This could be accomplished by implementing an improved pre-test screening or triage strategy.[26] I modelled scenarios in which I reduced and increased the TB prevalence among presumptive cases tested and assessed the effect on the cost per TB case detected (Chapter 4).[21] I also assessed the effect on cost per TB case detected if the price per Xpert cartridge was reduced.

The model indicated that the best approach to improve affordability would be a combined approach of increasing the TB prevalence among presumptive cases tested using either a triage test or other pre-screening strategies, and a reduction in the price of Xpert cartridges. For example, if the TB prevalence among presumptive cases was 10.6% and with a 50% reduction in the price of Xpert cartridges, the cost per TB case

detected was still high, at US$142. With an increase in TB prevalence among presumptive cases tested to between 25.9% – 30.8% and the price of the Xpert cartridge reduced by 50%, the cost per TB case detected would range from US$50 to US$59, a level that is comparable with the cost per TB case detected in the smear/culture-based algorithm (US$48.77) found in the PROVE IT empirical laboratory costing study.[20]

The model indicated that unless alternative triage strategies are identified, the approach of increasing case-finding will not be sustainable, even if Xpert cartridge prices are reduced.

A study using a decision analytical model showed that a hypothetical triage test with sensitivity equivalent to that of the Xpert test, 75% specificity and cost of US$5 per test, would reduce the total diagnostic cost by 39% in South Africa.[27] No triage test is currently available, and this has been identified as one of the priorities in the development of new diagnostics for TB.[28]

It has been shown that pre-screening presumptive TB cases with smear microscopy with a follow-up Xpert test for all those with a smear-negative tests had a higher sensitivity (81.9%, 95% CI 74.9 – 87.2) than testing only with smear microscopy (sensitivity = 68.5%, 95% CI 60.6 – 75.4) or testing only with Xpert (sensitivity = 77.2%, 95% CI 69.8 – 83.2). This strategy would result in a 28.7% reduction in the cost per TB case detected from US$516 when Xpert was used on all cases to US$401 when used on all smear-negative cases.[29]

6.8 Modelling the rollout of future tests

In many countries, the detection of TB is still reliant on old technology such as smear microscopy and culture. However, over the last decade, there has been an increase in the development of new diagnostic tests. A pipeline analysis of new TB diagnostic technologies reported that, in 2015, there were about 50 different new TB diagnostic technologies.[12] One of these new technologies, Xpert MTB/RIF Ultra (Ultra) (Cepheid, Sunnyvale, CA, United States), has been developed to replace the current version of Xpert MTB/RIF (Xpert).[30,31] The development and rollout of Xpert was a major improvement over previous diagnostic test, such as smear microscopy and culture, for

the simultaneous detection of TB and RMP-R TB. However, Xpert still had imperfect sensitivity especially in HIV-positive TB cases and some limitations in detecting RMP-R TB. Ultra was developed to address these limitations and showed higher sensitivity and lower specificity than Xpert.[30,31]

A prospective multicentre diagnostic accuracy study compared the performance of Ultra to that of Xpert for the detection of TB and RMP-R TB.[30] This study found an overall 4.9% increase in sensitivity with Ultra (87.8%) compared to Xpert (82.9%). The increase in sensitivity was higher among HIV-positive individuals with an increase of 12.3% (Ultra = 87.8%, Xpert = 75.5%) compared to 1.3% (Ultra = 90.6%, Xpert = 89.3%) among HIV-negative individuals. The overall specificity was lower by 3.2% with Ultra (94.8%) compared to Xpert (98%). The decrease in specificity was higher among individuals with a previous history of TB treatment (5.4%, Ultra = 91.5%, Xpert = 96.9%) compared to individuals with no previous history of TB treatment (2.5%, Ultra = 95.9%, Xpert = 98.4%). Sensitivity and specificity for detecting RMP-R TB was similar between Ultra (sensitivity = 94.8%, specificity 98.2%) and Xpert (sensitivity = 95.5%, specificity 97.9%).

The model indicated that using Ultra as a replacement for Xpert (Chapter 5) would only increase TB yield by 3.4% (if 60% know their HIV status). The increase in TB yield was even smaller (0.9%) if 100% of presumptive TB cases know their HIV status. This was balanced by a 167% increase in the number of false positive presumptive cases detected (when 100% know their HIV status). The model indicated a 3.5% (if 60% know their HIV status) increase in the number of RMP-R TB cases detected and a 0.8% decrease in the number of RMP-R TB cases detected if 100% of presumptive TB cases know their HIV status.

The small increase in TB and RMP-R TB yield has to be weighed against the massive increase in the number of false positive cases detected and unnecessarily treated. The increase in false positive cases, especially in settings with high proportions of presumptive TB cases with a history of previous TB treatment, would place a large burden on the health system and patients. Decision makers would have to take the high number of false positive cases in consideration, if Ultra replace Xpert, and find a

balance between increased TB case detection and unnecessarily starting patients on TB treatment.

6.9 Summary: What did I find with the operational model?

The model outputs presented in this dissertation showed that there was an increase in TB yield in the Xpert-based compared to a smear/culture-based algorithm, though this increase was not as high as expected (Chapter 2). The model indicated that a decrease in TB prevalence as well as different levels in adherence to the diagnostic algorithms were likely reasons that the empirical study did not find an increase in TB yield in the Xpert-based algorithm. The model also indicated that the context of the health system has to be taken into consideration when evaluating the impact of a new TB diagnostic test. In our setting, the high efficiency of the central laboratory as well as extensive use of culture testing for smear-negative cases in the smear/culture-based algorithm limited the observed benefit of the Xpert-based algorithm.

The model indicated that the real benefit of the Xpert-based algorithm is the ability of Xpert to simultaneous test for TB and RMP-R (Chapter 3). The small increase in TB yield and the high laboratory cost of the Xpert-based algorithm have to be weighed against the efficiency of Xpert in diagnosing RMP-R TB cases. The model did however indicate that this benefit in diagnosing RMP resistance is highly dependent on adherence to the Xpert-based algorithm.

The high laboratory cost and high cost per TB case detected with the rollout of the Xpert-based algorithm is a concern. The long-term sustainability of the high cost to the health system is questionable, particular if TB case-finding efforts are increased. The model indicated that alternative, more cost-effective strategies will need to be implemented in settings where the TB prevalence among presumptive cases is low or declining (Chapter 4). We showed that a reduction in the price of Xpert cartridges would not be sufficient to bring the cost per TB case detected down and alternative strategies such as better pre-screening or a triage screening test will need to be implemented with increased case-finding efforts.

The model showed that replacement of Xpert with Ultra, which has higher sensitivity but lower specificity for TB detection, would increase TB and RMP-R TB case

detection slightly (Chapter 5). However, there would be a significant increase in the number of false-positive TB cases detected. The small increase in the number of TB cases detected has to be weighed against the increased number of false positive cases detected and unnecessarily treated.

6.10 Strengths and Limitations

The model developed and used in this dissertation had several strengths, including the availability of detailed routine data and information on health and laboratory processes collected within the PROVE IT empirical study. This allowed me to develop a precise operational model to assess the impact of TB and RMP-R TB detection in terms of number of cases detected and laboratory costs. The model input parameters were based mostly on these detailed routine data, and only a few assumptions, based on literature, were made. We assumed that TB prevalence among presumptive cases was higher among HIV-positive presumptive cases than among HIV-negative cases[32,33], and among previously treated than among new TB cases;[14] we assumed a decrease in TB prevalence among presumptive TB cases over time based on the empiric yield data, which showed a decrease in yield over time despite similar proportions of the population being tested.[16]

We had detailed information for both the previously used smear/culture-based algorithm and the newly introduced Xpert-based algorithm and therefore the model could be developed for both algorithms. This made a direct comparison between the algorithms possible taking into account differences in population characteristics and adherence to algorithms. A further strength of the model is the fact that we could validate the model against data for seven-time points, as reported by the empirical study, which built confidence in the outputs from the model and confirmed that the outputs were credible.

Generalisability of findings from the model and the use of the model for other settings may be limited as the model was validated against data from a well-resourced, urban setting, with good health and laboratory infrastructure and therefore may not reflect reality in other settings, such as rural areas. The rollout of the Xpert-based algorithm in Cape Town was different to the Xpert-based algorithm rolled out nationally. In the

Cape Town Xpert-based algorithm, two sputum specimens are required compared to only one specimen required in the national Xpert-based algorithm.

The highly centralised diagnostic infrastructure in Cape Town as well as the extensive use of culture testing may also limit generalisability of findings from the model and therefore make a direct comparison to countries with decentralised diagnostic infrastructure and no culture testing difficult.

A limitation of the model is that we did not consider time delays in the model, such as the time it takes to process a sputum specimen and have a test result available. We did include time delays as part of the model input parameters and model logic, however, these were not reported as part of the model output as they did not add to the findings from the empirical study.

6.11 Innovation

This dissertation used an operational model for the detection of TB and RMP-R TB cases to compare diagnostic algorithms in routine operational settings. The model did not only evaluate the impact of a single test on the health system, but rather took the complete testing protocol stipulated in each algorithm into consideration. New diagnostic tests are implemented as part of a diagnostic algorithm and not used in isolation and using this approach allowed for a more realistic comparison between algorithms.

It would not have been possible to develop the operational model without operational data being available. Whilst it would thus not have been feasible to use this model to inform decisions about the implementation of Xpert, it could be used to provide data on the benefits to be expected from health system strengthening efforts such as improved adherence to diagnostic algorithms and increased HIV testing amongst presumptive TB cases. The model provides useful data on the benefits to be expected if Ultra were to replace Xpert, providing a sobering picture of the potential number of cases treated unnecessarily, in order to detect a relatively small number of additional TB and RMP-R TB cases. To my knowledge an operation model has not, to date, been used to comprehensively evaluate diagnostics in the way that I have done in this dissertation.

6.12 What does modelling contribute to the evidence base?

This dissertation and the modelling approach followed demonstrates that modelling is not just a useful tool to make future projections of burden of a disease, but could be used to assess the potential impact of new diagnostic tools under routine operational conditions and provide insights on how to increase impact.

The operational model used in this dissertation was developed as part of the PROVE IT study undertaken after the rollout of Xpert in South Africa. The empirical analyses from PROVE IT identified inefficiencies in the health system that contributed to the findings on TB and RMP-R TB yield and laboratory costs when comparing algorithms. These need to be addressed to ensure the optimal use of Xpert, for example, ensuring adherence to the Xpert-based algorithm and therefore that all presumptive TB cases receive Xpert as a first-line test and that all HIV-positive presumptive TB cases with a negative Xpert result receive a culture test.

The modelling allowed us to answer several important questions. With the model, the above factors to strengthen the health system for TB and RMP-R TB detection could be evaluated, and gaps in data (HIV status) could be addressed. This research contributes important evidence to decision makers as to which intervention strategies would result in better TB and RMP-R TB case detection as well as the impact of these interventions on laboratory cost.

The effect of culture testing for HIV-positive presumptive TB cases, on TB and RMP detection, was however not possible in the empirical study due to the incomplete data available in the routine laboratory on HIV status .

An important challenge for the health system is to ensure that everyone has access to health services and to new technologies, in particular the poor and marginalised groups.[34] The model indicates that unless a concerted effort is made to use the newly introduced technology optimally, the investment in the new technology would not fully benefit the health system and patients.

The empirical study as well as output from the model indicate that with the rollout of Xpert there were definite benefits, in particular an increase in the detection of RMP-R

TB cases. Other benefit were also identified by the empirical study such as reduced initial loss to follow-up and reduced treatment delay for TB cases, reduced delays to MDR-TB treatment initiation and reduced costs to MDR-TB patients.[35] These benefits came at a very high cost to the health system and therefore additional strategies (such as a pre-screening or triage testing) would need to be considered to bring these costs down in order to be sustainable to the health system.

Cepheid, the developers of Xpert® MTB/RIF, has developed an upgrade to Xpert® MTB/RIF namely Xpert® MTB/RIF Ultra. The company plan to slowly phase-out Xpert® MTB/RIF to be eventually completely replace by Xpert® MTB/RIF Ultra.[30,31] Ultra has a higher sensitivity but lower specificity than Xpert. The model indicated that even though more TB and RMP-R TB cases will be detected by Ultra, the lower specificity (in particular for individual with a history of previous TB treatment) will result in more individuals incorrectly being detected with TB and unnecessarily been started on TB treatment. Alternative strategies, such as alternative diagnostic algorithms, will have to be considered to find a balance between increased detection of TB cases and unnecessarily starting patients on TB treatment due to false positive results.

The findings from the studies presented in this dissertation highlight the important role that an operation model can play in informing decision maker on the optimal use of new diagnostic test in an operational setting, even after the rollout of the new test. Operational modelling can therefore be an effective tool to be used to assist the health department to optimise the way in which tests are currently used and could serve to inform policy decisions about the implementation of new more sensitive diagnostic tests.

6.13 Recommendations for further research

In this dissertation, I used an operational model to model the effect of interventions for health system strengthening on TB and RMP-R TB detection, however, we did not model all possible interventions. Future studies are required to identify and test further health system interventions with the operational model, for example, interventions to further reduce the delay in starting TB and MDR-TB treatment and initial loss to treatment. Studies conducted in South Africa indicated that 15.5% to 34.7% of laboratory confirmed TB cases did not start TB treatment.[9,10,36–38] A nationwide

retrospective cohort study conducted in South Africa to assess second-line treatment initiation and delay among laboratory confirmed RMP-R TB cases[39] indicated that in 2013 (after full rollout of Xpert in South Africa), only 51% to 73% of laboratory confirmed RMP-R TB cases initiated MDR-TB treatment with the median delay in starting treatment of between 15 and 36 days. These cases not initiating TB and MDR-TB treatment as well as delays in initiating treatment contribute to the ongoing transmission of TB and MDR-TB in the community.

Further studies are required to determine the long-term population level impact of introducing new TB and RMP-R TB diagnostic tests. The long-term population level impact of health system strengthening interventions for the optimal use of these new diagnostics also needs to be determined. Such studies will use transmission modelling to predict the long-term impact on the community by projecting TB incidence, prevalence, and mortality.[19,40] There are however few studies that combine the strengths of both transmission modelling and operational modelling. Such a study was conducted to determine the effects of new diagnostic tests from the patient, health system, and population perspective in United Republic of Tanzania by incorporating and linked a detailed operational model with a transmission model.[41] We therefore propose a study to follow a similar approach, as was done for United Republic of Tanzania, and develop a combined operational and transmission model.

6.14 References

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Supplement

A list of manuscripts I contributed to as part of Policy Relevant Outcomes from Validating Evidence on ImpacT.

1. du Toit E, Squire SB, Dunbar R, Machekano R, Madan J, Beyers N, Naidoo P. Comparing multidrug-resistant tuberculosis patient costs under molecular diagnostic algorithms in South Africa. Int J Tuberc Lung Dis. 2015 Aug;19(8):960–8.

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5. Naidoo P, Dunbar R, Lombard C, du Toit E, Caldwell J, Detjen A, Squire SB, Enarson DA, Beyers N. Comparing tuberculosis diagnostic yield in smear/culture and Xpert® MTB/RIF-based algorithms using a non-randomised stepped-wedge design. PLoS One. 2016;11(3):e0150487.