Evaluating the Impact of an Xpert® MTB/RIF- based TB Diagnostic Algorithm in a Routine Operational Setting in Cape Town

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DECLARATION

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the authorship owner thereof (unless to the extent explicitly otherwise stated) and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

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To my family Al, Ethan and Keryn – for their love and support and for every day joys.

CONTENTS

ABSTRACT

Decades of reliance on slow, inaccurate diagnostic tests have contributed to poor case detection and impeded tuberculosis (TB) control efforts globally. The development of an accurate, rapid molecular diagnostic test, Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) (Xpert), offers the prospect of identifying more cases, detecting them rapidly and enabling quicker treatment initiation. Xpert is a nucleic acid amplification test that simultaneously detects genetic sequences for *Mycobacterium tuberculosis* complex and the presence of mutations conferring resistance to rifampicin. Xpert sensitivity is substantially higher than smear microscopy (88% compared to 53.8% for a single smear) and provides a test result within a day (compared to 8-16 days for liquid culture). Whilst laboratory and demonstration studies suggest that Xpert has the technical capacity to address the limitations of conventional smear and culture tests, very little is known about how this translates into patient and public health benefits in routine operational conditions.

The overall **aim** of this thesis was to undertake rigorous scientific research into the impact of an Xpert® MTB/RIF-based TB diagnostic algorithm in a routine operational setting in Cape Town. This entailed a pragmatic comparison between the existing smear/culture-based TB diagnostic algorithm and the newly introduced Xpert-based algorithm. The magnitude and range of benefits for laboratory confirmed cases of TB and MDR-TB were assessed.

Impact analysis was guided by the Impact Assessment Framework which ensured a systematic and comprehensive approach to the evaluation of the new diagnostic algorithm. This framework addresses five aspects of impact: ***Effectiveness Analysis*** assesses the impact on the numbers of cases diagnosed and appropriately started on treatment as well as the timeliness of results and of treatment initiation. ***Equity Analysis*** assesses whether marginalised groups who may be more affected benefit from the new test – poor people, women and HIV-infected specifically. ***Health Systems Analysis*** assesses the human resource, laboratory infrastructure, procurement and quality assurance implications. ***Scale-up Analysis*** assesses the economic costs and benefits of scaling up the new technology from both a provider and a patient perspective. ***Horizon Scanning*** assesses what other similar technologies are available or likely to become available and how these compare in their projected performance.

The stepped-wedge analysis of TB yield *(Chapter 2)* in five sub-districts between 2010 and 2013 showed that among the 54,393 presumptive cases tested, the proportion with a bacteriological diagnosis of TB was not increased in the Xpert-based algorithm. We found a decline in TB yield over time, possibly attributable to a declining TB prevalence. When the time-effect was taken into consideration, there was no difference TB yield – yield was 19.3% (95% CI 17.7% to 20.9%) in the Xpert-based algorithm compared to 19.1% (95% CI 17.6% to 20.5%) in the smear/culture-based algorithm with a risk difference of 0.3% (95% CI -1.8% to 2.3%, p=0.796). Inconsistent implementation of the Xpert-based algorithm and the frequent use of culture tests in the smear/culture-based algorithm may have contributed to the yield parity.

The multidrug-resistant (MDR)-TB yield study *(Chapter 3)* found that amongst the 10,284 TB cases identified in the five sub-districts, the Xpert-based algorithm was more effective in identifying MDR-TB than the smear/culture-based algorithm. Pre-treatment, there was a higher probability of having drug susceptibility tests undertaken (RR=1.82, p<0.001) and of being diagnosed with MDR-TB (RR=1.42, p<0.001) in the Xpert-based algorithm than in the smear/culture-based algorithm. Overall 8.5% of TB cases were detected with MDR-TB in the Xpert-based algorithm compared to 6% in the smear/culture-based algorithm, translating to approximately

375 additional MDR-TB cases diagnosed in Cape Town annually.

The study on TB treatment initiation and treatment success undertaken in five sub-districts in October – December 2011 *(Chapter 4)* found that a higher proportion of cases initiated TB treatment in the Xpert group (84%, 508/603) than in the smear/culture group (71%, 493/693, p<0.001). The adjusted odds ratio for treatment initiation in the Xpert group was 1.98 (p<0.001). Cases >44 years in age (AOR=0.49, p<0.001) and previously treated cases (AOR=0.64, p=0.020) were less likely to initiate treatment. Laboratory delay was associated with non-initiation (AOR=0.96 per day, p<0.001). The reduction in TB treatment delay from a median of 15 days in the smear/culture group to 7 days in the Xpert group did not translate into improved TB treatment outcomes and treatment success rates were 80% in both groups (AOR=0.95, p=0.764).

The MDR-TB treatment commencement study *(Chapter 5)* undertaken in 10 high TB burden facilities found that the time from test taken to treatment initiation was reduced from 43 days in the smear/culture-based algorithm (n=375) to 17 days in the Xpert-based algorithm (n=120) with a mean reduction of 25 days (p<0.001). Median laboratory turnaround time from test taken to result available in the laboratory was reduced from 24 days to <1 day with a mean reduction of 20 days (P<0.001) between algorithms.

The qualitative study on MDR-TB patient pathways *(Chapter 6)* showed that patients experienced substantial delays before being diagnosed – these delays may not have been reflected using the data from the laboratory and clinics. Avoidable health system delays resulted from providers not testing for TB at initial health contact, non-adherence to testing algorithms, results not being available and failure to promptly recall patients with positive results. Negative perceptions of the public sector (as over-burdened, with long waiting times, negative staff attitudes and lack of privacy) were prevalent and contributed to deferred health-seeking, interruptions to the diagnostic process and to patient's preferential use of the private sector, contributing to delays in both algorithms.

The MDR-TB patient costing study *(Chapter 7)* assessed direct (out-of-pocket expenses) and indirect costs (lost productivity costs for patient's time) incurred. The median patient cost from initial health visit to treatment initiation was reduced from $68.1 in the smear/culture-based algorithm to $38.3 (p=0.004) in the Xpert-based algorithm. Median direct costs were low at $6.7 and $4.4 (p=0.321) respectively. The difference in costs was attributable to time costs as the median number of visits to MDR-TB treatment was reduced from 20 in the smear/culture-based algorithm to 7 in the Xpert-based algorithm (p<0.001). Further details are provided below in the section on equity.

From a laboratory costing perspective *(Chapter 8)* we found a 43% increase in overall PTB laboratory costs at the central laboratory, from $440,967 in the smear/culture-based algorithm to $632,262 in the Xpert-based algorithm for 3-month periods. 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 MDR-TB case diagnosed was similar at $190.14 in the smear/culture-based algorithm compared to $183.86 in the Xpert-based algorithm.

From an ***effectiveness*** perspective, the Xpert-based algorithm did not result in an increase in the number TB cases diagnosed or improve treatment outcomes amongst those initiating treatment. It did however significantly reduce treatment delay and increased the proportion of TB cases initiating treatment. The Xpert-based algorithm resulted in a higher proportion of MDR-TB cases being diagnosed and reduced MDR-TB treatment commencement time.

From an ***equity*** perspective the Xpert-based algorithm helped reduce health inequities through improving effectiveness as described above. However, these benefits did not shield patients from economic losses. The proportion unemployed increased (from symptom onset to the time of the interview) in both groups: from 39% to 73% in the smear/culture group (p<0.001) and from 53% to 89% in the Xpert group (p<0.001). From symptom onset to the time of the interview there was a 16% decrease in median household income in the smear/culture group and 13% decrease in the Xpert group and "catastrophic" costs were experienced by 38% and 27% (p=0.165) in respective groups who lost >10% of monthly household income.

Health system failures at several levels from poor initial planning for Xpert implementation to human resource and IT infrastructure deficits, to poor accountability and inefficient service delivery as well as low community preparedness are likely to have diminished the full potential impact of the Xpert-based algorithm. Urgent attention needs to be paid to these issues to optimise the benefit of Xpert.

From a ***scale-up perspective*** the increase in laboratory costs in our study are offset to some extent by the cost-saving to MDR-TB patients.

As part of broader work we have developed a discrete event simulation model and validated it using the results from the studies presented in this thesis. This model will be used to evaluate more cost-effective diagnostic options and the benefits of a more sensitive test such as Xpert Ultra, which our ***horizon scanning*** suggests is the most likely current replacement for Xpert.

These studies have limitations. It was difficult to control for bias - for example the non-random allocation of facilities to different study arms was ouside our control. Generalisability to other settings, especially rural settings, is limited as these studies were undertaken within a well-resourced, urban setting, with relatively good health and laboratory infrastructure. It was possible to address temporal trends in some studies (for example the stepped-wedge analysis of TB yield) but not in others (for example the MDR-TB treatment commencement study where decentralization of services may have contributed to the findings).

The studies presented in this thesis have several novel aspects: they were undertaken at the level of the Xpert-based diagnostic *algorithm* and not the individual test, reflecting how tests were used in clinical practice. They reflect the patient, provider and health system factors that influenced outcomes and that are essential to understanding the impact of the new diagnostic algorithm in routine programmatic conditions. In addition, the use of Impact Assessment Framework provided a comprehensive view of the benefits and limitations of Xpert.

These studies highlight the effect of the early introduction of new tools into under-prepared and inefficient health systems and provide insights into some of the health system weaknesses that could be addressed to optimise the impact of Xpert. Unless concerted efforts are made to address these weaknesses, the investment in this expensive new technology will not provide the full range of benefits possible.

OPSOMMING

Omdat daar oor dekades heen op stadige, onakkurate diagnostiese toetse staatgemaak is, het die opsporing en beheer van tuberkulose (TB) wêreldwyd daaronder gely. Die ontwikkeling van ’n akkurate, vinnige molekulêre diagnostiese toets, Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, VSA) (Xpert), bring die moontlikheid dat meer gevalle nou dalk vinniger geïdentifiseer kan word sodat behandeling gouer kan begin. Xpert maak van nukleïensuurversterking gebruik om terselfdertyd genetiese reekse vir *Mycobacterium tuberculosis* kompleks sowel as weerstandigheidsmutasies teen rifampisien op te spoor. Xpert is meer sensitief as smeermikroskopie (88% vergeleke met 53.8% vir ’n enkele smeer), en die toetsresultaat is binne ’n dag beskikbaar (vergeleke met 8-16 dae vir vloeistofkweking). Hoewel laboratorium- en demonstrasiestudies daarop dui dat Xpert oor die tegniese vermoë beskik om die beperkings van konvensionele smeer- en kwekingstoetse te bowe te kom, is weinig nog bekend oor die werklike voordele wat dit in normale bedryfsomstandighede vir pasiënte en openbare gesondheid inhou.

Die oorkoepelende doel met hierdie tesis was om streng wetenskaplike navorsing te onderneem oor die impak van ’n Xpert® MTB/RIF-gebaseerde algoritme vir TB-diagnose in ’n normale bedryfsomgewing in Kaapstad. Hiervoor is ’n pragmatiese vergelyking onderneem van die bestaande smeer/kwekingsgebaseerde algoritme vir TB-diagnose, en die nuut ingestelde Xpert-gebaseerde algoritme. Die omvang van én verskeidenheid voordele vir laboratoriumbevestigde TB- en MDR-TB-gevalle is beoordeel.

Impakontleding is deur die impakbeoordelingsraamwerk gerig, wat ’n stelselmatige en omvattende benadering tot die beoordeling van die nuwe diagnostiese algoritme verseker het. Hierdie raamwerk ondersoek vyf aspekte van impak: ***Doeltreffendheidsontleding*** beoordeel die impak op die getal gevalle wat gediagnoseer word en met gepaste behandeling begin, sowel as die tydigheid van resultate en behandelingsaanvang. ***Billikheidsontleding*** beoordeel of gemarginaliseerde groepe wat dalk erger geraak word – in die besonder arm mense, vroue en MIV-geïnfekteerde persone – by die nuwe toets baat vind. ***Gesondheidstelselontleding*** beoordeel die implikasies vir menslike hulpbronne, laboratoriuminfrastruktuur, verkryging en gehalteversekering. ***Opskaleringsontleding*** beoordeel die ekonomiese koste en voordele verbonde aan die opskalering van die nuwe tegnologie uit sowel ’n verskaffer- as ’n pasiënteoogpunt. ***Horisonbespieding*** beoordeel watter ander soortgelyke tegnologieë beskikbaar is of waarskynlik beskikbaar sal kom, en hoe die verwagte prestasie daarvan van Xpert s’n verskil.

Die trapsgewyse wigontleding van TB-opbrengs *(hoofstuk 2)* in vyf subdistrikte tussen 2010 en 2013 toon dat onder die 54 393 vermoedelike gevalle wat getoets is, die persentasie met ’n bakteriologiese TB-diagnose nie met die Xpert-gebaseerde algoritme verhoog het nie. Die navorsing dui op ’n afname in TB-opbrengs oor tyd, moontlik as gevolg van ’n afname in TB-voorkoms. Toe die tydeffek in ag geneem is, was daar geen verskil in TB-opbrengs nie – 19.3% (95% CI 17.7% tot 20.9%) met die Xpert-gebaseerde algoritme vergeleke met 19.1% (95% CI 17.6% tot 20.5%) met die smeer-/kwekingsgebaseerde algoritme, met ’n risikoverskil van 0.3% (95% CI -1.8% tot 2.3%, p=0.796). Inkonsekwente implementering van die Xpert-gebaseerde algoritme en die gereelde gebruik van kwekingstoetse in die smeer-/kwekingsgebaseerde algoritme kon tot die pariteit in opbrengs bygedra het.

Die studie van multimiddelweerstandige (MDR-) TB-opbrengs *(hoofstuk 3)* bevind dat onder die 10 284 TB-gevalle wat in die vyf subdistrikte geïdentifiseer is, die Xpert-gebaseerde algoritme MDR-TB doeltreffender as die smeer-/kwekingsgebaseerde algoritme gediagnoseer het. Voor behandeling, was die waarskynlikheid dat

middelweerstandigheidstoetse gedoen sal word (RR=1.82, p<0.001) en dat MDR-TB gediagnoseer sal word (RR=1.42, p<0.001), hoër met die Xpert-gebaseerde algoritme as met die smeer-/kwekingsgebaseerde algoritme. Die Xpert-gebaseerde algoritme het 8,5% van TB-gevalle as MDR-TB geïdentifiseer, vergeleke met 6% wat deur die smeer-/kwekingsgebaseerde algoritme geïdentifiseer is. Dít kom neer op die diagnose van sowat 375 bykomende MDR-TB-gevalle in Kaapstad per jaar.

Die studie van TB-behandelingsaanvang en -behandelingsukses wat van Oktober tot Desember 2011 in vyf subdistrikte onderneem is (*hoofstuk 4)*, het bevind dat ’n hoër persentasie in die Xpert-groep met TB-behandeling begin het (84%, 508/603) as in die smeer-/kwekingsgroep (71%, 493/693, p<0.001). Die waarskynlikheid van behandelingsaanvang was hoër in die Xpert-groep (AOR=1.98, p<0.001). Gevalle bo 44-jarige ouderdom (AOR=0.49, p<0.001) en voorheen behandelde gevalle (AOR=0.64, p=0.020) het ’n laer waarskynlikheid getoon om met behandeling te begin. Laboratoriumvertraging het ’n verband met die gebrek aan behandelingsaanvang getoon (AOR=0.96 per dag, p<0.001). Die daling van ‘n mediaan van 15 dae in TB-behandelingsvertraging in die smeer-/kwekingsgroep tot 7 dae in die Xpert-groep het nie in die praktyk tot beter TB-behandelingsuitkomste gelei nie, en behandelingsuksessyfers was 80% in albei groepe (AOR=0.95, p=0.764).

Die studie van MDR-TB-behandelingaanvangtyd *(hoofstuk 5)* wat in 10 fasiliteite met ’n swaar TB-las onderneem is, bevind dat die tydsduur vandat die toets gedoen word totdat behandeling begin, verkort is van 43 dae met die smeer-/kwekingsgebaseerde algoritme (n=375) tot 17 dae met die Xpert-gebaseerde algoritme (n=120), met ’n gemiddelde verkorting van 25 dae (p<0.001). Die mediane laboratoriumomkeertyd vandat die toets geneem is totdat die resultaat beskikbaar was in die laboratorium, is verkort van 24 dae tot <1 dag, met ’n gemiddelde verkorting van 20 dae (p<0.001) tussen algoritmes.

Die kwalitatiewe studie van MDR-TB-pasiëntbehandelingsroetes *(hoofstuk 6)* toon dat pasiënte beduidende vertragings ervaar voordat hulle gediagnoseer word – hierdie vertragings kom moontlik nie na vore uit die data van die laboratorium en klinieke nie. Voorkombare gesondheidstelselvertragings kan daaraan toegeskryf word dat verskaffers nie met die eerste kontakbesoek reeds vir TB toets nie, dat toetsalgoritmes nie nagekom word nie, dat resultate nie beskikbaar is nie, en dat verskaffers versuim om pasiënte met positiewe resultate dadelik te laat terugkeer. Negatiewe opvattings oor die openbare sektor (soos oorlading, lang wagtye, negatiewe personeelingesteldheid en ’n gebrek aan privaatheid) is algemeen en het bygedra tot die uitstel van die soeke na gesondheidshulp, onderbrekings in die diagnostiese proses, en pasiënte se voorkeur vir die privaat sektor, wat tot vertragings in albei algoritmes gelei het.

Die studie van MDR-TB-pasiëntkoste *(hoofstuk 7)* het direkte koste (uitgawes uit die pasiënt se sak) sowel as indirekte koste (die pasiënt se tydkoste vir verlore produktiwiteit) beoordeel. Die mediane pasiëntkoste van die eerste gesondheidsbesoek tot en met behandelingsaanvang is verminder van $68.1 met die smeer-/kwekingsgebaseerde algoritme tot $38.3 (p=0.004) met die Xpert-gebaseerde algoritme. Die mediane direkte koste was laag teen $6.7 en $4.4 (p=0.321) onderskeidelik. Die verskil in koste kan toegeskryf word aan tydkoste aangesien die mediane getal besoeke tot en met MDR-TB-behandeling verminder is van 20 met die smeer-/kwekingsalgoritme tot 7 met die Xpert-gebaseerde algoritme (p<0.001). Die ekonomiese impak op pasiënte word hieronder in die afdeling oor billikheid bespreek.

Uit die oogpunt van laboratoriumkoste *(hoofstuk 8)* dui die studie op ’n toename van 43% in algehele PTB-laboratoriumkoste by die sentrale laboratorium, van $440,967 met die smeer-/kwekingsgebaseerde algoritme

tot $632,262 met die Xpert-gebaseerde algoritme oor tydperke van 3 maande. Die koste per gediagnoseerde TB-geval het met 157% toegeneem van $48.77 met die smeer-/kwekingsgebaseerde algoritme tot $125.32 met die Xpert-gebaseerde algoritme. Die gemiddelde totale koste per gediagnoseerde MDR-TB-geval was soortgelyk, naamlik $190.14 met die smeer-/kwekingsgebaseerde algoritme vergeleke met $183.86 met die Xpert-gebaseerde algoritme.

Wat ***doeltreffendheid*** betref, het die Xpert-gebaseerde algoritme nie tot ’n toename in die getal gediagnoseerde TB-gevalle óf beter behandelingsuitkomste onder diegene wat met behandeling begin het, gelei nie. Dit het egter behandelingsvertraging beduidend verkort en die persentasie TB-gevalle wat met behandeling begin het, verhoog. Die Xpert-gebaseerde algoritme het daartoe gelei dat ’n groter persentasie MDR-TB-gevalle gediagnoseer is, en het MDR-TB-behandelingaanvangtyd verkort.

Wat ***billikheid*** betref, het die Xpert-gebaseerde algoritme gesondheidsonbillikheid help verminder deur doeltreffendheid te verbeter, soos wat hierbo beskryf is. Tog het hierdie voordele nie pasiënte teen ekonomiese verliese beskerm nie. Die persentasie werklose persone in albei groepe het toegeneem (van aanvang van simptome tot en met tyd van die onderhoud): van 39% tot 73% in die smeer-/kwekingsgroep ($p < 0.001$) en van 53% tot 89% in die Xpert-groep ($p < 0.001$). Van die aanvang van simptome tot en met die tyd van die onderhoud was daar ’n afname van 16% in die mediane huishoudelike inkomste in die smeer-/kwekingsgroep, en ’n afname van 13% in die Xpert-groep. Altesaam 38% en 27% ($p=0.165$) in die onderskeie groepe het “katastrofiese” koste ondervind en het sodoende meer as 10% van hulle maandelikse huishoudelike inkomste verloor.

Mislukking van ***gesondheidstelsels*** op verskeie vlakke, van swak aanvanklike beplanning vir Xpert-implementering, en tekorte in menslike hulpbronne en IT-infrastruktuur, tot swak verantwoordbaarheid, ondoeltreffende dienslewering en swak gemeenskapsgereedheid, het waarskynlik gekeer dat die Xpert-gebaseerde algoritme sy volle potensiële impak gehad het. Hierdie kwessies verg dringende aandag om die voordele van Xpert te optimaliseer.

Wat ***opskalering*** betref, word die toename in laboratoriumkoste in hierdie studie in ’n sekere mate geneutraliseer deur die kostebesparing vir MDR-TB-pasiënte.

As deel van ’n groter projek is ’n diskrete gebeurtenissimulasiemodel ontwikkel en met behulp van die resultate van die studies in hierdie tesis bekragtig. Hierdie model sal gebruik word vir die beoordeling van meer kostedoeltreffende diagnostiese moontlikhede, sowel as van die voordele van ’n gevoeliger toets soos Xpert Ultra, wat volgens die ***horisonbespieding*** tans die mees waarskynlike plaasvervanger vir Xpert blyk te wees.

Hierdie studies het bepaalde beperkings. Dit was moeilik om vir sydigheid te kontroleer – die nie-lukrake toewysing van fasiliteite aan verskillende afdelings van die studie was byvoorbeeld buite die navorsers se beheer. Veralgemeenbaarheid na ander omgewings, veral landelike omgewings, is beperk omdat hierdie studies in ’n stedelike omgewing met goeie hulpbronne en betreklik goeie gesondheids- en laboratoriuminfrastruktuur onderneem is. Tydtendense kon in party studies in ag geneem word (byvoorbeeld die trapsgewyse wigontleding van TB-opbrengs), maar nie in ander nie (byvoorbeeld die studie van MDR-TB-behandelingaanvangstyd, waar desentralisasie van dienste moontlik tot die bevindinge bygedra het).

Die studies in hierdie tesis bevat verskeie nuwe en oorspronklike aspekte: studies is op die vlak van die Xpert-gebaseerde diagnostiese *algoritme* in plaas van die individuele toets onderneem, en weerspieël hoe toetse in kliniese praktyk gebruik word. Dit reflekteer die pasiënt-, verskaffer- en gesondheidstelselfaktore wat uitkomste beïnvloed en noodsaaklik is om die impak van die nuwe diagnostiese algoritme in normale programmatiese omstandighede te verstaan. Daarbenewens bied die gebruik van die impakbeoordelingsraamwerk 'n omvattende blik op die voordele en beperkings van Xpert.

Hierdie studies beklemtoon die effek van die vroeë bekendstelling van nuwe toetse in swak toegeruste en ondoeltreffende gesondheidstelsels, en bied insig in van die swakpunte in gesondheidstelsels wat aangespreek behoort te word om die impak van Xpert te optimaliseer. Tensy doelbewuste pogings aangewend word om hierdie swakpunte te verbeter, sal die belegging in hierdie duur nuwe tegnologie nie die volle omvang van moontlike voordele oplewer nie.

Chapter 1: Introduction

Decades of reliance on slow, inaccurate diagnostic tests have contributed to poor case detection and impeded global tuberculosis (TB) control efforts. The development of an accurate, rapid molecular diagnostic test, Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) (Xpert), its validation and uptake offers the prospect of identifying more cases (including those with drug-resistance), detecting them rapidly and enabling quicker treatment initiation. This thesis seeks to contribute evidence on whether this technical advance in TB diagnostics has translated into patient and public health benefits.

This chapter will provide an overview of the current TB epidemiological context globally and in South Africa. The limitations of previous diagnostic tests and how these have contributed to the current TB burden will be discussed. The benefits of Xpert will be addressed and theoretical means through which the implementation of Xpert could impact on patients and on public health proposed. I will define the overall goal of this research, discuss the framework used in impact assessment and provide an overview of each of the subsequent chapters contributing to impact assessment.

1.1 Global context

Despite being a curable disease, TB remains a major global health challenge. The burden of disease, high mortality rates, emergence of drug resistance and diagnostic challenges all contribute to the current situation. Globally, there were an estimated 9.6 million TB cases in 2014 at an incidence rate of 133 per 100,000 population (1). The burden of disease is geographically concentrated with 22-high burden countries accounting for 83% of incident cases at a rate of 176 per 100,000 population (1). Human immunodeficiency virus (HIV) infection is a key driver of the TB epidemic; depending on HIV prevalence, it increases the risk of developing TB by 20 to 37-fold (2). Of the 1.2 million HIV co-infected cases, 74% occur in Africa (1).

A substantial proportion of estimated incident cases are either not detected or not reported. The TB case detection rate (estimated incident cases that were reported in notification systems) of 63% reported for 2014 (1) could be an under-estimate, due to the difficulty in estimating TB incidence (3). Direct measures of incidence from prospective cohort studies are generally not feasible, as this would require an assessment of the number of TB cases in a cohort of about 400,000 individuals (based on TB incidence of 100/100,000 population) over the period of a year (4). Various indirect estimates are therefore used and all of these have limitations: TB notification rates (if there is strong evidence that all TB cases diagnosed are notified) with expert opinion on case detection gaps; TB prevalence (where prevalence studies have been conducted) divided by duration of disease (which cannot be determined accurately); and number of TB deaths divided by the estimated case-fatality rate (however, cause of death is difficult to determine) (3)(4). Even at the reported levels, over one third of incident cases were not detected. Undetected cases contribute to ongoing transmission with each infectious case estimated to infect 10 individuals every year (5).

Undetected TB is particularly common in HIV co-infected individuals. A systematic review of post-mortem studies from resource-limited settings found TB to be the cause of death in 37.2% of adult HIV/AIDS-related deaths. TB remained undiagnosed at death in 45.8% of these cases (6). Untreated TB is associated with extremely high case fatality. The mean fatality rate in HIV-uninfected cases of 70% amongst smear-positive cases and 20% amongst smear-negative cases (7) is likely to be substantially higher in HIV-infected cases.

Whilst only 12% of cases were HIV-infected globally, these contributed to 33% of the estimated 1.5 million TB deaths in 2014 (1). The past reliance on insensitive smear microscopy tests has contributed to poor TB case-detection, particularly among HIV-infected cases, and high TB mortality rates.

The number of multi-drug resistant (MDR) TB cases, defined as resistance to both isoniazid and rifampicin, remains high, with a substantial proportion of these cases remaining undetected. An estimated 3.3% of new cases and 20% of previously treated cases have MDR-TB. Only 123,000 (26%) of the estimated 480,000 cases in 2014 were diagnosed (1), partly due to the limited availability of drug susceptibility tests (DST). Among the 36 high TB or MDR-TB burden countries, only 16 met the benchmark of one laboratory with culture and DST capabilities per five million population in 2010 (8). Improving MDR-TB control requires expanded access to accurate and rapid diagnostics for the detection of drug resistance (9–11).

Despite global progress towards achieving the Millennium Development Goals of reducing TB incidence, the key targets of reducing prevalence and death rates in 2015 to 50% of their 1990 levels (12) have not been achieved, with mortality rates reduced by 47% and TB prevalence rates reduced by 42% (1). To reach the ultimate goal of eliminating TB by 2050 (defined as ≤1 case per 1 million population), incidence rates need to decline by an average of 20% annually, a rate that has never been achieved to date (13). A modelling study suggests that reducing and sustaining decreases in TB incidence requires improvements in TB case-detection beyond the current target of 70% (14).

1.2 National context

Amongst the 22 high burden countries, South Africa had the highest estimated TB incidence rate with 834 cases per 100,000 population in 2014, equivalent to 450,000 incident cases (1). Sixty percent of cases were HIV co-infected (1) and the generalised HIV epidemic in South Africa remains the major driver of TB disease. There were an estimated 5.5 million individuals living with HIV in 2014 (10.2% of the population) (15). Antenatal surveys undertaken amongst women attending public sector services suggest that HIV prevalence rates have remained static over a 10 year period at 29.5% (95% CI 28.5 to 30.5) in 2004 (16) compared to 29.7% (95% CI 28.9 to 30.5) in 2013 (17).

Despite this, TB incidence rates have declined from their peak of 977 per 100,000 in 2008 (1). This may partly be attributable to the national increase in antiretroviral treatment (ART) uptake from just under 50,000 cases in 2004 to almost 2.7 million in 2014 (http://www.hst.org.za/content/health-indicators) (Figure 1). A decrease in TB prevalence following antiretroviral treatment roll-out has been reported in one community in Cape Town: between 2005 and 2008 overall prevalence decreased from 3.0% to 1.6%, attributable to a decrease in prevalence amongst HIV-infected individuals from 9.2% to 3.6% (prevalence remained unchanged in HIV-uninfected individuals at 1.2% and 1.0% in respective years) (18). However, regardless of ART, HIV-infected individuals have a sustained increased risk of TB disease compared to uninfected individuals (19).

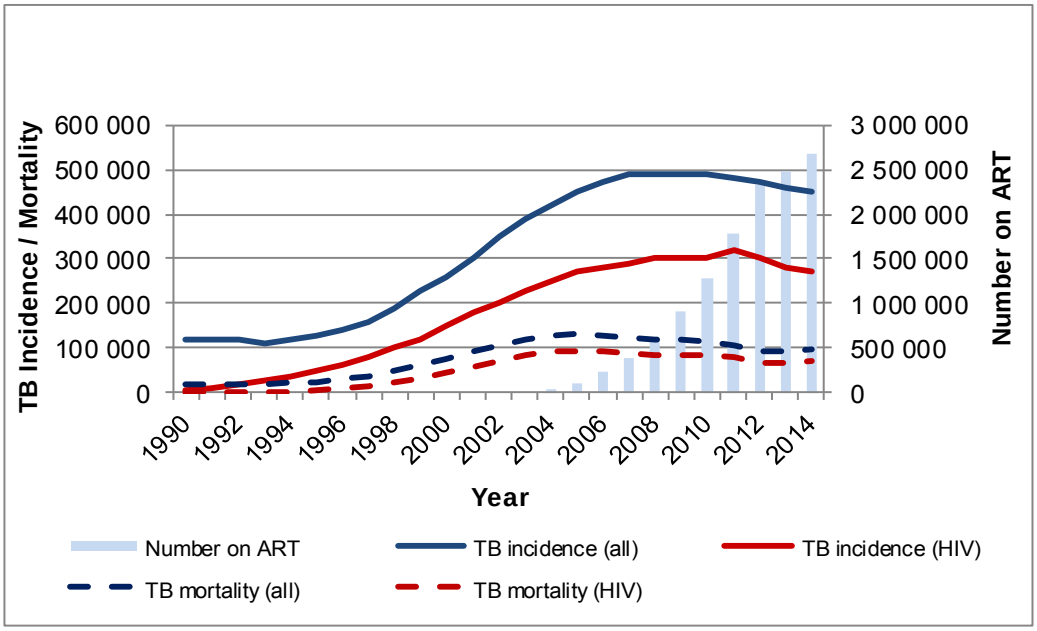

Fig 1: TB incidence and mortality and ART uptake in South Africa. The graph shows World Health Organisation estimates for tuberculosis (TB) incidence and mortality data for all cases and for human immuno-deficiency virus (HIV)-infected cases for 1990 to 2014 on the primary y-axis (Source: http://www.who.int/tb/country/ data/ download/en/). Data for all individuals reported to be on antiretroviral treatment (ART), including those in the private sector, are shown on the secondary y-axis (Source: http://www.hst.org.za/ content/ health-indicators)

Only 318,193 TB of the estimated 450,000 incident cases in 2014 were notified, with a case detection rate of 68% (1). This could be an under-estimate as South Africa has never had a TB prevalence survey and incidence estimates are based on TB case notification which is incomplete for two reasons – firstly due to cases on treatment that are not registered (20–22) and secondly because laboratory confirmed cases that fail to initiate treatment are not reported. South African studies show that between 15.5% and 34.7% of laboratory confirmed cases were not recorded in treatment registers (20,22–27).

Although MDR-TB case detection rates have been consistently high since 2009 (28), the treatment gap is significant: only 11,538 (62%) of the 18,734 cases rifampicin cases diagnosed in 2014 were initiated on treatment (1). This gap contributes to MDR-TB transmission and 24% of the 2009-2011 MDR-TB treatment cohort had primary infection (29). A 2012-2014 DR-TB prevalence survey in South Africa (30) reported rifampicin resistance rates of 3.4% amongst new and 7.1% amongst previously treated TB cases (4.6% overall). Applying this figure to the estimated TB incidence for 2014 suggests a total of 21,700 cases with rifampicin resistance and the 18,734 notified cases would comprise 91% of these. Comparing this to the TB case detection rate of 68% highlights the serious inaccuracies that are likely in routine reporting.

South Africa has made poor progress towards achieving the Millennium Development Goal targets for TB control. Whilst TB incidence rates are declining, TB prevalence rates were 49% higher and mortality rates were 271% higher in 2014 compared to their 1990 values (http://www.who.int/tb/country/ data/download/en/). Low case detection rates, delays in diagnosis and the treatment gap contribute to ongoing transmission, high TB incidence and prevalence and high TB mortality rates.

1.3 Diagnostic limitations in the pre-molecular diagnostic era

Sputum smear microscopy has formed the basis of TB diagnosis in many resource-limited settings, including South Africa. Despite the advantages of light microscopy, including simplicity, low cost, high specificity in TB endemic areas and the ability to identify the most infectious cases, its low and variable sensitivity, particularly in HIV prevalent areas is a major limitation (31–33). Conventional light microscopy has an average sensitivity of 53.8% for a single smear, with an increase of 11.1% from a second smear (34). Sensitivity is increased by 10% using fluorescence microscopy (35) and by 18% overall with chemical treatment and centrifugation when compared to unprocessed direct smears (36). Amongst HIV-infected cases, sensitivity for a single smear ranges between 23% and 50% (37–41).

Sputum culture, considered the gold standard for TB diagnosis (42), is slow, expensive and requires sophisticated laboratory infrastructure and technical expertise. Whilst culture in solid media takes 6-8 weeks, newer Mycobacterial Growth Inhibitor Tube (MGIT) liquid culture methods reduces the mean time to detection to 8-16 days (31). Laboratory infrastructure for sputum culture is limited and has focused on case detection rather than drug susceptibility testing, limiting the capacity to identify MDR- TB cases. Less than half of the 22 high TB-burden countries have 3 or more laboratories in their countries able to perform DST (33).

The low sensitivity of smear microscopy and poor availability of laboratory infrastructure to perform culture has serious consequences including missed cases, diagnostic delays and frequent empirical TB treatment based on clinical signs and chest x-rays, both of which have poor specificity. This results in incorrect treatment for many patients, wasted resources and over-burdening of treatment programmes (33). TB diagnosis is a particular challenge amongst HIV-infected individuals due to the difficulty and delay in diagnosing smear-negative TB, commonly found with immuno-suppression. The low sensitivity of smear microscopy and limited availability of culture in HIV prevalent areas (31) account for this, and has particular relevance in South Africa where the burden of HV is high. The risk of acquiring TB amongst these individuals is increased throughout the course of HIV infection, and diagnostic delays are likely to contribute to high mortality rates (19).

Preventing TB transmission through early case detection and treatment is a key goal of TB control programmes (43). Diagnostic delay is associated with initial TB treatment default (laboratory confirmed cases that fail to initiate treatment) (26), increased individual morbidity and mortality as well as ongoing TB and MDR-TB transmission. The lack of rapid, accurate diagnostics for TB thus presents a major challenge to TB control efforts (11).

1.4 Molecular diagnostic tests for TB and their uptake in South Africa

Rapid, more sensitive molecular diagnostic tests have the technical capacity to address the limitations of conventional TB diagnostic tests. These nucleic acid amplification tests detect genetic sequences for *Mycobacterium tuberculosis* complex and simultaneously, the presence of ‘wild type’ or mutations conferring resistance to TB drugs. The process involves DNA extraction from clinical specimens or culture isolates, amplification of specific genetic sequences and their identification through hybridisation to labelled, oligonucleotide probes. Two molecular tests have been introduced in South Africa since 2008.

The World Health Organisation (WHO) policy statement on “Molecular Line Probe Assays for Rapid Screening of Patients at Risk of Multidrug-Resistant Tuberculosis” released in June 2008 recommended the use of these

assays in testing smear-positive clinical specimens and culture isolates (44). Data from published studies were used to assess the efficacy and feasibility of programmatic implementation of two assays, GenoType® MTBDRplus (Hain LifeScience GmbH, Nehren, Germany) and INNO-LiPA Rif.TB (Innogenetics, Zwijndrecht, Belgium) (45). Whilst both assays simultaneously detect *M. tuberculosis* complex and "wild type" or mutations in the rpoB gene conferring rifampicin resistance, Genotype® MTBDRplus has several advantages including simultaneous detection of mutations in the katG gene (conferring high-level isoniazid resistance) and the inhA gene (conferring low-level isoniazid resistance), being validated for use in both liquid and solid culture media compared to only in solid media and lower costs. South Africa was an early adopter of Genotype® MTBDRplus Line Probe Assay as a replacement for conventional first-line DST in 2008.

The efficacy of Genotype® MTBDRplus Line Probe Assay (LPA) has been well established in laboratory and demonstration studies (46–48). A meta-analysis of ten LPA studies showed high sensitivity (98.1% (95% CI 95.9 to 99.1)) and specificity (98.7% (95% CI 97.3 to 99.4)) for rifampicin resistance and lower, more variable sensitivity of 84.3% (95% CI 76.6 to 89.8) and specificity of 99.5% (95% CI 97.5 to 99.9) for isoniazid (49).

The first generation test was approved for use only in smear-positive, but not smear-negative specimens. Although the test provides a result for smear-positive specimens in 1-2 days (50), delays were encountered with smear-negative specimens as the first generation test used culture isolates for testing. The test has several additional limitations: it requires initial processing in a bio-safety cabinet; has separate processes for DNA extraction, amplification and hybridisation and is prone to contamination. LPA requires substantial technical skills and the equipment and is only suitable for large, central laboratories.

Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) (Xpert) which simultaneously detects *Mycobacterium tuberculosis* and rifampicin resistance-conferring mutations directly from sputum addresses these complexities and has several advantages over LPA. It uses an integrated system in which sample preparation, DNA extraction, amplification and identification are automated and take place within a closed cartridge, reducing the risk of contamination (51). The test is approved for use with smear-negative specimens. The equipment is suitable for use in decentralised settings, such as at district and sub-district level, and does not require a high level of technical skills. Test results are available <1 day as processing takes about 2 hours (compared to 1 day for microscopy, 17 days for liquid culture and >30 days for solid culture) (51). Rifampicin resistance is detected in <1 day with Xpert compared to an average of 75 days with phenotypic DST (51). The equipment does however require a temperature controlled environment, a stable electrical supply and annual calibration (52).

Xpert has the ability to detect low bacteria loads (limit of detection of 131 colony forming units (CFU) per ml (53) compared to 10,000 CFU per ml for smear and 10-100 CFU per ml for culture (31)) and is useful in diagnosing the smear-negative TB typically found in HIV-infected individuals. The accuracy and feasibility of Xpert has been well established in laboratory and demonstration studies (54, 55). A Cochrane Review of fifteen studies where Xpert was used as the initial test replacing smear microscopy, showed a pooled sensitivity of 88% (95%CrI [1] 83% to 92%) and specificity of 98% (95% CrI 97% to 99%) for detecting *Mycobacterium tuberculosis*. Pooled sensitivity was 98% (95% CrI 97% to 99%) for smear-positive, culture-positive cases; 68% (95% CrI 59% to 75%) for smear-negative, culture-positive cases; and 80% (95% CrI

[1] The 95% CrI (credible interval) is the Bayesian equivalent of the classical, frequentist 95%CI (confidence interval)[21].

67% to 88%) for HIV-infected cases. In eleven of the studies, pooled sensitivity was 94% (95% CrI 87% to 97%) and specificity was 98% (95% CrI 97% to 99%) for rifampicin resistance (56).

Based on policy recommendations on its use as the initial diagnostic test in individuals suspected of MDR-TB or HIV-associated TB (51), Xpert was introduced as a replacement for smear microscopy for **all** presumptive TB cases in South Africa in 2011. This was a significant shift as prior to this, screening for MDR-TB amongst presumptive TB cases was undertaken only in those previously treated for TB, with an MDR-TB contact or from a congregate setting and in TB cases where 1st line regimens were failing. LPA was retained as a confirmatory test for rifampicin resistance or diagnosis of MDR-TB and for evaluation of cases on failing 1st line TB regimens.

1.5 The potential benefit of Xpert for patient and public health in South Africa

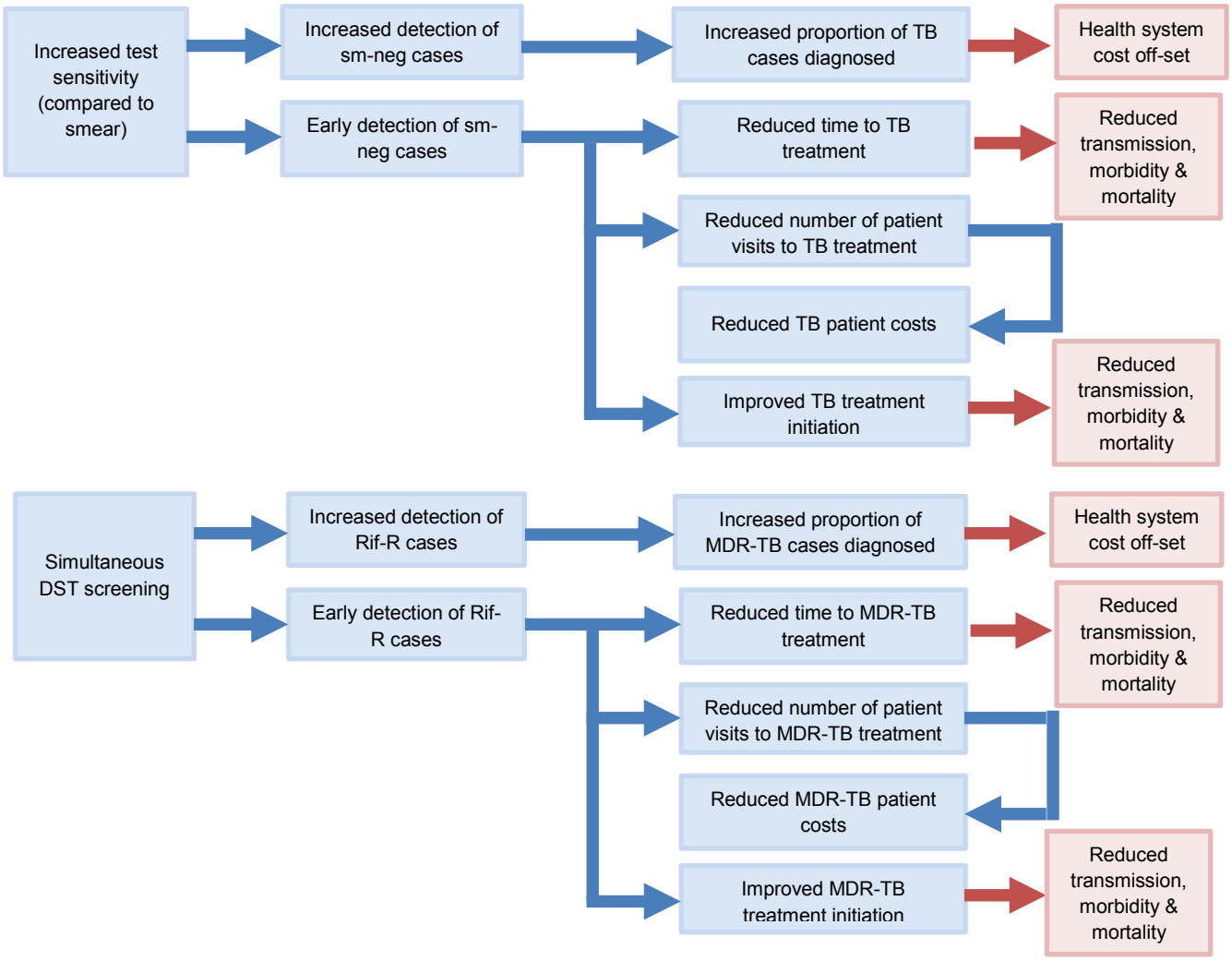

Fig 2: Potential benefits of an Xpert-based algorithm. Abbreviations: TB=tuberculosis; sm-neg=smear negative; DST-drug susceptibility test; Rif-R=rifampicin resistant; MDR-TB=multidrug resistant tuberculosis.

In the previous smear/culture-based algorithm, all presumptive TB cases were screened with two smear microscopy tests. Previously treated TB cases had a culture and DST undertaken and new cases that were

HIV-infected and smear-negative submitted a 3rd specimen for culture testing. In the Xpert-based algorithm, initial screening of all presumptive TB cases with the more sensitive Xpert test was expected to increase the proportion of TB cases initially identified. Previously, some of the presumptive TB cases initially missed with smear may have gone on to be diagnosed by culture, resulting in substantial delays to diagnosis and treatment initiation. From a patient's perspective, an early Xpert result could translate to fewer health care visits to TB diagnosis and treatment initiation and consequently reduced patient costs (Fig 1). Reductions in the proportion of missed cases and in delay may contribute to reductions in TB transmission, morbidity and mortality.

Simultaneous screening for TB and rifampicin resistance with Xpert could increase the proportion of MDR-TB cases diagnosed and substantially reduce the time to MDR-TB treatment as South African guidelines recommend that all patients with rifampicin resistance on Xpert are commenced on MDR-TB treatment whilst awaiting confirmation of their DST results (57). The reduction in health care visits and costs is likely to be higher for new compared to previously treated cases as in the smear/culture-based algorithm they would only have been evaluated for drug susceptibility when 1st line TB treatment regimens failed. From a health system perspective, improved case detection with Xpert is expected to off-set to some extent the expected increase in cost per TB and MDR-TB case diagnosed.

1.6 The policy-practice divide

WHO policy recommendations for Xpert were based largely on the accuracy data from laboratory and demonstration studies, evaluated through the GRADE process (51). Test sensitivity and specificity were used as proxy measures for patient-important outcomes based on the relative importance of false-negative and false-positive results, for example, through assessing the consequences of morbidity, mortality and disease transmission as a result of missed cases in tests with poor sensitivity or of serious adverse events to treatment for patients receiving false-positive results in tests with poor specificity.

This approach has shortcomings as tests are not assessed under operational conditions, evidence linking accuracy to patient important outcomes such as rapid access to treatment and costs incurred by patients is lacking, health system requirements are not adequately addressed and the public health impact is uncertain (58). A further limitation of the current evidence base is that although new molecular tests are introduced as part of an algorithm, tests are often assessed in isolation (59). In South Africa for example, a direct comparison of smear and Xpert tests that fails to account for the use of culture may overstate the benefit of Xpert.

Test performance in demonstration studies tends to over-estimate effectiveness due to greater resource availability than would be found in routine operational settings (59–61). In operational conditions, the accuracy of tests, may not always translate into appropriate clinical decisions for patients or for public health management.

Following The WHO endorsement of tests there is a need for a broader evidence base for the scale-up of new diagnostic tests within routine operational settings, including affordability and cost-effectiveness (59,62). This has particular relevance in a country like South Africa where Xpert has been introduced as a replacement for smear microscopy resulting in an estimated increase of annual TB diagnostic costs by 53-57% to $ 48-70

million per year at full Xpert coverage (63). Whilst the need for a strong, comprehensive evidence base to support decision making is clearly warranted, the question of how to do this in a systematic manner remains.

1.7 Aim of this thesis and research overview

The overall aim of this thesis was to undertake rigorous scientific research into the impact of an Xpert® MTB/RIF-based TB diagnostic algorithm in a routine operational setting in Cape Town. The research entailed a pragmatic comparison between the existing smear/culture-based TB diagnostic algorithm and the newly introduced Xpert-based algorithm. The magnitude and range of benefits for TB and MDR-TB cases and magnitude and nature of inputs required were assessed.

The research was implemented in Cape Town, South Africa between January 2010 and March 2014. Data was collected for the periods prior to, during and following completion of the phased introduction of the Xpert-based algorithm which commenced in August 2011 and was completed in January 2013. The scope of each study varied according to the research needs, from involving 26 MDR-TB patients at four primary health care (PHC) facilities for a qualitative study to involving all presumptive TB cases evaluated at 142 PHC facilities for a costing study. The majority of studies used data from five of the eight health sub-districts in Cape Town. All studies assessed laboratory confirmed cases of TB or MDR-TB only.

This research was part of the PROVE IT (Policy Relevant Outcomes from Validating Evidence on ImpacT) study supported by The Technology, Research, Education and Technical Assistance for TB (TREAT TB) initiative at The International Union Against Tuberculosis and Lung Disease. The research was undertaken by the Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, South Africa. It was funded by the United States Agency for International Development (USAID, TREAT TB – Agreement No. GHN-A-00-08-00004-00).

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.

1.8 Research Framework

An impact evaluation framework was sought that provided a methodological approach to collecting and synthesising data and that included effectiveness in field conditions, the contribution to patient care and the implications for the health system. I considered several frameworks for use in impact assessment and selected the Impact Assessment Framework for use in this thesis.

"Health Technology Assessment" defined as the "systematic evaluation of properties, effects, and/or impacts of health technology" (64) addresses technical performance, efficacy, effectiveness and appropriateness for a specific setting. Although it shares many similarities with the Impact Assessment Framework, it was not considered appropriate as it includes "upstream" aspects of technical performance akin to the GRADE evaluation process (65) that are not the subject of this evaluation.

"Health Impact Assessment" aims to predict positive and negative (including unanticipated) consequences of

health and other projects or policies with recommendations to maximise the former, minimise the latter and reduce impacts on health inequalities (66). It lacks a standard approach, using multiple frameworks that vary in scope from a narrow to a broad focus and in the quality of information gathered, rarely utilising quantitative data and was thus also deemed inappropriate for this evaluation.

The Impact Assessment Framework (IAF) (67), adopted by the WHO in "Pathways to better diagnostics for tuberculosis: a blueprint for the development of TB diagnostics" (62), aims to ensure a more comprehensive approach to the evaluation of new diagnostics. The IAF consists of 5 layers: ***Effectiveness Analysis*** takes efficacy beyond test accuracy to assess the impact on the numbers of cases diagnosed and appropriately started on treatment as well as the timeliness of results and of treatment initiation. ***Equity Analysis*** assesses whether marginalised groups who may be more affected benefit from the new test – poor people, women and HIV-infected specifically. ***Health Systems Analysis*** assesses issues such as the human resource, laboratory infrastructure, procurement and quality assurance implications. ***Scale-up Analysis*** assesses the economic costs and benefits of scaling up the new technology from both a provider and a patient perspective. ***Horizon Scanning***, adapted since the original publication[2], assesses what other similar technologies are available or likely to become available and how these compare in their projected performance.

The IAF was selected as appropriate for the intended purpose as it provides a clear guide to impact assessment. Each of the studies described below and in subsequent chapters of this thesis feed into one or more layers of the IAF.

1.9 Research studies, hypotheses and layout of this thesis

Chapter 2 *"Comparing tuberculosis diagnostic yield in smear/culture and Xpert® MTB/RIF-based algorithms using a non-randomised stepped-wedge design"* presents findings from a study assessing the proportion of presumptive TB cases diagnosed with TB over seven time-points in five of the eight sub-districts in Cape Town. A stepped-wedge design was used to assess changes in TB yield prior to, during and after the introduction of the Xpert-based algorithm. Presumptive TB cases screened in the time-frames shown in Figure 3 were included in this study. The following hypotheses were tested:

Ho: TB diagnostic yield is not increased in an Xpert-based algorithm compared to a smear/culture-based algorithm

Ha: TB diagnostic yield is increased in an Xpert-based algorithm compared to a smear/culture-based algorithm

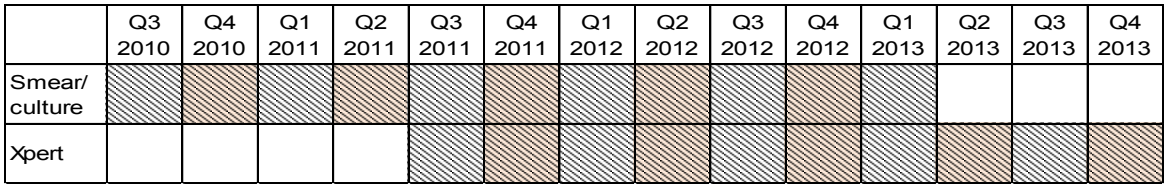

Fig 3: Timeframes used in the TB and MDR-TB yield analysis. Hatched cells indicate the period when the smear/culture and Xpert-based algorithms were in place. Shaded cells indicate the timeframes used in this analysis

[2] Personal communication S.B. Squires

Chapter 3 addresses the question *"Has universal screening with Xpert® MTB/RIF increased the proportion of multidrug-resistant tuberculosis cases diagnosed in a routine operational setting?"* A binomial regression analysis was used to assess the proportions of laboratory confirmed TB cases in each algorithm (identified in the TB yield analysis above) that were screened and diagnosed with MDR-TB pre-treatment and during the course of 1st-line TB treatment in the five sub-districts. TB cases identified in the time-frames shown in Figure 3 were included in this study. The following hypotheses were tested:

Ho: The proportion of TB cases screened and diagnosed with MDR-TB is not increased in an Xpert-based algorithm compared to a smear/culture-based algorithm

Ha: The proportion of TB cases screened and diagnosed with MDR-TB is increased in an Xpert-based algorithm compared to a smear/culture-based algorithm

Chapter 4 addresses the question *"Does an Xpert® MTB/RIF-based algorithm increase TB treatment initiation and treatment success rates in a routine operational setting?"* This study included cases from two sub-districts using the Xpert-based algorithm and three sub-districts using the smear/culture-based algorithm. Laboratory and treatment delay and other factors influencing 1st line TB treatment initiation and treatment success rates were assessed using a binomial regression analysis. Presumptive TB cases screened and diagnosed with TB in the time-frames shown in Figure 4 below were included in this study. The following hypotheses were tested:

Ho: TB treatment initiation and treatment success rates are not increased in an Xpert-based algorithm compared to in a smear/culture-based algorithm

Ha: TB treatment initiation and success rates are increased in an Xpert-based algorithm compared to a smear/culture-based algorithm

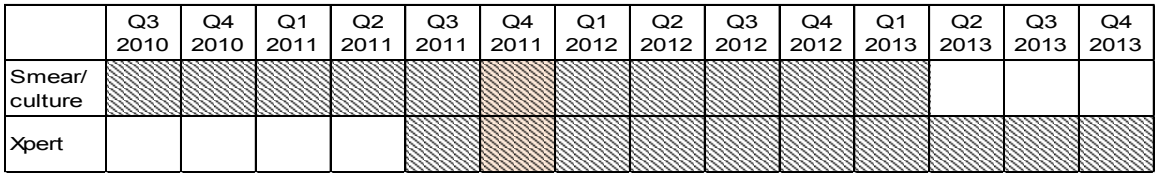

Fig 4: Timeframes used in the analysis of TB treatment initiation and treatment success rates. Hatched cells indicate the period when the smear/culture and Xpert-based algorithms were in place. Shaded cells indicate the timeframes used in this analysis

Chapter 5 *"A comparison of multidrug-resistant tuberculosis treatment commencement times in MDRTBPlus Line Probe Assay and Xpert® MTB/RIF-based algorithms in a routine operational setting in Cape Town"* presents findings from a study assessing MDR-TB treatment commencement times in the smear/culture and Xpert-based algorithms in 10 high TB-burden primary health care facilities. Kaplan Meier time-to-event analysis was used to analyse MDR-TB treatment commencement times for all cases and for subsets, including HIV-infected cases, previously treated cases and women. MDR-TB cases identified in the time-frames shown in Figure 5 were included in this study. The following hypotheses were tested:

Ho: MDR-TB treatment commencement time is not reduced in an Xpert-based algorithm compared to a smear/culture-based algorithm

Ha: MDR-TB treatment commencement time is reduced in an Xpert-based algorithm compared to a smear/culture-based algorithm

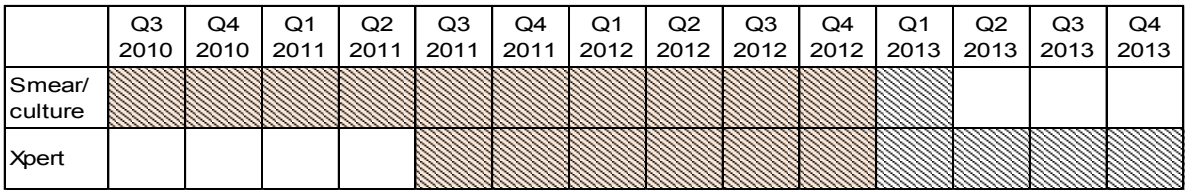

Fig 5: Timeframes used in the analysis of MDR-TB treatment commencement times. Hatched cells indicate the period when the smear/culture and Xpert-based algorithms were in place. Shaded cells indicate the timeframes used in this analysis.

Chapter 6 *"Pathways to multidrug-resistant tuberculosis diagnosis and treatment initiation: a qualitative comparison of patients' experiences in the era of rapid molecular diagnostic tests"* presents findings from a qualitative study of patients' experiences from the onset of symptoms to initial care-seeking and MDR-TB diagnosis and treatment initiation. Experiences of 26 purposively selected MDR-TB patients were explored using in-depth guided interviews. Key issues and themes in each stage of the care pathway were identified using open coding with constant comparison within and between groups. A combination of deductive (having explored specific aspects of the care pathway and the motivation behind patients' actions) and inductive analysis was used, identifying common and divergent themes emerging from the data that were not specifically elicited. MDR-TB cases identified in the time-frames shown in Figure 6 were included in this study.

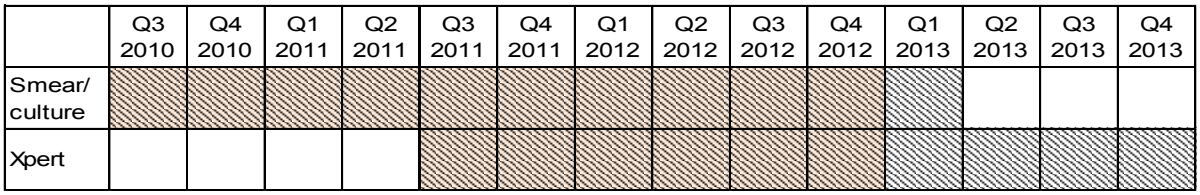

Fig 6: Timeframes used in the analysis of MDR-TB patient pathways and MDR-TB patient costs. Hatched cells indicate the period when the smear/culture and Xpert-based algorithms were in place. Shaded cells indicate the timeframes used in this analysis

Chapter 7 *"Comparing multidrug-resistant tuberculosis patient costs under molecular diagnostic algorithms in South Africa"* presents findings from a study that was undertaken in 10 high TB burden primary health care facilities. MDR-TB patient's health-seeking visits, including time spent in travel and at the health care facility, out of pocket payments, employment status, loss of individual and household income and socio-economic status were assessed. Patient costs included direct costs (medical and transport) and indirect costs (opportunity costs related to patient's time). MDR-TB cases identified in the time-frames shown in Figure 6 were included in this study. The following hypotheses were tested:

> **Ho:** MDR-TB patient costs are not reduced in an Xpert-based algorithm compared to a smear/culture-based algorithm
>
> **Ha:** MDR-TB patient costs are reduced in an Xpert-based algorithm compared to a smear/culture-based algorithm

Chapter 8 *"Comparing laboratory costs of smear/culture and Xpert® MTB/RIF-based tuberculosis diagnostic algorithms"* used an ingredients-based costing approach to calculate economic costs at a central laboratory. Cost effectiveness was based on the mean cost per TB and MDR-TB patient diagnosed. An incremental cost-effectiveness ratio was calculated per MDR-TB case diagnosed. All laboratory costs incurred for the periods shown in Figure 7, presumptive TB cases screened and TB and MDR-TB cases diagnosed were included in

the analysis. The following hypotheses were tested:

Ho: Laboratory costs per TB and MDR-TB patient diagnosed are not reduced in an Xpert-based algorithm compared to a smear/culture-based algorithm

Ha: Laboratory costs per TB and MDR-TB patient diagnosed are reduced in an Xpert-based algorithm compared to a smear/culture-based algorithm

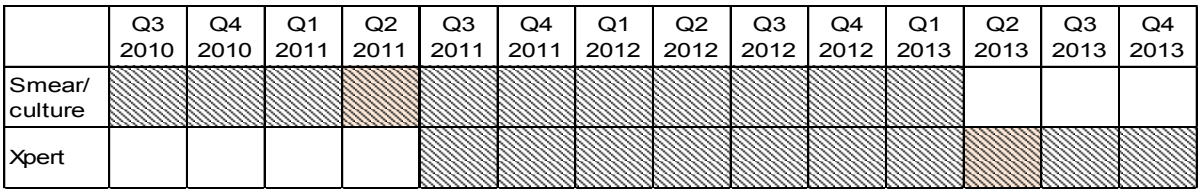

Fig 7: Timeframes used in the analysis of laboratory costs. Hatched cells indicate the period when the smear/culture and Xpert-based algorithms were in place. Shaded cells indicate the timeframes used in this analysis

Chapter 9 presents a synthesis of findings from the studies undertaken to evaluate the impact of molecular diagnostic tests for TB, using the Impact Assessment Framework. The extent to which the study goal was reached and the contribution of these studies to the emerging evidence base on impact of molecular diagnostic tests for TB is discussed. The strengths and limitations of the research are addressed and suggestions made for future research.

A **supplementary chapter** *"Global to Local Policy Transfer in the Introduction of New Molecular Tuberculosis Diagnostics in South Africa"* that was undertaken as part of the PROVE IT study is included. This chapter presents findings from a qualitative study that examined policy transfer for both Genotype® MDRTBplus Line Probe Assay and Xpert® MTB/RIF to understand policy development, uptake and implementation in South Africa. A Policy Transfer Analysis framework that integrates the key dimensions of policy transfer into one coherent model was used. This framework addressed the policy contexts and nature of policy innovation; the main actors, networks and resources involved; the forms of communication and cooperation that emerged; and the stages of policy initiation, uptake and diffusion, implementation, and maintenance as well as the dynamic relationships between these. The study used two phases of key informant interviews with 40 stakeholders, complemented with reviews of quarterly reports from 10 health facilities and from health and laboratory managers, as well as a desk-top review. Although policy analysis is not a component of the Impact Assessment Framework, many of the health system issues identified and addressed in the synthesis emanate from this study.

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Chapter 2: Comparing tuberculosis diagnostic yield in smear/culture and Xpert® MTB/RIF-based algorithms using a non-randomised stepped-wedge design

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ABSTRACT

Setting: Primary health services in Cape Town, South Africa.

Study Aim: To compare tuberculosis (TB) diagnostic yield in an existing smear/culture-based and a newly introduced Xpert® MTB/RIF-based algorithm.

Methods: TB diagnostic yield (the proportion of presumptive TB cases with a laboratory diagnosis of TB) was assessed using a non-randomised stepped-wedge design as sites transitioned to the Xpert® based algorithm. We identified the full sequence of sputum tests recorded in the electronic laboratory database for presumptive TB cases from 60 primary health sites during seven one-month time-points, six months apart. Differences in TB yield and temporal trends were estimated using a binomial regression model.

Results: TB yield was 20.9% (95% CI 19.9% to 22.0%) in the smear/culture-based algorithm compared to 17.9% (95%CI 16.4% to 19.5%) in the Xpert® based algorithm. There was a decline in TB yield over time with a mean risk difference of -0.9% (95% CI -1.2% to -0.6%)($p<0.001$) per time-point. When estimates were adjusted for the temporal trend, TB yield was 19.1% (95% CI 17.6% to 20.5%) in the smear/culture-based algorithm compared to 19.3% (95% CI 17.7% to 20.9%) in the Xpert® based algorithm with a risk difference of 0.3% (95% CI -1.8% to 2.3%)($p=0.796$). Culture tests were undertaken for 35.5% of smear-negative compared to 17.9% of Xpert® negative low MDR-TB risk cases and for 82.6% of smear-negative compared to 40.5% of Xpert® negative high MDR-TB risk cases in respective algorithms.

Conclusion: Introduction of an Xpert® based algorithm did not produce the expected increase in TB diagnostic yield. Studies are required to assess whether improving adherence to the Xpert® negative algorithm for HIV-infected individuals will increase yield. In light of the high cost of Xpert, a review of its role as a screening test for all presumptive TB cases may be warranted.

INTRODUCTION

The World Health Organisation identified five priorities to accelerate progress towards achieving the 2015 United Nation's Millennium Development Goals for tuberculosis (TB) [1]. The first was to "reach the missed cases", the estimated 2.9 million TB cases that were not diagnosed or reported in national notification systems. Expanding diagnostic services, including access to rapid tests, was identified as one of the strategies to achieve this.

South Africa, which ranks second on the list of 12 countries contributing 75% of missed cases [1] introduced Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) (Xpert) as a replacement for smear microscopy for all presumptive TB cases in 2011. Xpert is recommended as the initial diagnostic test in individuals suspected of multidrug-resistant (MDR)-TB or human immunodeficiency virus (HIV)-associated TB [2], both of which are prevalent in South Africa. Full Xpert coverage was predicted to identify 30% more TB cases in South Africa in 2013 compared to smear and culture [3].

Xpert has higher sensitivity than smear microscopy. A Cochrane Review of fifteen studies with Xpert replacing smear microscopy as the initial test, yielded a pooled sensitivity of 88% (95%CrI: 83% to 92%) and specificity of 98% (95% CrI: 97% to 99%) for detecting *Mycobacterium tuberculosis* (MTB) [4]. In comparison conventional light microscopy has an average sensitivity of 53.8% for a single smear and 64.9% for two smears [5] with a 10% increase from fluorescence microscopy [6]. Despite the advantages of light microscopy, including simplicity, low cost, high specificity in TB endemic areas and the ability to identify the most infectious cases of TB, its major limitation is low and variable sensitivity, with particularly low sensitivity in HIV prevalent areas [7–9].

Sputum culture, considered the gold standard in TB diagnosis and important in the diagnosis of smear-negative TB, is able to diagnose paucibacillary disease at concentrations as low as 10 bacteria per ml [8] compared to 10,000 bacteria per ml for conventional light microscopy. However, culture is slow, taking 6-8 weeks on solid Löwenstein-Jensen medium and 8-16 days with Mycobacterial Growth Inhibitor Tube (MGIT) liquid culture [7]. Culture is also more expensive than smear microscopy [10,11] and requires sophisticated laboratory infrastructure and technical expertise.

Whilst rapid, more sensitive molecular diagnostic tests such as Xpert have the technical capacity to address the limitations of smear and culture, very little has been reported on their use in routine operational conditions, particularly within diagnostic algorithms. Increased test sensitivity may not on its own translate into an increase in the proportion of bacteriologically confirmed TB cases. The role of the test within the algorithm, how effectively it is used, the use of follow-on tests such as culture and the number of presumptive TB cases screened may all play a role.

The aim of this study was to compare the proportion of presumptive TB cases with a laboratory diagnosis of TB (TB diagnostic yield) in an existing smear/culture-based algorithm and a newly introduced Xpert-based algorithm within a routine operational setting. Other factors influencing the proportion of TB cases identified, including adherence to diagnostic algorithms and changes in the proportion of the population tested, were assessed.

This study was part of a PROVE IT (**P**olicy **R**elevant **O**utcomes from **V**alidating **E**vidence on **I**mpac**T**) evaluation (http://www.treattb.org/) to assess the impact of new molecular diagnostics on the diagnosis and treatment of tuberculosis.

METHODS

Setting

The study was undertaken in Cape Town, South Africa, a city with a high TB burden with 28,658 cases registered in 2011. The TB case notification rate was 752/100,000 population. Amongst the 97% of TB cases tested for human immunodeficiency virus (HIV), 47% were co-infected. (Source: J. Caldwell, Routine TB Programme Data, Cape Town Health Directorate).

Provincial and municipal health authorities provided free TB diagnostic services at 142 primary health care (PHC) facilities in eight sub-districts. Prior to August 2011, a smear/culture-based algorithm was used (Fig 1). Policy required all presumptive TB cases to be evaluated through two spot sputum specimens, taken 1-hour apart. Both specimens were chemically treated (using bleach or sodium hydroxide / n-acetyl cysteine), centrifuged, stained with auramine and examined by fluorescence microscopy. In high MDR-TB risk cases, the second specimen underwent liquid culture (BACTEC™ MGIT™ 960) and drug susceptibility testing (DST) using the GenoType® MTBDR*plus* (Hain LifeScience GmbH, Nehren, Germany) line probe assay (LPA). Smear-negative, HIV-infected, low MDR-TB risk cases were required to submit a third specimen for culture.

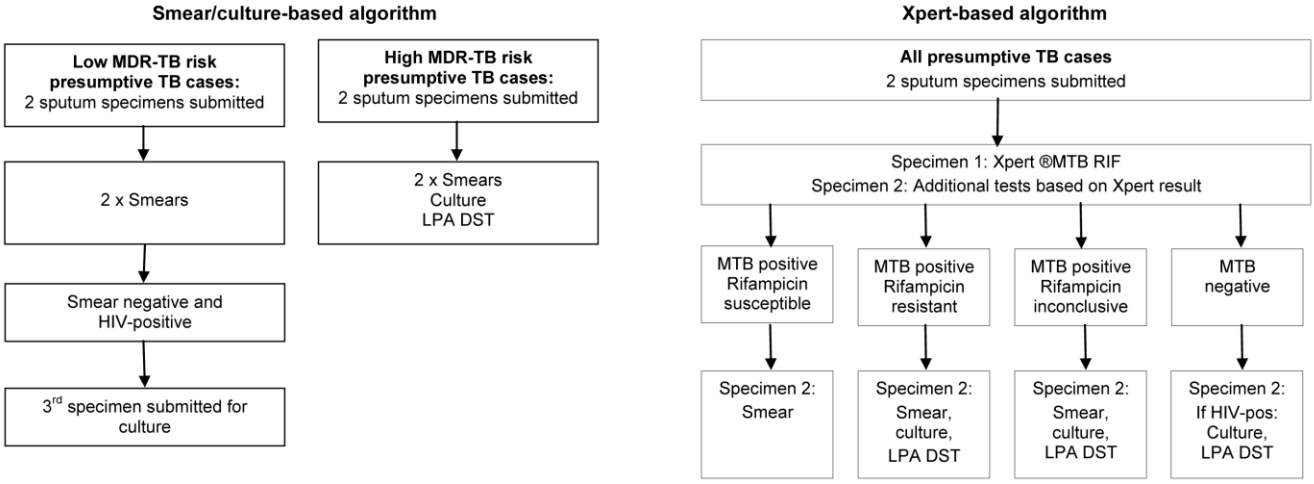


Figure 1: Testing protocols in the smear/culture and Xpert® based TB diagnostic algorithms in PHC facilities in Cape Town. The diagram shows the simplified sequence of TB diagnostic tests recommended in each algorithm and the action taken based on test results. Low MDR-TB risk was defined as ≤four weeks previous TB treatment and high MDR-TB risk as >four weeks previous TB treatment, from congregate settings or with a known MDR-TB contact. Abbreviations: TB - tuberculosis, LPA - line probe assay, DST - drug susceptibility testing, HIV – human immunodeficiency virus, MTB – mycobacterium tuberculosis, PHC - primary health care.

From August 2011 to February 2013 an Xpert-based algorithm was phased into the eight health sub-districts with Xpert replacing smear microscopy (Fig 1). All presumptive TB cases submitted two sputum specimens. The first was tested with Xpert; if MTB was detected the second underwent smear microscopy to enable smear-conversion monitoring during treatment. In HIV-infected cases with negative Xpert tests, the second specimen underwent culture (in view of the lower Xpert-sensitivity in these cases [4]).

Samples were initially tested at a central national health laboratory. Three sub-district laboratories were established in 2013 to perform Xpert tests and smear microscopy. Results for all samples were entered into a networked electronic laboratory database.

Definitions

A *presumptive TB case* was defined as an individual with pre-treatment sputum samples submitted for diagnostic purposes and a *TB case* as an individual with one or more smears positive and / or culture positive for MTB and / or MTB detected on Xpert.

Low MDR-TB risk was defined as ≤four weeks previous TB treatment and *high MDR-TB risk* as >four weeks previous TB treatment, from congregate settings or with a known MDR-TB contact.

A *PHC site* consisted of municipal and provincial health facilities linked to their satellite and mobile facilities and to each other if within a single geographic location (to account for shared diagnostic services).

Study design, population and timeframes

We used a non-randomised stepped-wedge study design to assess TB yield in five groups of PHC sites over seven one-month time-points (T1 to T7) as they changed from using the smear/culture-based algorithm to the Xpert-based algorithm (Fig 2).

Facilities	Nov 2010 (T1)	May 2011 (T2)	Nov 2011 (T3)	May 2012 (T4)	Nov 2012 (T5)	May 2013 (T6)	Nov 2013 (T7)
Group A (12 PHC sites)	Smear/culture	Smear/culture	Xpert	Xpert	Xpert	Xpert	Xpert
Group B (9 PHC sites)	Smear/culture	Smear/culture	Xpert	Xpert	Xpert	Xpert	Xpert
Group C (16 PHC sites)	Smear/culture	Smear/culture	Smear/culture	Xpert	Xpert	Xpert	Xpert
Group D (9 PHC sites)	Smear/culture	Smear/culture	Smear/culture	Smear/culture	Xpert	Xpert	Xpert
Group E (14 PHC sites)	Smear/culture	Smear/culture	Smear/culture	Smear/culture	Smear/culture	Xpert	Xpert

Figure 2: A non-randomised stepped-wedge evaluation of TB yield in five PHC groups as they transitioned from the smear/culture to the Xpert® based algorithms in Cape Town This figure shows the TB diagnostic algorithm in place in 5 groups of PHC sites over the seven time-points (T1 to T7) used in the analysis. All sites initially had a smear/culture-based algorithm in place. The Xpert-based algorithm was introduced in August 2011 in Group A, in October 2011 in Group B, in February 2012 in Group C, in October 2012 in Group D and in February 2013 in Group E. With the exception of one PHC site, the groups represent all the sites within a sub-district. Abbreviations: TB – tuberculosis, PHC - primary health care.

We included 60 PHC sites (five of the eight sub-districts in Cape Town) that had implementation of either the smear/culture or the Xpert-based algorithm in October to December 2011. The three sub-districts transitioning in this quarter were excluded to avoid overlap between algorithms within the time-point. Other time-points were selected to also avoid overlap.

The study population included all presumptive TB cases with sputum test results recorded in the electronic laboratory database in Cape Town for the selected facilities and time periods.

Data sources and management

The National Health Laboratory Services provided TB test data from the electronic laboratory database for 2010-2013. Data included patient demographic information, MDR-TB risk category, test type (smear, culture, or Xpert) and result.

Data for each time-point and the preceding and following months (i.e. a quarter's data) were imported into MS-SQL. The full sequence of tests for individuals at T1 to T7 were derived by identifying all tests done in that month as well as in the preceding and following months using a combination of name, surname, clinic folder number and age or birth date.

Analysis

TB diagnostic yield was calculated by dividing the number of TB cases identified (based on the full sequence of tests performed) by the total number of presumptive TB cases screened by algorithm and time-point.

Adherence to the smear/culture-based algorithm was assessed by calculating the proportion of cases with two smear tests and the proportion of smear-negative cases with culture tests. Adherence to the Xpert-based algorithm was assessed by calculating the proportion of cases with an Xpert test and the proportion of Xpert-negative cases with culture tests.

The proportion of presumptive TB cases tested in the five sub-districts was calculated by dividing the number of individuals tested in the quarter by the mid-year population estimates from Statistics South Africa [12].

Descriptive statistics by algorithm are presented using frequencies, means and standard deviation. We used a binomial regression model, adjusted for site-level clustering, to estimate the differences in TB yield between algorithms and assess temporal trends. This model was used to assess the effect of MDR-TB risk on TB yield and to evaluate trends in testing over time. All analyses were undertaken using STATA 12 (StataCorp).

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. A waiver of informed consent was granted for use of routine data. The City Health Directorate, Western Cape Health Department and National Health Laboratory Service granted permission to use routine health data. Data sharing is possible following approval by the National Health Laboratory Service.

RESULTS

Comparing the characteristics of presumptive TB cases evaluated by algorithm

The smear/culture-based algorithm included 24,000 presumptive TB cases and the Xpert-based algorithm 30,393 (Table 1). Age and gender distributions were similar. The smear/culture-based algorithm contained a larger proportion of high MDR-TB risk cases (26% compared to 24%, $p<0.001$).

Table 1: Comparing the characteristics of presumptive TB cases evaluated by algorithm

		Smear/culture-based algorithm n=24,000	Xpert-based algorithm n=30,393	p-value
Age (Years)	Mean	36	36	0.222
	SD	15	15	
	Range	2 to 98	1 to 100	
Gender	Female (%)	11,402 (48)	14,310 (48)	0.983
	Male (%)	11,788 (49)	14,789 (49)	
Patient category	Low MDR-TB risk (%)	15,070 (63)	19,674 (65)	<0.001
	High MDR-TB risk (%)	6,233 (26)	7,245 (24)	

Summary data are shown for presumptive TB cases evaluated in the existing smear/culture and newly introduced Xpert-based algorithm in primary health sites in Cape Town. Data are shown for recorded variables only. Missing data are included in the calculation of percentages. Low MDR-TB risk was defined as ≤four weeks previous TB treatment and high MDR-TB risk as >four weeks previous TB treatment, from congregate settings or with a known MDR-TB contact. Abbreviations: TB - tuberculosis, MDR-TB –multidrug-resistant tuberculosis, SD – standard deviation.

Comparing TB yield by algorithm and trends over time

TB yield was 20.9% (95% CI 19.9% to 22.0%) in the smear/culture-based algorithm compared to 17.9% (95%CI 16.4% to 19.5%) in the Xpert-based algorithm with a risk difference of -3.0% (95% CI -4.3% to -1.7%) (p<0.001) (Table 2). Adjusting for the differences in MDR-TB risk produced similar TB yields: 20.1% in the smear/culture-based algorithm compared to 17.2% in the Xpert-based algorithm and a risk difference of -2.9% (p<0.001).

Amongst *low MDR-TB risk cases*, TB yield in the smear/culture-based algorithm was 20.3% (95% CI 19.0% to 21.5%) compared to 17.1% (95% CI 15.1% to 19.1%) in the Xpert-based algorithm with a risk difference of -3.2% (95% CI -4.9% to -1.4%) (p<0.001). Amongst *high MDR-TB risk cases*, TB yield was 24.4% (95% CI 23.2% to 25.6%) and 22.1% (95%CI 21.0% to 23.3%) respectively with a risk difference of -2.3% (95% CI -3.8% to -0.7%) (p=0.004).

There was a declining trend in TB yield in both the smear-culture and Xpert-based algorithms (Fig 3). Overall, TB yield was 23.6% (95% CI 22.2 to 25.1%) at T1 compared to17.5% (95% CI 15.0% to 20.0%) at T7 with a mean risk difference of -0.9% (95% CI -1.2% to -0.6%) (p<0.001) per time-point (Table 2).

When estimates were adjusted for the temporal trend, there was no significant difference between the algorithms: the proportion of TB cases identified in the smear/culture based algorithm was 19.1% (95% CI 17.6% to 20.5%) compared to 19.3% (95% CI 17.7% to 20.9%) in the Xpert-based algorithm with a risk difference of 0.3% (95% CI -1.8% to 2.3%) (p=0.796) (Table 2).

Table 2: A comparison of TB yield in smear/culture and Xpert-based algorithms and trends over time

	TB yield	95% CI	Risk difference (95% CI)	p-value
All cases (simple model)				
Smear/culture-based algorithm	20.9%	19.9% to 22.0%	-3.0% (-4.3% to -1.7%)	<0.001
Xpert-based algorithm	17.9%	16.4% to 19.5%		
All cases adjusted for MDR-TB risk				
Smear/culture-based algorithm	20.1%	18.8% to 21.5%	-2.9% (16.4% to 19.5%)	<0.001
Xpert-based algorithm	17.2%	15.4% to 19.0%		
Amongst low MDR-TB risk cases (simple model)				
Smear/culture-based algorithm	20.3%	19.0% to 21.5%	-3.2% (-4.9% to -1.4%)	<0.001
Xpert-based algorithm	17.1%	15.1% to 19.1%		
Amongst high MDR-TB risk cases (simple model)				
Smear/culture-based algorithm	24.4%	23.2% to 25.6%	-2.3% (-3.8% to -0.7%)	0.004
Xpert-based algorithm	22.1%	21.0% to 23.3%		
For cases in both the smear/culture and Xpert-based algorithms by time-point (simple model)				
T1 (November 2010)	23.6%	22.2% to 25.1%	-0.9% (-1.2% to -0.6%)[a]	<0.001
T2 (May 2011)	20.4%	19.1% to 21.8%		
T3 (November 2011)	19.4%	18.3% to 20.5%		
T4 (May 2012)	17.4%	15.8% to 19.1%		
T5 (November 2012)	19.5%	17.8% to 21.2%		
T6 (May 2013)	16.6%	15.0% to 18.2%		
T7 (November 2013)	17.5%	15.0% to 20.0%		
All cases adjusted for temporal trends				
Smear/culture-based algorithm	19.1%	17.6% to 20.5%	0.3% (-1.8% to 2.3%)	0.796
Xpert-based algorithm	19.3%	17.7% to 20.9%		

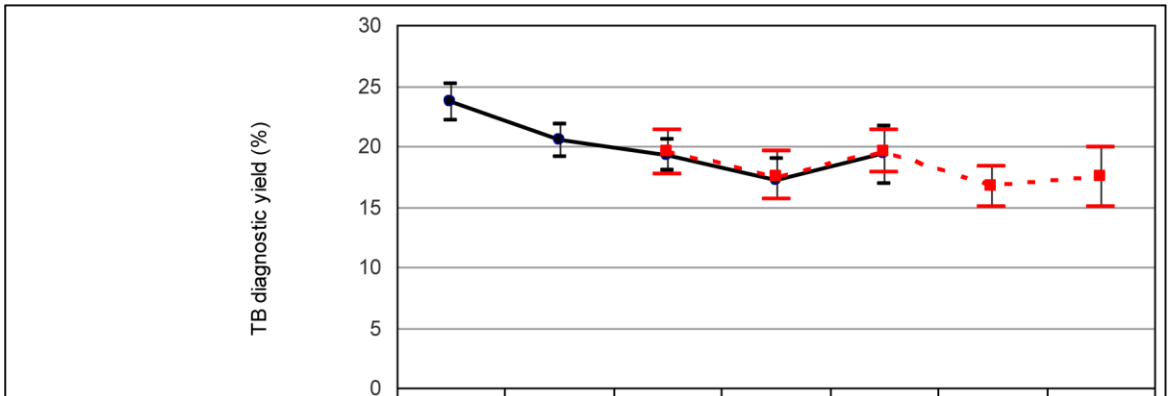
The table shows TB yield comparisons between the smear/culture and Xpert-based algorithms and temporal trends in yield at time-points T1 to T7 in primary health sites in Cape Town. The outputs are from a binomial regression model, adjusted for clustering of presumptive TB cases at sites. In the simple model adjustments have not been made for differences in MDR-TB risk profiles between the algorithms or for temporal trends. [a]This figure shows the mean risk difference per time point and 95% confidence interval. Abbreviations: TB - tuberculosis, MDR-TB –multidrug-resistant tuberculosis, CI – confidence interval.

Adherence to algorithms

Amongst *low MDR-TB risk* presumptive TB cases, 83.9% in the smear/culture-based algorithm had two smear tests and 35.5% of smear-negative cases had a culture test (Table 3). In the Xpert-based algorithm in comparison, 77.2% had an Xpert test and 17.9% of Xpert-negative cases had a culture test. The proportion of smear and Xpert-negative cases with culture tests could not be stratified by HIV-status as HIV data were unavailable for time-points T1 to T5. Amongst all low MDR-TB risk cases, the proportion with either two smear tests or an Xpert test increased from 84.6% at T1 to 94.3% at T7. The binomial regression analysis showed a mean increase in cases with either two smears or an Xpert test of 1.8% (95% CI 1.1% to 2.6%) (p<0.001) per time-point and a mean decrease of 3.7% (95% CI -4.8% to -2.6%) (p<0.001) in smear or Xpert-negative cases receiving culture tests per time-point.

Amongst *high MDR-TB risk* presumptive TB cases, 81.5% in the smear/culture-based algorithm had two smear tests and 85.2% of smear-negative cases had a culture test (Table 3). In the Xpert-based algorithm in comparison, 64.6% had an Xpert test and 40.6% of Xpert-negative cases had a culture test. Amongst all high MDR-TB risk cases, the proportion with either two smear tests or an Xpert test increased from 81.9% at T1 to 93.1% at T7. The binomial regression analysis showed a mean increase in cases with either two smears or an Xpert test of 2.3% (95% CI 1.7% to 3.0%) (p<0.001) per time-point and a mean decrease of 8.0% (95% CI -9.0% to -7.0%) (p<0.001) in smear or Xpert-negative cases receiving culture tests per time-point.

The proportion of presumptive TB cases with a culture test was higher in the smear/culture-based algorithm (51.5%) than in the Xpert-based algorithm (32.8%) (Table 3). The binomial regression analysis showed a mean decrease in cases with a culture test of 4.7% (95% CI -5.1% to -3.8%) (p<0.001) per time-point.



	T1	T2	T3	T4	T5	T6	T7
Smear/culture-based algorithm	23.6	20.4	19.2	17.2	19.3		
Upper 95% CI	25.1	21.7	20.4	18.9	21.6		
Lower 95% CI	22.1	19.0	18.0	15.5	16.9		
Xpert-based algorithm			19.5	17.5	19.5	16.6	17.4
Upper 95% CI			21.3	19.5	21.3	18.2	19.9
Lower 95% CI			17.6	15.5	17.8	15.0	15.0

Figure 3: TB yield in the smear/culture and Xpert® based algorithms at PHC sites in Cape Town by time-point. The graph shows the proportion of presumptive cases identified with TB (and 95% confidence intervals) in the smear/culture and Xpert-based algorithms as PHC sites changed from the former to the latter over seven time-points (T1 to T7). Estimates derived from the binomial regression analysis were adjusted for clustering of cases at PHC sites. Time-points were as follows: T1=November 2010, T2=May 2011. T3=November 2011, T4=May 2012, T5=November 2012, T6=May 2013, T7=November 2013. Abbreviations: TB – tuberculosis, PHC - primary health care, CI – confidence interval.

Trends in the proportion of the population tested over time

The trend in the proportion of the population tested over time varied from a high of 0.95% at T1 to a low of 0.80% at T5 and up to 0.89% at T7 (Table 3). There was a small decline in the proportion of the population tested over time (slope -0.00007, p<0.001).

Table 3: Temporal trends in TB testing in the smear/culture and Xpert® based algorithms

			Proportion of presumptive TB cases with tests done at each time-point (%)							
TB category	**Algorithm**	**Tests**	**T1**	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**	**All**
For low MDR-TB risk cases	Smear/ culture-based	Two smears	84.6	84.7	86.0	89.5	59.9	-	-	83.9
		Smear-negative with culture	34.3	36.8	33.4	41.5	30.3	-	-	35.5
	Xpert-based	Xpert	-	-	64.3	75.6	68.3	82.3	84.9	77.2
		Xpert-negative with culture	-	-	26.6	16.6	18.7	18.3	15.5	17.9
	Overall	Two smears	84.6	84.7	61.6	38.8	32.2	12.5	9.3	45.4
		Xpert	-	-	25.3	52.1	61.2	82.3	84.9	44.7
		Smear-negative with culture	34.3	36.8	34.2	39.6	37.1	50.9	25.2	36.2
		Xpert-negative with culture	-	-	26.3	16.7	18.8	18.3	15.5	17.9
For high MDR-TB risk cases	Smear/ culture-based	Two smears	81.9	81.7	82.7	84.4	67.9	-	-	81.5
		Smear-negative with culture	84.6	86.7	84.2	85.7	82.7	-	-	85.2
	Xpert-based	Xpert	-	-	53.0	56.0	56.7	71.3	78.0	64.6
		Xpert-negative with culture	-	-	44.8	35.4	39.4	42.9	40.2	40.6
	Overall	Two smears	81.9	81.7	56.8	47.4	38.6	22.5	15.1	51.2
		Xpert	-	-	25.7	38.6	50.6	71.3	78.0	35.3
		Smear-negative with culture	84.6	86.7	85.0	80.4	76.9	70.3	75.4	82.6
		Xpert-negative with culture			44.3	35.4	39.3	42.9	40.2	40.5
All cases	Smear/ culture-based	Culture	51.9	52.9	48.1	58.3	40.9	-	-	51.5
	Xpert-based	Culture	-	-	42.9	34.2	36.8	33.5	24.5	32.8
	Overall	Culture	51.9	52.9	45.9	41.3	37.5	33.5	24.5	41.1
			Trends in laboratory testing over time							
			T1	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**	**All**
All cases	Smear/ culture-based	Presumptive TB cases screened	8,083	7,842	4,465	2,269	1,341	-	-	24,000
		TB cases diagnosed	1,911	1,601	804	427	276	-	-	5,019
	Xpert-based	Presumptive TB cases screened	-	-	3,309	5,371	5,873	7,714	8,126	30,393
		TB cases diagnosed	-	-	702	906	1,133	1,281	1,422	5,444
Proportion of the population tested per quarter			0.95	0.93	0.85	0.84	0.80	0.84	0.89	-

Data on the proportion of presumptive TB cases with appropriate tests undertaken is shown by MDR-TB risk profile, algorithm and time-point. The analysis includes the full sequence of tests undertaken for individuals identified at each time-point, including tests in the preceding and following months. The proportion of the population tested per quarter was calculated based on the number of presumptive TB cases tested in the quarter divided by the mid-year population estimates for the five sub-districts included in the analysis. Abbreviations: TB - tuberculosis, MDR-TB –multidrug-resistant tuberculosis.

DISCUSSION

South Africa introduced Xpert as a replacement for smear microscopy for all presumptive TB cases in 2011. Since Xpert [4] has a higher sensitivity than smear microscopy [5,6,13] we expected to find a higher TB yield in the Xpert-based algorithm. The introduction of an Xpert-based algorithm however had no impact on TB yield in this routine operational setting.

A study in the rural Western Cape also found comparable TB yields amongst cases tested centrally through smear microscopy and Xpert [14]. Another study amongst HIV-infected cases enrolling for antiretroviral treatment in Zimbabwe found that the proportion of TB cases identified with Xpert was not significantly different to that from smears evaluated through fluorescence microscopy at a central laboratory [15]. The latter differs from a similar study in Cape Town that showed significant differences in the proportion of TB cases identified with Xpert and with smear microscopy amongst culture-confirmed cases enrolling for antiretroviral treatment [16].

Demonstration studies done on a moderate scale and at sites selected for good performance tend to over-estimate test efficacy [17] and may not reliably reflect findings in routine practice. Many of the studies reporting a significant increase in sensitivity for Xpert compared to smears used direct light microscopy for comparison in the majority or all or their sites [18–21]. Smear microscopy performance at our high throughput central laboratory may be better than that reported from peripheral microscopy units due to both greater proficiency and to technical aspects including chemical treatment, centrifugation and fluorescence microscopy, which have all been shown to increase yield [5,6,13]. The frequent use of culture tests in the smear/culture-based algorithm may also have contributed to the yield parity between algorithms and is discussed further below.

We found a decline in TB yield over time; the decline in the smear/culture-based algorithm was continued under the Xpert-based algorithm, with no change point observed. To assess whether adherence to algorithms may have contributed to this temporal trend, we assumed “diagnostic equipoise” i.e. that sensitivity was not lower with Xpert than with two smears. We assessed the proportion of low and high MDR-TB risk cases with either two smears or an Xpert test at each time-point. Both showed increases over time, indicating that although adherence to the Xpert-based algorithm was sub-optimal, cases were better-off than previously for initial testing.

As HIV data for presumptive TB cases were not available for all time-points, we could not assess adherence to the second step of the algorithm (i.e. the proportion of HIV-infected, smear- or Xpert-negative cases with a culture test). Overall, we found a higher proportion of smear-negative cases compared to Xpert-negative cases with culture tests. Since a higher proportion of HIV-infected cases may initially have been diagnosed by Xpert than by smear, the extent to which this may reflect poorer adherence to the algorithm cannot be ascertained. It is possible that poor adherence to the Xpert-negative algorithm for HIV-infected cases contributes to the temporal trend to some extent.

The last few years has seen national efforts to intensify TB case-finding. As the proportion of the population tested increases, one would expect to find a decrease in TB yield. Our study found a minimal decline in the proportion of the population tested over time and this is therefore unlikely to have contributed to the temporal decline in TB yield.

We do not have local TB prevalence estimates. A Cape Town study reported a decrease in TB prevalence following antiretroviral treatment roll-out in one community [22]. It is possible that the rapid scale-up of antiretroviral treatment in South Africa may have contributed to a declining TB prevalence and to the temporal decline in TB yield in this study. This postulate is supported by a study reporting a decrease in the number of laboratory confirmed PTB cases in South Africa from 2011 to 2012 [23].

Strengths and limitations

Diagnostic tests are rarely used in isolation. A unique aspect of this study is that we assessed TB diagnostic yield from each algorithm and not from individual tests. This reflected the variability that occurs in routine clinical practice, including both poor adherence to algorithms as well as the appropriate pursuit of a TB laboratory diagnosis after initial negative tests. Many presumptive TB cases are likely to undergo a sequence of tests and although this has been assessed in modelling studies [24,25], it is rarely reported from empirical field studies.

We used a stepped-wedge analysis, deemed appropriate where practical, financial or logistic constraints prevent the intervention being simultaneously introduced to all facilities [26]. An advantage of this method is that clusters act as their own controls and time-points prior and subsequent to the transition allow temporal trends to be assessed. In our study the introduction of the Xpert-based algorithm was determined by the health services based on operational requirements and not randomly assigned. Allocation bias may have influenced TB yield at time-points T3 to T5. The impact is difficult to quantify as the new algorithm was first introduced in areas with both high TB and HIV prevalence.

The extent to which results can be generalised is limited by the urban setting and good health and laboratory infrastructure, including access to liquid culture. Additional evidence is required from other settings particularly where culture is not routinely available.

Implications for policy and practice

The failure to find an increase in TB notification rates following Xpert implementation has been attributed to high rates of empirical treatment [15,20,27]. The efficiency of the diagnostic algorithm in some settings may also contribute. Our data showed comparable TB diagnostic yields in the smear/culture and Xpert-based algorithms, perhaps partly attributable to the high proportion of cases with a culture test in the former.

Several studies have reported other benefits with Xpert, including early TB [21,28] and MDR-TB treatment initiation [29,30] and reduced MDR-TB patient costs [31]. However, the high health system costs of Xpert [3,32] and lack of impact on TB morbidity and/or mortality [15,21,33] are cause for concern. These factors together with the failure to find an increase in TB diagnostic yield suggests that Xpert may not have the anticipated impact on TB control and its role may need to be reviewed. Studies are required to assess whether Xpert can be used more cost-effectively, for example as a rapid screening test for rifampicin resistance in smear or culture-positive cases.

CONCLUSION

Despite South Africa making great strides in expanding diagnostic services, including access to rapid tests through nation-wide implementation of Xpert, the proportion of TB cases diagnosed through laboratory tests in Cape Town has not increased. The historic smear/culture-based algorithm was as effective in identifying TB cases as the newly introduced Xpert-based algorithm. Additional studies are required to assess whether improving adherence to algorithms, particularly for Xpert-negative, HIV-infected individuals, will increase TB yield. Ultimately, difficult questions may need to be asked and answered about the future use of Xpert in resource-constrained settings where effective smear and culture-based algorithms are in place.

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Author contributions:

All authors were involved in the study design. RD extracted, matched and managed the data. PN, RD and CL developed the data analysis plan and undertook the analysis. PN wrote the manuscript. All authors provided input to the manuscript and approved the final draft for submission

Conflicts of interest:

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

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Chapter 3: Has universal screening with Xpert® MTB/RIF increased the proportion of multidrug-resistant tuberculosis cases diagnosed in a routine operational setting?

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ABSTRACT

Setting: Primary health services in Cape Town, South Africa where the introduction of Xpert® MTB/RIF (Xpert) enabled simultaneous screening for tuberculosis (TB) and drug susceptibility in all presumptive cases.

Study Aim: To compare the proportion of TB cases with drug susceptibility tests undertaken and multidrug-resistant tuberculosis (MDR-TB) diagnosed pre-treatment and during the course of 1st line treatment in the previous smear/culture and the newly introduced Xpert-based algorithms.

Methods: TB cases identified in a previous stepped-wedge study of TB yield in five sub-districts over seven one-month time-points prior to, during and after the introduction of the Xpert-based algorithm were analysed. We used a combination of patient identifiers to identify all drug susceptibility tests undertaken from electronic laboratory records. Differences in the proportions of DST undertaken and MDR-TB cases diagnosed between algorithms were estimated using a binomial regression model.

Results: Pre-treatment, the probability of having a DST undertaken (RR=1.82)($p<0.001$) and being diagnosed with MDR-TB (RR=1.42)($p<0.001$) was higher in the Xpert-based algorithm than in the smear/culture-based algorithm. For cases evaluated during the course of 1st-line TB treatment, there was no significant difference in the proportion with DST undertaken (RR=1.02)($p=0.848$) or MDR-TB diagnosed (RR=1.12)($p=0.678$) between algorithms.

Conclusion: Universal screening for drug susceptibility in all presumptive TB cases in the Xpert-based algorithm resulted in a higher overall proportion of MDR-TB cases being diagnosed and is an important strategy in reducing transmission. The previous strategy of only screening new TB cases when 1st line treatment failed did not compensate for cases missed pre-treatment.

INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB), defined as resistance to rifampicin and isoniazid, presents a major global health challenge with an estimated 480,000 incident cases in 2014 [1]. Whilst MDR-TB rates are substantially higher among previously treated cases (20%) than among new cases (3.3%), the latter contribute substantially to the total burden, accounting for an estimated 53% of MDR-TB cases among the pulmonary TB cases notified in 2014 [1]. The high proportion of new TB cases with MDR-TB (primary MDR-TB) suggests significant disease transmission.

Persistent diagnostic gaps due to both inadequate TB case-detection and limited drug susceptibility testing among detected cases contribute to transmission of MDR-TB. Only 6 million of the estimated 9.6 million TB cases in 2014 were detected. Among notified pulmonary TB cases, 300,000 were estimated to have MDR-TB; however just 12% of new and 58% of previously treated cases were tested for drug susceptibility and 123,000 MDR-TB cases were notified globally [1]. Thus it is estimated that 180,000 of the missed MDR-TB cases were among those with undetected TB and 177,000 among detected TB cases not screened for drug susceptibility.

The past reliance on insensitive smear microscopy tests [2–4] as the cornerstone of laboratory diagnosis has contributed to poor TB case-detection, particularly among human immunodeficiency virus (HIV)-infected cases, where sensitivity can be as low as 23% to 50% [5–9]. Limited laboratory capacity for culture and drug susceptibility testing (DST) contributes to poor MDR-TB case-detection: among the 36 high TB or MDR-TB burden countries, only 16 met the benchmark of one laboratory with culture and DST capabilities per five million population in 2010 [10]. In many developing countries these limitations have led to DST being rationed for use among previously treated cases as they are most at risk of MDR-TB [11–13].

The availability of the more sensitive Xpert® MTB/RIF (Xpert)(Cepheid, Sunnyvale, CA, USA) test offers the possibility of improving TB case-detection and simultaneously screening for drug susceptibility. Xpert is a nucleic acid amplification test that detects genetic sequences for *Mycobacterium tuberculosis* (MTB) complex and simultaneously, the presence of 'wild type' or mutations conferring resistance to rifampicin. Xpert has the ability to detect low bacteria loads (limit of detection 131 colony forming units (CFU) per ml) [14] compared to 10,000 CFU per ml for smear [15]) and is particularly useful in diagnosing the smear-negative TB typically found in HIV-infected individuals. Xpert has high sensitivity and specificity for detecting both TB and rifampicin resistance. In a meta-analysis of fifteen studies where Xpert was used as the initial test replacing smear microscopy, pooled sensitivity was 88% (95%CrI 83% to 92%) and specificity was 98% (95% CrI 97% to 99%) for detecting MTB. In eleven of these studies, pooled sensitivity was 94% (95% CrI 87% to 97%) and specificity was 98% (95% CrI 97% to 99%) for rifampicin resistance [16].

While Xpert has the technical capacity to help close MDR-TB diagnostic gaps, very little has been reported on its use in universal drug susceptibility screening under routine operational conditions. A study in India found that routine, up-front use of Xpert in children under 14-years of age almost tripled the number of Rif-R cases diagnosed (from 22 to 60 among the 8,370 presumptive TB cases screened), than would have been achieved through screening of presumptive DR-TB cases only [17].

Our study compared the proportion of TB cases with DST undertaken and MDR-TB diagnosed pre-treatment in the previous smear/culture-based algorithm and the newly introduced Xpert-based algorithm. Among cases without MDR-TB diagnosed pre-treatment, we compared the proportion with DST undertaken and MDR-TB diagnosed during the course of 1st-line TB treatment. Comparisons were made for new and previously treated

TB cases. The study was part of PROVE IT (Policy Relevant Outcomes from Validating Evidence on ImpacT), an evaluation to assess the impact of new molecular diagnostics on TB and MDR-TB diagnosis and treatment initiation in a routine operational context.

METHODS

We had previously undertaken and published results of a non-randomised stepped-wedge study to assess TB yield [18]. The current study assessed drug susceptibility screening and MDR-TB diagnosis among the TB cases identified in the previous study. Some details are highlighted here for completeness.

Setting

The study was undertaken in Cape Town, South Africa where free TB diagnostic services were provided at 142 primary health care (PHC) facilities in eight health sub-districts. Prior to August 2011, a smear/culture-based diagnostic algorithm was used (Fig 1). All presumptive TB cases were evaluated through two spot sputum specimens, taken 1-hour apart and examined by fluorescence microscopy. In previously treated TB cases, those from congregate settings or with an MDR-TB contact, the second specimen also underwent liquid culture (BACTEC™ MGIT™ 960) and DST with GenoType® MTBDR*plus* (Hain LifeScience GmbH, Nehren, Germany) line probe assay (LPA).

Between August 2011 and February 2013 an Xpert-based algorithm was phased into the eight health sub-districts with Xpert replacing smear microscopy for *all* (new and previously treated) presumptive TB cases (Fig 1). The first of two sputum specimens submitted was tested with Xpert; if rifampicin resistance was detected, the second specimen underwent smear, culture and LPA.

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.

Routine TB Programme data collected during the study period, indicated that the number of notified TB cases declined from 28,644 in 2011 (752/100,000 population) to 25,846 in 2013 (663/100,000 population). HIV co-infection rates were 47% (97% tested) and 44% (98% tested) in respective years. The number of MDR-TB cases notified increased from 1,020 to 1,134, comprising 3.6% and 4.4% of TB cases respectively (Routine TB Programme Data, Cape Town Health Directorate, April 2016).

Definitions

A presumptive TB case was defined as an individual with pre-treatment sputum samples submitted for diagnostic purposes.

A TB case was defined as an individual with one or more smears positive and / or culture positive for MTB and / or MTB detected on Xpert. TB cases were categorised as *new* (an individual with no or less than four weeks of previous TB treatment) or *previously treated* (an individual with more than four weeks of previous TB treatment).

An MDR-TB case was defined as a TB case with rifampicin resistance on LPA or Xpert, diagnosed either pre-treatment or whilst on 1st line TB treatment. Rifampicin resistance was used as a proxy indicator of MDR-TB.

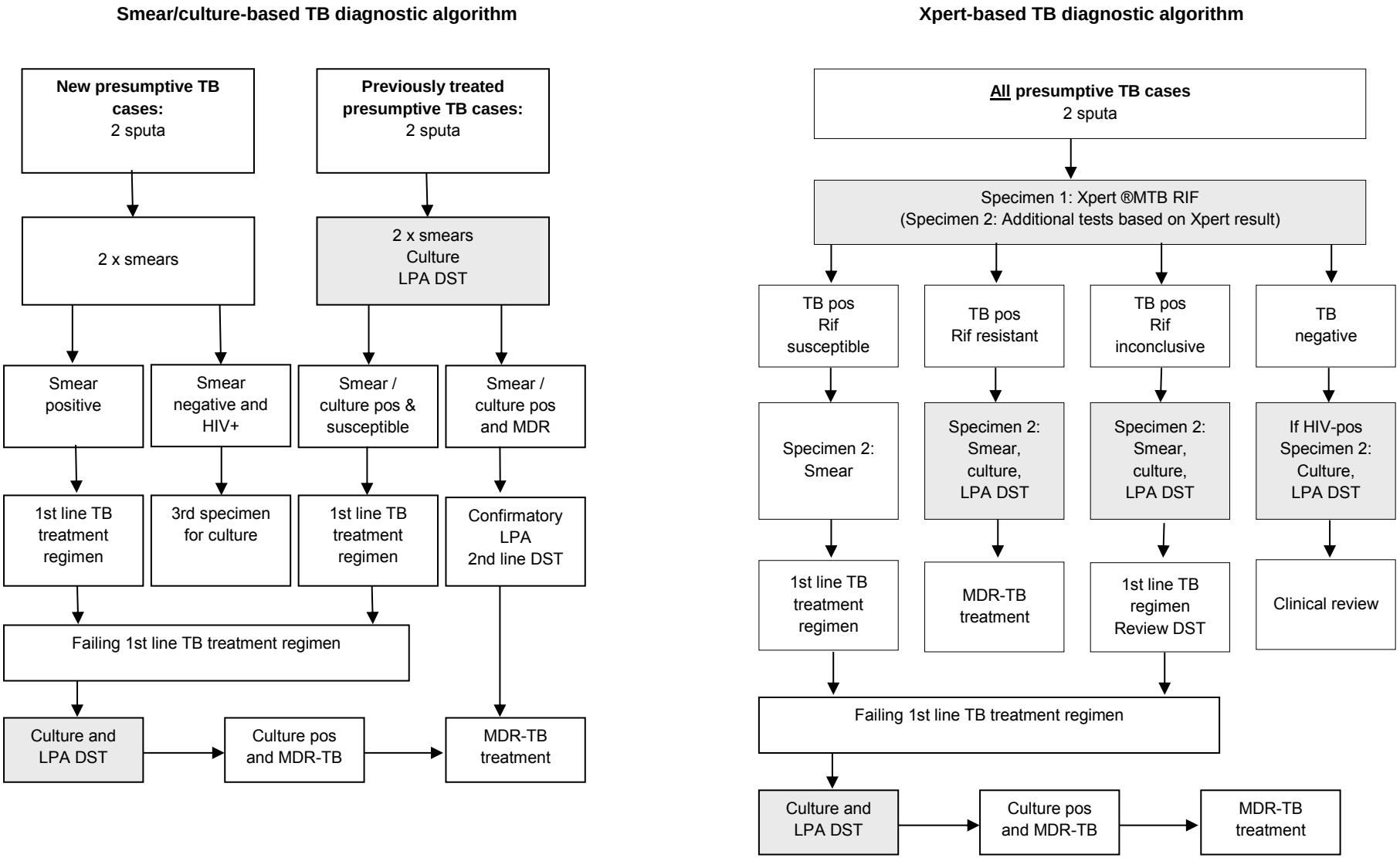

Figure 1: Testing in the smear/culture and Xpert-based TB diagnostic algorithms. The sequence of diagnostic tests in each algorithm and the action taken based on test results is shown. Shaded blocks indicate possible MDR-TB diagnostic points. Abbreviations: MDR-TB - multidrug-resistant tuberculosis; LPA - GenoType® MTBDR*plus* line probe assay; DST - drug susceptibility testing; HIV – human immunodeficiency virus; Rif – rifampicin; Pos – positive

Study design, timeframes and population

The previously published stepped-wedge study assessed TB yield in five sub-districts over seven one-month time-points (T1 to T7) prior to, during and after the introduction of the Xpert-based algorithm [18]. The current study population included all presumptive TB cases with a bacteriological diagnosis of TB in the smear/culture-based algorithm (T1 to T5) and in the Xpert-based algorithm (T3 to T7) (Fig 2).

Facilities	Nov 2010 (T1)	May 2011 (T2)	Nov 2011 (T3)	May 2012 (T4)	Nov 2012 (T5)	May 2013 (T6)	Nov 2013 (T7)
Group A (12 PHC sites)	Smear/ culture	Smear/ culture	Xpert	Xpert	Xpert	Xpert	Xpert
Group B (9 PHC sites)	Smear/ culture	Smear/ culture	Xpert	Xpert	Xpert	Xpert	Xpert
Group C (16 PHC sites)	Smear/ culture	Smear/ culture	Smear/ culture	Xpert	Xpert	Xpert	Xpert
Group D (9 PHC sites)	Smear/ culture	Smear/ culture	Smear/ culture	Smear/ culture	Xpert	Xpert	Xpert
Group E (14 PHC sites)	Smear/ culture	Smear/ culture	Smear/ culture	Smear/ culture	Smear/ culture	Xpert	Xpert

Figure 2: TB cases from the stepped-wedge analysis of TB yield included in this analysis. This figure shows the TB diagnostic algorithm in place in 5 groups of PHC facilities over seven time-points (T1 to T7) during the transition from the smear/culture-based algorithm to the Xpert-based algorithm. All TB cases identified in the smear culture-based algorithm (T1 to T5) and in the Xpert-based algorithm (T3 to T7) were included in the current analysis. We did not assess a time effect as the change in the proportion with DST over time was inherent to the phased introduction of the Xpert-based algorithm. Abbreviations: PHC=primary health care

Data Sources & Management

The National Health Laboratory Services provided TB test data from the electronic laboratory database for 2010-2014. Data included clinic identification, patient clinical folder number, patient demographics, TB category (new, previously treated), test type (smear, culture, LPA or Xpert), diagnostic point (pre-treatment or on 1st-line treatment), test date and result.

Laboratory data for all primary health facilities and all hospitals in Cape Town were imported into Microsoft SQL. We used a combination of patient name, surname, birth date, address and clinical folder number to identify all DSTs undertaken (i.e. a rifampicin result on Xpert / LPA) for the TB cases diagnosed at T1 to T7 and to identify duplicates cases (individuals diagnosed at multiple facilities). DSTs were classified as pre-treatment if recorded as a pre-treatment test or if taken within 7 days of this test. DSTs were classified as taken during 1st line treatment if taken >7 days and up to 9 months after the pre-treatment test. All matches and classification as “pre-treatment” or “treatment” were manually verified.

Data Analysis

Cases were allocated to algorithm based on the algorithm in place at the facility at the time-point i.e. we used an intention to treat approach in the analysis. We compared the proportion of TB cases with DST undertaken and MDR-TB diagnosed pre-treatment in the smear/culture-based algorithm and the Xpert-based algorithm. Among cases without MDR-TB diagnosed pre-treatment, we assessed the proportion with DST undertaken and MDR-TB diagnosed during the course of 1st-line TB treatment in both algorithms. Analyses were done for new and for previously treated TB cases.

Descriptive data are presented using proportions and frequencies. Normally distributed continuous outcomes were analysed using the t-test and categorical outcomes using the chi-squared test. A binomial regression model, adjusted for clustering at 60 primary health care sites, was used to estimate differences in the proportions of DST undertaken and MDR-TB cases diagnosed between algorithms and the interaction of age, gender and treatment category variables. We undertook a sub-analysis for new and previously treated cases. We did not consider a time-effect, as the change in the proportion with DST undertaken over time was inherent to the phased introduction of the Xpert-based algorithm. All analyses were undertaken using STATA 13 (StataCorp).

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. A waiver of informed consent was granted for the use of routine data. The City Health Directorate, Western Cape Health Department and National Health Laboratory Service granted permission to use routine health data. Data sharing is possible following approval by these authorities.

RESULTS

A total of 5,019 TB cases were diagnosed in the smear/culture-based algorithm and 5,444 in the Xpert-based algorithm. Among these, 7 and 3 cases were excluded from respective algorithms as they were known MDR/XDR-TB cases (with tests incorrectly reported as pre-treatment) and 97 and 72 from respective algorithms were merged with corresponding records as they belonged to individuals diagnosed at multiple facilities. The remaining 4,915 TB cases in the smear/culture group and 5,369 in the Xpert group were included in the analysis.

Characteristics of TB cases and those with DST undertaken by algorithm

There were no significant differences in age, gender or TB category (new or previously treated) between TB cases in the smear/culture and Xpert groups (Table 1). For those with DST undertaken pre-treatment, cases in the smear/culture group were slightly older and contained a lower proportion of new cases (45% compared to 65% in the Xpert group). Among those with DST undertaken on treatment, the smear/culture group contained a higher proportion of females (43% compared to 32% in the Xpert group).

Table 1: Characteristics of TB cases evaluated by algorithm

		Smear/culture-based algorithm	Xpert-based algorithm	p-value
TB cases	Total	4,915	5,369	-
	Mean age (Years) [SD]	35 [13]	35 [12]	0.905
	Number male (%)	2,702 (55)	2,995 (56)	0.811
	Number female (%)	2,086 (42)	2,290 (43)	
	Number new cases (%)	2,990 (61)	3,322 (62)	0.309
	Number previously treated cases (%)	1,490 (30)	1,583 (29)	
DST undertaken pre-treatment	Total	2,099	4,235	-
	Mean age (Years) (SD)	36 (11)	35 (12)	0.043
	Number male (%)	1,165 (56)	2,396 (57)	0.784
	Number female (%)	879 (42)	1,781 (42)	
	Number new cases (%)	946 (45)	2,733 (65)	<0.001
	Number previously treated cases (%)	1015 (48)	1,253 (30)	
DST undertaken for cases on 1st line TB treatment	Total	221	247	-
	Mean age (Years) (SD)	35 (12)	37 (11)	0.135
	Number male (%)	122 (55)	164 (66)	0.013
	Number female (%)	96 (43)	80 (32)	
	Number new cases (%)	102 (46)	122 (49)	0.469
	Number previously treated cases (%)	101 (46)	105 (43)	

The smear/culture and Xpert groups were compared using chi-squared tests. Missing values are not shown but have been included in the calculation of percentages. These have been excluded when comparing groups and calculating p-values. Abbreviations: TB – tuberculosis; DST – drug susceptibility test; SD – standard deviation.

Proportion of TB cases with drug susceptibility testing and MDR-TB diagnosed by algorithm

DSTs were undertaken pre-treatment for 42.7% of TB cases in the smear/culture group compared to 78.9% in the Xpert group and 5.5% and 7.7% of TB cases in respective groups had MDR-TB diagnosed (Table 2). Among cases not initially diagnosed with MDR-TB, 4.8% and 5.0% in respective groups had DST undertaken during the course of 1st-line TB treatment and 0.6% and 0.9% respectively were diagnosed with MDR-TB. In these MDR-TB cases, a lower proportion of cases had received an initial pre-treatment DST in the smear/culture group (5/28) than in the Xpert group (21/43)(p=0.008).

Among new TB cases, DSTs were undertaken pre-treatment for 31.6% of TB cases in the smear/culture group compared to 82.3% in the Xpert group and 2.7% and 5.5% of new TB cases in respective groups had MDR-TB. Among new TB cases not initially diagnosed with MDR-TB, similar proportions had DST undertaken (3.5% and 3.9% respectively) and were diagnosed with MDR-TB (0.3% and 0.5% respectively) during the course of 1st-line TB treatment.

Among previously treated TB cases, DSTs were undertaken pre-treatment for 68.1% of TB cases in the smear/culture group compared to 79.2% in the Xpert group and 10.6% and 11.5% of previously treated TB cases in respective groups had MDR-TB diagnosed. Among previously treated TB cases not initially diagnosed with MDR-TB, similar proportions had DST undertaken (7.6% and 7.5% respectively) and were diagnosed with MDR-TB (1.4% in both algorithms) during the course of 1st-line TB treatment.

Table 2: Drug susceptibility testing and MDR-TB cases diagnosed by TB diagnostic algorithm

	Smear/culture-based algorithm Number of cases (%)			Xpert-based algorithm Number of cases (%)		
	All TB cases	New TB cases	Previously treated cases	All TB cases	New TB cases	Previously treated cases
Number of TB cases	4915	2990	1490	5369	3322	1583
DST undertaken pre-treatment	2099 (42.7)	946 (31.6)	1015 (68.1)	4235 (78.9)	2733 (82.3)	1253 (79.2)
MDR-TB diagnosed pre-treatment	269 (5.5)	82 (2.7)	158 (10.6)	415 (7.7)	184 (5.5)	182 (11.5)
DST undertaken on 1st line TB treatment	221 (4.8)	102 (3.5)	101 (7.6)	247 (5.0)	122 (3.9)	105 (7.5)
MDR-TB diagnosed on 1st line TB treatment	28 (0.6)	9 (0.3)	18 (1.4)	43 (0.9)	15 (0.5)	20 (1.4)
Total MDR-TB diagnosed	297 (6.0)	91 (3.0)	176 (11.8)	458 (8.5)	199 (6.0)	202 (12.8)

Data is not shown for cases with TB category “unknown” (435 cases (8.9%) in smear/culture group and 464 (8.6%) in Xpert group) but can be calculated based on the numbers shown. DST (drug susceptibility tests) and MDR-TB (multidrug-resistant tuberculosis) pre-treatment are expressed as a percentage of TB cases. DST and MDR-TB on 1st line TB treatment are expressed as a percentage of TB cases not initially diagnosed with MDR-TB. Abbreviations: TB – tuberculosis; MDR-TB - multidrug-resistant tuberculosis

Comparing TB cases with DST undertaken pre-treatment and MDR-TB diagnosed by algorithm

The probability of having a DST undertaken pre-treatment was 1.82 times higher in the Xpert group than in the smear/culture group ($p<0.001$)(Table 3). Previously treated TB cases were more likely to have DST undertaken (RR=1.09, $p=0.001$) than new cases.

The likelihood of being diagnosed with MDR-TB was 1.42 times higher in the Xpert group than in the smear/culture group ($p<0.001$). Previously treated cases were more likely to be diagnosed with MDR-TB pre-treatment than new cases (RR=2.67, $p<0.001$).

Table 3: Comparison of TB cases with DST undertaken pre-treatment and MDR-TB diagnosed

	Variable	Risk ratio	Standard error	95% CI	p-value
All TB cases					
DST undertaken	Xpert-based algorithm	1.82	0.07	1.69 to 1.97	<0.001
	Age	~1.00	<0.01	1.00 to 1.00	0.037
	Female gender	0.98	0.01	0.96 to 1.00	0.052
	Previously treated category	1.09	0.03	1.03 to 1.14	0.001
	Constant	0.46	0.02	0.41 to 0.50	<0.001
MDR-TB diagnosed	Xpert-based algorithm	1.42	0.13	1.19 to 1.70	<0.001
	Age	0.99	<0.01	0.99 to <1.00	0.008
	Female gender	1.09	0.10	0.91 to 1.30	0.335
	Previously treated category	2.67	0.27	2.19 to 3.25	<0.001
	Constant	0.05	0.01	0.03 to 0.06	<0.001
New TB cases					
DST undertaken	Xpert-based algorithm	2.64	0.19	2.29 to 3.05	<0.001
	Age	1.00	<0.01	1.00 to 1.00	0.129
	Female gender	0.97	0.02	0.94 to 1.00	0.091
	Constant	0.33	0.03	0.28 to 0.38	<0.001
MDR-TB diagnosed	Xpert-based algorithm	2.09	0.33	1.53 to 2.84	<0.001
	Age	0.99	<0.01	0.98 to <1.00	0.088
	Female gender	1.03	0.15	0.78 to 1.36	0.821
	Constant	0.04	<0.01	0.02 to 0.05	<0.001
Previously treated TB cases					
DST undertaken	Xpert-based algorithm	1.15	0.03	1.10 to 1.21	<0.001
	Age	1.00	<0.01	1.00 to 1.00	0.024
	Female gender	0.99	0.02	0.94 to 1.03	0.553
	Constant	0.76	0.03	0.70 to 0.83	<0.001
MDR-TB diagnosed	Xpert-based algorithm	1.09	0.11	0.90 to 1.34	0.376
	Age	0.99	<0.01	0.98 to 1.00	0.047
	Female gender	1.15	0.13	0.91 to 1.43	0.237
	Constant	0.14	0.03	0.10 to 0.20	<0.01

The table shows outputs from binomial regression models for all TB cases with drug susceptibility tests (DST) undertaken pre-treatment and multidrug-resistant tuberculosis (MDR-TB) diagnosed and for sub-categories of new and previously treated cases. Facility level clustering has been taken into account in the binomial regression models. Abbreviations: TB – tuberculosis; MDR-TB - multidrug-resistant tuberculosis

Among new TB cases, the likelihood of a DST being undertaken pre-treatment was 2.64 times higher (p<0.001) and of MDR-TB being diagnosed was 2.09 times higher (p<0.001) in the Xpert group than in the smear/culture group. Among previously treated TB cases, the likelihood of a DST being undertaken pre-treatment was 1.15 times higher in the Xpert group than in the smear/culture group (p<0.001); however, the risk of being diagnosed with MDR-TB was not increased (RR=1.09, p=0.376).

Comparing cases with DST undertaken whilst on 1st line TB treatment by algorithm and MDR-TB diagnosed

Among TB cases not initially diagnosed with MDR-TB, there was no significant difference in the proportion with DST undertaken during the course of 1st-line TB treatment in the Xpert group (RR=1.02; p=0.848) compared to with smear/culture group (Table 4). Females were less likely to be screened for drug susceptibility than males (RR= 0.77; p=0.015). Previously treated TB cases were more likely to be screened for drug susceptibility than new cases (RR=2.02, p<0.001).

The likelihood of being diagnosed with MDR-TB during the course of 1st-line TB treatment was similar in the Xpert (RR=1.12; p=0.678) and smear/culture groups. Previously treated TB cases were 3.96 times more likely to be diagnosed with MDR-TB than new cases (p <0.001).

Table 4: Comparison of TB cases with DST undertaken whilst on 1st line TB treatment and MDR-TB diagnosed

	Variable	Risk ratio	Standard error	p-value	95% CI
DST undertaken	Xpert-based algorithm	1.02	0.13	0.848	0.80 to 1.31
	Age	1.00	<0.01	0.760	0.99 to 1.00
	Female gender	0.77	0.08	0.015	0.62 to 0.95
	Previously treated cases	2.02	0.25	<0.001	1.59 to 2.58
	Constant	0.04	<0.01	<0.001	0.03 to 0.06
MDR-TB diagnosed	Xpert-based algorithm	1.12	0.34	0.678	0.63 to 2.03
	Age	0.99	<0.01	0.435	0.98 to 1.01
	Female gender	0.84	0.22	0.520	0.50 to 1.41
	Previously treated cases	3.86	0.84	<0.001	2.52 to 5.90
	Constant	<0.01	<0.01	<0.001	<0.01 to 0.01

This table shows outputs from a binomial regression model for all TB cases with drug susceptibility tests (DST) undertaken and for multidrug-resistance tuberculosis (MDR-TB) diagnosed during the course of 1st-line TB treatment. Facility level clustering has been taken into account in the models.

DISCUSSION

Previously treated TB cases are at significantly higher risk of MDR-TB than new cases [11–13]. Many countries including South Africa have historically rationed the use of DST in favour of these cases. Thus, in the previous smear/culture-based algorithm drug-susceptibility testing in presumptive TB cases was limited to those at high risk of MDR-TB, namely those who were previously treated for TB, with MDR-TB contacts or from congregate settings. The assumption was that the smaller proportion of new TB cases with drug

resistance would be detected during the course of 1st-line treatment.

In comparison, the Xpert-based algorithm required all presumptive TB cases to be screened with Xpert. As expected, our study found that a higher proportion TB cases were screened for drug susceptibility pre-treatment in the Xpert-based algorithm (78.9%) compared to in the smear/culture-based algorithm (42.7%). Overall, TB cases were 82% more likely to be screened for drug susceptibility and 42% more likely to be diagnosed with MDR-TB pre-treatment in the Xpert-based algorithm than in the smear/culture-based algorithm. These differences were accentuated among new cases (RR=2.64 for DST and RR= 2.09 for MDR-TB). Although previously treated cases were also more likely to have a DST in the Xpert-based algorithm (RR=1.15) there was no significant increase in the likelihood of an MDR-TB diagnosis.

Interestingly, similar proportions of cases were screened for drug susceptibility (RR=1.02; p=0.848) and identified with MDR-TB (R=1.12; p=0.678) during the course of 1st-line TB treatment in the Xpert-based algorithm compared to in the smear/culture-based algorithm. The assumption that new cases with MDR-TB that were initially missed in the smear/culture-based algorithm would be picked up during the course of treatment appears not to hold true. We speculate that there may have been cases that died or were lost to follow-up before the opportunity to screen them for drug resistance presented.

It is notable that women were less likely to have a DST undertaken during the course of 1st line TB treatment than men. It is difficult to know whether this is due to reduced perceptions of risk (perhaps due to better adherence to treatment) or to women receiving a poorer quality of service [19–23].

There were over double the number of new compared to previously treated TB cases in the Xpert-based algorithm. Although the proportion of MDR-TB is higher among previously treated TB cases than among new cases, the large number of new TB cases means that they contributed almost equally to the number of MDR-TB cases diagnosed pre-treatment with Xpert. Failure to identify these cases early has serious consequences. It contributes to ongoing transmission of MDR-TB which is substantially more expensive [24] and difficult to treat successfully [25]. Inappropriate treatment leads to amplification of drug resistance [26,27] and exacerbates costs [24] and poor treatment outcomes [25]. The direct impact on patients of failing to identify MDR-TB pre-treatment should not be under-estimated. Interviews undertaken as part of PROVE IT illustrated the physical and emotional suffering endured by patients when 1st line TB regimens failed, how socio-economic difficulties were compounded and the devastating impact on families, particularly when children were infected [28,29].

Strengths and Limitations

The strength of an operational evaluation is that it reflects the reality of routine practice, including the impact of inconsistent implementation of diagnostic procedures. The evaluation was undertaken in the early phase of Xpert implementation which may have contributed to sub-optimal implementation of this algorithm, as not all presumptive TB cases received an Xpert test as required, resulting in an under-estimation of effect. However, even in the well-entrenched smear/culture-based algorithm, fewer previously treated cases had DST undertaken as required than in the newly introduced Xpert-based algorithm.

A major strength of the study was that we were had retrospective data that enabled us to assess DST undertaken during the course of treatment. This allowed us to assess whether limited initial DST and MDR-TB

diagnosis was compensated by screening and diagnosis during the course of 1st-line TB treatment; we found this not to be the case.

The completeness of routine data, with missing age (<5%), gender (<3%) and treatment category (<9%) variables in both groups is a limitation but is unlikely to have influenced overall findings at these levels. We were unable to analyse the interaction of HIV as this data was not available in the electronic laboratory dataset.

Our case definitions did not take account of discordant Rif-R results. Among the 223 cases with Rif-R on Xpert, 24 did not have confirmatory LPA and 12 had a discordant first LPA result (the majority of these did not have further tests undertaken). This may have resulted in an over-estimation of the proportion of true positive Rif-R cases in the Xpert-based algorithm. An intention to treat approach was adopted with the analysis based on the algorithm in place at the facility and not the tests undertaken. During the transition between algorithms, some contamination occurred with facilities in the smear/culture based algorithm testing patients via Xpert, resulting in a slight over-estimation of pre-treatment DST undertaken (additional 102 cases) and MDR-TB cases diagnosed (additional 3 cases).

Implications for policy and practice

Overall 8.5% of TB cases were detected with MDR-TB in the Xpert-based algorithm compared to 6% in the smear/culture-based algorithm. If one applies these proportions to the approximately 15,000 bacteriologically diagnosed PTB cases in all eight sub-districts in Cape Town annually, it translates to a substantial programmatic effect – an additional 375 MDR-TB cases diagnosed annually.

A recent national DR-TB prevalence survey in South Africa reported high rates of rifampicin resistance - 3.4% among new cases and 7.1% among previously treated cases in 2012-2014 [30], confirming high rates of transmission and a substantial national burden. The use of Xpert MTB/RIF as a screening tool for all presumptive TB cases is important in detecting these cases and reducing transmission, but comes at a high cost. A laboratory costing study undertaken as part of PROVE-IT reported an incremental cost-effectiveness ratio of $6,274 per MDR-TB case identified in the Xpert-based algorithm [31].

In addition to identifying patients with MDR-TB, reduced transmission will also be influenced by the proportion who initiate treatment, treatment delay and treatment success. Routine data from South Africa shows that only 62% of detected MDR-TB cases (11,538/18,734) initiated treatment in 2014 [1]. Whilst studies have reported reductions in delay from MDR-TB diagnosis to treatment [32,33], pre-diagnostic delays are unknown. Two systematic reviews in TB patients reported average (mean or median) time delays from symptom onset to first health care visit of 5–162 days [34] and 7-69 days [35] respectively. These may well be longer for MDR-TB patients. Treatment success rates are dismal: MDR-TB treatment success rates of 39% were reported for cases registered nationally in 2009-2011 [25]. Decentralised treatment models also reported low success rates: 52% in a study in the Western Cape [36] and in Kwa-Zulu Natal, 54% from centralised treatment compared to 58% from decentralised treatment [37]. Health system improvements, appropriate support for patients and improved regimens are required to improve treatment initiation, adherence and outcomes in order to help reduce MDR-TB transmission.

CONCLUSION

Universal drug susceptibility testing (i.e. among all presumptive TB cases) in the Xpert-based algorithm detected a significantly higher proportion of MDR-TB cases than the rationed approach used in the smear/culture-based algorithm. The previous strategy of only screening new TB cases when 1st line treatment failed did not compensate for cases missed pre-treatment. However, universal screening with Xpert is an expensive strategy – in order to justify this expenditure, patient and diagnostic delays must be decreased; health services strengthened and new treatment regimens introduced to improve MDR-TB treatment initiation and outcomes. The cost of Xpert needs to be reduced to ensure sustainability.

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Author contributions:

All authors were involved in the study design. RD extracted and managed the data. RD, PN and CL analysed the data. PN wrote the manuscript. All authors provided input to the manuscript and approved the final draft for submission.

Conflicts of interest:

RD, JC, CL and NB declare that they have no financial or non-financial conflicts of interests. PN undertakes and receives payment for unrelated work from the Bill and Melinda Gates Foundation (BMGF). The BMGF has not been involved in this work in any way or in the publication of this manuscript.

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Chapter 4: Does an Xpert® MTB/RIF-based algorithm increase TB treatment initiation and treatment success rates in a routine operational setting?

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ABSTRACT

Setting: Primary health services in Cape Town, South Africa.

Study Aim: To compare TB treatment initiation and treatment success rates in cases diagnosed in an Xpert MTB/RIF-based algorithm with those diagnosed in a smear/culture-based algorithm.

Methods: This cohort study included 5 of the 8 sub-districts in Cape Town in October – December 2011. We identified all tests undertaken for TB cases diagnosed from electronic laboratory records and matched these to electronic TB register records for all 8 sub-districts for a year prior to and after the study period. We used a binomial regression model, adjusted for facility level clustering, to estimate differences in TB treatment initiation and success between the Xpert and smear/culture groups, the interaction of potential confounders and the association with diagnostic and treatment delay.

Results: Median laboratory delay was reduced from 2 days (IQR 1 to 16) to 1 day (IQR <1 to 4, p<0.001) and treatment delay reduced from 15 days (IQR 4 to >365) to 7 days (IQR 3 to 35, p<0.001) in the Xpert group.

A higher proportion of cases initiated treatment in the Xpert group (84%) than in the smear/culture group (71%, p<0.001). The adjusted odds ratio (AOR) for TB treatment initiation in the Xpert group was 1.98 (95% CI 1.38 to 2.84, p<0.001). Cases >44 years in age were less likely to initiate treatment than cases ≤44 years old (AOR=0.49, p<0.001). Previously treated cases were less likely to initiate treatment than new cases (AOR= 0.64, p=0.020). Laboratory delay was associated with non-initiation: for every day of delay, AOR for treatment initiation was 0.96 (p<0.001).

There was no significant difference in the TB treatment success rate in the Xpert group (AOR=0.95, 95% CI 0.67 to 1.35, p=0.764). Treatment delay was associated with poorer treatment success (AOR=0.99, p<0.001).

Conclusion: Whilst the introduction of the Xpert-based algorithm has reduced treatment delays and increased treatment initiation rates, about 1 in 6 bacteriologically confirmed TB cases did not initiate treatment under this algorithm with implications for ongoing transmission, morbidity and mortality. Urgent efforts are required to address this.

INTRODUCTION

Rapid case-finding of infectious cases and treatment initiation is the cornerstone of tuberculosis (TB) control efforts and is key to reducing transmission. Patients with bacteriologically confirmed TB who fail to commence treatment, contribute to ongoing transmission; these patients are at also at high risk of mortality (1–3). The extent of TB treatment non-initiation at a global level has been poorly quantified. A systematic review of 23 studies reported non-initiation rates ranging between 4 and 38% with weighted values from studies in Africa of 18% (95% CI: 13 to 22) and in Asia of 13% (95% CI: 10 to 15) (4). Studies undertaken within routine operations in South Africa showed that between 15.5% and 34.7% of bacteriologically confirmed TB were not recorded in treatment registers (2,3,5–9). Diagnostic delay has been reported as one of the factors contributing to TB treatment non-initiation (3,8).

Diagnostic delay is partly a consequence of the use of insensitive laboratory tests such as smear microscopy. Conventional light microscopy has an average sensitivity of 53.8% for a single smear, with an increase of 11.1% from a second smear (10). Among HIV-infected cases, sensitivity for a single smear is much lower – ranging from 23% to 50% (11–15). A large proportion of TB case would initially be missed by smear microscopy and the need for return visits and additional culture tests all contribute to delay. The introduction of the more sensitive Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) (Xpert) as the initial screening test for all presumptive TB cases in South Africa has the potential to reduce diagnostic delays and thus increase the proportion of bacteriologically confirmed TB cases initiating treatment. When used as the initial test replacing smear microscopy, Xpert had a pooled sensitivity of 88% (95%CrI: 83% to 92%) and specificity of 98% (95% CrI: 97% to 99%) for detecting *Mycobacterium tuberculosis* (16), substantially above that of smear. However sensitivity is considerably lower among smear-negative, culture-positive cases at 68% (95% CrI 59% to 75%) (16).

The aim of this study was to compare TB treatment initiation and treatment success rates for bacteriologically confirmed cases diagnosed in Xpert MTB/RIF-based and smear/culture-based algorithms, within a routine operational setting. The effects of laboratory and treatment delay on treatment initiation and treatment success were assessed. This study was part of the PROVE IT (**P**olicy **R**elevant **O**utcomes from **V**alidating **E**vidence on **I**mpac**T**) initiative which assessed the impact of new molecular diagnostics on the diagnosis and treatment of TB.

METHODS

Setting

The study was undertaken in a high TB burden setting in Cape Town, South Africa, where 28,644 cases were notified in 2011 (752/100,000 population). Among the 97% of TB cases tested, 47% were HIV co-infected (Source: Routine TB Programme Data, Cape Town Health Directorate, April 2016). Free TB diagnostic services were provided at 142 primary health care (PHC) facilities.

Historically, a smear/culture-based TB diagnostic algorithm was used: all presumptive TB cases were evaluated through two spot sputum specimens, taken 1-hour apart. Both specimens were examined by

fluorescence microscopy. In *previously treated TB cases*, the second specimen underwent liquid culture (BACTEC™ MGIT™ 960). New cases that were *HIV-infected and smear-negative* submitted a third specimen for culture. An Xpert-based algorithm was introduced in August 2011, with Xpert replacing smear microscopy for *all presumptive TB cases*. The first of two sputum specimens submitted was tested with Xpert; if MTB was detected the second underwent smear microscopy. In HIV-infected cases with negative Xpert tests, the second specimen underwent culture. A daily courier delivered specimens to a central laboratory where tests were done and results recorded in a networked, electronic laboratory database. Positive results were faxed to facilities on a daily basis and printed copies of all results returned by courier.

Free TB treatment was provided at 101 PHC facilities. Nurses completed standardised clinical records for patients initiating treatment and recorded summary demographic, clinical and outcome data into paper-based TB registers. Completed, self-carbonated copies of TB register pages were sent to sub-district level and entered into the electronic TB register (ETR). Dispatches from sub-district level were collated at district level before submission to the Provincial and National Departments of Health.

Definitions

A presumptive TB case was defined as an individual with pre-treatment sputum samples submitted for diagnostic purposes. *A TB case* was defined as an individual with one or more smears positive and / or culture positive for MTB and / or MTB detected on Xpert. These were categorised as *new* (an individual with no or less than four weeks of previous TB treatment) or *previously treated* (an individual with more than four weeks of previous TB treatment).

Bacteriologically confirmed TB cases that were not registered in the electronic TB register within a 1-year period post diagnosis were defined as treatment *non-initiators*.

TB treatment outcome was classified as *treatment cure* for a case whose pre-treatment smear (or culture) was positive and whose smear (or culture) was negative in the last month of treatment and on at least one previous occasion at least 30 days prior. The outcome was classified as *treatment completion* for a case whose pre-treatment smear (or culture) was positive, and who completed treatment but who did not have a negative smear (or culture) in the last month of treatment and on at least one previous occasion more than 30 days prior. This definition was only applicable if 150 calendar days of treatment were completed for new cases and 210 days for re-treatment cases (17)(18).

Study design, population, sample size and timeframe

This cohort study included all primary health facilities in 5 of the 8 health sub-districts in Cape Town: three sub-districts used the smear/culture-based algorithm and two used the Xpert-based algorithm in October – December 2011. Patients diagnosed in these algorithms are referred to as the smear/culture and Xpert groups respectively. The three sub-districts in the process of introducing the Xpert-based algorithm in this period were excluded.

Estimation of the sample size required to show a 40% reduction in TB treatment non-initiation was based on a two-sided significance level of 95%, a power of 80% and the assumption (from routine data) that 15% in the smear/culture group would be non-initiators. This required a study sample size of 982 (491 in each group).

The study population included all presumptive pulmonary TB cases in the 5 sub-districts tested in November 2011 and with a laboratory diagnosis of TB from the current diagnostic episode (which included all tests undertaken for these individuals in October – December 2011). The number of cases diagnosed in this period ensured an adequate sample size for the study.

Data Sources and Management

The National Health Laboratory Services provided TB test data from the electronic laboratory database for 2011. Data included clinic identification, patient clinical folder number, patient demographics, patient category (new or previously treated), test type (smear, culture or Xpert), diagnostic point (pre-treatment or on treatment), test date and result.

Laboratory data were imported into Microsoft SQL. We used a combination of patient name, surname, birth date, address and clinical folder number to identify all tests undertaken for presumptive TB cases in this diagnostic episode. We identified cases diagnosed with TB, those with rifampicin resistance and duplicates (i.e. an individual diagnosed at multiple facilities). The date on which the first test was undertaken in this diagnostic episode and the date that a first positive result was available in the laboratory were used in our analyses.

ETR data received from the City of Cape Town Health Directorate were imported into Microsoft SQL. We used a combination of patient name, surname, birth date and address to match laboratory confirmed TB cases from the 5 sub-districts to ETR records from across all 8 sub-districts in Cape Town for the period October 2010 to December 2012. All matches were manually confirmed. Cases not electronically identified were manually searched for in ETR using name and surname and confirmed using date of birth and address. We recorded treatment initiation date and treatment outcomes for cases recorded as initiating treatment in ETR.

Data Analysis

Basic descriptive data for cases in the Xpert and smear/culture groups were compared using proportions and frequencies. Normally distributed continuous outcomes were analysed using the t-test and categorical outcomes using the chi-squared test. We plotted Kaplan Meier time-to-event graphs for laboratory delay (time from the first test taken in this diagnostic episode to the first positive result available in the laboratory) and for treatment delay (time from the first test taken in this diagnostic episode to treatment initiation). We compared the time-to-event curves using the log-rank test to assess for overall differences and reported median time to event and interquartile ranges.

We used a binomial regression model, adjusted for clustering in 60 sites, to estimate differences in TB treatment initiation and treatment success between the Xpert and smear/culture groups. We assessed the interaction of age, gender, patient category (new or previously treated) and delay in the model. Delay was expressed as a continuous variable. We expressed age as a categorical variable based on summary data showing higher rates of non-initiation in the >44 year age group. Analyses were undertaken using STATA 13 (StataCorp).

Ethics Statement

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. A waiver of informed consent was granted for the use of routine data. The City Health Directorate, Western Cape Health Department and National Health Laboratory Service granted permission to use routine health data.

RESULTS

TB cases included in the analyses

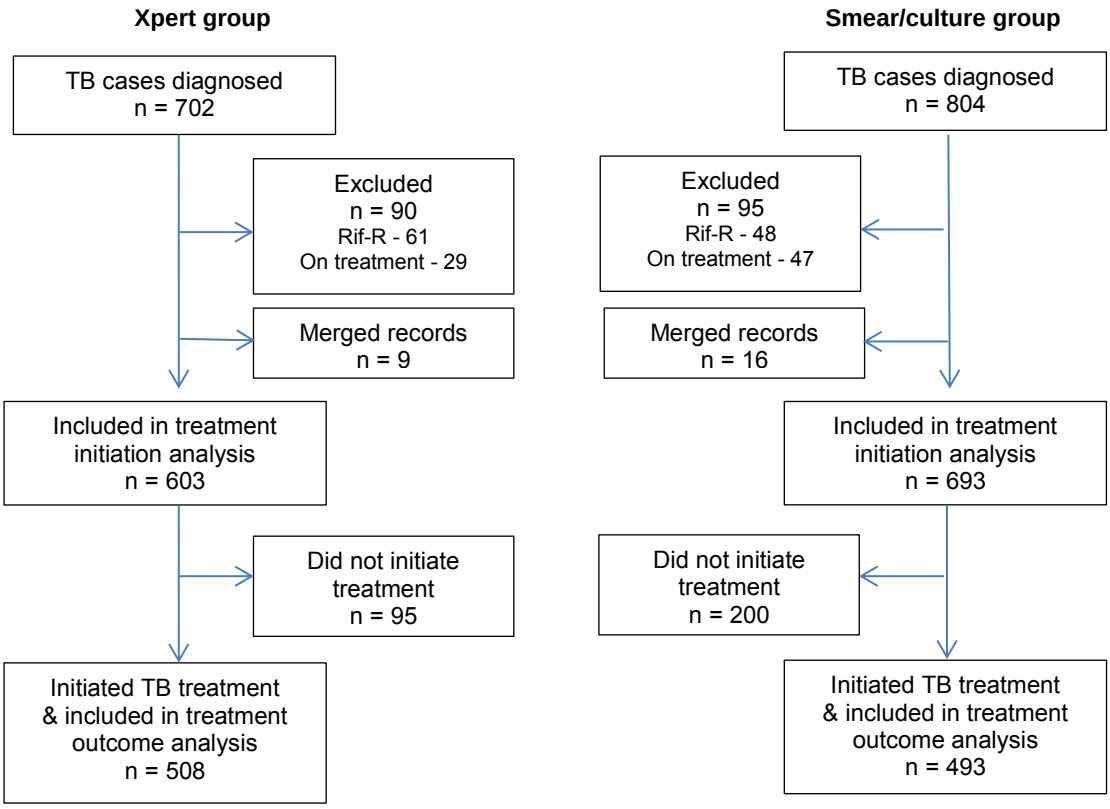


Figure 1: TB cases in the Xpert and smear/culture groups included in the analyses. This figure shows cases diagnosed in each algorithm, those included in the treatment initiation analysis and those that initiated TB treatment. Only cases initiating treatment were included in the analysis of TB treatment outcomes. Abbreviations: n=number of cases; TB=tuberculosis; Rif-R=rifampicin resistance

There were 702 laboratory diagnosed cases in the Xpert group and 804 in the smear/culture group (Fig 1). Amongst these, we excluded 61 and 48 cases from the respective groups with rifampicin resistance (as these cases would be registered in a separate electronic DR-TB register) and 29 and 47 cases respectively that were initiated on TB treatment prior to October 2011 (as we were unable to determine whether these cases were being re-evaluated after interrupting treatment or whether they were incorrectly recorded as pre-treatment tests). We merged 9 and 16 records in respective groups belonging to individuals diagnosed at multiple sites and used their earliest test data. The remaining 603 in the Xpert group and 693 on the

smear/culture group were included in the analysis of treatment initiation. We included only the 508 cases in the Xpert group and the 493 cases in the smear/culture group that initiated treatment in the analysis of TB treatment success.

Comparison of TB cases included in the treatment initiation analysis

There were no significant differences in mean age (p=0.644) between TB cases in the Xpert and smear/culture groups (Table 1). However the Xpert group had a smaller proportion of cases >44 years of age (18% compared to 23%, p=0.017). There were no significant differences in gender (p=0.282) or patient category (0.306) between TB cases in the Xpert and smear/culture groups.

Table 1: Comparison of laboratory confirmed TB cases in the Xpert and smear/culture groups

		Xpert	Smear/culture	p-value
TB cases analysed	Total number	603	693	-
Age	Mean (Years) *[SD]*	35 *[11]*	35 *[13]*	0.644
	Number in age bracket ≤44 years (%)	475 (79)	507 (73)	0.017
	Number in age bracket >44 years (%)	106 (18)	158 (23)	
Gender	Number male (%)	320 (53)	394 (57)	0.282
	Number female (%)	267 (44)	291 (42)	
Patient category	Number new cases (%)	407 (68)	497 (72)	0.306
	Number previously treated cases (%)	166 (28)	178 (26)	

Missing data are not shown but can be calculated based on the numbers provided. Missing data have not been included in determining the p-value from chi-square and T-tests.

Laboratory and Treatment Delay

Median delay from the first test taken to the first positive result available in the laboratory was 1 day (IQR <1 to 4) in the Xpert group compared to 2 days (IQR 1 to 16) in the smear/culture-based group (p<0.001) (Fig 2).

A significantly lower proportion of cases had initial negative or invalid tests in the Xpert group (21%) than in the smear/culture group (36%)(p<0.001). There was no significant difference in the proportion that initiated TB treatment before a result was available (18% in the Xpert group compared to 22% in the smear/culture group, p=0.114).

Fig 2: Laboratory delay

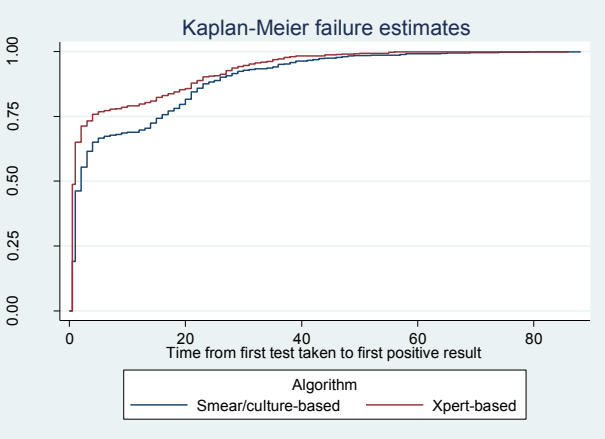
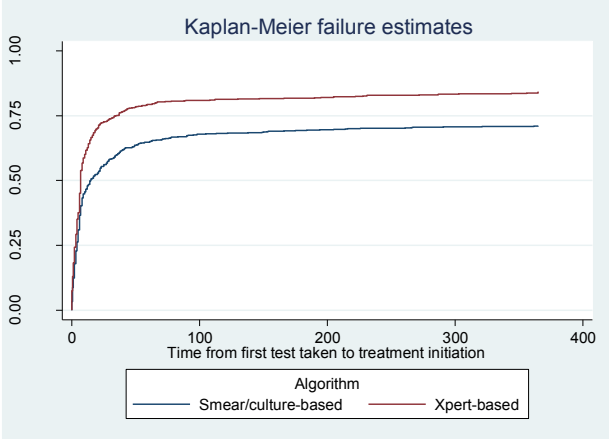


Fig 3: Treatment delay



Median delay from the first test taken to treatment initiation was 7 days (IQR 3 to 35) in the Xpert group compared to 15 days (IQR 4 to >365) in the smear/culture group (p<0.001) (Fig 3).

TB Treatment initiation

A higher proportion of cases initiated TB treatment in the Xpert group (84%) than in the smear/culture group (71%)(p<0.001)(Table 2). This difference was accentuated amongst cases >44 years of age with 81% initiating treatment in the Xpert group compared to 59% in the smear/culture group (p<0.001) and in cases previously treated for TB with 83% initiating treatment in the Xpert group compared to 60% in the smear/culture group (p<0.001).

Table 2: Univariate analysis of factors influencing TB treatment initiation

Treatment initiation		Xpert-based algorithm Number (%)		Smear/culture-based algorithm Number (%)		Algorithm comparison
Variable	Category	Initiation	Non-initiation	Initiation	Non-initiation	p-value
TB cases	Total number	508 (84)	95 (16)	493 (71)	200 (29)	<0.001
Age	≤44	407 (86)	68 (14)	383 (76)	124 (24)	<0.001
	>44	86 (81)	20 (19)	93 (59)	65 (41)	<0.001
Gender	Male	275 (86)	45 (14)	289 (73)	105 (27)	<0.001
	Female	219 (82)	48 (18)	202 (69)	89 (31)	0.001
Patient category	New cases	351 (86)	56 (14)	380 (76)	117 (24)	<0.001
	Previously treated cases	137 (83)	29 (17)	106 (60)	72 (40)	<0.001

Missing data are not shown but can be calculated based on the values shown.

After adjusting for potential confounders in the binomial regression model, the odds ratio for treatment initiation was 1.98 in the Xpert group (95% CI 1.38 to 2.84, p<0.001) (Table 3). Gender had no significant effect in the model, with an AOR of 0.84 (95% CI 0.65 to 1.09, p=0.192) for males compared to females. Cases >44 years in age were less likely to initiate treatment than cases aged ≤44 years (AOR 0.49, 95% CI 0.34 to 0.70, p<0.001). Previously treated cases were less likely to initiate treatment than new cases (AOR 0.64, 95% CI 0.44 to 0.93, p=0.020). Laboratory delay (time from the first diagnostic test taken to a positive result in the laboratory) was associated with non-initiation (AOR 0.96 for every day of delay, 95% CI 0.95 to 0.97, p<0.001).

Table 3: Binomial regression analysis for co-variables influencing TB treatment initiation

Variable	Adjusted odds ratio	95% CI	Standard error	p-value
Xpert	1.98	1.38 to 2.84	0.36	<0.001
Gender – male	0.84	0.65 to 1.09	0.11	0.192
Age >44 years old	0.49	0.34 to 0.70	0.09	<0.001
Patient category - previously treated cases	0.64	0.44 to 0.93	0.12	0.020
Laboratory delay	0.96	0.95 to 0.97	0.01	<0.001
Constant	5.97	4.55 to 7.83	0.83	<0.001

TB treatment outcomes

Treatment success rates were similar in the Xpert and smear/culture groups (80% in both, p=0.753) (Table 4). In the Xpert group 45% had a documented cure compared to 55% in the smear/culture group. Unsuccessful treatment outcomes were similar: 3% and 2% in respective groups died; 11% and 10% respectively were lost to follow-up; 0% and 2% respectively failed 1st line treatment and 6% in both groups did not have their treatment outcome evaluated (including cases that had moved or transferred out and whose outcomes were unknown).

In the univariate analysis, there was no significant difference in successful treatment outcome by age, gender or patient category between the groups (Table 4).

Table 4: Univariate analysis of factors influencing TB treatment success

Treatment initiation		Xpert-based algorithm Number (%)		Smear/culture-based algorithm Number (%)		Algorithm comparison
Variable	Category	Treatment successful	Treatment unsuccessful	Treatment successful	Treatment unsuccessful	p-value
TB cases	Total number	404 (80)	104 (20)	396 (80)	97 (20)	0.753
Age	≤44	320 (79)	87 (21)	304 (79)	79 (21)	0.796
	>44	76 (88)	10 (12)	78 (84)	15 (16)	0.385
Gender	Male	214 (78)	61 (22)	239 (83)	50 (17)	0.145
	Female	179 (82)	40 (18)	155 (77)	47 (23)	0.205
Patient category	New cases	284 (81)	67 (19)	307 (81)	73 (19)	0.967
	Previously treated cases	102 (74)	35 (26)	84 (79)	22 (21)	0.382

Missing data are not shown but can be calculated based on the values shown. The definitions used for TB treatment outcomes are as per the standard South African Department of Health definitions (17)(18). These are in line with World Health Organisation definitions (19).

After adjusting for potential confounders in the binomial regression model, there was no significant difference in treatment success in the Xpert group (AOR 0.95, 95% CI 0.67 to 1.35, p=0.764) in the Xpert. Gender (AOR

0.94, p=0.674), age (AOR 1.55, p=0.090) and patient category (AOR 0.73, p=0.090) were not significant factors in the model. Treatment delay was associated with poorer treatment success (AOR 0.99 for every 1 day delay in treatment initiation, p<0.001).

Table 5: Binomial regression analysis for co-variables influencing TB treatment success

Variable	Adjusted odds ratio	95% CI	Standard error	p-value
Xpert	0.95	0.67 to 1.35	0.17	0.764
Gender – male	0.94	0.70 to 1.26	0.14	0.674
Age >44 years old	1.55	0.93 to 2.58	0.40	0.090
Patient category - previously treated cases	0.73	0.51 to 1.05	0.14	0.090
Laboratory delay	0.99	0.99 to 1.00	<0.01	<0.001
Constant	4.99	3.70 to 6.72	0.76	<0.001

DISCUSSION

Since Xpert has a higher sensitivity than smear (10)(16), it was expected that this would reduce the need for additional culture tests and thus reduce laboratory and treatment delay. Although we found a small reduction in median laboratory delay in the Xpert-based algorithm (from 2 days to 1), results were available for 75% of cases within 4 days with Xpert compared to within 16 days with smear/culture. As was to be expected, a lower proportion of cases had initial negative tests in the Xpert-based algorithm (21% compared to 36%).

As with other studies (3,8) we found that diagnostic delay was associated with TB treatment non-initiation (AOR 0.96 for every one day of delay). A higher proportion of cases initiated treatment in the Xpert group (84%) than in the smear/culture group (71%); after accounting for potential confounders, the odds ratio for initiating treatment with Xpert was almost doubled. Our results are in a similar range to results from a pragmatic randomised controlled trial assessing the implementation of Xpert in Cape Town that reported a reduction in non-initiation rates from 25% with smear/culture to 13% with Xpert at 3 months (risk ratio 0.51, p=0.005) (20). However our results differ from the XTEND study that reported similar non-initiation rates in both arms - 17% with Xpert compared to 14.9% with smear (risk ratio 0·97, p=0·93) at 4 weeks (21). These findings are likely to have been influenced by the limited use of culture tests for cases with negative Xpert or smear tests in the XTEND study (22).

Whilst the proportion with non-initiation was substantially reduced with Xpert, it still presents a significant challenge to TB control efforts with about 1 in every 6 cases laboratory confirmed cases not initiating treatment within a one year period post-diagnosis. Apart from diagnostic delay, several other factors have been found to contribute to treatment non-initiation, including: inefficient diagnostic processes with multiple visits, failure to do tests, results not being available; long queues and poor referral mechanisms between the public and private sector and within the public sector (3)(5); the inability to contact patients due to poor recording of address or the provision of incorrect addresses (3)(9)(23); insufficient resources available for community–based follow-up (2); delays in contacting patients (24); early mortality (3)(2); low knowledge about TB and the importance of returning for treatment (3); and poor patient health (for example as a result of high

TB bacillary load, HIV co-infection, low CD4 and psychological distress)(9)(15). Interventions to improve health system efficiencies and to improve TB knowledge and health-seeking behaviour are urgently required to address the persistent high levels of TB treatment non-initiation. The introduction of the Xpert-based algorithm on its own will not suffice.

Median treatment delay from the first test taken to TB treatment initiation was reduced from 15 to 7 days in the Xpert group. The Cape Town study referenced above reported a reduction in median treatment delay from 9 days with smear to 4 days with Xpert in the per protocol analysis (20). The shorter delays found in this study compared to ours may partially reflect the effect of their decentralised use of smear and Xpert. Our data on laboratory delay reflects when the test result was available in the laboratory and not necessarily when it was available to clinicians. Whilst the electronic laboratory results system makes it theoretically feasible for clinician's to have real-time access to results from the central laboratory, this is limited by the low availability of computers at health facilities. Both the inefficient processing of printed laboratory results and delays in referral from health facilities offering only diagnostic services to treatment sites are likely to have contributed to the longer delays in our study.

For those initiating treatment, success rates were 80% in both the Xpert and smear/culture groups. After adjusting for potential confounders, there was no significant difference in the odds of treatment success. It is important to point out however that the treatment outcomes have been calculated only for the cohort recorded as having initiated TB treatment. Harries et al coined the term "sloppy DOTS" to highlight the limitation of failing to record non-initiators in TB treatment cohorts (25) and how this inflates treatment success rates. If the treatment cohort was defined as all cases with a bacteriological diagnosis of TB in our study, and the assumption made that all those that did not initiate treatment had unsuccessful outcomes, then treatment success rates would be 67% in the Xpert group compared to 57% in the smear/culture group. Whilst these percentages could be moderated upwards as a proportion of the untreated cases may have self-cured (estimated at an annual rate of 10%) (26), these figures provide a sobering view of TB control efforts.

Strengths and Limitations

One of the strengths of this study is that we assessed TB laboratory testing over an entire diagnostic episode (defined as a three month period). This allowed us to include test data for cases with initial negative or invalid tests (21% in the Xpert and 36% in the smear/culture group) in our assessment of delay. The study reflects the reality of a test being used in operational conditions including the failure to follow diagnostic algorithms and the collection of poor quality specimens; both may have contributed to the high proportion of cases with initial negative results.

This study only reports on bacteriologically confirmed TB cases and does not include data on patients evaluated clinically and commenced on treatment on empirical grounds. We could not assess HIV status as a confounder as this data was not reflected in laboratory records. The study relied on routinely collected information. We may have over-estimated non-initiation rates as some TB cases on treatment may not have been registered in ETR as has been found in other studies (7)(27). The extent to which results can be generalised is limited by the urban setting and good health and laboratory infrastructure. Additional evidence is required from less well-resourced and rural settings.

The data is based on laboratory records and not patient interviews and therefore does not reflect delays that may have occurred prior to this, for example as a result of clinicians failing to test presumptive TB cases presenting to health facilities, as has been reported in several studies (28)(29)(30). Patient-related delays have also not been quantified. A systematic review on TB diagnostic delays reported average (mean or median) overall delay of 25-185 days, with patient delay from symptom onset to first healthcare visit of 5–162 days (average 29) and health system delay from first health care visit to diagnosis of 2–87 days (average 25)(31). A second review reported average (mean or median) overall delay of 21-136 days with patient delays ranging from 7-69 days and health system delays from 2-120 days (32); neither of these studies reported on treatment initiation.

CONCLUSION

TB treatment non-initiation has been a blind-spot in TB control efforts in South Africa. Despite many local studies reporting high rates of non-initiation it remains largely unrecognised and difficult to address due to the disjunction between clinical and laboratory systems. Whilst the introduction of the Xpert-based algorithm has reduced diagnostic delays and increased treatment initiation rates, about 1 in 6 bacteriologically confirmed TB cases did not initiate treatment under this algorithm with implications for ongoing transmission, morbidity and mortality. Urgent efforts are required to link laboratory and clinical systems to improve the monitoring of non-initiation. However, until the rate of non-initiation is included as an indicator in TB control programmes and used in performance management, the current situation is unlikely to change.

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Author contributions:

All authors were involved in the study design. RD extracted and managed the data. , RD and PN matched the data. PN, RD and CL developed the data analysis plan and undertook the analysis. PN wrote the manuscript. All authors provided input to the manuscript and approved the final draft for submission

Conflicts of interest:

RD, JC, CL and NB declare that they have no financial or non-financial conflicts of interests. PN undertakes and receives payment for unrelated work from the Bill and Melinda Gates Foundation (BMGF). The BMGF has not been involved in this work in any way or in the publication of this manuscript.

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Chapter 5: A comparison of multidrug-resistant tuberculosis treatment commencement times in MDRTBPlus Line Probe Assay and Xpert® MTB/RIF-based algorithms in a routine operational setting in Cape Town.

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ABSTRACT

Background: Xpert MTB/RIF was introduced as a screening test for all presumptive tuberculosis cases in primary health services in Cape Town, South Africa.

Study Aim: To compare multidrug-resistant tuberculosis (MDR-TB) treatment commencement times in MDRTB*plus* Line Probe Assay and Xpert MTB/RIF-based algorithms in a routine operational setting.

Methods: The study was undertaken in 10 of 29 high tuberculosis burden primary health facilities, selected through stratified random sampling. An observational study was undertaken as facilities transitioned to the Xpert MTB/RIF-based algorithm. MDR-TB diagnostic data were collected from electronic laboratory records and treatment data from clinical records and registers. Kaplan Meier time-to-event analysis was used to compare treatment commencement time, laboratory turnaround time and action delay between algorithms. A facility-level paired analysis was done: the median time-to-event was estimated per facility in each algorithm and mean differences between algorithms compared using a paired t-test. Cox proportional hazards regression was used to assess the effect of patient-level variables on treatment commencement time. The difference between algorithms was compared using the hazard ratio.

Results: The median treatment commencement time in the Xpert MTB/RIF-based algorithm was 17 days (95% CI 13 to 22 days), with a median laboratory turnaround time (to result available in the laboratory) of <1 day (95% CI <1 to 1 day). There was a decrease of 25 days (95% CI 17 to 32 days, p<0.001) in median MDR-TB treatment commencement time in the Xpert MTB/RIF-based algorithm. We found no significant effect on treatment commencement times for the patient-level variables assessed.

Conclusion: MDR-TB treatment commencement time was significantly reduced in the Xpert MTB/RIF-based algorithm. Changes in the health system may have contributed. However, an unacceptable level of delay remains. Health system and patient factors contributing to delay need to be evaluated and addressed to optimise test benefits.

INTRODUCTION

Improving multidrug-resistant tuberculosis (MDR-TB) control requires access to accurate and rapid diagnostics for drug susceptibility testing [1–3]. A rapid diagnosis has both patient and public health benefits: it enables early, appropriate treatment which can reduce morbidity and mortality for patients as well as transmission within communities. This is of particular importance in South Africa which has a high TB and MDR-TB burden with 349,582 and 15,419 cases respectively reported in 2012 [4]. South Africa's early adoption of new molecular diagnostic tests is one of the responses to the TB crisis: Hain-MDRTB*plus* line probe assay (LPA) was introduced following the WHO Policy statement in 2008 [5] and Xpert MTB/RIF (Xpert) following the 2011 policy statement [6].

The efficacy of both tests has been well established [7–12] and confirmed by systematic reviews [13–15]. Policy recommendations for both diagnostics have been based largely on accuracy data from laboratory and demonstration studies. This has limitations, as test performance under operational conditions and evidence linking accuracy to patient important outcomes are not considered, making it difficult to translate "scientific progress into public health impact" [16].

Few studies have reported on the effect of molecular diagnostics on MDR-TB treatment delay [17–19]. Studies from South Africa that compared conventional drug susceptibility tests (DST) to LPA showed a reduction in median treatment commencement time from 72 days with conventional DST to 24 days with LPA in a demonstration study [17] and from 80 to 55 days in a rural TB hospital [18]. Although studies have reported a reduction in treatment delay with Xpert for drug-susceptible cases [12,20], we are not aware of any publications that address its effect on MDR-TB treatment delay.

This study is part of a broader PROVE IT (**P**olicy **R**elevant **O**utcomes from **V**alidating **E**vidence on **I**mpac**T**) (http://treattb.org) evaluation undertaken in Cape Town, South Africa, to assess the impact of new molecular diagnostics on the diagnosis and treatment of tuberculosis. Guided by the Impact Assessment Framework [21], the magnitude and range of benefits for patients (from clinical presentation to treatment initiation), the magnitude and nature of inputs required and factors that influence policy change were evaluated.

Study Aim

We compared MDR-TB treatment commencement times (TCT) in LPA and Xpert-based algorithms in a routine operational setting. Treatment non-initiation rates and the association between MDR-TB TCT and patient level variables such as age, sex, HIV-status, MDR-risk profile, MDR-TB diagnostic time-point and treatment initiation site were also assessed.

METHODS

This observational cohort study compared cases in a LPA-based algorithm to those in an Xpert-based algorithm, as facilities transitioned to the latter in 2011-2012.

Setting

The study was undertaken in Cape Town, South Africa. The City had a high TB burden with 28,658 TB cases and 953 MDR-TB cases recorded in 2011 and a TB case notification rate of 752/100,000 population (Source: J. Caldwell, Routine TB Programme Data, Cape Town Health Directorate). Free TB diagnostic services were provided at 142 primary health care (PHC) facilities and treatment at 101 of these. A daily courier delivered all specimens to a central laboratory where tests were done and results recorded in an electronic laboratory database. Positive TB results were faxed to facilities on a daily basis and hard copies of all results returned by courier.

Patients diagnosed with MDR-TB received standardised treatment regimens. Historically, patients initiated MDR-TB treatment at a central TB-hospital. From 2005, doctors at the TB hospital reviewed case records and prescribed treatment but patients could initiate treatment at PHC facilities. In 2012, doctors at the PHC facilities offering TB treatment initiated standardised MDR-TB treatment without the need for prior review of the case at the TB-hospital.

TB Algorithms

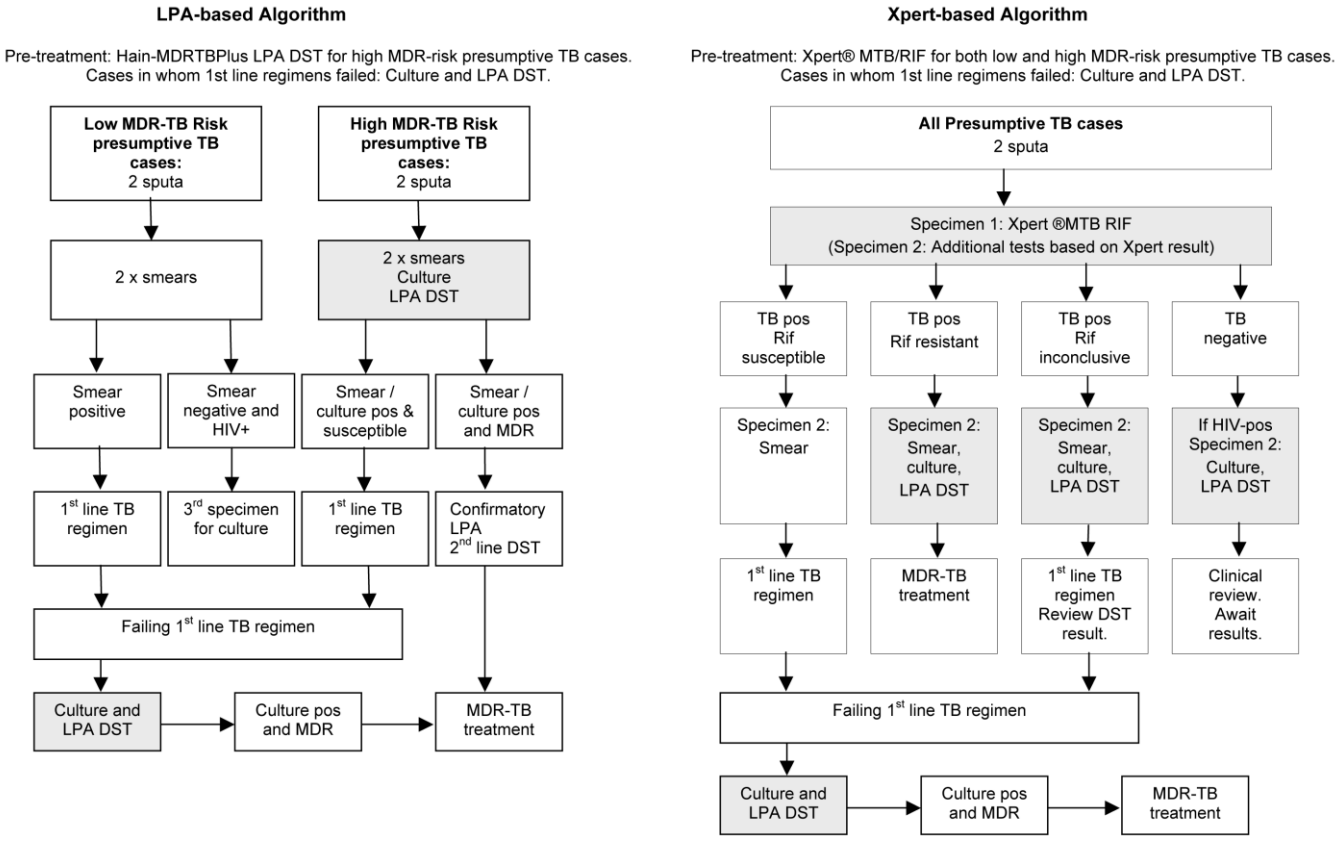

Figure 1: TB Testing in the LPA and Xpert-based Algorithms. The sequence of diagnostic tests in each algorithm and the action taken based on test results is shown. Shaded blocks indicate possible MDR-TB diagnostic points. Abbreviations: MDR-TB - multidrug-resistant tuberculosis; LPA - line probe assay; DST - drug susceptibility testing; HIV – human immunodeficiency virus; Rif – rifampicin; Pos – positive.

From 2011 to 2013 Xpert was sequentially introduced into the eight health sub-districts in Cape Town, replacing smear microscopy for *all* presumptive TB cases and referred to in this study as the Xpert-based algorithm (Figure 1).

In both algorithms, cases in whom 1st line regimens failed (i.e. those with positive smears during the course of treatment and or clinical deterioration) were evaluated for MDR-TB though culture and LPA (Figure 1).

Study Population

This study was undertaken in a routine operational setting in 10 high TB-burden government PHC facilities, selected from a total of 29 that met the criteria of a TB caseload of >350 in 2009. Two facilities were excluded due to competing research studies. The remaining facilities were ordered according to their smear-positive treatment success rates in 2009 and five were randomly selected from each group above and below the median.

All individuals with sputum samples taken at these facilities between January 2008 and December 2012 and with a laboratory diagnosis of pulmonary MDR-TB were included in the study (Figure 2). Cases diagnosed at other public health facilities in Cape Town that had received treatment at the selected facilities were also included. Cases with previous MDR-TB treatment or without results from the national health laboratory were excluded. Only cases from the 9 facilities that transitioned to the Xpert-based algorithm in the study period were included in the analysis.

Data Sources, Collection and Management

Patients diagnosed with MDR-TB in selected facilities were identified from the electronic laboratory database using the facility name and location code; those diagnosed elsewhere, but on treatment at the selected facilities, were identified through facility DR-TB paper registers and patient clinical records. Professional nurses undertook clinical record reviews of all cases that met the inclusion criteria and recorded demographic, laboratory and clinical data on case report forms. Data were quality checked, dual entered into a Microsoft SQL database and corrected. Where clinical records could not be found, treatment data were extracted from electronic in-patient records at the TB hospital and from sub-district electronic DR-TB registers. Data from these sources were linked to electronic laboratory data, which provided information on the specimen tested, test dates, type of test and results.

Study data will be made available to other researchers on request, with permission from the relevant authorities.

Definitions

In both algorithms, a specimen with rifampicin and isoniazid resistance was defined as MDR-TB; in the Xpert-based algorithm, rifampicin-resistance on Xpert was considered a proxy indicator of MDR-TB.

The primary outcome measure of *MDR-TB TCT* was calculated from first MDR-TB diagnostic sputum collection date to MDR-TB treatment commencement date and comprised two intermediary times:

1. *Laboratory turnaround time* was calculated from date of sputum collection to date result was available in the laboratory.
2. *'Action' delay* was calculated from date result was available in the laboratory to treatment commencement date.

Non-initiation of MDR-TB treatment was defined as no record of treatment initiation in facility records, the electronic DR-TB register or the in-patient hospital database within 6 months of the MDR-TB test sputum being collected.

The *MDR-TB diagnostic time-point* was defined as either *pre-treatment,* for a presumptive TB case being concurrently evaluated for TB and drug resistance, or as *treatment,* for a case on a 1st-line TB regimen being evaluated for drug resistance.

Low MDR-TB risk was defined as ≤four weeks previous TB treatment and *high MDR-TB risk* as >four weeks previous TB treatment, from congregate settings or with a known MDR-TB contact, based on clinical records.

Statistical Analysis

Demographic characteristics were analyzed using the t-test for normally distributed continuous outcomes and chi-square for categorical outcomes. Kaplan Meier time-to-event analysis was used to compare treatment commencement time, laboratory turnaround time and action delay between algorithms. Kaplan Meier survival distribution was used to estimate median time-to-event, defined as the length of time corresponding to the probability of 0.5 [22]. A facility-level paired analysis was used to generate summary statistics: the median time-to-event was estimated per facility and mean differences between diagnostic algorithms compared using a paired t-test.

Cox proportional hazards regression using the Breslow method for ties with a facility-level stratification was used to assess the effect of patient-level variables such as age, gender, HIV-status, MDR-TB risk profile and treatment initiation site on MDR-TB TCT. We adjusted for these variables and used the hazard ratio to compare the overall difference in MDR-TB TCT between diagnostic algorithms. Analyses were undertaken using STATA 12 (StataCorp).

Ethics Statement

The City Health Directorate, Western Cape Health Department and National Health Laboratory Service granted permission to use the routine health data. 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. A waiver of informed consent was granted for the use of routine data.

RESULTS

Of the 642 MDR-TB cases identified, 541 met the criteria for inclusion in the analysis (Figure 2). Amongst the 414 cases in the LPA-based and 127 in the Xpert-based algorithm, there were no significant differences in

sex, age, HIV-status or MDR-TB risk profile (Table 1). In the LPA-based algorithm, 68% were diagnosed at the pre-treatment MDR-TB diagnostic time-point compared to 83% in the Xpert-based algorithm (p=0.002).

Non-initiation rates did not differ between the LPA (9%) and Xpert-based algorithm (6%) (risk ratio 1.7, p=0.167). Comparative data for those who did and did not initiate treatment found that only HIV contributed significantly to non-initiation in the LPA-based algorithm (85% HIV-positive in the non-initiation group compared to 57% for those on treatment, p=0.014).

Amongst cases on MDR-TB treatment (Table 1), there were no significant differences in sex, age, HIV-status or MDR-TB risk profile between the algorithms. More patients initiated treatment at PHC-level in the Xpert (98%) than in the LPA-based algorithm (88%)(p<0.001).

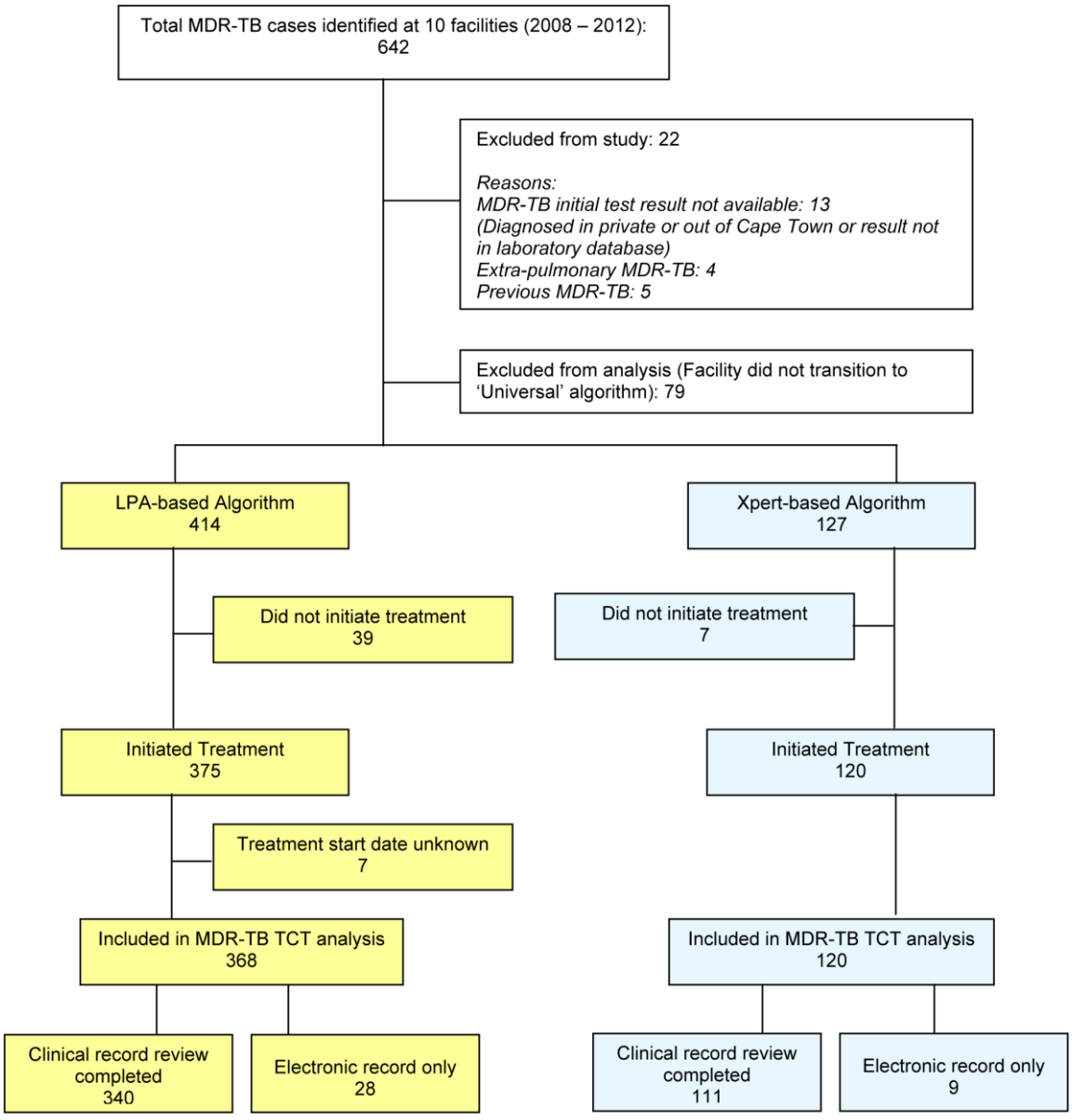

Figure 2: Study Population. MDR-TB cases identified from selected facilities and those included and excluded from the study and from the final analysis are shown. Abbreviations: MDR-TB – multidrug-resistant tuberculosis; DST- drug susceptibility test; TCT - treatment commencement time.

Table 1: Comparison of Baseline Characteristics of MDR-TB Cases by Algorithm

		Total Cohort			Did Not Initiate Treatment			Initiated Treatment		
		LPA-based Algorithm	Xpert-based Algorithm	*p-value*	LPA-based Algorithm	Xpert-based Algorithm	*p-value*	LPA-based Algorithm	Xpert-based Algorithm	*p-value*
Total cases		414	127		39 (9%)	7 (6%)	*0.167*	375 (91%)	120 (94%)	
Sex	Female n (%)	184 (44%)	53 (42%)	*0.590*	15 (38%)	5 (71%)	*0.213*	169 (45%)	48 (40%)	*0.330*
	Male n (%)	230 (56%)	74 (58%)		24 (62%)	2 (29%)		206 (55%)	72 (60%)	
Age	Mean (Years)	35	35	*0.483*	35	35	*0.504*	35	35	*0.478*
	SD (Years)	11	11		12	9		11	11	
	Range (Years)	8 – 81	12 – 68		19-81	25-53		8 - 71	12 - 68	
HIV-status	HIV-positive n (%)	216 (59%)	71 (60%)	*0.828*	17 (85%)	3 (75%)	*0.624*	199 (57%)	68 (59%)	*0.691*
	HIV-negative n (%)	153 (41%)	48 (40%)		3 (15%)	1 (25%)		150 (43%)	47 (41%)	
MDR-TB risk profile	Low-risk n (%)	155 (38%)	59 (46%)	*0.077*	16 (44%)	3 (43%)	*1.000*	138 (37%)	56 (47%)	*0.059*
	High-risk n (%)	255 (62%)	68 (54%)		20 (56%)	4 (57%)		235 (63%)	64 (53%)	
MDR-TB diagnostic time-point	Pre-treatment n (%)	253 (68%)	101 (83%)	*0.002*	19 (79%)	5 (71%)	*0.667*	234 (67%)	96 (83%)	*0.001*
	Treatment n (%)	118 (32%)	21 (17%)		5 (21%)	2 (29%)		113 (33%)	19 (17%)	
Treatment initiation site	TB Hospital n (%)							43 (12%)	2 (2%)	*<0.001*
	PHC Facility n (%)							313 (88%)	114 (98%)	

Percentages shown were calculated based on recorded data only. Missing data is not reflected but can be calculated based on totals in the cohort and the recorded data shown.
Abbreviations: HIV – human immunodeficiency virus; MDR-TB – multi-drug resistant tuberculosis; PHC – primary health care.

There was a reduction in median time-to-event between the LPA and Xpert-based algorithms (Table 2): MDR-TB TCT was reduced from 43 to 17 days (Figure 3a); laboratory turnaround time from 24 days to <1 day (Figure 3b) and 'action' delay from 14 to 10 days. The facility-level paired analysis showed a difference of 25 days (95% CI 17 to 32 days)(p<0.001) in median MDR-TB TCT, 20 days (95% CI 14 to 27 days)(P<0.001) in median laboratory turnaround time and 5 days (95% CI 1 to 9 days)(p=0.015) in median 'action' delay between algorithms.

Table 2: MDR-TB TCT, Laboratory Turnaround Time and Action Delay by Algorithm

		LPA-based Algorithm	Xpert-based Algorithm
MDR-TB TCT (days)	Median (95% CI) *Interquartile range*	43 (40-46) *30-64*	17 (13-22) *7-36*
Laboratory Turnaround Time (days)	Median (95% CI) *Interquartile range*	24 (22-25) *18-33*	<1 (<1-1) *<1-17*
Action delay (days)	Median (95% CI) *Interquartile range*	14 (13-15) *9-30*	10 (8-14) *6-21*
Median MDR-TB TCT for different categories of patients (days) (95% CI)	Female	43 (37-47)	14 (10-19)
	Male	43 (40-47)	22 (14-29)
	HIV-positive	43 (40-47)	17 (12-28)
	HIV-negative	44 (36-49)	17 (8-22)
	Low MDR-TB risk	42 (38-46)	14 (10-27)
	High MDR-TB risk	44 (40-49)	18 (13-23)
	MDR-TB diagnostic time-point: Pre-treatment	43 (39 – 47)	14 (10 – 20)
	MDR-TB diagnostic time-point: Treatment	43 (38 – 48)	36 (19 – 51)
	MDR-TB treatment initiation TB hospital	44 (34-52)	23*
	MDR-TB treatment initiation PHC facility	43 (40-46)	16 (13-22)

Table showing median time-to-event for cases included in the final analysis in each algorithm. Abbreviations: MDR-TB TCT - Multidrug-resistant tuberculosis treatment commencement time' HIV - human immunodeficiency virus; CI – Confidence interval; PHC – primary health care. *95% CI not reported due to small sample (n=2).

A univariate analysis showed no significant association between MDR-TB TCT and age (p=0.429), sex (p=0.064) (Figure 4a), HIV-status (p=0.056) (Figure 4b) or treatment initiation site (p=0.340). There was a significant association between MDR-TB TCT and MDR-TB risk profile (p=0.032): TCT decreased for both risk profiles (Figure 4c), but more so in the low-risk category (hazard ratio (HR) 3.3, 95% CI 2.4 to 4.6, p<0.001) than the high-risk category (HR 2.0, 95% CI 1.4-2.8, p<0.001). A significant association was also found between MDR-TB TCT and the MDR-TB diagnostic time-point (p=0.001): the difference was greater for cases at the pre-treatment diagnostic time-point (HR 3.9, 95% CI 2.5 to 5.9, p<0.001) than at the treatment time-point (HR 3.4, 95% CI 2.6 to 4.4, p<0.001) (Figure 4d).

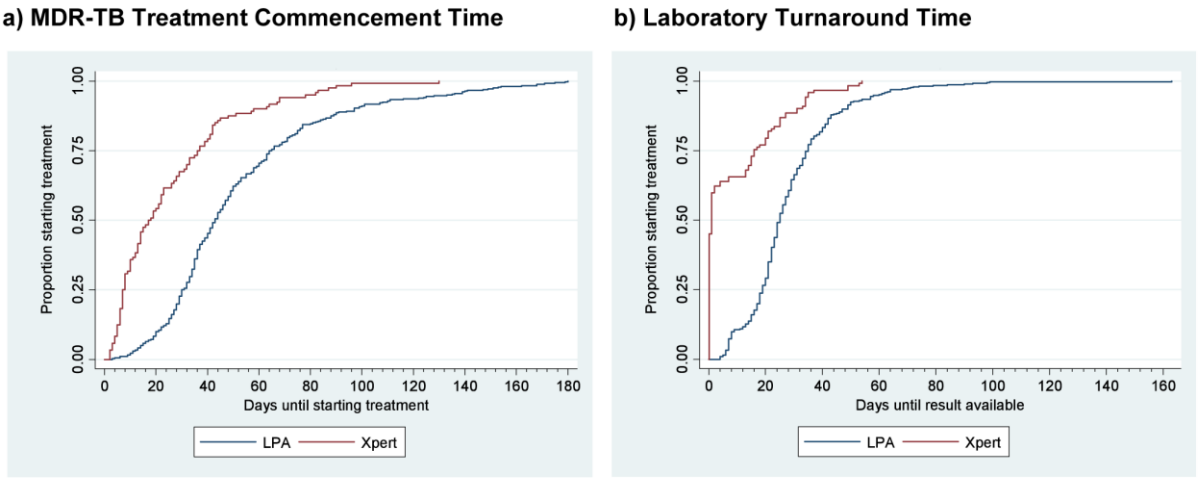

Figure 3: Cumulative Time-to-event Plots by Algorithm. Kaplan Meier time-to-event plots are shown for MDR-TB treatment commencement time (sample taken to treatment commencement) in Figure 3a and for laboratory turnaround time (to result available in the laboratory) in Figure 3b for cases included in the final analysis in the LPA- and Xpert-based algorithms. Abbreviation: MDR-TB - multidrug-resistant tuberculosis.

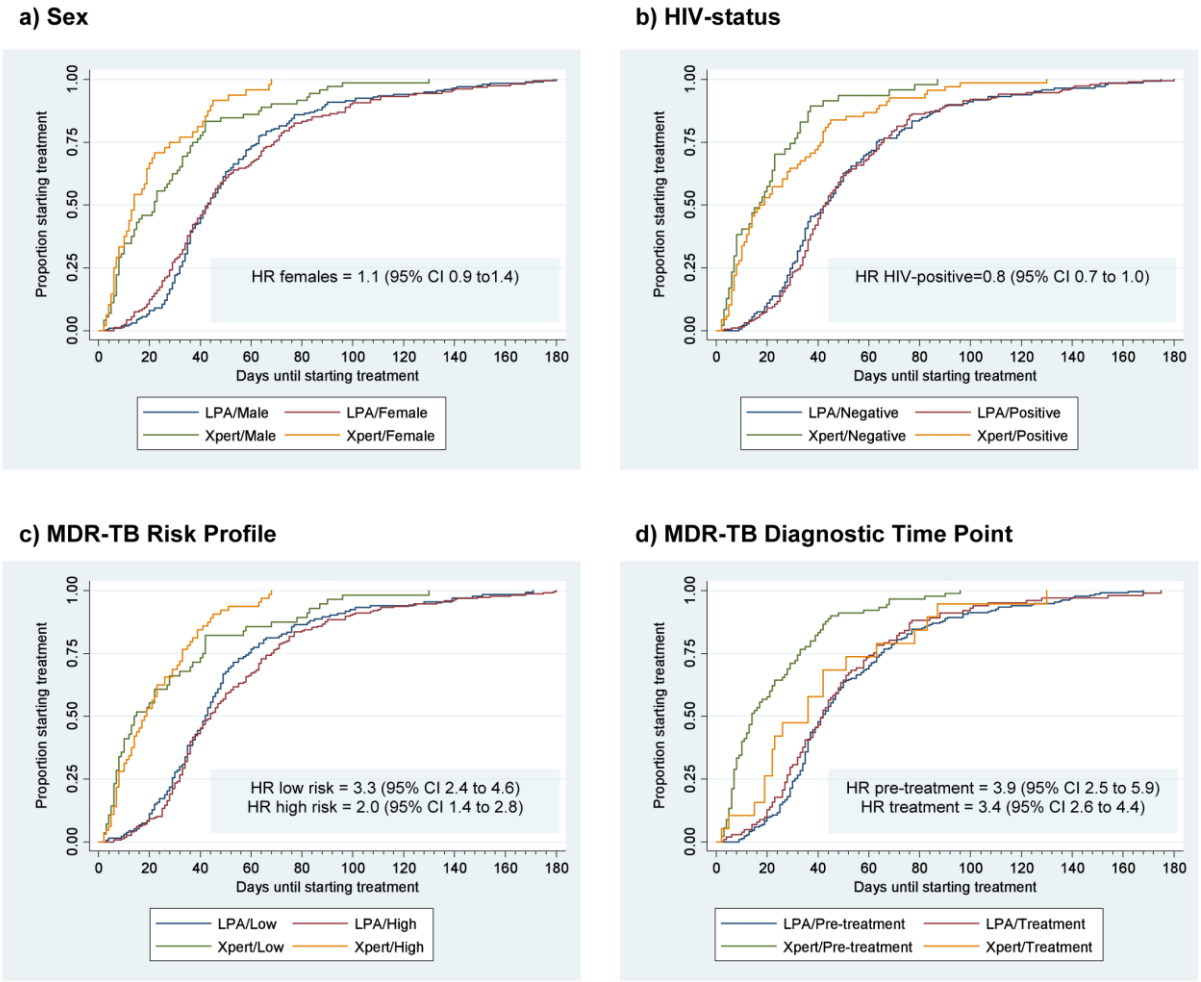

Figure 4: Cumulative Time to MDR-TB TCT Plots for Co-variables Assessed by Algorithm. Kaplan Meier time-to-event plots are shown for patient level variables assessed in the LPA-and Xpert-based algorithms: a) Sex; b) HIV-status; c) MDR-TB Risk Profile and d) MDR-TB Diagnostic Time-point. Inserts show Hazard Ratio (HR) for the univariate Cox regression analysis. Abbreviations: MDR-TB - multidrug-resistant tuberculosis; TCT – treatment commencement time.

However, in the extended Cox regression model that adjusted for all these patient level variables, only the algorithm produced a significant effect, with a hazard ratio of 2.7 (95% CI 2.1 to 3.4, p<0.001) in the Xpert compared to LPA-based algorithm.

DISCUSSION

This is one of the first studies to report on MDR-TB TCT in an Xpert-based algorithm under routine operational conditions. A reduction of 25-days in median MDR-TB TCT was found with the introduction of the Xpert-based algorithm. Most of the gain (80%) resulted from a reduced laboratory turnaround time with only 20% due to a reduction in the 'action' delay.

In this before-and-after comparison, a range of health system improvements that were introduced may have contributed to the reduction in MDR-TB TCT in the Xpert-based algorithm. At PHC-level, for example, care was fully decentralised for patients not requiring hospitalisation. From 2012, standard MDR-TB drug regimens were made available at PHC-level and sub-district medical officers could initiate treatment without prior review of cases or prescriptions from the TB-hospital. A nurse was also employed in each of the eight sub-districts to trace MDR-TB patients, refer to appropriate social services, arrange screening of contacts and ensure work-up and treatment commencement.

Considering the median laboratory turnaround time of <1 day and the health system improvements that were introduced, the median MDR-TB TCT of 17 days (95% CI 13 to 22 days) in the Xpert-based algorithm showed an unexpected level of delay. This partly reflected the time taken for pre-MDR-TB treatment clinical requirements such as chest x-rays, liver function tests and audiometry (done centrally at the TB hospital). Since the Xpert algorithm was only introduced for a period of 18 months during the study, it is possible that as the changes that have been introduced are entrenched, further reductions in MDR-TB TCT will be achieved.

Several factors may have contributed to 'action' delays, including inefficiencies in accessing results and recalling patients. 'Action' delays have also been found in other studies. In the Western Cape of South Africa, Jacobsen et al [18] found median delays from result being sent to the facility to treatment commencement of 20 days with LPA compared to 19 days with conventional DST. In two health regions in Peru, Yagui et al [23] showed that delays due to slow bacterial growth on solid media and "action" delays at various time-points contributed equally to the median TCT of almost 5 months. Patient factors may have also contributed to delays [24], including patients' failure to return promptly for their results due to work and family commitments and to perceptions of long waiting times and poor services.

There was no significant difference in MDR-TB treatment non-initiation rates between algorithms, due possibly to the small sample size in the Xpert-based algorithm. However, we found substantially lower non-initiation rates in both algorithms than those reported for South Africa [4,25]. The 6-month cut-off used in our definition of non-initiation has contributed to this. Standardisation of the definition will enable comparisons between studies. It is unclear to what extent the changes in the health systems may have also contributed and this requires further investigation.

As was expected based on the health system changes, a higher percentage of patients initiated treatment at PHC-level in the Xpert-based than in the LPA-based algorithm (98% compared to 88%, p<0.001). An unexpected finding however in the LPA-based algorithm was the similarity in MDR-TB TCT for patients initiating treatment at the TB-hospital compared to at PHC-level with a median of 44 and 43 days respectively. The need for prior case reviews and prescriptions from the TB-hospital for those initiating treatment at PHC-level may account for this. It is not possible to make inferences about the impact of decentralised care in the Xpert-based algorithm due to the small number initiating treatment at the TB-hospital.

The extent to which vulnerable groups benefit from a new diagnostic test is an important aspect of impact assessment [21]. The failure to find a significant reduction in MDR-TB TCT for HIV-positive individuals in the Xpert-based algorithm is surprising. Based on the increased sensitivity of Xpert for smear-negative TB cases [12], we expected to find that a higher proportion of HIV-positive individuals would be diagnosed by Xpert and would not require lengthy culture and DST. Our finding could however be attributed to the small sample in the Xpert-based algorithm and is a limitation of the study. There were also no benefits in MDR-TB TCT by age or gender.

New molecular tests need to be evaluated within the context of a diagnostic algorithm [21] and this is a unique aspect of this study. We found that not all patients in the Xpert-based algorithm received an Xpert test: 17% of this group were TB cases evaluated through culture and LPA when a first-line regimen failed. Studies that report on TCT based solely on a positive Xpert test fail to take this and other factors into account, including cases in whom the correct test was not requested or could not be done (due to an inadequate sputum volume, for example).

Whilst an operational evaluation provides important insights into the benefits possible in real-world settings, it has limitations. The quality and completeness of routine data is the first of these. Clinical records did not provide adequate information to assess the time between the onset of symptoms and MDR-TB testing. The 25-day reduction in TCT needs to be viewed in relation to this delay.

Another limitation of the study is that MDR-TB TCT was calculated from the point at which the MDR-TB test was taken and not necessarily the starting point on the algorithm. Treatment delay was thus potentially underestimated in the LPA-based algorithm as new TB cases did not have initial DST and may have had undiagnosed primary MDR-TB when evaluated for TB. We also did not assess the impact of the algorithm on MDR-TB treatment outcomes.

The extent to which our results can be generalised is limited by the setting: all facilities in the study were urban or peri-urban; Cape Town has a relatively good laboratory and health infrastructure with access to rapid liquid culture and decentralised MDR-TB treatment. During the study period all tests were done at a central laboratory. Additional evidence is therefore required from studies in rural settings, where liquid culture is not available and where there is decentralised use of Xpert, to provide a broader understanding of potential benefits.

In South Africa, where Xpert has been introduced as a replacement for smear microscopy, annual TB diagnostic costs are estimated to increase by 53-57% to USD 48-70 million per year at full Xpert coverage [26]. The reduced MDR-TB TCT in the Xpert-based algorithm needs to be assessed within the context of the cost-effectiveness of the algorithm. A more thorough understanding of impact also requires an assessment of

other potential benefits including, for example, TB yield, treatment outcomes and benefits from a patient's perspective.

CONCLUSION

We require evidence that new diagnostic tests which perform well in controlled settings can have an impact when implemented in operational settings [27]. This study showed that median MDR-TB TCT was reduced by 25 days with the introduction of an Xpert-based algorithm in a routine operational setting. However, when considered against a median laboratory turnaround time of <1-day, the median TCT of 17-days in the Xpert-based algorithm showed an unacceptable level of delay, exceeding the national target of five days [28].

Despite the substantial investment in the new technology [26], patients did not benefit fully from the use of Xpert, due possibly to both health system and patient factors. These need to be evaluated and addressed. Strengthening the health care system is important in controlling MDR-TB [29]; unless health system improvements are actively pursued, the full benefits of the rapid laboratory test are unlikely to be realised.

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Author Contributions:

Conceived and designed the experiments: PN EDT RD CL JC AD SBS DAE NB. Performed the experiments: PN EDT RD. Analyzed the data: PN EDT RD CL DAE NB. Contributed reagents / materials / analysis tools: PN EDT RD CL JC AD SBS DAE NB. Wrote the paper: PN EDT RD CL JC AD SBS DAE NB.

Competing interests:

The authors have declared that no competing interests exist.

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Chapter 6: Pathways to multidrug-resistant tuberculosis diagnosis and treatment initiation: a qualitative comparison of patients' experiences in the era of rapid molecular diagnostic tests

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ABSTRACT

Background: Although new molecular diagnostic tests such as GenoType MTBDR*plus* and Xpert® MTB/RIF have reduced multidrug-resistant tuberculosis (MDR-TB) treatment initiation times, patients' experiences of diagnosis and treatment initiation are not known. This study aimed to explore and compare MDR-TB patients' experiences of their diagnostic and treatment initiation pathway in GenoType MTBDR*plus* and Xpert® MTB/RIF-based diagnostic algorithms.

Methods: The study was undertaken in Cape Town, South Africa where primary health-care services provided free TB diagnosis and treatment. A smear, culture and GenoType MTBDR*plus* diagnostic algorithm was used in 2010, with Xpert® MTB/RIF phased in from 2011-2013. Participants diagnosed in each algorithm at four facilities were purposively sampled, stratifying by age, gender and MDR-TB risk profiles. We conducted in-depth qualitative interviews using a semi-structured interview guide. Through constant comparative analysis we induced common and divergent themes related to symptom recognition, health-care access, testing for MDR-TB and treatment initiation within and between groups. Data were triangulated with clinical information and health visit data from a structured questionnaire.

Results: We identified both enablers and barriers to early MDR-TB diagnosis and treatment. Half the patients had previously been treated for TB; most recognised recurring symptoms and reported early health-seeking. Those who attributed symptoms to other causes delayed health-seeking. Perceptions of poor public sector services were prevalent and may have contributed both to deferred health-seeking and to patient's use of the private sector, contributing to delays. However, once on treatment, most patients expressed satisfaction with public sector care. Two patients in the Xpert® MTB/RIF-based algorithm exemplified its potential to reduce delays, commencing MDR-TB treatment within a week of their first health contact. However, most patients in both algorithms experienced substantial delays. Avoidable health system delays resulted from providers not testing for TB at initial health contact, non-adherence to testing algorithms, results not being available and failure to promptly recall patients with positive results.

Conclusion: Whilst the introduction of rapid tests such as Xpert® MTB/RIF can expedite MDR-TB diagnosis and treatment initiation, the full benefits are unlikely to be realised without reducing delays in health-seeking and addressing the structural barriers present in the health-care system.

BACKGROUND

The World Health Organisation (WHO) identified the need to address multi-drug resistant tuberculosis (MDR-TB) as a public health crisis as one of five key priorities [1]. Improving MDR-TB control requires rapid, accurate diagnostics to enable early and appropriate treatment [1, 2] with benefit to both patients and the public through reductions in morbidity, mortality and transmission within communities [2, 3]. Advances have been made in the development, evaluation and routine use of rapid, accurate molecular diagnostic tests for MDR-TB. South Africa was an early adopter of two WHO approved tests, GenoType MTBDR*plus* (Hain Lifescience GmbH, Nehren, Germany) line probe assay (LPA) [4] and Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) (Xpert) [5].

Studies have shown that both LPA [6, 7] and Xpert [8] reduced MDR-TB diagnostic and treatment initiation times in comparison to previous tests. Test performance, as well as both patient and health system factors influence the potential of rapid diagnostics to reduce diagnostic and treatment delays [9]. Although not specific to MDR-TB, studies have found a number of factors associated with patient delay in accessing care in sub-Saharan Africa [10]. Fear of a positive human immunodeficiency virus (HIV) test or the stigma associated with this [11–13], the belief that symptoms, like cough, would resolve spontaneously or improve with self-medication [11, 13, 14], uncertainty about the cause of their illness and visits to multiple providers [13–15] all contributed to delays in seeking care. Health provider delays were influenced by the availability of laboratory resources, initial screening efficacy, timely and correct request for laboratory investigations and the coordination of patient management between different health-care providers [13, 16, 17].

There is a paucity of literature detailing MDR-TB patients' experience of diagnosis and treatment initiation. This study aimed to explore and compare MDR-TB patients' experiences of their pathway to diagnosis and treatment initiation in LPA and Xpert-based diagnostic algorithms. The study was part of a broader PROVE IT (Policy Relevant Outcomes from Validating Evidence on ImpacT) (http://treattb.org) evaluation that assessed the impact of new molecular tests on the diagnosis and treatment of TB in routine operational conditions. Impact analysis was guided by the Impact Assessment Framework [18] which provides a systematic, comprehensive approach to generating evidence to support decision-making for new diagnostics.

METHODS

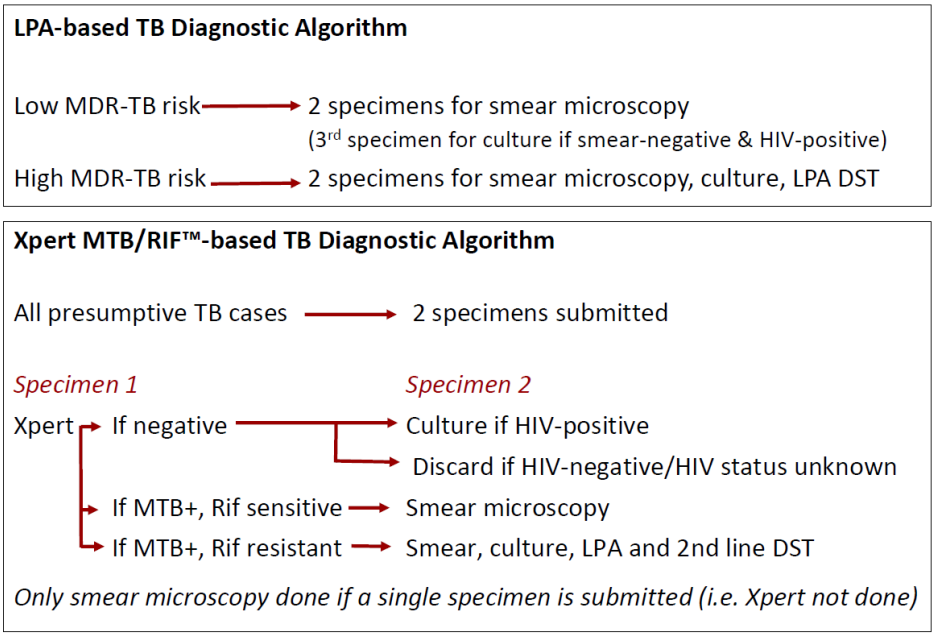
Study setting

The study took place in Cape Town, South Africa. Cape Town has a high TB burden with 28,658 TB cases and 953 MDR-TB cases notified in 2011 and a TB case notification rate of 752/100,000 population. Free TB diagnostic services were provided at 142 primary health-care (PHC) facilities offering two different service platforms. Community Health Centres (CHC) were large, busy facilities treating acutely ill adults and most offered only TB diagnostic services. Clinics tended to be smaller, focused on disease prevention and offered both TB diagnostic and treatment services. All TB tests were done at a central laboratory that received daily specimens via courier and recorded results in a networked, electronic laboratory database. Rapid, on-site HIV-testing was routinely offered to presumptive TB cases.

In 2010, a smear, culture and LPA-based diagnostic algorithm was used (Figure 1) with LPA done on culture isolates or clinical specimens of *high* MDR-TB-risk presumptive cases (those with previous TB, an MDR-TB contact or from a congregate setting). Doctors at the TB-hospital reviewed case records and prescribed MDR-TB treatment but patients could initiate treatment at PHC facilities.

From 2011-2013, Xpert was phased in, replacing smear microscopy for *all* presumptive TB cases (Figure 1). Full decentralisation of treatment occurred from 2012 with doctors at PHC facilities initiating standardised MDR-TB treatment without the need for prior case review at the TB-hospital.

Figure 1: Testing in the LPA and Xpert-based TB diagnostic algorithms



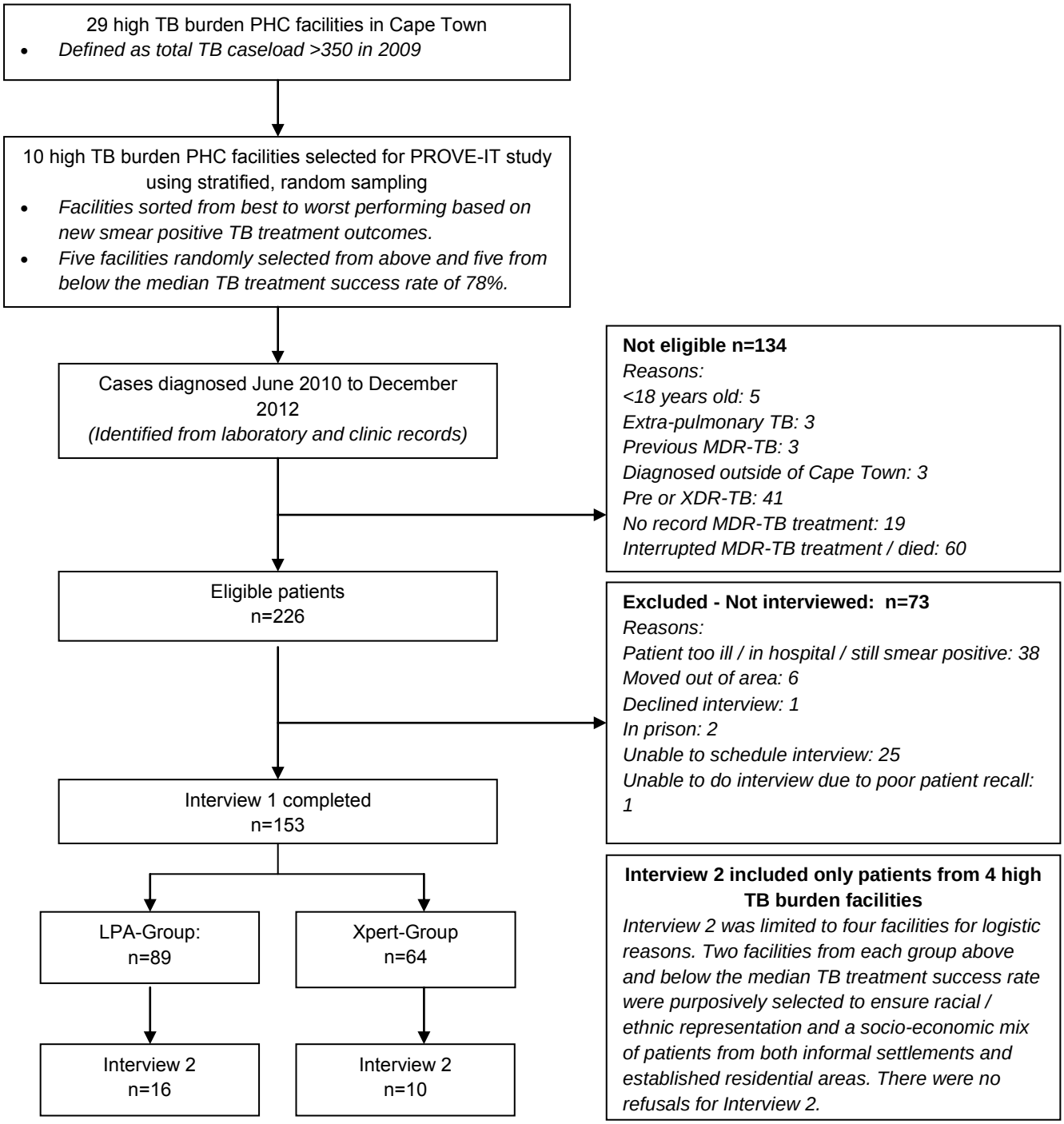
High MDR-TB-risk presumptive cases refer to those with previous TB, an MDR-TB contact or from a congregate setting. In the LPA-based algorithm, only these cases were initially screened for drug susceptibility. Low MDR-risk presumptive TB cases would only be identified when 1st-line TB treatment regimens failed. In the Xpert-based algorithm in comparsion, all presumptive TB cases were simultaneously screened for TB and rifampicn resistance using Xpert.

Sampling

Patients in this study were part of a PROVE-IT observational cohort in 10 high TB-burden PHC facilities selected from a total of 29 that met the criteria of a TB caseload of >350 in 2009. Health facility and patient sampling details are provided in Figure 2. We limited the number of facilities in this study for logistic reasons and purposively selected four of these facilities to ensure racial / ethnic representation and a socio-economic mix of patients from both informal settlements and established residential areas.

Eligible patients were >18-years of age, had been diagnosed with rifampicin or rifampicin and isoniazid resistance from sputa taken and tested in Cape Town between June 2010 and December 2012, and had received MDR-TB treatment at one of the four PHC facilities. Patients with previous MDR-TB treatment were excluded as their pathway to care may have been different. Patients with additional drug-resistance, in hospital or in prison, still smear-positive or with loss to follow-up at the time of the scheduled interview were excluded (Figure 2).

Figure 2: Primary health facility and MDR-TB patient selection



Patients in this study were part of a PROVE-IT observational cohort in 10 high TB-burden PHC facilities selected from a total of 29 that met the criteria of a high TB caseload in 2009. The flowchart indicates the selection of health facilities and patients for this study. Data from Interview 1 elicited quantitative information related to duration of illness, health-seeking visits and providers, cost incurred and socio-economic status data (used for costing purposes, to evaluate delay and to supplement information on patient pathways). Interview 2 was an in-depth qualitative interview exploring patients' perspectives of their pathways to care and formed the basis for this manuscript.

Patients diagnosed at the selected facilities were identified from an electronic laboratory database; those diagnosed elsewhere, but on treatment at these facilities, were identified through facility registers and clinical records. As patients in each diagnostic algorithm became eligible, PHC facility nurses enquired whether they

were willing to participate and provided their contact details to researchers for structured interviews. We purposively sampled a subset from the four facilities for qualitative interviews, stratifying participants by age, gender and MDR-TB risk profiles. PHC facility nurses asked selected patients if they were willing to participate in the second interview. Recruitment continued until an appropriate range of participants was interviewed and saturation was achieved in terms of key findings in both algorithms and no new themes appeared to emerge. We interviewed 16 patients diagnosed in the LPA-based algorithm between 2010 and 2012 and 10 patients diagnosed in the Xpert-based algorithm between 2011 and 2012.

The research team

The research team comprised a senior social scientist with oversight for this qualitative study (NL), two social science field researchers, two professional nurses, a health sciences researcher (MvN), a PhD enrolled medical researcher who was the principal investigator (PN) and a clinician (EdT). None of the researchers were involved in the delivery of health services or care of patients.

Data collection

As part of the broader PROVE IT study, professional nurses reviewed clinical records and completed a case record form (CRF) with demographic and clinical information. Three to six months after MDR-TB treatment had commenced, field researchers contacted eligible patients, obtained informed consent, interviewed patients and completed a structured questionnaire (Interview 1) detailing the care-seeking pathway, health-care visits and services received. Shortly thereafter, field researchers contacted the patients selected for this study, took informed consent again and conducted in-depth qualitative interviews in English or the patient's mother tongue (Interview 2). We elected to use interviews to elicit patients' first-hand experiences of their pathway to care. For infection control purposes, interviewers and patients wore N95-respirators and interviews were conducted in well-ventilated, private spaces at PHC facilities. Both the CRF and structured questionnaire were reviewed prior to interviews and the information was used to probe and clarify responses provided by the patients.

A semi-structured interview guide with open-ended questions was used. Patients were asked to provide a detailed account of their experiences from symptom onset to MDR-TB treatment initiation. Aspects of the care pathway explored in detail included patients' recognition of their initial symptoms, their decisions around where they sought medical care, their experience of these health services and their MDR-TB diagnostic and treatment initiation process. All interviews were digitally recorded, translated into English where necessary and transcribed.

Data analysis

Data analysis was undertaken by three of the authors (PN, MvN, NL). Each analyst read interview transcripts several times during the course of the study to familiarise themselves with their content. Analysts used open coding to independently identify key issues and themes in each stage of the care pathway with constant comparison within and between groups. We jointly recorded key events and issues for each patient on a treatment journey matrix based on data from the interview, supplemented by data from the case report forms and structured questionnaires. Consensus was reached through discussion. We used a combination of deductive (having explored specific aspects of the care pathway and the motivation behind patients' actions)

and inductive analysis, identifying common and divergent themes emerging from the data that were not specifically elicited [33].

Ethics

The City Health Directorate and Western Cape Health Department granted permission to undertake the study. 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 and provided a waiver of informed consent for the use of routine data. Written informed consent, in the patient's preferred language, was obtained prior to completion of the structured questionnaire and qualitative interviews. Patients were provided with refreshments but were not reimbursed financially for interviews.

RESULTS

We interviewed 12 female (6 in each group) and 14 male participants ranging from 20 to 58 years in age. Thirteen patients had previously been treated for TB and 17 were co-infected with HIV.

We present key themes in four components of the care-pathway: symptom recognition, health-care access, testing for MDR-TB and MDR-TB treatment initiation. We have combined the description of patients' experiences for both the LPA and Xpert-based algorithms and have highlighted similarities and differences. We identified both enablers and barriers to early MDR-TB diagnosis and treatment and summarise these in Table 1.

Symptom recognition

Patients described their symptoms, what they attributed these to and what led them to seek care. Most described symptoms typically associated with TB such as cough, night sweats, loss of appetite, weight loss, fever, chest pain and general malaise. Some, particularly those with HIV, described symptoms related to their co-morbidity as their primary concern, for example painful feet for a patient on antiretroviral treatment.

The role of previous TB treatment or social contact with TB patients

Half the patients had previously been treated for TB and many recognised their symptoms as a recurrence. Several responded by quickly seeking help at a PHC facility as this patient explained: *"I had all the symptoms that I had the last time when I had TB. So I wanted them to check [for TB]" (Xpert-4)*. Having had TB before did not always mean that patients recognised recurring symptoms or sought timely help. One patient explained: "*I did not believe it could be TB again because I completed my treatment the first time" (Xpert-9).* Several patients reported that contact with someone on TB or MDR-TB treatment heightened awareness of their symptoms: *"I thought I had TB because I stayed with someone who had TB and he did not take his treatment" (LPA-15).* Another explained: *"I did not know much about MDR-TB. My [relative] had MDR-TB and she told me to check if I don't have it" (Xpert-7).*

Table 1: Barriers and enablers in the pathway to early MDR-TB diagnosis and treatment initiation

	Enablers	Barriers
Symptom recognition	• Symptom recognition based on history of previous TB • Social contact with TB/MDR-TB patients • Awareness of increased risk of TB amongst HIV-infected patients	• Failure to recognise TB symptoms • Minimisation or denial of symptoms • Lack of awareness that TB can recur • Incorrectly ascribing symptoms to HIV or other medical condition
Accessing health-care	• Perceptions of good quality service • Convenience of free, accessible local services. • Familiarity with service • Family support • Responsiveness of provider at first health contact	• Negative perceptions of the public sector (over-burdened; long waiting times; negative staff attitudes; lack of privacy) • Fear of an HIV diagnosis • Social construct of "being a man", not admitting illness (weakness)
MDR-TB Testing	• Attendance at facilities geared towards TB (i.e. offering both TB diagnosis and treatment) • Availability of Xpert MTB/RIF • Screening of all presumptive TB cases for drug resistance • Patient's agency in specifically requesting TB screening services that were not offered • Patient's agency in pursuing diagnostic processes after initial negative tests	• Entry point to care through the private sector • Accessing facilities providing TB diagnostic but not treatment services. • Health providers failure to test for TB / MDR-TB at initial health contact • Health providers' failure to follow diagnostic algorithms • Interruptions to the diagnostic process due to dissatisfaction with the service, work and family commitments • Lack of money for transport to return to facility • Insensitive tests that fail to diagnose TB • Patients diagnosed clinically or on chest x-ray and started on 1st-line TB treatment • Failure to respond early to clinical deterioration for patients on 1st-line TB treatment
Initiating MDR-TB Treatment	• Health provider scheduling early return visits for MDR-TB test results • Patients returning for scheduled appointments • Availability of decentralised MDR-TB treatment • Perceptions that staff cared about their patient's well-being	• Patients failure to return for follow-up appointments • Delays in recalling patients • Results not being available at follow-up appointments • Family commitments preventing a return to facilities • Cultural beliefs and seeking traditional healthcare (often in another province)

The interaction with HIV

For some HIV-infected patients, awareness of their increased risk of TB motivated their response: *"I was coughing, my bones pained and I was losing weight…I thought I had TB …I went to the ARV doctor because I had an appointment … and told him how I feel. I asked him to send me for a TB test" (LPA-15).* However other HIV-infected patients incorrectly ascribed their symptoms to HIV and delayed seeking care. Fear of being diagnosed with HIV presented a barrier to accessing early care as one patient explained *"My mother said I must go to the clinic for a TB test. She was worried that I may have TB because my [relative] also had TB. I did not want to go ...too scared that if I go for a TB test they will also test me for HIV" (LPA-2).*

Failure to recognise or acknowledge TB symptoms

Patients who did not recognise symptoms as TB–related, tended to minimise their significance. Several attributed symptoms to other factors, including smoking tobacco and the weather: *"I was having a terrible cough and I was sweating at night, but this did not ring an alarm for me, because I still thought this was just a*

fever and the change of season and that everything was going to be fine" (LPA-3). Others mistook symptoms for "flu", asthma or other medical conditions: *"My grandfather had TB in 2006. I knew the symptoms of TB are when a person is coughing and getting very thin…I did not think about TB… I thought it was swine flu...Everyone was talking about swine flu"* (*LPA-16).*

Some patient's minimised their symptoms to avoid causing undue worry to their family. Family roles and responsibilities and the expectations that come with these contributed, as one patient reported: *"at the time when I started to feel sick I felt that I had to act a little bit strong, to not let the family know how weak I really felt. I must not let them down. Although I could feel some pain I felt I must be a man to face this disease" (Xpert-7).*

Patients tended to show considerable tolerance for their symptoms, referring to these as "just a cough" or "just losing weight". A patient who completely dismissed his symptoms said: *"But at all these times I was not sick. It was just a cough, sweat at night and I felt that I was also losing weight, nothing else, not a day I ever felt like I was sick" (LPA-8).* Symptom tolerance or denial resulted in some patients presenting for care when they were extremely ill, having lost substantial weight or being too ill to walk.

There was wide variation in the time from symptom onset to seeking health-care. Some, especially those who recognised they may have TB, took early action. Others delayed seeking care, sometimes for several months, until their symptoms were much worse. The stigma of possibly having TB did not emerge as an issue influencing patients' actions. The findings on symptom recognition were similar for patients in both the LPA and Xpert-based algorithms. It was interesting to note that none of the patients in the Xpert group reported a heightened awareness of TB or of the newly introduced test.

Accessing health-care

Patients described when and where they first sought care and what motivated their choice of provider. Although the public sector was the most common entry-point to care, several (about one third) first visited the private sector.

Public sector as the entry-point to care

Convenience, accessibility, familiarity with the services and cost were the commonest reasons for patients choosing the public health sector. Patients accessed and moved between CHCs and clinics and experiences differed between these. Several patients who first attended a CHC were treated with antibiotics for an acute chest infection and were not initially screened for TB; in comparison, most patients attending clinics were initially screened for TB, although not necessarily for MDR-TB.

Previously treated patients tended to return to their local clinic for care due to familiarity and satisfaction with the previous service: *"I had TB before and knew the symptoms of TB. I decided to go to the clinic where I stay…I was very satisfied with the treatment that I got [previously]" (Xpert-7).* Several patients chose to go to the clinic or CHC providing their antiretroviral treatment and requested TB tests at scheduled appointments; others were screened during antiretroviral treatment re-initiation.

A few patients specifically chose a CHC, because of the services offered, including emergency services and the availability of chest x-rays. A patient who attended for these reasons commented: *"I was very worried because I could not walk. I thought something serious is wrong with me. My [friend] called the ambulance"*

(LPA-10). Like other patients who had attended a CHC, this patient commented on the difficulties in accessing care: *"[the CHC] was very full. I don't like [the CHC] and would not like to go there again… Lots of chaos. The nurses rushed me, they don't give me time to talk and explain what's wrong with me. This is not right for me. They don't care about the patient. Once I was there and the nurses just went on tea, even if the very sick people are waiting on them. I told the nurse about a sick, old man and she said "he must just wait". They just don't care about the patients" (LPA-10).*

Although long waiting times were a common complaint, a few accepted this status quo: *"I waited for a long time before I was attended, but I understand that is the way it is. There are lots of people that need to be attended to everyday here at the clinic. But I knew that at the end of the day I was going to get assisted. I just told myself that... I am sick already and I need help and in order for me to get help I must be patient" (LPA-5).*

In contrast, some patients reported positive experiences: *"…I was sure I was going to stand in a long queue, but I explained to the TB nurse what was wrong with me and without me standing in a queue she told me to go to the TB room" (LPA-8).* Another explained *"I was expecting long queues and sitting for ages before getting help. I am not sure what the situation is at the other clinics, but …there was no queues and I got helped within 10 minutes…Staff in the TB room is very helpful and treats the patients with respect" (Xpert-9).*

Private sector as the entry-point to care

Several patients first visited the private sector, most commonly general practitioners (GP), due to perceptions of better services. They perceived the public sector to be over-burdened, with long waiting times, negative staff attitudes and a lack of privacy. Waiting times, in particular, were considered a barrier: *"I don't like coming to the clinic when I'm not feeling well…You wait for a long time before they can attend to you…At the doctors room the treatment and waiting time was very reasonable. I only had to wait for 20 minutes. Here at the clinic, you wait…you can wait for 8-hours here" (LPA-4).*

Having financial resources enabled patients to visit a GP; however, in some cases, they did not return as recommended due to financial constraints. Reflecting on their management in the private sector, several patients felt that visiting a GP had been a waste of time and money. One patient had the following advice for those with TB symptoms: *"I can advise them all to go to the clinic…. There are much better options at the clinic than the private doctors…lots of test which can be taken…lots of tests which will find out what is wrong with you….For someone to get those things you have to be patient though" (LPA-6).*

Patients that first sought help at a pharmacy often underestimated the seriousness of their symptoms, assumed these were self-limiting and self-medicated with cough mixtures.

We found no significant differences between the LPA and Xpert-based algorithms in the point of first health-care access or in patients' experiences. Despite perceptions of long waiting times, lack of privacy and poor staff attitudes, most patients reported that they would recommend that family and friends with TB symptoms go directly to PHC facilities, to reduce the cost and time to diagnosis.

Testing for MDR-TB

Patients described how they came to be diagnosed with MDR-TB; the steps involved and the time it took. With the exception of two patients, most experienced lengthy delays due to providers not testing for TB or MDR-TB

at initial visits, failure in the testing technology and patient-related delays, including interruptions to the diagnostic process and missed follow-up appointments.

Delays due to the first health provider not testing for TB

None of the patients who initially visited a pharmacy were referred for TB tests; a few subsequently visited a general practitioner, before eventually being investigated for TB at their local PHC facility. This contributed to MDR-TB diagnostic delays. In one extreme example, a patient with persistent cough described visits to the same pharmacy over a 6-month period: *"I went back again and again to the pharmacy and got different medication every time. I must have gone there five times" (LPA-13).*

Most patients who visited general practitioners were diagnosed with acute respiratory infections and treated with antibiotics, without TB investigations. Some had chest x-rays taken and a few had sputum tests. Some patients who did not respond to initial treatment had early referral to PHC facilities; others who could not afford to continue with private sector care attended the public sector when their health deteriorated. Several patients who visited general practitioners experienced lengthy delays as a result of numerous visits and courses of antibiotics, before seeking or being referred to a PHC facility for investigation.

In the public sector too, particularly at CHCs, some patients with a chronic cough were treated with several courses of antibiotics before a TB test was done. After an initial general practitioner one patient reported: "*I was at [the CHC] for 24 hours in December …they told me that I had infection in my lungs and gave me the drip and antibiotics…In the same month I didn't feel so well so I went back… and they gave me the same drip and antibiotics" (LPA-16).*

In the most extreme example of missed diagnostic opportunities a young woman was started on MDR-TB treatment 15 months after first seeking health-care. Despite repeated visits to both the private and public sector, the patient was not adequately evaluated for TB, including during pregnancy. She was diagnosed several months after her baby's birth with serious consequences including her baby contracting MDR-TB (see Figure 3).

Delays due to the first health provider not testing for drug susceptibility

In the LPA-based algorithm, low MDR-TB risk patients did not have initial drug susceptibility tests (DST); this was done only when 1st-line TB treatment failed, resulting in substantial delays to MDR-TB treatment. In comparison, in the Xpert-based algorithm, *all* presumptive TB cases were required to have an Xpert test and were concurrently evaluated for tuberculosis and rifampicin resistance, theoretically reducing these delays. In both algorithms however, there were many instances where the correct tests were not initially done, contributing to diagnostic delays.

Patients who experienced delays commented on the distress they felt whilst on 1st-line TB treatment. For one patient, diagnosed on smear microscopy by a general practitioner and referred to a PHC facility, a series of health service failures contributed to delay. The patient was at high MDR-TB-risk and despite the clinician requesting an Xpert test, only smear microscopy was done and the patient was started on 1st-line TB treatment.

Figure 3: Delayed access to treatment - in their own words

"It was winter and I was coughing non-stop". I went to [the general practitioner] frequently…. I never gave in sputum… [The GP] gave me cough medicine and antibiotics and the 2nd time he sent me for an x-ray…..I had to pay R300 for the x-ray and R200 for the doctor. They did not see anything on my x-ray. I had to buy cough medicine every month, one bottle after another. I finished [these], but nothing changed… I could not afford the private doctor anymore."

She visited a local clinic three months later and had two smear negative microscopy tests. She subsequently went back to a private practitioner. A few months later she fell pregnant and attended regular antenatal services at a CHC. Her health deteriorated. *"I was coughing and having sharp pains under my breast. Now that I know more about TB, I think that could have been where the TB was sitting…I was feeling cold all the time, even shaking. They said they could not help me because I am pregnant. They cannot give me anything strong. I remember when I was seven months pregnant I became very sick. The pain under my breast became very strong. I told them to give me a pill so that the baby can be born so that they can treat me for the pain. They said 'no', they don't work like that. My blood pressure is good and they cannot jeopardise my health. The pain was unbearable. I went three times a week to [the CHC] for help. They only gave me panados. They could do nothing for my pain. It was a very bad pregnancy….I even lost weight" "I only went for a HIV test and my results were negative. They did not think that there was something else wrong with me, only that I was pregnant. They did not even mention any TB test." "…They said since you're pregnant we cannot help you with anything. The medicine can be too strong and will not be good for the baby. They told me to be patient. They will deal with this pain after I give birth. For the 9 months I really suffered."*

After her pregnancy she initially felt better but then deteriorated and went to back to the CHC saying *"do not forget that I reported to you that I was sick during my pregnancy. Now I'm sick again. Since I had my baby, maybe you can do something about it. The doctor who attended to me first gave me painkillers and antibiotics. He thought it could just be a chest infection. When I told him for how long I felt sick, he then also decided that I must go for a TB test."*

The patient was started on MDR-TB treatment about 15 months after first presenting for care. The devastating impact of these missed opportunities was not limited to the patient, but also to her family, as her baby was diagnosed with MDR-TB and had to be hospitalised. This caused the mother huge feelings of guilt as well as concern that the bonding with her child was in jeopardy. She describes her baby as *"no longer happy….it seems as if he is forgetting us, it makes me feel bad to think that my baby is forgetting me". "I am very sad to think that I gave my baby MDR-TB."*

(Xpert-10)

Nurses did not respond to the patient's complaint of worsening symptoms. After sputa were taken to evaluate response to treatment the patient reported: *"When the results came back they told me I do not take my tablets. I told them 'but I take my pills every day'. They could not understand why my results were 3-plus positive. I told them 'my [spouse] sees when I take my tablets in the morning'. This made me very troublesome… In all the time that I took the treatment I felt the same. The treatment did not help….I started to give up hope" (Xpert-6*). The patient started MDR-TB treatment almost 5-months after initial tests; following routine screening the patient's child was also diagnosed with MDR-TB.

Delays due to initial negative or invalid tests

Patients in both algorithms were sometimes diagnosed on chest x-ray after negative initial smear or Xpert tests and commenced on 1st-line TB treatment as this patient explained: *"So finally after three days the results came back…. and a few days later they said I was negative, but I was still getting sicker." (Xpert-8).* This patient persisted, seeking care from another facility: "*I went to [the CHC] again like someone who does not know what's wrong with them. I told the doctor 'I already gave sputum' and I went for x-rays and that's when*

she saw the x-ray and sent me straight here and they … put me on treatment". As per policy, this HIV-negative patient did not have an initial sputum culture test; this was only done two months after 1st-line TB treatment was started, contributing to a 4-month delay in MDR-TB treatment.

In comparison, a patient who was investigated for TB shortly after commencing antiretroviral treatment reported: "*I gave in the sputum and came back to the clinic after 3 days. The result was negative…I went again to the ARV clinic and they sent me for chest x-ray .My chest x-ray was also negative….I went back to work. [One day] I was preparing to go to work. My phone rang and it was the clinic that said I must come to them immediately" (Xpert-5).* The patient was diagnosed on a culture test, resulting in a 6-week delay to MDR-TB treatment.

Patients' roles

Patient narratives presented several examples of their agency in persisting with the diagnostic process when symptoms did not resolve and in requesting tests that should have been offered but were not. One patient explained: *"I knew I was HIV positive, and that made me more worried when I felt sick. Even when my TB results were negative…I went again for a TB test" (LPA-14).* Whilst not playing a major role, patient factors contributed to delays during the diagnostic process due, for example, to work and family commitments and being unable to pay for transport to return to facilities.

A comparison between the LPA and Xpert-based Algorithms

There were many examples of remarkably similar patients' experiences between the LPA and Xpert-based algorithms, with a 1-2 month delay between submitting the MDR-TB test sputum and treatment initiation. Delays overall were longer for patients in whom initial tests were negative with 1st-line TB treatment started on clinical or chest x-ray findings.

With Xpert, there were two examples of rapid MDR-TB diagnosis where a test submitted at the first health contact diagnosed rifampicin resistance (see Figure 4). A patient elucidated: *"At the clinic I was given the bottle to give sputum… After that I was given a follow-up date to come the following week for my results, and when I came back I was told that it looks like I have TB and that this TB is not like the first one…. I was told that I needed to see the doctor because I have a "big TB, MDR-TB" a more serious TB, not the normal one" (Xpert-2).*

MDR-TB treatment initiation

Patients described their experiences of receiving test results and initiating treatment. We identified both health system and patient factors contributing to delays.

Health system factors contributing to delay

Problems were experienced with facilities failing to receive laboratory results, resulting in multiple return trips, as one patient explained: *"After returning for my results and waiting for a long time, I was told that I needed to come back again after two days. After another two days I was told my results were not received due to a broken fax machine. After this day I decided not to come back because I was waiting too long in the queue for my results and I was feeling better at this stage" (LPA-5).*

Figure 4: Expedited access to treatment - in their own words

"I went to [the CHC]… because I was coughing, sweating at night, basically I had all the symptoms that I had last time when I had TB. So I wanted them to check the TB…. I went there specifically because I wanted to see whether I was healed properly from the previous TB."

"At [the CHC] TB screening was conducted and I was told to come back for results within a week's time." I think [the CHC] sent a letter to this clinic and I was recalled immediately….they sent people from this clinic...home to recall me." "They told me that I had TB and my TB is not a normal one. I have MDR-TB. At the time I did not understand, but they told me that this is a more strong TB. I was sat down and the TB nurse explained to me everything about MDR-TB treatment, how it is used, and that I was going to undergo treatment of two years, first six months including injection. At that time I did not have any information on MDR. The explanation assisted a lot in understanding what was expected from me and the process that I was going to undergo. Also when I brought back my CXR… the doctor explained to me exactly what was happening with me and the processes that I was going to go through."

"The nurses in the TB room furnish me with information every time I come for my treatment, so education was not once off." "The treatment was good here at the clinic. The sisters are friendly and they explain stuff to you."

"I …had mixed feelings [when I was told about the MDR-TB]. [I was] relieved, because at least I knew what was wrong with me. Again the treatment I got from the staff at the clinic made me feel better. At first because I did not understand this MDR-TB, I thought it was the end of time for me, but when the treatment process was explained to me I felt much better and looked forward to the treatment."

The patient was started on MDR-TB treatment within a week of first presenting for care.

(Xpert-4)

Once the PHC facility received the MDR-TB test result, there were delays in recalling patients, although from patient accounts, the reasons for this were not always clear. Several patients indicated that a health worker was able to contact them telephonically or visited their home. Some indicated that the PHC facility struggled to contact them initially, for instance, when messages were not relayed to them. Substantial delays occurred in recalling some patients. One patient who tested smear-negative in April and went to visit family in another province to recuperate reported: *"In mid-August the ..clinic phoned me to check when I will be back home. They did not say why. I only went back at the .end of August and was informed…that I have MDR-TB. This was another shock for me. I was very disturbed that the clinic [had] not told me this while I was [away]. I was living unaware of this very contagious disease...I think this was very irresponsible of the clinic. I told them… when they explained the seriousness of MDR-TB to me….I was a danger to my family and could have been on treatment 2-weeks earlier" (Xpert-9).* In this extreme example, the patient was not aware that her results were in fact available three months prior to the patient being contacted.

Patient factors contributing to delay

Delays occurred when patients failed to return for scheduled appointments and had to be recalled. For a few, seeking traditional health-care at their family home in another province contributed to delays, as did family commitments. One patient explained: *"The day..I was told I have MDR-TB, my family phoned…with the news that my sister passed away. Everything then went crazy. All I could think about then was the fastest way to get [home.] I am the eldest son and must make all the preparation and decisions for the funeral. I left very early*

the next morning…not thinking about my MDR-TB treatment, maybe because my mind was very occupied with my family responsibilities and also because I did not feel that sick" (LPA-12).

The impact of an MDR-TB diagnosis

Patients spoke at length about the range of emotions they experienced on receiving an MDR-TB diagnosis. Although devastating for most patients, the diagnosis was often accompanied by a sense of relief at finally knowing what was wrong with them. For many experiencing financial and other hardships, diagnostic delays exacerbated their difficulties. There were also feelings of guilt about infecting others, especially children: *" it hurts me a lot, I don't even want to go there, I am feeling very bad, very, very bad, because if this was detected earlier I was not going to go through some difficulties that I went through. You know… when I think that I even infected my child it makes me feel very bad. Because if this was detected early and [I was] started on the right treatment, maybe some of the problems would have been eliminated" (LPA-3).* Overall, six children in the households of the 26 patients interviewed were diagnosed with MDR-TB.

DISCUSSION

Limited data are available on the impact of new molecular diagnostic tests on MDR-TB patients. Two studies comparing conventional DST to LPA showed reductions in median treatment commencement times from 72 to 24 days [6] and 80 to 55 days [7] respectively. The PROVE-IT evaluation found a reduction from 43 days in the LPA-based algorithm to 17 days in the Xpert-based algorithm [8]. These findings however provide a limited view, excluding the period prior to MDR-TB tests being taken and do not explain, for example, why it takes 17 days to get a patient onto treatment despite a laboratory turn-around time of <1 day [8]. There is a paucity of literature detailing patients' experiences of MDR-TB diagnosis and treatment initiation and this is one of the few studies to report specifically on this.

Our findings show that patients' pathways to MDR-TB care varied: some were expedited, with treatment initiated within a week of first health provider contact, thus achieving the anticipated benefit of Xpert. However obstacles at all stages in the pathway delayed treatment for many patients in both the LPA and Xpert-based algorithms. Some of these delays could be considered as unavoidable (perhaps due to the complexity of the disease and the limitations of tests), but some, especially those related to health service failures, are clearly avoidable. We reflect on the implications of these findings for reducing delays in the pathway to MDR-TB treatment initiation.

Symptom recognition

We found no differences in patients' recognition of their symptoms in the LPA and Xpert-based algorithms. The media coverage during the launch of Xpert in South Africa did not appear to impact on patient's health-seeking behaviour. Instead, factors that contributed to early symptom recognition and health-seeking in both algorithms included a previous history of TB, social contact with someone on treatment (both of which are unhelpful from a public health perspective) and awareness amongst some co-infected with HIV of their increased risk of TB. However, many patients deferred health-seeking for lengthy periods of time. As was found in other studies, some waited to see if symptoms like cough resolved spontaneously or improved with self-medication [11, 13, 14]; others deferred for fear of an HIV diagnosis [11–13] and patients who were

uncertain of the cause of their illness delayed health-seeking or visited multiple providers [13–15]. The extent to which patients deferred health-seeking is difficult to ascertain bearing in mind the tendency to tolerate, underplay or deny TB symptoms. This is likely to be a significant issue in our setting, considering the chronic nature of TB and how ill many patients were at their first health contact.

Studies have reported equivocal findings on the role of TB knowledge in treatment delay [10, 19, 20], with some finding an association between poor knowledge and delay [21–24] and others not [15, 25]. Our findings suggest that knowledge about symptoms and perceptions of risk influenced health-seeking. Raising awareness of TB symptoms and the need to seek early care may contribute to reducing patient delays. Perhaps the heightened awareness amongst those with previous TB presents an opportunity: these individuals could be targeted by education programmes to assume the role of “cough advocates” in their communities, with benefits for their own health too, as they are at higher risk of re-infection [26, 27]. The introduction of a new test like Xpert presents an opportunity to influence health-seeking behaviour through awareness campaigns that increase demand for the test.

Health-care access

About one third of the patients in our study first sought care in the private sector, due to perceptions of poor treatment in the public sector, particularly long waiting times and poor staff attitudes. Poor TB screening practices in the private sector contributed to delays for many patients. Other studies have also found that visits to private providers and facilities not equipped to diagnose and treat TB contributed to delays [13, 14, 19, 22, 28, 29]. Perceptions of poor public sector services are frequently cited as contributing to delay [11, 13–15] and may have contributed both to deferred health-seeking and to patient’s choice of the private sector in our study. Avoidance of free public sector services calls for serious reflection on how to improve service delivery. Improved TB screening practices in the private sector and early referral to the public sector are required to help reduce delays.

It is important to note that despite widespread negative perceptions of the public sector, several patients reported positive experiences at their first contact and almost all reported positive experiences once on treatment and indicated that they would recommend these services to family and friends. We do not feel that conducting the interviews at the health facilities influenced this sentiment as patients spoke candidly about negative experiences. Efforts to improve public health services could build on the positive sentiments expressed by patients.

Testing for MDR-TB and treatment initiation

Despite most patients, including those who were HIV-infected, presenting with symptoms typical of TB, one of the commonest factors contributing to delay in both diagnostic algorithms was health provider’s failure to test for TB at initial contact. This occurred most frequently when patients visited pharmacies, general practitioners and facilities not providing TB treatment. Large population-based surveys of health-seeking behaviour in other countries reported similar findings: the majority with chronic cough presented for care [23, 25, 30, 31] but only a small percentage were evaluated for TB [30, 31]. Efforts need to be made to increase the “index of suspicion” of TB amongst both private and public sector providers, especially those not providing TB treatment, to ensure appropriate testing.

An advantage of the Xpert-based algorithm is that by targeting all presumptive TB cases and not only those at high MDR-TB risk, it should diminish the problem of patients with primary MDR-TB being placed on 1st-line TB treatment and the ensuing suffering that patients described as their health deteriorated.

The potential of an Xpert-based algorithm to substantially reduce delay is highlighted by two examples of rapid initiation of MDR-TB treatment, within 6 and 8 days of the first health contact, respectively. Early access to treatment was enabled by the correct tests being requested which yielded a positive result, results being available when patients returned and decentralised treatment being available. In comparison, the earliest access for three patients in the LPA-based algorithm was within 31-38 days of the first health contact, reflecting the time taken for a culture and DST result with LPA.

However, more often than not, health system factors including failure to adhere to testing algorithms, problems with receiving the results, scheduling follow-up visits and recalling patients with positive results, all contributed to substantial delays. The introduction of rapid diagnostics therefore needs to be coupled with measures that address these structural barriers and minimize organizational delay [20, 32]. Patient-related delays (due to missed follow-up appointments, competing family demands and seeking traditional health-care) contributed to a lesser extent.

Our findings highlight not only the factors influencing the pathway to MDR-TB treatment, but also the impact on the lives of patients. Patients described how their physical and emotional suffering during the long and sometimes, tortuous pathway to treatment initiation compounded already difficult socio-economic and family circumstances. For some, the impact on their families was experienced as devastating, in particular, when children were infected. There was recognition (and anger) amongst some, that reducing diagnostic delays may have averted some of these infections.

Limitations and Strengths

The study has limitations. It was undertaken in Cape Town which is urban, relatively well resourced and with decentralized MDR-TB care. Obstacles to care may be greater in poorly resourced areas, in rural settings and with centralized care. The study does not reflect the experience of the sickest MDR-TB patients (those in hospital or still smear positive), those not initiating MDR-TB treatment and those who were lost to follow-up, and may therefore present a more optimistic view of pathways to care. One of the major strengths of this study is that we were able to increase the validity of patient reports by triangulating data from interviews with clinical information and data from a structured questionnaire on health visits and services received. This also provided important context to patient's narratives and deepened our understanding of pathways to care. Whilst the small sample included in the study may not have been statistically representative of all MDR-TB patients, we felt that we had captured an adequate range of experiences. Qualitative research, where patients are required to convey their experiences and the meaning they attribute to these [33] contributes important evidence on the impact of molecular diagnostic tests.

CONCLUSION

The history of TB control efforts around the world has shown that having the right technology will not by itself resolve complex medical and public health challenges [34, 35]. We are likely to confront a range of barriers in making the most of new diagnostic technologies [36]. Whilst the introduction of Xpert clearly has the potential

to reduce MDR-TB diagnostic and treatment delays, this alone does not suffice. Addressing patient delays in health-seeking is important. However, unless the structural barriers to care (correct evaluation at the first health contact, appropriate referral between sectors, developing patient-friendly health systems that are better organised to access results and commence treatment) are also addressed, the potential of rapid molecular diagnostic tests such as Xpert are unlikely to be fully realised. We hope that patients' perspectives will be a call to action to address the obstacles identified in the pathway to MDR-TB treatment initiation.

COMPETING INTERESTS: The authors declare that they have no financial or non-financial competing interests.

AUTHORS' CONTRIBUTIONS: All authors designed the study. MVN and EDT identified study participants. MVN, EDT and NL supervised the field researchers. PN, MVN and NL reviewed interview transcripts and undertook analysis. PN wrote the manuscript and MVN, EDT, NB and NL contributed to the first and subsequent drafts and approved the submission.

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Chapter 7: Comparing multidrug-resistant tuberculosis patient costs under molecular diagnostic algorithms in South Africa

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ABSTRACT

Setting: Ten primary health care facilities in Cape Town, South Africa, 2010–2013.

Objective: A comparison of costs incurred by patients in GenoType® MDRTB*plus* line-probe assay (LPA) and Xpert® MTB/RIF-based diagnostic algorithms from symptom onset until treatment initiation of multidrug-resistant tuberculosis (MDR-TB).

Methods: Eligible patients identified from laboratory and facility records were interviewed 3–6 months after treatment initiation and a cost questionnaire completed. Direct and indirect costs, individual and household income, loss of individual income and change in household income were recorded in local currency, adjusted to 2013 costs and converted to $US.

Results: Median number of visits to initiation of MDR-TB treatment was reduced from 20 to 7 (P<0.001) and median costs fell from US$68.1 to US$38.3 (P=0.004) in the Xpert group. From symptom onset to being interviewed, the proportion of unemployed increased from 39% to 73% in the LPA group (P<0.001) and from 53% to 89% in the Xpert group (P<0.001). Median household income decreased by 16% in the LPA group and by 13% in the Xpert group.

Conclusion: The introduction of an Xpert-based algorithm brought relief by reducing the costs incurred by patients, but loss of employment and income persist. Patients require support to mitigate this impact.

BACKGROUND

"TB is the child of poverty - and also its parent and provider" [Archbishop Desmond Tutu.]

TUBERCULOSIS (TB) disproportionately affects the poor[1] due to a complex interaction between many factors, including poor nutrition, overcrowded living or working conditions and concomitant disease, such as human immunodeficiency virus (HIV) infection.[2,3] TB perpetuates a cycle of poverty, with affected families losing household income through disability or death and confronting costs in the diagnosis and treatment of the disease. TB also affects the most economically viable, being among the top three causes of death among women aged 15–44 years.[4]

TB patients incur significant costs from the onset of their illness until diagnosis, with costs, as a percent- age of household income, being higher for poor patients.[5–9] There are generally considerable delays between the onset of TB symptoms and initiation of anti-tuberculosis treatment, attributable to both the patient and the health system.[10,11] The longer the delay, the more likely a patient is both to transmit TB[12] and to incur costs for transport, accessing health care, purchasing pharmaceuticals and loss in work time and productivity.

Several systematic reviews have reported on the diagnostic and treatment costs faced by TB patients. Costs ranged widely between countries, with one review reporting the greatest costs being incurred for hospitalisation, medication, transportation and private health care.[6] Ukwaja et al. reported mean diagnostic costs for patients in Africa ranging between 10.4% and 35% of mean annual income, and concluded that average diagnostic costs for TB were 'catastrophic',[13] defined in different studies as costs >10% of monthly or annual household income, >40% of non-subsistence household income, or the use of non-reversible coping strategies.[5,14] Patients in the lowest income bracket face the greatest risk of 'catastrophic' costs.[5] Tanimura et al. found that direct medical costs on average accounted for 20%, direct non-medical costs for 20% and income loss for 60% of total cost for patients in low- and middle- income countries.[14] Pre-treatment costs accounted for half of total costs. In Burkina Faso, 72% of patients were found to have incurred direct medical costs during the pre-diagnostic phase.[15]

Those with multidrug-resistant TB (MDR-TB) face an even greater economic burden, with low cure rates and lengthy treatment of up to 2 years.[16–18] Three studies reported by Tanimura et al. disaggregated the total costs for TB and MDR-TB patients and showed that costs were higher for those with MDR-TB.[14] In one of these studies pre-diagnostic costs for MDR-TB patients were just over double those for TB patients.[17] No studies from sub-Saharan Africa pertaining specifically to MDR-TB patient diagnostic costs were found.

The implementation of Xpert has reduced the time taken to diagnose MDR-TB[19] and it is anticipated that patients will benefit economically through fewer pre-treatment health care visits and the potential for an earlier diagnosis to reduce morbidity and mortality. It is important to ascertain the benefits that new technology affords to vulnerable groups.[20] This study compared costs incurred by patients in MDRTB*plus* line-probe assay (LPA) and Xpert-based diagnostic algorithms from symptom onset until MDR-TB treatment initiation.

METHODS

Setting

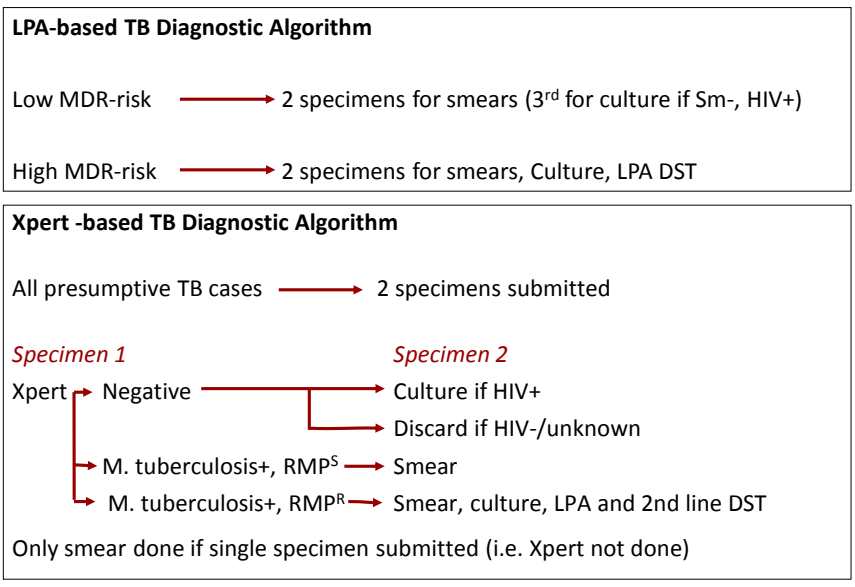
The study was conducted in a routine operational setting in Cape Town, South Africa. South Africa has high levels of poverty, with 56.8% of people living below the poverty line.[21] Household incomes show persistent disparities along racial lines, with an average annual household income of South African rand (ZAR) 387 011 among white households com- pared to ZAR69632 among black households; 48.7% of black households had an annual household income <ZAR9886.[22] The government has implemented a range of social protection measures to combat this, including both conditional (child sup- port and disability grants) and unconditional (pensions for men aged >65 and women aged >60 years) cash transfers and the provision of free primary health services.[23]

Free TB diagnostic services were provided at 142 primary health care (PHC) facilities in Cape Town; 101 of these, together with the dedicated TB hospital, offered free anti-tuberculosis treatment. There was a PHC facility within about a 5 km radius of all households. TB tests were performed at a central laboratory and results were recorded in an electronic laboratory database.

In 2010, a smear, culture and LPA-based diagnostic algorithm was in place (Figure 1), with LPA performed on culture isolates in high-risk presumptive MDR-TB cases. From 2011, Xpert was sequentially introduced into facilities, replacing smear microscopy for all presumptive TB cases (Figure 1). In both algorithms, cases with a failing first-line anti- tuberculosis treatment regimen were evaluated for MDR-TB using culture and LPA. We refer to patients diagnosed under these algorithms as the LPA and Xpert groups, respectively.

MDR-TB patients received standardised treatment regimens. At the start of data collection in 2010, doctors at the TB hospital reviewed case records and prescribed treatment; however, most patients initiated treatment at PHC facilities. Since 2012 (mid-way through the study), doctors have been able to initiate MDR-TB treatment at PHC facilities, without the need for prior review of case records at the TB hospital.

Study Figure 1: Testing in the LPA and Xpert-based TB Diagnostic Algorithms. LPA=line-probe assay; TB=tuberculosis; MDR-TB=multidrug-resistant TB; HIV=human immunodeficiency virus; +=positive; DST=drug susceptibility testing; –=negative; RMP^S=rifampicin-susceptible; RMP^R=RMP-resistant.



Study population

The study was part of an observational cohort in 10 high TB burden PHC facilities selected from a total of 29 that met the criteria of a TB caseload of .350 in 2009. We sorted facilities from best to worst performing based on new smear-positive treatment outcomes, and randomly selected five facilities above and five below the median treatment success rate of 78%.

Eligible patients diagnosed in either algorithm were aged >18 years, had been diagnosed with rifampicin (RMP) or RMP and isoniazid resistance from sputum samples tested in Cape Town between June 2010 and December 2012, and had received MDR-TB treatment at one of the 10 PHC facilities. Patients with previous MDR-TB treatment were excluded, as their pathway to care may have been different. Those with extensively or pre-extensively drug-resistant TB or who had interrupted MDR-TB treatment at the time of the scheduled interview were excluded. For infection control and the safety of the researchers, only patients who had been on MDR-TB treatment for at least 3 months and who were smear-negative were interviewed.

Data sources and collection

Patients diagnosed at selected facilities were identified from the electronic laboratory database; those who were diagnosed elsewhere but were on treatment at the selected facilities were identified from facility drug-resistant TB paper registers and clinical records.

Trained professional nurses located patient folders, reviewed study eligibility and recorded demographic, laboratory and clinical data and the patients' health care visits on case report forms. The clinical coordinator used this information to populate a timeline on a patient cost questionnaire with the number and dates of visits. This was used to probe and clarify responses provided by the patient during the interview.

Three to six months after the start of treatment, one of two graduate social scientists conducted interviews with patients at the PHC facility in their language of choice after obtaining informed consent. A structured cost questionnaire was completed detailing the patient's care-seeking visits from the reported onset of symptoms to MDR-TB treatment initiation. This included time spent at health care facilities, travel time and out-of-pocket payments. Employment status and individual and household income were assessed both before the onset of symptoms and at the time of the interview. The clinical coordinator checked the questionnaire and the text relating to care-seeking visits, and transcribed the data onto a coded spreadsheet.

Costs assessed

Direct costs comprised medical (for private practitioner consultation, diagnostic tests and medication) and non-medical (travel for return trips to the health care provider) expenditure as reported by patients. Money spent on food and expenditure incurred for persons accompanying the patient was not assessed. Indirect costs comprised opportunity costs for patient time. The number of health care visits was determined from the folder review and patient interview. Patient time comprised time spent in a health care facility (8 h per day in the case of hospitalised patients), and time spent in travel to the health care facility. The cost/h for patient time was calculated for all patients using the hourly wage (ZAR11.17) of a municipal worker in Cape Town in 2013.[24] We decided to use a basic wage for all patients, as it was difficult to calculate an average hourly wage for the large percentage of patients who were unemployed or self-employed and worked variable hours. The implications of this method are addressed in the discussion.

The total cost to the patient was calculated as the sum of the direct and indirect costs. All costs were calculated in local currency (ZAR) for that year, adjusted to 2013 costs using the annual consumer price index[25] and converted to $US based on average United Nations treasury operational rates in 2013.[26]

Definitions

Healthcare visit: A health care visit was defined as any visit made to a pharmacy, private practitioner, traditional healer or medical facility to seek care from the reported onset of symptoms with the current illness to MDR-TB treatment initiation. This included directly observed treatment (DOT) visits for those on first-line anti- tuberculosis treatment prior to MDR-TB treatment initiation; non-TB-related visits were excluded.

MDR-TB diagnostic timepoint: MDR-TB diagnostic timepoint was defined as either pre-treatment, for a presumptive TB case being concurrently evaluated for TB and drug resistance, or on first-line anti-tuberculosis treatment, for a case on a failing first-line TB regimen being evaluated for drug susceptibility.

Data management and statistical analysis

Data from the case report forms and cost questionnaire were double-entered into a Microsoft SQL database (MicroSoft, Redmond, WA, USA), corrected and analysed using STATA 12 (StataCorp, College Station, TX, USA). Some information on the variables collected was incomplete, and only reported data have been analysed. We compared differences between the algorithms and between MDR-TB diagnostic time points. Categorical data were summarised using proportions and compared using the chi-squared test. Continuous data were summarised using means and standard deviations or medians and interquartile ranges. Continuous variables were assessed using either the two-sample t-test or the Wilcoxon rank sum test, depending on the distribution of the variable.

Median as opposed to mean visits and costs are presented, as the data were skewed and medians are considered a more representative reflection of the sample. Mean values are presented in the appendix. We used a quantile regression model to assess the effect of potential confounders such as age, sex, previous TB and HIV status on median visits and costs.

Ethics

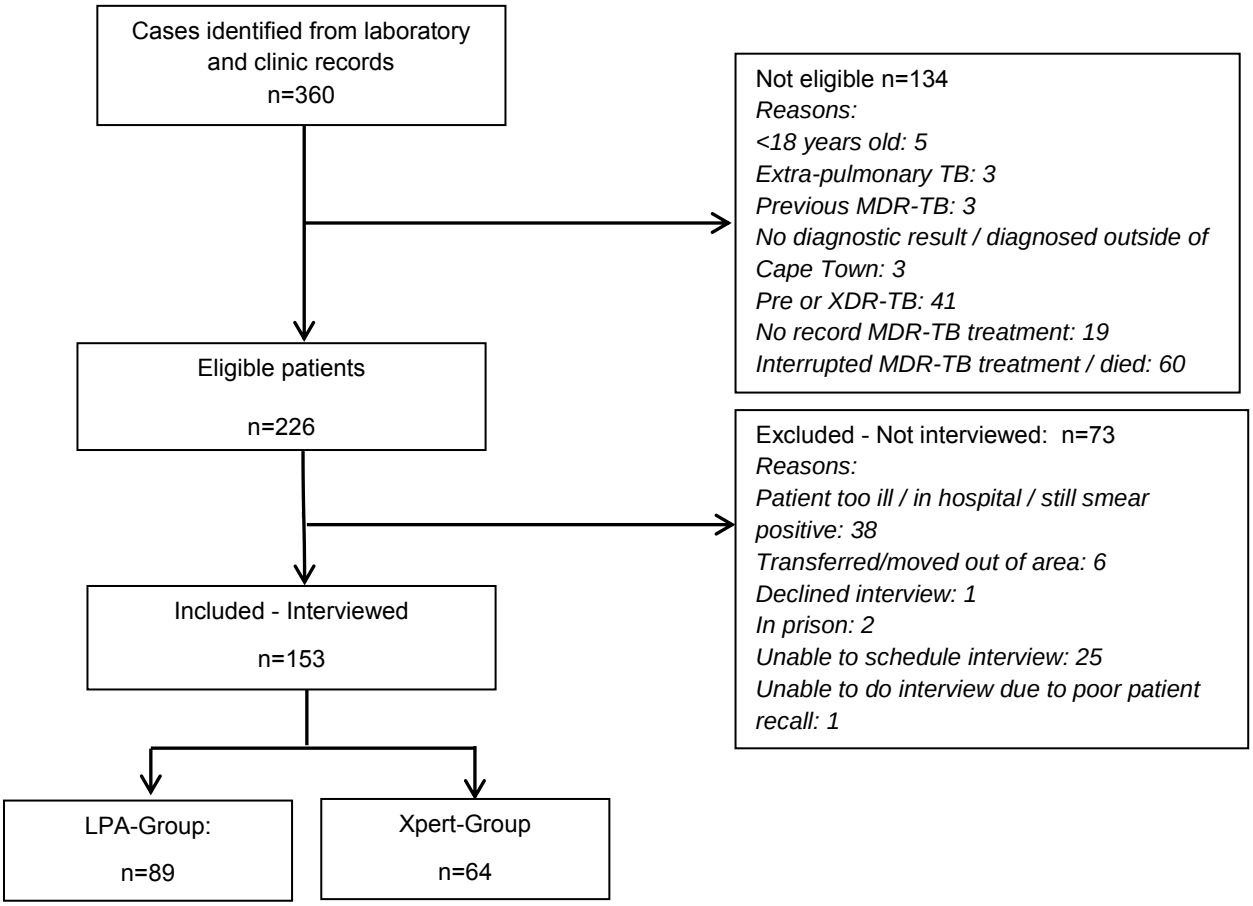
The Health Research Ethics Committee at Stellenbosch University (IRB0005239)(N10/09/308) and Ethics Advisory Group at The International Union Against Tuberculosis and Lung Disease (59/10) approved the study. The City Health Directorate, Western Cape Health Department and National Health Laboratory Service granted permission to use routine health data for which a waiver of informed consent was granted. All study participants provided informed consent for interviews.

RESULTS

Demographic and clinical characteristics

Of the 226 eligible patients, 153 were interviewed and 73 were excluded (Figure 2). Excluded patients did not differ significantly in gender (p=0.344), age (p=0.561), HIV status (p=0.893), previous TB treatment (p=0.101), or MDR-TB diagnostic time-point (p=0.471) from those included.

Figure 2: Study Population. TB = tuberculosis; MDR-TB = multidrug-resistant TB; XDR-TB =extensively drug-resistant TB; LPA=line-probe assay.



Demographic and clinical data are presented in Table 1 for the 89 patients in the LPA and 64 in the Xpert groups. There were no significant differences in sex, age, HIV status, and previous TB treatment between the groups. The majority of patients were diagnosed at the pre-treatment diagnostic time-point in both groups. The median household size was smaller in the LPA than the Xpert group (p=0.001).

Table 1: Demographic, Socioeconomic and Clinical Characteristics of Study Patients

Variable	LPA Group (n=89)	Xpert Group (n=64)	p-value
Sex, Female (number, %)	44 (49%)	27 (42%)	0.375
Mean Age, years	36.8	35 .3	0.300
SD	10.7	9.7	
(Range)	(19-70)	(19-63)	
HIV-positive (number, %)	57 (64%)	34 (53%)	0.175
Previous TB treatment (number, %)	45 (51%)	30 (47%)	0.653
MDR-TB diagnostic time-point: Pre-treatment (number, %)	74 (83%)	55 (86%)	0.640
Highest education level attained[1] (number, %) • No education • Primary school education (Grade 1-Grade 7) • Some high school education (Grade 8- Grade 11) • Completed high school education (Grade 12) • Tertiary education	 2 (2%) 29 (33%) 44 (49%) 13 (15%) 1 (1%)	 0 (0%) 15 (24%) 36 (57%) 7 (11%) 5 (8%)	0.112
Median number of people in household	3	4	0.001
IQR	2-4	3-5.5	
Median number of dependents	2	1	0.278
IQR	1-3	0-2.5	

[1]Education level was missing for one patient in the Xpert group. Abbreviations: LPA= MDRTB*plus* line probe assay; Xpert = Xpert MTB/RIF; SD= Standard Deviation; HIV=Human Immunodeficiency Virus; TB=Tuberculosis; MDR-TB= Multidrug Resistant Tuberculosis; IQR= Interquartile Range

Healthcare visits from symptom onset to MDR-TB treatment initiation

The median number of health visits to MDR-TB treatment initiation was reduced from 20 in the LPA group to 7 in the Xpert group (p<0.001) (Table 2). For those diagnosed at the pre-treatment diagnostic time-point, the median number of visits was reduced from 16 in the LPA group to 6 in the Xpert group (p<0.001). There were no significant differences between the groups for those diagnosed whilst on 1st-line TB treatment (p=0.375).

In the quantile regression model (see Appendix), age, sex, HIV status and previous TB were not significantly associated with the number of visits. When adjusting for these potential confounders, there were 12 (95% CI 3-21, p=0.009) fewer visits in the Xpert group. Cases diagnosed at the pre-treatment diagnostic time-point had 10 fewer visits (95% CI 4-15, p>0.001) in the Xpert group. For those diagnosed whilst on 1st-line TB treatment, there was no significant difference in the number of visits between the groups (p=0.624).

The proportion of patients who visited a private practitioner was similar, 30% in the LPA and 31% in the Xpert group (p=0.905). The proportion hospitalized at some point prior to MDR-TB treatment initiation was also similar, at 19% in both groups (p=0.957). A higher proportion attended a healthcare facility or a community site for DOT relating to their 1st-line TB regimen in the LPA group than in the Xpert group (69% vs 39%, p<0.001).

Table 2: Median Number of Healthcare Visits in the LPA and Xpert Groups

	Median	IQR	Min-Max	p-value
LPA Group - all patients (n=89)	20	10-44	2-171	p<0.001
Xpert Group - all patients (n=64)	7	4-23	2-184	
LPA Group – pre-treatment (n=74)	16	7-28	2-164	p<0.001
Xpert Group –pre-treatment (n=55)	6	4-12	2-73	
LPA Group – on 1st line TB treatment (n=15)	77	48-126	25-171	p=0.375
Xpert Group - on 1st line TB treatment (n=9)	51	46-77	19-184	

The table shows unadjusted data. Healthcare visits include all visits to both the public and private health sector. Visits for directly observed therapy (DOT) are included both for patients commenced on a 1st line TB regimen whilst awaiting drug susceptibility test results and for those diagnosed whilst on a failing 1st line TB regimen. Only 1.4% of visits in the LPA group and 3.2% in the Xpert group were to the private sector. Abbreviations: LPA = MDRTB*plus* line probe assay; Xpert = Xpert MTB/RIF; TB = Tuberculosis; IQR = Interquartile Range; Min-Max = Minimum – Maximum. Data on mean visits are presented in the appendix.

Cost to the patient

The total median cost to the patient from symptom onset to MDR-TB treatment initiation was reduced from $68.1 (IQR 32.0-142.0) in the LPA group to $38.3 (IQR 14.1-79.3) in the Xpert group (p=0.004)(Table 3). Median direct costs were $6.7 (IQR $1.1-$28.2) in the LPA group and $4.4 (IQR 0.0-$22.2) in the Xpert group (p=0.321). Median indirect costs were reduced from $40.0 (IQR $20.4-$105.9) in the LPA group to $22.1 (IQR $11.0-$54.5) in the Xpert group (p=0.003).

All patients incurred indirect costs, but only 34 patients (38%) in the LPA group and 22 (34%) in the Xpert group incurred direct medical costs with medians of $22.9 (IQR $17.2-$28.9) and $22.0 (IQR $15.7-$26.0) (p=0.756) respectively. Direct transport cost were incurred by 66 patients (74%) in the LPA group and 41 (64%) in the Xpert group with medians of $5.3 (IQR 2.7-8.1) and $4.6 (IQR 1.6-10.3) (p=0.483) respectively.

For those diagnosed at the pre-treatment diagnostic time-point, the total median cost to the patient was reduced from $49.8 (IQR 23.7-96.4) in the LPA group to $29.0 (IQR 12.5-57.6) in the Xpert group (p=0.004). For those diagnosed whilst on 1st-line TB treatment the total median cost to the patient was $167.6 (IQR 105.1-273.2) in the LPA group compared to $179.4 (IQR 65.8-228.7) in the Xpert group (p=0.531).

In the quantile regression model (see Appendix), sex, HIV status and previous TB were not significantly associated with costs. When adjusting for these potential confounders, there was a reduction of $35.4 (95% CI 6.1-64.7, p=0.018) in median costs in the Xpert group. Cases diagnosed at the pre-treatment diagnostic time-point had a reduction of $23.5 (95% CI $1.7-$45.2, p>0.035) in the Xpert group. There was no significant difference in costs between the groups (p=0.583) for those diagnosed whilst on 1st-line TB treatment. Costs for those diagnosed on 1st-line TB treatment were $102.6 higher (p<0.001) in LPA group and $147.9 higher in the Xpert group compared to those diagnosed pre-treatment in each group.

Table 3: Median Patients Costs in the LPA and Xpert Groups

	N	Median Direct Costs ($) (IQR)				Median Indirect Costs ($) (IQR)				Median Total Cost to Patient (IQR)	
		Transport Costs	Medical Costs	Direct Costs	p-value	Cost of Transport Time	Cost of Time in Health Facility	Indirect Costs	p-value	Total Costs	p-value
LPA Group – all patients	89	3.4 (0-6.9)	0 (0-18.1)	6.7 (1.1-28.2)	0.321	12.3 (6.2-29.6)	23.7 (11.7-64.4)	40.0 (20.4-105.9)	0.003	68.1 (32.0-142.0)	0.004
Xpert Group – all patients	64	1.5 (0-6.5)	0 (0-16.0)	4.4 (0.0-22.2)		4.6 (2.6-14.3)	13.4 (8.2-39.0)	22.1 (11.0-54.5)		38.3 (14.1-79.3)	
LPA Group – Pre-treatment	74	3.2 (0-6.9)	0 (0-18.1)	6.5 (1.1-25.9)	0.345	9.9 (5.8-23.2	19.9 (8.9-46.1)	33.7 (17.5-87.1)	0.005	49.8 (23.7-96.4)	0.004
Xpert Group – Pre-treatment	55	1.5 (0-6.5)	0 (0-15.7)	4.2 (0.0-20.3)		4.0 (2.5-9.9)	12.1 (7.3-30.3)	17.3 (10.9-46.7)		29.0 (12.5-57.6)	
LPA Group - on 1st line TB treatment	15	4.5 (0-6.2)	0 (0-24.1)	27.5 (0.0-30.0)	0.928	54.8 (30.1-91.2)	86.4 (31.9-117.0)	164.7 (76.1-234.5)	0.297	167.6 (105.1-273.2)	0.531
Xpert Group - on 1st line TB treatment	9	3.4 (0-21.7)	0 (0-22.9)	4.6 (0.0-44.6)		25.4 (21.6-46.9)	37.0 (19.1-155.6)	61.3 (46.7-202.4)		179.4 (65.8-228.7)	

Costs and time associated with seeking help were calculated from the onset of symptoms to MDR-TB treatment initiation in South African Rands, adjusted to 2013 values based on the consumer price index, and converted to US$ at a rate of 9.75 (average United Nations Treasury operational rates in 2013). The total cost to the patient is the sum of the direct and indirect costs.

The table shows data for all patients in both groups. However, only 67patients (75%) in the LPA group and 45 (70%) in the Xpert group incurred direct costs, with medians of $20.5 (IQR 5.0 to 30.3) and $12.4 (IQR $3.4 to $30.4) (p=0.462) respectively. Direct medical costs were incurred by 34 patients (38%) in the LPA group and 22 (34%) in the Xpert group with median costs of $22.9 (IQR $17.2 to $28.9) and $22.0 (IQR $15.7 to $26.0) (p=0.756) respectively. Direct transport cost were incurred by 66 patients (74%) in the LPA group and 41(64%) in the Xpert group with median costs of $5.3 (IQR 2.7 -8.1) and $4.6 (IQR 1.6-10.3) (p=0.483) respectively.

Abbreviations: LPA = MDRTB*plus* line probe assay; Xpert = Xpert MTB/RIF; IQR = Interquartile Range

Mean costs are presented in the Appendix.

Change in employment status

From symptom onset to being interviewed the proportion unemployed increased from 39% to 73% in the LPA group (p<0.001) and from 53% to 89% in the Xpert group (p<0.001) (Table 4). In the LPA group 36% lost employment after symptom onset compared to 27% in the Xpert group (p=0.222); 94% in both groups reported this to be directly attributable to having contracted MDR–TB. Both patients who stopped schooling or tertiary education in the LPA group and 6 of the 7 in the Xpert group reported this as attributable to MDR-TB.

Change in individual and household income

In the LPA group, 58% earned an income from employment prior to symptom onset compared to 36% in the Xpert group. Of those earning an income, 67% in the LPA group and 65% in the Xpert group lost income between symptom onset and MDR-TB treatment initiation (Table 4).

Table 4: A Comparison of Employment Status and Individual and Household Income

	LPA Group (n = 89)	Xpert Group (n = 64)	p-value
Number unemployed prior to symptom onset (%)	35 (39%)	34 (53%)	0.091
Number unemployed at time of interview (%)	65 (73%)	57 (89%)	0.015
Median monthly income from salary amongst employed prior to symptom onset ($) (IQR)[1]	228.9 (153.4-330.9)	265.6 (194.7-303.6)	0.628
Median loss of monthly income from salary amongst employed from symptom onset to time of interview ($) (IQR)	224.4 (144.2-320.5)	251.9 (160.3-303.6)	0.719
Number receiving money from any grant pre symptom onset (as % of total)	20 (22%)	17 (27%)	0.560
Of those receiving a grant pre symptom onset: number receiving money from a disability grant (%)	1 (1%)	5 (8%)	-
Additional number receiving money from a disability grant at time of interview (not including those above) [2]	36 (40%)	14 (22%)	0.016
Median monthly grant amount ($) pre symptom onset (IQR)	32.4 (30.9-80.5)	60.7 (30.4-137.3)	0.298
Median monthly additional grant amount at the time of the interview($)[3] (IQR)	123.6 (121.4-125.9)	126.6 (123.1-130.1)	0.593
Median monthly household income from all sources prior to symptom onset ($) (IQR)	259.3 (130.5-427.9) n = 86	356.6 (130.5-618.2) n = 62	0.057
Median monthly household income from all sources at time of interview ($) (IQR)	216.8 (123.6-343.5) n = 86	308.9 (130.1-471.6) n = 60	0.043
Number of households losing monthly household income after symptom onset (reported at time of interview) (%)[4]	33 (38%) n = 86	17 (27%) n = 62	0.165

Where data was incomplete or refers to a subset, we specify the denominator as: n = number reported.
All income or loss thereof was recorded in South African Rands, adjusted to 2013 values based on CPI, and converted to US$ at a rate of 9.75 (average United Nations Treasury operational rates in 2013).
[1]52 patients in the LPA and 23 patients in the Xpert group earned an income from their occupation prior to symptom onset and 52 in the LPA and 22 in the Xpert groups were able to report their income.
[2] 19 previously employed patients in the LPA group and 4 in the Xpert group received a monthly disability grant of $129.2
[3]Additional grants were all temporary disability grants linked to their illness.
[4]All households losing income lost >10% of monthly household income.
Abbreviations: LPA = MDRTB*plus* line probe assay; Xpert = Xpert MTB/RIF; IQR = Interquartile Range; MDR-TB = Multidrug Resistant Tuberculosis.

Before symptom onset, 20 (22%) patients in the LPA group and 17 (27%) in the Xpert group received money from a social grant, of which 1 in the LPA group and 5 in the Xpert group comprised a temporary or

permanent disability grant (Table 4). At the time of the interview an additional 36 (40%) in the LPA group and 14 (22%) in the Xpert group (p=0.016) received temporary disability grants, linked to their illness.

In both groups 97% knew or could estimate their monthly household income with 38% in the LPA group and 27% in the Xpert group losing >10% of monthly household income between symptom onset and time of the interview (Table 4). Overall there was a 16% decrease in median household income in the LPA group compared to 13% in the Xpert group.

DISCUSSION

This study compared costs incurred by MDR-TB patients in an existing LPA-based diagnostic algorithm to that in a newly introduced Xpert-based algorithm from the reported onset of symptoms to MDR-TB treatment initiation. The number of health visits (and thus costs) was expected to decrease in the Xpert-based algorithm for two reasons: first, Xpert provided a quicker drug susceptibility testing (DST) result than LPA (median <1 day compared to 24 days to a result being available in the laboratory[19]); thus fewer patients would be started on first-line anti-tuberculosis treatment while awaiting a DST result. Second, all presumptive TB cases were simultaneously screened for TB and underwent DST in the Xpert group; in comparison, those at low risk of MDR-TB in the LPA group only underwent DST when first-line anti-tuberculosis treatment failed (usually after 2–3 months of treatment). An algorithm where all presumptive cases are tested for drug resistance, irrespective of the test used, will reduce the number of pre-treatment visits due to earlier identification of drug resistance for many patients.

The introduction of the Xpert-based algorithm led to a reduction in the number of pre-treatment health care visits from a median of 20 in the LPA group to 7 in the Xpert group. However, the number of visits remains high, particularly for patients diagnosed while on first-line treatment. A large contributor to this was DOT visits while awaiting a DST result. Visits to private practitioners (similar in both algorithms) and to health centres not offering anti- tuberculosis treatment increased the number of pre- treatment visits, as patients often made several visits, were not appropriately tested and had to eventually be referred for MDR-TB testing and/or treatment.

There was a significant reduction in median costs for patients in the Xpert group, from US$68.1 to US$38.3. As direct medical costs were similar in both groups (all related to private sector care, as public sector services were free) and travel costs were low, this was largely attributable to indirect costs related to time spent in travel and at the health care facility. Other TB costing studies have also found higher indirect than direct costs.[17,18]

Improved health system efficiencies with the Xpert-based algorithm can help to further reduce indirect costs. To achieve this, health care professionals need to adhere to the testing algorithm, and health delivery issues, such as leaking sputum containers, broken fax machines and mislaid results need to be minimised to eliminate unnecessary pre-treatment visits.

Other studies have found income loss to be the largest financial burden faced by patients contracting TB.[14] We found a high proportion of patients in both algorithms who lost both employment and income due to illness, highlighting the devastating impact MDR- TB can have on a patient's livelihood, irrespective of the

speed at which they are diagnosed. 'Catastrophic' costs[14] were experienced by 38% in the LPA group and 27% in the Xpert group who lost >10% of monthly household income. A controlled follow-up study is required to assess the long-term economic consequences of early diagnosis; given the poor treatment outcomes for MDR-TB,[27] these are likely to be severe.

When estimating costs, different approaches may influence the cost estimate. In this study, indirect costs for patient's time were calculated for all patients based on a basic municipal worker wage. This may have overestimated indirect costs for unemployed patients, although the effect may be counterbalanced, as the study did not cost unpaid work in the household or costs to the unemployed who lost time that could have been used to seek employment.

There are also alternative methods of calculating indirect costs—we have used the traditional human capital method, which assumes a loss equivalent to the productivity that could have occurred in the time lost, using hourly wages to value this productivity.[28] Alternative methods, such as the friction cost approach,[29] assumes some reorganisation to minimise disruption (e.g., individuals substituting leisure time for paid or unpaid work). Our approach may therefore overstate indirect costs by not accounting for such flexibility, although it is not possible to quantify the impact of this method.

Strengths and Limitations

As patients were interviewed 3–6 months after the start of MDR-TB treatment, recall bias may have influenced findings. A strength of our study was that we were able to triangulate visit data from patient interviews with clinical records, which is likely to have reduced reporting bias.

However, the study had limitations. First, this was an observational study conducted in routine operational conditions. Temporal changes such as the full decentralisation of MDR-TB treatment may have contributed to the findings. Second, the patients sampled were not representative of all MDR-TB patients. Cases who did not start treatment (initial defaulters) were not included. To reduce the risk of infection to researchers, only patients who had been on MDR-TB treatment for at least 3 months and had smear converted were interviewed. Patients who were lost to follow-up, which may have been influenced by the high cost of illness, or had failed to smear convert were not included. Healthier people were thus more likely to be interviewed, which may have underestimated costs, but this is unlikely to have differed between the two algorithms. Third, we did not assess coping strategies that patients may have resorted to, such as the sale of assets and borrowing. Finally, we have not assessed visits or costs based on clinic performance, as the clinic ranking changed each year and the number of patients was too small. The study included the early phase of Xpert implementation, which may have increased the median number of pre-treatment visits in the Xpert group as staff became familiar with the new algorithm and adjusted to new practices.

Implications of Study Findings

Given the high loss of employment attributable to developing MDR-TB, many of these patients and their households are in need of financial support. There have been international calls by the World Health Organization and the International Labour Office for countries to invest in social protection mechanisms such as income replacement and social support for those affected by illness.[30]

Although disability grants (monthly value US$129.2) are available to support MDR-TB patients and offer a measure of income replacement, access to these was poor, with fewer patients receiving a disability grant at the time of the interview in the Xpert (22%) than in the LPA group (40%). This may reflect the time it takes to process a grant, and it may not yet have taken place for those diagnosed in the Xpert-based algorithm. Expedited access to disability grants is required: the provision of unconditional disability grants could be considered for diseases such as MDR-TB, as the means-testing process (undertaken by a doctor) contributes to delay. On a positive note, the low direct medical costs incurred by patients bear testimony to the social protection offered by the free public health services in South Africa.

CONCLUSION

Assessing the economic relief to patients and their households is important in understanding the impact of new molecular TB diagnostics. This study has shown that the introduction of an Xpert-based algorithm brought relief by reducing patient costs, mostly by reducing the number of visits before treatment initiation. Improved health service efficiencies can help further reduce costs.

There is a strong link between TB and poverty.[1,31] In our setting, although MDR-TB diagnosis and treatment are free and easily accessible, the economic impact of MDR-TB was considerable, with many patients losing both employment and individual and household income. It is important for health planners to be cognisant of the fact that, irrespective of how quickly treatment is initiated with a rapid MDR-TB test, a high number of patients will be vulnerable to the effects of increased poverty. Increased efforts need to be made to break the poverty-illness cycle.

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Conflicts of interest:

The authors declare that there are no conflicts of interest

Author contributions:

EdT, SBS, NB and PN were involved in the study design, EdT, PN in the data collection, EdT, RD, RM, JM in the data analysis, EdT, SBS, RD, RM, JM, NB, and PN in writing the manuscript

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Appendix

Quantile Regression Model Outputs for Number of Healthcare Visits and Patient Costs

Variable	Coefficient	Standard Error	p-value	95% Confidence Interval
Adjusted Data for Median Number of Healthcare Visits – All patients				
Xpert Group	-11.9	4.5	0.009	-20.8 to -3.1
Sex	5.4	4.5	0.224	-3.4 to 14.3
HIV status	-0.9	4.5	0.843	-9.8 to 8.0
Age	-0.1	0.2	0.742	-0.5 to 0.4
Previous TB	-0.4	4.4	0.921	-9.2 to 8.3
Constant	20.8	9.2	0.026	2.5 to 39.1
Adjusted Data for Median Number of Healthcare Visits – Patients at Pre-treatment Diagnostic Time Point				
Xpert Group	-9.6	2.7	0.001	-14.9 to -4.2
Sex	2.3	2.7	0.401	-3.1 to 7.6
HIV status	-0.1	2.7	0.979	-5.4 to 5.3
Age	-0.1	0.1	0.524	-0.4 to 0.2
Previous TB	1.8	2.7	0.509	-3.5 to 7.1
Constant	17.2	5.8	0.004	5.6 to 28.7
Adjusted Data for Median Number of Healthcare Visits – Patients at Treatment Diagnostic Time Point				
Xpert Group	-13.4	26.8	0.624	-69.8 to 43.0
Sex	16.6	24.7	0.510	-35.3 to 68.5
HIV status	15.7	25.4	0.545	-37.7 to 69.2
Age	-0.9	1.1	0.405	-3.3 to 1.4
Previous TB	57.9	35.2	0.117	-16.0 to 131.8
Constant	88.7	42.2	0.050	0.1 to 177.3
Adjusted Median Patient Cost Data ($) – All patients				
Xpert Group	-35.4	14.8	0.018	-64.7 to -6.1
Sex	9.4	14.7	0.524	-19.7 to 38.5
Previous TB	-15.2	14.6	0.298	-44.0 to 13.6
HIV status	-0.7	15.0	0.962	-30.4 to 28.9
Constant	74.3	16.5	<0.001	41.7 to 107.0
Adjusted Median Patient Cost Data ($) – Patients at Pre-treatment Diagnostic Time Point				
Xpert Group	-23.5	11.0	0.035	-45.2 to -1.7
Sex	7.3	10.9	0.506	-14.3 to 28.8
Previous TB	1.9	10.8	0865	-19.6 to 23.3
HIV status	-1.7	11.1	0.880	-23.6 to 20.3
Constant	48.8	12.9	<0.001	23.2 to 74.3
Adjusted Median Patient Cost Data ($)– Patients at Treatment Diagnostic Time Point				
Xpert Group	-55.4	99.1	0.583	-262.8 to 152.1
Sex	48.8	90.3	0.595	-140.3 to 237.9
Previous TB	114.1	130.2	0.392	-158.4 to 386.5
HIV status	3.4	92.7	0.972	-190.7 to 197.4
Constant	121.2	86.8	0.179	-60.5 to 302.9
Adjusted Median Cost Comparison at the different Diagnostic Time Points in the LPA-based Algorithm				
On 1st line TB treatment	102.6	25.0	<0.001	52.8 to 152.4
Constant	69.2	21.3	0.002	26.8 to 111.6
Adjusted Median Cost Comparison at the different Diagnostic Time Points in the Xpert-based Algorithm				
On 1st line TB treatment	147.9	24.3	<0.001	99.3 to 196.5
Constant	14.6	15.5	0.349	-16.4 to 45.6

Mean Number of Healthcare Visits in the LPA and Xpert Groups

	Mean	95% CI	SD	p-value
LPA Group - all patients (n=89)	36.2	27.6 - 44.8	40.9	0.005
Xpert Group - all patients (n=64)	19.7	12.2 - 27.2	30.1	
LPA Group – pre-treatment (n=74)	25.9	18.6 - 33.2	31.6	0.001
Xpert Group –pre-treatment (n=55)	11.5	7.7 - 15.3	14.1	
LPA Group – on 1st line TB treatment (n=15)	86.9	62.2 – 111.6	44.6	0.390
Xpert Group - on 1st line TB treatment (n=9)	69.7	31.1 - 108.3	50.2	

The table shows unadjusted data. Healthcare visits include all visits to both the public and private health sector. Visits for directly observed therapy (DOT) are included for patients on a 1st line TB regimen, either whilst awaiting drug susceptibility test results or for those diagnosed whilst on 1st line TB treatment. Only 1.4% of visits in the LPA group and 3.2% in the Xpert group were to the private sector. Abbreviations: LPA = MDRTB*plus* line probe assay; Xpert = Xpert MTB/RIF; TB = Tuberculosis; CI = Confidence Interval; SD = Standard Deviation

Chapter 8: Comparing laboratory costs of smear/culture and Xpert® MTB/RIF-based tuberculosis diagnostic algorithms

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ABSTRACT

Setting: Cape Town, South Africa, where Xpert® MTB/RIF was introduced as a screening test for all presumptive tuberculosis (TB) cases.

Study Aim: To compare laboratory costs of smear/culture- and Xpert-based TB diagnostic algorithms in routine operational conditions.

Methods: Economic costing was undertaken from a laboratory perspective, using an ingredients-based costing approach. Cost allocation was based on reviews of standard operating procedures and laboratory records, timing of test procedures, measurement of laboratory areas and manager interviews. We analysed laboratory test data to assess overall costs and cost per pulmonary TB and multidrug-resistant TB (MDR-TB) case diagnosed. Costs were expressed as 2013 Consumer Price Index-adjusted values.

Results: Total TB diagnostic costs increased by 43% from $440,967 in the smear/culture-based algorithm (April-June 2011) to $632,262 in the Xpert-based algorithm (April-June 2013). The cost per TB case diagnosed increased by 157% from $48.77 (n=1601) to $125.32 (n=1281) respectively. The total cost per MDR-TB case diagnosed was similar at $190.14 and $183.86 with 95 and 107 cases diagnosed in the respective algorithms.

Conclusion: The introduction of the Xpert-based algorithm resulted in substantial cost increases. This was not matched by the expected increase in TB diagnostic efficacy, calling into question the sustainability of this expensive new technology.

INTRODUCTION

New molecular diagnostic tests for tuberculosis (TB) such as GenoType® MTBDR*plus* line probe assay (Hain LifeScience GmbH, Nehren, Germany) (LPA) and Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) (Xpert) hold the promise of improving TB and multidrug-resistant (MDR)-TB diagnosis as both are sensitive and faster than culture and conventional drug susceptibility tests (DST). The accuracy of these tests is well established from laboratory and demonstration studies.[1,2] A meta-analysis of ten LPA studies showed high sensitivity (98.1% (95% confidence interval (CI) 95.9-99.1)) and specificity (98.7% (95% CI 97.3-99.4)) for rifampicin (RMP) resistance and lower, more variable sensitivity of 84.3% (95% CI 76.6-89.8) and specificity of 99.5% (95% CI 97.5-99.9) for isoniazid resistance.[3] A Cochrane Review of fifteen studies where Xpert was used as the initial test replacing smear microscopy, showed a pooled sensitivity of 88% (95% credibility interval [CrI] 83%-92%) and specificity of 98% (95% CrI 97%-99%) for detecting *Mycobacterium tuberculosis*. In eleven of these studies, pooled sensitivity was 94% (95% CrI 87%-97%) and specificity 98% (95% CrI 97%-99%) for RMP resistance.[4]

Policy recommendations[5,6] have been based mainly on accuracy data from laboratory and demonstration studies.[7–9] However demonstration studies tend not to reflect the realities of a test being used within an operational context.[8,9] There is a tendency towards overestimation of effectiveness partly due to greater resource availability than would be found in routine settings[8]. Insufficient emphasis is placed on costs and an overestimation of effectiveness may provide a more optimistic view of cost-effectiveness than would be found in routine settings.

Cost estimates are essential to making decisions on the most effective use of limited resources. One of the challenges to evaluating costs and cost-effectiveness is the lack of standard accepted evaluation methods.[10,11] Current guidelines are too broad and generalised and poor adherence to guidelines contributes to the failure to provide consistent and comparable cost data to policy makers.[12] For example, two studies in South Africa reported Xpert costs of $25.90 (in 2010 $US)[13] and $14.93 (in 2012 US$)[14] respectively. Differences in costs were partly attributable to the exclusion of cartridge shipping costs and specimen transport costs in the latter.

A guideline on laboratory costs[15] emphasises the importance of an ingredients-based approach to costing that includes all resource elements, including quality assurance and control. It emphasises the need to accurately allocate overhead costs and deal with capital assets in a way that takes “time preference” into account i.e. that $1 in 2 years is worth less than $1 today, reflecting a societal and individual preference to have money and resources today rather than in the future. Capital costs need to be discounted to reflect this preference.[16]

Xpert is an expensive test and making the case for additional expenditure requires empirical data to supplement the estimates used in decision-making. Operational data can help improve the reliability of estimates used in cost and cost-effectiveness analyses and is particularly important in high-burden settings with resource constraints.

The aim of the present study was to compare laboratory costs for the diagnosis of pulmonary TB (PTB) and MDR-TB in a new Xpert-based algorithm to that in the previous smear/culture-based algorithm in a routine

operational context. The study was part of a PROVE IT (Policy Relevant Outcomes from Validating Evidence on ImpacT) evaluation (http://www.treattb.org/) to assess the impact of new molecular diagnostic tests.

METHODS

Setting

The study was undertaken in Cape Town, South Africa, a city with a high TB and MDR-TB burden with 28,644 TB cases (752/100,000 population) and 1,020 MDR-TB cases notified in 2011. In comparison, 25,846 TB cases (663/100,000 population) and 1,134 MDR-TB cases were notified in 2013. Human immunodeficiency virus (HIV) co-infection rates amongst TB cases were 47% (97% tested) and 44% (98% tested) in respective years (Source: J. Caldwell, Routine TB Programme Data, Cape Town Health Directorate, April 2016).

Free TB diagnostic services were provided at 142 primary health care facilities in eight sub-districts. All sputum specimens collected at primary health care facilities were sent by courier to the National Health Laboratory Services (Cape Town, South Africa). Test results were entered into a networked, electronic laboratory database.

TB diagnostic algorithms

A smear/culture-based algorithm (Figure 1) was used in the 'comparator' period (April–June 2011 = T1). All presumptive TB cases were evaluated using smear microscopy from two spot sputum specimens taken 1 h apart. In high MDR-TB risk cases (>4 weeks of previous anti-tuberculosis treatment, from congregate settings or with an MDR-TB contact), the second specimen underwent liquid culture (BACTEC™ MGIT™ 960; BD, Sparks, MD, USA) and DST using the GenoType® MTBDR*plus* LPA and second-line testing, as required. Smear-negative, HIV-infected, low MDR-TB risk cases were required to submit a third specimen for culture.

An Xpert-based algorithm was used in the 'intervention' period (April–June 2013 = T2), with Xpert replacing smear microscopy for all presumptive TB cases (Figure 1). Two sputum specimens were evaluated: the first was tested with Xpert; if M. tuberculosis was detected, the second underwent smear microscopy. In HIV-infected cases with negative Xpert tests, the second specimen underwent culture. Confirmatory LPA and second-line DST were undertaken for cases with RMP resistance.

Costing methods

Economic costing was undertaken from a laboratory perspective for the high throughput central laboratory in Cape Town. Only costs related to the dedicated TB laboratory were assessed. Costs were calculated from the time the courier collected specimens from health facilities to the time results were returned. Costs were assessed only for PTB tests for smear, culture, LPA and Xpert.

An Excel-based costing tool was developed (Microsoft, Redmond, WA, USA), based on that used in the Foundation for Innovation and Development (FIND) GenoType® MTBDR*plus* demonstration study. We used an ingredients-based costing approach, with test costs based on the cost per unit and quantities utilised for

buildings, equipment, consumables, staff and overheads. Cost allocation was determined using reviews of standard operating procedures and laboratory records, direct observation and timing of the test procedures outlined in Figure 2, measurement of laboratory areas used for test processes and interviews with managers. Quality assurance samples were included in batch costs and outputs adjusted accordingly.

Building costs per square metre, including air conditioning and consoles, were provided by the Council for Scientific and Industrial Research, Pretoria, South Africa, for a Level 2 laboratory for 2013. Equipment and consumables costs were sourced from laboratory financial records and quotes from suppliers for 2013. These costs were corrected by the consumer price index (CPI) to derive 2011 costs.[17] Staff and overhead costs were provided from laboratory financial records for both years. 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. Further information on costs is provided in Appendix Tables A.1 and A.2 and Appendix Figure A.*[3] Building and equipment costs were spread over their expected lifespan and discounted to present values at a 'risk- free' rate of 3%,[11,18] with maintenance based on expenditure or estimated at 10% of annual costs. Laboratory utilisation was based on a 10 h week day for 21 days per month and a 4 h Saturday shift. The cost of staff time was based on a 40 h week for 46 weeks of the year, with efficiency estimated at 80%.

All costs were calculated in local currency (South African rand [ZAR]). For comparative purposes, 2011 costs were expressed as 2013 CPI-adjusted values and converted to US$ based on average United Nations treasury operational rates in 2013 (ZAR9.75=US$1.00).[19]

Study population and analysis

All sputum specimens processed in the laboratory in T1 (smear/culture-based algorithm) and T2 (Xpert-based algorithm), and resources related to the processing of these specimens, were included in the assessment of laboratory and test costs. Overall laboratory costs were based on the cost per test and test volumes for microscopy (bleach-treated specimens), microscopy and culture, LPA and Xpert.

We used laboratory data for presumptive PTB cases from five of the eight subdistricts to estimate the cost per TB and MDR-TB case diagnosed. These subdistricts were included in a previous analysis of TB yield and their selection criteria have been described elsewhere.[20] The analysis required the full sequence of tests undertaken for presumptive TB cases. We therefore identified cases with specimens submitted in May 2011 and May 2013, and linked all diagnostic tests from the preceding and following months to identify the full sequence of tests undertaken for each case. Linkage was undertaken with MS-SQL, using a combination of facility name, patient folder number, name, surname and age or date of birth.

[3] The appendix is available in the online version of this article, at http://www.ingentaconnect.com/content/iuatld/ijtld/2016/00000020/000000010/art00022

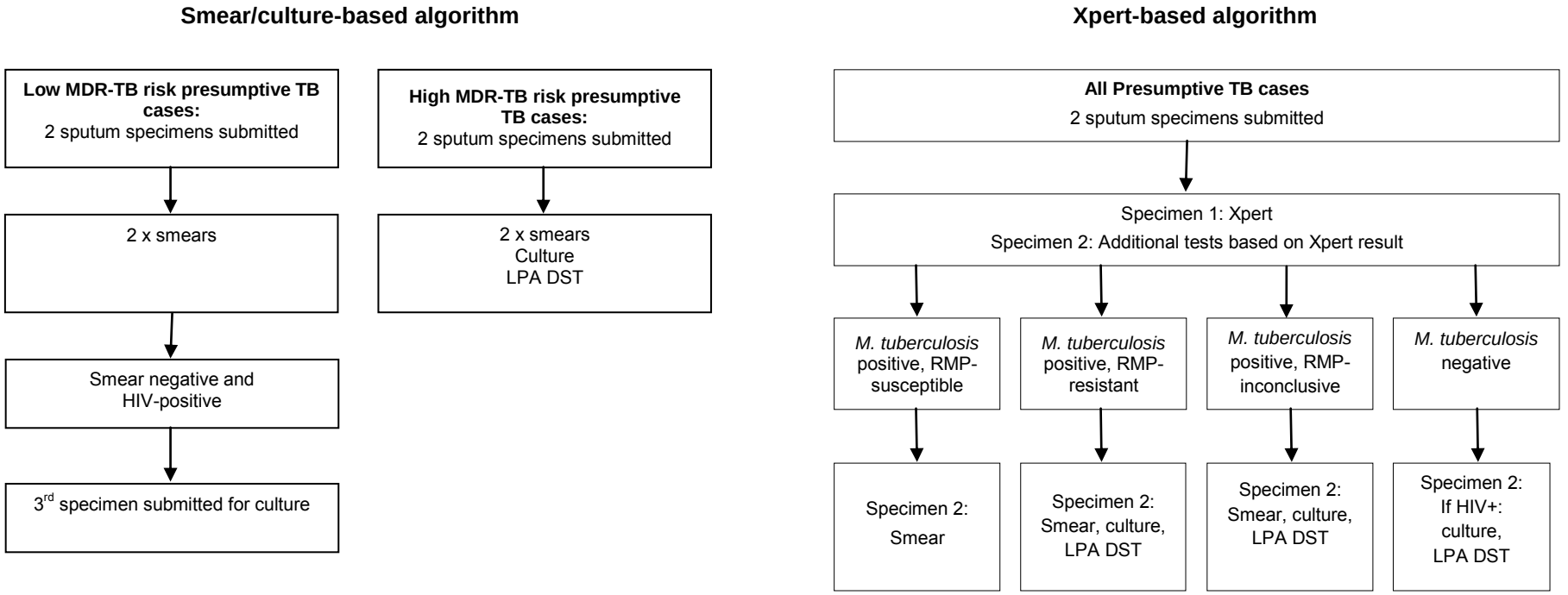
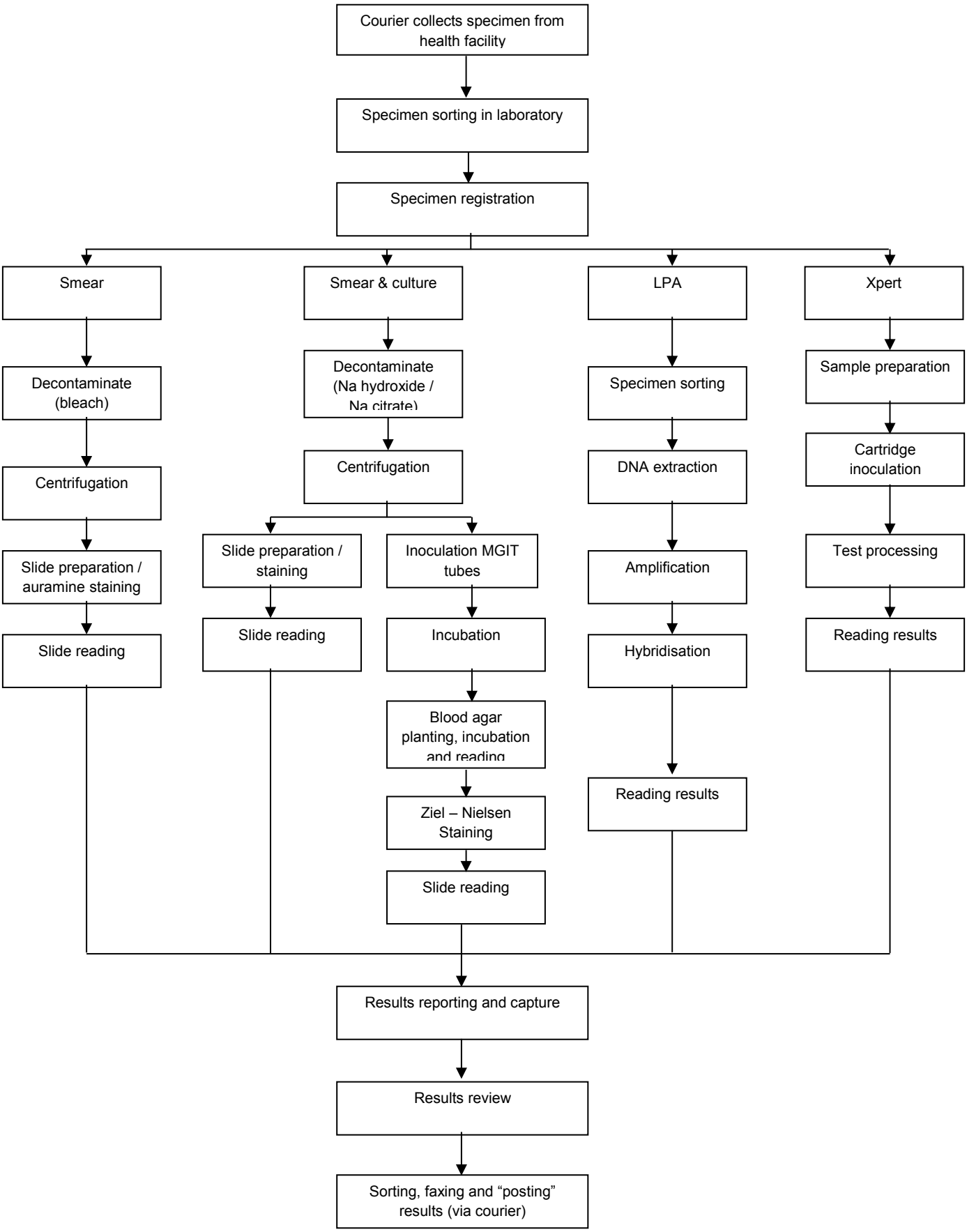


Figure 1: Testing protocols in TB diagnostic algorithms. The simplified sequence of diagnostic tests in each algorithm and the action taken based on test results is shown. MDR-TB = multidrug-resistant TB; TB = tuberculosis; LPA = line-probe assay (GenoType® MTBDR*plus*); DST = drug susceptibility testing; HIV = human immunodeficiency virus; RMP = rifampicin. Reprinted from Naidoo et al.[20]

Figure 2: Laboratory workflow and test processes



We defined a TB case as an individual with one or more smears positive and/or culture positive for *M. tuberculosis* and/or *M. tuberculosis* detected using Xpert. An MDR-TB case was defined as an individual with RMP resistance on LPA or Xpert. We compared the mean cost per patient diagnosed with TB and MDR-TB in each algorithm. MDR-TB costs were reported as additional to a TB diagnosis.

Ethics statement

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

RESULTS

Comparison of total laboratory costs and activities

In T1, 79 544 specimens were tested at the central laboratory compared to 59 238 in T2. The majority (96% and 94% respectively) were for PTB tests.

Total laboratory costs for PTB tests increased from $440 967 in T1 to $632 262 in T2 (Table 1). Costs for bleach treated smears decreased by 49% from $128 916 to $65 799; smear and culture costs decreased by 35% from $247 771 to $161 707 and LPA by 50% from $64 279 to $32 339, all driven by reduced test volumes. The increase in total cost was attributable to the Xpert test which accounted for 59% of total laboratory costs in the Xpert-based algorithm.

Annual overhead costs increased by 12% from $137 101 in T1 to $153 628 in T2. The largest contributors to the increase were specimen transport costs, utilities, biohazardous waste and janitorial services (Appendix). Overhead costs were allocated based on test volume as this was identified as the key driver for these costs. Overhead costs per test were increased by 47% from $1.80 in the smear/culture-based algorithm to $2.63 in the Xpert-based algorithm, due to both increases in overhead costs and reductions in test volumes.

Comparison of test costs

Smear microscopy costs (per bleach-treated specimen) increased from US$2.85 in the smear/culture- based algorithm to US$3.70 in the Xpert-based algorithm. Overhead costs were the main driver, accounting for 63% of costs in the smear/culture- based algorithm and 71% in the Xpert-based algorithm.

Microscopy and culture costs (per sodium hydroxide [NaOH]/sodium citrate-treated specimen) increased from US$8.75 in the smear/culture-based algorithm to US$9.62 per test in the Xpert-based algorithm. Consumables (44% and 40% in the respective algorithms), staff costs (respectively 25% and 23%) and overheads (respectively 21% and 27%) were the key cost drivers. The highest cost component for consumables was for BACTEC MGIT tubes and supplement.

MTBDR*plus* LPA costs per test were similar, at US$16.12 in the smear/culture-based algorithm and US$16.98 per test in the Xpert-based algorithm. Most tests were performed on culture isolates, and culture costs have not been included in these totals. Consumables were the greatest cost driver (79% and 75% in the respective algorithms), due mostly to the cost of the GenoType® MTBDR*plus* kit.

The Xpert cost per test was $19.03. The largest cost driver was consumables (77%), due mostly to the cost of the Xpert MTB/RIF cartridges (Table 1).

Table 1: Comparison of test costs in the smear/culture and Xpert-based algorithms

		Smear microscopy (Bleach treated)	**Smear microscopy & culture**	**Culture confirmation**	**MTBDR*plus* Line Probe Assay**	**Xpert MTBRif**
Smear/culture-based algorithm (April – June 2011)(T1)	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**	-
	Number of tests	45 252	27 508	4 747	3 987	-
	Total costs	**$128 916**	**$240 706**	**$7 065**	**$64 279**	-
Xpert-based algorithm (April – June 2013)(T2)	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**
	Number of tests	17 770	16 503	2 020	1 905	19 565
	Total costs	**$65 799**	**$158 700**	**$3 007**	**$32 339**	**$372 418**

Test costs and volumes are for the central National Health Laboratory only. Total laboratory costs were $440,967 in the smear-culture-based algorithm compared to $632,262 in the Xpert-based algorithm for respective 3-month periods. All costs are expressed in 2013 CPI-adjusted values.

Cost per tuberculosis case diagnosed

In May 2011, 7842 presumptive TB cases were tested using the smear/culture-based algorithm. The full sequence of tests for these individuals included 10 472 bleach-treated microscopy tests, 5347 NaOH/ sodium citrate-treated microscopy and culture tests and 980 tests for *M. tuberculosis* culture confirmation, at a total cost of US$78 080. The mean cost per TB case diagnosed (n = 1601) was US$48.77 (Table 2).

Table 2: Costs per pulmonary TB and MDR-TB case diagnosed in the smear/culture and Xpert-based algorithms

	Costs in the smear/culture-based algorithm	Costs in the Xpert-based algorithm	Changes with the Xpert-based algorithm
Smear microscopy (Bleach treated)	$29 833.23 (n=10,472)	$10 038.29 (n=2,711)	-$19 794.94
Smear microscopy & culture (Sodium hydroxide/sodium citrate-treated)	$46 788.44 (n=5,347)	$35 475.12 (n=3,689)	-$11 313.32
Culture confirmation	$1 458.51 (n=980)	$641.53 (n=431)	-$816.98
Xpert MTB Rif	_	$114 380.73 (n=6,009)	$114 380.73
Total TB diagnostic costs	$78 080.18	$160 535.67	$82 455.50
Number of presumptive TB cases evaluated	7 842	7 714	-128
Number TB cases identified	1 601	1 281	-320
Mean cost per TB case identified	$48.77	$125.32	$76.55
Total costs for MTBDR*plus* Line Probe Assay	$13 429.75 (n = 833)	$6 264.02 (n = 369)	-$7 165.73
Number of MDR-TB cases diagnosed	95	107	12
Mean additional cost per MDR-TB case diagnosed	$141.37	$58.54	-82.82
Mean total cost per MDR-TB case diagnosed	$190.14	$183.86	-$6.27

In May 2013, 7714 presumptive TB cases were tested using the Xpert-based algorithm. The full sequence of tests for these individuals included 2711 bleach-treated microscopy tests, 3689 NaOH/sodium citrate-treated microscopy and culture tests, 431 tests for M. tuberculosis culture confirmation and 6009 Xpert tests, at a total cost of US$160 536. The mean cost per TB case diagnosed (n = 1281) was US$125.32.

The cost per TB case is influenced by the proportion of TB cases identified, which decreased in the Xpert-based algorithm, probably due to a decline in prevalence (see Discussion for further details). We assessed a scenario where TB diagnostic yield in the Xpert-based algorithm was similar to that in the smear/culture-based algorithm, which reduced the cost per TB case diagnosed to US$101.94.

Cost per MDR-TB case diagnosed

There were 833 LPA tests done for TB cases in the smear/culture-based algorithm at a cost of $13 430 and mean additional cost per MDR-TB case (n = 95) of $141.37 (Table 2). In comparison 369 LPA tests were done amongst TB cases in the Xpert-based algorithm at a cost of $6264 and mean additional cost per MDR-TB case (n=107) of $58.54. When these costs were added to the “base” cost of the TB diagnosis, the total cost per MDR-TB case diagnosed was $190.14 in the smear-culture-based algorithm compared to $183.86 in the Xpert-based algorithm.

As our prior analysis showed no difference in TB yield between the algorithms[20], we apportioned all additional costs to the additional MDR-TB cases diagnosed. This produced an incremental cost-effectiveness ratio (ICER) of $6274 per additional MDR-TB case diagnosed.

DISCUSSION

The use of the more sensitive Xpert test[4,21,22] as a replacement for smear microscopy was expected to increase the number of TB cases diagnosed, and simultaneous drug-susceptibility screening for all presumptive TB cases (not only those at high MDR-TB risk) expected to increase the number of MDR-TB cases diagnosed. A modelling study in South Africa, estimated that at full coverage Xpert would increase annual TB diagnostic costs by 53-57% to $48-70 million per year but that this would be partially offset by a 30% to 37% increase in TB and 69 to 71% increase in MDR-TB cases diagnosed annually.[23]

Our study found a 43% increase in PTB laboratory costs, from US$440 967 in the smear/culture-based algorithm to US$632 262 in the Xpert-based algorithm for each 3-month period. However, the increase in laboratory costs was not matched by an increase in TB diagnostic efficacy. Although the number of presumptive TB cases evaluated was similar in the smear/culture (n = 7842) and Xpert-based algorithms (n = 7714), the proportion of TB cases diagnosed (yield) decreased from 20.4% (n = 1601) to 16.6% (n = 1281). A previous stepped-wedge analysis undertaken as part of PROVE IT for 2010–2013 showed a temporal decline in TB diagnostic yield in both algorithms.[20] This may have been partly attributable to a declining TB prevalence, possibly due to the rapid scale-up of antiretroviral treatment in South Africa. When estimates were adjusted for the temporal trend, the study showed no significant difference in TB yield between the algorithms.

The increase in total costs and the decrease in the number of cases identified in the current study increased the cost per TB case diagnosed by 157%, from US$48.77 in the smear/culture-based algorithm to US$125.32 in the Xpert-based algorithm. On the other hand, even a scenario with a similar proportion of TB cases identified in the Xpert-based algorithm to that in the smear/culture-based algorithm would increase the cost per TB case diagnosed by 109%, to US$101.94.

The cost per MDR-TB case diagnosed was similar, at US$190.14 in the smear/culture based algorithm and US$183.86 in the Xpert-based algorithm. In the smear and culture-based algorithm, DST was only undertaken in high MDR-TB risk presumptive TB cases. One of the advantages of Xpert is that it provides simultaneous screening for TB and RMP resistance. The use of Xpert for all presumptive TB cases contributed to the 13% increase in the number of MDR-TB cases identified. While these additional cases may have been diagnosed later in the smear/ culture-based algorithm (i.e., after first-line treatment failed), early diagnosis potentially reduces transmission, prevents the amplification of drug resistance and reduces patient morbidity and mortality. This modest benefit has to be weighed against the heavy overall expenditure, as shown by the MDR-TB ICER of US$6274. This figure needs to be viewed with some caution, as possible changes in TB, and thus MDR-TB prevalence, have not been taken into consideration. Additional studies are required to assess whether Xpert or another method of DST can be targeted more cost-effectively.

The cost-effectiveness of newly introduced laboratory tests is influenced by how these services are re-organised and whether underutilised assets can be redeployed. In the short-term it may be difficult to reduce costs until new systems and workloads are well established; however, in the future, efforts could be made to reduce overhead costs. Overhead costs per test could be reduced by increasing test volumes, through additional case-finding efforts, for example. However, consumable costs were by far the greatest cost-drivers, accounting for 40% and 60% of total costs in the respective algorithms. It remains to be seen whether global increases in test volumes or the availability of generic tests can reduce these costs substantially.

Strengths and limitations

The major strength of the analysis was that we collected detailed information to accurately estimate the cost per TB and MDR-TB case diagnosed. By including the full sequence of tests undertaken for individuals, we were able to make the analysis reflect real-life variations found in diagnostic practices, including, for example, additional culture testing for smear- and Xpert-negative cases in the respective algorithms.

The extent to which our results can be generalised is limited by the setting, as Cape Town has a relatively good laboratory and health infrastructure. Additional evidence is required from poorly resourced settings, including areas where culture is not available, as the benefit of Xpert may be greater in areas that previously used only smear microscopy, and from rural settings, where specimen transport costs may be higher, economies of scale cannot be readily achieved and expertise may differ. The possible difference in TB prevalence between the two time periods is a limitation, and has been taken into consideration in the analysis. The analysis was undertaken from a laboratory perspective only; the impact of new molecular diagnostic tests on patient costs is important, and has been reported elsewhere.[24]

Implications for policy and practice

The increase in total laboratory costs is in a similar range to that projected by two South African studies.[13,23] However, we did not find the expected increases in TB yield. Our findings are in keeping with a national study showing an 8% reduction in the number of laboratory-confirmed PTB cases from 2011 to 2012, despite the introduction of Xpert.[25] Even when temporal trends of a possible declining prevalence were taken into account in our study, costs remained high. It is difficult to justify the increased laboratory costs incurred due to the introduction of Xpert, and cost implications should not be underestimated. If the US$160 411 spent on TB diagnosis in the Xpert-based algorithm was used for testing as per the smear/culture-based algorithm, the number of presumptive TB cases screened could have been increased by over 100%, from 7714 to 16 158.

There is strong impetus to increase the use of Xpert. To mid-2014, 7.5 million Xpert cartridges had been procured internationally, with more than half being procured by South Africa.[26] However, the broader impact of Xpert remains questionable. Although studies have reported early TB[21,27,28] and MDR-TB[29,30] treatment initiation, Xpert had no impact on TB morbidity and mortality.[27,31,32] This, together with the increased costs, warrants a review of the role of Xpert in TB diagnosis.

Having invested heavily in this new technology, reversion to a smear/culture-based algorithm is unlikely. Thus, either technical adjustments need to be sought to improve Xpert sensitivity and/or the price of Xpert has to be substantially reduced to improve cost-effectiveness in our setting. Urgent efforts need to be made to optimise costs through improved efficiency of the Xpert-based algorithm, including exploring alternative options. Theron et al., for example, showed that pre-screening with smear reduced the cost of a TB diagnosis in their model by more than 20%.[33] A discrete event simulation model has been developed and validated as part of PROVE IT, and will be used to evaluate more cost-effective diagnostic options.

This study highlights the need for thorough costing during early implementation to inform scale-up. As new diagnostic technologies become available, consideration should also be given to the wider costs of serial implementation of different technologies, over- lapping of different technologies and redundancies that are created when existing technologies are also retained.[9]

CONCLUSION

Economic costing is a key component in the decision to implement new TB diagnostic tests, and careful consideration should be given to cost implications, particularly in resource-constrained, high-burden settings. The introduction of the Xpert-based algorithm has resulted in substantial increases in cost, which are in line with modelling exercises under- taken in South Africa. However, these were not matched by an increase in TB diagnostic efficacy; massive cost increases persist even when temporal trends of a possible declining TB prevalence were taken into consideration. One of the benefits of the Xpert-based algorithm was the modest increase in the number of MDR-TB cases diagnosed, which comes at high cost.

In view of the limited benefits, we have serious concerns about the sustainability of this expensive new technology. More sensitive tests that are comparable to culture and considerably cheaper than Xpert (at

current prices) are required, particularly if TB screening is to be substantially scaled up, as suggested by the Global Plan to Stop TB 2016–2020.[34]

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Author contributions:

All authors were involved in the study design. PN, RD and MVN collected the data. PN, RD and JM analysed the data. PN wrote the manuscript. All authors provided input to the manuscript and approved the final draft for submission.

Conflicts of interest:

The authors declare that they have no conflicts of interest.

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Online Appendix 1: Costing Details

Cost category	Costing details
Building costs	• Costs (including air-conditioning and basic consoles) were provided by the Council for Scientific and Industrial Research for a Level 2 laboratory for 2013 at ZAR12,732 per m^2. Additional costs included professional fees at 6.5% and value added tax at 14%. • Annual costs were calculated based on an expected building lifespan of 30 years and annuitized at a 'risk-free' rate of 3%. • Maintenance was calculated at 10% of the annual building cost. • Building space for each activity was measured. Space included the entire work area used for the activity / test procedure. For test procedures, space was divided into workstations and costs were allocated per workstation. For other activities the total area was used. • Per minute cost of space utilised was calculated based on a 10-hour weekday for 21 days per month and a 4-hour shift every Saturday.
Equipment	• The cost of new equipment was based on purchases, quotes from suppliers and for basic items, catalogue prices and included value added tax at 14%. • The expected lifespan of equipment was determined from interviews with managers. • Costs were annuitized at a 'risk-free' rate of 3%. • Maintenance costs included routine equipment checks, equipment malfunction, module replacement (Xpert), replacement of disposable parts (e.g. air filters) and quality/safety control (eg smoke tests for bio-safety cabinets and equipment calibration). • Where specific maintenance costs were not available (serviced by the "in-house" unit for example), maintenance was calculated at 10% of the annual cost of the equipment. • The use of equipment was timed per batch of tests for each test procedure. • Per minute costs of equipment utilised was calculated based on a 10-hour weekday for 21 days per month and a 4-hour shift every Saturday.
Consumables	• Consumables included tests, reagents and other disposables that could be specifically attributable to individual tests. • Consumable costs were based on actual laboratory expenditure for items purchased from suppliers or from the in-house Direct Media Production unit and included value added tax at 14%. • Consumable costs were calculated based on reviews of standard operating procedures and direct observation of test procedures. • Costs were calculated based on the cost per unit and the quantities utilized per batch of tests or per test
Staff	• Staff salaries reflected the mid-salary band for each staff level and were provided by the laboratory. • The "usual" category of staff performing each test procedure was used • The time spent on each test procedure per batch of tests was measured over several days and averaged • Per minute staff costs were based on a 40-hour week for 46 weeks of the year (with flexible working hours to cover laboratory operational hours). • Non-test specific staff costs were included in overhead costs (see below)
Overheads	• Overheads included non-test specific costs for buildings, equipment, consumables and staff related to specimen sorting and registration, results processing, procurement, stores, training, supervision and management. Staff time was based on the proportion of time allocated to these TB laboratory activities, assuming an 80% staff efficiency level. • Transport: 50% of courier costs (based on test volume) were allocated to the TB laboratory for transport of specimens from health facilities to the laboratory. • Utilities: 50% of costs for electricity, water, sanitation and municipal waste and 70% of costs for biohazardous waste were allocated to the TB laboratory • Cleaning and janitorial: actual costs for outsourced cleaning and laundry services were included • Communication: 50% of costs for telephone and internet services were allocated to the TB laboratory • Security: 50% of costs outsourced security services were allocated to the TB laboratory • Training: External training was not costed as it was included in equipment supply arrangements. Internal training costs were included in non-test specific activities. • Overhead costs were allocated based on test volumes. The rationale was that courier costs (39%) and costs related to specimen sorting, registration, results processing, procurement and the supervision of these activities (24%) were influenced by test volume. • To allocate overhead costs to tests we assessed all tests done at the laboratory in April – June 2011 and 2013, annualised these and calculated the proportion of PTB tests (95% and 92% respectively). • We divided 95% of total overhead costs in 2011 and 92% in 2013 by the annualised number of PTB tests done to allocate an overhead cost per specimen tested.

Online Appendix 2: Examples of laboratory costs (2013)

i) Consumables

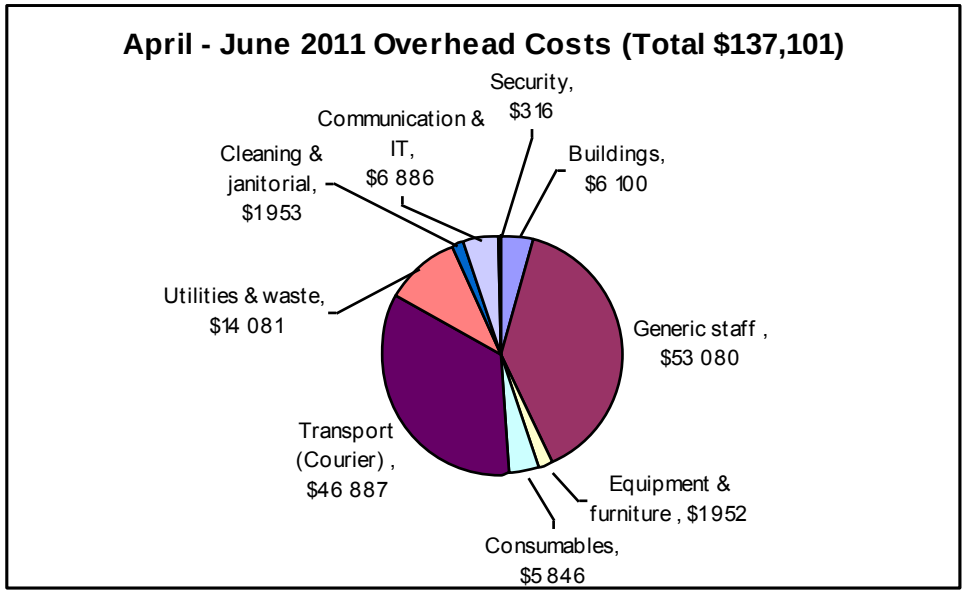
	Package amount per g/ml/test	Unit Measure (g/ml/test)	Price $US	Price per g/ml/test
BACTEC MGIT tubes	100	unit	246	2.46
BACTECT MGIT 960 Supplement KIT (inc PANTA)	100	test	82	0.82
Biohazard waste bin - disposable 50L	1	item	4	4.44
Biohazard waster bag + box	1	item	8	7.86
Blood agar plate	1	unit	0	0.42
Genotype MTBDR*plus* kit - 2nd generation	96	test	1 142	11.90
XPERT MTB RIF cartridge	50	test	721	14.42

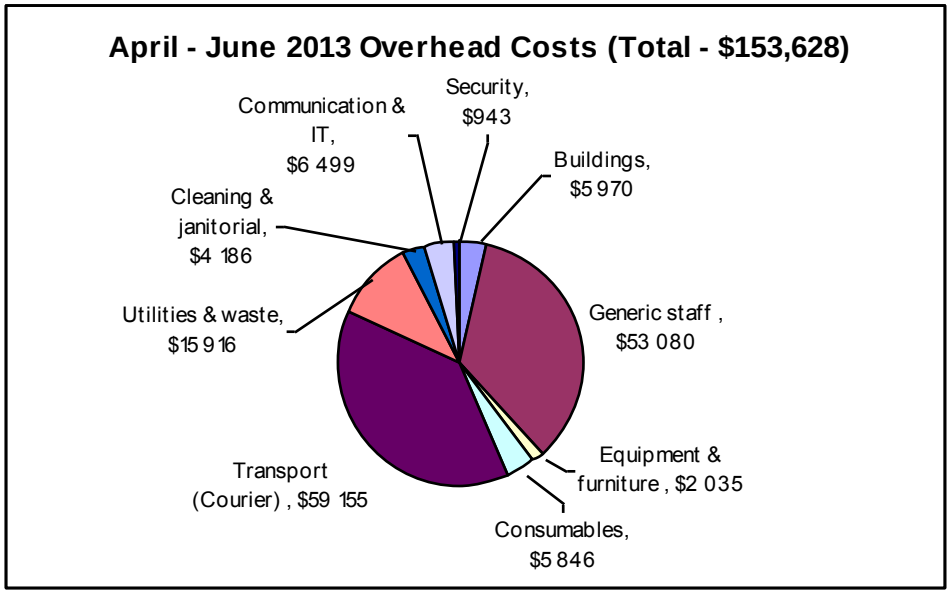
ii) Equipment

	Capacity	ELY	Annuity 3%	Price $US	Annuitised Cost $US	Annual Maintenance Costs $US	Total Annual Costs $US
Biosafety cabinet - class II	1	10	8.5302	8 894	1 043	2 258	3 301
Centrifuge - refrigerated benchtop	Up to 30	15	11.9379	17 203	1 441	77	1 518
LED microscope	1	10	8.5302	3 441	403	61	464
Bactec MGIT 960 system	Up to 960	10	8.5302	50 811	5 957	596	6 552
Aerospray	Up to 30	5	4.5757	15 063	3 292	329	3 621
Light microscope	1	15	11.9379	3 097	259	58	318
Genotype MTBDR*plus* Genoscan	Up to 48	10	8.5302	16 368	1 919	192	2 111
Genotype MTBDR*plus* GT-Blot-48	Up to 48	10	8.5302	22 798	2 673	267	2 940
Genotype MTBDR*plus* thermal cycler	Up to 96	10	8.5302	6 079	713	71	784
Microcentrifuge w/ aerosol-tight rotor	Up to 24	5	4.5757	2 867	627	63	689
Xpert GX XVI module & desktop computer	16	10	8.5302	19 995	2 344	3 177	5 521

The tables above provide examples of some of the 2013 costs used in the analysis. Abbreviations: g = gram, ml – millilitres, ELY – expected life years.

Online Appendix 3: Overhead costs





Overhead costs were calculated based on annual expenditure and allocated on an equal quarterly basis. All costs are expressed in 2013 CPI-adjusted values.

Chapter 9: Conclusion

The overall aim of this thesis was to undertake rigorous scientific research into the impact of an Xpert® MTB/RIF-based TB diagnostic algorithm in a routine operational setting in Cape Town. The magnitude and range of benefits for patients and magnitude and nature of inputs required were assessed. The research entailed a pragmatic comparison between the existing smear/culture-based TB diagnostic algorithm and the newly introduced Xpert-based algorithm.

Impact analysis was guided by the Impact Assessment Framework (1) which aims to ensure a systematic and more comprehensive approach to the evaluation of new diagnostics. This framework addresses five aspects of impact:

- ***Effectiveness Analysis*** assesses the test impact on the numbers of cases diagnosed and started on treatment as well as the timeliness of results and time to treatment initiation
- ***Equity Analysis*** addresses patient important outcomes and assesses whether marginalised groups, who may be more affected, benefit from the new test
- ***Health Systems Analysis*** assesses issues such as the human resource, laboratory infrastructure, procurement and quality assurance requirements, to evaluate the feasibility of implementation and to identify key constraints in the health system to achieving the desired impact
- ***Scale up Analysis*** assesses the economic costs and benefits of scaling up the new technology from both a provider and a patient perspective
- ***Horizon Scanning*** assesses what other similar technologies are available or likely to become available and how these compare in their projected performance.

This chapter sets out to synthesise the findings from each study included in this thesis using the impact assessment framework and to use this to provide an overall assessment of the impact of the Xpert® MTB/RIF-based TB diagnostic algorithm. I address the strengths and limitations of this research and discuss what it contributes to the evidence base on new molecular diagnostics. Finally I make recommendations for future research that could contribute to a better understanding of the impact of new molecular diagnostic tests.

9.1 Effectiveness Analysis

Whilst the need for new evidence based interventions to improve TB control efforts is well recognised, the type of evidence required is rarely available when policy decisions are taken. Policy decisions are based largely on *efficacy* data. These are undertaken in optimally controlled conditions (often ideal settings that are resource rich), on selected populations, with strictly enforced standardised interventions delivered by experienced, well-trained providers (2,3). Whilst these are essential to make direct attribution possible, questions remain as to how this translates to *effectiveness* in real-world programmatic settings, amongst heterogeneous populations, with varying levels of adherence to protocols and a range of experience amongst providers (2,3). Efficacy and effectiveness studies exist on a continuum, with laboratory studies at the efficacy end of the spectrum and demonstration studies closer to, but not fully reflecting, the effectiveness end. Analysis of effectiveness in a routine setting accounts for the patient, provider and health system factors that

influence the outcome and these are all essential to understanding the impact on the numbers of cases diagnosed and started on treatment as well as the timeliness of results and time to treatment initiation.

Were more TB cases identified in the Xpert-based algorithm?

Our stepped-wedge analysis of TB yield *(Chapter 2)* showed that the proportion of TB cases diagnosed in the Xpert-based algorithm was not increased compared to in the smear/culture-based algorithm. Although the proportion of TB cases identified (TB yield) overall was lower in the Xpert-based algorithm (5,444/30,393=17.9% vs. 5,019/24,000=20.9%), this was attributed to a declining TB prevalence, which resulted in a decrease in yield over time. When the time-effect was taken into consideration, TB yield was 19.3% (95% CI 17.7% to 20.9%) in the Xpert-based algorithm compared to 19.1% (95% CI 17.6% to 20.5%) in the smear/culture-based algorithm with a risk difference of 0.3% (95% CI -1.8% to 2.3%)(p=0.796)(4).

Inconsistent implementation is one of the factors that can contribute to lower effectiveness under programmatic conditions. In our study, fewer culture tests were undertaken for Xpert-negative than for smear-negative cases (17.9% vs. 35.5% for low MDR-TB risk cases and 40.5% vs. 82.6% for high MDR-TB risk cases) in respective algorithms. Our ability to interpret this difference is limited in the absence of HIV data, as culture testing was required for HIV-infected cases whose Xpert tests were negative. Since a higher proportion of TB cases were likely to have initially been diagnosed by the more sensitive Xpert test than by smear, it is difficult to know whether this reflects poorer use of ongoing culture testing or better detection of TB by Xpert amongst HIV-infected individuals. The XTEND trial found that amongst HIV infected cases, 28% of smear-negative compared to 11% of Xpert-negative cases had culture tests (5). The difference was attributed to nurses having greater confidence in Xpert compared to smear and is possibly a factor contributing to lower use of culture amongst Xpert-negative cases in our context. A reflex laboratory testing algorithm in which all HIV-infected cases with negative Xpert tests automatically have a culture test undertaken on a second sputum specimen is a potential way to address this deficit; this would require improved HIV-testing amongst presumptive TB cases and for clinicians to indicate the patient's HIV status on laboratory request forms.

The frequent use of culture tests in the smear/culture-based algorithm, and in particular "routine" use amongst previously treated presumptive TB cases, may have also contributed to the yield parity between algorithms in our setting.

Were more MDR-TB cases identified in the Xpert-based algorithm?

Amongst the TB cases identified in the study described above, the Xpert-based algorithm was more effective in identifying MDR-TB than the smear/culture-based algorithm *(Chapter 3).* The probability of having a DST undertaken pre-treatment was 1.82 (p<0.001) times higher and of being diagnosed with MDR-TB was 1.42 (p<0.001) times higher in the Xpert-based algorithm than in the smear/culture-based algorithm.

Importantly, we did not find the compensatory detection of MDR-TB expected during the course of 1st-line TB treatment in the smear/culture-based algorithm. Similar proportions of cases were screened for drug susceptibility (RR=1.02; p=0.848) and identified with MDR-TB (R=1.12; p=0.678) during the course of 1st-line TB treatment in the Xpert and smear/culture-based algorithms. The assumption that new cases with MDR-TB that were initially not detected in the smear/culture-based algorithm would be picked up during the course of treatment appears not to hold true. We speculate that there may have been cases that died or were lost to follow-up before the opportunity to screen them for drug resistance presented.

Overall 8.5% of TB cases were detected with MDR-TB in the Xpert-based algorithm compared to 6% in the smear/culture-based algorithm. If one applies this to the approximately 15,000 bacteriologically confirmed PTB cases diagnosed annually in Cape Town, it translates to a substantial programmatic effect – an additional 375 MDR-TB cases diagnosed, despite sub-optimal implementation of the Xpert-based algorithm. By definition all presumptive TB cases should be screened with Xpert and thus all those diagnosed with TB would have a DST; only 79% of TB cases had a DST in our study, reflecting cases tested only with smear microscopy. Improved monitoring of diagnostic processes is required to optimise use of the Xpert-based algorithm.

Did more cases initiate TB treatment in the Xpert-based algorithm?

A higher proportion of cases initiated TB treatment in the Xpert group (84%) than in the smear/culture group (71%) (p<0.001) *(Chapter 4).* After adjusting for potential confounders, the odds ratio for initiating treatment in the Xpert group was 1.98 (p<0.001). Several co-variables were found to influence TB treatment initiation. Cases >44 years old were less likely to initiate treatment (AOR=0.49, p<0.001) than cases ≤44 years old. Previously treated cases were less likely to initiate treatment (AOR= 0.64 p=0.020) than new cases.

Laboratory delay was associated with non-initiation: for every 1 day of delay, the odds ratio of treatment initiation was 0.96 (p<0.001). Laboratory delay, calculated from the first test taken to the first positive result available in the laboratory, was reduced from 2 days (IQR 1 to 16) in the smear/culture-based algorithm to 1 day (IQR <1 to 4) in the Xpert based-algorithm (p<0.001).

Whilst the introduction of the Xpert-based algorithm reduced diagnostic delays and increased treatment initiation rates, over 1 in 6 bacteriologically confirmed TB cases did not initiate treatment within a year under this algorithm, with serious implications for ongoing transmission, morbidity and mortality. Urgent efforts are required to link laboratory and clinical systems to improve monitoring of non-initiation. The inclusion of non-initiation rates as a TB control programme indicator can play a role in focussing attention on this important gap in TB control efforts.

Did more cases successfully complete TB treatment in the Xpert-based algorithm?

Median delay from the first test taken to treatment initiation was reduced from 15 days (IQR 4 to >365) in the smear/culture group to 7 days (IQR 3 to 35) (p<0.001) in the Xpert group. Treatment success was inversely associated with treatment delay: for every 1 day delay in treatment initiation the adjusted odds ratio for treatment success was 0.99 (p<0.001) *(Chapter 4)*.

TB treatment success rates were similar in the Xpert (80%) and smear/culture groups (80%) (p=0.753) *(Chapter 4).* After adjusting for potential confounders, the OR for treatment success was 0.95 (p=0.764) in the Xpert group. Gender, age and patient category had no significant interaction in the model.

It is important to point out that treatment outcomes were calculated for the cohort recorded as having initiated TB treatment, which inflates treatment success rates in both groups. If the treatment cohort was defined as all cases with a bacteriological diagnosis of TB, treatment success rates would be higher in the Xpert (67%) than in the smear/culture group (57%). The reduction in treatment delay in the Xpert-based algorithm is likely to contribute to reduced TB transmission; however this potential benefit has to be assessed against the duration of pre-diagnostic delay.

Did MDR-TB cases initiate treatment more rapidly in the Xpert-based algorithm?

Median MDR-TB treatment commencement time (TCT) from test taken to treatment initiation was reduced from 43 days in the smear/culture/LPA-based algorithm to 17 days in the Xpert-based algorithms with a mean reduction of 25 days (p<0.001). Median laboratory turnaround time from test taken to result available in the laboratory was reduced from 24 days to <1 day with a mean reduction of 20 days (P<0.001) between algorithms *(Chapter 5)* (6). In the extended Cox regression model that adjusted for co-variables, none of the patient-level variables assessed (age, gender, treatment category, HIV-status) had a significant effect on treatment commencement times. Only the algorithm produced a significant effect, with a hazard ratio of 2.7 (p< 0.001) for cases in the Xpert compared to smear/culture/LPA-based algorithm. We did not assess the impact of reduced treatment delay on MDR-TB treatment outcomes.

There was no significant difference in MDR-TB initiation rates at 6 months in the Xpert compared to the smear/culture-based algorithm (91% vs 94% p=0.167) based on clinical records (6). These figures contrast substantially with routine TB data from South Africa shows that only 62% of detected cases (11,538/18,734) initiated treatment in 2014 (7). It is possible that cases lost to follow-up early during treatment are not registered in the electronic MDR-TB register, contributing to these differences.

The assessment of MDR-TB TCT is limited as the initial time-point is defined by the time at which the first positive test was taken; this does not reflect the patient's diagnostic journey as it fails to capture prior healthcare visits, including those where the patient was not screened for TB or drug susceptibility. Interviews with MDR-TB patients *(Chapter 6)* showed that when the health system was operating optimally, MDR-TB treatment was initiated in 6 to 8 days with Xpert compared to 31 to 38 days with smear/culture/LPA, reflecting the time for a culture and LPA result. More often than not however, health system failures including failure to test for TB at initial visits; incorrect use of algorithms; results not being available when patients returned; and failure to promptly recall patients, contributed to lengthy delays (8). This is addressed further in the Health System Analysis.

Overall effectiveness of the Xpert-based compared to the smear/culture-based algorithm

In summary, the Xpert-based algorithm did not result in an increase in the number of bacteriologically identified TB cases or improve treatment outcomes amongst those initiating treatment. It did however significantly reduce time to TB treatment initiation from a median of 15 to 7 days and reduced non-initiation rates from 29% to 16%. There were broader benefits for MDR-TB cases. It resulted in significantly more MDR-TB cases being diagnosed (8.5% compared to 6%) and reduced MDR-TB treatment commencement time by a mean of 25 days. We did not assess MDR-TB treatment outcomes.

9.2 Equity Analysis

Health inequity is defined as systematic differences in healthcare access or outcomes that are considered to be avoidable, unfair and unjust within that context (9). Equity analysis addresses patient important outcomes and assesses whether marginalised groups, who may be more affected, benefit from the new test. Although systematic reviews are widely used in making policy decisions and considered to be effective for this purpose, these rarely consider the effects on equity (10). There are several underlying reasons for this including

challenges in defining the theoretical mechanism by which the intervention influences health equity; the fact that randomised control trials rarely provide data that is "fit for purpose" as these generally come from observational studies; the need to understand context and how changes in context influence effectiveness and transferability as well as the need to assess the processes by which the intervention is delivered, including whether it was delivered as planned (10)(11).

The gap between efficacy and effectiveness is not equally distributed within socio-economic strata. Tugwell et al describe a "staircase effect" with efficacy reduced at each step for the poor compared to the wealthy due to lower awareness and access; poorer screening and diagnosis as well as poorer compliance of providers and adherence by patients (12). A specific focus on equity is therefore an important aspect of assessing impact.

Health providers need to consider both "horizontal equity" (equal access for those with equal need) and "vertical equity" (differentiated access according to differentiated need) to reduce unfair disparities in healthcare access and outcomes (13)(14). In assessing the impact of new technologies, policies or guidelines, the question then is not only whether the health system performance and outcomes improve, but how the improvement is distributed across socio-economic strata and vulnerable groups and whether the new intervention ameliorates or exacerbates inequity.

Poverty increases vulnerability to TB resulting in a socio-economic gradient in the burden of TB. In South Africa the poorest socio-economic quintile bear 37% of the TB burden compared to the wealthiest quintile that bear 17% of the burden (15). We did not collect socio-economic data from TB patients. However the data collected from MDR-TB patients suggests that they come from amongst the poorest households in South Africa. The 2010/2011 Income and Expenditure Survey found average annual household income in SA of ZAR119,542 (US$15,791), with substantial disparities along racial lines: amongst "white" households average annual household income was ZAR387,011 (US$ 51,124) compared to ZAR 69,632 ($9,198) amongst "black" households (16)[4]. In comparison median annual household incomes was US$3,112 for patients diagnosed in smear/culture/LPA algorithm and S$4,279 for those diagnosed in the Xpert-based algorithm (expressed as 2013 CPI adjusted values) *(Chapter 7)*. These patients also have lower educational levels, with 15% and 11% in respective groups completing secondary education in comparison to the national average of 28% in 2013 (17).

Whilst many of the socio-economic determinants of health that drive health inequities, including education, employment, income and housing lie beyond the purview of the health sector, the health sector can play a role in reducing health inequities by reducing morbidity and preventing impoverishment due to health care expenses (18). Failure to address this results in the "medical poverty trap" (19) where untreated morbidity by those who cannot afford services; reduced access to care amongst the poorest; long term impoverishment due to forced, unanticipated payments for medical care; reduced expenditure on food; withdrawing children from school to reduce schooling costs and to assist with subsistence work all coalesce to produce a cycle that increases impoverishment and reduces the health and well-being of individuals and families.

A diagnostic algorithm that identifies more TB cases, identifies them more rapidly and results in more cases

[4] US$ conversion is based on average UN operational rates in 2010/2011 of ZAR7.57=US$1

initiating and successfully completing TB treatment potentially reduces morbidity and mortality amongst those infected as well as exposure and potential transmission to other vulnerable individuals. As discussed in the previous section, individuals diagnosed in the Xpert-based algorithm received their results earlier and were more likely to commence treatment, reducing inequity for these patients as well as all those at risk. These benefits were limited as there was no increase in the proportion of TB cases identified.

Previously treated TB cases are at greater risk of recurrent TB (20–22) and can be considered to have a "differential need". Inequity could be considered to have increased in the Xpert-based algorithm for this group as fewer cases had more sensitive culture tests than cases in the smear/culture-based algorithm, potentially contributing to lost diagnostic opportunities. Another group with differential need are HIV-infected individuals given their sustained increased risk of TB regardless of antiretroviral treatment (23). A limitation of the study is that we did not have data on HIV status and could not evaluate the likelihood of these individuals being diagnosed with Xpert.

However, the Xpert-based algorithm can be considered to have reduced inequity as it was more effective in identifying MDR-TB cases. The probability of being diagnosed with MDR-TB pre-treatment was 1.42 times higher in the Xpert-based than in the smear/culture-based algorithm. Previously treated TB cases can be considered to be a group with differential need as they are at significantly higher risk of MDR-TB than new cases (24–26). In the previous smear/culture-based algorithm DST was rationed to previously treated presumptive TB cases. Our findings suggest that this policy was iniquitous: almost half the MDR-TB patients identified were new presumptive TB cases; failing to screen them initially did not result in compensatory detection during the course of 1st -line TB treatment, with potential long term harm to these individuals and their families.

Whilst women were less likely to have a DST undertaken during the course of 1st line TB treatment than men, it is difficult to know whether this is due to reduced perceptions of risk (perhaps due to better adherence to treatment) or to women receiving a poorer quality of service (27–31). We found no gender bias for DSTs undertaken pre-treatment *(Chapter 3).*

Patients in the Xpert-based algorithm also initiated MDR-TB treatment more rapidly than those in the smear/culture-based algorithm. There was equal benefit by age, gender, treatment category and HIV status amongst these cases. Other benefits to MDR-TB patients included the higher proportions diagnosed pre-treatment and initiating MDR-TB treatment at decentralised sites, with potentially reduced morbidity, increased convenience and reduced costs for these individuals (6).

Since MDR-TB patients come from amongst the poorest households in the country, the impact on patient costs is important *(Chapter 7).* The total median cost from symptom onset to MDR-TB treatment initiation was reduced from $68.1 in the smear/culture/LPA group to $38.3 in the Xpert group (p=0.004)(32). Median direct costs (out of pocket payments) were similar at $6.7 in the smear/culture/LPA group and $4.4 in the Xpert group (p=0.321). The low median direct costs are testament to the primary health infrastructure and free services with zero median medical costs in both groups. The cost saving is attributable largely to a time saving: the median number of health visits to MDR-TB treatment initiation was reduced from 20 in the LPA group to 7 in the Xpert group (p<0.001). For those diagnosed at the pre-treatment diagnostic time-point (i.e. when being evaluated as presumptive TB cases), the median number of visits was reduced from 16 in the LPA group to 6 in the Xpert group (p<0.001). We used the human capital method to cost the time of all

patients, including the unemployed, to reflect the opportunity costs of the time spent is seeking healthcare that could have been used for seeking employment or contributing to sustaining families in other ways (childcare and other household chores for example) and this may have resulted in an overstatement of these benefits.

Despite the social protection offered by access to free primary health services and the reduced time and number visits to treatment commencement with Xpert, there was a decrease of 16% in median household income in the smear/culture/LPA group and 13% in the Xpert group and "catastrophic" costs (33) were experienced by 38% and 27% (p=0.165) in respective groups who lost >10% of monthly household income *(Chapter 7).* These already low income households (median monthly household income prior to symptom onset of US$259.3 and $356.6 respectively) may have substantially less flexibility in dealing with these costs. Loss of employment contributed significantly, increasing from 39% to 73% in the LPA group (p<0.001) and from 53% to 89% in the Xpert group (p<0.001) and earlier access to treatment did not impact on this. The faster treatment initiation may well have contributed to the finding that fewer patients had received a disability grant at the time of the interview in the Xpert (22%) compared to the smear/culture/LPA-based algorithm (40%), reflecting the time taken to process a grant (32).

One of the goals of the End TB strategy is that no households should face catastrophic costs from TB by 2025 (34). The relief provided to MDR-TB patients in terms of reducing time and total costs to treatment initiation with Xpert and the existing social protection offered by free primary healthcare and disability grants in South Africa were not adequate to counter the financial losses experienced, and a substantial proportion of these households faced catastrophic costs. Although we do not have data on the costs for TB patients, a study embedded in the national rollout of Xpert showed that TB diagnostic and treatment cost consumed 12% of annual individual income, with about 40% due to expenditure in the diagnostic phase, suggesting high costs for these individuals as well (35). Irrespective of how quickly treatment is initiated with a rapid test, a high number of patients will be vulnerable to the effects of increased poverty and additional government efforts are required to counter this.

9.4 Health Systems Analysis

Health systems analysis assesses issues such as the human resource, laboratory infrastructure, procurement and quality assurance requirements to evaluate the feasibility of a new intervention and to identify key constraints in the health system to achieving the desired impact.

Many complementary approaches exist to health system analysis, varying in terms of scope, focus, utility and purpose (36–39). The World Health Organisation's Building Blocks framework, one of the best known of these, identifies six essential functions of a health system and the desirable attributes of each: service delivery; health workforce; information; medical products, vaccines and technologies; financing; leadership and governance (38). The Health Systems Dynamics Framework (39), which expands upon WHO's Building Blocks framework, places a greater emphasis on the relational nature of the health system and has been selected for this analysis. This framework (Figure 1) views the health system as a dynamic interaction between leadership and governance, resources, service delivery and the population, operating within a specific context and underpinned by a set of values and principles, in producing health outcomes and goals.

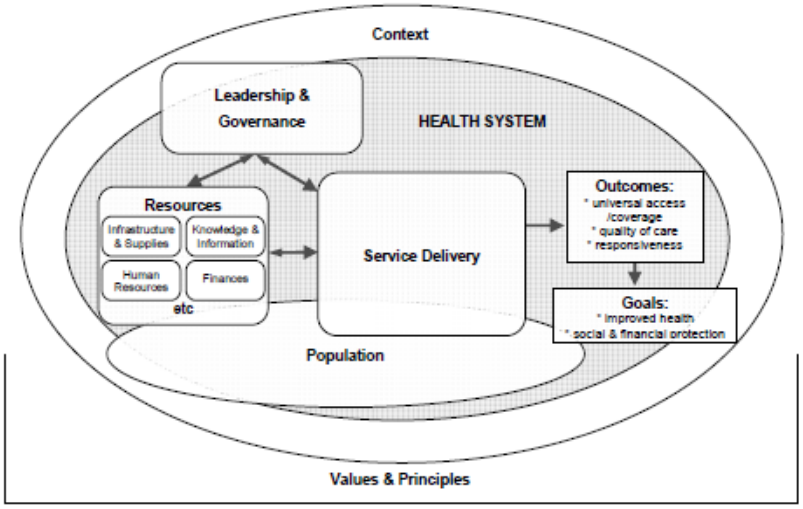


Figure 1: Health systems dynamics framework. From van Olmen J et al, Analysing Health Systems Dynamics. Studies in Health Services Organization & Policy. 2012 (40)

Context: This element of the framework recognises that health systems are shaped by wider societal influences including political decision-making and historical developments. A policy transfer analysis (see supplement) undertaken in South Africa as part the PROVE-IT evaluation highlighted the strong political pressure from the Health Minister to adopt Xpert, to the extent where national implementation preceded the release of the global policy (41). Important contextual factors at play included the international concern around the growing DR-TB problem and the spotlight cast on South Africa by the 'Tugela Ferry' XDR-TB outbreak (42). This was also a period when South Africa was emerging from the HIV denialist era under President Mbeki and the new political leadership were determined to demonstrate renewed commitment to tackling the public health crises facing the country, including the TB and HIV epidemics (41).

The policy transfer analysis recognised the critical importance of private sector, donor and non-profit organisations in catalysing the development and implementation of Xpert, but suggested that this also entails risks. Complex conflicts of interest are possible between these organisations with respect to advocating for particular platforms and creating reliance on a single provider for a crucial health technology. Concern was expressed amongst South African managers that to some extent, international interests may have driven the rapid implementation of Xpert and contributed to poor planning and implementation.

Leadership and governance: The policy transfer analysis (41) found a lack of transparency in national policy and planning processes for Xpert. Implementation, maintenance and expansion were characterised by poor communication and coordination, insufficient attention to resource implications, technical challenges and a lack of broader health systems thinking in integrating the diagnostic tests into the TB control programme.

We provided two possible interpretations to help explain this. The first was the tension between 'rescue' and 'management' in health services which reflects the urgent desire to save lives through medical rescue on the one hand and the need to carefully manage change in the system, evaluate impact and produce strong evidence on the other. The second was an over-reliance on technological solutions to complex public health challenges. Confidence in the basic Xpert technology and optimism about the potential impact may have crowded out careful thinking about how best to integrate the tests into routine practice, with a failure to

recognise that even an easy to use technology entails health system challenges that need to be anticipated and managed.

Overall, whilst the Ministry of Health's role in South Africa has been characterised by good policies, an insufficient emphasis on implementation, monitoring, and assessment of these policies throughout the system and poor accountability have undermined their impact (43). Effective transformation of the health system would necessitate organisational restructuring with greater delegation of authority to frontline managers (44). Facility managers have a crucial role to play in using local information to optimise care and to drive change. Training and support that is directly responsive to managers' needs could help to optimise the health system to ensure that patients benefit from the implementation of Xpert.

Resources: ***Finances:*** One the greatest challenges posed by the introduction of Xpert has been the cost issue. Our analysis showed a 43% increase in laboratory costs for PTB, an increase of 157% per TB case diagnosed, and an incremental cost-effectiveness ratio of $6,274 per MDR-TB case diagnosed (45). Costing is discussed in detail in the section on Scale-Up. The policy transfer analysis drew attention to how the availability of donor funding, though an important catalyst for Xpert implementation, may have distorted perceptions of feasibility by masking start-up and recurrent costs, and led to insufficient attention being paid to resource requirements with risks to its sustainability (41).

Human resources: A comparative analysis of six countries with similar population size, per capita GDP, GINI co-efficient and GDP growth indicates that South Africa has similar numbers of health professionals to these countries but substantially higher infant and maternal mortality rates (Table 1). Although South Africa has the lowest proportion of doctors (5.4 per 10,000 population compared to 17.3 in Brazil and 8.7 per 10,000 population in Thailand, both countries with nurse-driven primary health services), the 36.1 nurses per 10,000 population was on a par with several other countries including Thailand (33.2) but was substantially lower than Brazil (65.6) (46).

Table 1: Comparative benchmarks for staffing per 10,000 population and health outcomes for six countries

	International benchmarks													
Indicator	Brazil		Chile		Costa Rica		Colombia		Thailand		Argentina		SA current	
Population	193 733 795		16 970 265		4 578 945		45 659 709		67 764 033		40 276 376		49 320 150	
GDP per capita (USD)	4 399		6 083		5 043		3 102		2 567		9 880		3 689	
%GDP Health	9.05		8.18		10.47		6.42		4.31		9.53		8.51	
GDP growth (annual %)	-0.64		-1.53		-1.50		0.83		-2.25		0.85		-1.78	
GINI index	53.9		52.06		50.31		58.49		53.57		45.77		57.77	
DOCTORS	17.31	17%	15.71	42%	20.42	39%	19.43	58%	8.72	19%	31.96	62%	5.43	12%
NURSES	65.59	64%	10.45	28%	22.19	42%	5.83	17%	33.21	71%	4.87	10%	36.1	80%
PHARMACY	5.81	6%	3.72	10%	5.34	10%	0	0.0	2.92	6%	5.08	10%	2.29	5%
ORAL HEALTH	13.69	13%	7.44	20%	4.85	9%	8.26	25%	1.73	4%	9.28	18%	1.2	3%
Total	102.39		37.32		52.8		33.52		46.59		51.19		45.02	
IMR (per 1,000 live births)	17.3		7.0		9.6		16.2		12.0		13.0		43.1	
MMR (per 100,000 live births)	75		18.2		26.7		75.6		12.2		40		165.5	

From: Department of Health, South Africa. Human Resources for Health South Africa. Strategy for Health 2012/13-2016/17. 2011 (46)

However these figures mask the disproportionate allocation of health professionals to the private sector. In 2014, only 48% of national health expenditure was in the public sector that catered to the 82% of the

population without medical aid coverage (http://apps.who.int/gho/data/view.main.HEALTHEXPRATIOZAF) (47). These figures suggest that the public health sector may be under-resourced in terms of the numbers of health care professionals available to provide effective services. The number of nurses available also does not reflect their skill levels and competence. The inefficiencies identified in the implementation of Xpert including the missed diagnostic opportunities, incorrect use of diagnostic algorithms and delays in linkage to care may partially reflect an under-resourced public health sector.

Information technology infrastructure: Information technology and health information systems in South Africa are fragmented and poorly integrated for supporting healthcare delivery, clinical decision-making and monitoring and evaluation of the health system's performance (48). Even though the Western Cape has one of the most advanced information architectures nationally, there was still heavy reliance on paper-based systems that impeded the follow-up of patients (for example for newly diagnosed TB cases or those requiring additional tests). Whilst a laboratory result for Xpert may have been available within a day, a clinician's real-time access to laboratory results, whilst theoretically feasible, was limited by the low availability of computers at health facilities. Although this has now been addressed through a web-based system that allows clinicians access through cell-phones, it is dependent on the willingness of clinicians to use their private cell phones for this purpose. Importantly there is no electronic mechanism in place to flag patients that fail to initiate treatment, to monitor action that has been taken, or their outcomes. Existing systems did not allow adherence to diagnostic algorithms to be readily assessed to enable appropriate action. Information systems were all heavily dependent on paper based records that were onerous to manage and which prevented optimum patient management and the evaluation of healthcare delivery beyond treatment outcomes.

Infrastructure and supplies: Cape Town has a relatively good laboratory and health infrastructure that have supported the implementation of Xpert. Although the laboratory infrastructure is highly centralised, a courier system enabled daily delivery of specimens to the laboratory. The MGIT liquid culture and smear microscopy infrastructure have been retained with the introduction of Xpert as they are integral components of the new diagnostic algorithm and used to monitor the response to treatment. The laboratory has external and internal quality assurance processes in place and adequate stock management and procurement systems.

There is an extensive public primary health care infrastructure with 142 primary health care (PHC) facilities within the 2440 square km geographic boundary of Cape Town and an average distance to PHC facilities of less than 3 km (http://www.hst.org.za/publications/district-health-barometer-201415-1, Data File 2014/15). However, there is some fragmentation of services with only 101 of 142 offering both TB diagnostic and treatment services and TB diagnostic services poorly integrated into obstetric services, all contributing to treatment delay. Although only a small proportion (7%) of cases are diagnosed in the private health sector in South Africa (49) our studies found that about one third of patients had engaged the private sector prior to attending the public sector, contributing both to increased patient costs and to delay.

Service delivery: Laboratory resources were substantially re-organised to optimise the impact of Xpert. For example, twice daily courier collection was introduced for larger facilities and as well as extended laboratory hours during the week and on Saturday mornings. Parallel efforts were made to improve clinicians' access to laboratory test results to supplement the faxed and printed copies of results provided. However, as our MDR-TB patient interviews reflected (8), delays in treatment initiation occurred as a result of facilities not having the result available, for example, due to broken fax machines. The poor management of laboratory results

appeared to contribute substantially to delay; it is unclear why staff sometimes delayed taking action on positive results (occasionally for several months) even in situations where community health care workers were available to trace patients and nurses were able to telephonically contact patients.

Full decentralisation of MDR-TB services is likely to have contributed to earlier MDR-TB treatment initiation for patients not requiring hospitalisation in the Xpert-based algorithm. From 2012, standard MDR-TB drug regimens were made available at PHC-level and sub-district medical officers could initiate treatment without prior review of cases or prescriptions from the TB-hospital. A nurse and counsellor was also employed in each of the eight sub-districts to trace MDR-TB patients, refer to appropriate social services, arrange screening of contacts and ensure work-up and treatment commencement (6).

Our studies identified several service delivery constraints to optimising the implementation of the Xpert-based algorithm. Chief amongst these was poor compliance with standards of care including failure to undertake TB tests in those with classical symptoms of TB and poor adherence to diagnostic algorithms (4)(8). Almost 2 years after Xpert was introduced, only 85% of new and 78% of previously treated presumptive TB cases received an Xpert test as per algorithm (4). Insufficient training, poor monitoring and accountability may all have contributed. Clinical acumen is also called into question by the failure to respond early to patients' deteriorating health whilst on 1st line TB regimens in individuals that were eventually diagnosed with MDR-TB (8).

Negative perceptions of the public sector (as over-burdened, with long waiting times, negative staff attitudes and a lack of privacy) were prevalent and contributed to deferred health-seeking, interruptions to the diagnostic process and to patient's preferential use of the private sector, contributing to delays in both algorithms (8).

Population: We found generally low awareness of TB amongst the MDR-TB patients interviewed *(Chapter 6)* (8). Incorrect symptom attribution was common as was tolerance of ill-health, both contributing to delays in health- seeking. Cultural influences in terms of men not admitting to illness to avoid displaying signs of weakness and to patients seeking traditional healthcare contributed to delays to a minor extent. Although TB-related stigma did not emerge as an issue in our study, HIV-related stigma contributed to delays in health-seeking amongst individuals fearful of having an HIV test (8). Whilst the supply side of the new diagnostic test was addressed (at least theoretically, as all facilities had access to the test) we found no evidence of efforts to improve the demand side, both of which are required to increase utilisation (39).

There was some evidence of transformation of power relationships between patients and service providers compared to findings from a previous study (50); on the one hand there were several examples of patients being in too disempowered a position to demand the service expected, and on the other examples of patients that were able to do so (8). Empowering patients is an important step to reducing inequity (39) and further efforts are required to advance this.

Values and principles: The white paper on "Transforming Public Service Delivery" sets out eight "Batho Pele" (People First) principles for improving the efficiency and effectiveness of services (51). Citizens should expect consultation on the level and quality of services; adherence to service standards; access to services; courtesy; information on services they are entitled to receive; openness and transparency about how services are managed, resources are allocated and who is accountable; redress and effective remedy; and value for money. We found little consistent evidence of these principles in our studies. Whilst the South African

constitution binds the state to work towards achieving the progressive realisation of the right to health for all citizens, massive challenges in transforming health institutions and promoting equity persist (43)(44).

From an allocative efficiency perspective, resources should be moved from cost-ineffective interventions to cost-effective interventions in a way that maximises population health overall. However, allocative efficiency is not the only determinant of budget allocations, reducing health inequities and prioritising the sick are important considerations in a context where health should be considered a social good and not only an economic good. This has particular relevance in a country like South Africa where the socio-economic determinants of health are deeply rooted in the colonial and apartheid past and continue to produce the disparities in disease incidence and mortality found today (43). An argument could be made that the cost of Xpert needs to be viewed through this lens.

Health system failures at several levels from poor initial planning for Xpert implementation to human resource and IT infrastructure deficits, to poor accountability and inefficient service delivery and as well as low community preparedness are likely to have diminished the full potential impact of the Xpert-based algorithm. Urgent attention needs to be paid to these issues to optimise the benefit of this expensive new investment.

9.5 Scale-up Analysis

Scale-up analysis assesses the economic costs and benefits of scaling up the new technology from both a provider *(Chapter 8)* and a patient perspective *(Chapter 7).*

From a provider perspective, we found a 43% increase in overall PTB laboratory costs at the central laboratory, from $440,967 in the smear-culture-based algorithm to $632,262 in the Xpert-based algorithm over 3-month periods (45). Although the number of presumptive TB cases evaluated was similar in the smear/culture (n=7,842) and Xpert-based algorithms (n=7,714), the proportion of TB cases diagnosed decreased from 20.4% (n=1,601) to 16.6% (n=1,281), possibly due to a decline in TB prevalence. 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 (45). Since the TB yield study showed no difference in yield between the algorithms when time trends were taken into account (4), we estimated the cost per TB case diagnosed if yields were similar: the cost per TB case diagnosed in this scenario would increase by 109%, to $101.94.

The mean added cost per MDR-TB case was $141.37 (n = 95) in the smear-culture-based algorithm compared of $58.54 (n=107) in the Xpert-based algorithm. When these costs were added to the “base” cost of a TB diagnosis, the total cost per MDR-TB case diagnosed was $190.14 in the smear/culture-based algorithm compared to $183.86 in the Xpert-based algorithm. As our analysis showed no difference in TB yield between the algorithms, we apportioned all additional diagnostic costs to the 12 additional MDR-TB cases identified, resulting in an incremental cost-effectiveness ratio (ICER) of $6,274 per additional MDR-TB case diagnosed (45). The high ICER from this universal screening strategy has to be weighed against potential cost savings that may be realised through reducing MDR-TB transmission. A costing study undertaken in Cape Town found MDR-TB diagnostic and treatment costs to be $6,772 in 2011, 26-times the cost for a drug-sensitive case (52).

We did not estimate cost effectiveness in terms of disability adjusted life years (DALY) from our data. Despite

its limitations (53) DALYs are widely used in comparing relative costs and impacts of intervention to inform health policy. Vassal et al used decision analytic modelling to compare the cost-effectiveness of a base case of two smears and clinical diagnosis to the use of Xpert for all presumptive TB cases (54). Although diagnostic costs increased from $28 to $137 per TB case diagnosed in South Africa, the mean incremental cost-effectiveness ratio per DALY averted was $138, within the World Health Organisation's suggested "willingness to pay" threshold (defined as the cost per DALY averted of the country's per capita GDP i.e. US$5,786 for South Africa in 2010) and was thus deemed to be cost-effective. Several authors suggest a cautious interpretation of this threshold (55,56). The ease with which interventions meet this threshold and the issue of whether this represents the best use of a country's health budget in relation to other feasible, necessary interventions have been highlighted as cause for concern (56). Cost-effectiveness does not necessarily imply an affordable strategy: in India for example, the implementation of Xpert for 15% of presumptive TB cases would consume the entire Revised National TB Programme budget (57). In South Africa, where Xpert has been introduced as a replacement for smear microscopy, it is estimated that annual TB diagnostic costs will increase by 53-57% to $48-70 million per year at full Xpert coverage (58). Serious questions have to be asked about whether these resources could be used more cost-effectively in a way that also reduces health inequities.

A full analysis of facility costs was not done for this thesis. It is unlikely that the unit costs per visit type changed, as categories of staff involved, processes, infrastructure and overheads were similar in both algorithms. However, the facility cost to MDR-TB treatment initiation is likely to have decreased in line with the decreased number of patient visits, the majority of which were to the public health sector. The decrease would be non-linear, as the greatest difference in visits related to those for the less costly directly observed therapy ("DOT") visits.

Resources used in health should be valued from a societal perspective and costs to the patient are also important (59). We assessed both the direct and indirect costs incurred by patients (32). The median patient cost from initial health visit to treatment initiation was reduced from $68.1 in the smear/culture/LPA-based algorithm to $38.3 (p=0.004) in the Xpert-based algorithm. Median direct costs (out-of-pocket payments) were low at $6.7 and $4.4 (p=0.321) respectively. The difference was attributable to time costs as the median number of visits to MDR-TB treatment was reduced from 20 to 7 (p<0.001 in the Xpert-based algorithm). We used the human capital method to allocate lost productivity costs to all patients, based on the wage of a municipal health worker. An argument could be made that this overstates costs as 39% and 53% in respective algorithms were unemployed prior to their illness.

The increase in laboratory costs in our study is offset to some extent by the cost-saving to MDR-TB patients. We did not assess the costs incurred by TB patients and this is required to provide a more comprehensive view of costs from a societal perspective.

9.6 Horizon Scanning

Horizon scanning, adapted since the original IAF publication[5], assesses what other similar technologies are

[5] Personal communication S.B. Squires

available or likely to become available and how these compare in their projected performance.

A 2015 pipeline analysis identified almost 50 different TB diagnostic technologies at different stages of development and evaluation (60). Only two tests suitable for use amongst presumptive TB cases have been reviewed by The World Health Organisation. The first of these is TB LAMP (loop-mediated isothermal amplification) (Eiken Chemical Co., Japan), a moderate complexity test on a par with Xpert. TB-LAMP is a manual TB detection method designed to be simple and inexpensive enough for implementation in resource-limited countries as a replacement for smear microscopy. Advantages include speed (it takes 15-40 minutes to a result); minimal requirement for equipment (as it requires only a heat block); and that the result is visible to the naked eye through the detection of fluorescence under an ultraviolet light (61).

Evaluation studies from TB reference laboratories in South Africa, Vietnam, Peru and Brazil reported sensitivity of 97% for smear-positive/culture-positive cases and 53% for smear-negative/culture-positive cases and specificity of 94.7%, with the latter below target and attributed to problems with the test strips in humid conditions. Studies from settings where this test may potentially be used (i.e. rural or simple urban microscopy centres) in India, Uganda and Peru reported sensitivity of 97% for smear-positive cases and 62% for smear-negative cases and specificity of 96.3% (below the 97.3% achieved with microscopy) (61). Humidity and failure to adhere to protocols contributed to false positive results. An economic costing study reported a cost of $13.47 per test (at volumes of 10 runs per day) compared to $2.51 for two Ziehl-Neelsen stained sputum smears (61).

The Expert Group convened to review this data was of the opinion that the data on TB-LAMP was insufficient to make a recommendation either in favour of, or against its use as a replacement for sputum smear microscopy (61). In the South African setting with centralised laboratories where Xpert and efficient smear microscopy are in place, it seems unlikely that TB-LAMP would be considered as a viable alternative as a screening test for presumptive TB cases.

The second test that has been reviewed is LF-LAM (lateral flow urine lipoarabinomannan assay) (Alere DetermineTM TB LAM Ag, Alere Inc, Waltham, MA, USA) (62). This point of care urine-based test detects antigens to a lipopolysaccharide present in mycobacterial cell walls which is released from metabolically active or degenerating bacteria in individuals with active TB disease. Urine-based testing has advantages over sputum-based testing as it reduces the infection control risks associated with sputum collection. The test is performed by applying a small amount of urine to the test strip, incubating at room temperature for 25 minutes and inspecting the strip for the absence or presence of pink bands of varying intensity (related to antigen concentration), graded according to a reference card. In comparison to most other tests, LF-LAM shows improved sensitivity in those with TB/HIV co-infection, with higher sensitivity in those with lower CD4 counts. Possible explanations for this include a higher bacillary / antigen load, higher likelihood of genitourinary tract TB and increased glomerular permeability resulting in increased urinary antigen levels in these individuals.

In six studies comparing LF-LAM with a microbiological reference, sensitivity ranged from 23% to 84%, and specificity from 75% to 99% with pooled sensitivity of 44% (95% CrI=31- 60%) and specificity of 92% (95% CrI=83-96%). WHO made a strong recommendation that LF-LAM should not be used as a screening test for TB and a conditional recommendation that it can be used only to assist in the diagnosis of TB in HIV infected patients with signs and symptoms of pulmonary or extrapulmonary TB who have a CD4 count ≤100 cells/μL or who are seriously ill, as the test has the potential to reduce mortality in these individuals. Operational pilots

are currently underway to assess the use of these tests in hospital settings in South Africa as per the WHO recommendation and this test is not a potential replacement for Xpert.

Xpert MTB/RIF Ultra (Ultra) (Cepheid, Sunnyvale, CA, United States) is in an earlier phase of development to the tests described above. Ultra was developed in response to the poor sensitivity of Xpert amongst smear-negative cases and to the false positive rifampicin-resistance results generated. In sputum samples spiked with MTB H37Rv preliminary data showed a limit of detection of 5 CFU/ml with Ultra compared to 50 CFU/ml for Xpert (63). The assay contains new rpoB genes that increase Rif-R specificity. Preliminary specificity and sensitivity were reported at 100% (63). These data are limited in scope and there are no published data on how this translates into practice. However, if sensitivity exceeds that of Xpert and costs are similar, this test could be a replacement for Xpert.

As part of the PROVE IT evaluation we developed an operational model for the smear/culture and Xpert-based TB diagnostic algorithms in Cape Town. The model was developed using Witness (Lanner, Redditch, UK), a discrete event and continuous process simulator, to comprehensively represent PTB patient diagnostic pathways and processes in the smear/culture and Xpert-based diagnostic algorithms. This included sample flow from specimen collection, laboratory test procedures, provision of results and treatment initiation. The model was validated against the routine data presented in this thesis, building confidence in its reliability. As part of a separate doctoral thesis, the model will be used to test a variety of scenarios, including the replacement of Xpert with Ultra. The availability of our operational model allows us to test a range of possible Ultra sensitivities and specificities for MTB and Rif-R and to assess their effect on yield and costs. This validated model can provide important answers to assist policy makers in decision-making.

9.7 Strengths and limitations of this research

The use of the Impact Assessment Framework ensured that a broad range of perspective were assessed that included not only those of the health service and laboratory but also the patients'. The latter tends to be neglected area in TB research. The measurement of multiple outcomes, mix of quantitative and qualitative study methodologies and inclusion of costing studies provided a comprehensive view of the benefits and limitations of Xpert. The framework resulted in an important focus on equity; whilst equity is a key component of global strategies, and is included for example in the Millennium development goals, studies rarely address this aspect (1)(64). The use of the framework to guide impact evaluation enabled a systematic approach that could be replicated in other settings and for future new diagnostics.

These studies have several novel aspects: they were undertaken at the level of the Xpert-based diagnostic *algorithm* and not the individual test. New tests are used as part of a diagnostic algorithm and not in isolation and using this approach allowed for a more realistic comparison of benefit. For example, whilst the more sensitive Xpert test may correctly identify a higher proportion of TB cases than smear, this benefit could be muted by the large proportion of cases that also had a culture test in the smear/culture based algorithm.

The strength of these studies is that they account for the patient, provider and health system factors that influence outcomes; these are essential to understanding the impact of the new diagnostic algorithm in routine programmatic conditions, amongst heterogeneous populations, with varying levels of adherence to protocols and a range of experience amongst providers.

Whilst observational studies such as the ones included in this thesis are generally easier and less costly to implement than experimental studies, they have limitations. The levels of evidence tend to be lower in observational studies due to confounding which makes a direct attribution of outcome more difficult. We used a large amount of routine information that was collected for clinical and programme management purposes, not research, and which contained a limited number of variables. Risk factor data, particularly HIV status and basic socio-economic data (eg employment status, income) were not routinely collected, making it difficult to address potential confounders. Although the quality of routine data is often lower than would be found in studies where data is collected by well-trained and supervised research staff, missing data in our studies was at acceptabel levels.

Bias was difficut to control for in these studies, for example as a result of the non- random allocation of sites to different study arms. In the stepped-wedge analysis of TB yield *(Chapter 2)*, the introduction of the Xpert-based algorithm was non-random. Facilties in areas with both high TB and HIV prevalence were allocated to the Xpert-based algorithm first. The extent to which these factors influenced the findings is difficult to quantify. This allocation is also likely to have influenced findings in the TB treatment initiation and treatment outcome analyses *(Chapter 4)* as sub-districts in the Xpert-arm were likley to have had higher HIV prevalence than those in the smear/culture-arm. In studies addressing patient pathways *(Chapter 6)* and costs *(Chapter 7)* bias was introduced by excluding patients not initiating treatment and the sickest, however these were likely to have been similar between the comparison groups.

The ability to address temporal trends was limited. In the stepped-wedge analysis of TB yield *(Chapter 2),* we were able to address the possible decline in TB prevalence over time. Although the laboratory costing study *(Chapter 8)* had a “before and after” study design, we could assess the influence of a possible decline in TB prevalence on cost per TB case diagnosed. However, in the study comparing MDR-TB treatment commencement times *(Chapter 5),* the sample size was too small to allow an assessment of temporal trends. This meant that changes such as decentralisation of MDR-TB treatment could not adequately be accounted for, and may have contributed to the outcome of reduced MDR-TB treatment commencement times.

Generalisability to other settings is limited by the context. Whilst many of the studies in this thesis included a large number of facilities, these were all undertaken within a well-resourced, urban setting, with relatively good health and laboratory infrastructure. Whilst this may be applicable to the 65% of the population in South Africa that live in urban areas (http://databank.worldbank.org/data/reports), it does not reflect the reality within rural contexts where access to healh facilities and diagnostic infrastructure may differ substantially. The highly centralised diagnostic infrastructure in the South African context which adds to diagnostic delay and disrupts the link between diagnosis and care, makes it difficult to generalise these findings to countries with decentralised diagnostic infrastructure.

9.8 What does this research contribute to the evidence base?

Whilst the Impact Assessment Framework was intended to provide evidence to inform scale-up, the speed of Xpert implementation in South Africa and the time taken to implement these studies and analyse the results precluded this. The studies presented in this thesis highlight the effect of early introduction of new tools into under-prepared and inefficient health systems and provide insights into some of the health system

weaknesses that could be addressed to optimise the impact of Xpert, for example: ensuring the testing of presumptive TB cases with Xpert at their first health visit; routine culture testing for HIV-infected individuals with negative Xpert results; effectively managing results received from the laboratory; early recall of patients not returning for care and reducing barriers to care such as long waiting times and negative staff attitudes. Many of these issues are within the scope of control of facility managers and easily remediable through effective management practices, including ensuring accountability for the quality of services delivered. Health system weaknesses have been recognised as an important challenge to ensuring access to existing services as well as to new technology, particularly for the poorest and most marginalised individuals (65). Unless concerted efforts are made to address these weaknesses, the investment in this expensive new technology will not provide the full range of benefits possible.

The range of data collected allowed the many factors influencing the impact of Xpert to be identified. This research contributes important evidence not only from provider's perspectives but also patients' perspectives: the impact on livelihoods, costs and the difficulties that patients encounter in receiving the appropriate health care. These findings suggest that despite the many social protection measures in place in South Africa, including child support grants, disability grants and access to free primary health services (66), current measures need to be strengthened, particularly if the End TB goal that no households should face catastrophic costs from TB by 2025 (34) is to be achieved.

The findings from these studies highlight the complexity of making decisions about the investment in new technology. Whilst the reliance on modelling data to inform decision making and insufficient availability of operational data to populate these models may have resulted in less than optimum decision-making, the introduction of Xpert has provided undeniable benefits: reduced initial loss to follow-up and treatment delay for TB cases; an increase in the proportion of MDR-TB cases identified, reduced delays to MDR-TB treatment initiation and reduced costs to MDR-TB patients. However these come at a high cost and may be indefensible from an allocative efficiency perspective. Having invested heavily in this technology, we need to address the health system and patient factors that prevent optimal benefit to improve cost-efficiencies. The findings from the studies presented in this thesis could 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 Xpert elsewhere and for the future adoption of new diagnostic tests in South Africa. The cost-benefit ratio may also improve over time as a result of further technological advancements that increase Xpert sensitivity and as the cost of the technology is reduced.

9.9 Future research

Studies are required to assess improved cost-efficiency of the Xpert-based algorithm. Theron et al., for example, showed that pre-screening with smear reduced the cost of a TB diagnosis in their model by more than 20% (67). As part of PROVE IT study we have developed a discrete event simulation model and validated it using the results from the studies presented in this thesis. This model will be used to evaluate more cost-effective diagnostic options and the benefits of a more sensitive test such as Ultra.

We have not addressed the impact of health system optimisation on the impact of Xpert. Several aspects are worth testing, including the use of a reflex laboratory testing algorithm for routine culture amongst HIV-infected

cases with Xpert-negative test results (to assess the impact on TB yield) and improved management practices to address the issues described above.

One of the key benefits of the Xpert-based algorithm is the reduction in treatment delay (from diagnosis) for TB and MDR-TB patients. However, we need to evaluate pre-diagnostic delay (from symptom onset to first healthcare access) to fully assess this benefit. Two systematic reviews (70,71) suggested that patient delays contributed significantly to overall diagnostic delay. In one of these patients reported average delays from symptom onset to first health care visit of 5–162 days (33) and in the other 7-69 days (34). Our qualitative study on MDR-TB patient pathways *(Chapter 6)* suggested that these delays are lengthy. It is difficult to know whether delays are likely to be shorter in TB patients than they are in MDR-TB patients. Assessing this for both groups will provide a better understanding of the potential benefit of the Xpert-based algorithm in reducing overall delay.

Addressing the health system weaknesses that have been identified in these studies is a key priority before the next new diagnostic test is considered for South Africa. We need to ensure that systems are adequately prepared to fully realise the benefits of future investments.

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Supplementary Chapter: Global to Local Policy Transfer in the Introduction of New Molecular Tuberculosis Diagnostics in South Africa

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ABSTRACT

Setting: Lack of innovation in diagnostics has contributed to tuberculosis (TB) remaining a global health challenge. It is critical to understand how new diagnostic technologies are translated into policies and how these are implemented.

Objective: To examine policy transfer for two rapid molecular diagnostic tests, GenoType ® MDRTBplus and Xpert ® MTB/RIF, to understand policy development, uptake and implementation in South Africa.

Methods: A Policy Transfer Analysis framework that integrates the key dimensions of policy transfer into one coherent model was used. Two phases of key informant interviews were undertaken with a wide range of stakeholders.

Results: Both tests were developed through innovative partnerships and responded to urgent public health needs. GenoType was introduced through a process that was more inclusive than that for Xpert. National policy and planning processes were opaque for both. Implementation, maintenance and expansion suffered from poor communication and coordination, insufficient attention to resource implications, technical challenges and a lack of broader health systems thinking.

Conclusion: Our analysis identified the risks and benefits of partnerships for technological innovation, the complex intersections between global and national actors and impact of health systems on policy transfer, and the risks of rescue- and technology-focused thinking in addressing public health challenges.

Key words: tuberculosis; GenoType® MDRTBplus; line-probe assay; Xpert® MTB/RIF; health systems

INTRODUCTION

The lack of innovation in tuberculosis (TB) diagnostics has contributed to TB remaining a global health challenge. For decades, TB control programmes used long-standing methods of smear microscopy, culture, and conventional drug susceptibility tests for diagnosis of TB and drug resistance. The low sensitivity of smear microscopy, slow culture methods, and poor availability of laboratory infrastructure contribute both to under-diagnosis and delays in diagnosis and treatment, including drug resistance.[1]

The development of new rapid molecular diagnostic tests for TB has the potential to change this. Two of these, GenoType MTBDR*plus* (Hain Lifescience GmbH, Nehren, Germany) line probe assay (LPA) and Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) (Xpert) were approved for use by the World Health Organisation (WHO)[2, 3](see Table 1 for test details). These tests hold the promise of quicker diagnosis of TB and drug resistance and should enable quicker linkage to treatment, with concomitant patient- and population-level benefits of reduced morbidity and mortality.[1] Effective use of these new technologies thus holds the potential to improve TB control.

However, global TB control efforts have shown that having the right tools will not by itself resolve complex medical and public health challenges.[4, 5] We will likely confront numerous barriers in making the most of new diagnostic technologies. For example, strong evidence of test accuracy and support among experts for their use is often not enough to encourage national policymakers to adopt them.[6, 7] Even when good policies are taken up, health systems challenges often contribute to the failure to deliver optimal care.[8] It is critical to better understand how promising new technologies are translated into global and national health policies and how effectively and appropriately these policies guide local implementation.

'Policy Transfer' and Molecular Diagnostics for TB

Health policy analysis usually investigates how policy is shaped and is compatible with principles such as equity. Policy analysis often remains descriptive, explaining 'what happened' without investigating 'how' and 'why' it happened[9] and the implications for policy adoption, implementation and maintenance. Policy analysis tends to focus on the content of policies, and less on the pre-adoption and early policy formulation process.

The concept of 'policy transfer' has long been used in political science as a more expansive approach to policy analysis to examine how policy ideas 'travel' and the process by which actors borrow policies that were developed in one setting and apply them to another, including analyses of the power relations between actors.[10, 11] More recently, health policy analysts have used these concepts to investigate policy advocacy and development, policy diffusion, and translation of policy into practice—together referred to here as 'policy transfer'.[12, 13]

Policy Transfer Analysis (PTA) uses a conceptual framework that integrates the key dimensions of policy transfer into one coherent model.[13] While several studies have used core concepts of policy transfer to guide their analysis[14], having an explicit conceptual framework that defines and integrates these concepts helps to ensure that analyses are more rigorous internally, and more useful when drawing comparisons across studies.[11]

The Figure and Table 2 capture the key components of the PTA framework set out by Bissell et al[13], including the policy contexts and nature of policy innovation; the main actors, networks and resources involved; the forms of communication and cooperation that emerge; and the stages of policy initiation, uptake and diffusion, implementation, and maintenance. Also critical to the PTA framework are the dynamic relationships between these components. Taken together, the PTA framework can generate a thorough understanding of multiple factors that shape policy development and implementation.

Understanding policy transfer requires more than research into policymakers' perspectives and the movement of ideas and policies from one setting to another. It also requires an examination of the role and motivations of other decision-makers, programme managers, researchers, private sector stakeholders and frontline implementers. Finally, policy transfer analysis requires understanding the types of communication and decision-making processes across levels—from global to local — and through different stages and activities over time.[10]

The present study examined policy transfer for GenoType LPA and Xpert to understand how these promising new technologies were taken up, adapted and delivered within local health systems. It was part of a PROVE IT (**P**olicy **R**elevant **O**utcomes from **V**alidating **E**vidence on **I**mpac**T**) evaluation to assess the impact of new molecular diagnostics on the diagnosis and treatment of TB in routine operational conditions (http://treattb.org).

METHODS

Setting

TB is the leading cause of death in South Africa and the country is battling one of the largest TB epidemics in the world. In 2010, there were an estimated 490 000 TB cases in South Africa, with 396 554 (72%) notified.[15] Of the estimated 9,200 MDR-TB cases, 7386 were notified.[15] The burden of human immunodeficiency virus (HIV) infection is also extremely high, affecting 5.02 million individuals in 2010.[16] Amongst TB cases tested for HIV, 60% were co-infected.[15] The country has made progress towards international TB treatment outcome targets, but has failed to contain the epidemic and now has the highest risk of TB disease compared to similar-sized countries globally.[17]

TB is managed largely within the public healthcare system, with diagnosis and treatment at the primary healthcare (PHC) level. Secondary-level specialist TB hospitals treat more complex cases and DR-TB. The National Health Laboratory Services, a parastatal organisation, provides TB diagnostic services to the public sector, mostly through centralised laboratories that are concentrated in urban areas. Prior to the introduction of molecular diagnostic tests, sputum microscopy formed the basis for TB diagnosis; culture was available for smear-negative, HIV-infected cases with conventional drug susceptibility testing for previously treated patients.

In South Africa, the National Department of Health develops policies and Provincial Departments are tasked with their implementation. TB policies align with WHO recommendations. The country was an early adopter of molecular TB diagnostic tests. Following the WHO Policy statement in 2008,[2] GenoType LPA replaced conventional first-line drug sensitivity tests (DST) for rifampicin (RMP) and isoniazid (INH), with testing

recommended on smear-positive clinical specimens and culture isolates. Xpert was introduced prior to the release of WHO's 2011 policy statement[3], which recommended its use as the initial diagnostic test in individuals suspected of multidrug-resistant (MDR)-TB or HIV-associated TB. Xpert, which is more sensitive than smear microscopy[18], promised to bring molecular TB diagnostics closer to the point of care, reducing bottlenecks between diagnosis and treatment.

Study design

We used a longitudinal, qualitative evaluation to track policy transfer with the introduction of Xpert and GenoType LPA in South Africa. Two phases of key informant interviews were complemented with reviews of quarterly reports from health and laboratory services and other relevant documents.

Key Informants

Key informants were eligible for participation if they were involved in some component of the policy transfer process. Key informants were sampled purposively to ensure those selected had knowledge and experience of LPA and Xpert from development and production, to evaluation, policy formulation, national and local implementation. In cases with few potential participants (e.g. international policymakers), we aimed to include one or two key role-players in each setting. In cases with many potential participants (e.g. frontline staff), we sampled purposively to maximize the range of roles, perspectives and service contexts. Local implementation was limited to experiences in Cape Town, the second largest city in South Africa.

Data collection

Our research team comprised four senior social scientists (NL, CW, KB, CC) (the latter two with experience in policy analysis), two field researchers (KM, CP), a health sciences researcher (MvN) and two medical researchers (PN and EDT). None of the researchers were involved in policy development or test implementation.

The first phase of key informant interviews in 2011 assessed the adoption of LPA in 2008-2009. The second phase in 2012-13 evaluated more recent changes with implementation of Xpert. Interviews were conducted in person if possible, and via telephone if not. These lasted between 1 and 2 hours and were guided by a set of topic guides (based on the PTA framework), tailored to different participant types. We aimed to speak with the same people in each phase. When this was not possible, we recruited participants who played a similar role. Interviews were digitally recorded, transcribed and summary reports compiled.

We reviewed quarterly process evaluation reports from 10 health facilities, City and Provincial TB Managers, and the laboratory from 2011-12. A standard template assessed activities or events related to TB diagnostics, people or organisations involved, challenges experienced and adjustments to health systems and processes. We also reviewed policy documents, meeting minutes, and communiqués related to the development, evaluation and implementation of LPA and Xpert.

Data analysis

Data analysis began with thematic analysis of the interview transcripts and progressed towards an interpretive explanation of policy transfer. The PTA framework was used to organize findings and identify key aspects of

the process. Triangulation among participants and the two rounds of interviews was done to test emerging explanations and identify important variations in findings. Data analysis was iterative. Ongoing analysis of emerging findings was conducted regularly by the key interviewers (CC, NL, CW and MvN). The broader research team participated in several rounds of more formal data analysis after each phase of interviews.

Ethics

The Health Research Ethics Committee at Stellenbosch University, Cape Town, South Africa (IRB0005239) (N10/09/308) and Ethics Advisory Group of the International Union Against Tuberculosis and Lung Disease, Paris, France (59/10) approved the study. Written or verbal (for telephonic interviews) informed consent was taken from key informants.

OVERVIEW OF THE RESULTS

Key Actors and Timelines

We interviewed 40 participants each about LPA and Xpert. A table showing the key actors involved in policy transfer and those interviewed is provided as an online Appendix Table A1. At the global level, participants included global TB policymakers, executives and experts at the companies developing the diagnostic tests, advocates for TB diagnostics and South African researchers involved at the global level. At the national level, we spoke with policymakers and managers in the TB Programme and the National Health Laboratory Service (NHLS) and researchers involved in demonstration studies. At the provincial and local levels, participants included policymakers and managers as well as front-line staff working in clinics and the TB hospital.

We provide a timeline of key events related to policy transfer for LPA and Xpert as an online Appendix Table A2, starting with the establishment of the TB Diagnostics Initiative (TBDI) by the WHO in 1996 and tracing key events at the global level and in South Africa.

Organization of Findings

We have organized the findings into two main sections. The first tracks policy transfer at global level and the second at national level. We draw the distinction between these not by the location of actors, but by the aspects of policy transfer at stake. Global-level findings address the processes of developing new diagnostic technologies, producing evidence of accuracy and efficacy, and global policymaking. National-level findings address the translation of global policy recommendations into national and local policies for implementation.

Our description of policy transfer follows the key domains of the PTA framework. Some of these have been combined (e.g. ‘context’ and ‘policy innovation’) for simplicity and others have been omitted when less relevant (e.g. ‘implementation’ issues at the global-level). We have combined LPA and Xpert findings but have identified points where important differences between the two emerged.

POLICY TRANSFER AT THE GLOBAL LEVEL

Context and Policy Innovation

Over the last two decades, global public health institutions have identified an urgent need to develop new TB diagnostics that can rapidly diagnose TB and identify DR-TB strains to reduce barriers to timely, appropriate treatment.[19] In 1996, the WHO established the Tuberculosis Diagnostics Initiative (TBDI) to improve case detection.[20] Their survey of more than 50 companies with TB diagnostic tests in their research and development portfolios identified numerous barriers to developing new TB diagnostics, including lack of funding, poor understanding of the type of tests needed, limited access to reference clinical material, poor availability of clinical trial sites, and limited familiarity with markets in those parts of the world most affected by TB.[21, 22] Recognition of these barriers led, in 2003, with Gates Foundation support, to the creation of the Foundation for Innovative New Diagnostics (FIND). FIND's aim is to promote and facilitate the development, evaluation and use of improved diagnostics for tuberculosis and other infectious diseases.[22]

FIND played an important role in catalysing the development of GenoType LPA and Xpert® MTB/RIF tests and in bringing them to market. By 2006, FIND had identified GenoType LPA (developed by HAIN Diagnostics) and Xpert® MTB/RIF (developed by Cepheid) as promising tests and worked with the companies to build the business case for their development for public sector use in high-burden countries.[23]

Other developments within the broader global public health community complemented these efforts, most notably, the launch of the Stop TB Partnership's "Global Plan to Stop TB" in 2006, supported by funding from The Bill & Melinda Gates Foundation, the Global Fund to Fight AIDS, TB & Malaria and UNITAID.[24] The 'Tugela Ferry' outbreak in South Africa[25] heightened global concern around the growing problem of DR-TB. According to an international participant, *"it was the outbreak in Tugela Ferry that prompted"* the speed with which new diagnostics were brought to the field. There were also perceptions among some that it was not only the local epidemic that led to the rapid deployment of new diagnostics and in the words of a South African manager this *"appeared dependent on international interests and lobbies."*

Knowledge and Learning

Laboratory studies were followed by large-scale demonstration studies to determine test accuracy under field conditions. LPA studies were implemented in Russia, Uzbekistan, Nepal and in four South African provincial laboratories in July 2007 and for Xpert in Peru, Azerbaijan, India and South Africa in August 2009.

According to an international informant, South Africa was chosen as a demonstration site for both tests for several reasons. It was one of 22 high-TB burden countries initially consulted by the WHO as part of efforts to develop new diagnostics. South Africa was considered an excellent testing ground because of its high TB burden, being at *"the epicentre for the MDR and XDR outbreaks",* its *"relatively good health and laboratory infrastructure"*, its *"research expertise"* and *"existing relationships"* with research institutions**.**

In South Africa, FIND partnered with the National Department of Health (NDOH), NHLS and the South Africa Medical Research Council (MRC) for LPA and University of Cape Town (UCT) for Xpert to conduct demonstration studies.

Interactions among key players at the national level, however, differed significantly between the LPA and Xpert demonstration studies. For LPA, a wider range of role-players were involved, with close collaboration between FIND, WHO, the MRC, NDOH and NHLS. The NDOH provided national co-ordination, with provinces taking more control over planning and implementation (especially within laboratory services). MRC researchers were actively involved in coordinating the demonstration study with NHLS and NDOH, providing another layer of national-level interaction and a degree of credibility for the findings. In provinces with demonstration sites, there was also direct involvement of the Provincial Departments of Health (PDOH) and TB managers.

By contrast, the Xpert demonstration study was conducted in two sites (both in the Western Cape) and was reported to have involved primarily FIND, NHLS, UCT researchers, and the office of the National Minister of Health. National and Provincial Departments of Health and TB control programme were involved to a far lesser extent than with LPA, despite the fact that Xpert required extensive changes in routine operations.

Persuasion and decision-making

During the development and evaluation process, WHO played a central role, bringing leadership, structure and credibility to the process by advocating for better TB diagnostics, linking key actors in the policy and research communities with efforts by FIND and HAIN/CEPHEID, and providing the platform for translating the research evidence into recommendations. For both tests, WHO's involvement was reported to have been channelled through the Strategic and Technical Advisory Group (STAG), which reviewed early evidence from laboratory and demonstration studies using its well-established guideline development process [26], and made policy recommendations. In the words of an international informant, this proceeded *"in a very systematic way"*. For LPA, WHO convened an Expert Group to review the findings in March 2008 and released its policy statement in June of 2008.[2] For Xpert, an Expert Group was convened in September 2010 and the policy statement released in May 2011.[3]

POLICY TRANSFER AT THE NATIONAL LEVEL

Context and policy innovation

International attention after the Tugela Ferry XDR-TB outbreak catalysed the national response for LPA. A health department participant noted that after the *"massive XDR outbreak at Tugela Ferry….WHO descended on the country." "We were under pressure, and at the TB conference in June the Minister pronounced that we will scale up this test [LPA] from January 2009".*

The Tugela Ferry outbreak cast a spotlight on a problem that many health providers knew had been quietly brewing for years, driven by both HIV and government's inadequate response to both diseases. This same period marked the beginning of the end, however, of the denialist era in the National Department of Health, and by 2008, President Mbeki and his Health Minister were both out of office. A concerted effort soon emerged among national political leadership to demonstrate renewed commitment to tackling public health crises facing the country, evidenced for example by the increased pace of the public sector rollout of antiretroviral therapy.

Participants reported that the DR-TB focus produced other shifts. Monitoring and evaluation of DR-TB control efforts were strengthened through the creation of paper-based and electronic registers. In Cape Town, health worker roles in TB control were re-assigned and capacity was added with a nurse and counsellor appointed in each sub-district to facilitate access to DR-TB treatment.

Despite the increased attention, however, participants expressed frustration that health services were still often unable to make substantial impacts on the management of DR-TB. When LPA was introduced, DR-TB treatment was still highly centralized to TB hospitals. One local manager said:

> *"We haven't shown any significant improvement because of this whole centralised way of managing things … we should be able to make an earlier diagnosis and initiate treatment a lot sooner … [but] we've got to reorganise and reengineer our services...to get the maximum benefit from the technology that's now available"*

In Cape Town, a limited form of decentralisation was started where treatment could be initiated at PHC level after patient's records were reviewed at the TB hospital and a prescription was sent to the clinic. Working under direction of the TB hospital created uncertainty about who took ultimate responsibility for treatment as expressed by a local manager:

> *"What you must take into account is that 80% of our patients do not get admitted to hospital according to the National Policy. They get managed at primary care level. So unless I strengthen the services at a primary care level how on earth can I expect good management of these patients when I get told it's somebody else's responsibility not ours and I don't empower the people* [at PHC level]?"

PHC staff reported being more proactive when directly responsible for treatment decisions after full decentralization of care with Xpert.

LPA and Xpert were both policy innovations consistent with the health system's renewed focus on improving DR-TB control. Their introduction, however, was not well integrated with other efforts to strengthen the health system and there were missed opportunities to take advantage of the reduced laboratory turnaround times, as explained by a local informant:

> *"[if] there is going to be a change, [we should] understand what else we need to do to improve the management of MDR patients … it is now a shorter period to getting a diagnosis, but systems issues also need to be addressed… e.g. starting treatment…or getting a script from the doctor … From the time that we get the result it takes another week to get patients onto treatment."*

Knowledge and Learning

The LPA and Xpert demonstration studies were designed to assess test accuracy in field conditions; they were not designed to assess their pragmatic effectiveness in operational conditions. Information on how these new tests could be integrated most effectively into the health services and cost effectiveness data was limited. As a result, very little knowledge was created about the potential role and function of these innovations in the local operational context.

For LPA, once the demonstration study concluded in 2007, the NHLS simply continued routine use of LPA at demonstration sites. The test had proven accuracy and feasibility and from their perspective, there was no reason to return to previous, slower forms of drug sensitivity testing. Clinic staff reported not knowing that a

new test had been introduced and many were not aware of its potential benefits in terms of reduced turnaround times. One health provider commented:

> *"We normally get a communication to say…this is going to happen, this is how processes are going to change, and this is going to be the impact. So we never formally received any of that information … there was never formal communication"*

A year later, national rollout of LPA commenced with donor support and continued slowly over the next few years; by 2011 only 12 of the 20 designated sites were reported to be "*fully operational*". A manager who commented on the obstacles to planned rollout noted that:

> *"They didn't articulate the practical issues that were required at the time, and even the infrastructural issues that were required."*

As changes brought about by LPA occurred largely at a laboratory-level, it passed under the radar for many and knowledge at facility level was limited. LPA demonstration study feedback to health staff in Cape Town only occurred in August 2011, after Xpert implementation had already commenced.

With Xpert, in contrast, the media attention during its introduction was considerable and awareness of Xpert as a potentially important innovation in TB control was relatively high, both among healthcare workers, and the public. However for both LPA and Xpert it appeared little effort was made to collect additional information during initial implementation to inform broader national rollout. Nor was there much attention to how to take advantage of the expected reductions in laboratory turnaround times.

Persuasion and Decision-making

In South Africa, decisions to adopt LPA and Xpert either closely followed (for LPA) or emerged in parallel with (for Xpert) global policy. In an ideal policy transfer process, policy innovations in one context spark a process of knowledge and learning, that leads to a period of persuasion and decision-making as policy is finalized and adopted. For both LPA and Xpert, however, these steps were significantly foreshortened. Participants reported that in neither case were there explicit processes of persuasion and decision-making that included relevant stakeholders.

For LPA, the involvement of national and provincial TB programme managers in the demonstration study resulted in some awareness of the new test and deliberation about its place in TB control efforts. Engagement of national and provincial DOH managers during the demonstration study appeared to have generated a positive sense of involvement and anticipation of the improvements promised by LPA.

This engagement, however, did not appear to have translated into changes at the level of service-delivery. While the NHLS perceived LPA's introduction as primarily an internal change, for clinicians, the new test meant quicker laboratory turnaround times. Taking advantage of this required clinicians to ask patients to return sooner to the clinic. Many of the clinicians we spoke to were unaware of its use, had not anticipated faster turnaround times and did not therefore take advantage of LPA benefits. In many cases, this was understandable as tests were performed on culture isolates rather than on positive smears, delaying test results:

> *"As far as I understood we would get the sensitivity test much sooner but I must say up to now I haven't noticed a difference in receiving this. We still get our culture and sometimes we get the culture*

> *and the sensitivity on the same page but it's still after the same [number of] days as when the culture was positive."*
>
> *"There wasn't a change at all like the way I understood it where PCR would maybe be done on the smear ... then immediately the sensitivity would be done and within two days we're supposed to get the sensitivity result, which hasn't happened yet."*

With Xpert, persuasion and decision-making was quicker and much less inclusive. It was characterized by strong, vertical interaction between FIND, WHO, the National Health Minister's office, and NHLS, sidelining to some extent key national and provincial actors in the TB programme. The National Minister took the lead in supporting and driving the implementation of Xpert. Managers observed that:

> *"The sheer pressure we had in the TB world then, with the minister taking TB … and even drug-resistance very seriously, the pressure was actually unbelievable at the time."*
>
> *"It happened very quickly. I think once it was endorsed and FIND said go, and WHO said go, it came. By March 21st[2011]… the message was clear that by the World TB Day they wanted to have so many instruments installed … "*

TB managers and local health services staff alike experienced the decision-making and implementation of Xpert as fast-paced, with little horizontal co-ordination or communication, despite the fact that Xpert involved more on-the-ground changes than LPA. Xpert was introduced in several sites before a national testing algorithm had been finalised. The rapid pace of implementation meant there was little time to assess its operation and integration into local contexts, and in the words of one manager, many staff felt that Xpert seemed to have just *"fallen out of the sky"* at a time when their focus was still on completion of the LPA rollout.

It would seem that these relatively thin, uneven processes of persuasion and decision-making were not only the result of particular sets of actors and agendas, they also reflected a broader disconnect between the Departments of Health and the NHLS, a semi-independent parastatal institution. While frontline health services constantly engage with NHLS, collaboration appears to vary between the two sets of actors at higher levels. Despite NHLS having provincial liaison officers working to improve the relationships with health services, serious gaps still exist.

Implementation

The ways in which LPA and Xpert were implemented in the health system were largely shaped by the character of policy transfer described above. While there were generally positive impressions of LPA among national, provincial and facility-level staff, and optimism it could dramatically improve time to appropriate treatment, there was little written or verbal communication about the specific changes LPA would entail or how to take advantage of them.

Similarly, the general view regarding Xpert among key informants, from national policy makers to frontline staff, was that there was a lack of communication and planning regarding implementation between the laboratory and health services and at all levels of the health system. One manager in Cape Town noted:

> *"The powers that be think of policies as this thing that gets done in an ivory tower with a group of experts that come together … they actually haven't a clue of what happens on the ground. There is a disconnection between what they think can be done and potentially what gets done … Once the*

> *policies are developed .... they feel good and they consider their job is done … They actually do not realise that after the policy is developed, the real work starts in turning that policy into reality".*

This was of particular concern not only because of potential missed opportunities but also because Xpert required more substantial changes at facility level, such as changes to TB testing algorithms (finalized only after implementation), and to laboratory test request forms and National TB registers that had not been adapted to reflect Xpert results. Several participants reported that insufficient attention was paid to changing the management processes required to optimise the impact of Xpert on service delivery. For some, there was also concern over a perceived lack of diagnostic performance with Xpert:

> *"… I think some of us have the perception that now with using the Gene Xpert up front, we would have diagnosed those [with negative smears who never came back for culture]… but the TB numbers seem to have remained the same and I am not sure why that is."*

During implementation, cost issues also came to the fore. LPA had human resource and infrastructure implications at the laboratory level, requiring dedicated space suitable for polymerase chain reaction testing and suitably trained technicians, in addition to the cost of consumables. There were no initial cost implications for the broader health system as donor funds were used for capital, start-up and initial recurrent costs. It is not clear, however, to what degree longer-term, ongoing costs of LPA were planned for. Although data on ongoing costs were not available during our research, managers and even some frontline staff expressed concerns about the high costs of LPA.

Similar concerns were expressed about the costs of Xpert. Both managers and staff perceived Xpert to be a very expensive test and expressed concerns about the costs of machines and cartridges. Frontline nursing staff identified this as their main concern about the test. It is unclear to what extent costing informed the rollout of Xpert. Participants reported that donor funding was an important catalyst for the quick initial implementation of both tests but this also may have led to insufficient attention being paid to ongoing resource requirements.

Beyond the direct costs of these tests, however, there were also concerns about the strategic and equitable use of resources during implementation. For example, although many anticipated using Xpert at point-of-care, only a few machines were initially purchased. Consensus amongst national laboratory and health managers that PHC facilities did not have the necessary infrastructure for Xpert resulted in machines being placed at hospital laboratories in selected, often well-functioning sub-districts. Provincial and district managers did not guide these decisions and some were unaware of the criteria used for selecting sites. Key informants expressed concern that Xpert machines went to laboratories that already had LPA and argued they would have been better placed in areas with no access to improved TB diagnostics.

Maintenance and Expansion

The final steps of the policy transfer process—maintenance and expansion—were marked by a similar set of challenges and missed opportunities. There was little attempt to understand the impact of either test on TB programme performance.

The technical challenges of LPA were highlighted by a participant:

> *"It very much depends on the level of proficiency of the technician … there were considerable barriers to implementing the technology in the typical developing country … there [were] high expectations on*

> *the one hand tempered by the realization that it did require expensive sophisticated lab infrastructure, additional resources … plus it was, and still is, an expensive technology."*

Technical concerns were expressed around the potential of false-positive RMP-resistant results with Xpert, an issue that is now well documented.[18,27] For those using Xpert, these concerns were in addition to numerous technical challenges for maintenance, calibration, repairs, and downtime of machines that were not well planned for or supported.

Many participants expressed the need for ongoing training and support among end-users. The once-off 'train on Friday and implement on Monday' approach adopted with Xpert did not adequately meet end-users' needs:

> *"Never underestimate the training requirements a new technology needs, not so much for the lab personnel as they caught on quite quickly in the instance of Xpert, but it's training the clinicians, the nurses, making them feel comfortable and confident with the result."*

Finally, a stock-out of Xpert cartridges posed a problem for maintenance and expansion of the test. The manufacturer did not anticipate the rapidly increasing demand as a consequence of the rapid rollout in South Africa and its transition to a new manufacturing plant resulted in a stock-out that lasted 6 weeks. While the availability of cartridges has been resolved for the time being, some policymakers expressed ongoing concerns about reliance on one company for key TB diagnostic supplies.

DISCUSSION

The findings presented above reveal a number of important commonalities and differences in policy transfer for GenoType and Xpert. Both tests were developed through innovative partnerships between global health governance, non-profit, for-profit, and academic sectors. Both responded to an urgent public health need and enjoyed strong political buy-in and the global policy development process, led by WHO, unfolded with relatively little controversy.

Nationally, there was greater variation in policy transfer. The introduction of the GenoType LPA test to South Africa as a demonstration study involved a range of stakeholders and enjoyed strong buy-in, but the eventual decision to adopt LPA was poorly communicated and its rollout relatively slow. On the other hand, the introduction of Xpert took a more rapid, verticalised approach, driven by the office of the Minister of Health. Xpert enjoyed high visibility, but the process of developing local policy for Xpert and planning its implementation was opaque in much the same way it was for LPA.

Although there were important differences in implementation, maintenance and expansion of LPA and Xpert, in both cases, processes were characterised by poor communication and coordination, insufficient attention to resource implications, technical challenges and a lack of health systems thinking in integrating these diagnostics into the TB control programme. The pace of National rollout of Xpert was such that emerging evidence showing a lack of impact on case-finding,[28, 29] morbidity,[28] and mortality[29, 30] had little influence.

Our interpretive explanation of the policy transfer process highlights a number of broad lessons, including the risks and benefits of strategies for technological innovation in health, the complicated intersections of global and national actors in policy transfer, the impact of local health systems on policy transfer, and the risks of rescue- and technology-focused thinking in addressing public health challenges. These are discussed below.

Risks and Benefits of Models for Catalysing Technological Innovation

One lesson at both the global and national levels is that private sector, donor and non-profit support can be critical in catalysing development and implementation of new technology, but their involvement also entails risks. Advocacy by FIND was crucial in catalysing development of GenoType LPA and Xpert and donor funding was crucial in producing evidence from demonstration studies and in the initial national rollout.

Complex conflicts of interest, however, are possible between FIND, the WHO and private companies with respect to advocating for particular platforms, and in particular how these efforts can end up establishing reliance on a single provider for crucial health technologies. It is unclear to what extent the establishment of the South African Health Products Regulatory Agency, tasked with independent assessment of diagnostics, will provide a neutral process that circumvents potential conflicts of interest and generates adequate evidence to inform scale-up.

The use of donor support to introduce new technologies can produce unintended consequences. It can distort perceptions of feasibility by masking start-up and recurrent costs. For Xpert, there appear to be real risks to its sustainability and cost effectiveness as a screening test for TB.

Intersections between Global and National Actors, Agendas and Activities and Impacts

Another important feature of both policy transfer processes was the closely intertwined character of actors, agendas and activities across levels. In both cases there was no clear division between finalisation of global policy recommendations, and commencement of local policy and decision-making. National policy decisions sometimes anticipated and even moved ahead of global policy recommendations. In the case of GenoType, this seems to have been largely the result of well-functioning demonstration sites simply continuing to use GenoType after the study was completed but before global or national policy recommendations. For Xpert, demonstration sites did not simply continue to use the test, but political pressure to adopt Xpert was strong and national policy preceded global policy.

An important explanation for the parallel character of global and national policy development is the fact that local and global experts and advocates often ‘cross’ levels at several stages in policy transfer. South African experts were involved in global policy development, partly as a result of their direct involvement in the demonstration studies, and their involvement helped smooth the way for the acceptance of Genotype and Xpert in South Africa. Conversely, global actors such as FIND played an important role at a national level in advocating for both tests and supporting the implementation of Xpert.

The Health System as Concept and Context for Policy Transfer

At the national level, the health system itself was a critical conceptual and contextual factor in policy transfer. On one hand, the *concept* of the health system seemed absent in many accounts of policy transfer. Both managers and frontline staff described numerous missed opportunities to adopt a health systems approach to implementing these tests, leading to unnecessary delays and inefficiencies. There was a perception among several informants that the net benefits of these tests were not being realised, except perhaps in a few facilities.

Overall, there appeared to be weak links between demonstration studies and policy development; lessons learnt were not transferred, and managers and frontline staff were left to make use of the new technologies with insufficient guidance or support. This gap was most tangible at the national level but was also found at the global level where the challenges of developing locally appropriate and sustainable translations of policy were given little attention and tools were not available to support countries through implementation.

It is also important to note that the structure and function (or dysfunction) of the health system in South Africa itself also acted as a critical *contextual* barrier to a more holistic health systems approach. Barriers included weak health system planning and management as well as a persistent disconnect (at all levels) between the Departments of Health and the NHLS. This disconnect is especially relevant since the diagnosis of TB requires a higher degree of coordination between clinicians and laboratory services than other diseases.

Habits of Thought: On Rescue and Techno-Optimism

Two 'habits of thought'[31] help to explain the lack of health systems thinking in implementing these new technologies. The first is the tension between 'rescue' and 'management' in health services planning and delivery. This is the tension between the urgent need—and desire—to save lives through medical rescue, and the often less readily apparent but equally important need to produce strong evidence, carefully manage change in the system, and evaluate the process and impact of new interventions. It is possible that a sense of medical, social, and moral urgency, particularly with Xpert, contributed to the rapid, poorly strategized implementation of the test, resulting in numerous missed opportunities This is not to say that Xpert has not had an impact, or that longer-term benefits will not outweigh shorter-term costs - answers to these questions are still emerging. What is clear, however, is that chances to strengthen implementation and avoid mistakes were missed as a result the tension between competing imperatives of rescue and management.

The second "habit of thought" that worked against health systems thinking is a familiar one in the history of global disease control efforts — an over-reliance on technological solutions to complex health challenges. Among our informants, there was widespread confidence in the basic technologies underlying GenoType and Xpert and optimism about their potential impact. This may have crowded out careful thinking about how best to integrate the tests into routine practice. This was especially true of Xpert, which garnered a great deal of praise for its straightforward, modularized, and 'portable' design. To be fair, there was no lack of recognition among informants about the practical challenges of implementing Xpert. What seemed to be lacking, however, was recognition from the outset that even the most trusted and easy to use technologies entail new, often considerable health systems challenges that need to be anticipated and actively managed.

Limitations

This study had several methodological limitations. LPA was implemented in 2008 but interviews on LPA were only conducted in 2011. This may have introduced recall bias in comparison to interviews about Xpert, which were conducted during implementation. Not all key informants were interviewed due to scheduling difficulties towards the end of the project; however, we feel adequate information was derived from completed interviews and saturation of key findings was reached. Interviews at the service delivery level were limited to Cape Town, a relatively well-resourced and managed urban setting with good health and laboratory infrastructure.

Documentation of decisions, events and processes, especially at the national level, was often poor. This meant we often had to rely on verbal information to document policy transfer. The wide range of stakeholders interviewed allowed triangulation of data and increased confidence in our findings.

Finally, we have not included the end users of TB services—the patients—in our analysis. As part of the PROVE-IT study, we evaluated MDR-TB patients' experiences and pathways to diagnosis and treatment, and these findings will be published elsewhere.

CONCLUSION AND RECOMMENDATIONS

Analysing global, national and local processes of policy uptake and implementation can help to inform rational and effective adoption and scale-up activities.[9, 13, 32] This analysis has highlighted process and programmatic issues that influenced policy transfer.[33] We summarise the key lessons learnt and offer some recommendations in Table 3.

Amongst our recommendations is the need to identify and manage conflicts of interest that may arise when innovative partnerships are established to address public health issues. We suggest that the role of committed leadership in fast-tracking processes needs to be matched with a national policy consensus process and careful, transparent planning. As scale-up requires evidence beyond that generated from demonstration studies, impact data should be collected during early implementation and used to inform national scale-up.

By incorporating both descriptive and explanatory components in the analysis we hope to contribute to the body of policy transfer research in a way that can strengthen policy development and implementation and help to ensure innovative new diagnostics lead ultimately to improved patient and population health.

Table 1 Characteristics and Performance of GenoType MTBDR*plus* and Xpert® MTB/RIF

	GenoType LPA	Xpert® MTB/RIF
Overview	• Simultaneously detects resistance to isoniazid and RMP from direct smear-positive clinical specimens or culture isolates • Provides a result for smear positive specimens in 1-2 days • Has separate processes for DNA extraction, amplification and hybridisation • Requires substantial technical skills and equipment and is only suitable for large, central laboratories • Specimen processing prior to DNA extraction produces aerosols and requires bio-safety precautions • The test is prone to contamination	• Simultaneously detects mycobacterium complex and resistance to RMP from direct clinical specimens (smear-positive and negative) • Test processing takes about 2 hours (can therefore provide results within 1-day) • Uses an integrated system in which sample preparation, DNA extraction, amplification and identification are automated and take place within a closed cartridge (preventing contamination) • Equipment is suitable for use in decentralised settings as it does not require a high level of technical skills • Equipment requires a temperature controlled environment, stable electrical supply and annual calibration and is thus not ideally suited to point of care testing
Test performance	• A meta-analysis of ten LPA studies showed high sensitivity (98.1% (95% CI 95.9 to 99.1)) and specificity (98.7% (95% CI 97.3 to 99.4)) for RMP resistance and lower, more variable sensitivity of 84.3% (95% CI 76.6 to 89.8) and specificity of 99.5% (95% CI 97.5 to 99.9) for isoniazid.[34]	• A Cochrane Review of fifteen studies where Xpert was used as the initial test replacing smear microscopy, yielded a pooled sensitivity of 88% (95%CrI 83% to 92%) and specificity of 98% (95% CrI 97% to 99%) for detecting Mycobacterium tuberculosis. In eleven of these studies, pooled sensitivity was 94% (95% CrI 87% to 97%) and specificity 98% (95% CrI 97% to 99%) for RMP resistance.[16]
Costs	• A multicentre study estimated reference laboratory costs (2010 $US) for MGIT liquid culture of $15.24 and for MGIT/LPA $33.01 in South Africa.[35]	• A multicentre study estimated costs (2010 $US) per Xpert test of $25.90 in peripheral and hospital laboratories in South Africa compared to smear microscopy at $1.58.[35] • Diagnostic costs increased from $28 to $137 per TB case diagnosed when Xpert replaced smear microscopy.[35]

LPA=line-probe assay; INH=isoniazid; RMP=rifampicin; CI=confidence interval; CrI=credibility interval; MGIT= Mycobacteria Growth Indicator Tube.

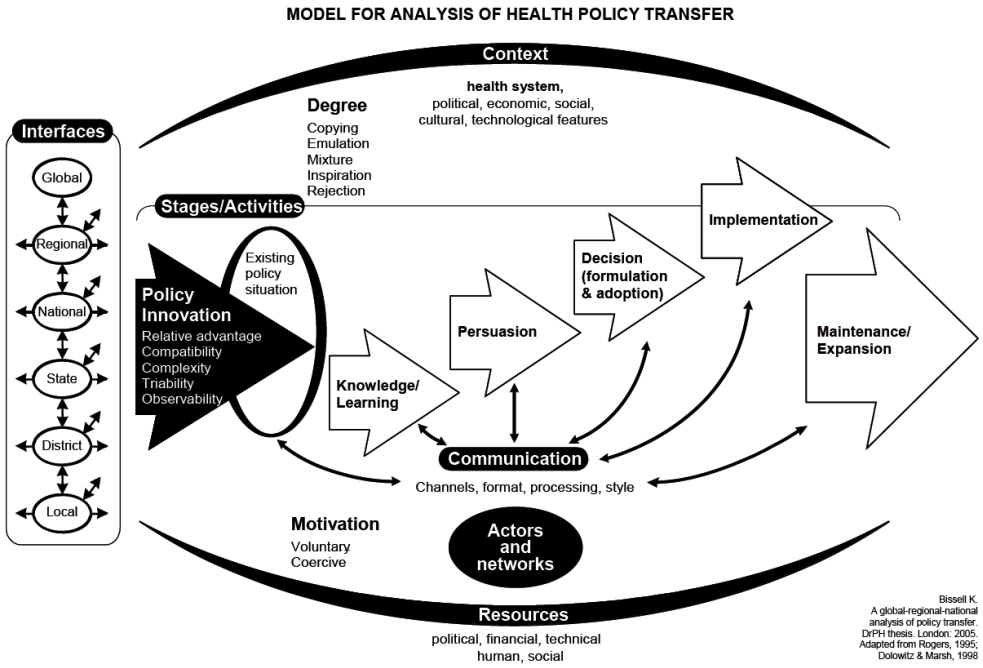

Figure: A model for the for the analysis of policy transfer[13] Reprinted with permission of the International Union Against Tuberculosis and Lung Disease. Copyright © The Union.

Table 2: Conceptual Framework for Policy Transfer Analysis [13]

Context	What was the prior policy environment? Why was there a need for innovation? What were the most significant contextual factors influencing the process? (e.g. health system, political, social, economic, cultural, technological) What was the motivation for change?
Policy innovation	What policy was adopted? Where did the policy innovation come from? What influenced selection in terms of: relative advantage; compatibility; level of complexity; triability and observability of results?
Actors, networks, interfaces	Who was involved and affected (global, national and local actors)? What role did they play? How were they linked? What shaped and mediated their action? Who supported or resisted the intervention? How do the existing structures and their dynamics influence the process? Were influences top down, bottom-up or diagonal?
Communication	What channels existed/were developed? Who communicated with whom? How was information shared? What effect did communication have in creating shared understanding? Were there misunderstandings?
Process Involved	
Knowledge and Learning	How did people learn about the policy innovation? What opportunities worked for learning? Where did ideas come from? Who had access to knowledge?
Persuasion	Who was convinced about the innovation? What evidence convinced them? Whom did they influence? How did they facilitate the transfer process?
Decision-making	What major decisions were taken? When were they made? What were they based upon? Who was involved? Who was informed? Who was excluded?
Implementation	What was implemented? What was the implementation process? Was the policy adapted?
Maintenance and Expansion	How was the policy expanded and maintained? What learning influenced expansion? What scale of change was required? What factors influenced maintenance and expansion (e.g. context, costs, degree and complexity of change)?
Resources	What are the most significant resource issues affecting the success of this process e.g. financial, technical, human, social

Table 3: Lessons Learnt and Recommendations

	Lessons Learnt	Recommendations
1. Risks and Benefits of Models for Catalysing Technological Innovation	• Development and uptake of TB diagnostics resulted from innovative partnerships between actors in the global health governance, donor, non-profit, for-profit, and academic sectors. • Donor funding, whilst important to fast-tracking implementation, can produce unintended consequences and distort perceptions of feasibility and sustainability.	• Complex conflicts of interests can arise from these partnerships. These should be identified and managed carefully. • Feasibility assessment should be based on transparent and comprehensive costing, including infrastructure development and ongoing maintenance and training costs.
2. Intersections between Global and National Actors, Agendas and Activities and Impacts	• Policy transfer was shaped by the intersection and sometimes overlapping agendas and activities across global and national levels, with national policy development sometimes moving ahead of global policies. • The urgent public health need (and response from a wide range of global and local actors), and strong support from government leadership, allowed the policy transfer for molecular diagnostic tests to be fast-tracked in South Africa.	• Urgent public health need and committed leadership can usefully contribute to fast-tracking global policy development, but this should this should be led by local policy consensus making processes (to improve buy-in) and adequate preparation at national, sub-national and local levels. • When implementation is fast-tracked, ensure that production and supply chains issues have been projected and planned for at the intended levels of use of the technology in recipient countries.
3. The Health System as Concept and Context	• On a national level, the efficiency of policy implementation was limited by poor communication between national, provincial, district and frontline managers and between laboratory services and clinical service management. • Insufficient health systems thinking weakened implementation, resulting in missed opportunities to integrate new diagnostics with broader TB control efforts. • Pre-existing health system weaknesses, such as inadequate planning processes and persistent disconnects between the health and laboratory services, impacted negatively on policy transfer.	• Develop a more cohesive and coherent approach to national-level policy transfer processes, including greater stakeholder consultation, more transparent decision-making, more thorough health system planning and budgeting and better use of existing platforms (e.g. standing quarterly meetings) for communication. • Better anticipate the needs and consequences of implementation on health system elements (such as coordination, infrastructure, supply chain and other logistics). Monitor implementation to contribute iteratively to the development, revision and adaption of local implementation guidelines.
4. Rescue and Techno-Optimism	• A tension between the need to 'rescue' (in response to urgent public health needs) and the need to carefully manage change may negatively affect the introduction of new technologies. • An over-reliance on technological solutions to complex challenges led to insufficient monitoring and support of implementation processes.	• Adopt a slower, more deliberate phased approach to national scale-up of new rapid diagnostics that includes an early phase of operational evaluation in different health contexts (e.g. high/low TB/HIV burden; urban/rural) prior to wide-scale national implementation.[36] • Once new diagnostic tests are scaled up, it is important to evaluate epidemiological impact in order to inform adaptation of policy.[27]

TB=tuberculosis; HIV=human immunodeficiency virus

Online appendices

Key Actors Involved in GenoType MDRTB*plus* and Xpert® MTB/RIF Policy Transfer

Timeline of Key Events in the Development of Molecular Diagnostic Tests for Tuberculosis

AUTHOR CONTRIBUTIONS

All authors designed the study. MVN and PN identified study participants. MVN and NL supervised the field researchers. CC, NL, CW and MVN undertook interviews, summarised key findings and identified emerging themes. All authors participated in the analysis. CC wrote the first draft. All authors provided input to this and subsequent drafts and the final manuscript and approved the submission.

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CONFLICTS OF INTEREST

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

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Table A1: Key actors involved in Genotype MTBDRplus line probe assay and Xpert® MTB/RIF policy transfer

Stakeholder	Number participants interviewed LPA/Xpert	Role in the development, approval and use of new molecular TB Diagnostic Tests and provision of clinical services
Global		
World Health Organisation	Genotype: 1 Xpert: 1	Convenes expert groups to review data from published papers, laboratory validation and demonstration studies. Develops and approves policy guidelines through the Strategic and Technical Advisory Group for Tuberculosis (STAG-TB). Involved in consensus-making and advocacy. Houses and is a partner to the Stop TB Partnership, an international body that aligns a wide range of international stakeholders in the fight against TB.
Foundation for Innovative New Diagnostics (FIND)	Genotype:1 Xpert: 1	A non-profit foundation created to facilitate the development, evaluation, and use of improved diagnostics for tuberculosis and other infectious diseases by linking industry, academia, international health agencies, donors and national governments.
Hain Lifescience (GmbH, Germany)	Genotype:1 Xpert: 0	Founded in 1988. Manufactures and distributes molecular diagnostic systems and instruments. Developed and produced one of the WHO approved line probe assay tests on the market. In October 2006 Hain Lifescience announced agreement with FIND to accelerate the development, evaluation and implementation of a molecular test to screen for MDR-TB (GenoType). The test, developed in 2004, was initially marketed for use with culture isolates and was adapted for use with direct clinical specimens.
Cepheid, Inc. (Sunnyvale, CA)	Genotype:0 Xpert: 1	A molecular diagnostics company that developed, manufactured, and marketed fully-integrated automated systems for testing in the clinical and bio-threat markets (against anthrax). Worked with the University of Medicine and Dentistry of New Jersey, Newark, NJ, USA, to develop the Xpert platform. After partnership agreement with FIND in May 2006, this platform was adapted for use with TB
National		
Ministry of Health	Genotype: 0 Xpert: 0	Leadership, advocacy, decision-making for health services. The South African Medical Research Council and National Health Laboratory Services report to the Minister.
Director General of Health	Genotype: 0 Xpert: 0	Decision making, national implementation of health programmes and services, resource allocation, financial accountability at national level.
National TB Control Programme	Genotype:1 Xpert: 1	Planning. Policy. Advocacy. Technical TB programme support at national level.
National Health Laboratory Services	Genotype:1 Xpert: 2	Planning and implementation of laboratory services for the public health sector, including procurement and financial responsibility. Involvement in laboratory and field demonstration studies.
South African Medical Research Council	Genotype:1 Xpert: 0	Research institution that aims to improve health and quality of life through promoting and conducting relevant research. Partnered in the Genotype demonstration study.
Provincial		
Western Cape Department of Health	Genotype: 0 Xpert: 0	Health policy development, planning and implementation at provincial level. Financial accountability.
Western Cape TB Control Programme	Genotype:1 Xpert: 2	Provides technical assistance for TB. Policy and protocol development. Planning. Training. Supports implementation. Monitoring and evaluation of TB Programme.
University of Cape Town	Genotype: 0 Xpert: 0	Tertiary education and research organisation. Partnered in the Xpert demonstration study.
District		
Sub-district / Sub-structure Managers	Genotype:3 Xpert: 3	Planning for health services. Management of health service delivery in sub-district / sub-structure. Financial accountability.
TB Control Programme Manager	Genotype:1 Xpert: 1	Provides technical assistance. Policy and protocol development. Planning. Training. Supports implementation. Monitoring and evaluation.
TB Hospital Managers	Genotype:1 Xpert: 2	Planning, implementation and monitoring of in and out-patient services at TB hospital.

Table A1 (continued)

Stakeholder	Number participants interviewed LPA/Xpert	Role in the development, approval and use of new molecular TB Diagnostic Tests and provision of clinical services
TB/HIV Sub-district Coordinators	Genotype:5 Xpert: 4	Planning, coordinating and implementing TB/HIV programmes at sub-district level. Training. Monitoring and evaluation of programmes.
DR-TB Nurses	Genotype:4 Xpert: 3	Follow-up patients diagnosed with DR-TB and facilitate access to treatment and other services. Monitoring and evaluation of DR-TB.
National Health laboratory Service: TB Manager	Genotype:1 Xpert: 1	Manages the national health laboratory providing tests for public health facilities in Cape Town. Responsible for planning, service provision, financial expenditure.
National Health laboratory Service: Scientist	Genotype:1 Xpert: 1	Responsible for doing Genotype tests at the central laboratory. Participated in laboratory evaluation of Genotype.
Medecins sans Frontiere	Genotype:1 Xpert: 1	Partner with health services in the delivery of TB and HIV health services. Involved in establishing community-based model for DR-TB care.
Health Facilities		
Facility manager	Genotype:3 Xpert: 4	Planning. Management of health service delivery at facility. Financial accountability.
TB Doctors/DR-TB Doctors	Genotype:5 Xpert: 5	Clinical service provider. Training and mentorship of nurses.
Nurses	Genotype:3 Xpert: 3	Clinical service provider. Monitoring and reporting for TB programme.
Reception Clerks	Genotype:1 Xpert: 0	Appointments. Processing clinical records.
TB Clerks/ Assistants	Genotype:4 Xpert: 4	Appointments. Completion of laboratory request forms. Filing test results. TB patient education. Community-based follow-up of patients who interrupt treatment, require tests or fail to return for results.

This table provides an overview of the key actors involved in the policy transfer process at various levels and those interviewed. TB=tuberculosis; WHO=World Health Organization; FIND=Foundation for Innovative New Diagnostics; LPA=line-probe assay; MDR-TB=multidrug-resistant TB; HIV=human immunodeficiency virus; DR-TB=drug-resistant TB.

Table A2: Timeline of key events in the development of molecular diagnostic tests for tuberculosis

Month/Year	Key Events
1996	TBDI established at the WHO to improve case detection and cure rates using the DOTS strategy
1999	The WHO and partners create the DOTS-Plus strategy for the treatment of MDR-TB. Prior to this, the treatment of MDR- TB was not considered feasible in low-resource settings. Few data existed on the extent of the global MDR-TB problem and second-line drugs were prohibitively expensive. Following surveillance projects in over 30 countries, MDR-TB treatment pilot projects were established (including in South Africa), and efforts were made to improve access to second-line drugs and to procure these at lower cost
2000	TBDI receives funding from Gates Foundation. TBDI undertakes an industry survey that identifies more than 50 companies with TB diagnostic tests in their research and development portfolios. Progress found to be hampered by lack of funding, poor specification of types of tests needed, limited access to reference clinical material, poor availability of clinical trial sites and limited familiarity with markets in the developing world
July 2003	FIND established through a grant from the Gates Foundation. FIND aims to promote and facilitate the development, evaluation and use of improved diagnostics for TB and other infectious diseases
2004	Cepheid launches Xpert platform. This fully integrated automated system for testing in the clinical and bio-threat markets (against anthrax) was developed in partnership with the UMDNJ, Newark, NJ, USA, and partly funded by the National Institutes of Health, Bethesda, MD, USA
	FIND evaluates several potential new molecular diagnostic tests and identifies Xpert as most suitable for development of a simple test to screen for MDR-TB
January 2006	The Stop TB Partnership launches Global Plan to Stop TB, 2006–2015. The plan was supported by funding from the Bill & Melinda Gates Foundation (Seattle, WA, USA), the Global Fund to Fight AIDS, TB & Malaria and UNITAID (Geneva, Switzerland)
May 2006	FIND signs agreement with Cepheid (Sunnyvale, CA, USA) and UMDNJ to develop the Xpert platform for M. tuberculosis and contributes to development and trial costs
August 2006	Outbreak of XDR-TB at Tugella Ferry, KwaZulu Natal, South Africa, discussed at the XVI International AIDS Conference in Toronto, ON, Canada, and puts South Africa in the global spotlight, heightening concerns and focusing attention on DR-TB
September 2006	Expert consultation on DR-TB held in Johannesburg, South Africa, calls attention to the problem of DR-TB in Southern African Development Community countries. Gaps in surveillance and steps required for these countries to address the problem of DR-TB identified
October 2006	The WHO convenes Global Task Force on XDR-TB in Geneva, Switzerland, to operationalise the DR-TB component of the Global Plan to Stop TB
October 2006	FIND and Hain Lifescience, Nehren, Germany, announce their agreement to accelerate the development, evaluation and implementation of a molecular LPA to screen for MDR-TB (GenoType MTBDRplus). The test, marketed for use with culture isolates, will be adapted for use with direct clinical specimens
January 2007	FIND and Hain Lifescience announce that GenoType is approved in Europe and sign agreement to begin large-scale demonstration projects in South Africa, Russia, Uzbekistan and Nepal
July 2007	Enrolment into the FIND GenoType demonstration project commences in five provinces in South Africa in collaboration with the South African Medical Research Council, the National Health Laboratory Service and the Department of Health (Pretoria, South Africa) and ends in December 2007
January 2008	Laboratory services continue the use of GenoType as replacement for conventional first-line drug susceptibility testing in Cape Town, South Africa. The test was used for presumptive TB cases with a history of previous anti-tuberculosis treatment for 74 weeks. The test was performed on culture isolates and later directly on smear-positive sputum specimens

Table A2 (continued)

Month/Year	Key Events
March 2008	WHO and partners convene Expert Group to assess available data on LPAs with a view to making policy recommendations. INNO-LiPA Rif.TB (Innogenetics, Zwijndrecht, Belgium), for use on M. tuberculosis isolates grown on solid culture, and GenoType assays, for use on isolates from solid and liquid culture as well as directly on smear-positive pulmonary specimens, were reviewed. GenoType offers advantages of identifying resistance to both rifampicin and isoniazid (compared to rifampicin alone) and lower cost (US$17–19 on smear-positive specimens and US$25–35 on culture isolates compared to US$116) than INNO-LiPA Rif.TB1
June 2008	WHO releases policy statement, 'Molecular line-probe assays for rapid screening of patients at risk of multidrug-resistant tuberculosis',1 approving the use of LPAs. GenoType is recommended in direct testing of sputum smear-positive specimens and on culture isolates
July 2008	Health Minister Manto Tshabalala-Msimang announces implementation of GenoType at the 1st South African TB Conference held in Durban, South Africa
January 2009	National rollout of GenoType in South Africa (beyond demonstration sites) commences
August 2009	Enrolment for the multicentre Xpert evaluation trial in Peru, Azerbaijan, South Africa and India commences, including at a site in Cape Town and in a rural area in the Western Cape Province
May 2010	South African Minister of Health joins the Stop TB Board
September 2010	WHO convenes Expert Group to assess available data on Xpert with a view towards policy recommendations. Findings and recommendations presented to the WHO STAG-TB
September 2010	National DoH and NHLS host Xpert stakeholders meeting in Johannesburg, South Africa, to discuss demonstration study findings and rollout plan
November 2010	WHO holds global consultation with national TB programmes to discuss the implementation and scale-up of Xpert and achieve consensus on the way forward, including agreement on interim diagnostic algorithms and implementation considerations for programmatic rollout
March 2011	South African Minister of Health, Dr Aaron Motsoaledi, unveils the country's first Xpert machine at Prince Mshiyeni Hospital in Durban, South Africa, on World TB Day
May 2011	WHO releases Xpert policy statement recommending its use as the initial diagnostic test in individuals suspected of having MDR-TB or HIV-associated TB
June 2011	South Africa commences Xpert national rollout plan. Xpert is used as a replacement test for smear microscopy
August 2011	The South African Medical Research Council and NHLS host feedback session on GenoType demonstration study findings in Cape Town, South Africa
August 2011	South Africa commences Xpert national rollout plan. Xpert is used as a replacement test for smear microscopy
December 2011	The South African DoH releases the National Strategic Plan for HIV/AIDS and TB. One of the five goals is to halve the number of new TB infections and deaths from TB (aligned with the United Nations Millennium Development Goals)
August 2012	PEPFAR, USAID (Washington DC, USA), UNITAID (Geneva, Switzerland) and the Bill and Melinda Gates Foundation (Seattle,WA, USA) announce a price reduction for Xpert from US$16.86 to US$9.98 for public sector use in countries eligible for preferential pricing
July 2013	The Stop TB Partnership Coordinating Board elects the Minister of Health of South Africa as its Chair

Reference: [1]World Health Organisation. Molecular Line Probe Assays For Rapid Screening Of Patients At Risk Of Multidrug-Resistant Tuberculosis. Expert Group Report. 2008.

TB=tuberculosis; TBDI=Tuberculosis Diagnostics Initiative; WHO=World Health Organization; MDR-TB=multidrug-resistant TB; FIND=Foundation for Innovative New Diagnostics; UMDNJ=University of Medicine and Dentistry of New Jersey; STAG-B=Strategic and Technical Advisory Group for Tuberculosis; DoH=Department of Health; NHLS= National Health Laboratory Service; XDR-TB=extensively drug-resistant TB; LPA=line-probe assay; HIV=human immunodeficiency virus; PEPFAR=President's Emergency Plan for AIDS Relief; USAID=United States Agency for International Development.