Feasibility, accuracy, and clinical effect of point-of-care Xpert MTB/RIF testing for tuberculosis in primary-care settings in Africa: a multicentre, randomised, controlled trial

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Summary

Background The Xpert MTB/RIF test for tuberculosis is being rolled out in many countries, but evidence is lacking regarding its implementation outside laboratories, ability to inform same-day treatment decisions at the point of care, and clinical effect on tuberculosis-related morbidity. We aimed to assess the feasibility, accuracy, and clinical effect of point-of-care Xpert MTB/RIF testing at primary-care health-care facilities in southern Africa.

Methods In this pragmatic, randomised, parallel-group, multicentre trial, we recruited adults with symptoms suggestive of active tuberculosis from five primary-care health-care facilities in South Africa, Zimbabwe, Zambia, and Tanzania. Eligible patients were randomly assigned using pregenerated tables to nurse-performed Xpert MTB/RIF at the clinic or sputum smear microscopy. Participants with a negative test result were empirically managed according to local WHO-compliant guidelines. Our primary outcome was tuberculosis-related morbidity (measured with the TBscore and Karnofsky performance score [KPS]) in culture-positive patients who had begun anti-tuberculosis treatment, measured at 2 months and 6 months after randomisation, analysed by intention to treat. This trial is registered with Clinicaltrials.gov, number NCT01554384.

Findings Between April 12, 2011, and March 30, 2012, we randomly assigned 758 patients to smear microscopy (182 culture positive) and 744 to Xpert MTB/RIF (185 culture positive). Median TBscore in culture-positive patients did not differ between groups at 2 months (2 [IQR 0–3] in the smear microscopy group *vs* 2 [0·25–3] in the MTB/RIF group; p=0·85) or 6 months (1 [0–3] *vs* 1 [0–3]; p=0·35), nor did median KPS at 2 months (80 [70–90] *vs* 90 [80–90]; p=0·23) or 6 months (100 [90–100] *vs* 100 [90–100]; p=0·85). Point-of-care MTB/RIF had higher sensitivity than microscopy (154 [83%] of 185 *vs* 91 [50%] of 182; p=0·0001) but similar specificity (517 [95%] 544 *vs* 540 [96%] of 560; p=0·25), and had similar sensitivity to laboratory-based MTB/RIF (292 [83%] of 351; p=0·99) but higher specificity (952 [92%] of 1037; p=0·0173). 34 (5%) of 744 tests with point-of-care MTB/RIF and 82 (6%) of 1411 with laboratory-based MTB/RIF failed (p=0·22). Compared with the microscopy group, more patients in the MTB/RIF group had a same-day diagnosis (178 [24%] of 744 *vs* 99 [13%] of 758; p<0·0001) and same-day treatment initiation (168 [23%] of 744 *vs* 115 [15%] of 758; p=0·0002). Although, by end of the study, more culture-positive patients in the MTB/RIF group were on treatment due to reduced dropout (15 [8%] of 185 in the MTB/RIF group did not receive treatment *vs* 28 [15%] of 182 in the microscopy group; p=0·0302), the proportions of all patients on treatment in each group by day 56 were similar (320 [43%] of 744 in the MTB/RIF group *vs* 317 [42%] of 758 in the microscopy group; p=0·6408).

Interpretation Xpert MTB/RIF can be accurately administered by a nurse in primary-care clinics, resulting in more patients starting same-day treatment, more culture-positive patients starting therapy, and a shorter time to treatment. However, the benefits did not translate into lower tuberculosis-related morbidity, partly because of high levels of empirical-evidence-based treatment in smear-negative patients.

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Introduction

A reversal in the incidence of tuberculosis is a key component of the UN Millennium Development Goals for 2015.[1] Although substantial progress has been made worldwide,[2] tuberculosis remains a major cause of morbidity and mortality in sub-Saharan Africa,[3] and several high-burden countries are not on track to substantively reduce their burden of tuberculosis.[4] Smear microscopy, which is often done in primary-care clinics in such settings, is frequently used for the diagnosis of tuberculosis, and it can rapidly affect treatment decisions. However, it misses 40–60% of cases, and does least well in people with advanced immunosuppression.[5] Tests that are rapid, accurate, and deployable at the point of care are projected to substantially reduce tuberculosis-related morbidity and mortality,[6,7] although empirical evidence is in very short supply.

The Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) is a US Food and Drug Administration-approved, automated nucleic-acid amplification test that can detect

both *Mycobacterium tuberculosis* (MTB) complex DNA and rifampicin (RIF) resistance within 2 h.[8] In 2011, it was endorsed by WHO,[9] and is being piloted or integrated into the national algorithms of a growing number of high-burden countries, where it will be based at subdistrict or district level.[10]

The accuracy of Xpert MTB/RIF is well validated: one test detects about 88% of culture-confirmed cases of pulmonary tuberculosis, correctly identifies about 98% of patients without tuberculosis, and can detect up to 67% of cases missed by smear microscopy.[11] It can detect 94% of rifampicin-resistant tuberculosis cases and correctly classify 98% of rifampicin-susceptible cases.[11] Preliminary data suggest Xpert MTB/RIF could accelerate and improve tuberculosis case detection,[8,12–14] and modelling studies project it to be cost effective[15] and have a substantial effect on patient health in HIV-endemic regions.[16]

Despite the continuing roll out and piloting of Xpert MTB/RIF, no randomised empirical data exist to show whether its improved accuracy relative to smear microscopy improves patient-important outcomes and endpoints such as morbidity and mortality. Although small observational studies in South Africa[13,17,18] have described the feasibility of Xpert MTB/RIF implementation at the point of care, whether their findings can be generalised to other countries is uncertain, as is whether point-of-care Xpert MTB/RIF improves same-day clinical decision making. The latter question is crucial because up to 40% of patients who test positive do not return for their results in tuberculosis-endemic settings.[8,19,20] To better understand these important issues, which inform policy decisions relevant to the scale-up of Xpert MTB/RIF, we did a randomised controlled trial to examine the feasibility, accuracy, and clinical effect of Xpert MTB/RIF deployed at the point of care compared with smear microscopy in five primary-care health-care facilities in areas of southern Africa with a high HIV prevalence.

Methods

Study design and participants

We did a pragmatic, randomised, parallel-group, multicentre trial. After obtaining written informed consent, we consecutively enrolled patients aged 18 years or older who presented to periurban primary-care tuberculosis clinics with attached treatment facilities and microscopy laboratories in Cape Town (South Africa; here the microscopy laboratory was close by rather than attached to the facility), Durban (South Africa), Harare (Zimbabwe), Lusaka (Zambia), and Mbeya (Tanzania). We enrolled patients who had one or more symptoms of pulmonary tuberculosis according to predefined WHO criteria,[5,21] were able to spontaneously expectorate two sputum specimens (each with a volume of 1 mL or greater), and had not received anti-tuberculosis treatment within the previous 60 days. We excluded patients who did not meet these criteria or were unwilling or unable to give informed consent. A description of each site and the tuberculosis symptoms required for eligibility are presented in the appendix. The study was approved by five local ethics committees at each site. This study is reported in accordance with the CONSORT statement for patient-outcome-orientated pragmatic randomised controlled trials.[22]

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See **Online** for appendix

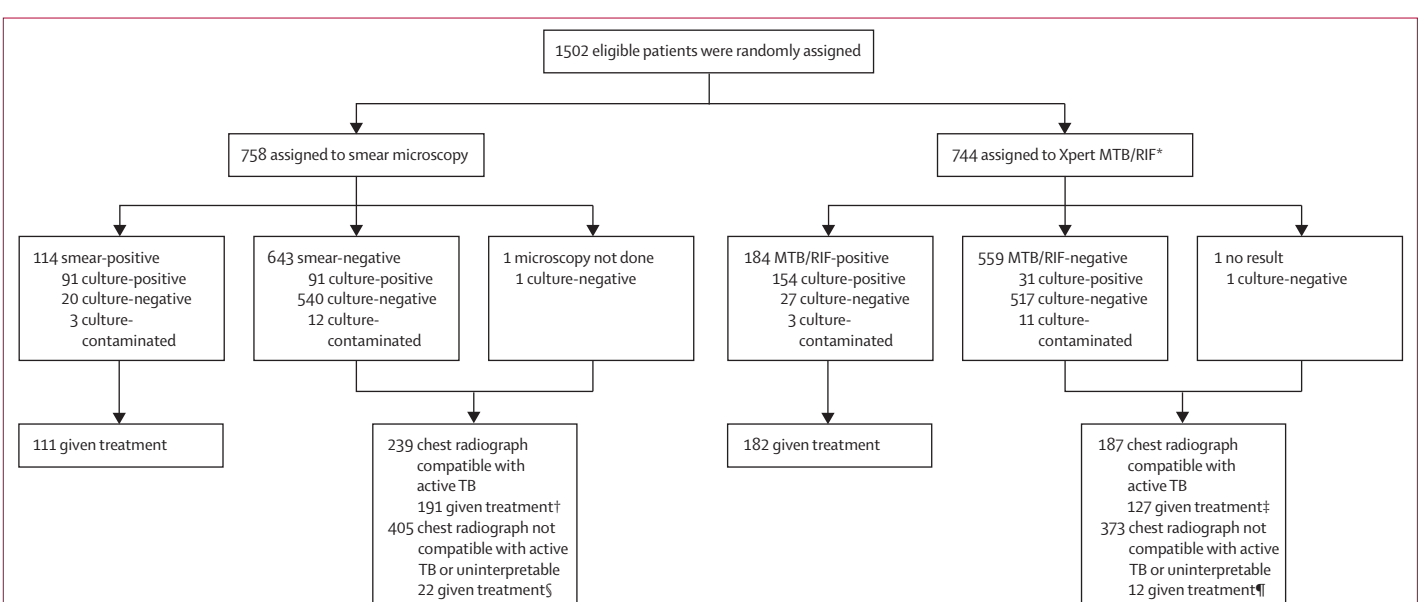

Figure 1: **Study profile**
Numbers were calculated at the end of study. TB=tuberculosis. *Six patients recorded an error MTB/RIF result, six recorded an invalid MTB/RIF result, and nine recorded no MTB/RIF result (eight due to a power failure). †12 (10%) patients were culture-positive; all but one 'no result' error were resolved when the test was repeated. ‡11 (50%) were culture-positive. §11 (50%) patients were culture-positive. ¶6 (50%) patients were culture-positive.

	Gugulethu TB Clinic (Cape Town, South Africa)	Mabvuku Polyclinc (Harare, Zimbabwe)	Kanyama TB Clinic (Lusaka, Zambia)	St Mary's Day Clinic (Durban, South Africa)	Ifisi Day Clinic (Mbeya, Tanzania)	Overall	p value for comparisons between sites
Number of patients	419	400	400	200	83	1502	..
Age, years	39 (31–49)	38 (32–45)	35 (30–41)	37 (30–50)	37 (31–54)	37 (30–46)	<0·0001
Women	160 (38%)	215 (54%)	131 (33%)	96 (48%)	41 (49%)	643 (43%)	<0·0001
Previous TB	178 (43%)	67 (17%)	85 (21%)	52 (26%)	2 (2%)	384 (26%)	<0·0001
HIV status (%)							
Infected*	133 (32%)	324 (81%)	268 (67%)	121 (61%)	49 (59%)	895 (60%)	<0·0001
Uninfected	278 (66%)	76 (19%)	130 (33%)	70 (35%)	34 (41%)	588 (40%)	..
Unknown	8 (2%)	0	2 (<1%)	8 (4%)	0	18 (<1%)	..
HIV-infected patients on ART at recruitment†	51/133 (38%)	96/324 (30%)	54/268 (20%)	29/121 (24%)	2/49 (4%)	232/895 (26%)	0·0010
Number of culture-positive patients‡	74 (18%)	77 (19%)	152 (38%)	35 (18%)	29 (35%)	367 (24%)	0·0001
TB-related morbidity at baseline in culture-positive patients							
TBscore§	5 (4–6)	5 (4–5)	6 (4–8)	6 (5–7)	8 (5·5–10)	5 (4–7)	<0·0001
KPS¶	90 (80–90)	50 (40–60)	70 (60–80)	90 (80–90)	70 (55–80)	70 (60–90)	<0·0001
Number of drug-resistant cases							
Rifampicin monoresistant	1/67 (1%)	7/73 (10%)	8/152 (5%)	0/32	0/26	16/350 (5%)	0·1550
Isoniazid monoresistant	5/67 (7%)	1/73 (1%)	3/152 (2%)	1/32 (3%)	3/26 (12%)	13/350 (4%)	0·0580
Multidrug resistant	5/67 (7%)	1/73 (1%)	0/152	0/27	0/25	6/345 (2%)	0·0090

Data are N, median (IQR), n (%), and n/N (%). A higher TBscore and a lower KPS score indicate more morbidity. TB=tuberculosis. ART=antiretroviral therapy. KPS=Karnofsky performance score. *A greater proportion of patients in Harare were infected with HIV compared with the other sites (p<0·0001 for all comparisons). †A greater proportion of patients infected with HIV were on ART in Cape Town compared with Lusaka, Durban, and Mbeya (p=0·0001, p=0·0137, and p<0·0001, respectively). ‡A greater proportion of patients in Lusaka and Mbeya were culture-positive for TB compared with Cape Town, Harare, and Durban (p<0·0001 for all comparisons with Lusaka, and p=0·0004, p=0·0017, and p=0·0014, respectively, for comparisons between Mbeya and Cape Town, Harare, or Durban). §The median TB score in patients from Cape Town or Harare was less than Lusaka, Durban, and Mbeya (p<0·0001 for all comparisons). ¶Patients from Cape Town and Durban had a higher KPS than those from Harare, Lusaka, or Mbeya (p<0·0001 for all comparisons).

Table 1: **Demographic and clinical characteristics by study site**

Randomisation and masking

Eligible patients were randomly assigned to undergo either Xpert MTB/RIF testing or smear microscopy using computer-generated allocation lists. Once an eligible patient was identified, a nurse at each site, blinded to these lists, telephonically contacted a centrally located data manager to obtain the assignment for each patient. Central laboratory personnel were masked to clinic-based results.

Procedures

At least two spot expectorated sputa were obtained sequentially from each patient at recruitment. One specimen, selected randomly, was used for smear microscopy or Xpert MTB/RIF. The other specimen underwent culture (if a patient was allocated to the microscopy group, a smear was also done on this specimen [not done in Harare]). There were no other interventional differences between allocation groups. If available, a third sputum specimen was stored at –20°C and used for Xpert MTB/RIF testing at the end of recruitment in a centralised reference laboratory (ie, at the same site at which culture was done) by a trained laboratory technician. We compared results from the first and last samples for a comparison between nurse-performed Xpert MTB/RIF in study clinics and that done by laboratory technicians in centralised laboratories.

Same-day smear microscopy was done onsite by a technician employed by the programme, as part of routine practice, in a laboratory attached to the health-care facility. In view of local infrastructure, same-day smear microscopy in Cape Town was done at a centralised laboratory close to the clinic. Patients were asked to wait until results of their smear microscopy or Xpert MTB/RIF were available, but did not receive any compensation to do so. The smear microscopy technique used at each site depended on local capacity (described in the appendix). Patients were classified as having smear-positive tuberculosis if any smear revealed acid-fast bacilli over 100 fields (1000× for light microscopy and 400× for fluorescence microscopy).

A four-module GeneXpert machine, desktop computer, and uninterrupted power supply were installed at each facility together with a thermometer and hygrometer. With the exception of a biosafety cabinet in Harare, no additional equipment or infrastructure were installed. Xpert MTB/RIF was done directly on sputum by a nurse who received a 1 day training session at study initiation. In Harare, the national review board required Xpert MTB/RIF to be done by a certified technician. Unannounced visits by an experienced laboratory technician were done at least eight times to monitor test adherence and survey user opinion (appendix). Nurses first estimated the volume of expectorated sputum using

	Gugulethu TB Clinic (Cape Town, South Africa)	Mabvuku Polyclinc (Harare, Zimbabwe)	Kanyama TB Clinic (Lusaka, Zambia)	St Mary's Day Clinic (Durban, South Africa)	Ifisi Day Clinic (Mbeya, Tanzania)	Overall
At recruitment						
Smear microscopy						
Sensitivity*						
n/N	22/36	15/37	38/78	7/16	9/15	91/182
% (95% CI)	61·2% (44·9–75·3)	40·6% (26·4–56·6)	48·8% (38–59·7)	43·8% (23·1–66·9)	60·0% (35·8–80·2)	50·0% (42·9–57·2)
p value (*vs* point-of-care Xpert MTB/RIF)	0·0253	<0·0001	<0·0001	0·40	0·28	0·0001
Specificity†						
n/N	171/172	161/163	105/116	82/83	21/26	540/560
% (95% CI)	99·5% (96·8–99·9)	98·8% (95·7–99·7)	90·6% (83·9–94·7)	98·8% (93·5–99·8)	80·8% (62·2–91·5)	96·5% (94·6–97·7)
p value (*vs* point-of-care Xpert MTB/RIF)	0·53	0·08	0·87	0·14	0·56	0·25
Point-of-care Xpert MTB/RIF						
Sensitivity*						
n/N	32/38	35/40	65/74	11/19	11/14	154/185
% (95% CI)	84·3% (69·6–92·6)	87·5% (73·9–94·6)	87·9% (78·5–93·5)	57·9% (36·3–76·9)	78·6% (52·5–92·5)	83·3% (77·2–88)
p value (*vs* lab-based Xpert MTB/RIF)	0·55	0·58	0·94	0·14	0·50	0·99
Specificity†						
n/N	161/163	151/158	113/124	72/76	20/23	517/544
% (95% CI)	98·8% (95·7–99·7)	95·6% (91·2–97·9)	91·2% (84·9–95)	94·8% (87·3–98)	87·0% (67·9–95·5)	95·1% (92·9–96·6)
p value (*vs* lab-based Xpert MTB/RIF)	0·57	0·25	0·0190	0·40	0·41	0·0173
Failed results before repeat on same specimen	4/208 (1·9%)	14/198 (7·1%)	13/200 (6·5%)	1/97 (1·0%)	2/41 (4·9%)	34/744 (4·6%)
Failed results after repeat on same specimen	1/208 (0·5%)	0/198	0/200	0/97	0/41	1/744 (0·1%)
Operating temperature, °C (95% CI)	23·2°C (21·3–25·3)	21·0°C (18·0–23·0)‡	26·45°C (24·9–27·7)	23·2°C (19·2–24·3)	27·4°C (24·9–28·0)	23·4°C (21·1–25·2)
Humidity, % (95% CI)	55% (48·25–61)	66% (66–66)	42% (26–61·5)	58·5% (44·25–67)	55% (52–63)	56% (50–63)
At study close						
Laboratory-based Xpert MTB/RIF§						
Sensitivity*						
n/N	54/68	61/73	134/152	24/31	19/27	292/351
% (95% CI)	79·5% (68·4–87·4)	83·6% (73·5–90·4)	88·2% (82·1–92·4)	77·5% (60·2–88·7)	70·4% (51·6–84·2)	83·2% (79–86·8)
Specificity†						
n/N	305/311	285/307	194/237	131/135	37/47	952/1037
% (95% CI)	98·1% (95·9–99·2)	92·9% (89·4–95·3)	81·9% (76·5–86·3)	97·1% (92·7–98·9)	78·8% (65·1–88·1)	91·9% (90–93·4)
Failed results before repeat on same specimen	6/385 (1·6%)	33/391 (8·5%)	34/391 (8·7%)	8/169 (4·8%)	1/75 (1·4%)	82/1411 (5·9%)
Failed results after repeat on same specimen	6/385 (1·6%)	14/391 (3·6%)	2/391 (0·6%)	4/167 (2·4%)	1/75 (1·4%)	27/1409 (2%)
Operating temperature, °C (95% CI)	21·0°C (20·0–21·7)‡	24·0°C (22·0–25·0)‡	25·0°C (25·0–25·0)‡	ND	23·2°C (19·2–24·3)‡	23·3°C (16·5–17·5)‡
Humidity, % (95% CI)	53·0% (47·0–57·0)	54·0% (47·0–67·0)	50·0% (50·0–50·0)	ND	58·5% (44·0–67·0)	23·7% (22·0–26·0)

A head-to-head comparison of point-of-care versus laboratory-based Xpert MTB/RIF testing restricted to only patients in the Xpert MTB/RIF group is presented in the appendix. TB=tuberculosis. ND=not done. *Sensitivity is the proportion of people with TB who had a positive test result. †Specificity is the proportion of people without TB who had a negative test result. ‡Room was air-conditioned. §Done on a paired specimen obtained at recruitment.

Table 2: **Performance of smear microscopy, clinic-based nurse-administered Xpert MTB/RIF, and laboratory-based technician-administered Xpert MTB/RIF, per treatment site and overall**

standards of known volume. Xpert MTB/RIF was thereafter done as previously described.[23] If the procedure failed, it was repeated on any remaining sputum-sample buffer mix. A qualified laboratory technician regularly assessed the proficiency of the nurse who undertook the Xpert MTB/RIF tests at the clinic using a standardised form (appendix).

Liquid culture (Mycobacteria Growth Indicator Tube, BD Microbiology Systems, Cockeysville, MD, USA) was done in central laboratories at each site on sputum decontaminated using sodium hydroxide (2% [4% was used in Harare]) with or without *N*-acetyl-L-cysteine. Speciation and drug susceptibility testing are detailed in the appendix. Culture results were reported to nursing staff. Patients were classified as having definite tuberculosis if sputum obtained at recruitment grew acid-fast bacilli identified as *M tuberculosis* complex.[24]

Patients were offered voluntary testing and counselling for HIV at recruitment, and received a chest radiograph while waiting for their smear microscopy or Xpert MTB/RIF result. If a positive smear microscopy, Xpert MTB/RIF, or culture result was obtained the patient was referred to the tuberculosis treatment office at the same clinic. Patients who were smear-negative or Xpert MTB/RIF-negative were

	TBscore			Karnofsky performance score		
	Smear microscopy (N=758)	Xpert MTB/RIF (N=744)	p value	Smear microscopy (N=758)	Xpert MTB/RIF (N=744)	p value
Baseline						
Score in patients given treatment	5 (4–7)	5 (4–7)	0·12	70 (50–80)	70 (50–80)	0·62
Culture-positive (153 patients in smear microscopy group and 168 in Xpert MTB/RIF group with complete morbidity data)	5 (4–7)	5 (4–7)	0·56	70 (60–80)	70 (57·5–90)	0·89
Culture-negative or contaminated (170 patients in smear microscopy group and 151 in Xpert MTB/RIF group with complete morbidity data)	5 (4–6)	5 (4–7)	0·08	60 (50–80)	70 (50–80)	0·59
2 months						
Score in patients given treatment	1 (0–3)	2 (0–3)	0·39	90 (80–90)	90 (80–90)	0·91
Culture-positive*	2 (0–3)	2 (0·25–3)	0·85	80 (70–90)	90 (80–90)	0·23
Culture-negative†	1 (0–7)	1 (0–3)	0·37	80 (70–90)	90 (80–90)	0·23
Per-patient change in score since recruitment in patients given treatment	3 (2–4)	4 (2–5)	0·17	20 (10–30)	10 (10–30)	0·87
Culture-positive	3 (2–4)	3 (2–5)	0·20	10 (0–22·5)	10 (10–30)	0·59
Culture-negative or contaminated	3 (2–4)	4 (2·5–5)	0·28	20 (10–30)	20 (10–30)	0·96
Patients with a >25% decrease (for TBscore) or increase (for KPS) in score from baseline	150/183 (82%)	168/197 (85%)	0·38	83/183 (45%)	93/197 (47%)	0·72
Culture-positive	66/87 (76%)	89/108 (82%)	0·26	32/87 (37%)	46/108 (43%)	0·41
Culture-negative or contaminated	84/96 (88%)	79/88 (90%)	0·63	51/96 (53%)	47/88 (53%)	0·97
6 months						
Score in patients given treatment	1 (0–3)	0 (0–3)	0·20	100 (90–100)	100 (90–100)	0·81
Culture-positive‡	1 (0–3)	1 (0–3)	0·35	100 (90–100)	100 (90–100)	0·85
Culture-negative§	0 (0–2)	0 (0–3)	0·80	100 (90–100)	100 (90–100)	0·87
Per-patient change in score since recruitment in patients given treatment	4 (3–5)	4 (2–5)	0·16	30 (10–40)	30 (10–40)	0·92
Culture-positive	4 (3–5)	4 (2·25–5)	0·35	20 (10–40)	30 (10–40)	0·44
Culture-negative or contaminated	4 (3–5)	4 (3–5·5)	0·38	30 (20–40)	40 (17·5–50)	0·53
Patients with a >25% decrease (for TBscore) or increase (for KPS) in score from baseline	146/167 (87%)	148/168 (88%)	0·85	76/167 (56%)	82/168 (59%)	0·55
Culture-positive	70/81 (86%)	85/97 (88%)	0·81	32/81 (39%)	42/97 (43%)	0·61
Culture-negative or contaminated	76/86 (88%)	62/71 (87%)	0·84	44/86 (51%)	40/71 (56%)	0·52

Data are median (IQR) or n/N (%) unless otherwise indicated. TB=tuberculosis. KPS=Karnofsky performance score. *87 (57%) of 153 in the smear microscopy group *vs* 108 (64%) of 168 in the Xpert MTB/RIF group were followed-up within 2 weeks (p=0·17); of the patients who were not followed up within 2 weeks, 11 (17%) of 66 *vs* 6 (10%) of 60 had died (p=0·2740), and 33 (50%) of 66 *vs* 36 (60%) of 60 were followed up >2 weeks before or after the specified date (p=0·2600). †96 (56%) of 170 in the smear microscopy group *vs* 88 (58%) of 151 in the Xpert MTB/RIF group were followed-up within 2 weeks (p=0·74); of those who were not followed-up within 2 weeks, 15 (20%) of 74 *vs* 8 (13%) of 63 had died (p=0·2373), and 22 (30%) of 74 *vs* 21 (33%) of 63 were followed up >2 weeks before or after the specified date (p=0·6506). ‡81 (53%) of 153 in the smear microscopy group *vs* 97 (58%) of 168 in the Xpert MTB/RIF group were followed up within 2 weeks (p=0·39); of those who were not followed-up within 2 weeks, 14 of 72 (19%) *vs* 14 of 71 (20%) had died (p=0·9671), and 23 (32%) of 72 *vs* 23 (33%) of 71 were followed up >2 weeks before or after the specified date (p=0·9541). §86 (51%) of 170 in the smear microscopy group *vs* 71 (47%) of 151 in the Xpert MTB/RIF group were followed up within 2 weeks (p=0·52); of those who were not followed-up within 2 weeks, 21 (25%) of 84 *vs* 14 (18%) of 80 had died (p=0·2413), and 28 (33%) of 84 *vs* 28 (35%) of 80 were followed up >2 weeks before or after the specified date (p=0·8220).

Table 3: **Tuberculosis-related morbidity at recruitment, 2 months, and 6 months, according to baseline culture status in patients given anti-tuberculosis treatment, per allocation group**

referred (with their chest radiographs) for routine clinical review done by non-study staff who had been briefed about Xpert MTB/RIF and whether it had been undertaken, and supplied with a copy of the WHO policy statement. Empirical treatment initiation was doctor led. The WHO guidelines for the treatment of smear-negative tuberculosis[5] are routinely used at each clinic.

Our primary outcome was tuberculosis-related morbidity (graded using the TBscore[25,26] and Karnofsky performance score [KPS];[27,28] see appendix for definitions) in culture-positive patients who had begun anti-tuberculosis treatment, measured at 2 months and 6 months after randomisation (within a range of 14 days before and after both timepoints). Our secondary outcomes were: feasibility of point-of-care Xpert MTB/RIF testing (accuracy, failure rates, operator protocol adherence, and user appraisals); time to diagnosis (overall and at days 1, 2, 3, 14, 28, and 56); time to anti-tuberculosis treatment initiation (overall and at days 1, 2, 3, 14, 28, and 56); and proportion of culture-positive patients not started on anti-tuberculosis treatment (dropout) or lost to follow-up (culture-positive patients started on treatment who were not retained in the study).

Statistical analysis

We designed the study to detect a difference in TBscore of 1 point and a difference in KPS of 10 points (the minimally important clinical differences for each score). With an α of 5% (two-sided) and a desired power of 80%, assuming equal numbers in each group, we would need about 63 culture-positive patients in each group. To account for deaths, loss to follow-up, withdrawals, and missing data, we inflated this by 30% (to about 82 culture-positive patients). We conservatively

estimated the overall study tuberculosis prevalence to be 15%, meaning we aimed to recruit about 550 patients in each group. Further information about the sample size calculations, including post-hoc calculations, can be found in the appendix.

We did an intention-to-treat analysis. We used culture positivity for *M tuberculosis* complex as a reference standard for diagnostic accuracy calculations. We used Fisher's exact test with mid-p correction for comparisons between proportions, and the Mann-Whitney test to compare differences in morbidity. We assessed inter-rater agreement between clinic-based and laboratory-based Xpert MTB/RIF using the kappa statistic (κ).[29] We did multivariable-linear (for morbidity scores) and logistic (for mortality) regression to adjust for potential confounding. We did a sensitivity analysis to assess the effect on the morbidity endpoint when the site with the highest loss to follow-up (Lusaka) was excluded. We did analyses using OpenEpi (version 2.3.1),[30] Graphpad Prism (version 6.0), GPower (version 3.1),[31] and R (version 3.0).[32]

This trial is registered with Clinicaltrials.gov, number NCT01554384.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between April 12, 2011, and March 30, 2012, we randomly assigned 758 patients to the smear microscopy group and 744 to the Xpert MTB/RIF group (figure 1), 182 and 185 of whom were culture positive, respectively (p=0·70). Six (2%) of the 345 culture-positive patients who were tested for multidrug resistance had multidrug-resistant tuberculosis. 439 (58%) of 758 patients in the smear microscopy group were infected with HIV compared with 456 (61%) of 744 in the Xpert MTB/RIF group (p=0·18). Demographic and clinical characteristics were similar between allocation groups (data not shown). Table 1 presents demographic and clinical characteristics by site, further details of which are presented in the appendix.

Smear microscopy detected 91 (50%) of 182 culture-positive patients, and Xpert MTB/RIF undertaken at the clinic by a nurse detected 154 (83%) of 185 culture-positive patients (table 2). Nurse-administered Xpert MTB/RIF possessed substantial agreement to that done by a laboratory technician on a paired sputum specimen (κ=0·69 [95% CI 0·64–0·74]), and had a similar sensitivity and proportion of unusable results (table 2; appendix). Repeat testing using the remaining sputum-sample buffer mix reduced the proportion of unusable results (from 34 [4·6%] of 744 to 1 [0·1%] of 744 for clinic-based Xpert MTB/RIF [p<0·0001], and from 82 [6%] of 1411 to 27 [2%] of 1409 for laboratory-based Xpert MTB/RIF [p<0·0001]). The sensitivity of Xpert MTB/RIF was reduced in patients with HIV; of culture-positive patients with a known HIV status, nurse-administered Xpert MTB/RIF test gave a positive result in 56 (93%) of 60 patients without HIV versus 97 (78%) of 124 HIV-infected patients (p=0·0103; appendix).

Culture-positive patients in both groups had similar median TBscores at baseline (5 [IQR 4–7] *vs* 5 [4–7]; p=0·12), 2 months from baseline (2 [0–3] *vs* 2 [0·25–3];

	Smear microscopy (N=758)	Xpert MTB/RIF (N=744)	p value
All patients with a positive result (by any means)*			
By day 1	99/758 (13%)	178/744 (24%)	<0·0001
By day 2	107/758 (14%)	183/744 (25%)	<0·0001
By day 3	109/758 (14%)	185/744 (25%)	<0·0001
By day 14	165/758 (22%)	196/744 (86%)	0·0380
By day 28	199/758 (26%)	212/744 (29%)	0·33
By day 56	204/758 (27%)	215/744 (29%)	0·39
Culture-positive patients with a positive result (by any means)*			
By day 1	79/182 (43%)	150/185 (81%)	<0·0001
By day 2	86/182 (47%)	153/185 (83%)	<0·0001
By day 3	87/182 (48%)	153/185 (83%)	<0·0001
By day 14	142/182 (78%)	166/185 (90%)	0·0023
By day 28	176/182 (97%)	182/185 (98%)	0·30
By day 56	181/182 (99%)	185/185 (100%)	0·31
Days to first positive result	0 (0–6)	0 (0–0)	0·0055
Days to culture result	10 (6–14)	9 (6–15)	0·86

Data are n/N (%) or median (IQR). *Positive results could be from smear microscopy or culture in the smear microscopy group, or by Xpert MTB/RIF or culture in the Xpert MTB/RIF group.

Table 4: **Patients with a positive smear microscopy, Xpert MTB/RIF, or culture result, and days to result, per allocation group**

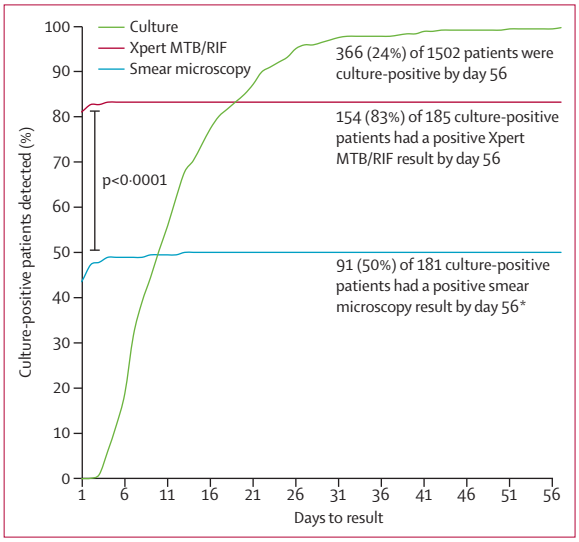

Figure 2: **Time to diagnosis by smear microscopy, Xpert MTB/RIF, or liquid culture in culture-positive patients**

*One patient's culture obtained at recruitment was positive after 59 days.

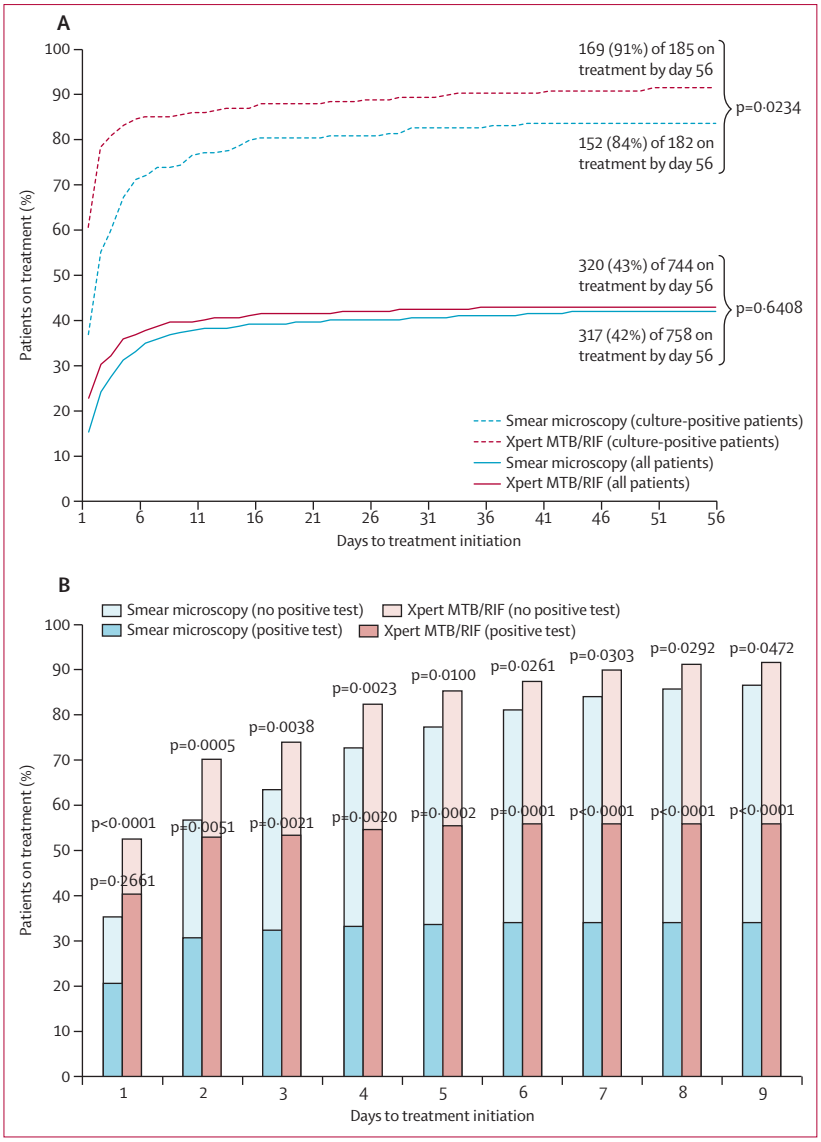

Figure 3: **Initiation of anti-tuberculosis treatment in all patients and culture-positive patients, per allocation group**

(A) Proportion of all patients in each group or of culture-positive patients only in each group given anti-tuberculosis treatment over the 56 days of the study. After day 9, the proportion of patients on anti-tuberculosis treatment in each group did not differ significantly. (B) Proportion of patients in the first 9 days after recruitment who began anti-tuberculosis treatment as a result of empirical evidence (ie, in the absence of positive smear microscopy, Xpert MTB/RIF, or culture result) and those who began anti-tuberculosis treatment as a result of a positive smear microscopy, Xpert MTB/RIF, or culture result. p values just above each pair of bars are a result of comparisons between groups of the overall number of patients on treatment, whereas the p values across each pair of bars are a result of comparisons between groups of the proportions of patients with no positive test who began treatment on empirical grounds.

p=0·85), and 6 months from baseline (1 [0–3] *vs* 1 [0–3]; p=0·35). The median per-patient change in TBscore from recruitment to 2 month or 6 month follow-up was similar in both groups, as was the proportion of culture-positive patients with a greater than 25% decrease in TBscore (table 3). KPSs at each timepoint displayed the same pattern (table 3). We detected no differences according to allocation group when data were stratified by HIV status, when multivariate adjustments were done, or when Lusaka was excluded (where loss to follow-up was comparatively high; appendix).

Xpert MTB/RIF diagnosed more patients who were culture positive than did smear microscopy on the day of presentation (154 [81%] of 185 *vs* 91 [43%] of 182; p<0·0001) and through to day 14 (table 4 and figure 2). Of the patients with a positive smear microscopy or Xpert MTB/RIF result available on the same day, 252 (90%) of 272 waited for their result and were informed that day. Of the culture-positive patients placed on treatment, 67 (44%) of 154 in the smear microscopy group and 112 (66%) of 170 in the Xpert MTB/RIF group started treatment on the day of presentation (p<0·0001). The proportion of patients who were given treatment remained higher in the Xpert MTB/RIF group than in the smear microscopy group through until day 9, and the proportion of culture-positive patients on treatment in the Xpert MTB/RIF group remained higher than in the smear microscopy group at day 56 (figure 3).

In the smear microscopy group, 197 (26%) of 758 patients began treatment as a result of empirical evidence by day 56 (ie, on the basis of a chest radiograph or clinical symptoms and in the absence of a positive bacteriological result) compared with 130 (17%) of 744 in the Xpert MTB/RIF group (p=0·0001; table 5). The proportion of patients initiated on same-day empirical-evidence-based treatment was 48 (6%) of 758 in the smear microscopy group and 38 (5%) of 744 in the Xpert MTB/RIF group (p=0·31). 313 (94%) of 333 patients who began treatment on empirical grounds had a chest radiograph compatible with active tuberculosis. In the smear microscopy group, 47 (87%) of 54 patients treated empirically and later identified with culture-positive tuberculosis were infected with HIV, whereas seven (57%) of nine smear-positive, culture-positive patients were infected with HIV (p=0·0001; appendix). A similar proportion of patients in each group were culture-negative and received treatment (163 [22%] of 758 patients in the smear microscopy group *vs* 145 [20%] of 744 in the Xpert MTB/RIF group; p=0·31). The time-specific proportion of culture-positive patients treated empirically is shown in the appendix.

The proportion of culture-positive patients who did not start treatment (ie, they dropped out) was greater in the smear microscopy group than in the Xpert MTB/RIF group (28 [15%] of 182 *vs* 15 [8%] of 185; p=0·0302; table 6). Of the 28 culture-positive patients who did not start treatment in the smear microscopy group, 17 (61%) were detected by a laboratory-based Xpert MTB/RIF at the end of the study. An overview of culture-positive patients who dropped out is in the appendix. Overall, a similar proportion of culture-positive patients who began treatment were not retained in the study (lost to follow-up) at 6 months in each group (50 [32%] of 154 patients in the smear microscopy group *vs* 50 [29%] of 170 patients in the Xpert MTB/RIF group; p=0·55); the appendix

	Smear microscopy (N=758)	Xpert MTB/RIF (N=744)	p value
Initiation of anti-TB treatment and reason for treatment initiation			
By day 1	115/758 (15%)	168/744 (23%)	0·0002
Positive smear or Xpert MTB/RIF	67/758 (9%)	130/744 (17%)	<0·0001
Empirical evidence*	48/758 (6%)	38/744 (5%)	0·31
Chest radiograph compatible with active TB	43/48 (90%)	35/38 (92%)	0·69
Later shown to be culture-positive	15/48 (31%)	2/38 (5%)	0·0027
By day 2	184/758 (24%)	225/744 (30%)	0·0094
Positive smear or Xpert MTB/RIF	99/758 (13%)	170/744 (23%)	<0·0001
Empirical evidence*	85/758 (11%)	55/744 (7%)	0·0109
Chest radiograph compatible with active TB	79/85 (93%)	52/55 (95%)	0·71
Later shown to be culture-positive	20/85 (24%)	5/55 (9%)	0·0294
By day 3	206/758 (27%)	238/744 (32%)	0·0410
Positive smear or Xpert MTB/RIF	105/758 (14%)	172/744 (23%)	<0·0001
Empirical evidence*	101/758 (13%)	66/744 (9%)	0·0060
Chest radiograph compatible with active TB	94/101 (93%)	63/66 (95%)	0·53
Later shown to be culture-positive	24/101 (24%)	7/66 (11%)	0·0325
By day 14	292/758 (39%)	303/744 (41%)	0·3827
Positive smear or Xpert MTB/RIF	105/758 (14%)	181/744 (24%)	<0·0001
Positive culture	3/758 (4%)	2/744 (3%)	0·67
Empirical evidence*	180/758 (24%)	121/744 (16%)	0·0003
Chest radiograph compatible with active TB	171/180 (95%)	118/121 (98%)	0·27
Later shown to be culture-positive	52/180 (29%)	9/121 (7%)	<0·0001
By day 28	304/758 (40%)	314/744 (42%)	0·4086
Positive smear or Xpert MTB/RIF	111/758 (15%)	181/744 (24%)	<0·0001
Positive culture	6/758 (8%)	5/744 (7%)	0·79
Empirical evidence*	189/758 (25%)	128/744 (17%)	0·0002
Chest radiograph compatible with active TB	179/189 (95%)	123/128 (96%)	0·57
Later shown to be culture-positive	54/189 (29%)	9/128 (7%)	<0·0001
By day 56	317/758 (42%)	320/744 (43%)	0·6408
Positive smear or Xpert MTB/RIF	111/758 (15%)	182/744 (24%)	<0·0001
Positive culture	9/758 (12%)	8/744 (11%)	0·84
Empirical evidence*	197/758 (26%)	130/744 (17%)	0·0001
Chest radiograph compatible with active TB	186/197 (94%)	124/130 (95%)	0·70
Later shown to be culture-positive	54/197 (27%)	9/130 (7%)	<0·0001
Days to anti-TB treatment initiation	1 (0–4)	0 (0–3)	0·0004
In culture-positive patients	1 (0–3)	0 (0–1)	<0·0001
In culture-negative patients or those with contaminated culture	2 (0–5)	1 (0–4)	0·12
In patients treated empirically*	1 (1–6)	1 (0–5)	0·38

Data are n/N (%) or median (IQR). TB=tuberculosis. *In the absence of a positive smear microscopy, Xpert MTB/RIF, or culture result.

Table 5: **Proportions of patients on anti-tuberculosis treatment, and days to treatment initiation according to reason for treatment initiation, per allocation group**

contains a site-by-site breakdown of patient retention. Culture-positive patients on treatment that were lost to follow-up had a higher median TBscore at baseline than did those retained in the study (6 [IQR 5–8] *vs* 5 [4–6]; p<0·0001).

At the end of the study, a similar proportion of patients in both groups had died (63 [8%] of 758 in the microscopy group *vs* 58 [8%] 744 in the Xpert MTB/RIF group; p=0·7135; appendix). When we made multivariable adjustments, predictors of death included baseline TBscore (p<0·0001; odds ratio 1·41, 95% CI 1·26–1·58) and HIV status (p=0·0095; odds ratio 2·01, 1·20–3·48), but not allocation group (p=0·68; appendix).

Discussion

This multicentre study is the first randomised controlled trial of Xpert MTB/RIF, and the first to compare its feasibility at the point of care to that in the laboratory and the effect on clinically important outcomes (panel). Xpert MTB/RIF did not reduce overall tuberculosis-related morbidity (our primary outcome), but our results do show that Xpert MTB/RIF undertaken by a minimally

	Smear microscopy (N=758)	Xpert MTB/RIF (N=744)	p value
Patients with a positive test result who were not given treatment			
Smear-positive or Xpert MTB/RIF-positive	3/114 (3%)	2/182 (1%)	0·32
Culture-positive (dropped out)	28/182 (15%)	15/185 (8%)	0·0302
Patients given treatment who were not retained in the study (lost to follow-up or deceased)*			
At 2 months	96/324 (30%)	83/321 (26%)	0·29
Culture-positive	44/154 (29%)	42/170 (25%)	0·43
Culture-negative or contaminated	52/170 (31%)	41/150 (27%)	0·52
At 6 months	106/324 (33%)	102/321 (32%)	0·48
Culture-positive	50/154 (32%)	50/170 (29%)	0·55
Culture-negative or contaminated	56/170 (33%)	52/150 (35%)	0·81

Data are n/N (%). *A site-by-site comparison and a comparison of baseline clinical and morbidity information are presented in the appendix.

Table 6: **Dropout and loss to follow-up data, per allocation group**

trained nurse in a primary-care setting is feasible, and has similar sensitivity, better specificity, and similar failure rates compared with that done by a technician at a laboratory. Additionally, Xpert MTB/RIF increased same-day tuberculosis detection and anti-tuberculosis treatment initiation, but did not increase the overall number of patients on treatment (when chest radiography was available)—although more of those patients were culture positive, resulting in a slight (about 7%) increase in the number of culture-positive patients who started treatment within 56 days.

We postulated that the placement of Xpert MTB/RIF at the point of care would assist same-day clinical decision making and improve patient retention and clinical outcomes.[36] We used a two-person team at each site that undertook Xpert MTB/RIF with similar accuracy to that in centralised laboratories using pre-existing infrastructure in clinics. These nurses, who had only 1 day of Xpert MTB/RIF training, had moderate to excellent protocol adherence, knowledge of the technical aspects of the test, and rated themselves as satisfied to confident with the procedure. Near-patient placement of Xpert MTB/RIF improved same-day rates of treatment initiation, and reduced dropout (patients with culture-proven tuberculosis who never began treatment). Thus, although the overall number of patients treated was similar between allocation groups, Xpert MTB/RIF allowed more patients with culture-confirmed tuberculosis to be placed on treatment, even though levels of empirical-evidence-based treatment were comparatively high. This issue is important for tuberculosis control, because these patients would have continued to transmit tuberculosis if left untreated.

So far, three observational studies, all in South Africa, have examined Xpert MTB/RIF at the point of care.[13,17,18] Collectively, they concluded that Xpert MTB/RIF improved case detection and time to anti-tuberculosis treatment initiation, but in our study only about half of patients who initiated treatment did so on the basis of a positive Xpert MTB/RIF result. These previous studies did not examine the effect of Xpert MTB/RIF on patient health, nor did they have a comparator group to detect improvements in the number of patients dropping out. In a previous study[37] in Cape Town, centralised Xpert MTB/RIF testing resulted in about 75% of test-positive patients starting treatment within 9 days. In our study, 179 (97%) of 184 Xpert MTB/RIF-positive patients started treatment within a week, and 130 (71%) started treatment on the day of presentation. In the microscopy group, the comparatively poor accuracy of the test was offset by high levels of treatment given on empirical grounds, but treatment decisions based on empirical evidence had suboptimal sensitivity, meaning about 15% of culture-confirmed tuberculosis cases were still missed. Since WHO guidelines recommend using better screening methods and diagnostics for reducing inappropriate anti-tuberculosis treatment, we did not detect a difference in the level of inaccurate empirical-evidence-based initiation of anti-tuberculosis treatment between groups.

Although validated markers of morbidity such as the TBscore and KPS are highly predictive of long-term outcome,[25,26,28] we did not detect intergroup differences in tuberculosis-related morbidity, despite sufficient power to detect less than the minimum clinically important difference in score. This finding might be explained by several factors. First, in the microscopy group, 67 (68%) of 98 patients who had a negative smear result but a positive Xpert MTB/RIF result obtained at the end of the study (using archived specimens collected at recruitment) were given treatment, 62 (93%) of whom were treated on the basis of empirical evidence. In view of the known problem of low sensitivity of smears in high-HIV-prevalence settings, doctors were presumably erring on the side of caution. Second, TBscore and KPS are composite measures that might be affected by different factors (eg, diet, treatment adherence, antiretroviral therapy). Third, diagnostic randomised controlled trials such as this study convert a diagnostic research question into a therapeutic question, in which diagnosis and treatment are combined into a package. As documented

by others,[38] the observed effects might therefore be a result of either the diagnostic test or subsequent management. Finally, tuberculosis is a slowly progressing illness and small improvements in time to treatment might therefore not affect patient-specific morbidity. Our findings emphasise the necessity of studying diagnostic interventions in a real-world pragmatic context,[34,39,40] in which patient outcomes might be modulated by diverse settings and patient-specific factors. Similarly, a recent randomised controlled trial assessing different methods of sputum acquisition for tuberculosis reported that although sputum induction increases diagnostic yield, it does not affect the number of patients on treatment because of pre-existing high rates of treatment initiated on the basis of empirical evidence.[40] Our data imply that the projected epidemiological effect of Xpert MTB/RIF might be overestimated.

Our study had several limitations. Loss to follow-up of patients with culture-confirmed tuberculosis in our study was about 20%. This result was largely ascribable to one site (Lusaka) and arose because of staffing problems. However, with Lusaka excluded as part of a sensitivity analysis, which was recommended by an independent data review committee, our conclusions remain unchanged, power was retained, and overall loss to follow-up was reduced to 13%, which is the norm in our settings. Xpert MTB/RIF did show a trend towards reduced 2 month mortality compared with smear microscopy in culture-positive patients (appendix); however, the trial was not explicitly powered for this outcome. We did not detect a difference in mortality at 6 months, and allocation group was not an independent predictor of mortality in the multivariable analysis. Nevertheless, it seems that placing Xpert MTB/RIF where it can have the biggest effect on same-day clinical decision making (such as at the point of care) is crucial to maximising its benefit and avoiding dropout. The availability of chest radiography in our study, although in routine use at four of the five sites, might not be representative of certain programmatic settings and would have caused increased levels of empirical-evidence-based treatment decisions in the microscopy group; however, it is recommended by WHO for investigation of smear-negative tuberculosis. We did not measure the clinical effect of Xpert MTB/RIF in patients with extrapulmonary tuberculosis or those who are seriously ill, which might have affected intergroup differences. We did not quantify the potential financial and administrative effect of point-of-care Xpert MTB/RIF implementation on local clinics, which can be substantial,[18] the need for improved infection control necessitated by increased same-day management, nor any decline in Xpert MTB/RIF ability arising from prolonged use.

Notably, we deliberately chose same-day smear microscopy as our comparator group, whereas many countries use the conventional protocol of two or three smears (eg, spot, morning, spot) done over 2–3 days. In other settings, the effect of Xpert MTB/RIF might be different and should be explored. For ethical and clinical reasons the nurse undertaking the test and the person initiating treatment (whether the national tuberculosis programme doctor or nurse) could not be masked to the test result, which would have affected their clinical decision making; however, this approach is reflective of what happens routinely in primary care. Finally, although Xpert MTB/RIF does not affect morbidity, substantial potential benefits caused by its implementation, such as a reduction in dropouts, should still be considered by health-care providers. An important future research question is whether minimally trained non-clinical personnel (such as community health-care workers) are able to do Xpert MTB/RIF. Our assessment of nurse-administered versus technician-administered Xpert MTB/RIF compared nurses in peripheral settings to technicians in centralised laboratories. Because laboratory personnel might be available in peripheral settings, an important comparison for future analyses of cost-effectiveness would be to compare nurse-administered Xpert MTB/RIF versus technician-administered Xpert MTB/RIF in the same clinical setting.

Overall, our findings suggest that Xpert MTB/RIF is feasible at the point of care when done by non-specialised personnel, and that its near-patient placement translates into higher rates of treatment initiation, lower rates of true-positive patient dropout, and lower rates of empirical-evidence-based treatment compared with an

Panel: Research in context

Systematic review

We searched PubMed for studies published in English up to Aug 1, 2013, that examined the use of Xpert MTB/RIF at the point of care or its effect on patient-important outcomes. We combined search terms for Xpert MTB/RIF ("Xpert", "MTB/RIF", "Xpert MTB/RIF") with those suggesting use at the point of care ("point of care", "primary care", "clinic") or effect ("time to result", "time to diagnosis", "time to treatment", "morbidity", "mortality", "outcome"). We identified two meta-analyses of Xpert MTB/RIF,[11,33] six studies[8,12,14,17,34,35] that examined short-term outcomes such as time to result or time to treatment, and three[13,17,18] that described the use of Xpert MTB/RIF at the point of care.

Interpretation

To our knowledge, our study is the first published randomised controlled trial of Xpert MTB/RIF, the first to assess feasibility when done by a nurse at the point of care, and the first to assess its effect on clinically important outcomes such as patient dropout and morbidity. Most previous studies have examined the diagnostic accuracy of Xpert MTB/RIF and none have examined its effect on patient health. Despite finding many advantages over smear microscopy, such as improved rates of diagnosis and time to treatment initiation, our results show that the overall morbidity of tuberculosis patients retained in care did not differ between groups. This finding suggests that although Xpert MTB/RIF at the point of care is feasible when done by non-technical personnel and leads to more patients with tuberculosis starting treatment, the potential long-term epidemiological effect of this test is probably overestimated because of pre-existing high rates of treatment given on the basis of empirical evidence. Future studies on cost-efficacy and the effect of Xpert MTB/RIF on mortality and incidence are awaited.

alternative best-case in which WHO-endorsed same-day smear microscopy and chest radiography are available. However, Xpert MTB/RIF at point of care did not result in clinically important long-term changes in morbidity. The cost-effectiveness of this deployment strategy needs to be assessed and our trial will provide input data for such planned analyses.

Contributors

GT, LZ, DC, PC, AR, MP, MH, PMw, AP, PMa, JP, and KD were involved in the conception and design. GT, LZ, DC, PC, AR, AP, WB, SM, MH, PMw, JP, and KD were involved in study implementation. GT, ML, JP, and KD did the analysis. GT, LZ, MP, DD, JP, and KD interpreted the data and provided important intellectual input. GT, JP, and KD wrote the first draft.

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