

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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TB NEAT

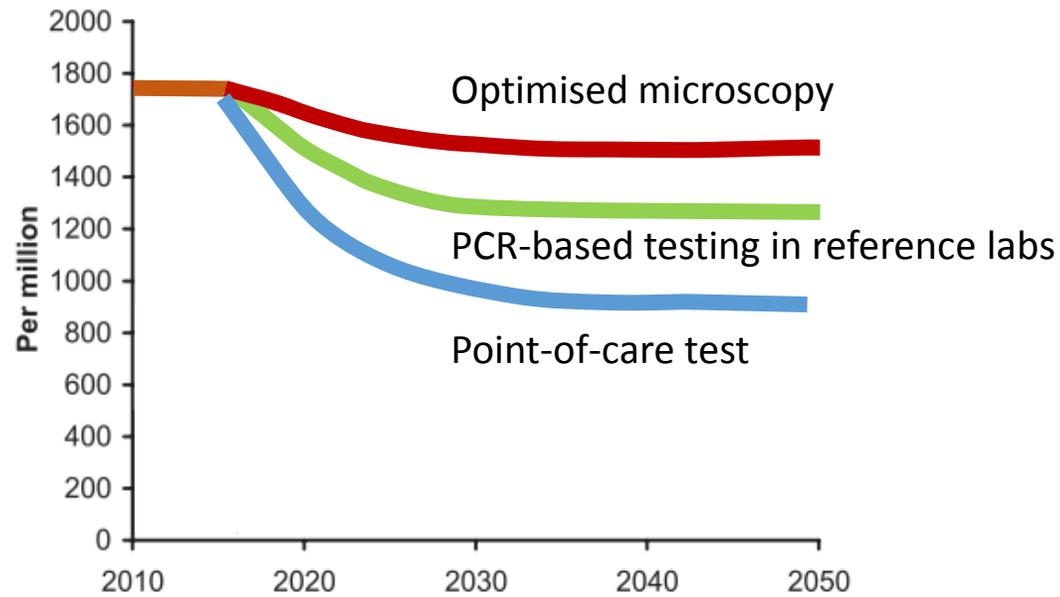


Outline

- Gaps in our knowledge about Xpert
- Study design, aims, and clinic setting
- Feasibility of nurse-performed Xpert at the clinic
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- Limitations and conclusions

Accurate TB diagnostics are needed, and their benefit may be maximised by point-of-care placement

Projected impact on incidence:



Abu-Raddad et al., PNAS, 2009

- 28% (4-38%) of patients who test positive in Africa do not start treatment

Macpherson et al., WHO Bull., 2013

6. Implementation considerations

As with any new technology, a range of implementation issues was identified, without which Xpert MTB/RIF use would not be optimal. These include:

- **Positioning:** Xpert MTB/RIF is suitable for use at **district and sub-district level**. Although testing with Xpert MTB/RIF does not require additional laboratory equipment, **the sophisticated nature of the device requires care of handling, i.e. stable and uninterrupted electrical supply to avoid interruption of the procedure and subsequent loss of results, security against theft, adequate storage space for the cartridges, dedicated staff to perform testing, and biosafety procedures similar to microscopy;**

WHO, 2010

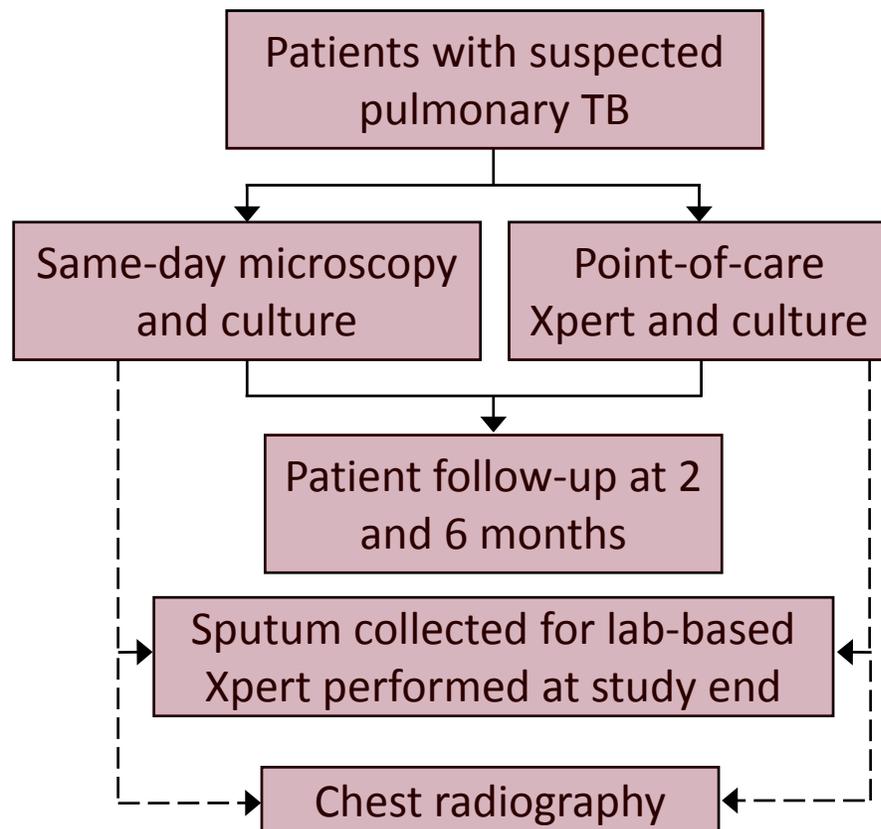
- Xpert will never substitute for an accurate bedside test, but does its far-patient placement undermine the potential of the most accurate and rapid test we currently have?
- Can a case be made for the rational placement of Xpert at the POC in well-resourced clinics within TB hotspots?

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Hypothesis, design, and endpoints

Hypothesis: One Xpert performed by a nurse at the **point-of-care** is **feasible**, and will **improve time-to-result, time-to-treatment and TB morbidity** amongst patients in primary care, **compared to same-day microscopy**.



Study staff did not initiate treatment. Patients were referred to routine clinical staff after diagnostic testing.

Endpoints

- **Feasibility** of Xpert by a nurse in the clinic vs. that by technician in a research or reference lab
- **Time-to-diagnosis**
- **Rates of treatment initiation**
- **Differences in TB morbidity score (TBscore) and Karnofsky Performance Score** between TB patients at 2 and 6 months

Clinic and nurse information

- Teams of **two nurses each** were placed at :
 - Gugulethu TB Clinic (Cape Town, South Africa), Mabvuku Polyclinic (Harare, Zimbabwe), Kanyama TB Clinic (Lusaka, Zambia), St. Mary's Day Clinic (Durban, South Africa), and Ifisi Day Clinic (Mbeya, Tanzania).
- Each had **an attached microscopy lab** (with the exception of Cape Town), **DOTS treatment facility**, and **a dedicated space for Xpert**
- Aside from security features and an IRB-required biosafety cabinet in Harare, **no other infrastructure** (e.g., power upgrades) **were installed**
- Nurses received **one day** of technical training
- Unannounced inspections by technicians were conducted **≥1 per month**, and **user appraisals** were regularly performed



Gugulethu Clinic, Cape Town.

Study profile

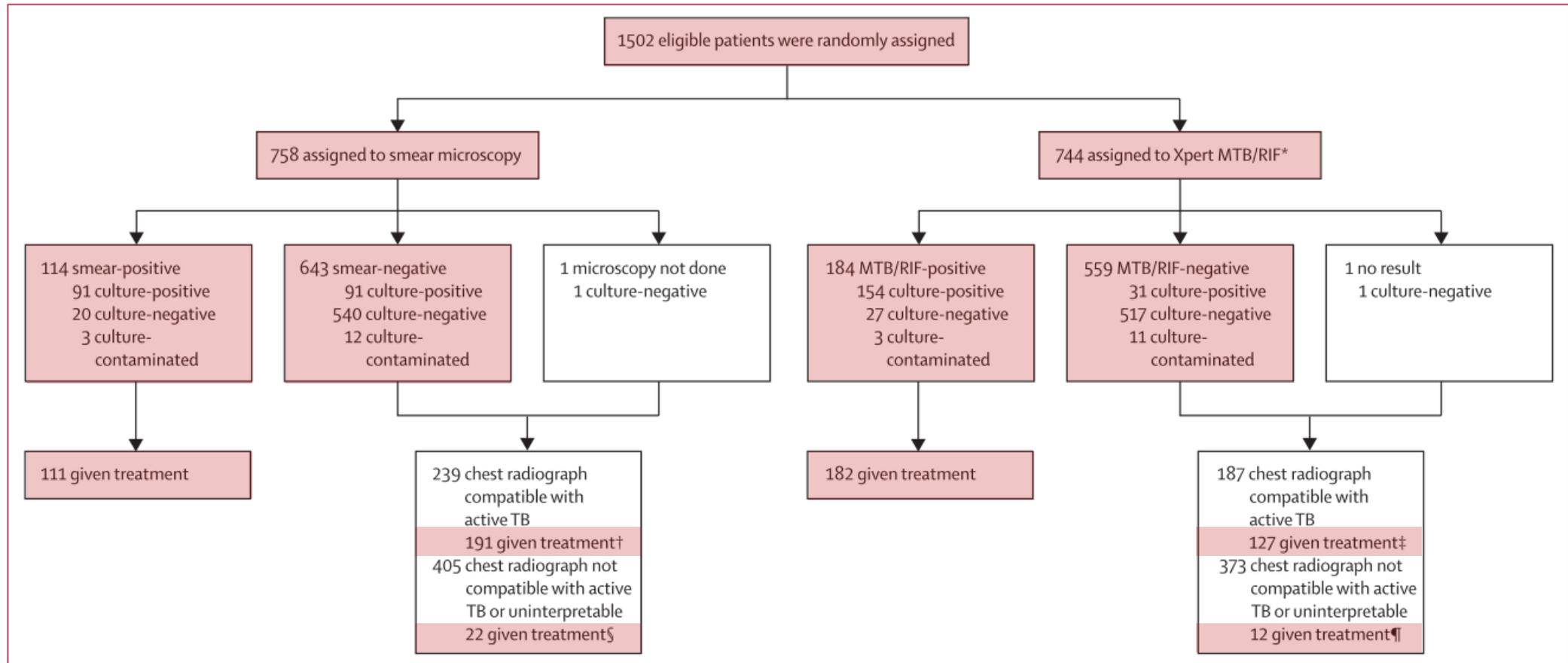


Figure 1: Study profile

Site characteristics

	Gugulethu TB Clinic (Cape Town, South Africa)	Mabvuku Polyclinic (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 across sites
Number of patients	419	400	400	200	83	1502	-
Age (IQR)	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 (1)	384 (26)	<0.0001
HIV Infected	133 (32)	324 (81)	268 (67)	121 (61)	49 (59)	895 (60)	<0.0001
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 TB culture-positive patients (%)	74 (18)	77 (19)	152 (38)	35 (18)	29 (35)	367 (24)	0.0001

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Feasibility of nurse-performed Xpert at the point-of-care

	At recruitment					At study close		
	Smear microscopy		Point-of-care Xpert			Lab-based Xpert		
	Sensitivity	Specificity	Sensitivity	Specificity	Failure rate	Sensitivity	Specificity	Failure rate
Overall	50% (42.9, 57.2) 91/182	96.5% (94.6, 97.7) 540/560	83.3% (77.2, 88) 154/185	95.1% (92.9, 96.6) 517/544	Before repeat: 4.7% (34/730) After repeat: 0.2% (1/730)	83.2% (79, 86.8) 292/351	91.9% (90, 93.4) 952/1037	Before repeat: 5.9% (82/1411) After repeat: 2% (27/1409)

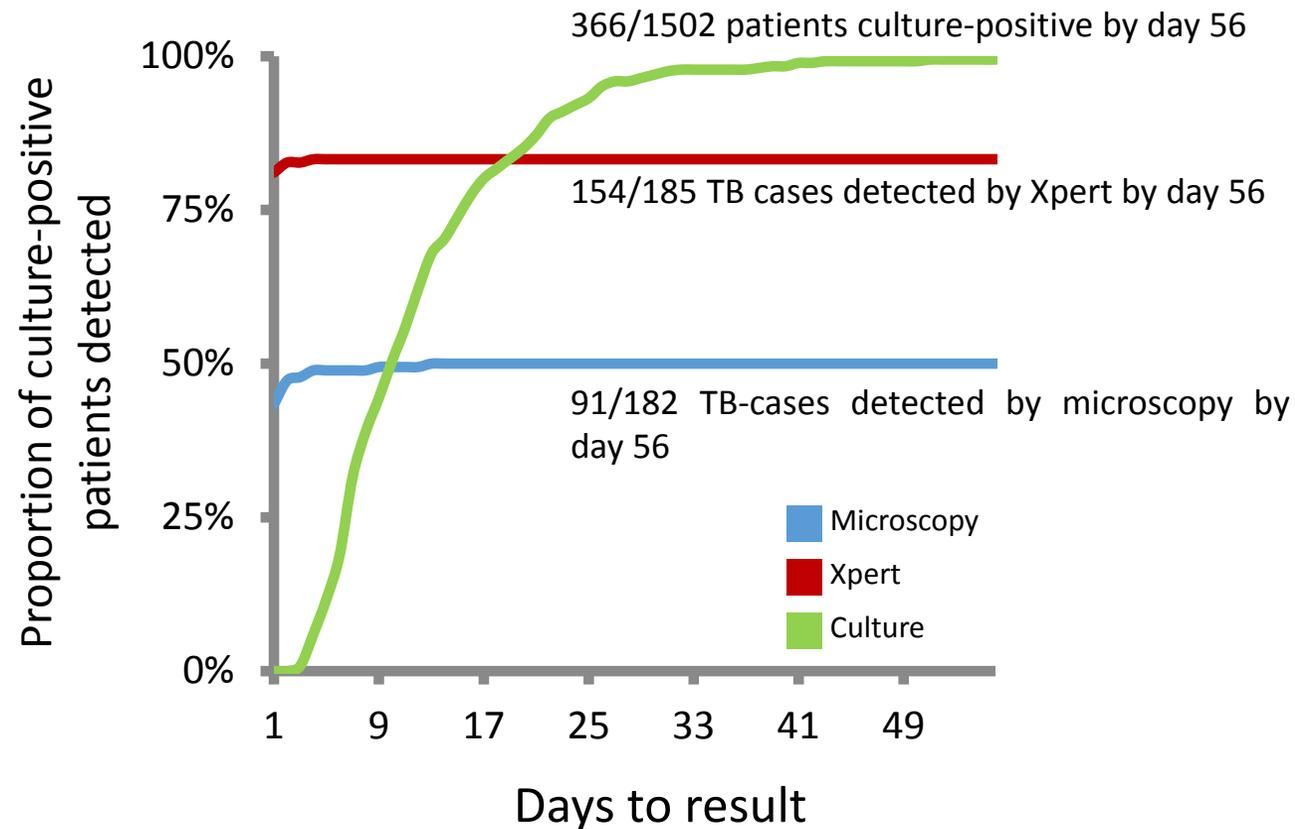
Kappa = 0.69 (“substantial agreement”)

	Gugulethu TB Clinic (Cape Town, South Africa)	Mabvuku Polyclinic (Harare, Zimbabwe)	Kanyama TB Clinic (Lusaka, Zambia)	St Mary’s Day Clinic (Durban, South Africa)	Ifisi Day Clinic (Mbeya, Tanzania)	Overall
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)

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Does Xpert improve time-to-diagnosis?

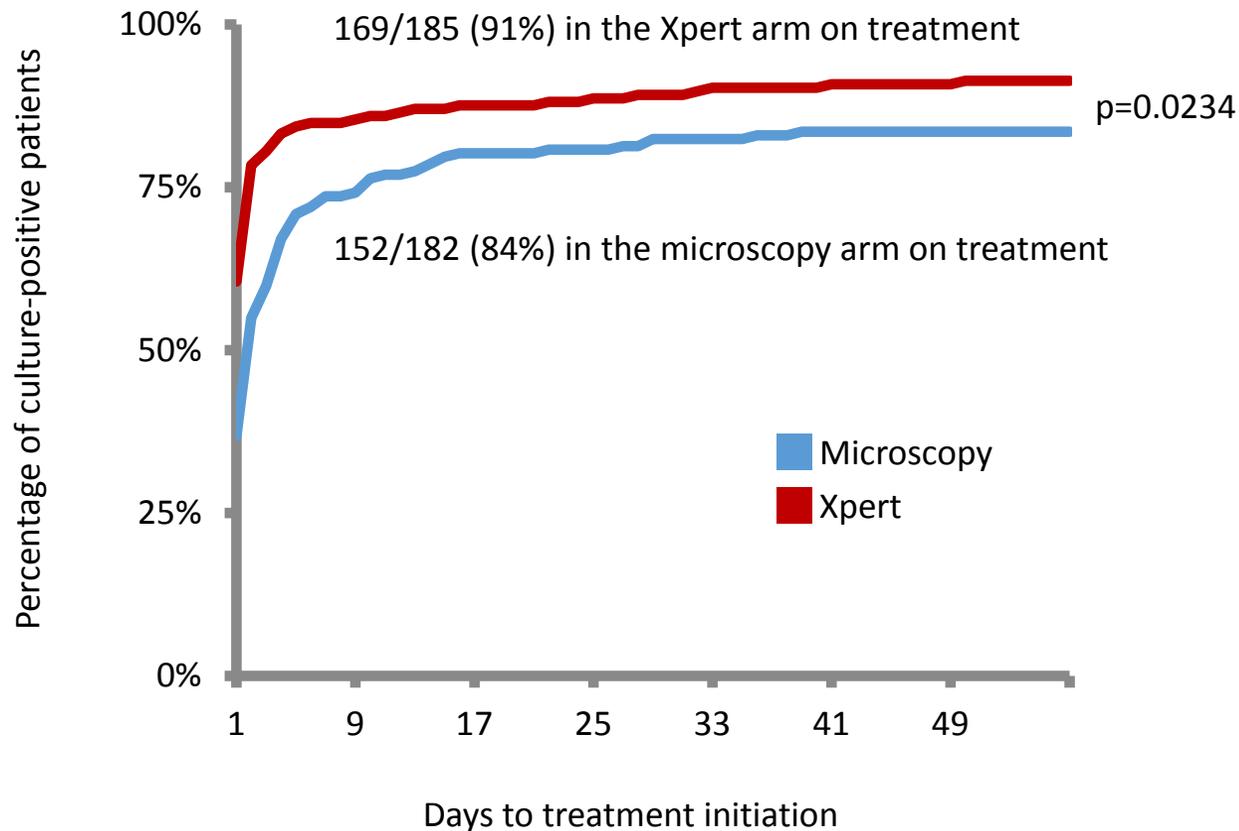


	Smear microscopy (N=758)	Xpert MTB/RIF (N=744)	p value
All patients with a positive result (by any means)*			
By day 1	99/758 (13%)	178/744 (24%)	<0.0001
By day 2	107/758 (14%)	183/744 (25%)	<0.0001
By day 3	109/758 (14%)	185/744 (25%)	<0.0001
By day 14	165/758 (22%)	196/744 (26%)	0.0380
By day 28	199/758 (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

Does Xpert improve time-to-treatment in culture-positive patients?

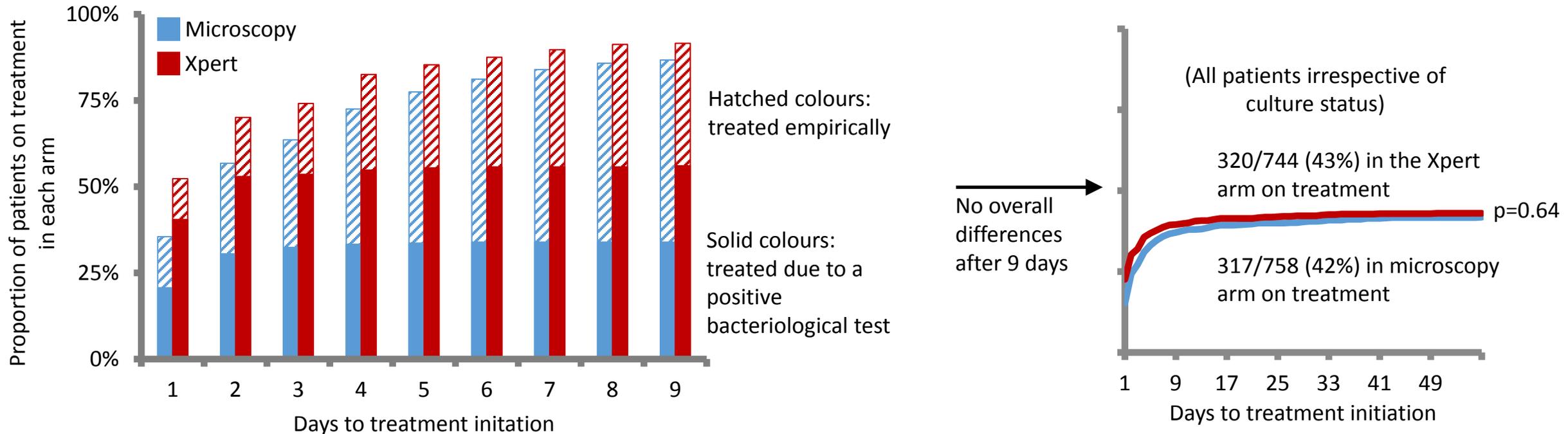


- Xpert reduced culture-positive drop-out from **16% to 9%**
- Median time-to-treatment was **2 days** in the microscopy arm versus **1 day** in the Xpert arm (p=0.0004)
- Culture had **little utility** :
 - 6% of culture-positive patients were initiated based on their culture-result (10/182 in smear arm, and 9/185 in Xpert arm)

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What is the role of empirical treatment?



- Proportion of patients treated empirically was less with Xpert (17% vs. 26%; $p < 0.0001$)
- Empirical treatment was rapid (median time of 3 days in either arm)
- 70% of smear-negative TB cases were detected by Xpert at the study end, yet 93% of these were treated rapidly on empirical grounds anyway

The “appropriateness” of empirical treatment did not change

- Although there is **overall less empirical treatment** with Xpert (due to more patients receiving a rapid bacteriological diagnosis) :
 - A **similar** number of “**false-negative**” **empirical treatment decisions** occurred in either arm: 26% of culture-negatives in smear arm vs. 22% in Xpert arm

<u>versus a single culture</u>	Specificity (%) (95 CI)
Empirical treatment in the microscopy arm	74.15 (70.05, 77.78) 416/561
Empirical treatment in the Xpert arm	78.35 (74.89, 81.80) 427/545

p=0.1013

Did Xpert improve TB-related morbidity?

	TBscore			Karnofsky performance score		
	Microscopy	Xpert	P-value	Microscopy	Xpert	P-value
Baseline (n=153 and n=168 in each arm)	5 (4-7)	5 (4-7)	0.56	70 (60-80)	70 (57.5-90)	0.89
Two month follow-up (87/153 and 108/168 in each arm; p=0.17)	2 (0-3)	2 (0.25-3)	0.85	80 (70-90)	90 (80-90)	0.23
Six month follow- up (81/153 and 97/168 in each arm; p=0.39)	1 (0-3)	1 (0-3)	0.35	100 (90-100)	100 (90-100)	0.85

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Drug-resistant TB in TB-NEAT

- In South Africa (and China), 80% of DR-TB is be caused by person-to-person transmission

Streicher et al., Infect. Gen. Evol., 2011; Zhao et al., NEJM, 2012

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Rifampicin monoresistant (%)	1/67 (1)	7/73 (10)	8/152 (5)	0/32 (0)	0/26 (0)	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
Multi-drug resistant (%)	5/67 (7)	1/73 (1)	0/152 (0)	0/27 (0)	0/25 (0)	6/345 (2)	0.0090

- Accuracy of lab-based Xpert for Rif^R TB in patients with complete data was sub-optimal:

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
MTBDR <i>plus</i> as a reference standard	23.6% (9.6, 47.3) 4/17	98.9% (96.8, 99.7) 264/267	57.2% (25.1, 84.2) 4/7	95.4% (92.2, 97.3) 264/277

Loss-to-follow-up and mortality

Loss-to-follow-up in patients placed on treatment			
	Microscopy arm	Xpert arm	P-value
Two months	70/324 (21)	69/321 (21)	p=0.9730
TB cases	33/154 (21)	36/170 (21)	p=0.9559
Non-TB cases	37/170 (22)	33/151 (22)	p=0.9845
Six months	71/324 (22)	74/321 (23)	p=0.7289
TB cases	36/154 (23)	36/170 (21)	p=0.6343
Non-TB cases	35/170 (21)	38/151 (25)	p=0.3288

Mortality			
	Microscopy arm	Xpert arm	P-value
Two months	26/324 (8)	14/321 (4)	0.0538
TB cases	5/67 (7)	11/154 (7)	0.1452
Non-TB cases	15/170 (9)	8/151 (6)	0.2216
Six months	35/324 (11)	28/321 (9)	0.3737
TB cases	14/154 (9)	14/170 (8)	0.7843
Non-TB cases	21/170 (12)	14/151 (9)	0.3766

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Limitations

- This was a short-term study in Southern Africa amongst TB suspects that needs to be viewed in the context of high burden settings with high rates of empirical treatment. Xpert in different populations will have a different effect.
- Programmatic monitoring, machine maintenance, and the task shifting implications of POC Xpert placement are important, but were outside the scope of this trial. Most sites in Africa have POC microscopy available, however.
- CXRs were available to clinicians, even though radiography is not standard-of-care everywhere. XTEND has, however, also reported high rates of empirical treatment (35% of patients starting treatment prior to Xpert were smear-negative).
- Xpert appeared to perform poorly for drug-resistance detection, however, this is not definitive due to the small number of cases.
- The selective placement of Xpert at the POC will be very expensive, but will it be worth it? This work will inform a cost-effectiveness study.

The way forward: taking new molecular tests into the community?



Concluding thoughts

- In our RCT, although Xpert did not impact morbidity, it
 - is feasible in primary care and does not require technical personnel
 - increased rates of same day treatment
 - resulted in less patients with TB “dropping-out”
- If POC placement has little clinical effect, how likely is it that centralised testing will? Will the key benefit arise from preventing TB patient drop-out? Other studies not using POC Xpert have been unable to demonstrate a reduction in pre-treatment drop-out.
- While Xpert reduces the volume of empirical treatment, it does not improve its accuracy or “appropriateness”
- Empirical TB treatment has many disadvantages, but have we underestimated it’s role when projecting the impact of new diagnostics?
- How will the clinical handling of test-negative patients change with the long-term implementation of Xpert?
- Does improving clinical decision making and training need to be given an as big a priority as merely rolling out a new test?

