Randomised controlled trials evaluating Xpert MTB/RIF

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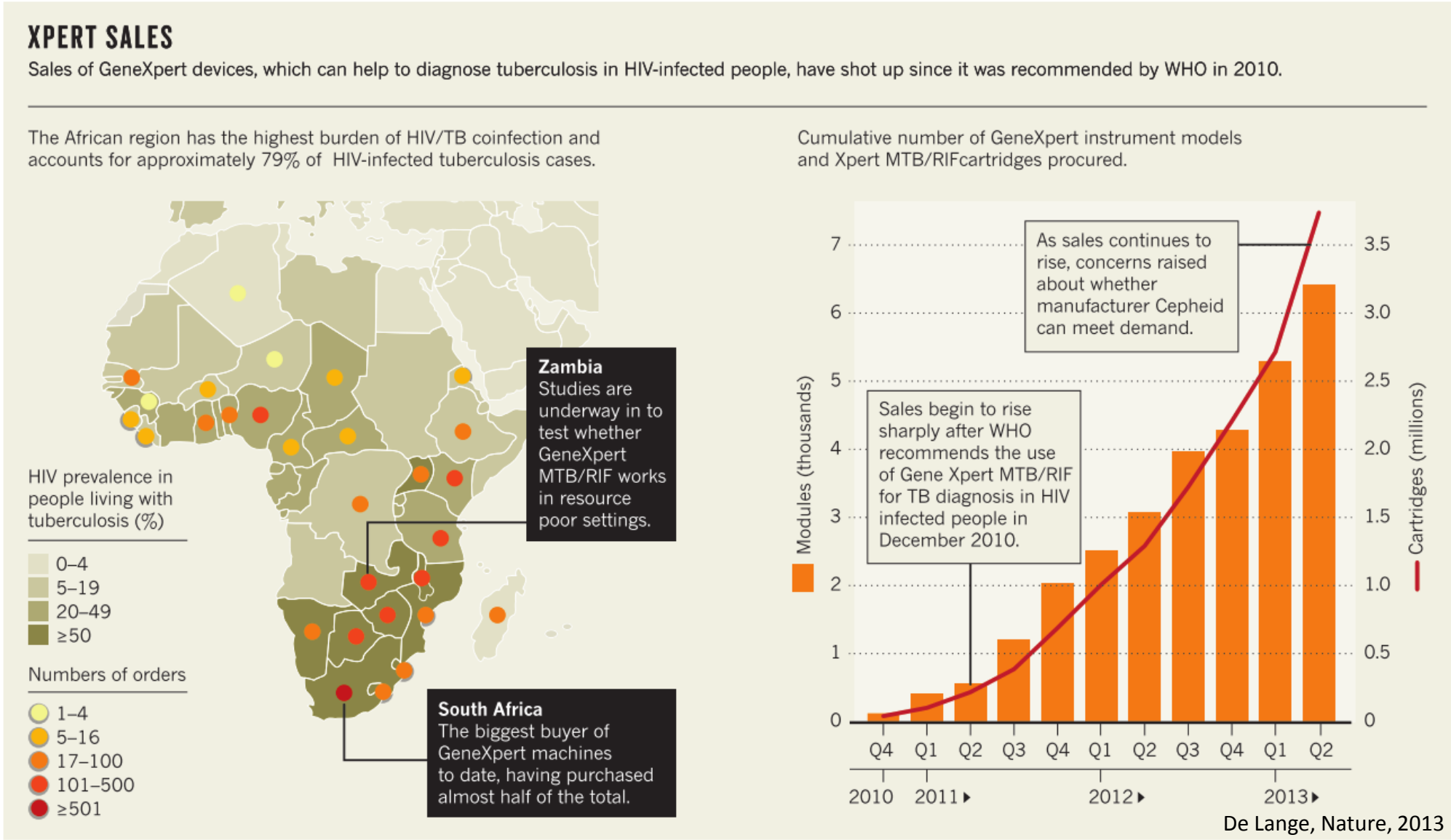
Rapid adoption of Xpert but hardly any RCTs



De Lange, Nature, 2013

Position of RCTs in the Xpert evaluation pathway

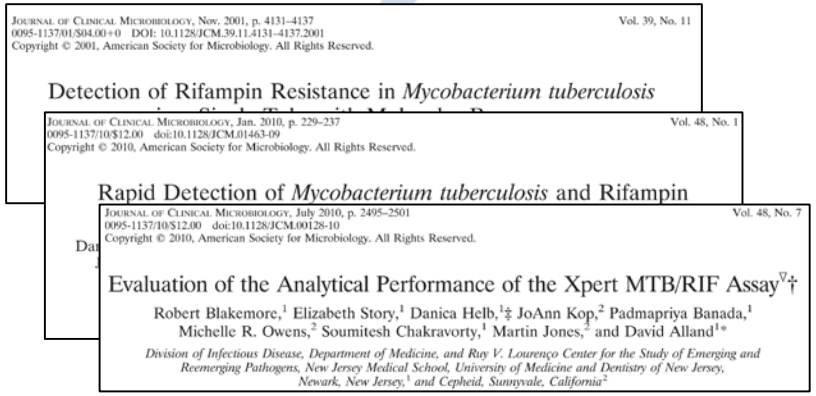
Early proof of concept studies

Large scale evaluation studies: what is the diagnostic accuracy?

Demonstration and implementation studies: What is the technical feasibility? Impact on the short-term patient outcomes like time-to-treatment initiation?

Diagnostic RCTs addressing long-term patient outcomes

Public health impact and evidence for scale up, impact on prevalence


JOURNAL OF CLINICAL MICROBIOLOGY, Nov. 2001, p. 4131–4137 Vol. 39, No. 11
0095-1137/01/$04.00+0 DOI: 10.1128/JCM.39.11.4131–4137.2001
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Detection of Rifampin Resistance in *Mycobacterium tuberculosis*

JOURNAL OF CLINICAL MICROBIOLOGY, Jan. 2010, p. 229–237 Vol. 48, No. 1
0095-1137/10/$12.00 doi:10.1128/JCM.01463-09
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Rapid Detection of *Mycobacterium tuberculosis* and Rifampin

JOURNAL OF CLINICAL MICROBIOLOGY, July 2010, p. 2495–2501 Vol. 48, No. 7
0095-1137/10/$12.00 doi:10.1128/JCM.00128-10
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Evaluation of the Analytical Performance of the Xpert MTB/RIF Assay▽†

Robert Blakemore,[1] Elizabeth Story,[1] Danica Helb,[1]‡ JoAnn Kop,[2] Padmapriya Banada,[1] Michelle R. Owens,[2] Soumitesh Chakravorty,[1] Martin Jones,[2] and David Alland[1]*

Division of Infectious Disease, Department of Medicine, and Roy V. Lourenço Center for the Study of Emerging and Reemerging Pathogens, New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark, New Jersey,[1] and Cepheid, Sunnyvale, California[2]

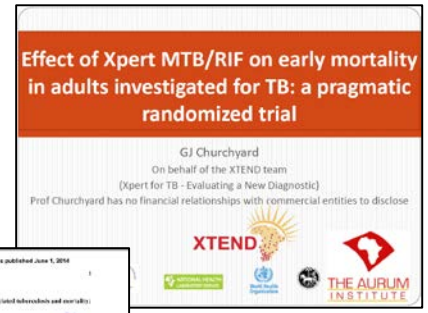

The NEW ENGLAND JOURNAL of MEDICINE

Rapid Molecular Detection of Tuberculosis and Rifampin Resistance


Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study


Articles

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


Effect of Xpert MTB/RIF on early mortality in adults investigated for TB: a pragmatic randomized trial

GJ Churchyard

On behalf of the XTEND team

(Xpert for TB - Evaluating a New Diagnostic)

Prof Churchyard has no financial relationships with commercial entities to disclose

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Accepted Manuscript


Pilot roll out for Xpert MTB/Rif for the diagnosis of pulmonary tuberculosis in two municipalities in Brazil

Befina Durovni

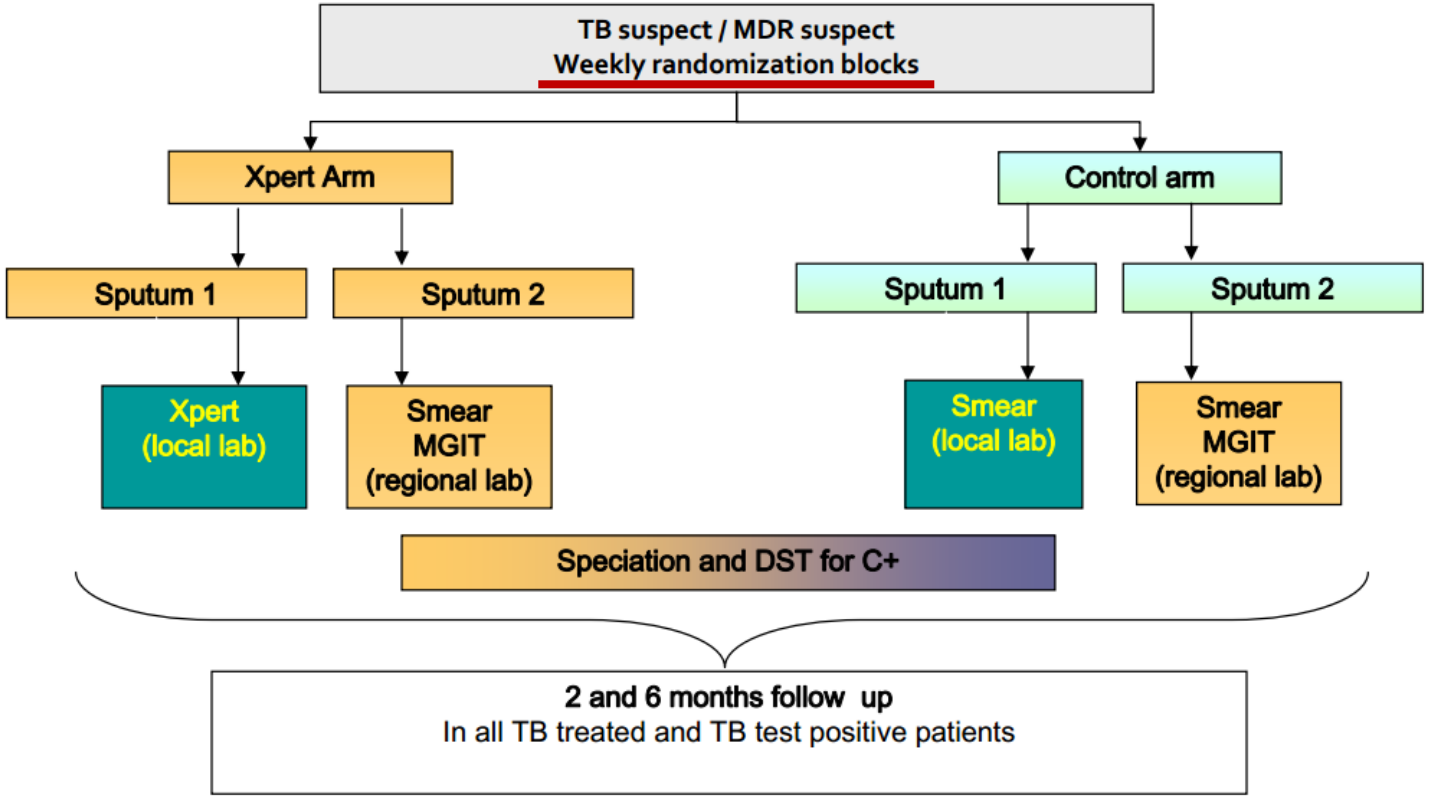
Rio de Janeiro Health Department, Brazil

BRASIL

Outline

- FIND demonstration study in Cape Town
- TB-NEAT Xpert RCT in Southern Africa
- XTEND roll-out study from South Africa
- Xpert roll-out study in Brazil
- RCT of Xpert for TB detection in Zimbabweans starting ART
- Other in progress RCTs that involve Xpert
  - CIDRZ 1201 - Clinical Outcomes in HIV-Infected Adults & Children Using Xpert in Zambia
  - STATIS (empirical treatment vs. Xpert in CD4<100)
  - Xpert in the ICU
  - XACT (Xpert used for active case finding)
- Summary and conclusions

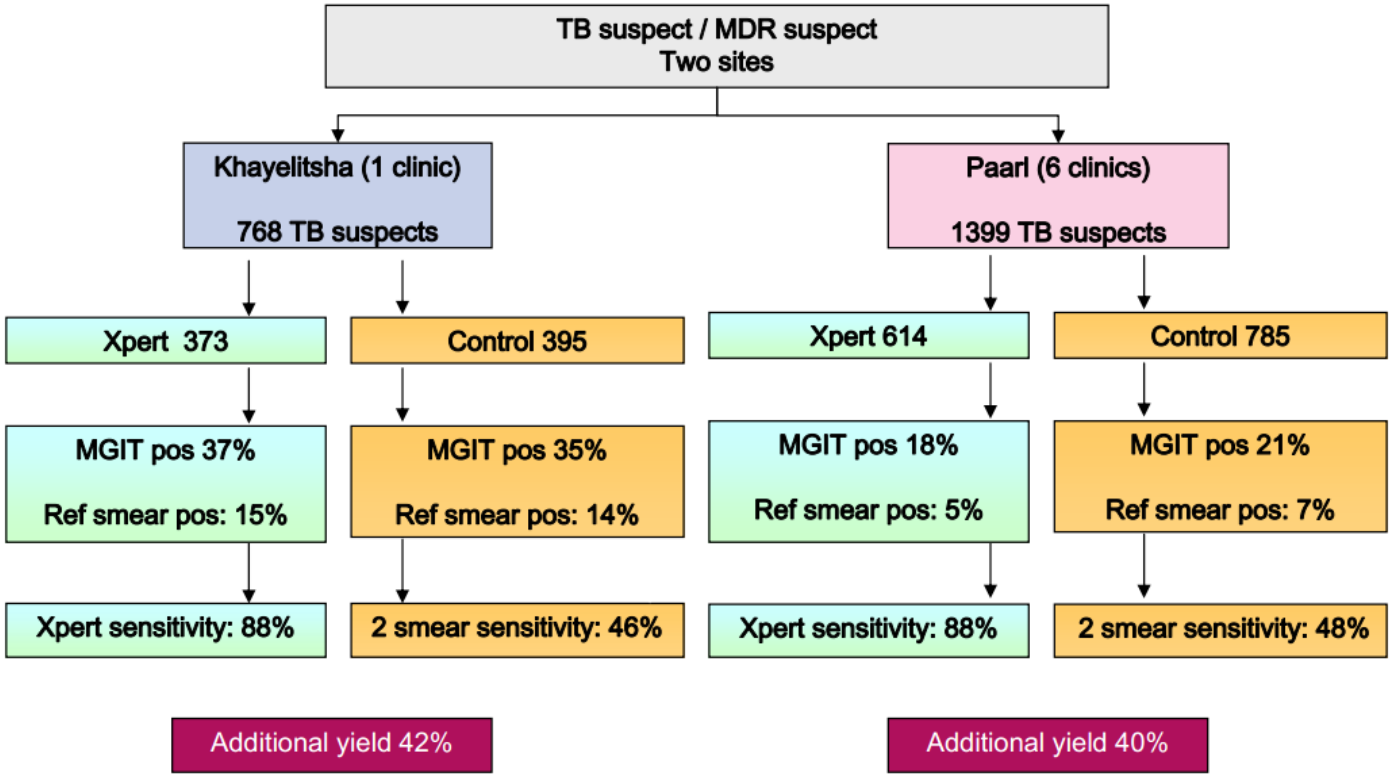
Cape Town-component of FIND Demonstration study



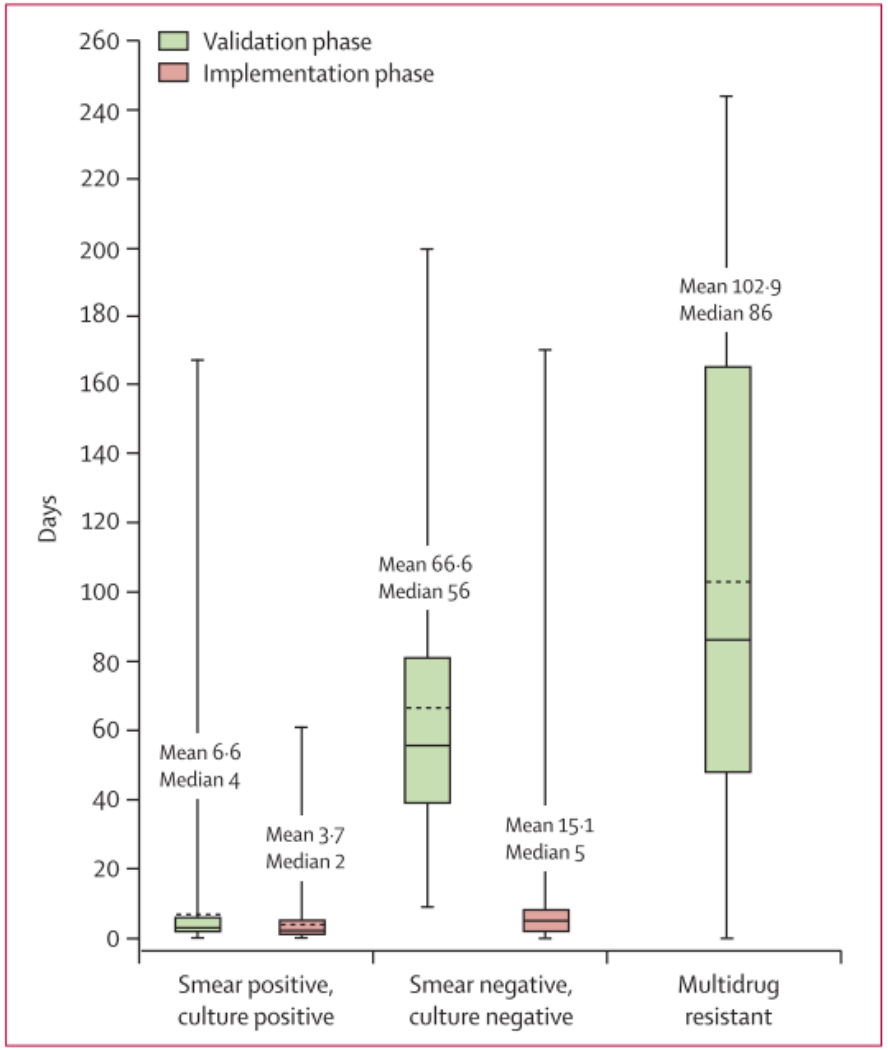
Population: 2522 patients with suspected TB from a clinic and a hospital in Cape Town
Intervention: Xpert + smear
Comparator: Smear
Outcome: Rates of diagnosis and treatment initiation

Nicol et al., Union Conference, 2010
Boehme et al., Lancet, 2011

Cape Town-component of FIND Demonstration study



Nicol et al., Union Conference, 2010
Boehme et al., Lancet, 2011



Outline

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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

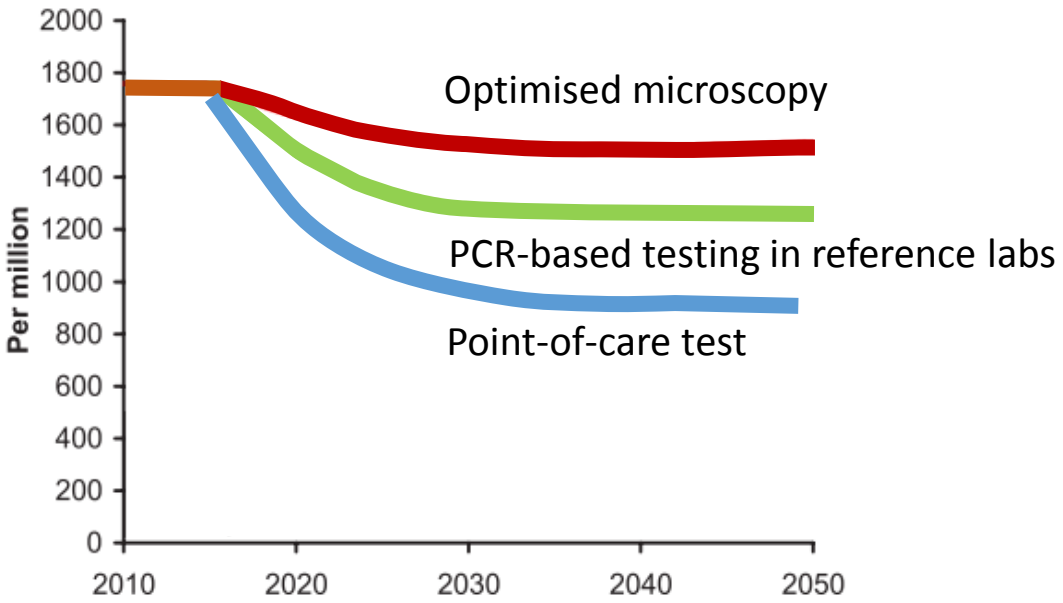
*Grant Theron, Lynn Zijenah, Duncan Chanda, Petra Clowes, Andrea Rachow, Maia Lesosky, Wilbert Bara, Stanley Mungofa, Madhukar Pai, Michael Hoelscher, David Dowdy, Alex Pym, Peter Mwaba, Peter Mason, Jonny Peter, Keertan Dheda, for the TB-NEAT team**

- Up to 40% of patients who test positive fail to return

Squire et al., IJTLD, 2005
Botha et al., IJTLD, 2008

> **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;

Projected impact on incidence:



Abu-Raddad et al., PNAS, 2009

- Xpert will never substitute for an accurate lateral flow assay, 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?

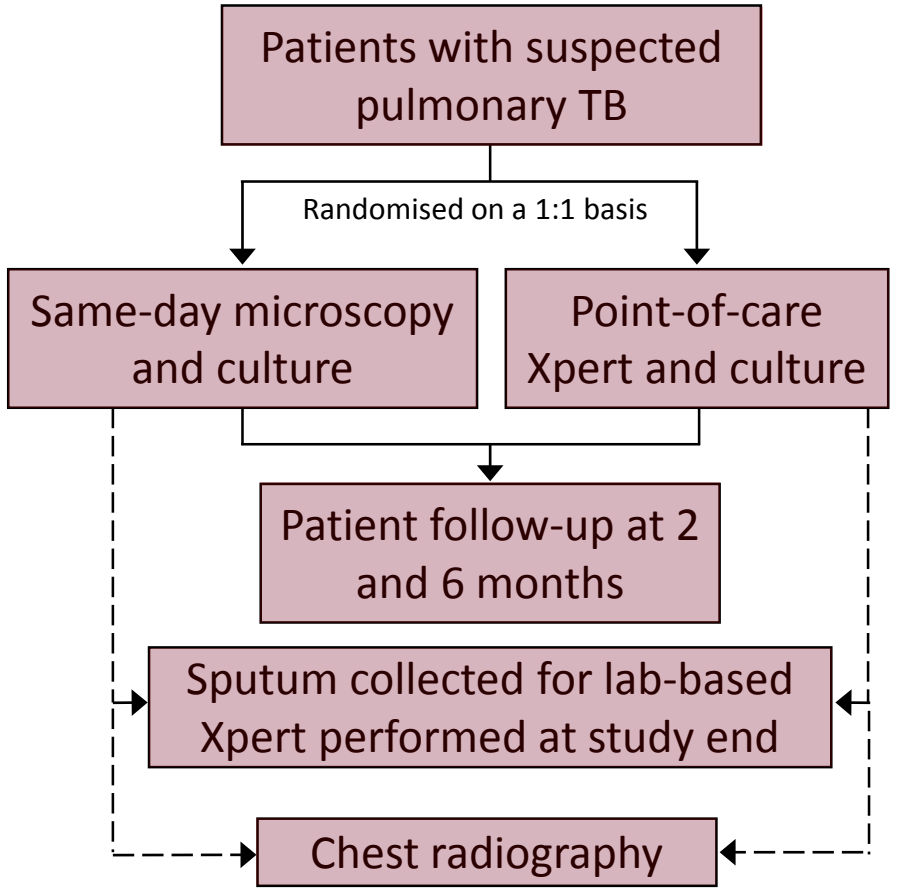
Feasibility, accuracy, and clinical effect of point-of-care Xpert MTB/RIF testing for tuberculosis in primary-care settings in Africa: a multicentre, randomised, controlled trial

*Grant Theron, Lynn Zijenah, Duncan Chanda, Petra Clowes, Andrea Rachow, Maia Lesosky, Wilbert Bara, Stanley Mungofa, Madhukar Pai, Michael Hoelscher, David Dowdy, Alex Pym, Peter Mwaba, Peter Mason, Jonny Peter, Keertan Dheda, for the TB-NEAT team**

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

Endpoints

- **Feasibility** of Xpert by a nurse in the clinic vs. by technician in 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



Study staff did not initiate treatment. Patients were referred to clinic staff after testing.

Site characteristics

	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 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 culture-positive patients (%)	74 (18)	77 (19)	152 (38)	35 (18)	29 (35)	367 (24)	0.0001

Clinic information

- Teams of **two nurses each** were placed at :
  - Gugulethu TB Clinic (Cape Town, South Africa), Mabvuku Polyclinc (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

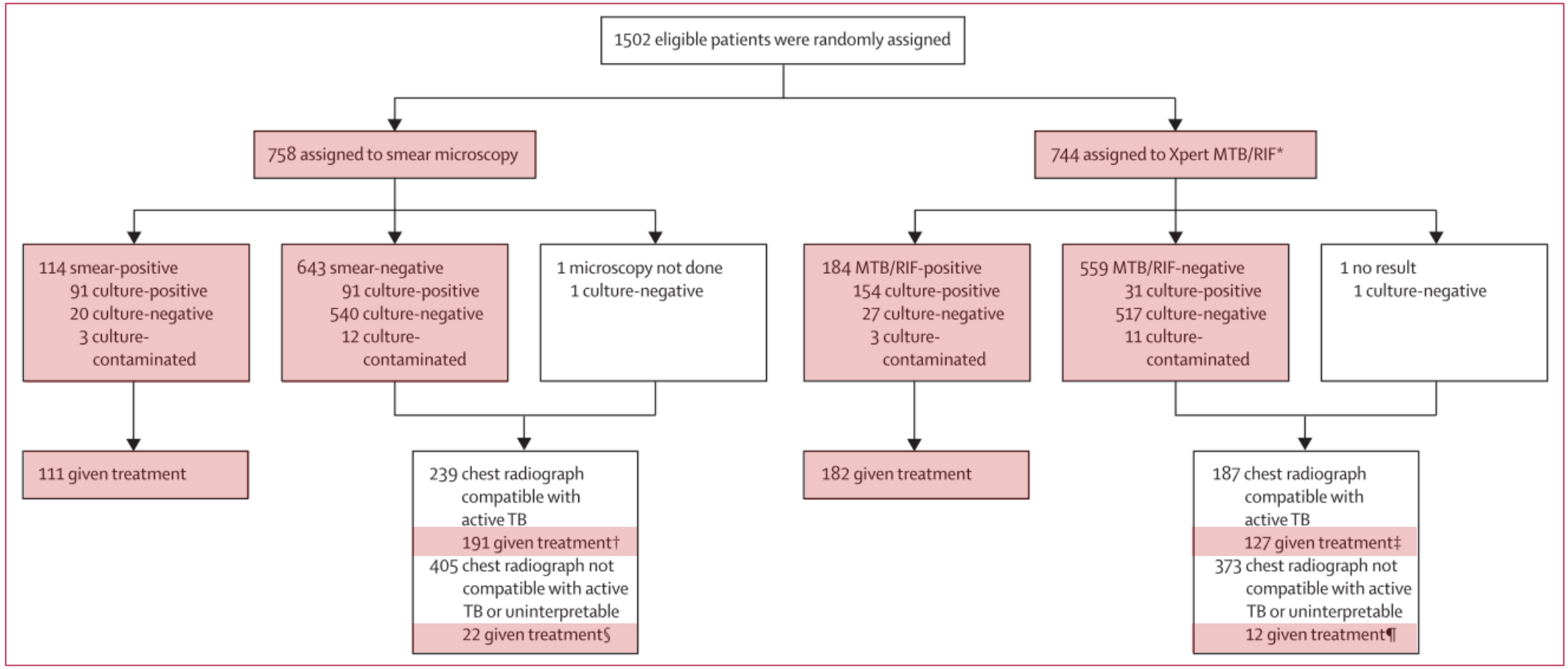


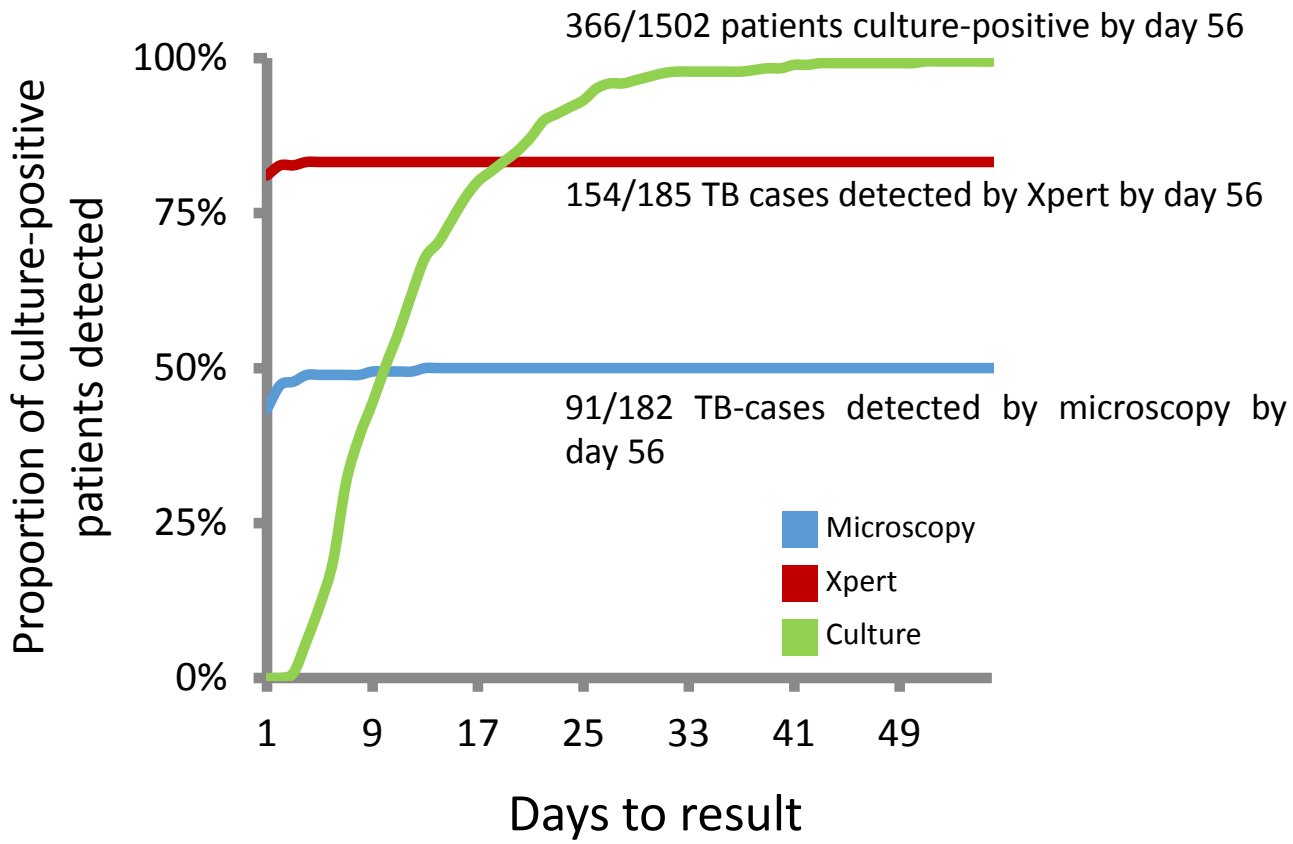
Figure 1: **Study profile**

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”)

Time-to-diagnosis

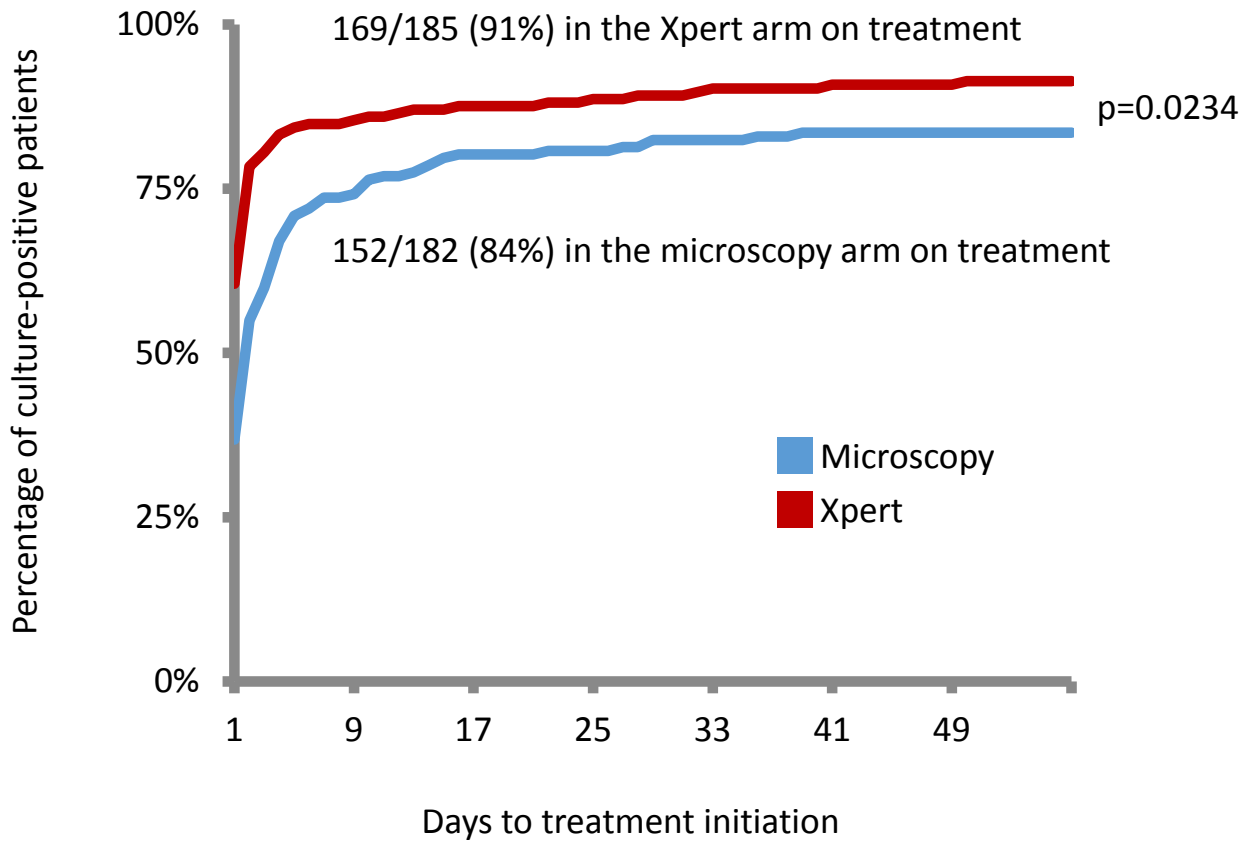


	Smear microscopy (N=758)	Xpert MTB/RIF (N=744)	p value
All patients with a positive result (by any means)*			
By day 1	99/758 (13%)	178/744 (24%)	<0·0001
By day 2	107/758 (14%)	183/744 (25%)	<0·0001
By day 3	109/758 (14%)	185/744 (25%)	<0·0001
By day 14	165/758 (22%)	196/744 (86%)	0·0380
By day 28	199/758 (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.

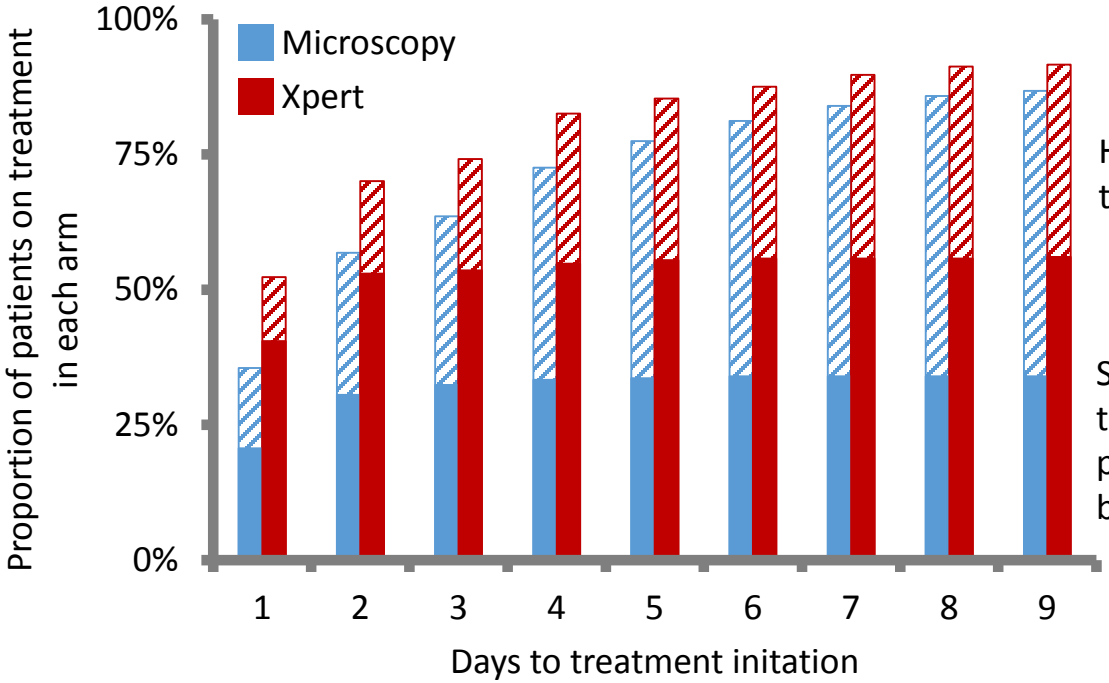
Table 4: **Patients with a positive smear microscopy, Xpert MTB/RIF, or culture result, and days to result, per allocation group**

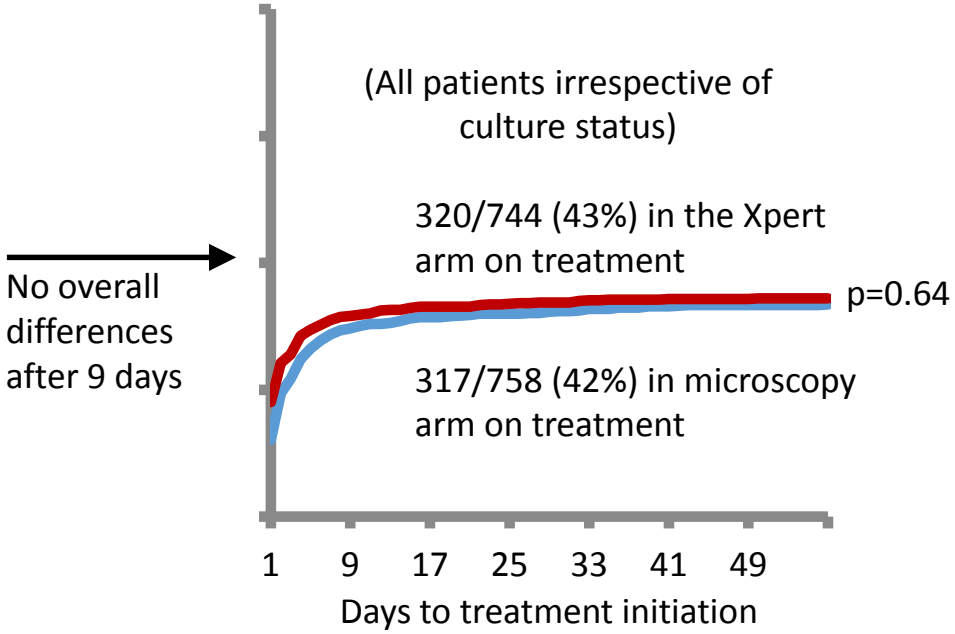
Time-to-treatment in culture-positive patients



- 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 diagnostic utility** :
  - 6% of culture-positive patients where initiated based on their culture-result (10/182 in smear arm, and 9/185 in Xpert arm)

What is the role of empirical treatment?





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

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

versus a single culture	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

TB-related morbidity

Table S1. Variables used to calculate the TB score as defined by Wejse *et al.* (2008)[4]. Each patient was scored at baseline, 2 months and 6 months.

Parameters	**Points assigned** (Maximum score is 13)
Self-reported	
Cough	1
Haemoptysis	1
Dyspnoea	1
Chest pain	1
Night sweats	1
Clinically examined	
Anaemic conjunctivae	1
Tachycardia	1
Positive finding at lung auscultation	1
Axillary temperature > 37.0 °C	1
BMI < 18.0	1
BMI < 16.0	1
MUAC < 220 mm	1
MUAC < 200 mm	1

Abbreviations: BMI, body mass index; MUAC, middle upper arm circumference.

Table S2. Karnofsky performance status scale currently as assessed by interviewer

100	Normal no complaints; no evidence of disease.
90	Able to carry on normal activity; Minor signs or symptoms of disease.
80	Normal activity with efforts; some signs or symptoms of disease.
70	Cares for self; unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his personal needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospital admission is indicated although death not imminent.
20	Very sick; hospital admission necessary; Active supportive treatment necessary.
10	Moribund; fatal processes progressing rapidly.
0	Dead

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

Challenges in the TB-NEAT RCT

Study progress:

May 2010

Study design & protocol development June 2010

Hiring of staff, rooms in clinics available

Ethics approval Oct 2010

Recruitment begins Feb 2011

Evaluation study NEJM Sept 2010

WHO endorsement Dec 2010

SA DOH implementation plan March 2011

Demo study Lancet April 2011

Phased rolled out of Xpert in Klipfontein district by DoH in Jan 2012

End of recruitment: March 2012

End of follow-up: October 2012


Articles

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

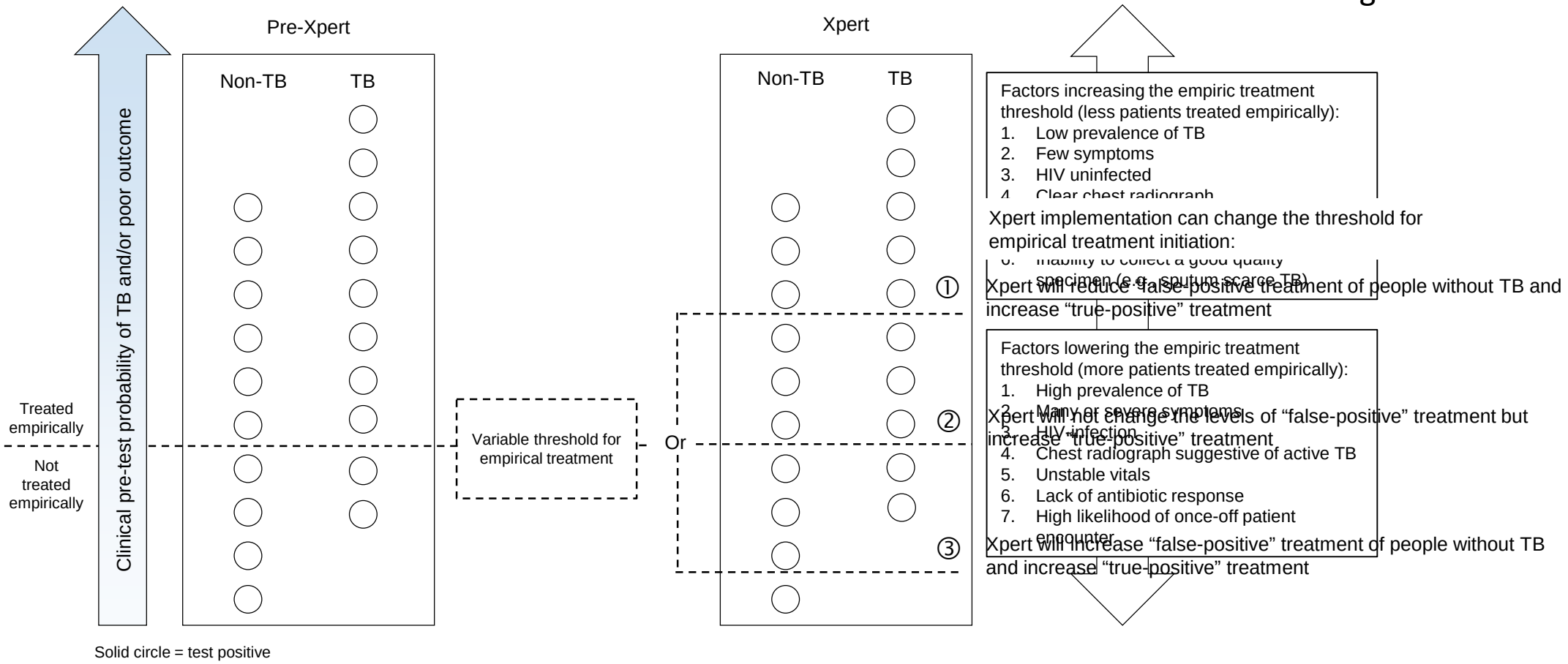
Publication in October 2013

→ Scientific relevance: 4 Xpert publications per month!

Do high rates of empirical treatment undermine the potential effect of new diagnostic tests for tuberculosis in high-burden settings?

Grant Theron, Jonny Peter, David Dowdy, Ivor Langley, S Bertel Squire, Keertan Dheda

Is Xpert merely displacing true-positive (and frequently rapid) empirical treatment in high burden settings?



Limitations of the TB-NEAT Xpert RCT

- 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 study clinicians. Although it is not standard-of-care everywhere, it is recommended by the WHO for the diagnosis of smear-negative TB.

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Effect of Xpert MTB/RIF on early mortality in adults investigated for TB: a pragmatic randomized trial

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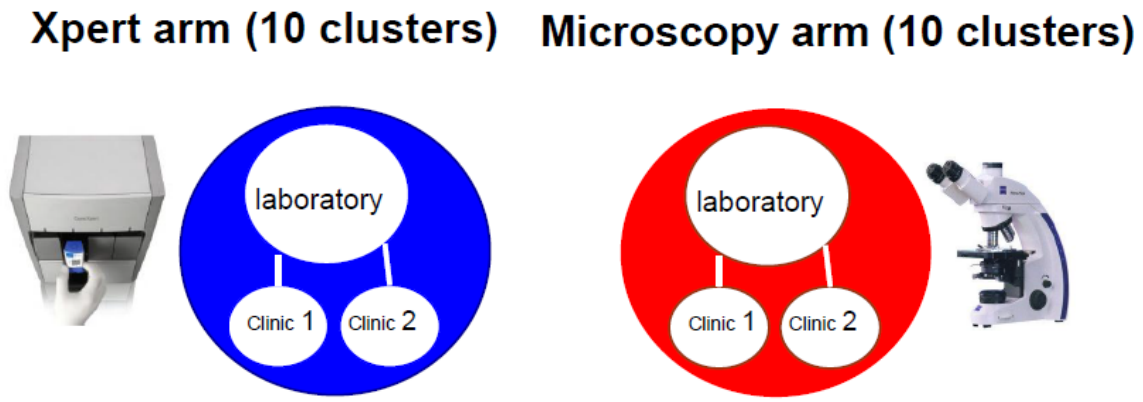
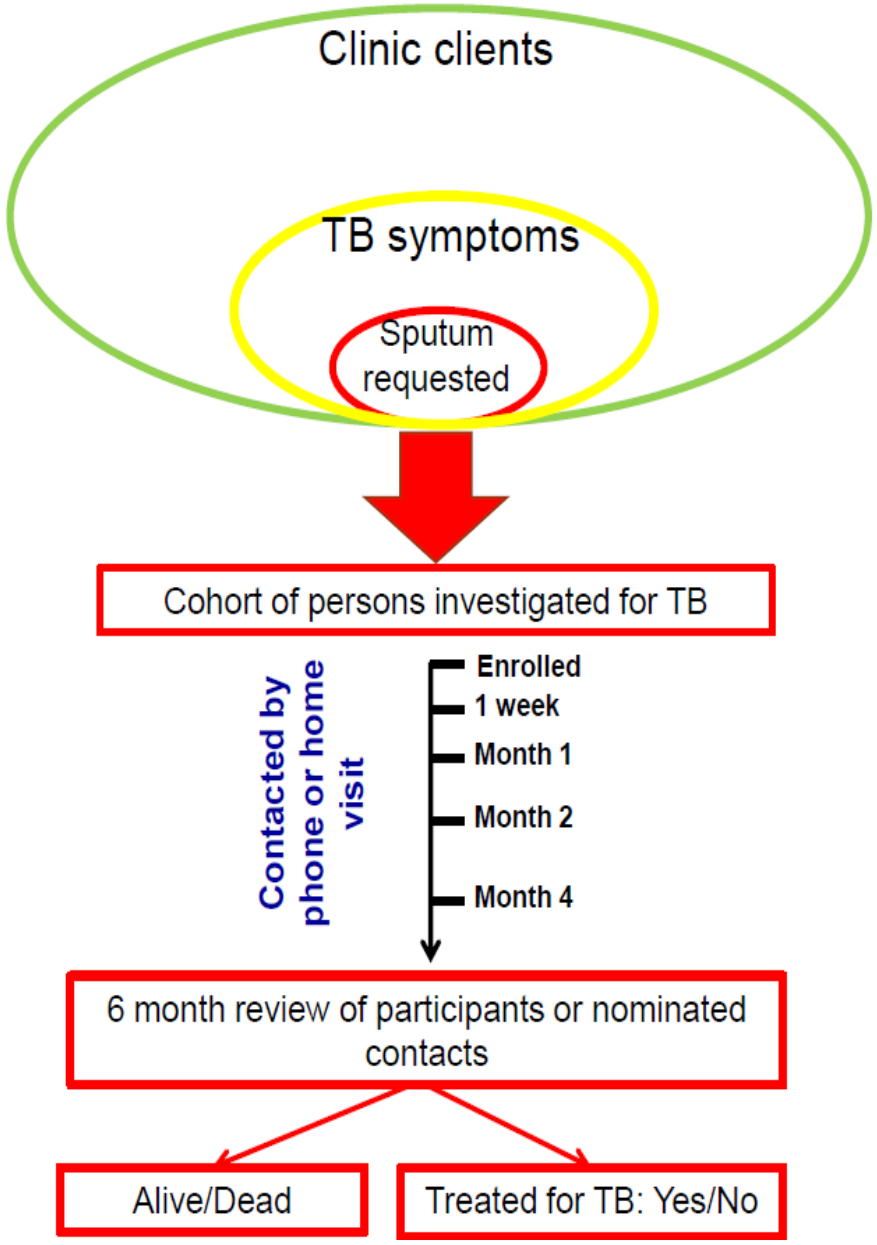
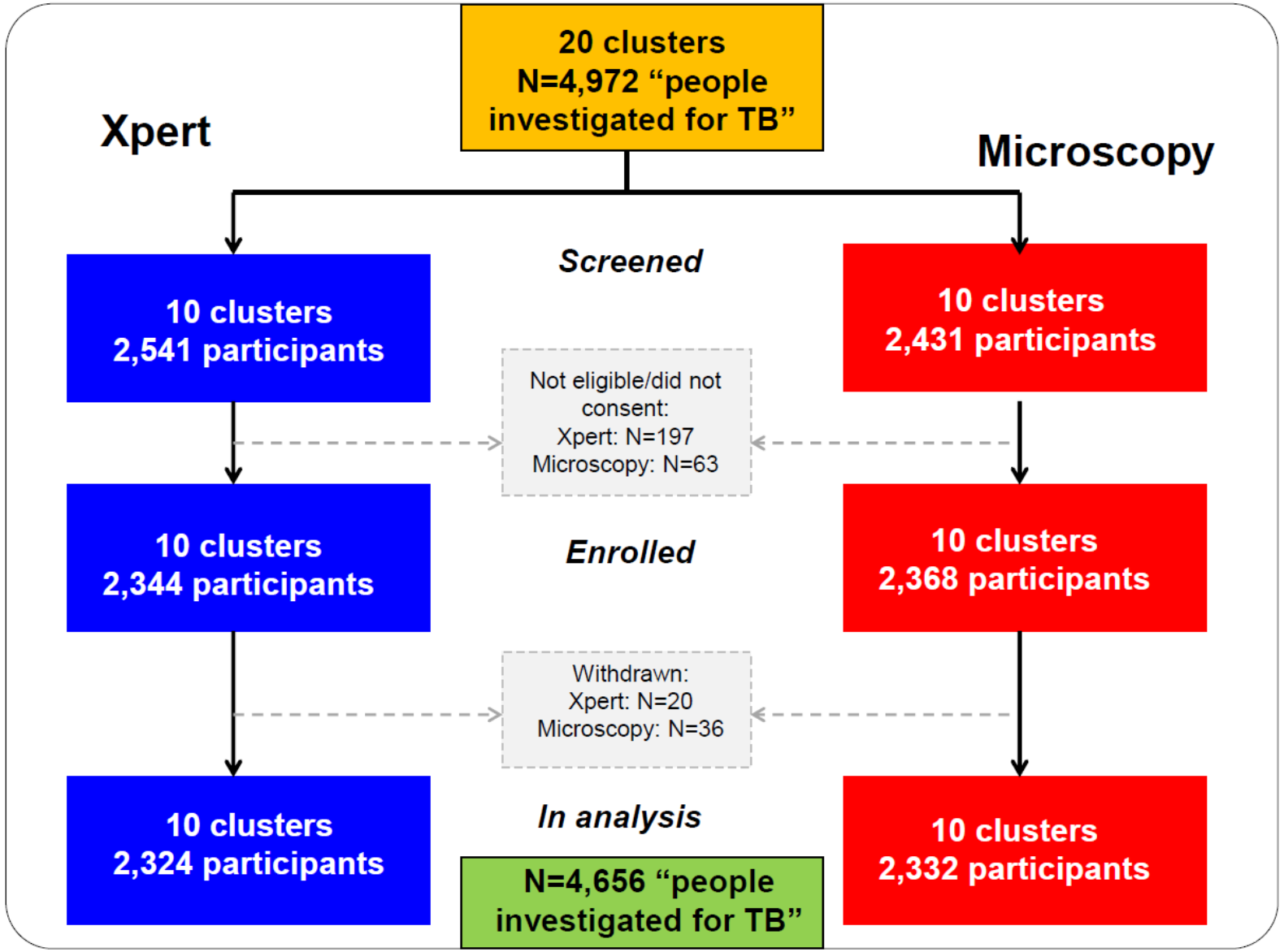
- A pragmatic, cluster-randomized trial was embedded within the Xpert South African national roll out to evaluate patient and programme relevant outcomes
- Primary objective: Effect of Xpert implementation on mortality among adults investigated for TB







Churchyard et al., CROI, 2014

Baseline characteristics

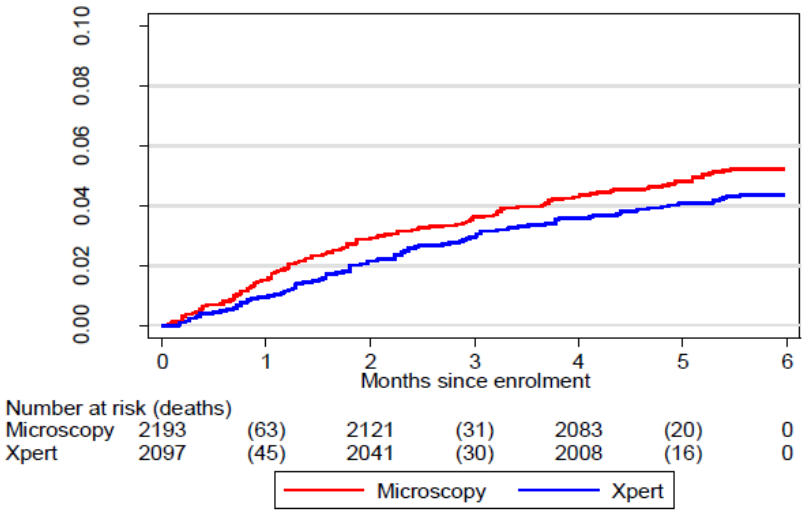
	Xpert (n=2324)	Microscopy (n=2332)
Age (median (IQR))	35 (28-45)	37 (29-48)
Female (%)	64.2%	59.9%
HIV status, self-report (%)		
Known	72.8%	79.4%
HIV positive	62.2%	62.3%
HIV+, ART ever (%)	33.5%	32.7%
CD4 count (median (IQR))	303 (171-457)	315 (192-480)
Body mass index (%)		
<18.5	8.7%	12.4%
18.5-25	45.7%	46.2%
>25	45.6%	41.5%
# TB symptoms (%)		
0	9.8%	6.0%
1	23.5%	19.6%
2	32.4%	27.0%
≥3	34.3%	47.5%

Churchyard et al., CROI, 2014

Effect of Xpert MTB/RIF on mortality risk over 6 months

Xpert		Microscopy		Risk ratio (95% CI)	
Deaths/N	%[1]	Deaths/N	%[1]	Unadjusted	Adjusted[2]
91/2324	3.9%	116/2332	5.0%	0.86 (0.56-1.28)	1.10 (0.75-1.62)

[1]summary ignores cluster, [2]adjusted for age group, sex, body mass index group, number of TB symptoms and HIV status



Kaplan-Meier failure curves for mortality among all study participants (N=4656), by study arm

Churchyard et al., CROI, 2014

Risk factor analysis for mortality

(six months from enrolment)

		OR	aOR	95% CI	P-value
# TB symptoms	0	0.18	0.23	0.05-0.98	<0.001
	1	0.52	0.52	0.33-1.06	
	2	1	1		
	3	1.80	1.58	1.04-2.38	
	4	3.12	2.51	1.66-3.80	
Body mass index (kg/m^2)	<18.5	1.68	1.40	0.94-2.07	0.003
	18.5-24.9	1	1		
	25-29.9	0.49	0.60	0.38-0.94	
	≥30	0.38	0.57	0.33-0.97	
HIV status, self report	HIV-	1	1		<0.001
	HIV+. ART-	3.15	3.32	2.03-5.41	
	HIV+, ART+	1.85	1.79	0.99-3.21	
	Unknown	2.78	2.41	1.47-3.98	

Churchyard et al., CROI, 2014

Summary of XTEND results

Primary outcome	n	Xpert %	Microscopy %	Adjusted Risk ratio (95% CI)
Mortality risk over 6 months	4656	3.9%	5.0%	1.10 (0.75-1.62)
Secondary outcomes	**n**	**Xpert %**	**Microscopy %**	**Adjusted Effect measure (95% CI)**
Index test positive	4412	9.2%	7.8%	1.49 (1.00, 2.23)
Initial loss to follow-up, over 28 days	374	17.0%	14.9%	0.96 (048-1.93)
% treated for TB over 6 months	4656	10.8%	12.5%	1.04 (0.76-1.43)
% with microbiological confirmation, among those treated for TB	*541*	*78.5%*	*65.0%*	*1.20 (0.98- 1.47)*

Churchyard et al., CROI, 2014

- Overall, 29% of patients were placed on treatment on empirical grounds in the absence of a positive microbiological test

Outline

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- RCT of Xpert for TB detection in Zimbabweans starting ART
- Other in progress RCTs that involve Xpert
  - CIDRZ 1201 - Clinical Outcomes in HIV-Infected Adults & Children Using Xpert in Zambia
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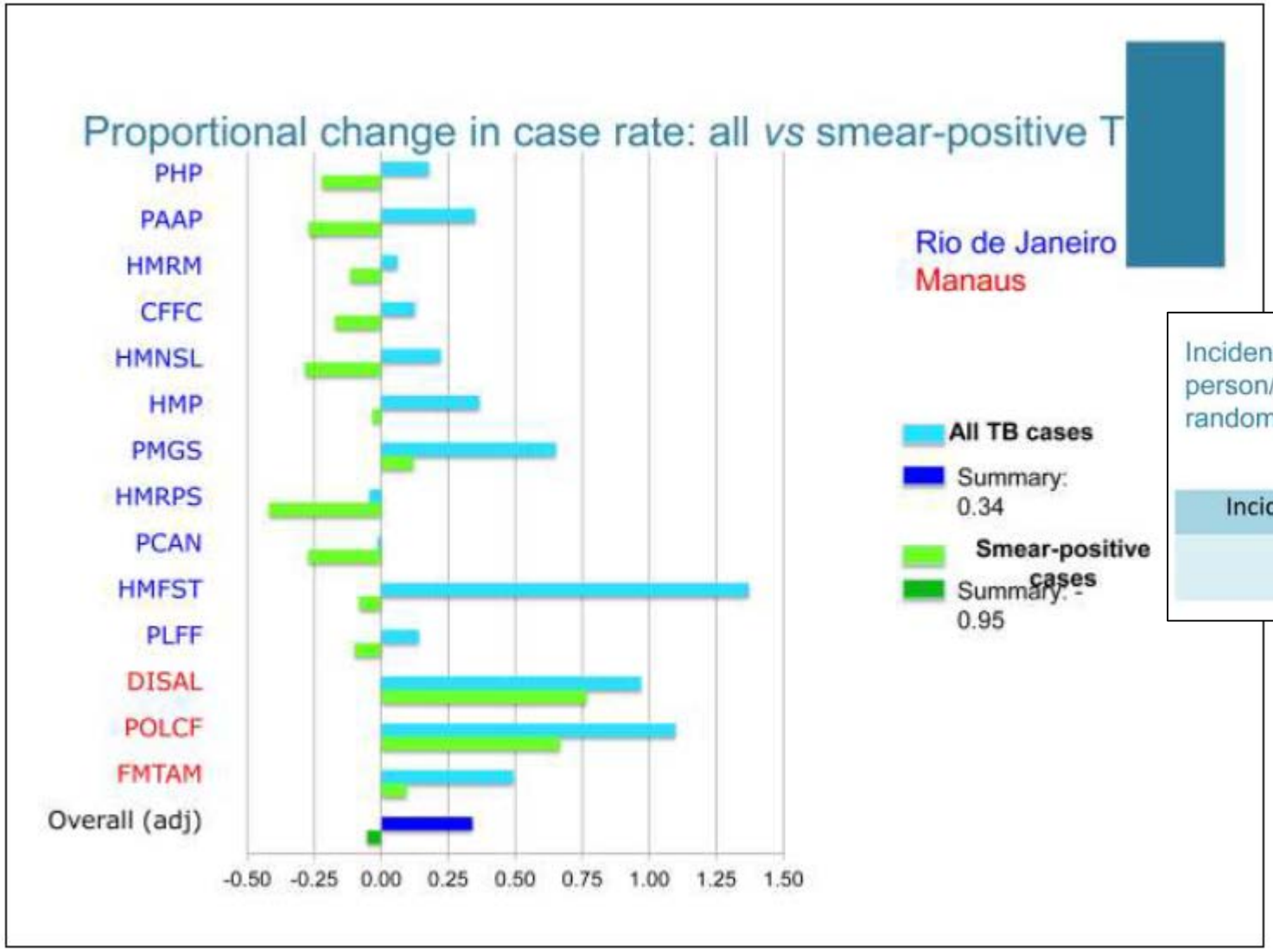
Durovni et al., Xpert Global Implementers' Meeting, 2013

Primary endpoint: Impact of Xpert implementation on pulmonary TB case detection

Control data: From routine microscopy performed during baseline

Intervention: Introduction of Xpert as microscopy replacement



Incidence Rate Ratio of positive pulmonary TB diagnosis per 100,000 person/years, comparing control and intervention phases, crude and random effects models.

Incidence Rate Ratio (crude)	Incidence Rate Ratio (RE)
1.45 (1.35 – 1.56) p<0.001	1.34 (1.23 - 1.46) p<0.001

- Did the number of patients placed on treatment change?

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Impact of Xpert MTB/RIF on Antiretroviral Therapy-Associated Tuberculosis and Mortality: A Pragmatic Randomized Controlled Trial

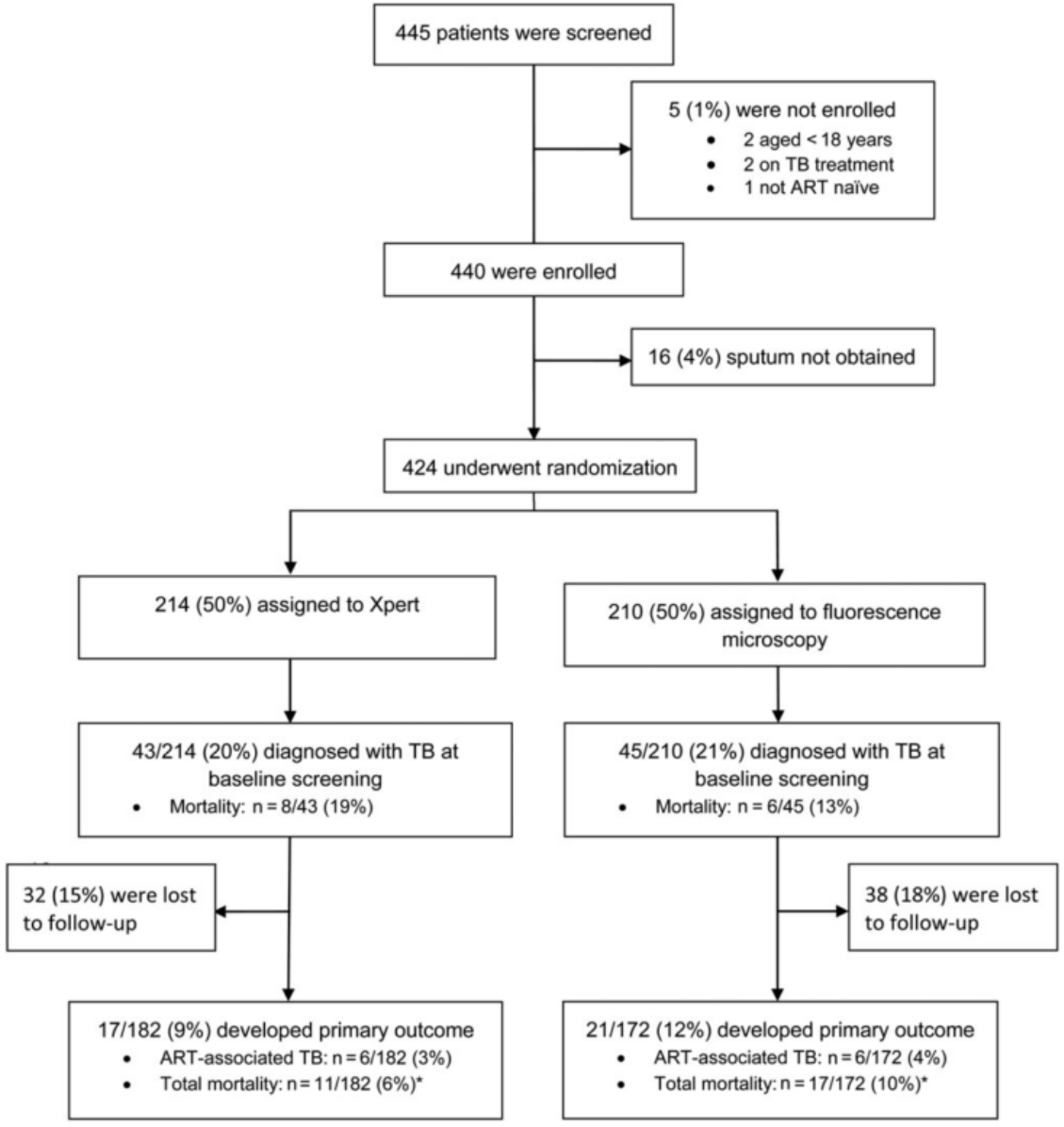
L. Mupfumi,[1,2] B. Makamure,[1,2] M. Chirehwa,[2] T. Sagonda,[2] S. Zinyowera,[3] P. Mason,[1,2] J. Z. Metcalfe,[4,a] and R. Mutetwa[2,a]

[8]. We hypothesized that compared with conventional TB screening with FM, intensified screening with Xpert at the time of ART initiation would "miss" fewer cases of prevalent TB, with resulting reduction in subsequent TB diagnoses and/or death during ART [9, 10].

Table 3. Results of Multivariate Analysis of Baseline Characteristics Prognostic for Mortality

Variable	Relative Risk (95% confidence interval)	*P* Value
Weight, per 1 kg increase	0.96 (.91–1.02)	.17
Gender		
Male	1	
Female	0.38 (.16–.91)	.03
CD4 count		
CD4 ≥100	1	
CD4 < 100	2.51 (1.12–5.64)	.03
Tuberculosis diagnosis[a]		
No	1	
Yes	2.30 (1.06–4.96)	.03
Diagnostic group		
Fluorescence microscopy	1	
Xpert	0.48 (.21–1.08)	.08

- Similar time to treatment (5 vs. 8 days; p=0.23)
- Similar proportion of patients in each arm initiated on treatment empirically (54 vs. 69%; p=0.12)



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Some unpublished and *in progress* RCTs involving Xpert

- CIDRZ 1201 - Optimizing Clinical Outcomes in HIV-Infected Adults & Children Using Xpert in Zambia
  - Per-patient parallel arm RCT of Xpert versus smear
  - Primary endpoint: Proportion of adults and children receiving treatment
- STATIS - Systematic Empirical vs. Test-guided Anti-TB Treatment Impact in Severely Immunosuppressed HIV-infected Adults Initiating ART With CD4 Cell Counts <100
  - Four site parallel arm RCT of intensive screening (Xpert, LAM, CXR) versus upfront empirical treatment
  - Primary endpoint: All-cause mortality and incidence of invasive bacterial infections

Some unpublished and *in progress* RCTs involving Xpert

- Xpert ICU – Effect of Xpert on all-cause mortality in the intensive care unit
  - Two arm RCT of Xpert + culture vs. smear + culture in any patient suspected of TB in the ICU of a hospital in Cape Town
  - Primary endpoint: All-cause mortality
- XACT - The Utility of Intensified Case Finding Combined With a Package of Novel TB Diagnostics Using a Mobile Clinic in Africa
  - Two arm active case finding RCT of testing in a van (Xpert, LAM) versus Xpert provided at a clinic
  - Primary endpoint: Proportion of TB patients completing treatment

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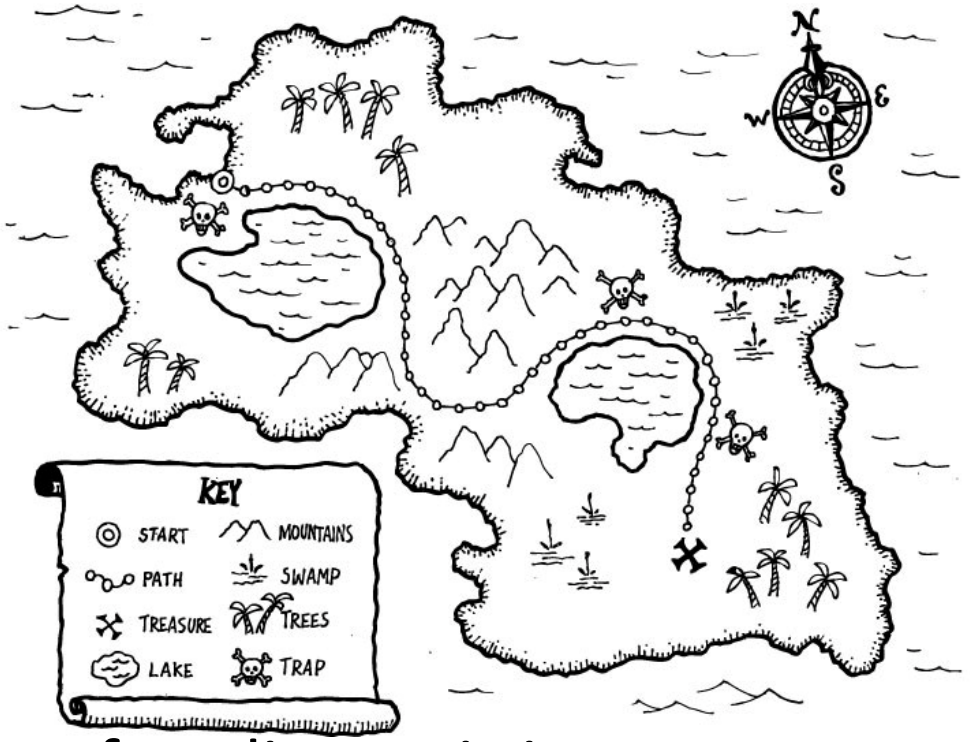
Lessons learnt and concluding thoughts

- Project management is paramount
- Xpert improves diagnosis, time-to-treatment, and drop-out
- Do you think the results of the TB-NEAT and XTEND studies will stop any countries rolling out Xpert?
- The path to cure is complex – can a simple test really be a panacea for broad healthcare systems problems? What happens after diagnosis in outcome-based trials is as important.
- What needs to change in your setting to get maximum benefit from a test?



Thank you!

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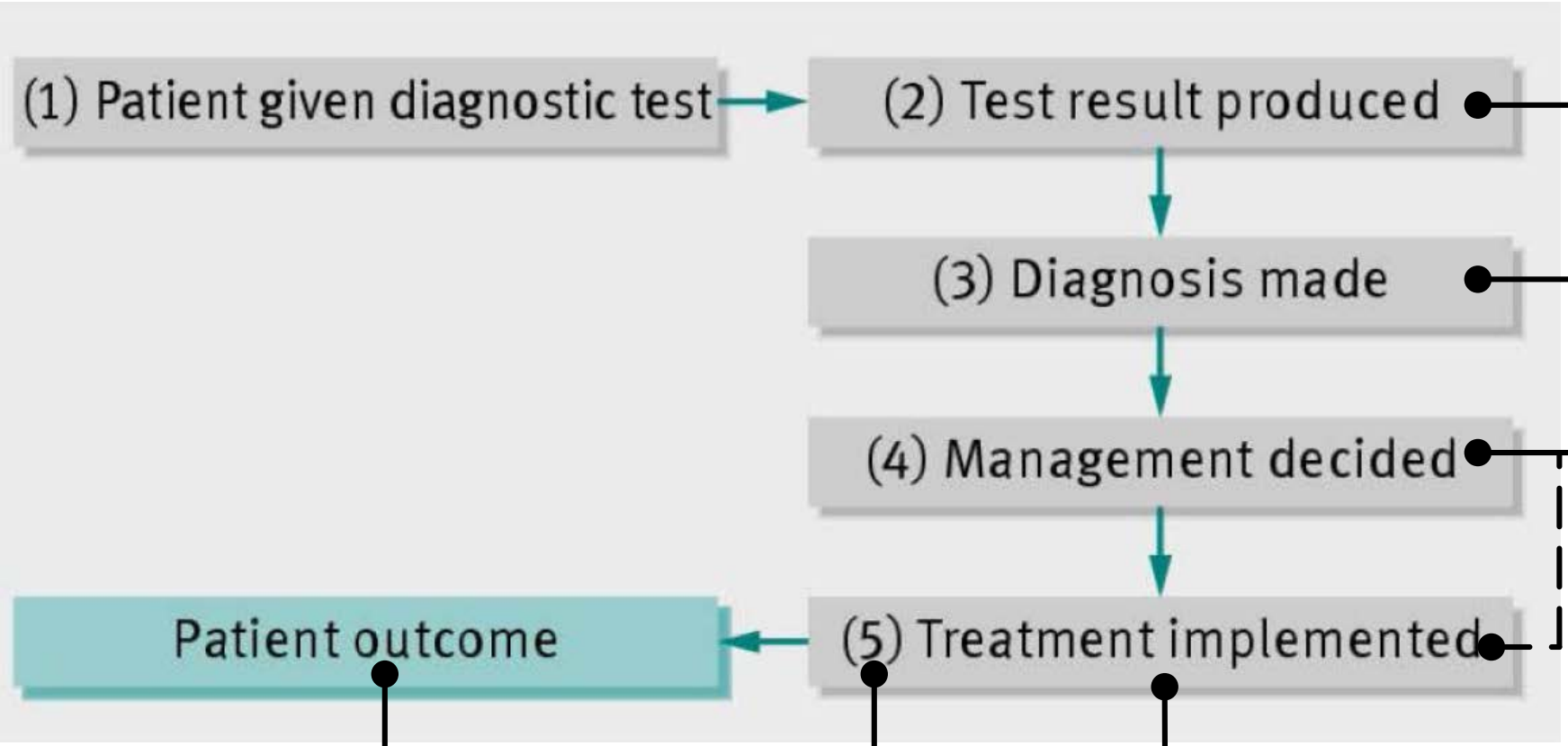
Test-treatment pathway



El-Hajj 2001
Helb 2010
Blakemore 2012

Boehme NEJM 2010

Boehme Lancet 2011

DiRuffano et al., BMJ, 2012

TB-NEAT (Theron, Lancet, 2013)
XTEND
Mupfumi Open Forum ID 2014

Brazil implementation study