

Xpert MTB/RIF for TB: *Evaluating a new Diagnostic (the XTEND trial)*

Results and ongoing evaluations

Implementing HIV and TB Diagnostics
in Resource-Limited Settings

Kerrigan McCarthy

MBBCh, DTM&H, FCPATH (Micro)

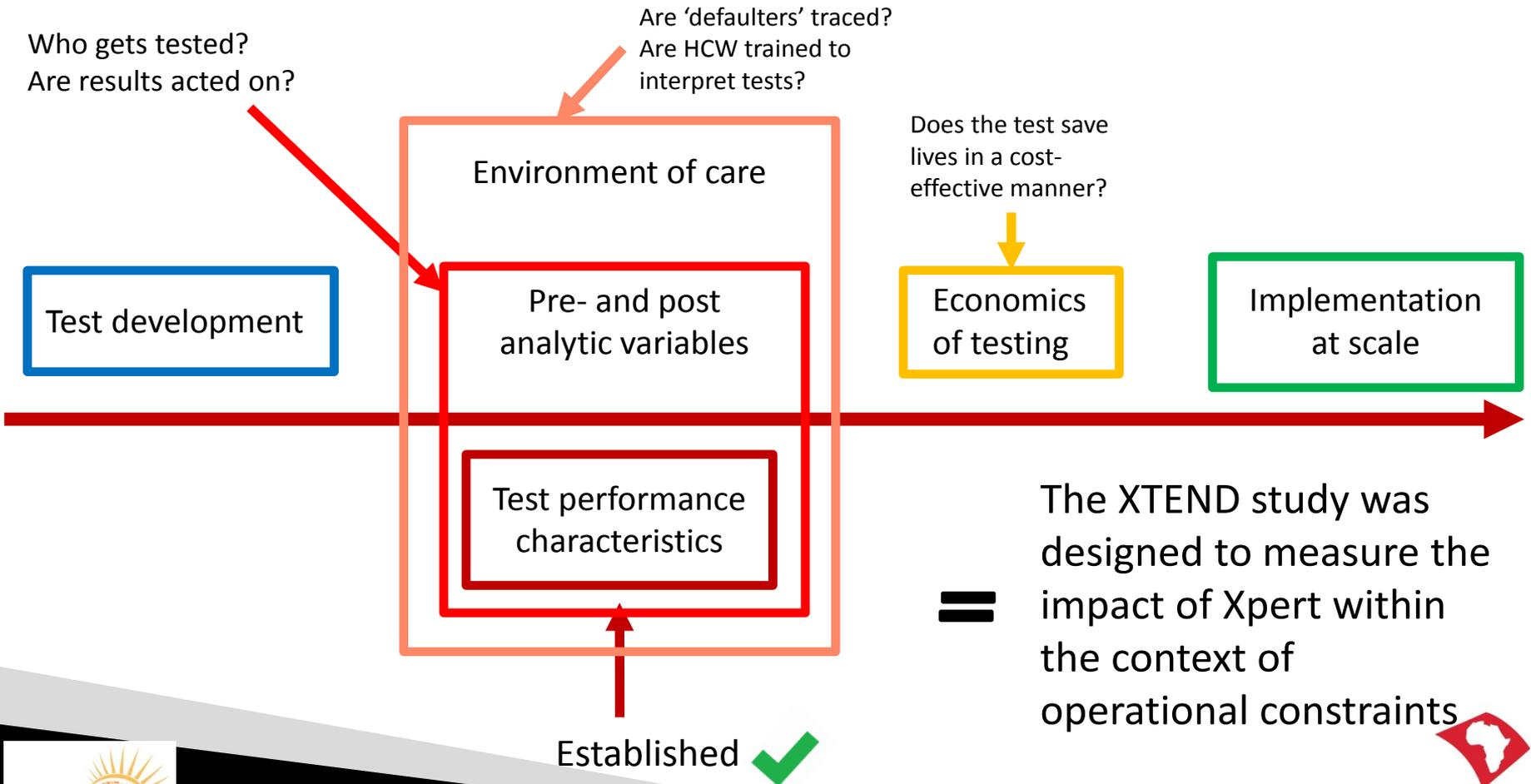
The Aurum Institute, and Wits School of Public Health
for Prof Gavin Churchyard



Overview

- Evaluation of diagnostic tests
- The XTEND trial – methodology and results
- How can we maximise the benefit from improved TB diagnostics?
 - Ongoing Aurum studies to address XTEND findings

Evaluation of diagnostic tests



The XTEND trial

- XTEND=“Xpert for TB – Evaluating a New Diagnostic”
- Pragmatic cluster randomised trial of Xpert MTB/RIF *vs* smear microscopy for the diagnosis of TB, nested in (Phase 3a/b) the NHLS roll out of Xpert MTB/Rif

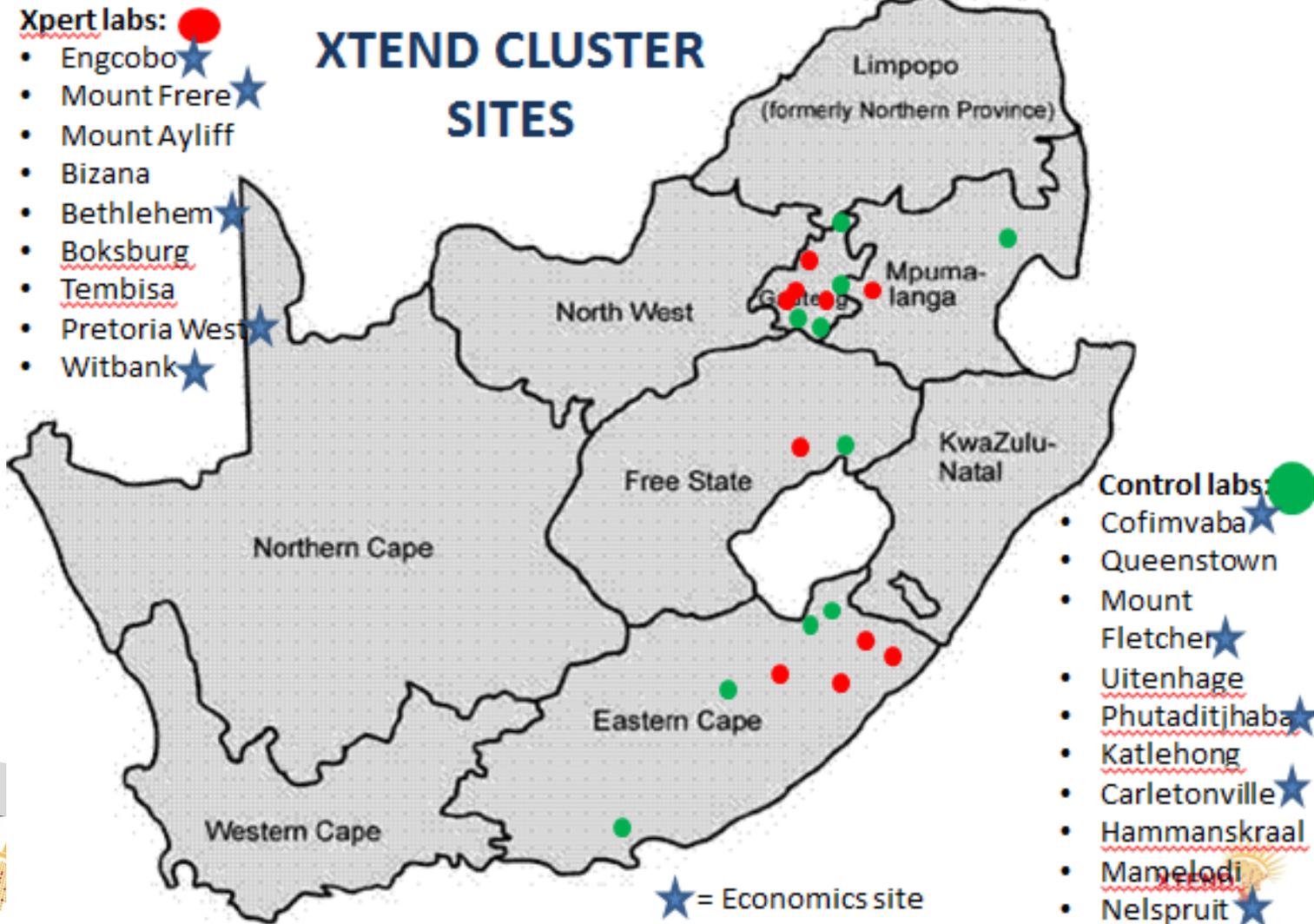
The XTEND trial

- Aims:
 - To measure the effectiveness of Xpert MTB/RIF in improving patient and programme outcomes.
 - To estimate the cost-effectiveness of Xpert MTB/RIF from a patient and health system perspective.

XTEND methodology -Study clusters

- During NHLS roll-out of GXP, districts with a 'medium TB burden' were identified for Phase III implementation.
- In 4 provinces (KZN, FS, EC, GT) only, 20 labs situated in these districts were randomised in a stratified manner based on urban/rural location to intervention (early Xpert) or control arm (late Xpert)
- Two primary health clinics were identified for each laboratory, to form a cluster.
 - 1 cluster= 1 laboratory + 2PHCs

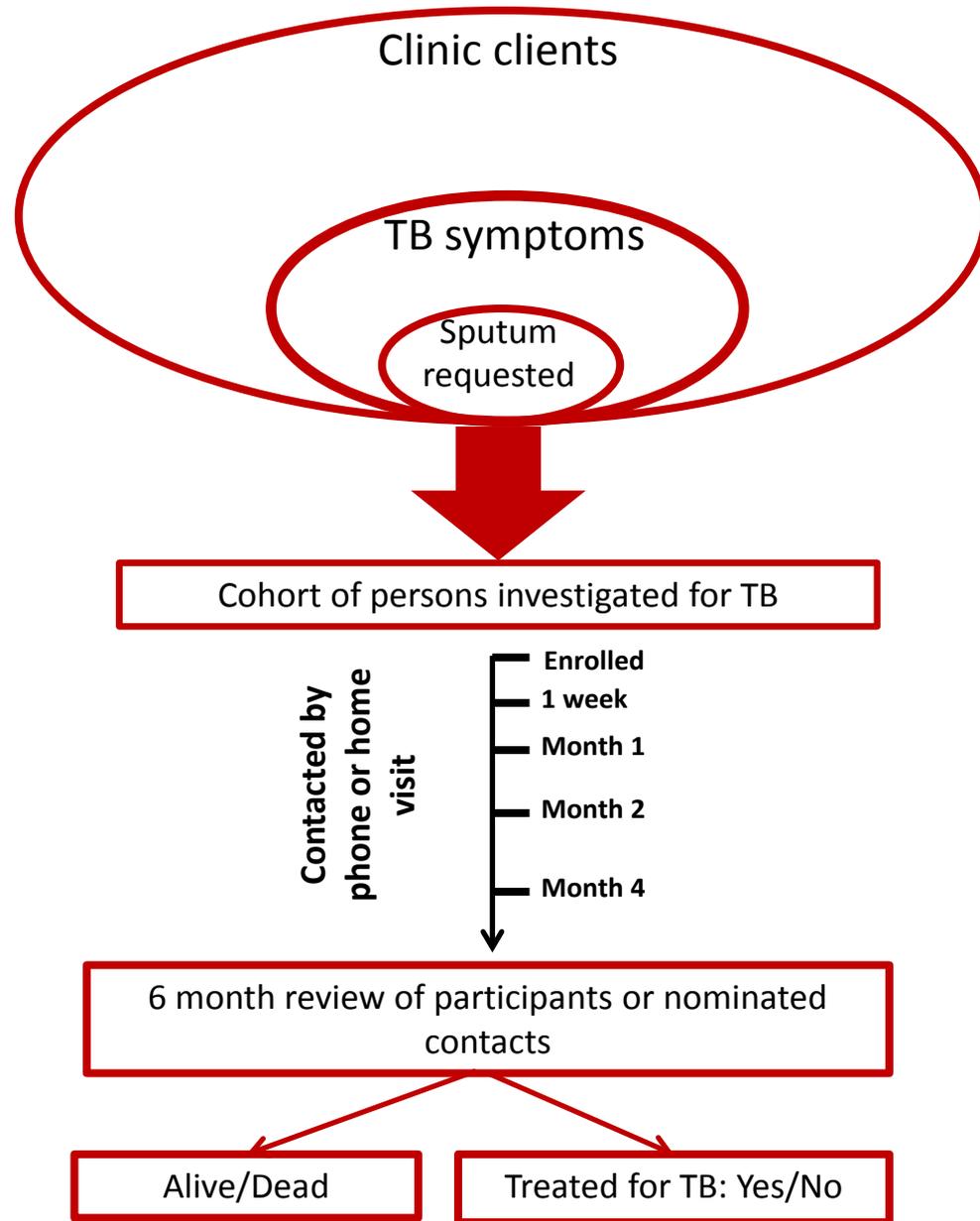
XTEND methodology - Study clusters



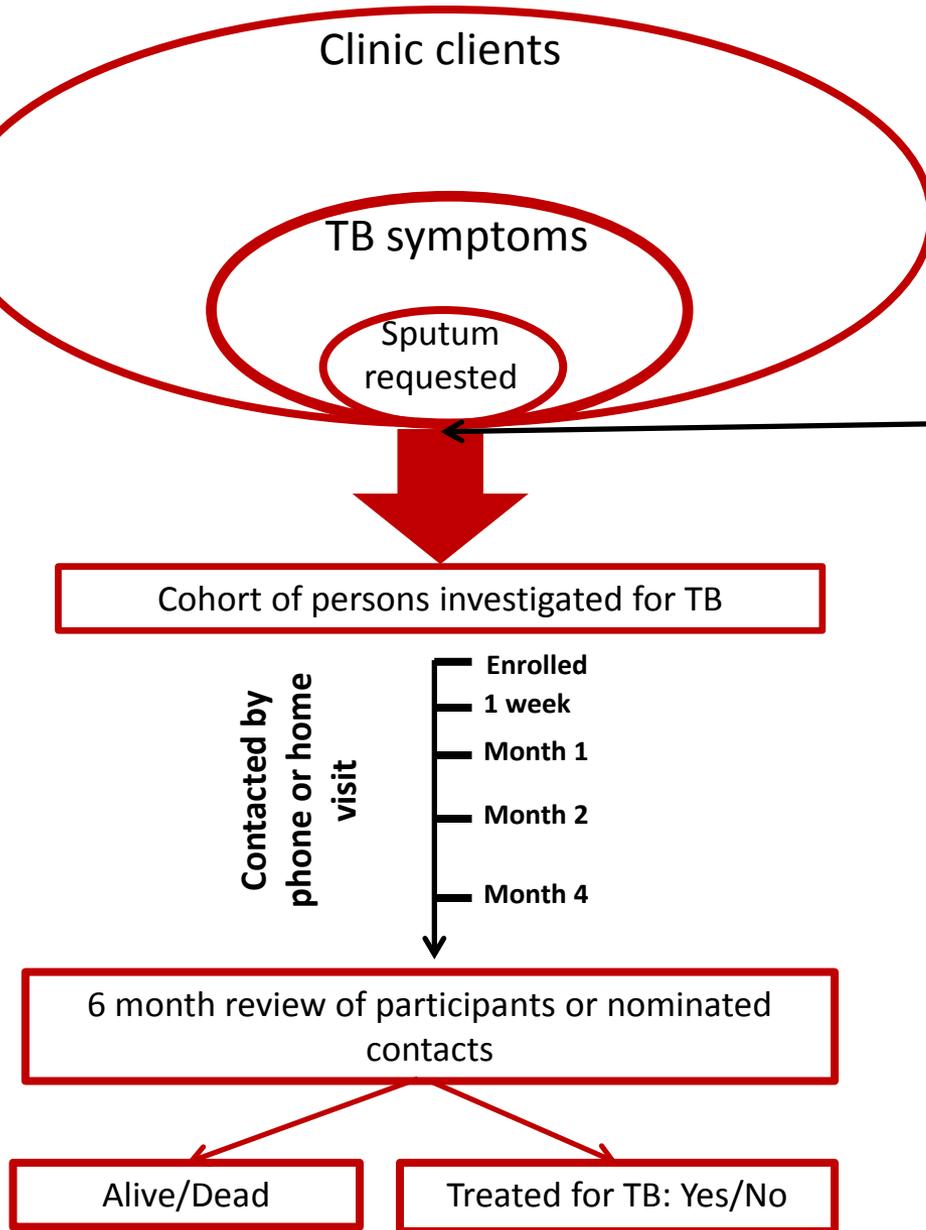
XTEND methodology – Lab implementation

- NHLS Priority Programme co-ordinated implementation.
 - GX 16-module instruments placed in Xpert arm laboratories
 - Training, instrument validation and ongoing quality monitoring, including cartridge stock levels were conducted by NPP
- Lab testing during participant recruitment:
 - Participant enrolment in the Xpert arm was initiated a median of 3.6 (range 1-7.4) months after starting routine use of GXP
 - Control arm continued using smear, but received Xpert MTB/RIF ~6 months after enrolment complete

XTEND methodology –enrolment and follow-up

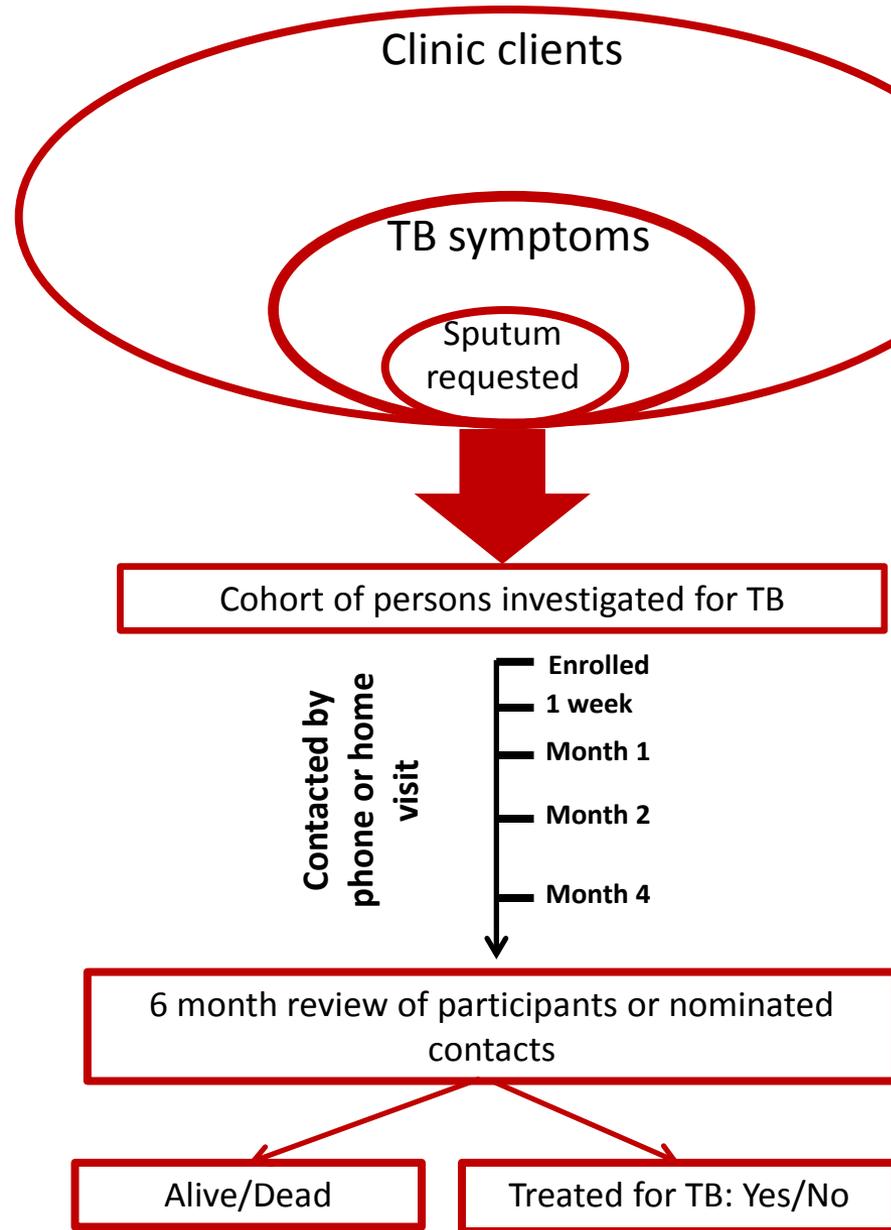


XTEND methodology –enrolment and follow-up



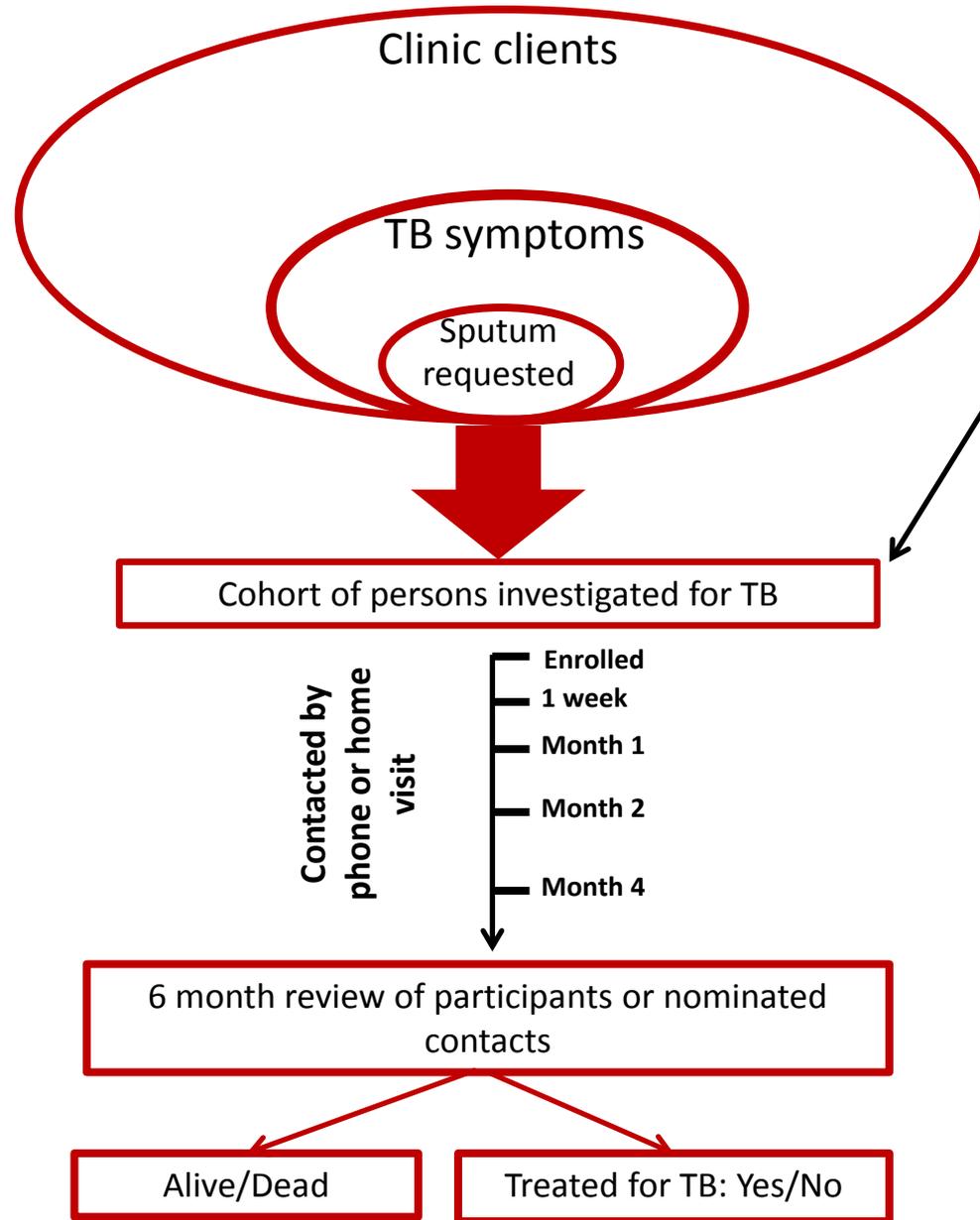
- Persons investigated for TB **by clinic staff**
 - **Xpert arm:** 1 sputum specimen collected for Xpert MTB/RIF
 - **microscopy arm:** 2 sputum specimens collected for fluorescence microscopy
 - CXR/ sputum for culture if requested by clinic staff, guided by relevant algorithm

XTEND methodology –enrolment and follow-up



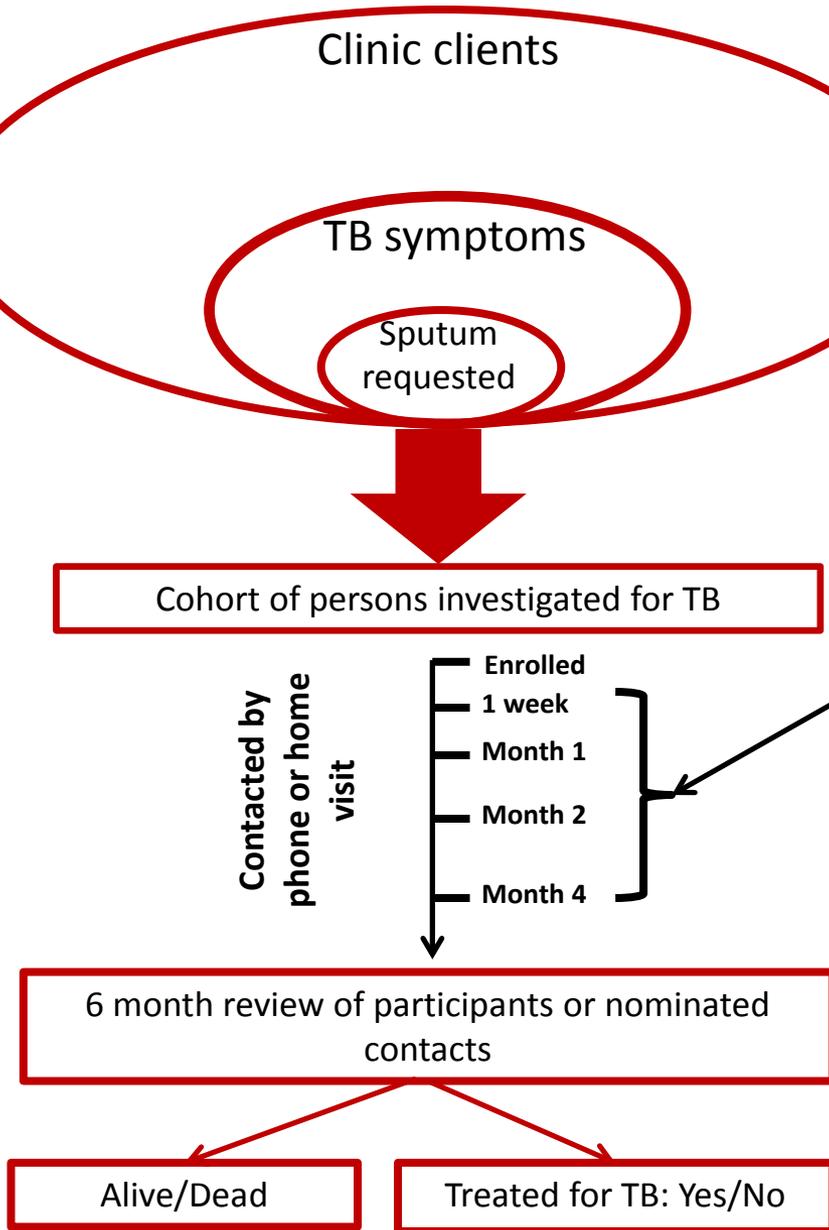
● A systematic sample of adults, not on TB treatment, who had had a sputum specimen requested by clinic staff to investigate for possible TB were recruited *by study staff*

XTEND methodology –enrolment and follow-up



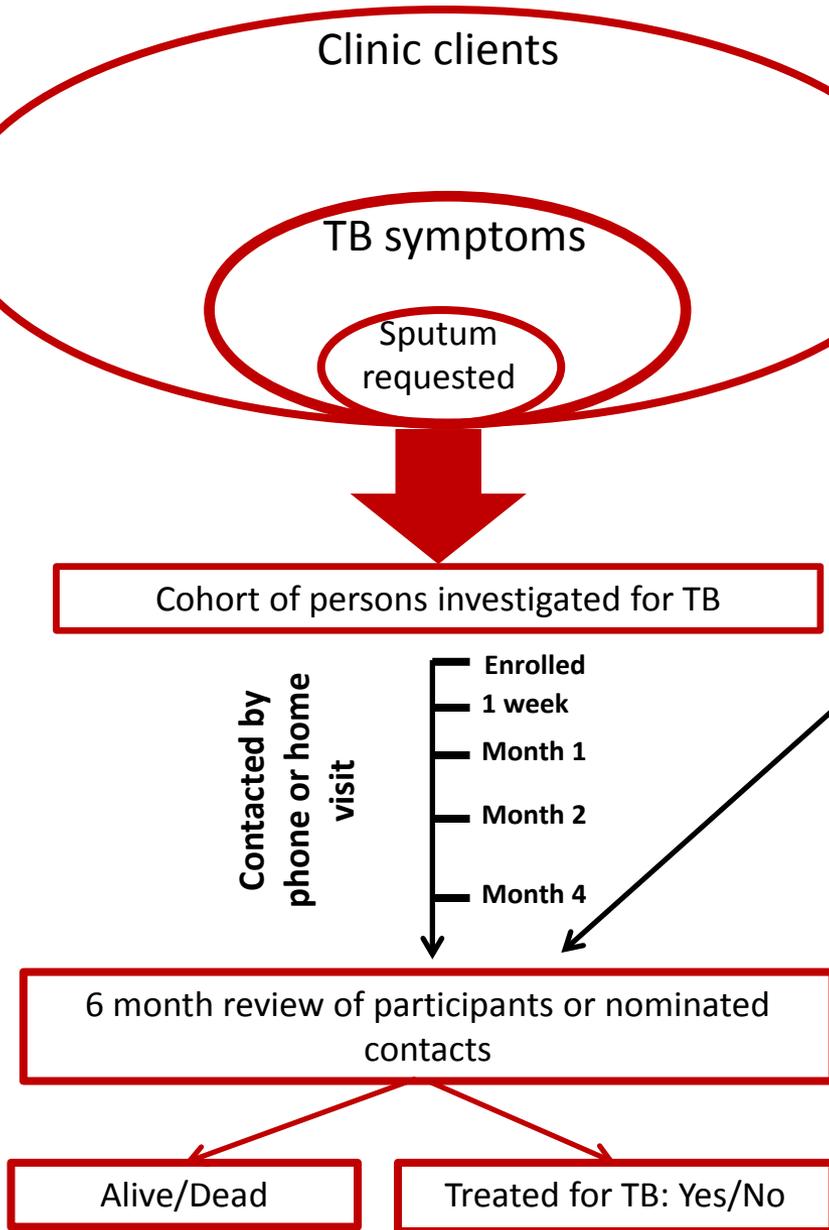
- At enrolment, personal identifiers, including SA identity number, locator information, demographic and clinical data relevant to TB and mortality risk were collected
- No extra tests for study purposes

XTEND methodology –enrolment and follow-up



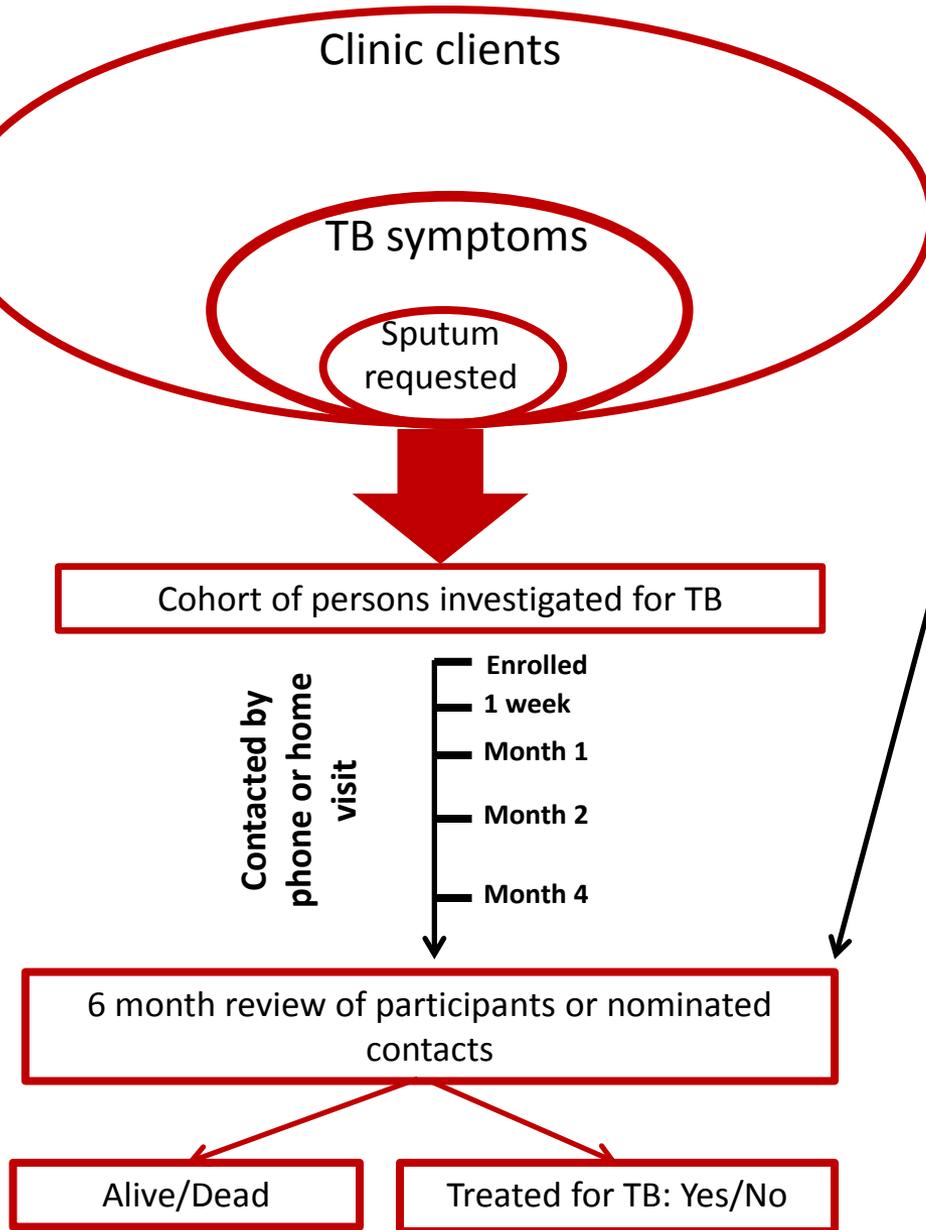
Participants were contacted telephonically by study staff in order to maintain contact and update locator information

XTEND methodology –enrolment and follow-up



- Prior to the 6-month interview, study staff reviewed patients' clinic records for information such as results of index and subsequent tests and TB treatment and/or ART start dates

XTEND methodology –enrolment and follow-up



• 6 months after enrolment, study staff interviewed participants telephonically, or by home visit, to ascertain whether they had started TB treatment or ART and treatment start dates

XTEND primary and secondary outcomes

Primary outcome

- To evaluate the effect of Xpert MTB/RIF implementation on mortality among adults investigated for TB

Secondary outcomes

To compare, in the XTEND study, by study arm:

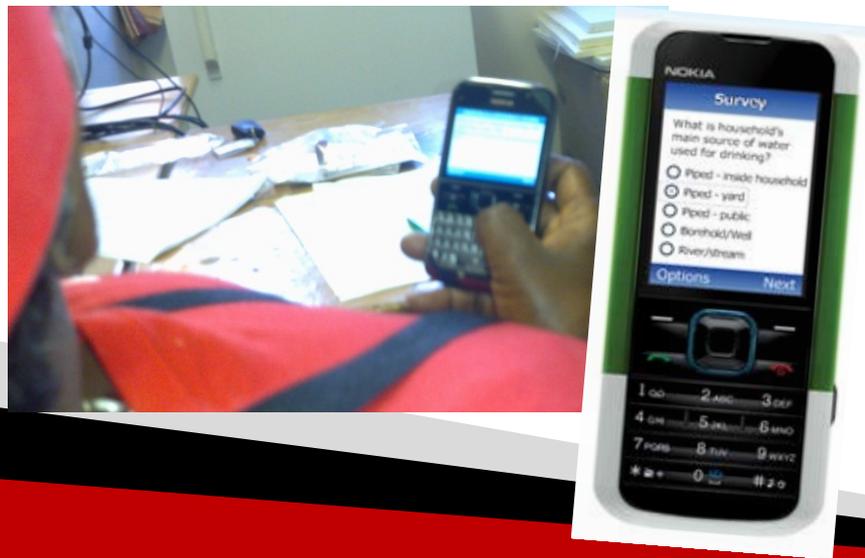
- Among clinic attendees investigated for TB
 - Proportion index test (GXP vs smear) positive for TB
 - Proportion starting TB treatment by 6 months
- Among those with a positive index test result
 - Proportion initially lost to follow-up



XTEND methodology - Data management and endpoint verification

Data Management

- Real-time, paperless data entry with celphones, and a web-based interface for data management and review



Endpoint verification

- Deaths
 - Through next of kin, and SAID on DoHA website (thro MRC)
- Index GXP/smear result
 - NHLS central data warehouse and case note abstraction of clinic records
- TB treatment start
 - case note abstraction of clinic records
 - Participant interview

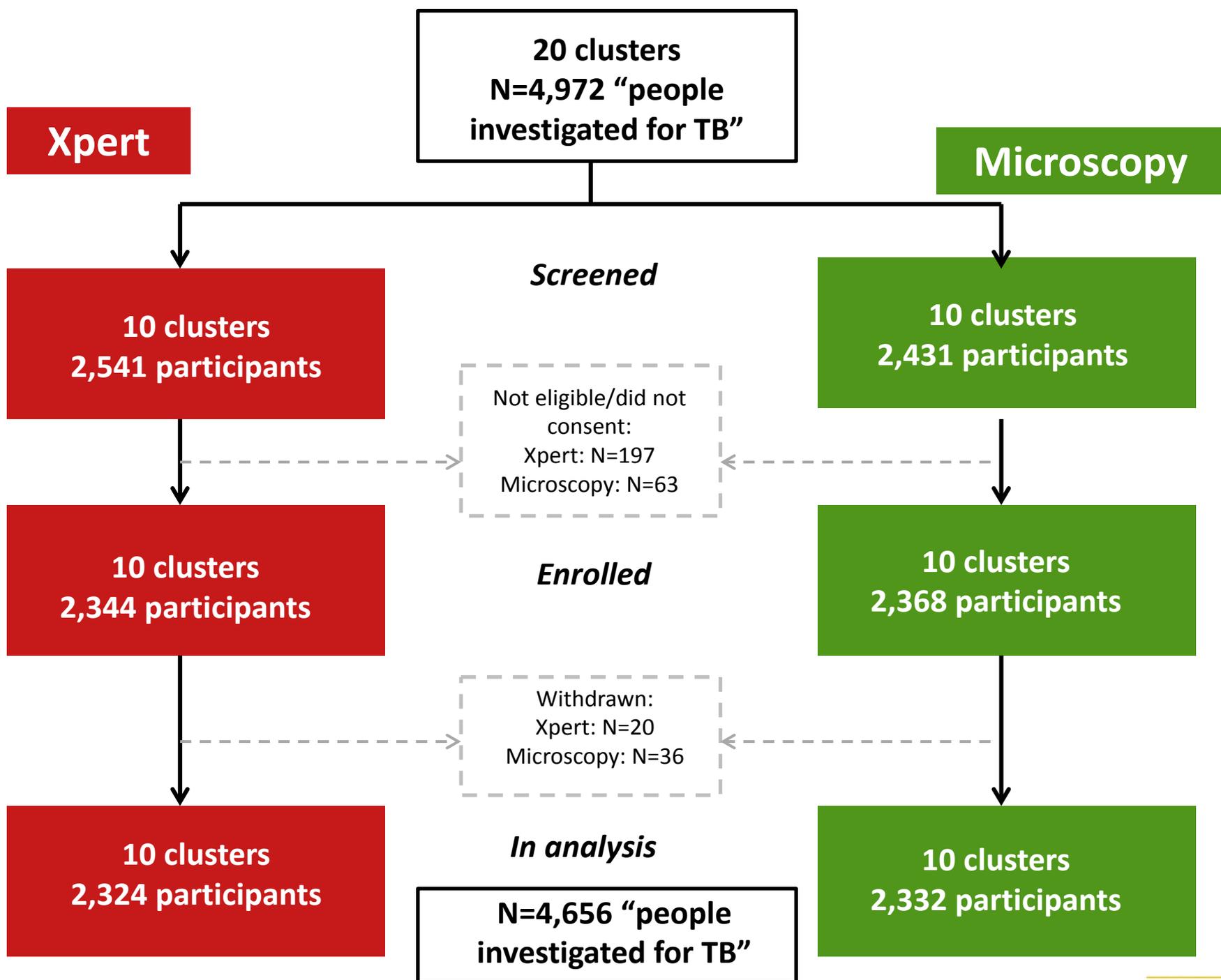


XTEND methodology- analysis

- Analysis was conducted using methods appropriate to the trial design, with a small number of clusters
- Adjustment for individual-level baseline factors showing imbalance by study arm

XTEND Results





XTEND Results -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%

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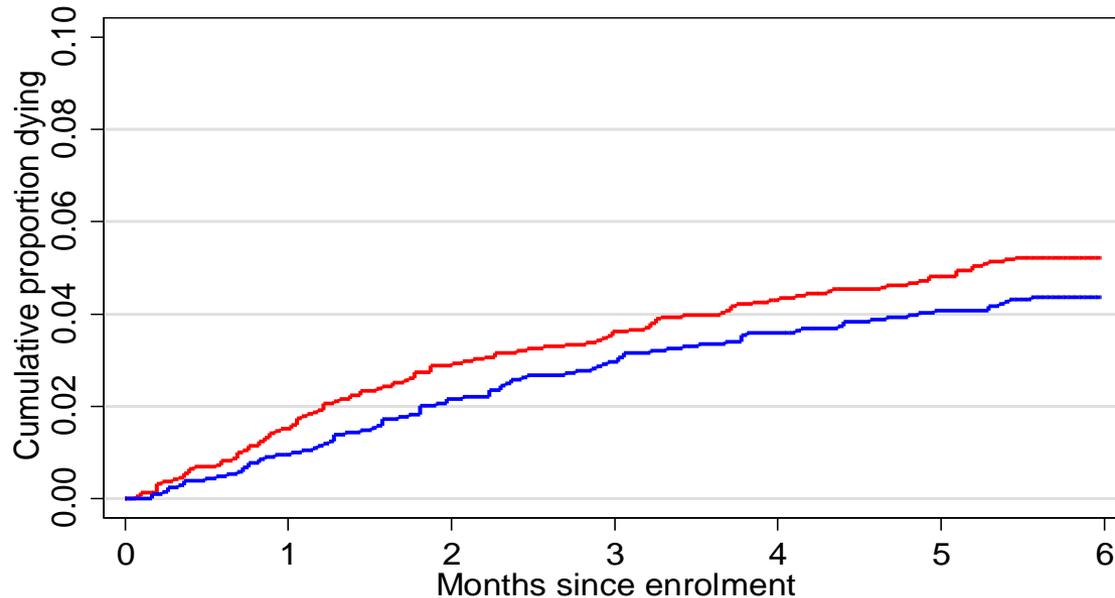
XTEND Results- Vital status at 6/12

	Xpert (n=2324)		Microscopy (n=2332)	
	%	n	%	n
Vital status known	98.9%	2299	99.0%	2309
Lost to follow-up	1.1%	25	1.0%	23



XTEND Results- Mortality over 6 months

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



Number at risk (deaths)

Microscopy	2193	(63)	2121	(31)	2083	(20)	0
Xpert	2097	(45)	2041	(30)	2008	(16)	0

— Microscopy — Xpert



XTEND Results- Mortality over 6 months

Study findings					
Xpert Arm		Microscopy Arm		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 ignores cluster

²adjusted for age group, sex, body mass index group, number of TB symptoms and HIV status



XTEND Results- Risk factors for mortality at 6 months

		OR	aOR	95% CI	P-value
Positive index test	No	1	1		0.06
	Yes	2.25	1.49	0.99-2.24	
Gender	Female	1	1		0.001
	Male	2.37	1.69	1.22-2.33	
Age	<30	1	1		0.001
	30-34.9	1.64	1.34	0.80-2.29	
	35-39.9	2.32	2.02	1.23-3.34	
	40-49.9	1.80	1.59	0.98-2.59	
	≥50	2.58	2.53	1.59-4.04	

XTEND Results- Risk factors for mortality at 6 months

		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	

XTEND Results – proportion with positive sputum for TB

- 97% (4411/4656) had index specimen result available

Xpert		Microscopy		Prevalence ratio (95% CI)	
positive /N	% ¹	positive /N	% ¹	Unadjusted	Adjusted ¹
200/2176	9.2%	174/2235	7.8%	1.27 (0.81-2.00)	1.49 (1.00-2.23)

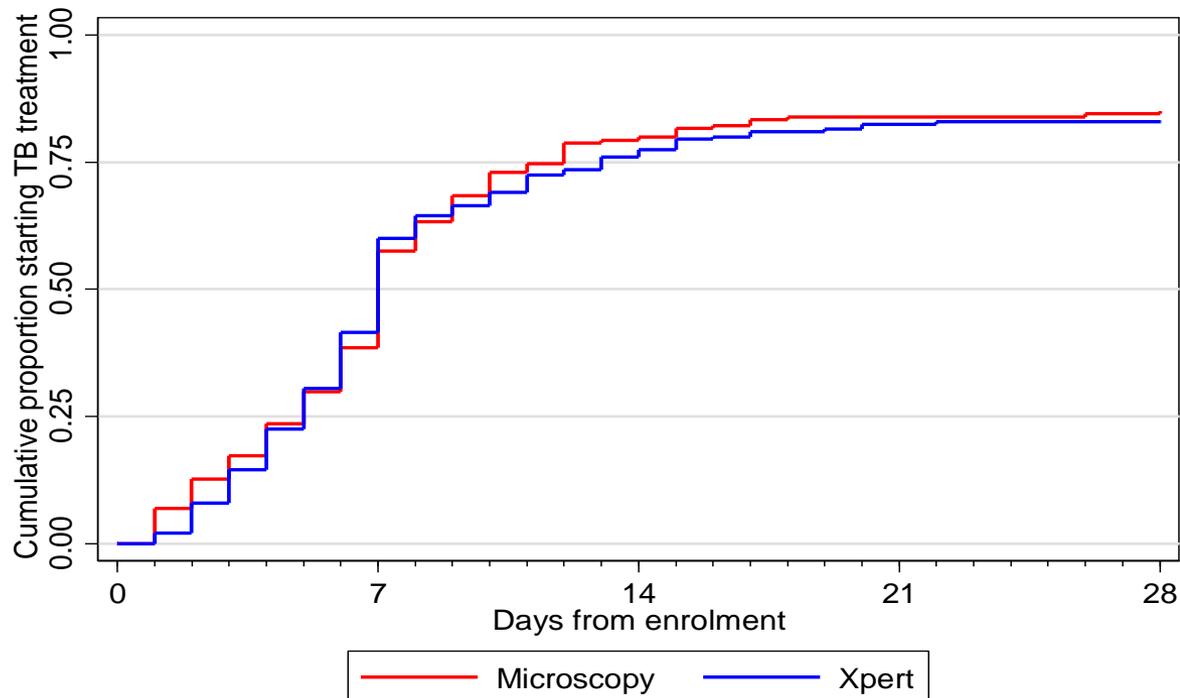
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²adjusted for age group, sex, body mass index group, number of TB symptoms and HIV status



XTEND Results- time to TB Rx start

Kaplan-Meier curves showing time to starting TB treatment, among those test positive, in each arm



XTEND Results- initial loss to follow-up

Among 374 with a positive index test result, 60 (16%) participants did not start TB treatment within 28 days from sputum collection

Xpert		Microscopy		Risk ratio (95% CI)	
no TB Rx /N	% ¹	no TB Rx/N	% ¹	Unadjusted	Adjusted ²
34/200	17.0%	26/174	14.9%	0.97 (0.48-1.96)	0.96 (0.48-1.93)

¹ ignores cluster

²adjusted for age group, sex, body mass index group, number of TB symptoms and HIV status



XTEND results - % treated for TB

- Overall 11.6 % (541/4656) were treated for TB during the 6 month follow-up period

Xpert		Microscopy		Risk ratio (95% CI)	
TB rx/N	% ¹	TB rx/N	% ¹	Unadjusted	Adjusted ²
250/2324	10.8%	291/2332	12.5%	0.88 (0.60-1.29)	1.04 (0.76-1.43)

¹ ignores cluster

²adjusted for age group, sex, body mass index group, number of TB symptoms and HIV status



XTEND results - % with microbiological confirmation of TB

- Microbiological confirmation: as any positive Xpert, microscopy or culture
- Overall 71.1 % (385/541) of individuals treated for TB had microbiological confirmation

Xpert		Microscopy		Prevalence ratio (95% CI)	
micro+/N	% ¹	micro+/N	% ¹	Unadjusted	Adjusted ²
196/250	78.4%	189/291	65.0%	1.21 (0.99-1.47)	1.20 (0.98-1.47)

¹ ignores cluster

²adjusted for age group, sex, body mass index group, number of TB symptoms and HIV status



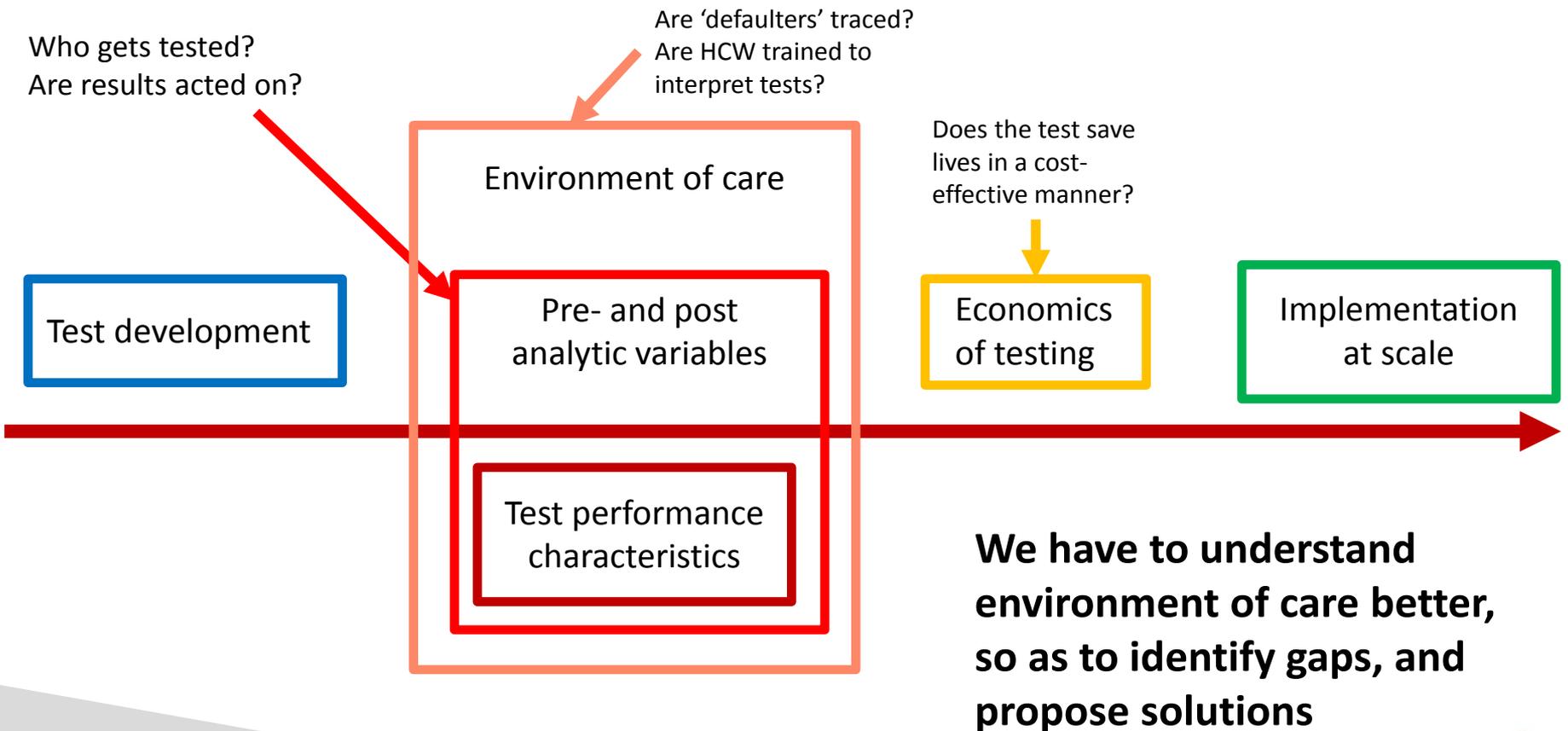
Study Limitations

- Small numbers of rifampicin resistant samples
 - we cannot comment on the effect of Xpert MTB/RIF on outcomes for drug resistant TB

XTEND summary findings

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 (0.48-1.93)
% 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)

How can we maximise the benefit from improved diagnostics?



How can we maximise the benefit from improved diagnostics?

- Review pre-analytic components of TB Dx
 - Does the current algorithm have the best analytic sensitivity for TB diagnosis?
 - Who gets screened and tested for TB?
- Review post-analytic components of TB Dx
 - Is the algorithm for diagnosis of TB adhered to, when Xpert results are negative?
 - Can initial loss to follow-up rates be reduced?
- Review the Economics of TB Dx
 - If Xpert does not save lives, what are the cost implications for the TB programme?

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Does the current algorithm have the best analytic sensitivity for TB diagnosis?

- XPHACTOR study
 - Xpert for People attending HIV/AIDS Care: Test Or Review?
 - an interventional cohort study
 - conducted amongst ART and pre-ART patients in public sector clinics
 - evaluating a novel algorithm which prioritises testing with Xpert MTB/RIF for those at highest risk, with watchful waiting for others

Does the current algorithm have the best analytic sensitivity for TB diagnosis?

- AIMS of the XPHACTOR study
 - To evaluate a novel TB screening algorithm (ie test vs wait) based on evaluation of TB symptoms, Body Mass Index and CD4 count
 - Compare repeat Xpert vs 'smear negative' algorithm amongst HIV+ adult TB suspects with negative Xpert MTB/RIF
 - describe spectrum of disease among HIV+ people with "TB symptoms" who don't have TB
 - To determine the natural history of TB symptoms among individuals without a final diagnosis of TB (to estimate the demand for repeat Xpert)

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Adherence to the algorithm for TB Dx

a sub-study of XTEND

- A mixed methods evaluation of factors that promote and impair adherence to the algorithm for TB diagnosis
- Part 1: Using the XTEND dataset,
 - Amongst those known to be HIV positive, to describe adherence to the NHLS/DoH algorithm

Principal Investigator Kerrigan McCarthy with
Gavin Churchyard and Alison Grant



Adherence to the algorithm for TB Dx

Summary results from XTEND dataset

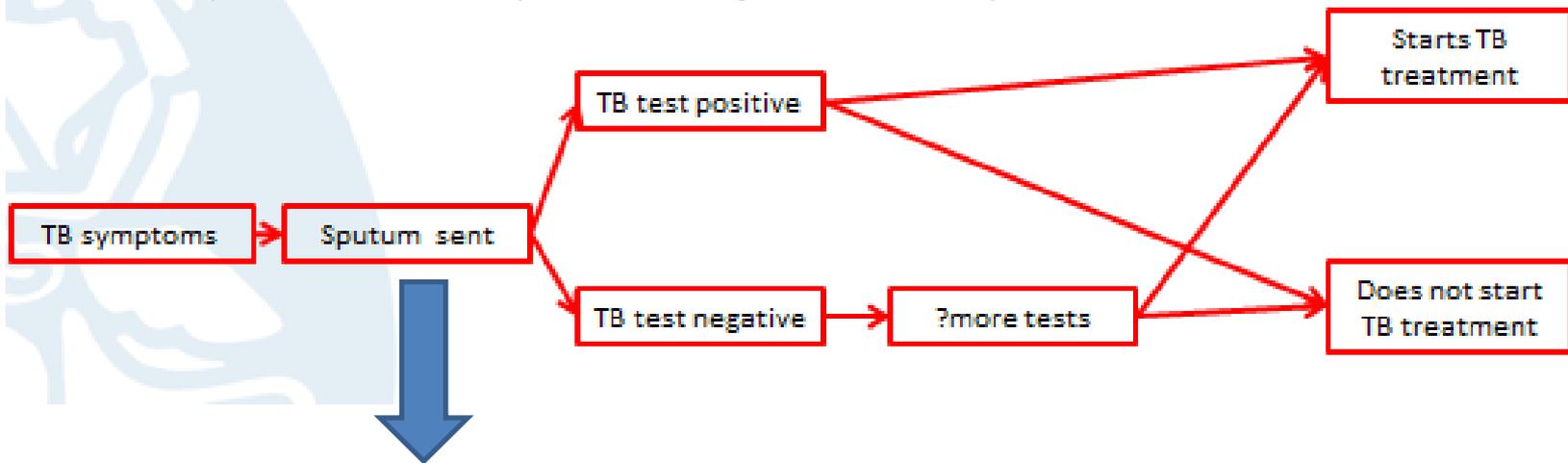
- Amongst 4665 persons enrolled
 - 1342 HIV negative by self-report
 - 540 (13%) HIV status unknown
 - Meaningful adherence to algorithm precluded
- Amongst 2153 persons known to be HIV positive
 - All of CXR, culture and antibiotics done in only 9(<1%)
 - One of CXR or sputum culture amongst only 868 (40%)
 - 1285 (59%) had no further investigations
- HCW in Xpert MTB/RIF arm LESS likely to take culture
 - 251 (22%) vs 52 (5%)
- HCW more likely to investigate persons who are ill with
 - ↓BMI, ↓Karnofsky score, more TB symptoms

Adherence to the algorithm for TB Dx

- A mixed methods evaluation of factors that promote and impair adherence to the algorithm for TB diagnosis
- Part 2: Through qualitative methodology
 - To explore the experience and practice of health administrators and facility-based health care workers with regard to TB diagnosis

Adherence to the algorithm for TB Dx

Some preliminary findings from qualitative assessment



Who gets tested for TB?

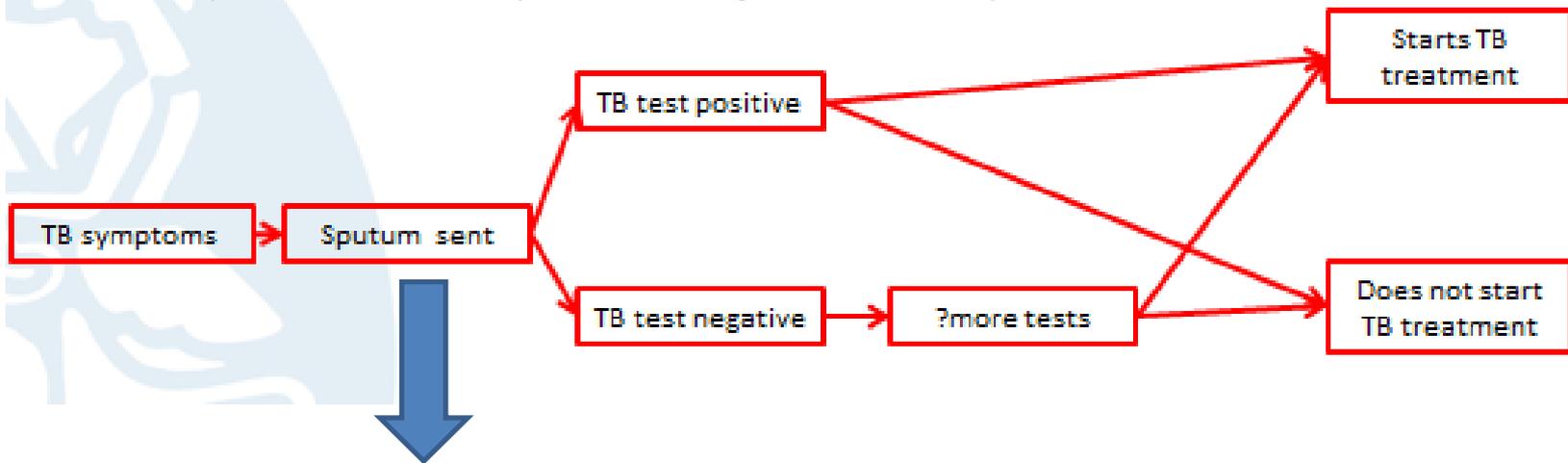
- Screening for TB

The screening thing is a challenge for most of the facilities. You see you have to fight with them to screen, because now they don't screen.

TB co-ordinator, District Z

Adherence to the algorithm for TB Dx

Some preliminary findings from qualitative assessment



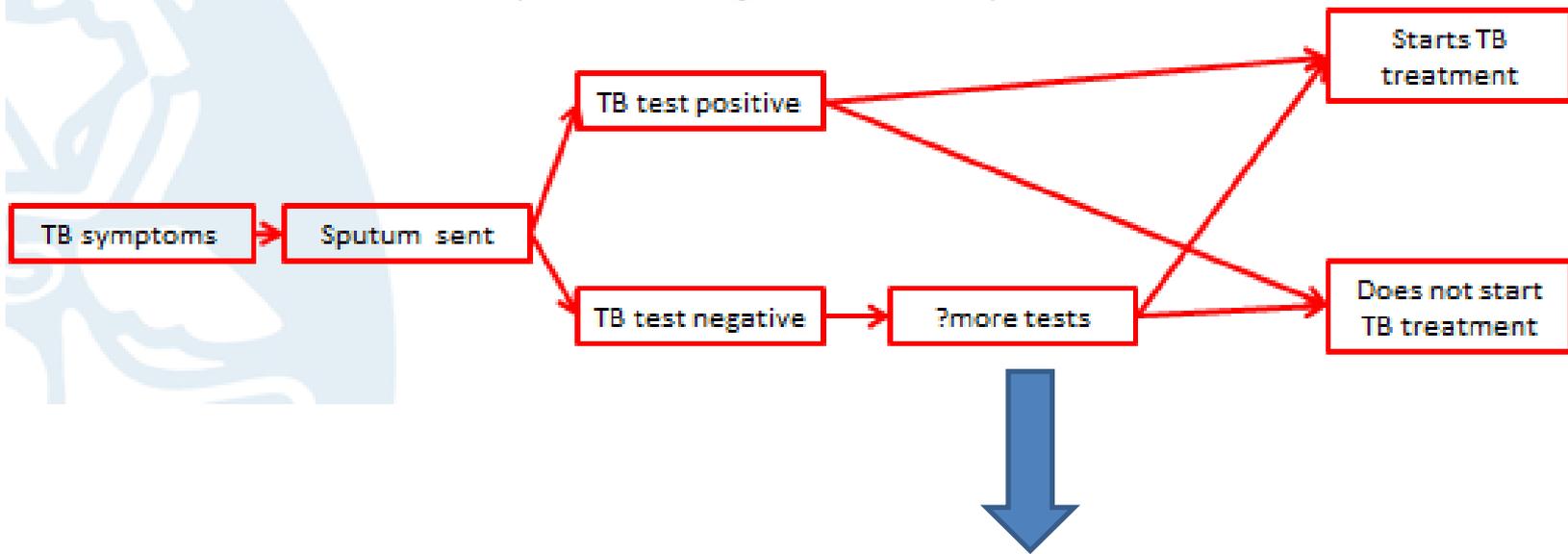
Who gets tested for TB?

- HCW motivation to use GXP and understanding of algorithm

The problem was not the GXP. It was the understanding within the facility. Because at that time they weren't used to it. There were some sisters who were understanding it, and there were others who were not. So there were some who didn't even want to bother themselves by doing GXP because of understanding.

Adherence to the algorithm for TB Dx

Some preliminary findings from qualitative assessment



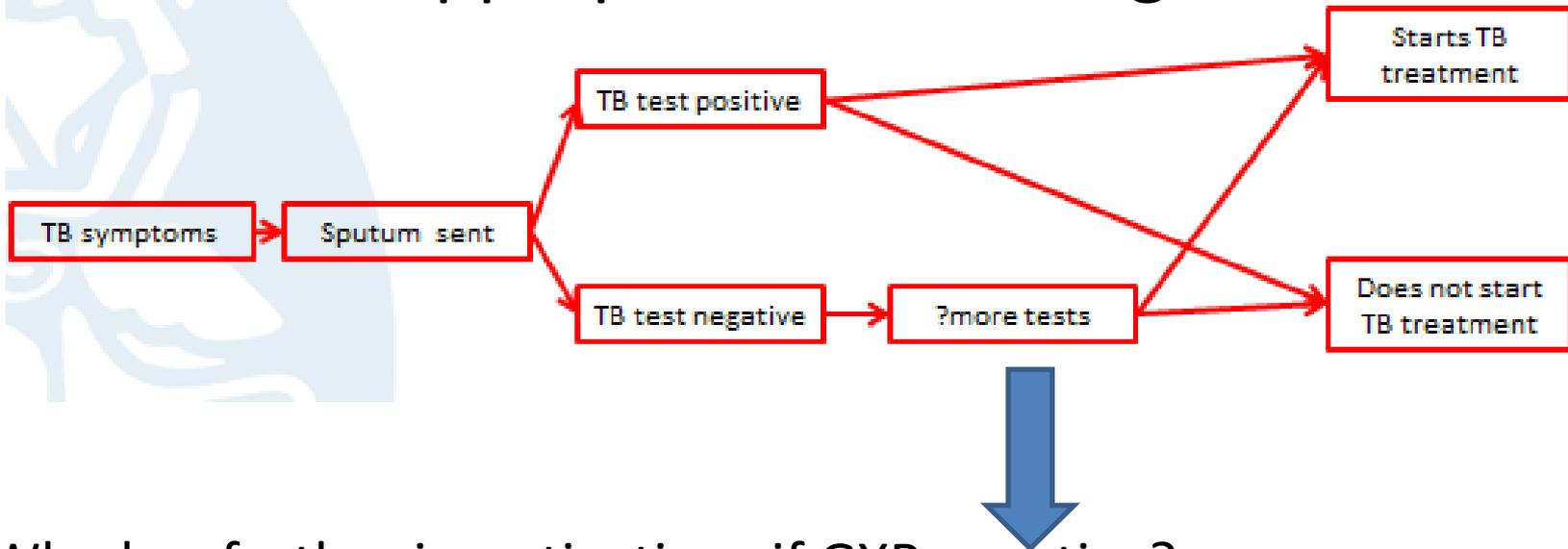
Who has further Investigations if GXP negative?

- Correct test interpretation by HCW

“if she is GXP negative , I tell her she doesn’t have TB. I ask the patient to come after some time to re-test again”

TB nurse, facility C

A preliminary sense of 'enablers and barriers to TB appropriate TB investigation'

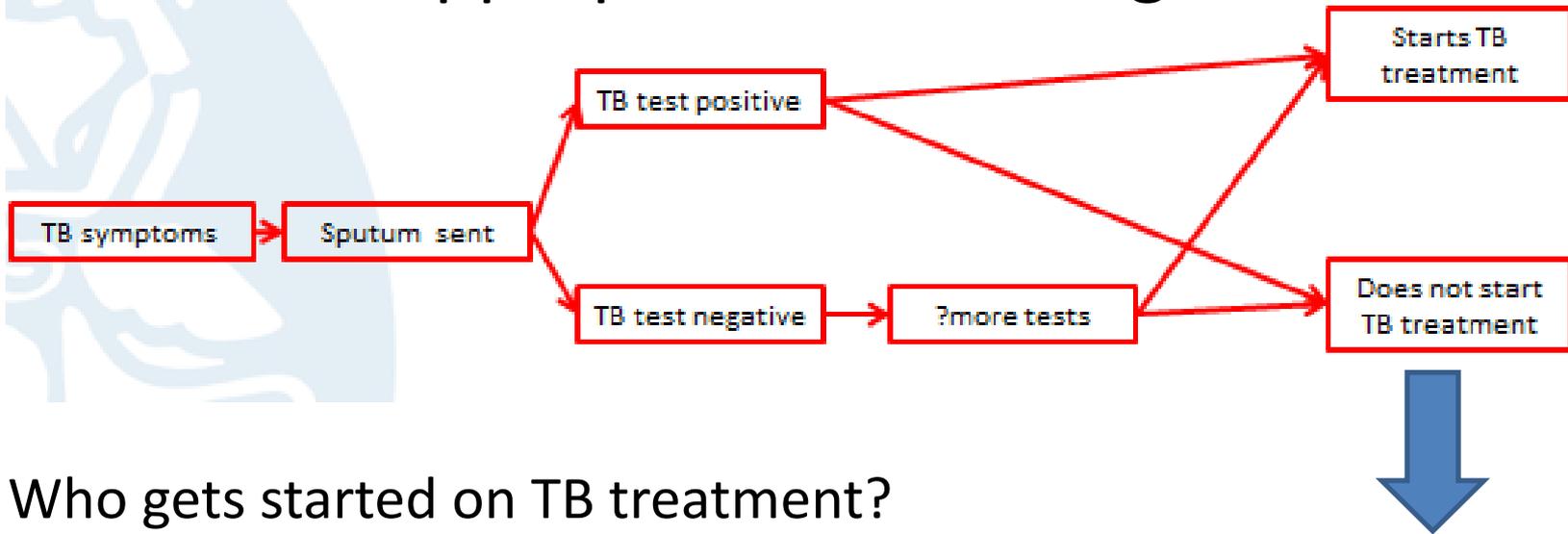


Who has further investigations if GXP negative?

- Pressure from the patient

“there was a person whose GXP was negative ne? and then the patient continues coughing, and the husband was worried about that. And he brings back the patient to the clinic, and booked the patient for the doctor. he ordered X ray..... And then when the X ray comes, it shows that the patient is having TB”

A preliminary sense of 'enablers and barriers to TB appropriate TB investigation'



Who gets started on TB treatment?

- Patient factors
- Facility Management

“ja I did explain to [the facility manager] “do you realise that since the DOT supporters are not here, we are having difficulty tracing of the patients that are positive?”, but since now he has not come with a solution”

TB nurse, Facility C

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Can initial loss to follow-up rates be reduced?

Two studies currently being conducted by Aurum

Case-manager study

- Aim: to determine if a case manager placed at a PHC facility will reduce initial loss to follow-up through linking persons being investigated for TB with appropriate TB and HIV services

Principal Investigator: Noriah Matabane with Alison Grant
Funded by Gates Foundation

The *iTB-project*: mHealth for TB

- Aim: to determine if mHealth-based relaying of Xpert sputum results to HCW and patients will reduce initial loss to follow up

Principal Investigator: Kerrigan McCarthy.
Funded by NIH Grant 1R21TW009894-01



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Xpert Health Economics

- A complete cost analysis has been conducted as part of XTEND
 - Laboratory, patient and programme costs (including costs of in- and out-patient treatment)
 - Top down and bottom up approach
 - Results available, but not released.... pending notification of Minister of Health

Principal Investigator, G Churchyard with Anna Vassal and Edina Sinanovic



Key message

In the XTEND study, Xpert MTB/RIF, although better than smear, was undermined by poor health systems, specifically poor linkage to care and inadequate HIV patient care, amongst other problems.

Therefore, scale-up of a more sensitive diagnostic test requires strengthened health systems in order to maximise impact on patient and programme outcomes

XTEND investigators

Aurum Institute

- Gavin Churchyard
- Kerrigan McCarthy
- Violet Chihota

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- Lerole D. Mametja
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- Lindiwe Mvusi

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Mpumalanga: Edith Becka, Fikile Khoza, Bongumusa Dlamini, Mary-Faith Malesoena, Ntoana Mbete, Solani Mthimunye



Partners and funders

- **Funders**

- Bill and Melinda Gates Foundation



- **Partners**

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- Gauteng Department of Health: Dr Dimakatso Moloji
 - City of JHB: Ms Antonia Barnard
 - City of Tshwane: Ms Julia Mokale
 - Ekurhuleni: Ms Sibongile Mokoena
- Mpumalanga Department of Health: Ms Duduzile Mbambo



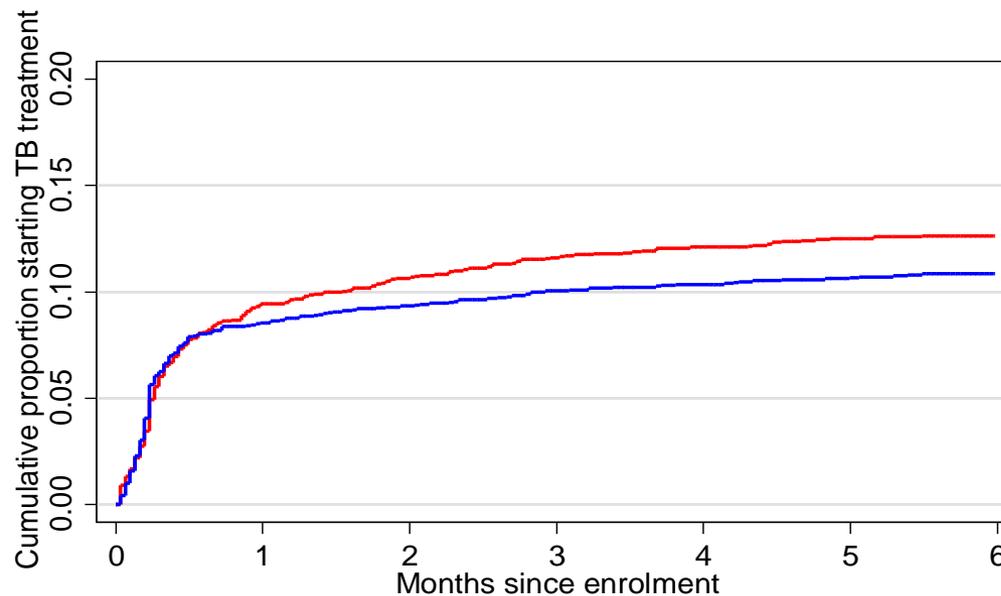


Summary of XTEND results

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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 (0.48-1.93)
% 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)

XTEND results - % treated for TB

Kaplan-Meier curves showing time to starting TB treatment, among all who started TB treatment, regardless of index test sputum result, in each arm



Number at risk (TB)		0	1	2	3	4	5	6
Microscopy	2332	(246)	2021	(33)	1961	(12)	0	0
Xpert	2324	(216)	2058	(23)	2003	(11)	0	0

— Microscopy — Xpert

