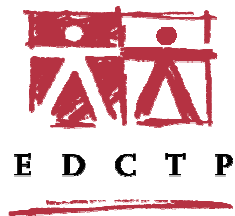


A randomized controlled trial of two sputum sample acquisition methods in smear-negative or sputum-scarce persons with suspected tuberculosis in primary-care practice

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“If TB and AIDS are a snake, then the head is in South Africa while the tail is quickly moving through other African countries... And if the head of the snake is in South Africa then the teeth are in Durban”

Dr Aaron Motaledi (SA minister of Health)
World TB Day, 24 March 2011

1 in 100 South Africans have TB

1 HIV-associated TB death every 6 minutes

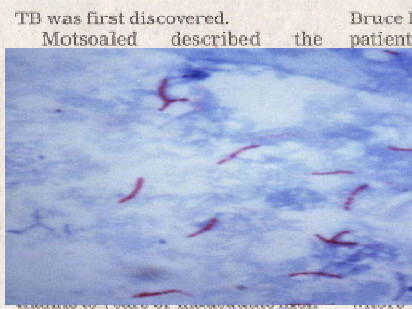
**1 out of 2 TB cases are smear-negative or
unable to produce (sputum-scarce)**

'Bazookas' will help fight TB says Motsoaledi

Xpert MTB/RIF to replace smear for frontline TB diagnosis in SA



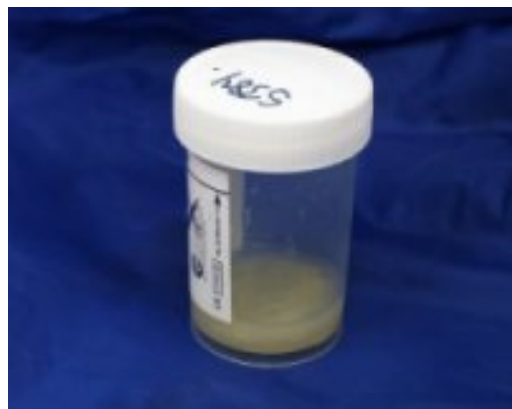
'REVOLUTION': Health Minister Aaron Motsoaledi



Motsoaledi described the machines as a "revolution", saying that these were the "bazookas" in the war against TB.

Cape Times, 25 March 2011.

Diagnosis = adequate sputum sample + effective diagnostic test



Sputum sampling methods

- Healthcare-provider instruction and supervision
- Sputum induction
- Nasopharyngeal aspirate
- Gastric washings
- Bronchoscopy

Cost & complexity

Sputum induction for primary care...

- Safe, easy-to-perform sputum sampling strategy
- Equivalent diagnostic yield to bronchoscopy & gastric washings in hospitals (10-30%)

BUT

- No primary care clinic data
- No impact data
- No comparative data to other simple, effective sampling strategies e.g. Healthcare-worker provided instruction



Battery powered-SI in Tanzania

Beyond accuracy to impact...

Hypothesis

Using sputum induction compared to healthcare-worker provided instruction to acquire a sample for diagnostic testing in smear-negative or sputum-scarce adults with suspected tuberculosis in a high HIV prevalent primary care setting will decrease the time-to-diagnosis and time-to-treatment initiation

Study design

An open-labeled pragmatic randomised controlled trial
(registered with clinicaltrials.gov - NCT01545661)

Primary outcome

- Time-to-treatment initiation
(Overall and time-specific proportions of patients initiating treatment by 3, 5, 7, 10, 14, 21, 56 days from enrolment)

Secondary outcomes

- Adequate (≥ 1 ml) sputum sample acquisition
- Safety and tolerability of sputum sampling methods
- Diagnostic yields of sputum smear microscopy and TB culture
- Diagnostic yield of Xpert MTB/RIF, using stored samples
- Comparative costing of induction and instruction in primary care clinics

Study participants

Inclusion criteria

- ≥ 18 years
- TB symptoms and either sputum-scarce or 2 x negative sputum smears (within preceding 4 weeks)
- Informed consent

Exclusion criteria

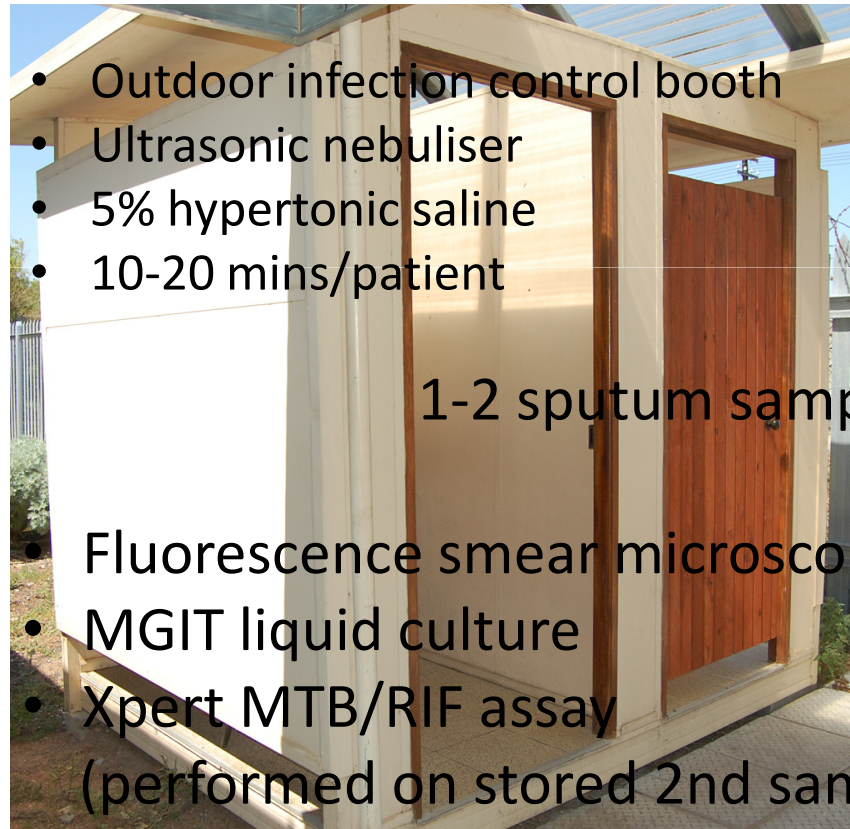
- Unable to provide consent
- Symptoms not suggestive of TB
- Initial sputum samples underwent MTB/RIF rather than smear microscopy

Screening and randomisation

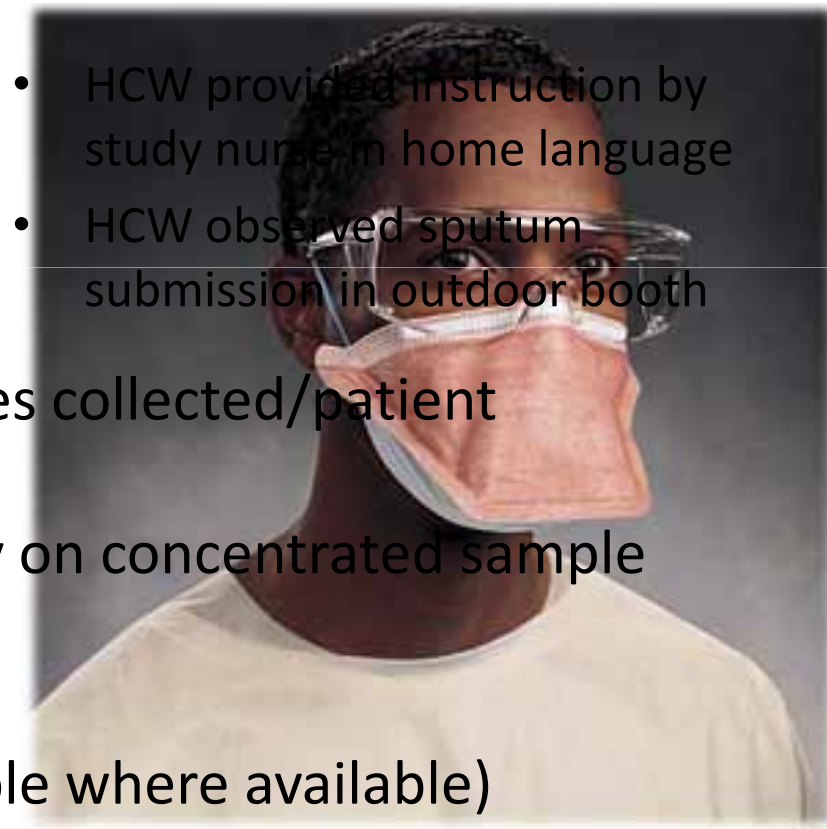
- Referred for screening by TB clinic nurse
- Assessed and enrolled by study research nurse, prior to either doctor's assessment or Chest x-ray (CXR) performance
- Simple randomisation strategy without stratification or blinding
- Opaque envelopes for allocation concealment
- After consenting, patients selected envelope with intervention card stored with patient clinical record forms
- Unannounced checks were made to confirm adherence to randomisation protocol

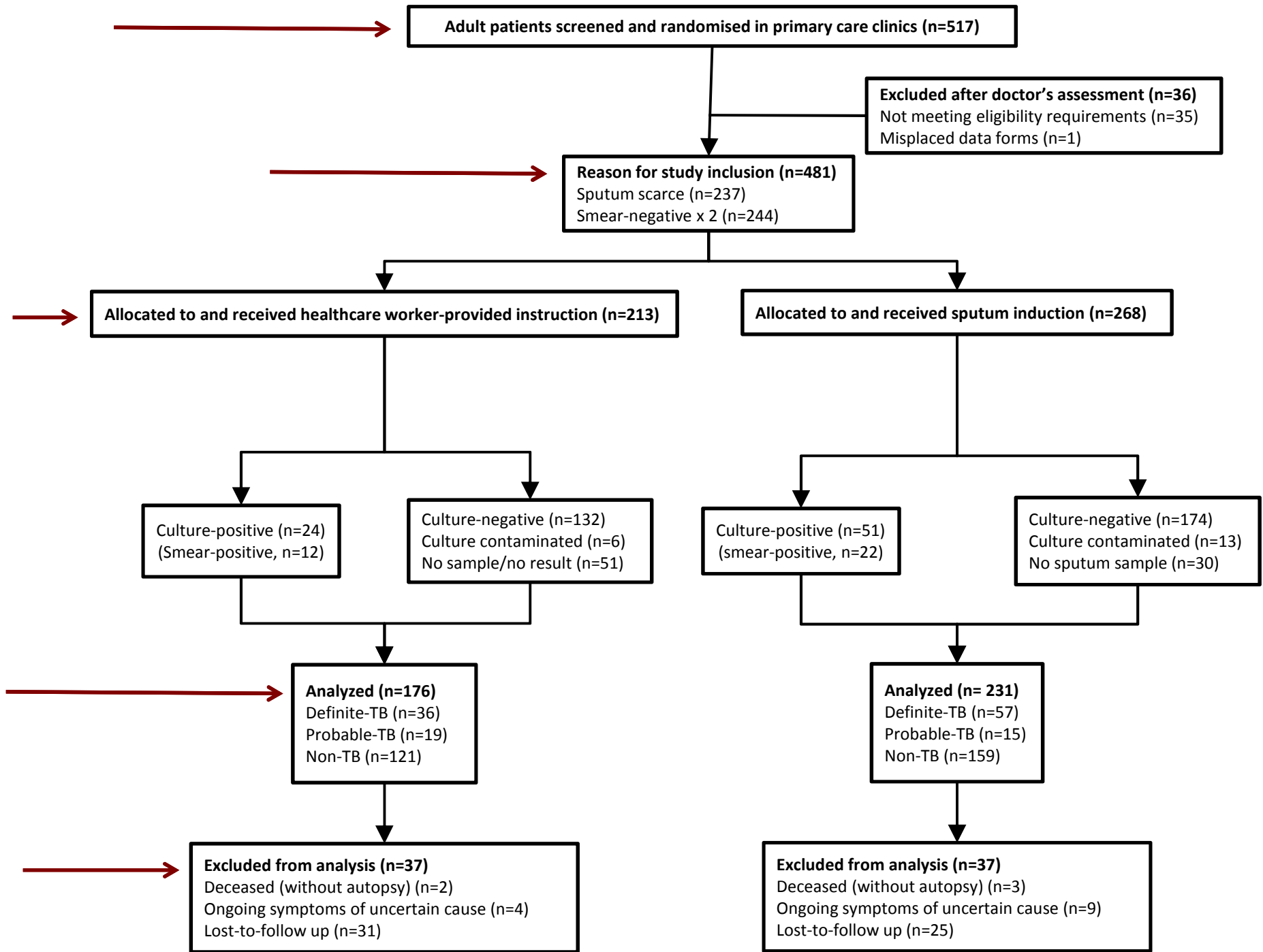
Intervention and diagnostic testing

Sputum induction



Healthcare-worker (HCW) provided instruction



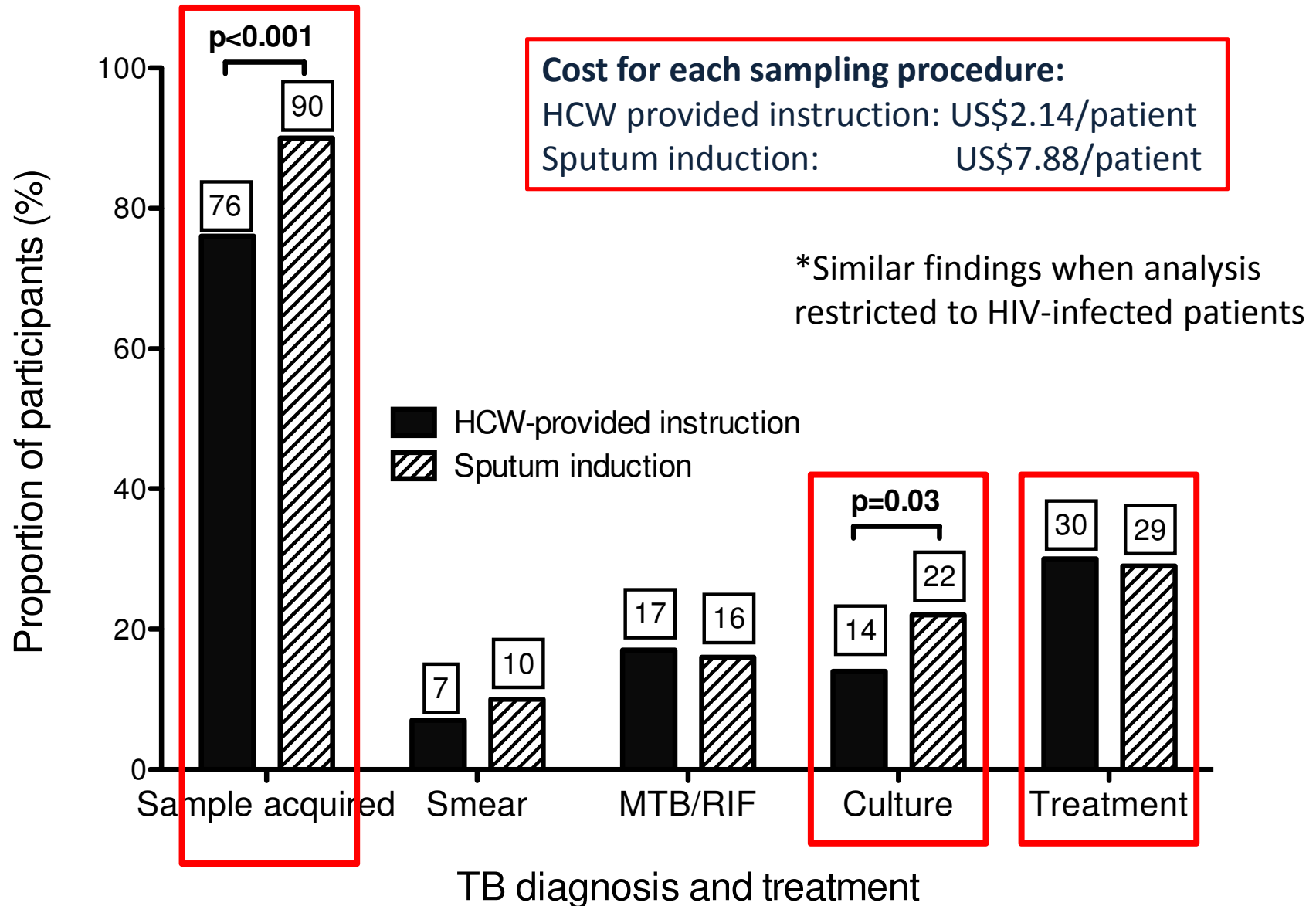


Demographic and clinical characteristic(s)	All (N=481)	HCW-provided instruction (N=213)	Sputum induction (N=268)
Demographic characteristics			
Median age (years, IQR)	39 (30-49)	40 (31-49)	38 (29-49)
Male sex (%)	262 (55)	122 (57)	140 (52)
HIV-infected (%)	171 (36)	75 (35)	96 (36)
Median CD4 cell count (cells/ml, IQR)	242 (146-358)	239 (136-345)	247 (149-379)
Current ARVs (%)	37 (22)	15 (20)	22 (23)
History of TB (%)	180 (37)	82 (39)	98 (37)
Diagnostic categorization at enrolment			
2 × sputum smear-negative (%)	244 (51)	117 (55)	127 (47)
Unable to produce sputum prior to enrolment (%)	237 (49)	96 (45)	141 (53)
Symptoms, signs and radiological features at enrolment			
Cough > 2 weeks (%)	430 (90)	189 (89)	241 (90)
Productive cough (%)	311 (65)	141 (67)	170 (64)
Night sweats (%)	344 (72)	152 (72)	192 (72)
Weight loss (%)	335 (70)	145 (68)	190 (71)
Appetite loss (%)	253 (54)	114 (55)	139 (54)
Weight (median kg, IQR)	62 (54-72)	62 (54-72)	63 (55-72)
CXR compatible with TB	179 (37)	85 (40)	94 (35)

2

No differences between induced and instructed patients

Primary and key secondary outcomes



Why similar treatment but different case detection?

Outcome	HCW-provided instruction	Sputum induction
Overall proportion of participants initiating treatment[†] (n/N, %)	52/176 (30)	68/231 (29)
Smear microscopy-based TB diagnosis and treatment initiation		
1. Proportion of participants treated based on smear-positive result (n/N, %)	13/52 (25)	22/68 (32)
Diagnosis based on clinico-radiological presentation with empiric treatment initiation		
2. Participants treated based on clinical and CXR findings (n/N, %)	32/52 (62) [*]	29/68 (43) [*]
i. HIV-infected participants only [§]	18/32 (56)	18/29 (62)
ii. HIV-uninfected participants only ^{&}	14/32 (44)	11/29 (38)
Culture-based TB diagnosis and treatment initiation		
3. Participants treated based on sputum (study sample 1) culture result (n/N, %)	6/52 (11)	15/68 (22)
4. Participants treated based on other (sputum/non-sputum) culture result/s (n/N, %)	1/52 (2)	2/68 (3)
5. Culture-positive patient not given any TB treatment during study period (n/N, %)	3/176 (2)	4/231 (2)

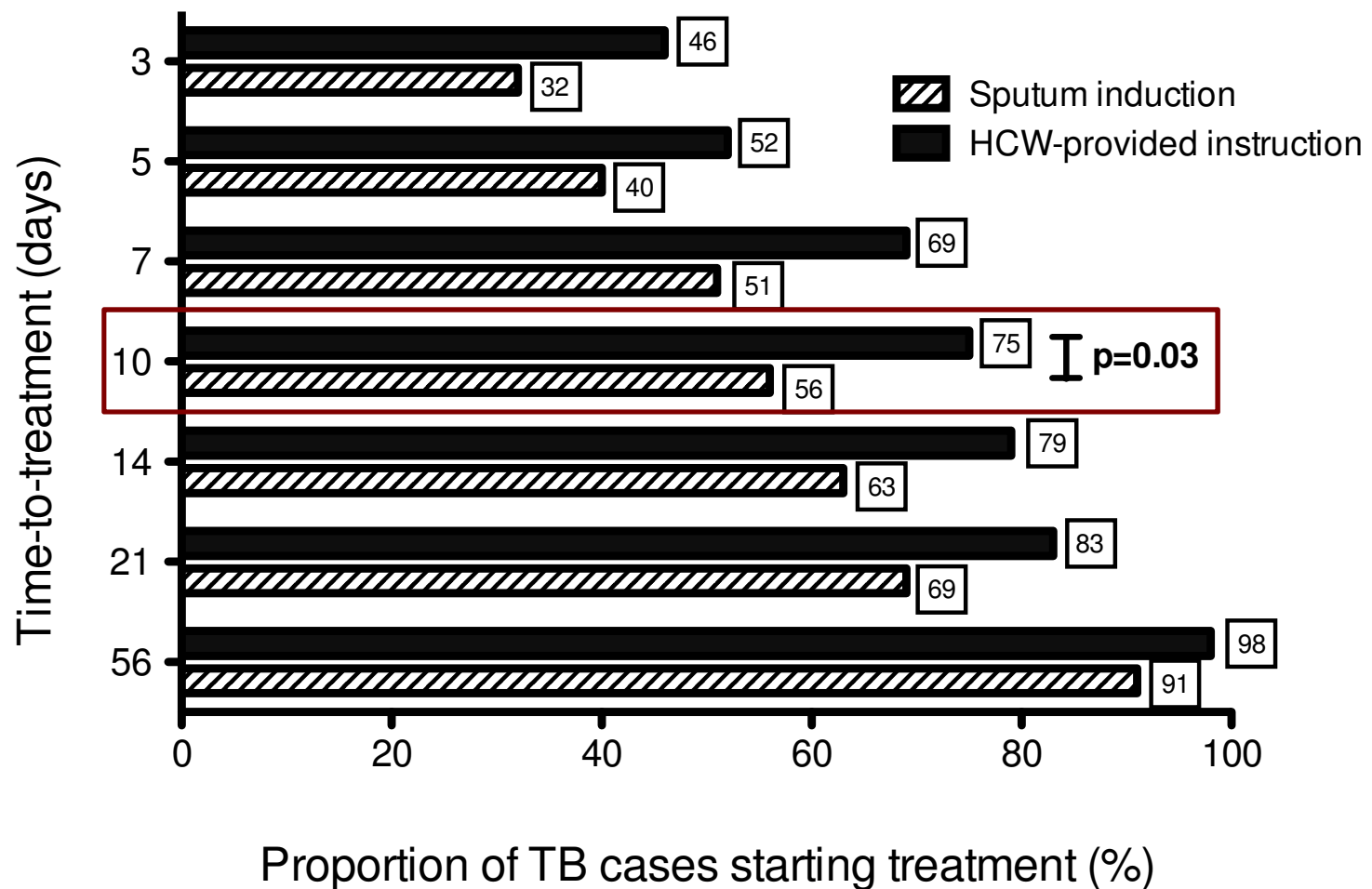
?

More HCW-provided instruction patients received empiric treatment

Time-specific proportions initiating treatment (All patients)

Median (IQR) time-to-treatment:

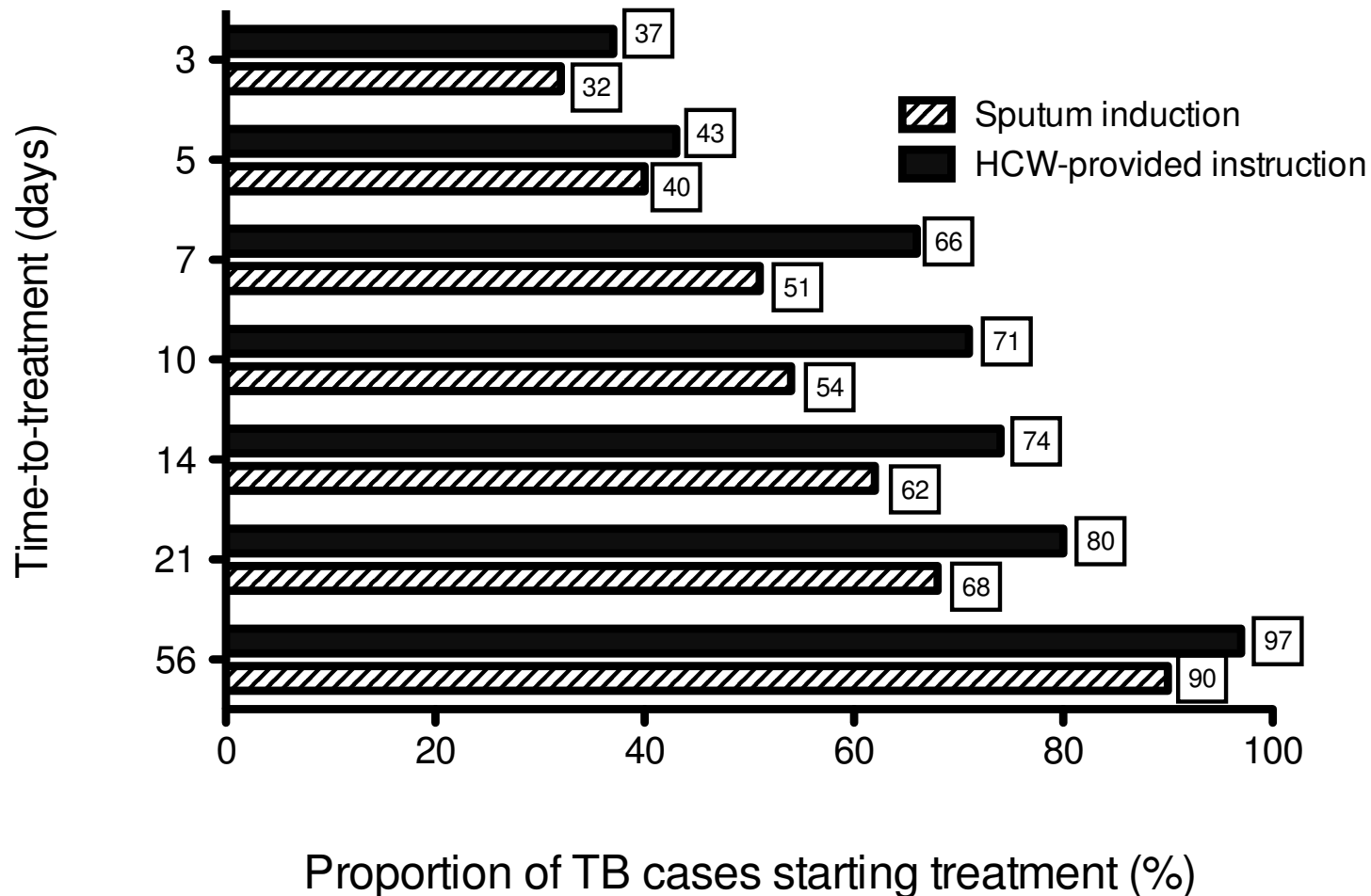
HCW-provided instruction: 4 (2-9) days vs. Sputum induction: 7 (2-30) days; $p=0.02$



Time-specific proportions initiating treatment (Only patients successfully providing a sputum)

Median (IQR) time-to-treatment:

HCW-provided instruction: 6 (2-14) days vs. Sputum induction: 7 (3-30) days; $p > 0.05$



Conclusions

- Sputum induction led to higher sampling success and culture-based TB detection
- Overall and time-specific proportions of patients initiating treatment was not improved by sputum induction
- Sputum induction did not improve diagnostic yield of rapid tools such as smear microscopy or Xpert MTB/RIF
- HCW-provided instruction had lower cost and complete absence of side-effects
- HCW-provided instruction should be recommended as the preferred initial sputum sampling strategy in adult smear-negative or sputum-scarce persons with suspected tuberculosis in primary care practice

Limitations

- Open-labeled opaque envelope randomisation strategy at risk of bias
- Higher empiric treatment rates – where these appropriate or overtreatment?
- MTB/RIF not used for treatment decisions
- Findings may only be applicable to high HIV prevalent settings

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