

# Diagnostic RCTs in TB: Same-day smear diagnosis



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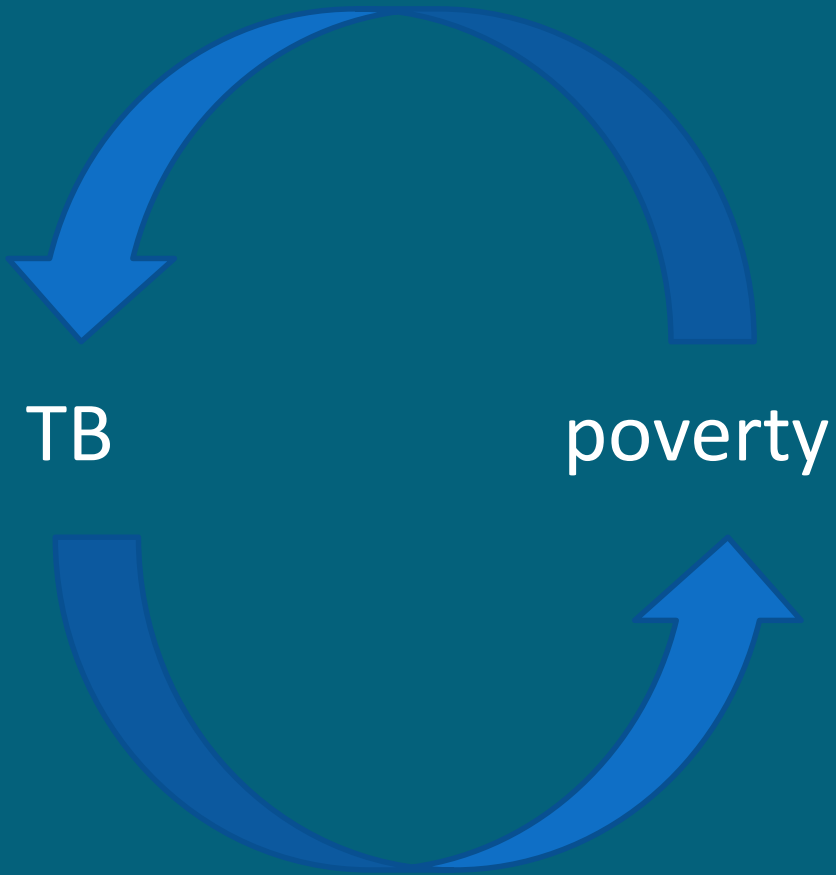
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# TB is a disease .....



# % POPULATION LIVING ON < 2 USD

Country	% living on <2 USD per day
India	68.7 (2010)
Bangladesh	76.5 (2012)
Pakistan	60.2 (2008)
Tanzania	87.9 (2007)
South Africa	31.3 (2009)
Brazil	10.8 (2009)
China	27.2 (2009)

(a) a one-positive-one-negative rule for definition of a sputum positive TB case,  
(b) the reduction of the three-month-treatment rule to a two-month treatment policy.

1. Policy recommendations should be prepared for ITAG review based on this work.



MIEMBROS DE LA FAO REUNIDOS EN ROMA PARA TRATAR DE RESOLVER EL PROBLEMA DEL HAMBRE EN EL MUNDO.



MIEMBROS DEL CONSEJO DE SEGURIDAD DE LA ONU REUNIDOS EN NUEVA YORK PARA TRATAR DE RESOLVER EL PROBLEMA DE LA ACTUAL INSEGURIDAD GLOBAL.



MIEMBROS DE LA OIT REUNIDOS EN GINEBRA PARA TRATAR DE RESOLVER EL PROBLEMA DE LA DESOCUPACIÓN MUNDIAL.



MIEMBROS DE UNICEF Y DE LA OMS REUNIDOS EN PARÍS PARA TRATAR DE RESOLVER PROBLEMAS COMO: LA NIÑEZ SIN EDUCACIÓN, EL DESAMPARO SANITARIO Y LA CRECIENTE ESCASEZ DE AGUA QUE AFECTA YA A VARIAS ZONAS DEL PLANETA.



MIEMBROS DE LA FAMILIA ROSALES REUNIDOS EN VILLA TACHITO PARA TRATAR DE RESOLVER SUS PROBLEMAS DE: HAMBRE, INSEGURIDAD, DESOCUPACIÓN, IMPOSIBILIDAD DE MANDAR LOS NIÑOS A LA ESCUELA, NO CONTAR CON ASISTENCIA MÉDICA, NO TENER AGUA CORRIENTE EN LA CASA, NI.....



Over 50 million smear microscopy  
investigation per year

# Background - Patient Perspective

Day 1. Present. Provide 1<sup>st</sup> "spot" specimen.

Day 2. Return. Morning spec and 2<sup>nd</sup> "spot"

Day 3. Return. Results. Referred/appointment

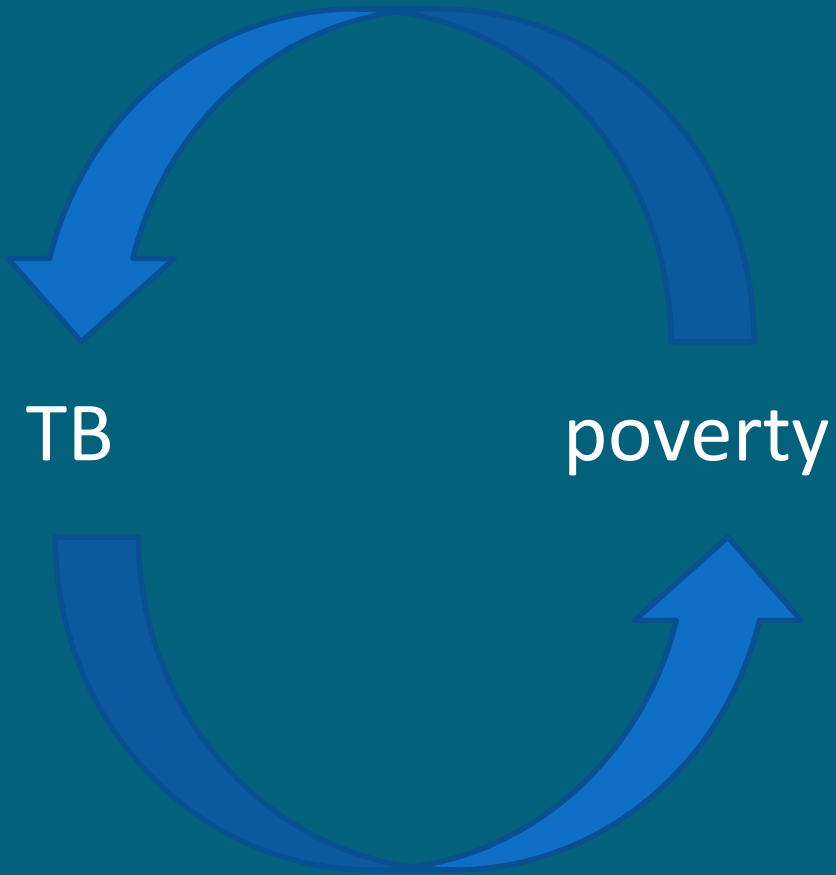
Day 4. Return. Start treatment.



- Less than 20% of those being investigated will have tuberculosis
- Less than 10% of those being investigated will have smear-positive tuberculosis
- Multiple visits required
- "Catastrophic" costs



# TB is a disease .....



# Background – Laboratory perspective

- District hospital/busy health centres
- Heavy workload
- Fatigue
- Quality
- M/T/W/T/F



# The "I Love Lucy Study"

- With thanks to Barry Kosloff, LSHTM, YAMBART Project, Lusaka, Zambia

<http://www.youtube.com/watch?v=8NPzLBSBzPI>

# LABORATORY PATHWAY

- Three specimens
- Ziehl-Neelsen
- Smear positive case – 2 positive specimens (1+)



## Initial default from tuberculosis treatment: how often does it happen and what are the reasons?

E. Botha,\* S. Den Boon,<sup>†</sup> S. Verver,<sup>†‡</sup> R. Dunbar,\* K-A. Lawrence,\* M. Bosman,<sup>§</sup> D. A. Enarson,<sup>¶</sup> I. Toms,<sup>#</sup> N. Beyers\*

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### SUMMARY

A study in 11 primary health care facilities in and around Cape Town determined the proportion of bacteriologically confirmed tuberculosis (TB) cases who did not start treatment (initial default) and identified reasons for it. Databases from centralised laboratories were compared with electronic TB treatment registers. Fourteen per cent (373/2758) of TB suspects were TB cases. Of the 58 (16%) initial defaulters, 14 (24%) died, while 26

(45%) could not be interviewed for address-related reasons. The 18 subjects who were interviewed indicated reasons for initial default that were (56%) or were not (44%) directly linked to services. High initial default rates require improvement in the quality of health services.

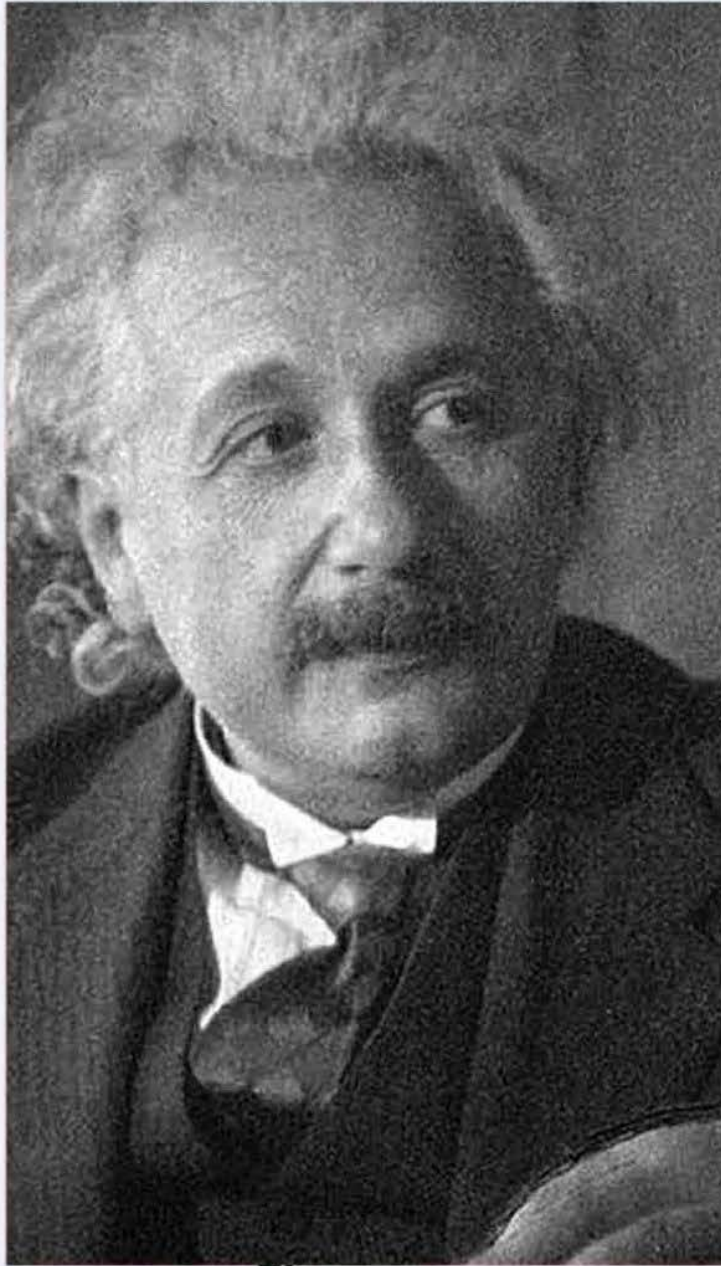
**KEY WORDS:** tuberculosis; South Africa; treatment; initial default

# Smear microscopy – is it worth improving it?

- Very good specificity
- Relatively low-cost
- Can be used to monitor treatment
- Employs people
- Possible at health centre level

## **BUT**

- Limited sensitivity – quality/workload
- Protracted and expensive pathway for patients
- Overwhelming workload for labs
- No direct information on drug resistance



**“Insanity:  
Doing the same  
thing over and over  
again and expecting  
different results.”**

**ALBERT EINSTEIN**

**1879 - 1955**

# Starting to rationalize (formally) .....

## Reducing workload to improve quality

- Are three specimens necessary?
- Could we reduce to two?
- (LED FM)?



## Improving patient experience

- If we reduced to two, could we do the smears on the same day and get a "one-stop shop"?



**STATE OF THE ART SERIES**

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NUMBER 10 IN THE SERIES

# Translating tuberculosis research into global policies: the example of an international collaboration on diagnostics

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# Are three specimens necessary?

## Yield of serial sputum specimen examinations in the diagnosis of pulmonary tuberculosis: a systematic review

S. R. Mase,<sup>\*†</sup> A. Ramsay,<sup>‡</sup> V. Ng,<sup>§</sup> M. Henry,<sup>¶</sup> P. C. Hopewell,<sup>\*†</sup> J. Cunningham,<sup>‡</sup> R. Urbanczik,<sup>#</sup> M. D. Perkins,<sup>\*\*</sup> M. A. Aziz,<sup>††</sup> M. Pai<sup>‡‡</sup>

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# Incremental yield of 3<sup>rd</sup> specimen

**Approx 85/12/3%**

Worked example:

- 1000 TB suspects
- 3 x 1000 smears
- 100 Sm+ TB patients (10%)
- First 1000 smears identifies 85 of 100 cases
- Second 1000 smears identifies additional 12
- Third 1000 smears identifies additional 3 cases

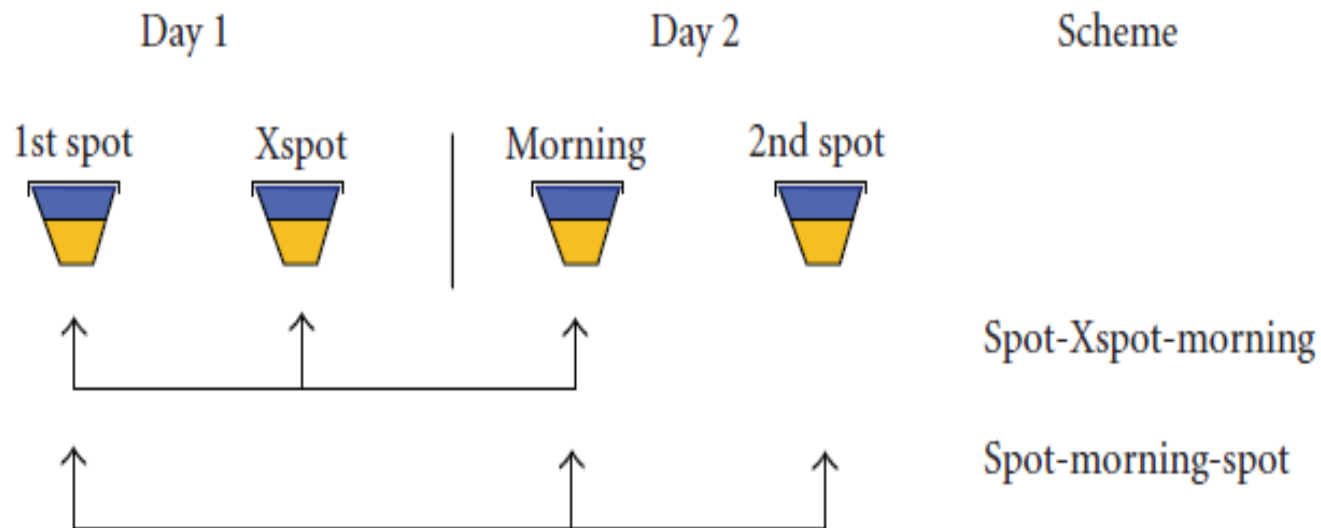
# New questions.....

- Is morning specimen important?
- Are two positive specimens really necessary to confirm a case of TB?
- How important is it that positive smears are graded 1+ and above? What about scanty smears (1-9 AFB per 100 fields)?

*Research Article*

## Front-Loading Sputum Microscopy Services: An Opportunity to Optimise Smear-Based Case Detection of Tuberculosis in High Prevalence Countries

Andy Ramsay,<sup>1,2</sup> Mohammed Ahmed Yassin,<sup>1,3</sup> Alexis Cambanis,<sup>1</sup>  
Susumu Hirao,<sup>1</sup> Ahmad Almotawa,<sup>1</sup> Mohamed Gammo,<sup>1</sup> Lovett Lawson,<sup>4</sup>  
Izabel Arbide,<sup>5</sup> Nasher Al-Aghbari,<sup>6</sup> Najla Al-Sonboli,<sup>6</sup> Jeevan Bahadur Sherchand,<sup>7</sup>  
Punita Gauchan,<sup>7</sup> and Luis Eduardo Cuevas<sup>1</sup>



## Reducing the number of sputum samples examined and thresholds for positivity: an opportunity to optimise smear microscopy

M. Bonnet,\* A. Ramsay,† L. Gagnidze,\* W. Githui,‡ P. J. Guerin,\* F. Varaine§

\* Epicentre, Paris, France; † Liverpool School of Tropical Medicine, Liverpool, UK; ‡ Centre for Respiratory Diseases Research, Kenya Medical Research Institute, Nairobi Kenya; § Médecins Sans Frontières, Paris, France

## Efficiency of a third serial sputum smear examination in the diagnosis of tuberculosis in Moldova and Uganda

A. Katamba,\* D. Laticevschi,† H. L. Rieder‡

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<b>Tuberculosis</b>	<p><b>The revised definition of a new sputum smear-positive pulmonary TB case is based on the presence of at least one acid fast bacilli (AFB+) in at least one sputum sample in countries with a well functioning external quality assurance (EQA) system.</b></p> <p><a href="#">Detailed background information [pdf 144kb]</a></p> <p><a href="#">Proposal for a revision of the case definition of "Sputum Smear-Positive Tuberculosis" [pdf 1.99Mb]</a> Background document prepared by Hans L. Rieder and Armand Van Deun</p>
<b>Stop TB Strategy</b>	<p><b>More information</b></p> <ol style="list-style-type: none"> <li><a href="#">Background documentation</a></li> <li><a href="#">Definition of a new sputum smear-positive TB case</a></li> <li><a href="#">Reduction of number of smears for the diagnosis of pulmonary TB</a></li> <li><a href="#">The use of liquid medium for culture and DST</a></li> </ol>
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**BACKGROUND**

As highlighted in the Stop TB Strategy, quality-assured bacteriological examination is an essential element for diagnosis and management of TB patients harbouring susceptible or resistant bacilli. During the last two years, an increasing number of countries are scaling up external quality assurance programmes for smear microscopy by means of blinded re-checking of slides. As a result, the quality of smear microscopy examination reached a satisfactory level in some countries. Evidence suggests that countries with a functional EQA system have very low frequency of false positive cases.

**KEY ISSUES FOR WHO ACTION**

A number of key meetings and workshops were held where the TB case definition was discussed. These meetings included the Stop TB Partnership Laboratory Strengthening Subgroup (SLCS), an expert group meeting organized by the UNION held in Belgium and a technical expert workshop held in the Netherlands. Recent scientific evidence [Ref. 1,2] was reviewed and it was concluded that where a functional EQA for smear microscopy is in place, the finding of a single AFB in at least one single sputum smear examination in a TB suspect would satisfy the criterion to report a patient as having "sputum smear-positive tuberculosis" and to subsequently start treatment.

It should be noted that the definition of bacteriological failures has not been reviewed; hence, no change in definition of failure cases is proposed at this stage.

Local intranet

<http://www.who.int/tb/dots/laboratory/en/index.html>

## Quantitative differences in sputum smear microscopy results for acid-fast bacilli by age and sex in four countries

H. L. Rieder,\* J. M. Lauritsen,<sup>†‡</sup> N. Naranbat,<sup>§</sup> A. Katamba,\*<sup>¶</sup> D. Laticevschi,<sup>###</sup> B. Mabaera<sup>††‡‡</sup>

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## Sputum, sex and scanty smears: new case definition may reduce sex disparities in smear-positive tuberculosis

A. Ramsay,\* M. Bonnet,<sup>†</sup> L. Gagnidze,<sup>†</sup> W. Githui,<sup>‡</sup> F. Varaine,<sup>§</sup> P. J. Guérin<sup>†</sup>

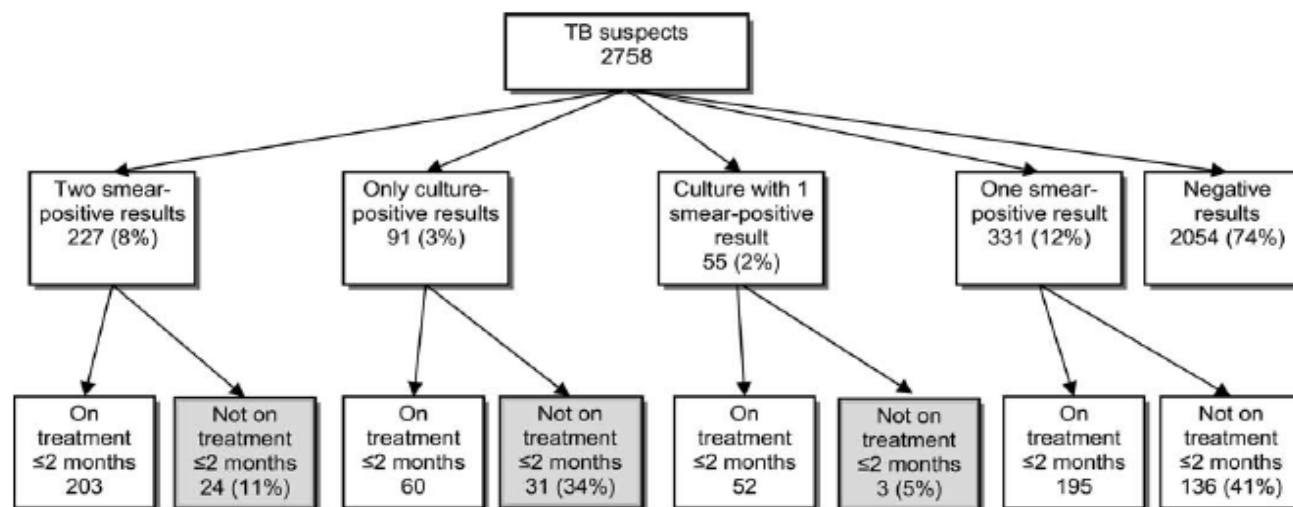
\* Liverpool School of Tropical Medicine, Liverpool, UK; <sup>†</sup>Epicentre, Paris, France; <sup>‡</sup>Kenya Medical Research Institute, Nairobi, Kenya; <sup>§</sup>Médecins Sans Frontières, Paris, France



## Initial default from tuberculosis treatment: how often does it happen and what are the reasons?

E. Botha,\* S. Den Boon,<sup>†</sup> S. Verver,<sup>†‡</sup> R. Dunbar,\* K-A. Lawrence,\* M. Bosman,<sup>§</sup> D. A. Enarson,<sup>¶</sup> I. Toms,<sup>#</sup> N. Beyers\*

\* Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Stellenbosch University, Tygerberg, South Africa; <sup>†</sup>KNCV Tuberculosis Foundation, The Hague, <sup>‡</sup>CINIMA, Academic Medical Centre, Amsterdam, The Netherlands; <sup>§</sup>National Health Laboratory Services, Cape Town, South Africa; <sup>¶</sup>International Union Against Tuberculosis and Lung Disease, Paris, France; <sup>#</sup>Department of Health, City of Cape Town, Cape Town, South Africa



**Figure** Diagnostic process of tuberculosis suspects who submitted a sputum sample between April and June 2005. Shaded boxes indicate initial defaulters. TB = tuberculosis.



# A Multi-Country Non-Inferiority Cluster Randomized Trial of Frontloaded Smear Microscopy for the Diagnosis of Pulmonary Tuberculosis

Luis Eduardo Cuevas<sup>1,2\*</sup>, Mohammed Ahmed Yassin<sup>1</sup>, Najla Al-Sonboli<sup>3</sup>, Lovett Lawson<sup>4</sup>, Isabel Arbide<sup>5</sup>, Nasher Al-Aghbari<sup>6</sup>, Jeevan Bahadur Sherchand<sup>7</sup>, Amin Al-Absi<sup>6</sup>, Emmanuel Nnamdi Emenyonu<sup>4</sup>, Yared Merid<sup>8</sup>, Mosis Ifenyi Okobi<sup>9</sup>, Juliana Olubunmi Onuoha<sup>4</sup>, Melkamsew Aschalew<sup>8</sup>, Abraham Aseffa<sup>10</sup>, Greg Harper<sup>1</sup>, Rachel Mary Anderson de Cuevas<sup>1</sup>, Kristin Kremer<sup>11</sup>, Dick van Soolingen<sup>11</sup>, Carl-Michael Nathanson<sup>2</sup>, Jean Joly<sup>2</sup>, Brian Faragher<sup>1</sup>, Stephen Bertel Squire<sup>1</sup>, Andrew Ramsay<sup>2</sup>

**Citation:** Cuevas LE, Yassin MA, Al-Sonboli N, Lawson L, Arbide I, et al. (2011) A Multi-Country Non-Inferiority Cluster Randomized Trial of Frontloaded Smear Microscopy for the Diagnosis of Pulmonary Tuberculosis. *PLoS Med* 8(7): e1000443. doi:10.1371/journal.pmed.1000443

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**Competing Interests:** AR is employed by WHO/TDR the organization which administered the USAID and BMGF grants that funded the study. AR is Secretary of the New Diagnostics Working Group, Stop TB Partnership.

**Abbreviations:** AFB, acid fast bacilli; EQA, external quality assessment; ITT, intention to treat; LMICs, low- and middle-income countries; NTP, national tuberculosis programme; PPA, per protocol analysis; SM, spot-morning; SMS, spot-morning-spot; SS, spot-spot; SSM, spot-spot-morning; TB, tuberculosis; WHO, World Health Organization

# Diagnostic accuracy of same-day microscopy versus standard microscopy for pulmonary tuberculosis: a systematic review and meta-analysis

*J Lucian Davis, Adithya Cattamanchi, Luis E Cuevas, Philip C Hopewell, Karen R Steingart*

**Findings** We identified eight relevant studies from five articles enrolling 7771 patients with suspected tuberculosis in low-income countries. Compared with the standard approach of examination of two smears with Ziehl-Neelsen light microscopy over 2 days, examination of two smears taken on the same day had much the same sensitivity (64% [95% CI 60 to 69] for standard microscopy *vs* 63% [58 to 68] for same-day microscopy) and specificity (98% [97 to 99] *vs* 98% [97 to 99]). We noted similar results for studies employing light-emitting diode fluorescence microscopy and for studies examining three smears, whether they were compared with two-smear strategies or with one another.

**Interpretation** Same-day sputum smear microscopy is as accurate as standard smear microscopy. Data from tuberculosis programmes are needed to document the changes required in the health system to successfully implement the strategy and understand its effects.

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S1473-3099\(12\)70232-3](http://dx.doi.org/10.1016/S1473-3099(12)70232-3)

(a) a one-positive-one-negative rule for definition of a sputum positive TB case,  
(b) the reduction of the three-month-treatment rule to a two-month treatment policy.

1. Policy recommendations should be prepared for ITAG review based on this work.





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## SAME-DAY-DIAGNOSIS OF TUBERCULOSIS BY MICROSCOPY

### POLICY STATEMENT

- **WHO recommends that:**
- Countries that have successfully implemented the current WHO policy for a two-specimen case-finding strategy consider a switch to the same-day-diagnosis approach, especially in settings where patients are likely to default from the diagnostic process;
- Countries that are still using the three-specimen case-finding strategy consider a gradual change to the same-day-diagnosis approach, once WHO-recommended external microscopy quality assurance systems are in place and good quality microscopy results have been documented;

# Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review

*Karen R Steingart, Megan Henry, Vivienne Ng, Philip C Hopewell, Andrew Ramsay, Jane Cunningham, Richard Urbanczik, Mark Perkins, Mohamed Abdel Aziz, Madhukar Pai*

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PLoS MEDICINE

## LED Fluorescence Microscopy for the Diagnosis of Pulmonary Tuberculosis: A Multi-Country Cross-Sectional Evaluation

**Luis Eduardo Cuevas<sup>1,2\*</sup>, Najla Al-Sonboli<sup>3</sup>, Lovett Lawson<sup>4</sup>, Mohammed Ahmed Yassin<sup>1</sup>, Isabel Arbide<sup>5</sup>, Nasher Al-Aghbari<sup>3</sup>, Jeevan Bahadur Sherchand<sup>6</sup>, Amin Al-Absi<sup>7</sup>, Emmanuel Nnamdi Emenyonu<sup>4</sup>, Yared Merid<sup>8</sup>, Mosis Ifenyi Okobi<sup>9</sup>, Juliana Olubunmi Onuoha<sup>4</sup>, Melkamsew Aschalew<sup>8</sup>, Abraham Aseffa<sup>10</sup>, Greg Harper<sup>1</sup>, Rachel Mary Anderson de Cuevas<sup>1</sup>, Sally Jane Theobald<sup>1</sup>, Carl-Michael Nathanson<sup>2</sup>, Jean Joly<sup>2</sup>, Brian Faragher<sup>1</sup>, Stephen Bertel Squire<sup>1</sup>, Andrew Ramsay<sup>2</sup>**

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# New Policies, New Technologies: Modelling the Potential for Improved Smear Microscopy Services in Malawi

Andrew Ramsay<sup>1\*</sup>, Luis E. Cuevas<sup>2</sup>, Catherine J. F. Mundy<sup>3</sup>, Carl-Michael Nathanson<sup>1</sup>, Petros Chirambo<sup>4</sup>, Russell Dacombe<sup>5</sup>, S. Bertel Squire<sup>2</sup>, Felix M. L. Salaniponi<sup>6</sup>, Sera Munthali<sup>7</sup>

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## Abstract

**Background:** To quantify the likely impact of recent WHO policy recommendations regarding smear microscopy and the introduction of appropriate low-cost fluorescence microscopy on a) case detection and b) laboratory workload.

**Methodology/Principal Findings:** An audit of the laboratory register in an urban hospital, Lilongwe, Malawi, and the application of a simple modelling framework. The adoption of the new definition of a smear-positive case could directly increase case detection by up to 28%. Examining Ziehl-Neelsen (ZN) sputum smears for up to 10 minutes before declaring them negative has previously been shown to increase case detection (over and above that gained by the adoption of the new case definition) by 70% compared with examination times in routine practice. Three times the number of staff would be required to adequately examine the current workload of smears using ZN microscopy. Through implementing new policy recommendations and LED-based fluorescence microscopy the current laboratory staff complement could investigate the same number of patients, examining auramine-stained smears to an extent that is equivalent to a 10 minutes ZN smear examination.

**Conclusions/Significance:** Combined implementation of the new WHO recommendations on smear microscopy and LED-based fluorescence microscopy could result in substantial increases in smear positive case-detection using existing human resources and minimal additional equipment.



# Population-Level Impact of Same-Day Microscopy and Xpert MTB/RIF for Tuberculosis Diagnosis in Africa

David W. Dowdy<sup>1</sup>, J. Lucian Davis<sup>2,3</sup>, Saskia den Boon<sup>4</sup>, Nicholas D. Walter<sup>5</sup>, Achilles Katamba<sup>6</sup>, Adithya Cattamanchi<sup>2,3\*</sup>

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## Abstract

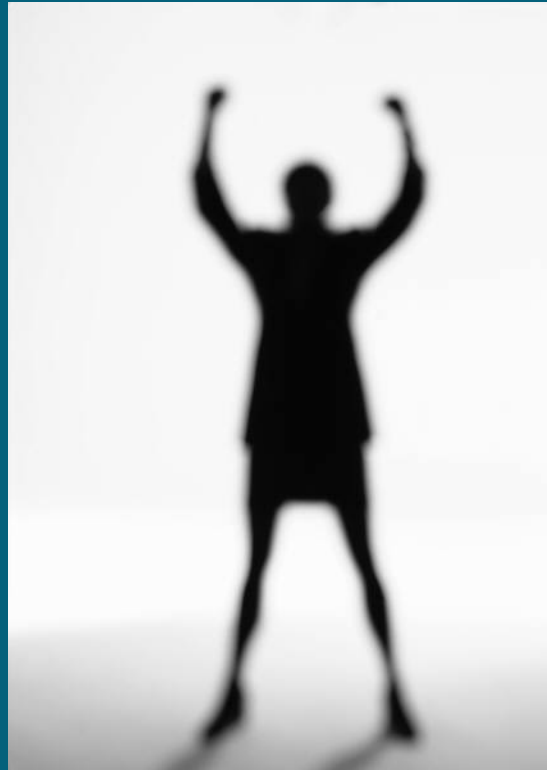
**Objective:** To compare the population-level impact of two World Health Organization-endorsed strategies for improving the diagnosis of tuberculosis (TB): same-day microscopy and Xpert MTB/RIF (Cepheid, USA).

**Methods:** We created a compartmental transmission model of TB in a representative African community, fit to the regional incidence and mortality of TB and HIV. We compared the population-level reduction in TB burden over ten years achievable with implementation over two years of same-day microscopy, Xpert MTB/RIF testing, and the combination of both approaches.

**Findings:** Same-day microscopy averted an estimated 11.0% of TB incidence over ten years (95% uncertainty range, UR: 3.3%–22.5%), and prevented 11.8% of all TB deaths (95% UR: 7.7%–27.1%). Scaling up Xpert MTB/RIF to all centralized laboratories to achieve 75% population coverage had similar impact on incidence (9.3% reduction, 95% UR: 1.9%–21.5%) and greater effect on mortality (23.8% reduction, 95% UR: 8.6%–33.4%). Combining the two strategies (i.e., same-day microscopy plus Xpert MTB/RIF) generated synergistic effects: an 18.7% reduction in incidence (95% UR: 5.6%–39.2%) and 33.1% reduction in TB mortality (95% UR: 18.1%–50.2%). By the end of year ten, combining same-day microscopy and Xpert MTB/RIF could reduce annual TB mortality by 44% relative to the current standard of care.

**Conclusion:** Scaling up novel diagnostic tests for TB and optimizing existing ones are complementary strategies that, when combined, may have substantial impact on TB epidemics in Africa.

# Scale-up of WHO-recommended diagnostic tools



# A Multi-Country Non-Inferiority Cluster Randomized Trial of Frontloaded Smear Microscopy for the Diagnosis of Pulmonary Tuberculosis

- Prospective
- Adults with suspected PTB
- SMS compared to SSM (and SM compared to SS)
- Cluster-randomized (4 week block-randomization)
- Non-inferiority vs superiority trial (Sample, cost, bias)
- Multi-country: Brazil, Ethiopia, Nepal, Nigeria, Yemen
- Rate of recruitment limited by culture w/load
- Intention To (diagnose and) Treat Analysis (ITT)
- Per Protocol Analysis (PP)

# Primary Objectives

- To determine sensitivity, specificity and predictive values of a "two samples in a single day" strategy for the diagnosis of TB and compare it to the standard strategy
- To determine the proportion of patients who could initiate, or be referred for, treatment within 24, 48 or 72 hours of initiating specimen collection.
- To describe the effect of different thresholds to define a positive smear and smear positive case.

# Secondary Objectives

Included:

- To describe the costs incurred by patients assigned to the different specimen collection arms.
- To describe initial default among patients assigned to the different specimen collection arms.

# Sites

- Brazil: Hospital General Otavio de Freitas, Recife. Government hospital.
- Ethiopia: Bushollo and Awassa Major Health Centres. Faith-based NGO and government.
- Nepal: Tribhuvan University Teaching Hospital. Kathmandu.
- Nigeria. Wuse General Hospital, Abuja. Government General Hospital.
- Yemen: National TB Institute, Sanaa.

Referral and self-presentation.

# Patients

- Consecutive patients
- $\geq 18$  years of age
- Cough  $\geq 2$  weeks
- Provides informed consent

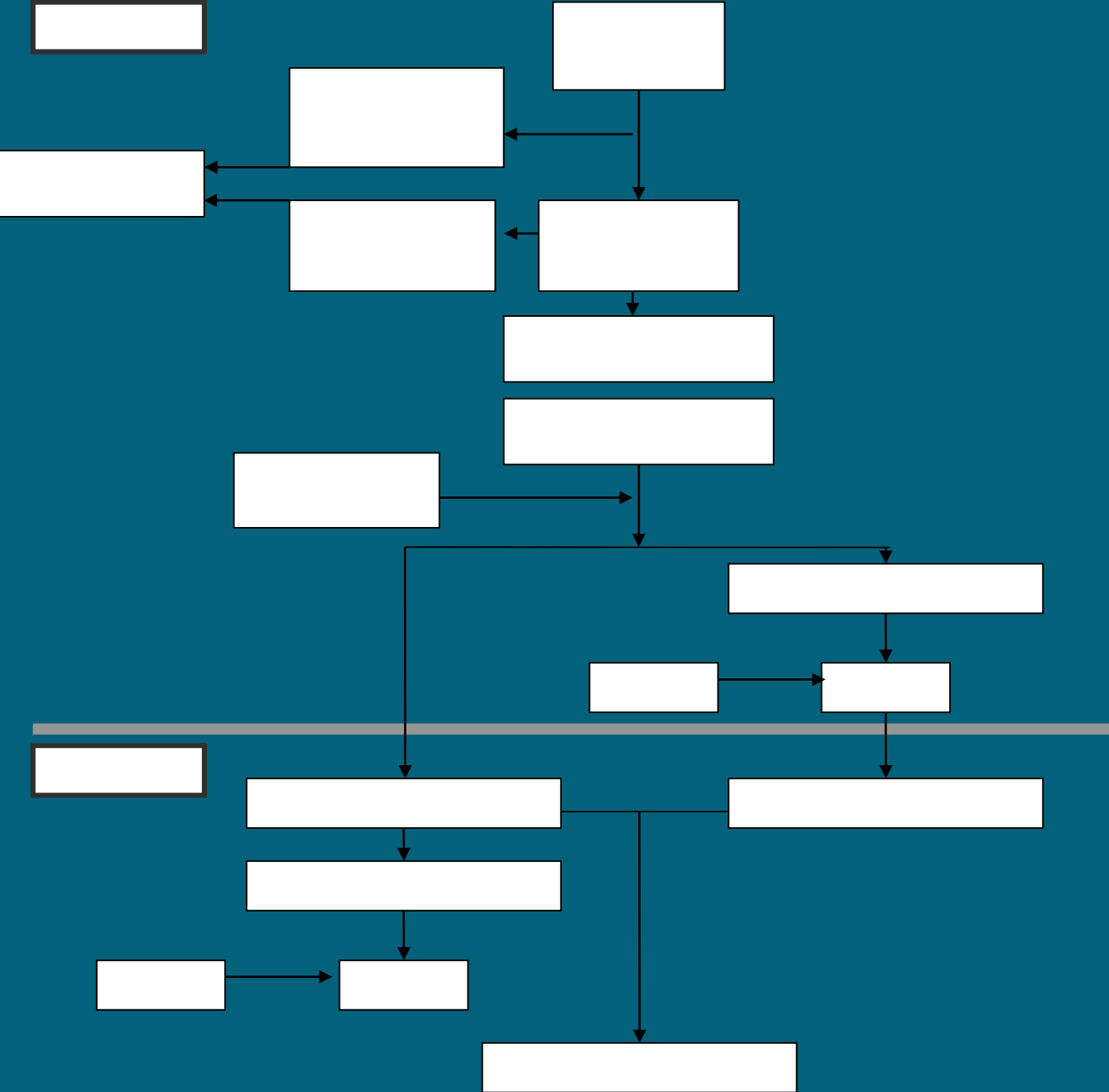
Rate of recruitment limited by ability  
to perform culture.

# Cluster-randomization

- Randomized by week (4 week block)
- Minitab Statistical Software – list of random numbers ranging from 1 – 5.
- AABB, ABAB, BABA, ABBA and BAAB.
- Sealed envelopes opened each week.
- Study coordinators unaware of block size.



Figure 1. Patient flowchart.



# Blinding

- All slides labeled with study and lab numbers.
- All slides identifiers masked with wrap-around tape and mixed (by coordinator) prior to microscopic examination.
- Microscopy result written on tape.
- Identifiers unmasked by a separate lab staff member when entering results in lab book

# Sample Size and Analysis

- Calculated to establish non-inferiority of frontloaded compared to standard
- Assumed Std Approach identifies 50% of patients with positive cultures
- Sample size of 1696 for each arm would achieve 90% power to detect a non-inferiority margin between the arms of 5%
- Significance level of the test targeted 0.05
- Assumption: 50% of patients will have +ve cultures
- No of patients to be recruited = 6,784 ( $1696 \times 2 \times 100 / 50$ )
- Analysis by ITT and PP (SMS vs SSM, subanalysis SM vs SS)

# Ethics and Standards

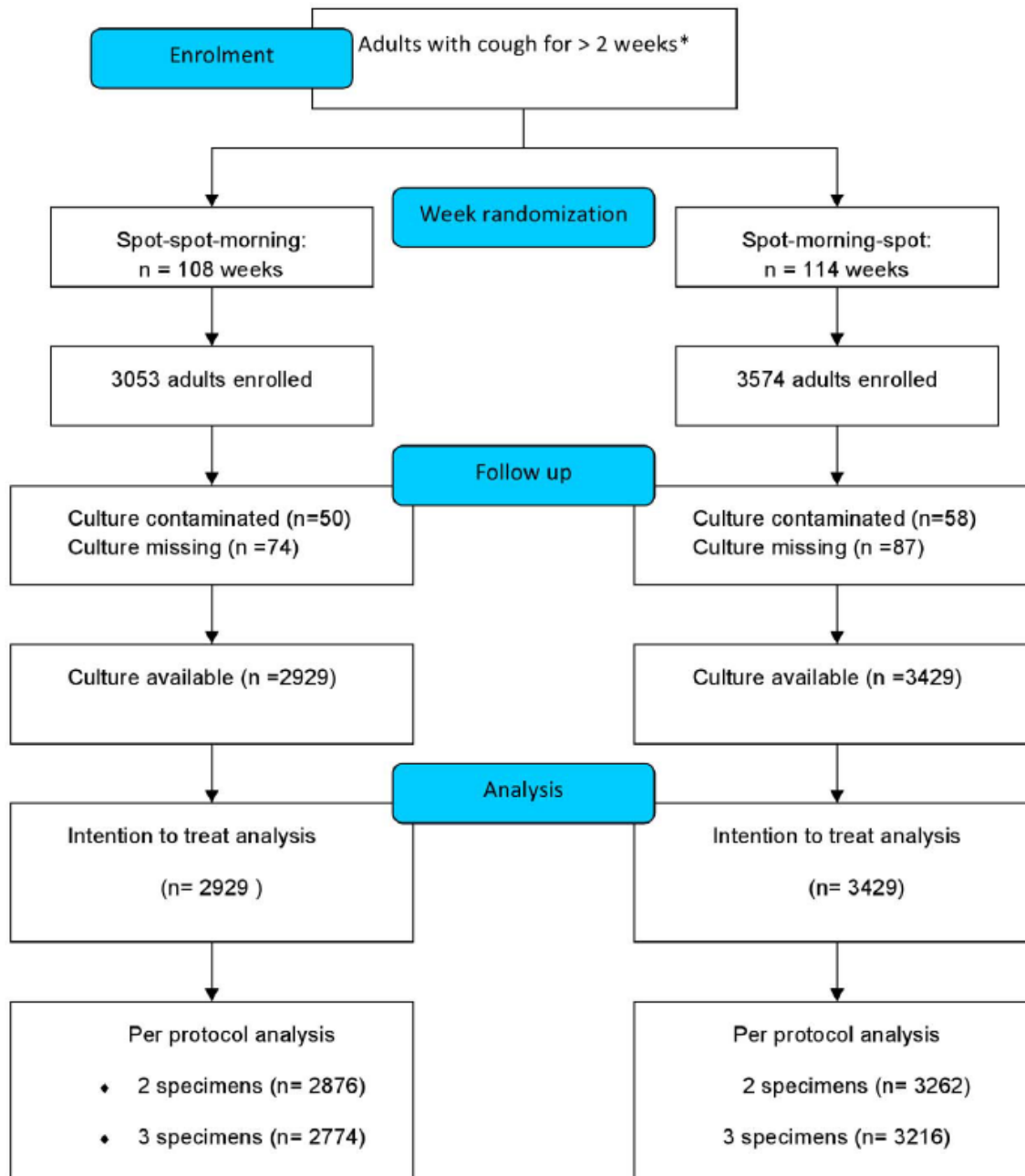
- Study approved by WHO Ethics Committee, LSTM Ethics Committee, national/institutional ERCs (as appropriate)
- Study registered with International Standard Randomized Controlled Trial Register.
- GCP
- GCLP

# Oversight

- Regular visits by LSTM and/or WHO TDR staff.

# Results

- 6,627 patients recruited
- 1,909 in Ethiopia, 630 in Nepal, 1,238 in Nigeria, 2,850 in Yemen.
- 3, 574 in Std App and 3,053 in frontloaded
- No statistically significant differences in the baseline characteristics of patients recruited in SMS vs SSM arms.



\*cough registers were not available.

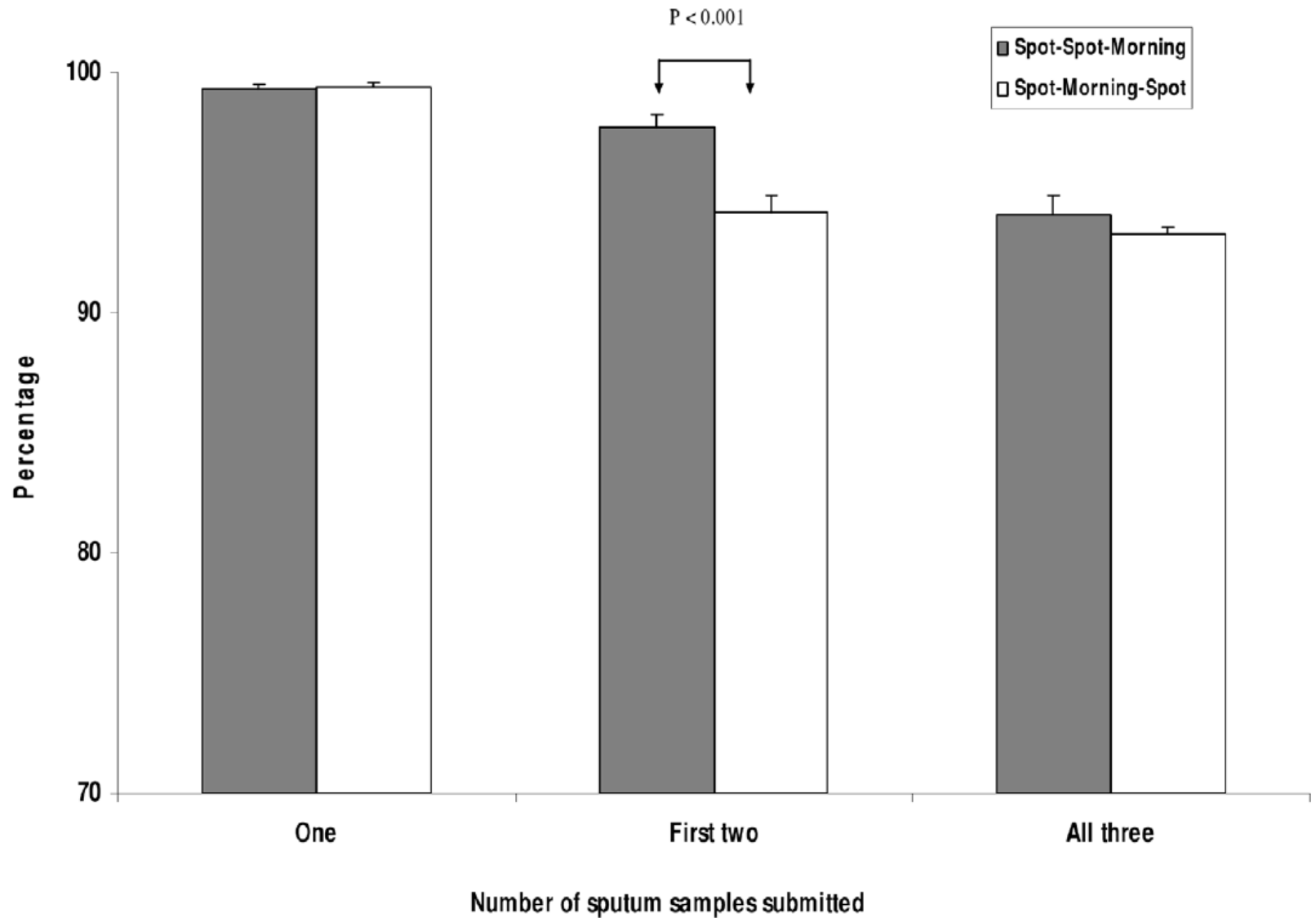
**Table 2.** Sensitivity and specificity of two and three smears, stratified by scheme by intention to treat and per protocol analysis.

Scheme	Smear Result <sup>a</sup>	Culture		Sensitivity (95% CI)	Specificity (95% CI)
		Positive	Negative		
<b>ITT</b>					
SS	Positive	453 (63.6)	57 (2.6)	63.6% (59.7%–67.5%)	97.4% (93.5%–99.9%)
	Negative	259 (36.4)	2,160 (97.4)		
SM	Positive	550 (64.8)	56 (2.2)	64.8% (61.3%–68.3%)	97.8% (94.3%–99.9%)
	Negative	299 (35.2)	2,524 (97.8)		
SSM	Positive	500 (70.2)	68 (3.1)	70.2% (66.5%–73.9%)	96.9% (93.2%–99.9%)
	Negative	212 (29.8)	2,149 (96.9)		
SMS	Positive	559 (65.8)	62 (2.4)	65.9% (62.3%–69.5%)	97.6% (94.0%–99.9%)
	Negative	290 (34.1)	2,518 (97.6)		
<b>PPA</b>					
SS	Positive	447 (63.6)	45 (2.4)	63.6% (59.6%–67.6%)	97.6% (93.6%–99.9%)
	Negative	256 (36.4)	2,121 (97.6)		
SM	Positive	535 (65.0)	54 (2.2)	65% (61.6%–68.4%)	97.8% (94.4%–99.9%)
	Negative	288 (35.0)	2,385 (97.8)		
SSM	Positive	485 (70.6)	63 (3.0)	70.6% (66.7%–74.5%)	97% (93.1%–99.9%)
	Negative	202 (29.4)	2,024 (97)		
SMS	Positive	542 (66.4)	60 (2.5)	66.4% (62.9%–69.9%)	97.5% (94.0%–99.9%)
	Negative	274 (33.6)	2,340 (97.5)		

<sup>a</sup>Smear-positive defined as having  $\geq 1$  smear with  $\geq 1$  AFB. Patients with missing smears were classified according to the smears available (e.g., a patient with first spot sample negative and morning sample missing was classified as negative) for ITT analysis.

doi:10.1371/journal.pmed.1000443.t002





**Figure 2. Number of patients submitting the first, the first two, and all three specimens, by scheme.** Error bars represent the upper limit of the 95% confidence limits.

doi:10.1371/journal.pmed.1000443.g002

# Findings

- Sensitivity and specificity of SSM were non-inferior to SMS
- Sensitivity and specificity of SS were also non-inferior to SM
- Patients screened using the SSM/SS scheme were more likely to submit two specimens.

Study was included in the systematic review

Would we do it this way again?

Should we do it this way again?

# Same-day light-emitting diode fluorescence microscopy for the diagnosis of tuberculosis in Chhattisgarh, India

**Authors:** Nayak, P.; Kumar, A. M. V.; Agrawal, T. K.; Chandraker, S.; Nair, S. A.

The International Journal of Tuberculosis and Lung Disease, Volume 18, Number 6, 1 June 2014, pp. 666-670(5)

## **SETTING:**

Three medical college hospitals using light-emitting diode fluorescence microscopy (LED-FM) for diagnosing tuberculosis (TB) in Chhattisgarh, India.

## **OBJECTIVES:**

To assess and compare the proportion of sputum smear-positive TB patients diagnosed through same-day microscopy (spot-spot) strategy or with the conventional (spot-morning) strategy.

## **METHODS:**

During November 2012 - March 2013, all consecutively enrolled presumptive TB patients (aged  $\geq 18$  years) were requested to provide three specimens: two spot specimens collected 1 h apart on the first day and one early morning specimen the next day; these were stained using auramine-O and examined using LED-FM.

- **RESULTS:**

Of 1716 (93% of total 1845) presumptive TB patients who provided all three specimens, 218 (13%) were smear-positive: 200 (11.7%) by same-day microscopy and 217 (12.7%) by the conventional method (McNemar's  $\chi^2$  13.5, df 1,  $P = 0.0002$ ). Eighteen (8.3%) cases were missed by the same-day method.

## **CONCLUSION:**

Although LED-FM is more sensitive to paucibacillary samples, 8% of smear-positive cases were missed using the same-day method. These findings indicate the need to revisit the global applicability of the current World Health Organization recommendation of switching to same-day diagnosis from the conventional policy.

# SO RT IT

*Improving health systems through research*

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International Union Against Tuberculosis and Lung Disease

*Health solutions for the poor*



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## REVIEW ARTICLE

# The Structured Operational Research and Training Initiative for public health programmes

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<http://dx.doi.org/10.5588/pha.14.0011>

Thank You

