



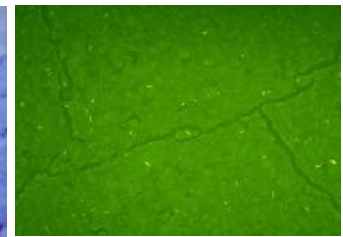
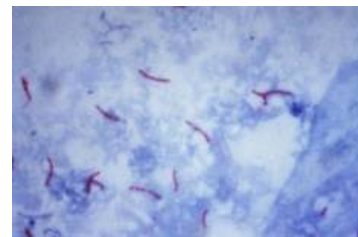
Novel Approaches and New Methods to Increase Case Detection by Microscopy

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Objectives

- Present “hot off the press” findings from 3 systematic reviews concerning sputum microscopy
- Summarize the findings of the reviews using the GRADE approach



Some definitions

- Systematic review is a review of a **clearly formulated question** that uses **systematic and explicit methods to identify, select, and critically appraise relevant research**, and to **collect and analyse data** from the studies that are included in the review.
- Meta-analysis is the use of **statistical techniques** in a **systematic review** to integrate the results of included studies.

Glossary of Terms, The Cochrane Collaboration, Version 4.2.5,
Updated May 2005

Systematic review questions

- Are **front-loaded** and standard microscopy strategies comparable for diagnosing pulmonary TB when 2 specimens are examined?
- What is the diagnostic accuracy of **LED fluorescence** microscopy for pulmonary TB and how does it compare to Ziehl-Neelsen and fluorescence microscopy?
 - What do users think?
- Does **bleach centrifugation** increase the diagnostic accuracy of sputum smear microscopy for pulmonary TB?

Why carry out these reviews?

- Direct smear microscopy
 - Most widely available test for TB diagnosis
 - Moderate to poor sensitivity
 - High drop-out rate
- Methods to optimize smear microscopy
 - Sputum processing
 - Fluorescence microscopy
 - Diagnostic test strategies
- High quality evidence is important for policy

Previous microscopy reviews

Review (Date of publication)	No. of studies	Median sample size	Principal findings
Sputum processing (2006)	83	256	↑ sensitivity (13%) with bleach centrifugation
Fluorescence microscopy (2006)	45	493	↑ sensitivity (10%) with fluorescence microscopy
Serial sputum examination (2007)	37	153	2-5% ↑ sensitivity with 3rd sputum specimen

What's new?

- New studies
- New technique
 - light emitting diode
- New diagnostic strategy
 - “front-loaded” microscopy
- New methods of data analysis and presentation

Standardized approach to systematic reviews of diagnostic accuracy

- Define review questions
- Identify and select studies
- **Assess study quality (QUADAS)**
- Extract, analyze, and present data
 - Graph results of individual studies
 - **Pooled estimates of sensitivity/specificity** by hierarchical summary ROC and bivariate random effects methods
 - Visualize and statistically assess heterogeneity
 - Explore reasons for heterogeneity
 - Forest plots, hierarchical summary ROC curves
- Interpret data

Leeflang et al on behalf of the Cochrane Diagnostic Test Accuracy Working Group.
Ann Intern Med. 2008;149:889-897



Quality assessment of diagnostic accuracy studies (QUADAS)

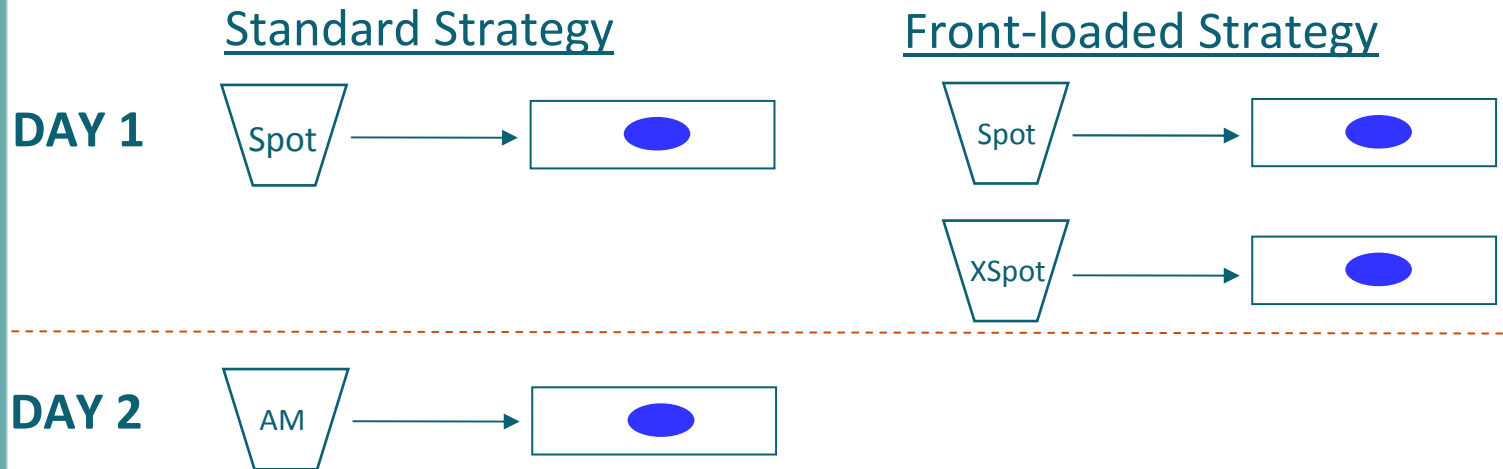
- Asks reviewers to assess 14 items
- Scores each item as ‘yes’, ‘no’, or ‘unclear’
 - Patient spectrum
 - Selection criteria
 - Appropriate reference test
 - Time between tests
 - Partial verification
 - Differential verification
 - Incorporation bias
 - Index test described
 - Reference test described
 - **Index test blinded**
 - **Reference test blinded**
 - Relevant data available
 - Indeterminate results
 - Study withdrawals

Whiting P, BMC Med Res Methodol, 3:25 (2003)

Systematic review questions

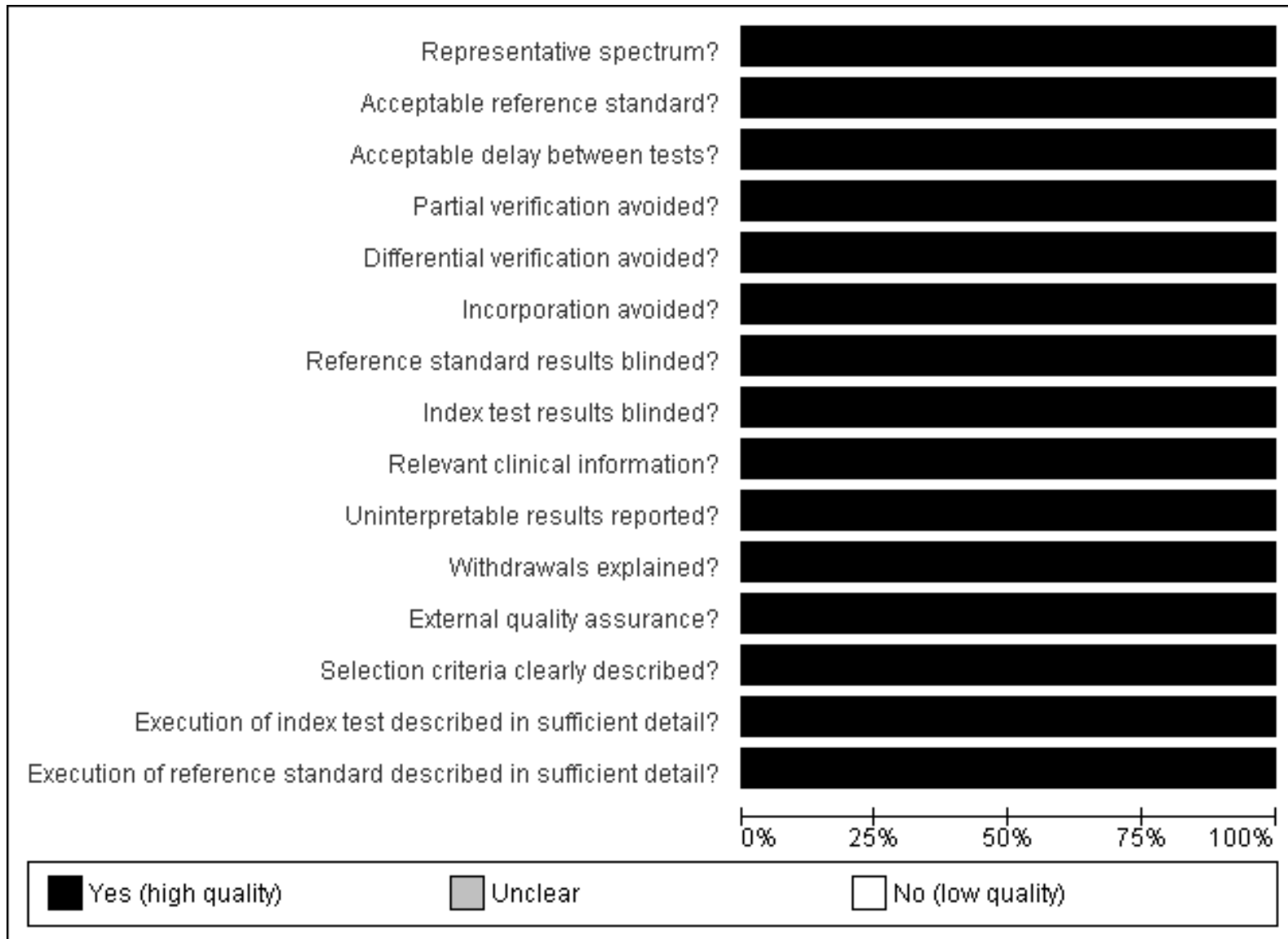
- **Are front-loaded and standard microscopy strategies comparable for diagnosing pulmonary TB when 2 specimens are examined?**
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Sputum collection

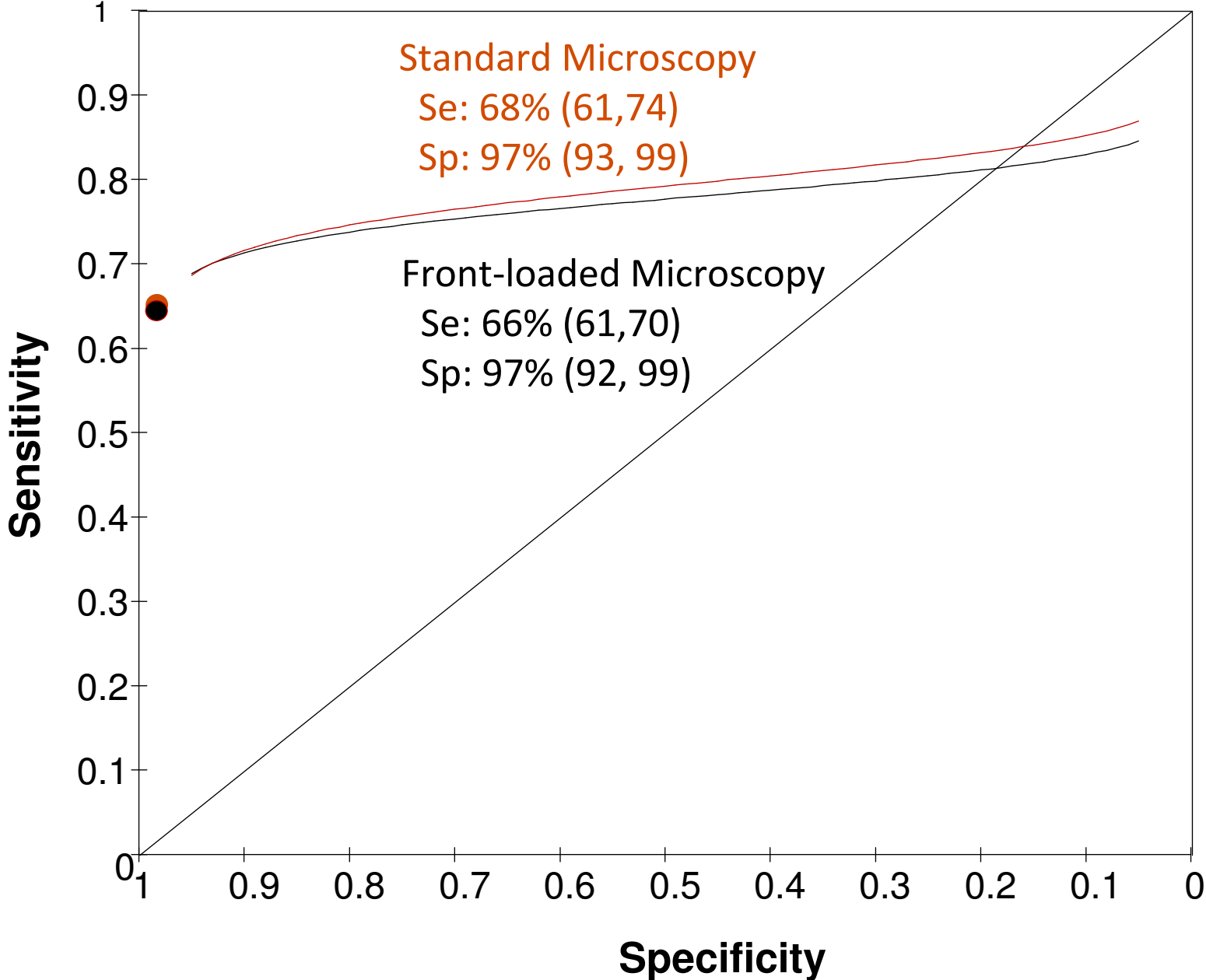


Smear preparation: Direct
Stain: Ziehl-Neelsen
Type of microscopy : Light
Reference standard: Culture

QUALITY ASSESSMENT (QUADAS)



HSROC curves



Systematic review questions

- Are front-loaded and standard microscopy strategies comparable for diagnosing pulmonary TB when 2 specimens are examined?
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 - **What do users think?**
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Light Emitting Diode (LED) microscopy

Fluorescence microscopy has been shown to be more sensitive than ZN and more time efficient

LED fluorescence microscopy uses ultra bright LED bulbs

- Less expensive
- Require less power (run on batteries)
- Very long half-life
- Lower maintenance
- No toxic components
- No UV production
- Perform equally well without a darkroom

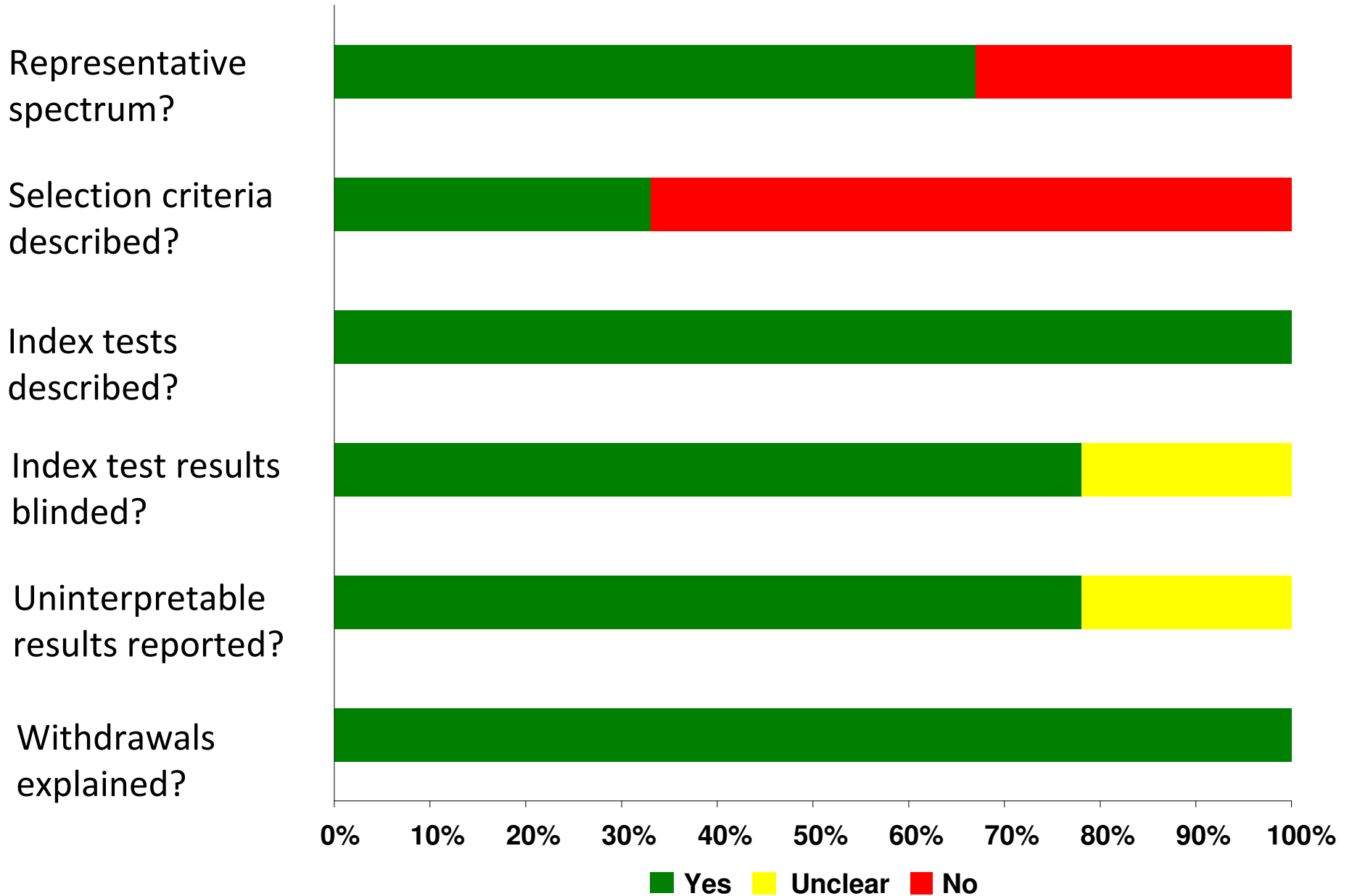
LED fluorescence diagnostic accuracy

- **Sensitivity 84% (76, 89); specificity 98% (97,99)**
- **Head-to head LED versus ZN**
 - 6% (0.1, 13) greater sensitivity, comparable specificity (8 studies)
 - 46% *less* time to examine smears (14 comparisons)
- **Head-to head LED versus conventional fluorescence**
 - 5% (95% CI 0, 11) greater sensitivity, comparable specificity (7 studies)
 - same time to examine smears (7 comparisons)
- **94-100% of users would recommend implementing an LED system over ZN (FIND)**

Systematic review questions

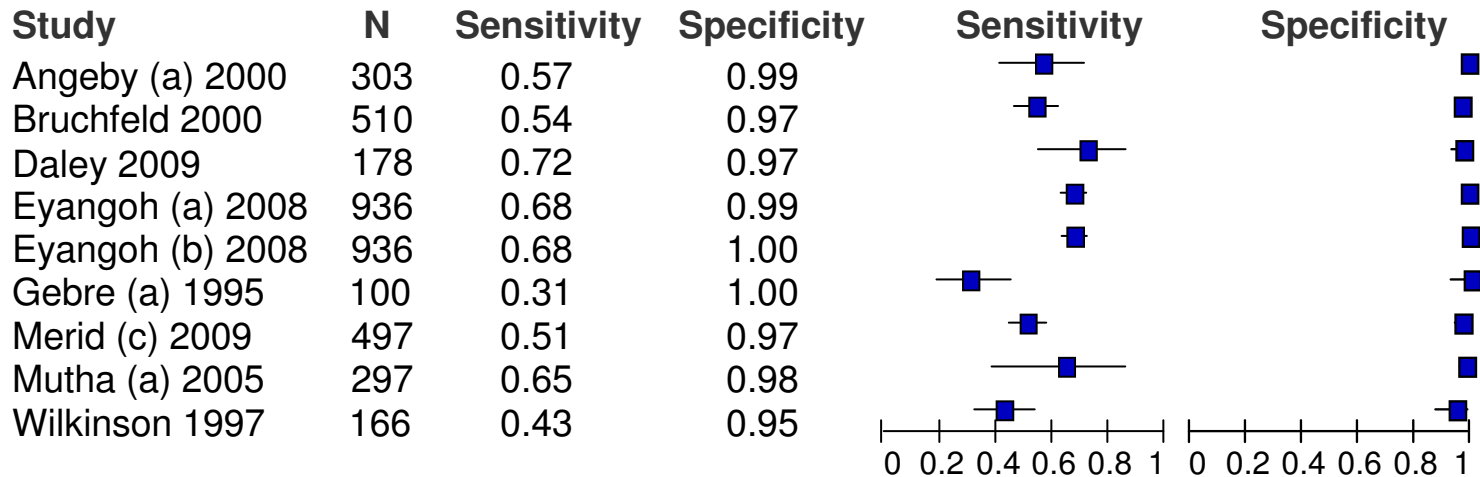
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QUALITY ASSESSMENT (QUADAS)

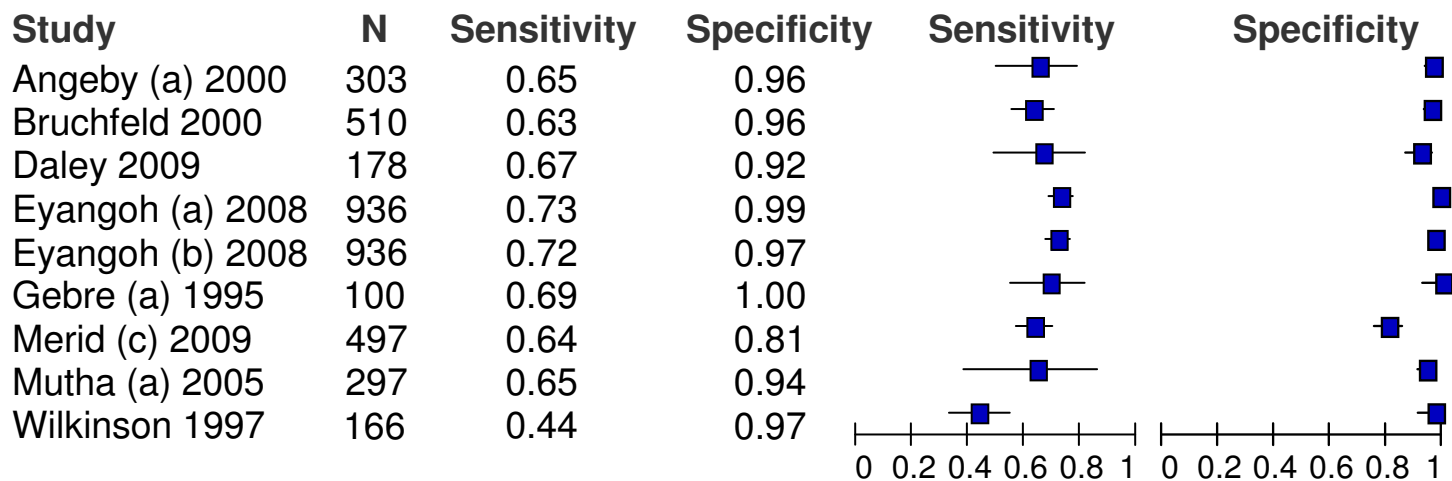


Forest plots, bleach centrifugation, culture reference

Direct microscopy

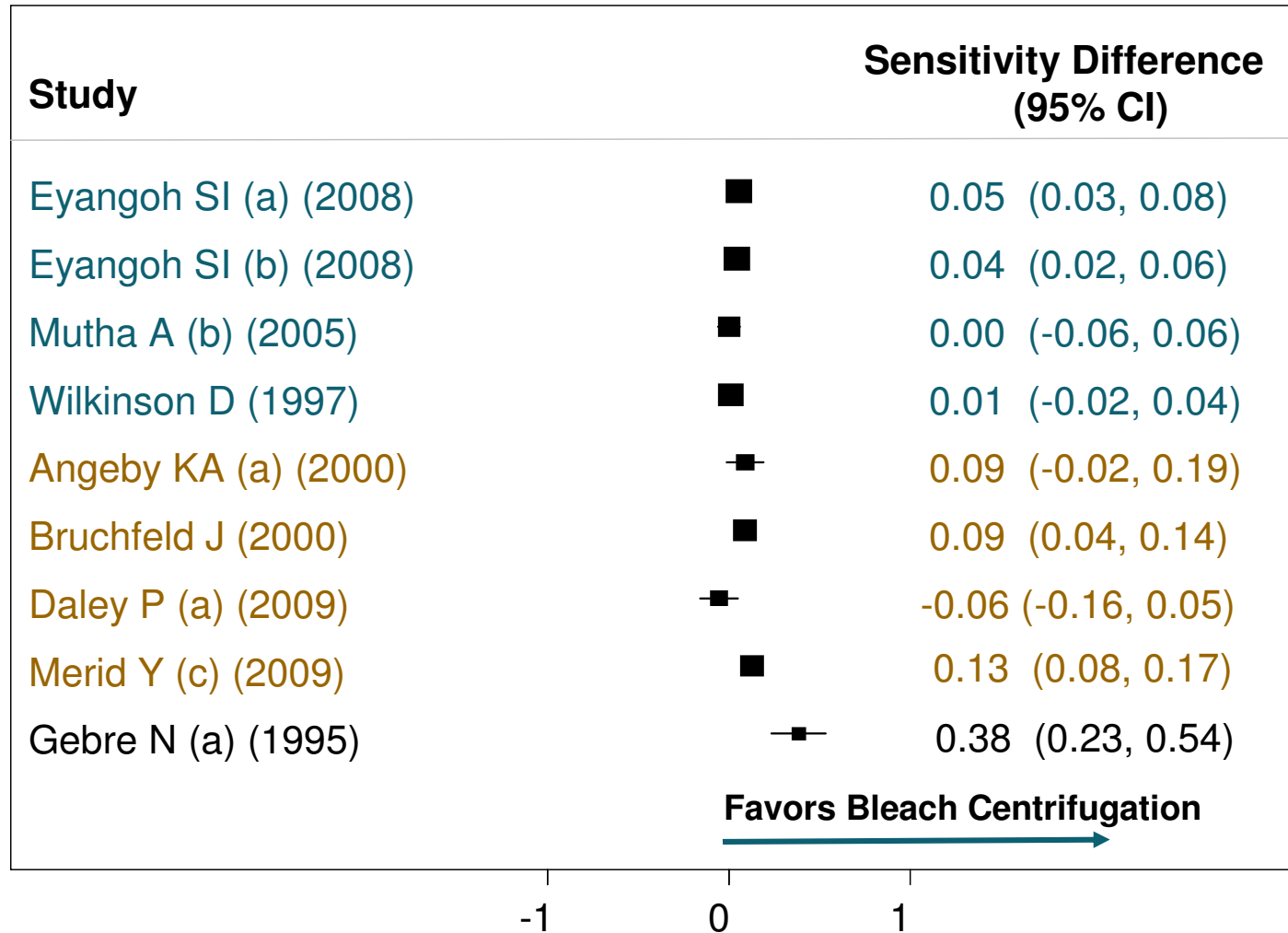


Bleach centrifugation



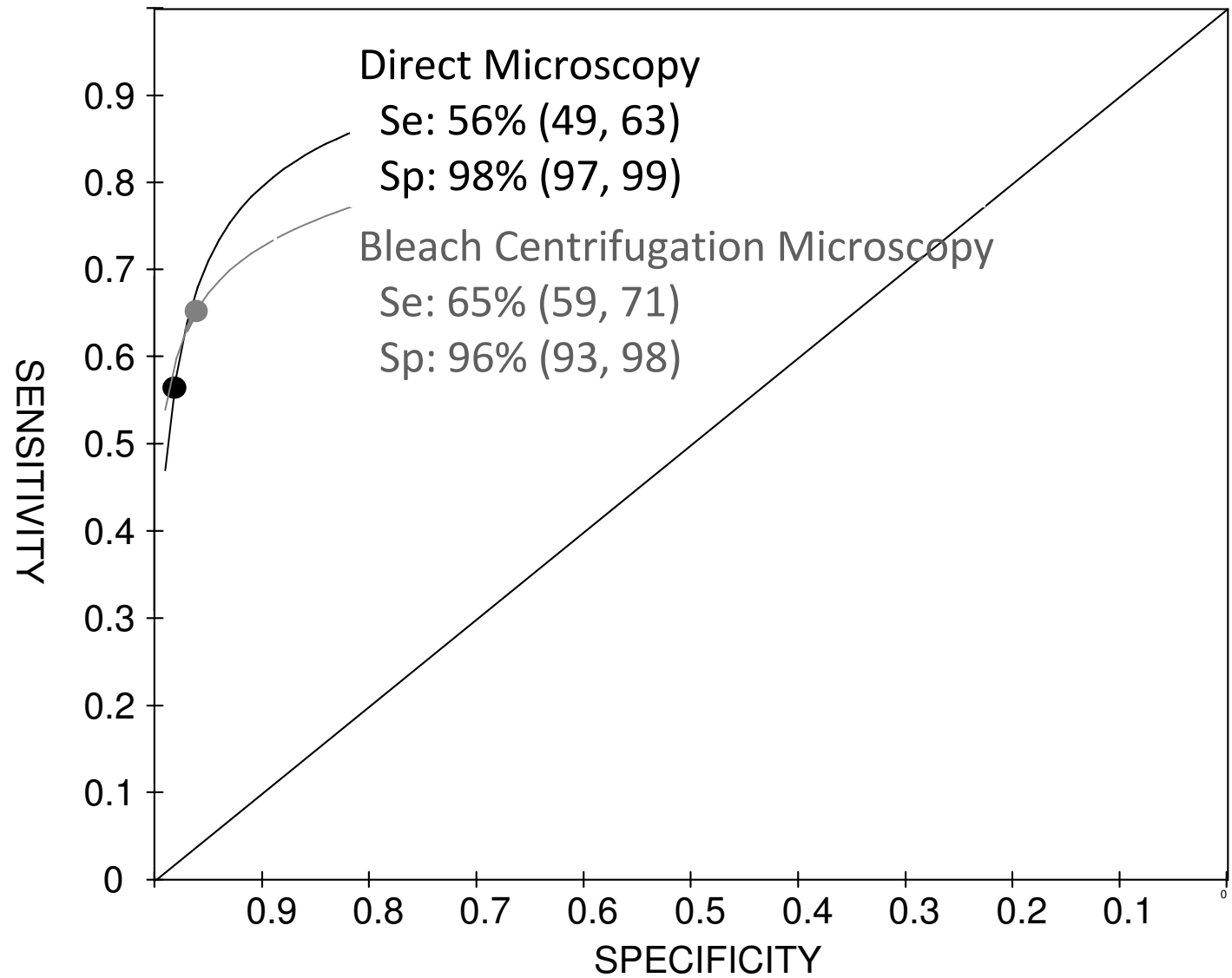


Forest Plot: Sensitivity Difference





HSROC curves





Strengths and limitations

- **Strengths**

- Standardized systematic review protocol
- Comprehensive search strategy
- Rigorous data analysis methods

- **Limitations**

- Variability in diagnostic accuracy estimates for sputum processing
- Limited data in HIV-infected patients



Concerns

- **Front-loaded**
 - risk of TB transmission in health care settings
 - loss of morning specimen for culture
- **LED versus conventional fluorescence**
 - increased cost of EQA because of fading of slides
- **Sputum processing**
 - primary analysis presented included only studies with culture reference



Arriving at a Recommendation





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San Francisco



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The Grading of Recommendations Assessment, Development and Evaluation - GRADE

“The GRADE approach provides a system for rating quality of evidence and strength of recommendations that is explicit, comprehensive, transparent, and pragmatic and is increasingly being adopted by organisations worldwide.”

www.gradeworkinggroup.org

The screenshot shows the homepage of the GRADE working group website. At the top, there is a blue header with the text "GRADE working group". Below the header is a navigation menu with links for Home, Introduction, Toolbox, Publications, Member login, Links, and Contact. The main content area is divided into two columns. The left column contains a sidebar with links for Learn more, FAQ, Organizations, Downloads, Courses, and About us. Below these links are sections for "What's new" and "Announcements". The "What's new" section lists "GRADEpro available now" and "New GRADE publication in BMJ". The "Announcements" section lists "More and more organizations chose GRADE". The right column features a large red "GRADE" logo and a "Welcome" section. The "Welcome" section contains a paragraph of text describing the working group's mission and a link to "learn more". At the bottom of the page, there are language selection options for español, français, deutsch, italiano, and polski, followed by a footer with links for About Us, Members, and Contact Us, and a copyright notice for 2005-2009.



GRADE and Patient-Important Outcomes

	With TB	Without TB
Test positive	True Positive TP	False Positive FP
Test negative	False Negative FN	True Negative TN

TP - benefit from earlier diagnosis and treatment

TN - spare patients unnecessary treatment

FP - likely anxiety, possible morbidity from additional testing and treatment; may halt further diagnostic evaluation

FN - increased risk of severe disease from delayed diagnosis; continued TB transmission in the community

GRADE Summary of Findings - Microscopy

Review Question (studies, participants)	Absolute Difference per 1000 persons (Prevalence 20%)				Quality of Evidence
	TP	TN	FP	FN	
Standard versus two-specimen front-loaded (7, 7308)	2	0	0	-2	Moderate
LED versus ZN light (8, 20155)	16	0	0	-16	Moderate
Bleach centrifugation versus direct (9, 3923)	18	-16	16	-18	Very Low

Acknowledgments

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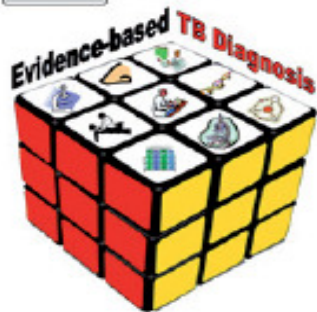
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Merci!

