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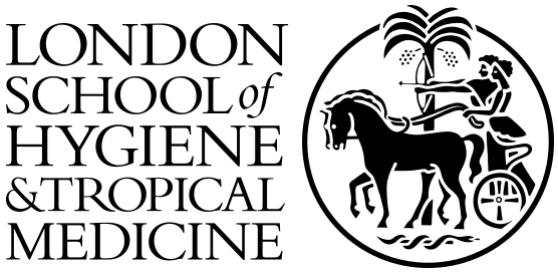

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Article type: systematic review

Running title: Quality improvement in TB laboratories

Title: Impact of quality improvement in TB laboratories in low and lower-middle income countries: a systematic review

Authors: Ioana D Olaru[1,2*], Heidi Albert[3], Julia Zallet[4], Ulf-Eike Werner[4], Nada Ahmed[5], Hans L. Rieder[6], Max Salfinger[7], Katharina Kranzer[4,8]

1. Division of Clinical Infectious Diseases, Research Center Borstel, Borstel, Germany

2. Department of Clinical Microbiology, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom

3. Foundation for Innovative New Diagnostics (FIND), Waverley Business Park 17-107, Wyecroft Road, Mowbray, Cape Town, South Africa

4. National Mycobacterium Reference Laboratory, Research Center Borstel, Borstel, Germany

5. Centre for Clinical Microbiology, University College London, London, United Kingdom

6. Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Switzerland and Tuberculosis Consultant Services, Kirchlindach, Switzerland

7. Mycobacteriology and Pharmacokinetics Laboratory and Department of Medicine, National Jewish Health, Denver, Colorado, USA

8. London School of Hygiene and Tropical Medicine, London, United Kingdom

***Correspondence:** Ioana D. Olaru, Dept. of Clinical Microbiology, University Hospitals of Leicester NHS Trust, Infirmary Square, LE1 5WW, Leicester, United Kingdom; e-mail: ioanad_olaru@yahoo.co.uk

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References: 38

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Summary

Objective:

The effect of quality improvement measures on performance of diagnostic tuberculosis laboratories in low- and lower-middle income countries is currently unknown and is the subject of this review.

Methods:

Three databases were searched for quality improvement studies presenting data on performance parameters before and after the implementation of quality improvement interventions.

Results:

A total of 21 studies were included in this review. Quality improvement measures were most frequently implemented by an external organization; settings targeted ranged from microscopy centers, hospitals, districts, regional and national reference laboratories. Quality improvement interventions and outcome measurements were highly heterogeneous. Most studies investigated interventions aimed at improving smear microscopy (n=17). Two studies evaluated comprehensive quality improvement measures (n=2) and another three studies focused on mycobacterial culture and drug susceptibility testing. Most studies showed an improvement in outcomes measured in a before-after or time trend analysis.

Conclusion:

Quality improvement measures implemented in tuberculosis laboratories showed a positive impact on various outcomes. Due to high heterogeneity of outcome reporting and interventions and the low quality of studies the effect size is unclear. Identification of standardized quality indicators and their link to quality of patient care would improve knowledge in this field.

Introduction

Worldwide, an estimated 10.4 million new tuberculosis cases occurred in 2015; a third remained undiagnosed.[1] Accurate, rapid diagnosis is critical for timely initiation of treatment and, ultimately, disease control. Today quality assurance (QA) is an essential for the diagnostic process. It comprises activities that enable the achievement and maintenance of high levels of proficiency and accuracy in laboratory testing[2] and includes staff training, quality control (QC), external and internal quality assessment (EQA and IQA) of laboratory proficiency, quality performance indicator monitoring and continuous quality improvement. Continuous quality improvement is a comprehensive management philosophy which employs scientific methods to increase knowledge and control on work processes variability[3] with the goal of customer satisfaction. EQA and IQA comprise systems aiming to continuously improve reliability and efficiency of laboratory processes.[4] Generally QA is the process of managing for quality, a strategy of prevention with focus on planning and documenting. QC on the other side is aimed at verifying the quality of the output, a strategy of detection including all activities designed to determine the level of quality. All these elements are managed by the quality management system (QMS) that documents processes, procedures and responsibilities for achieving quality policies and objectives that is critical for guiding laboratories towards international accreditation.[5]

In 2008, the need to expand and strengthen laboratory capacity was acknowledged by the World Health Organization (WHO) together with multiple international partners.[6] This was swiftly followed by Strengthening Laboratory Management Toward Accreditation (SLMTA) launched in 2009.[7-9] SLMTA is a large-scale effort aimed at improving the quality of laboratory services and patient care in resource-limited settings by developing a cadre of competent laboratory

managers. The program seeks to engage laboratories in continuous quality improvement and accelerate their preparations toward accreditation to international standards. WHO has also developed a framework for targets and indicators for laboratory strengthening as part of the "End TB Strategy", which includes indicators for EQA and implementation of QMS.[10] Although there has been progress towards the implementation of QMS in the African Region, more than 90% of National Tuberculosis Reference Laboratories (NRLs) are not yet accredited.[11]

However, whether quality improvement measures impact on quality outputs of tuberculosis laboratories in low- and lower-middle income countries[12] is currently unknown and subject of this review.

Methods

Studies were selected if they were conducted in tuberculosis laboratories or microscopy centers from low- and lower-middle income countries[12] and evaluated the implementation of QMS, their components, or more general interventions (such as training, competency checks, EQA with feed-back loops, etc.) using a comparator (either the same laboratory in a before/after comparison or other laboratories). Outcomes were extracted as defined by the authors.

MEDLINE, EMBASE and Web of Science were searched up to the 27th week of 2017 using a compound search strategy (Table S2). The results were cross-referenced with the list of low and lower-middle income countries from the World Bank from 2016.[12] No language restriction was applied.

Articles identified were imported in the bibliographic software manager EndNote^{TM} X7. Titles and abstracts were then screened for eligibility by KK and IDO. Full texts of eligible articles were retrieved and eligibility criteria applied (KK and IDO). Due to the variability in

intervention and outcomes a narrative approach was taken. Data extraction was performed using standardized tables. Quality was assessed using a modified Newcastle Ottawa scale (Table S3).[13] Meta-analysis was deemed inappropriate due to the heterogeneity in interventions and outcome measurements. Ethics approval was not required.

Results

Characteristics of the identified studies

971 unique citations were identified and screened, 78 were selected for full-text review and 21 were retained for further analysis (Figure 1). The majority of studies were conducted in India (n=5)[14-18] and Ethiopia (n=4),[19-22] the remaining were from the Democratic Republic of the Congo,[23] Ghana,[24] Kenya,[25] Malawi,[26] Mozambique,[27] Nigeria (n=2),[28, 29] Sierra-Leone,[30] and Uganda (n=2) (Table 2).[31, 32] Two studies reported data from multiple countries including 48 African countries[33] and 7 countries and regions from Europe, Africa, and the Middle East.[34] The number of participating laboratories ranged from one to 956.

Settings ranged from microscopy centers, hospitals, district, regional laboratories and NRLs. The implementing agency in most studies was an external organization, usually the national or regional reference laboratory. International partner organizations were often involved and supported the national implementing authority[21, 25, 27, 31] or were the sole implementers.[19] Three studies described quality improvement interventions implemented by laboratories themselves.[25, 26, 32] Two multisite, multinational studies investigated the effect of EQA schemes with feedback loops and troubleshooting on subsequent EQA results. Participants were NRLS and research laboratories.[33, 34]

Quality improvement interventions consisted of EQA schemes with feedback loops, supervisory visits conducted by an external agency, implementation of internal quality assurance (IQA), development of standard operating procedures (SOPs) and staff training. EQA comprised the evaluation of a lower-level laboratory or microscopy center by a higher-level laboratory (usually a regional, national or international organization), while IQA consisted of self-implemented measures within the laboratory with the aim of improving performance. In most studies, laboratories underwent repeated rounds of assessment at regular time intervals. Three studies presented laboratory assessment data obtained before and after implementation of interventions and comprised two evaluation rounds only.[14, 23, 27] The following indicators were reported: checklist or questionnaires scores across different dimensions, quality of AFB smears (preparation and staining), number and type of smear reading errors (high- or low-grade),[4] smear result concordance between observers (Table 2). Other reported indicators included culture contamination rates, proficiency of drug susceptibility testing (DST), and consumables wasted.

Interventions targeting microscopy

The majority of studies investigated interventions aimed at improving AFB smear microscopy (n=17) with EQA schemes featuring as the most frequent intervention.[14-16, 18-24, 26, 28-33] Slide panels were provided to laboratories as part of microscopy EQA or randomly selected slides were blindly rechecked. Slide panels sent by the higher-tier laboratories to the lower-tier facilities aimed to evaluate staining techniques and reading performance. Random blinded-rechecking of slides involved sending a proportion of slides from the lower-tier facility to the higher-tier laboratory to investigate slide preparation and staining techniques as well as reading performance. Reading errors were defined as false positive, false negative and quantification

errors. Smear quality was assessed across the following categories: staining, cleanliness, thickness, size and evenness. Most studies 10/17 reported an improvement in performance,[14, 15, 19-22, 24, 26, 28, 32] while the rest showed either no change or the results were difficult to interpret due to variability.[16, 18, 23, 29-31, 33] Although difficult to assess, studies of interventions showing no improvement had infrequent evaluation visits[23], did not provide timely feed-back[30], or were implemented in laboratories with a good baseline performance.[18, 33]

Three studies evaluated the impact of panel testing EQA schemes. Panels of 5-100 stained or unstained slides were provided[14, 16, 29, 33] and the proportion of errors made were fed back to participating laboratories. One study showed an improvement with no errors rated as "high-grade" and a decrease in the number of "low-grade" errors following two rounds of EQA.[14] A multi-country study evaluating the laboratory performance for a wide range of infectious diseases including TB showed stable high overall scores for AFB smear microscopy across all settings.[33] Variable performance across laboratories and times was observed in a study from India without any clear effect or trend.[16] Another study from Nigeria showed an initial increase in performance followed by a subsequent decrease but the number of slides sent for panel testing was very small.[29] A study conducted in a newly established research biosafety level 3 research laboratory showed overall excellent performance for microscopy while participating in two different EQA schemes.[32]

Nine studies provided data investigating the effect of random blinded rechecking of microscopy slides. At baseline, the proportion of false positive (0.1%-19%) and false negative errors (0%-21%) varied widely across studies. Post intervention, the proportion of false positive and false negative errors ranged between 0% to 1.8% and 0% to 3.6%. Six of the nine studies reported an overall improvement with a decrease in the proportion of false positives [15, 20, 21, 24, 28] and false

negatives.[20, 21, 24] Other studies reported a decrease in major errors[15], an increase in laboratories without any errors[21] and increased concordance between laboratory staff and supervisors performing the rechecking was reported.[22, 28] Two studies conducted in India and Nigeria showed a non-significant increase in the proportion of false negative errors.[15, 28] Three studies failed to show any impact.[18, 23, 30] Those studies were conducted in India, Sierra-Leone and the Democratic Republic of Congo and performed 2-12 rounds of random blinded rechecking.

Six studies reported on the effects of random blinded rechecking or slide reevaluation within an EQA scheme on the quality of AFB smear preparation and staining.[21, 22, 24, 26, 28, 30] Quality of staining improved in five studies[21, 22, 24, 26, 28] with 10-20% improvement on quantifiable effect.[21, 24, 28] One study from Sierra-Leone failed to show improvement in AFB smear quality, staining and reading. However, there was delayed feedback of findings to the submitting laboratory. These results lead to on-site training of staff.[30]

Interventions targeting culture and antimicrobial susceptibility testing

A study from Kenya conducted in a district laboratory reported on the implementation of quality improvement measures initiated by the laboratory management aiming for accreditation. Analytical SOPs, laboratory policies and a quality manual were developed. Regular analyses of quality indicators such as contamination frequency were implemented and optimization of processes was initiated when required. Culture contamination decreased from 15.4% to 5.3% on solid media and 15.2% to 9.3% in liquid media. External support was provided for conducting quality audits, implementing the QMS and gaining accreditation.[25]

A study conducted by the Italian supranational reference laboratory reported the impact of four rounds of EQA for phenotypic DST involving two low-income countries in Africa and several

laboratories in Europe. Following the first round of EQAs, the results were discussed with the national reference laboratories. Expert support was provided both remotely and on-site, if required, to struggling laboratories aimed to address shortcomings and improving performance. During subsequent EQA rounds, improvement across all performance parameters including efficiency and reproducibility was recorded.[34] Another study from Uganda periodically reviewed culture contamination rates and implemented corrective measures when targets were not attained. Additionally, the center participated in EQA schemes for mycobacterial identification and DST.[32]

Comprehensive quality improvement interventions

Studies implementing comprehensive quality improvement measures included on-site evaluations as part of EQA schemes, supervisory visits, staff training and development and implementation of SOPs and electronic inventories. Eight studies described on-site evaluation of laboratories assessing equipment, consumables, procedures, and levels of staff training.[14, 17, 19, 21, 23, 24, 27, 31] Results of evaluation visits were systematically reported back. Additionally, laboratories were supported to address shortcomings. Site visits were documented using standardized checklists and questionnaires in six studies.[14, 17, 19, 23, 27, 31] One study assessed the extent and accuracy of data documentation during site vists[24], while one study assessed the levels of theoretical and practical knowledge of staff.[23] All studies reported improvement in the checklist scores, decreased number of recommendations made over time and enhanced documentation practices.[14, 17, 19, 24, 27, 31] One study implemented an electronic inventory system to enable real-time control of stock, facilitate procurement and check product expiry dates.[25] This decreased expenses due to product expiry from 6% to 1%. Another study reported on the

implementation of a QMS at the NRL. The interventions comprised intensive staff training and mentoring to strengthen local capacity building. The SLIPTA checklist comprising over 250 items was used for outcome assessment.[35] The interventions led to a significant increase in checklist scores and from zero to a three-star rating.[27] Two studies conducted site visits, but did not report findings.[21, 23]

Quality of included studies

Nine studies were marked as moderate quality and twelve studies as low quality (Table 3). This was mostly due to the study design, lack of evaluation of secular trends, relatively short follow-up time in some studies and uncertainties concerning completeness of follow-up data.

Discussion

The results of this review suggest a measurable impact of quality improvement measures across different settings, analytic processes and interventions in tuberculosis laboratories in low- and lower-middle income countries. Unfortunately, results do not allow firm conclusions regarding effectiveness of specific interventions as both interventions and outcome measures were highly heterogeneous. Furthermore, only one study evaluated the effect of implementing a multicomponent QMS eventually resulting in accreditation of the laboratory.[25] The majority of studies evaluated a single component of a QMS, most frequently EQAs[15-18, 20, 22, 28-30, 33, 34] or aimed at improving a specific process for example documentation.[24] Additionally, the feedback following evaluation and the corrective measures were poorly described.

The SLMTA program was recently introduced with the scope of improving quality in laboratories in low-resource settings ultimately aiming to facilitate laboratory accreditation. In a

study including more than 600 laboratories across 47 countries in Africa, Asia, the Americas, SLMTA led to a substantial increase in laboratory performance and quality measured by a standardized checklist score. Although, this program was not specifically targeted at tuberculosis laboratories, it shows that training and mentoring of laboratory managers is highly effective in improving quality. In spite of these encouraging findings, only a small fraction of less than 1% of participating laboratories completed accreditation.[36] Unfortunately, laboratories in countries with high prevalence of multi-drug resistant (MDR)-tuberculosis such as some countries in Central-Asian were not included. Tuberculosis laboratories are key to MDR-tuberculosis diagnosis and treatment as results of first and second line DST are vital in guiding MDR-tuberculosis treatment. Therefore, TB laboratories in high MDR-tuberculosis-burden countries should be a priority for quality improvement.

Until recently AFB smear microscopy was the main tuberculosis diagnostic in low- and lower-middle income countries. Thus, quality improvement has largely focused on microscopy. National EQA schemes for microscopy as recommended by WHO[37] have been rolled out across many countries. It is therefore not surprising that the majority of studies included in this review investigated the effect of microscopy EQA schemes. Reassuringly these schemes had a positive effect. However, more comprehensive quality improvement measures are needed if broader culture and molecular diagnostic coverage is to succeed at least in regions with high MDR-tuberculosis prevalence, ultimately aiming to attain the indicators for laboratory strengthening proposed by the WHO.[10] This could include comprehensive interventions targeted at analytic tests other than microscopy, such as mycobacterial culture, drug susceptibility testing and molecular techniques. In addition, rather than focusing on individual diagnostic assays,

introduction of a quality management system which also manages areas such as staff, safety, procurement, pre- and post-analytic processes to name a few should be the ultimate aim.

The review highlights high heterogeneity of outcome measures. Ideally, outcome measures should be standardized to enable comparison across studies. The SLMTA checklist score provides such a standardized tool. However, completing the comprehensive checklist is time-consuming and requires expertise. This might impede its widespread use in future studies. A simpler and user-friendlier tool might be more appropriate. Alternatively, independent external assessors trained in tuberculosis diagnostics, QMS and ISO 15189 and 17043 standards should be considered to assess outcomes comprehensively. Other important outcome measures and quality performance indicators such as turn-around times, service interruptions, specimen rejection rates, QC results, cost-effectiveness and laboratory staff productivity[5] were not reported in any of the studies included in this review. Furthermore, the cost-effectiveness of implementing the additional step for attaining accreditation needs to be investigated. Additionally, standardized reporting on results of quality improvement projects should be attempted.[38]

The strengths of this review are its comprehensive search strategy across multiple databases and inclusion of all studies irrespective of language or year of publication. This review is limited by the small number of countries included. No studies from the Americas or Asia (except for India) could be identified. The large heterogeneity in interventions and outcomes prohibited comparisons across studies and meta-analysis. All studies had a before-and-after design. No study was identified using more stringent study designs such as quasi-experimental studies or cluster randomized controlled trials. Outcomes were often poorly defined and the quality of most studies was rated low.

In summary, this review shows that implementation of quality improvement measures in tuberculosis laboratories in low resources settings improves laboratory performance. Firm conclusions with regards to the effect size and the most important aspects of the interventions cannot be drawn due to high heterogeneity of outcomes and interventions and the overall low quality of studies. Recently, there have been extensive investments in laboratory QMS. This should be accompanied by research to investigate the impact of QMS interventions and their cost-effectiveness. Rather than performing before-after studies at one site, a multi-site cluster randomized trials design should be adopted.

Competing interests - The authors have no conflicts of interests to declare.

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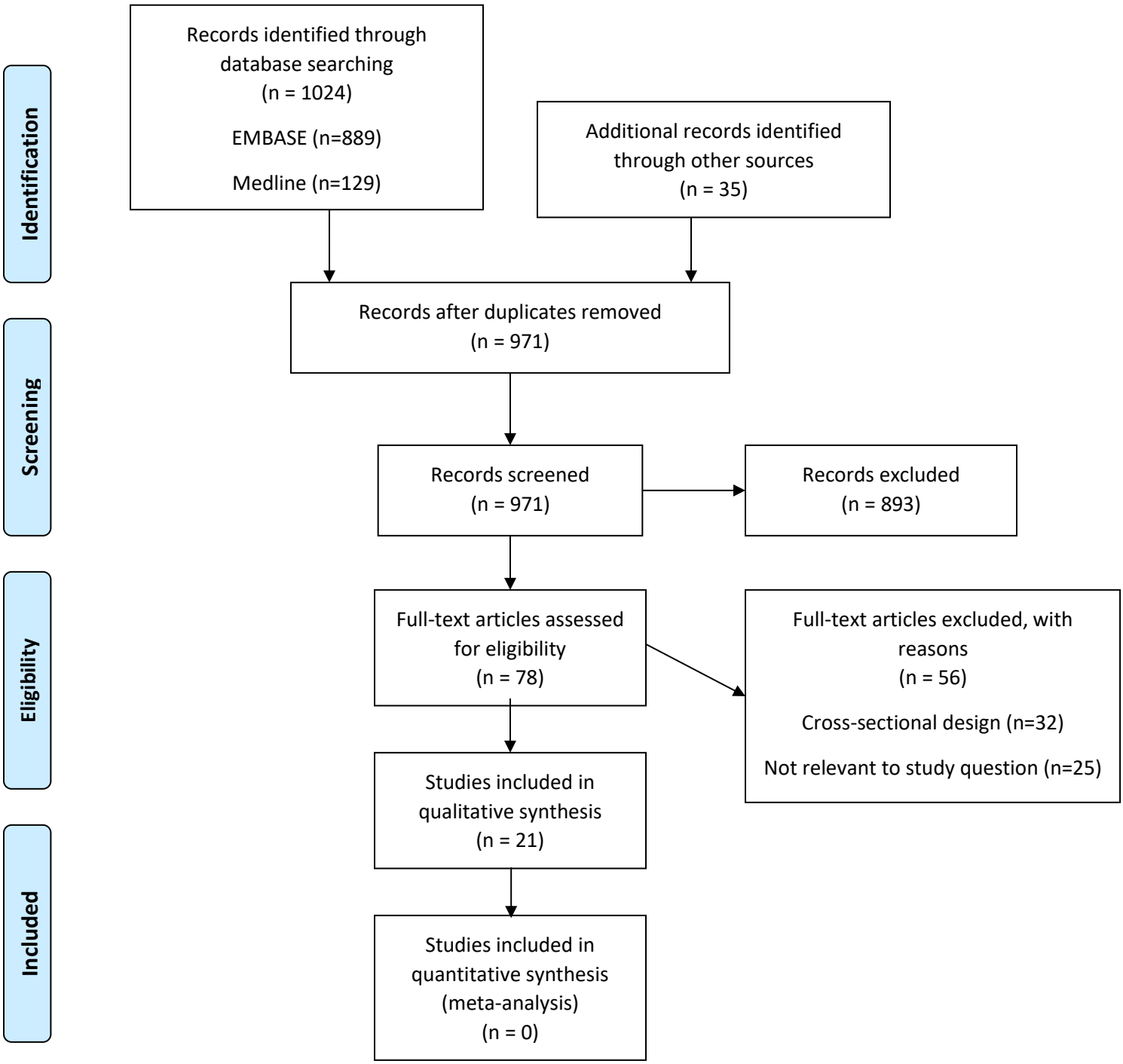
Author contributions: IDO contributed to the concept and design of the manuscript, acquisition, analysis and interpretation of the data, drafting and revising of the article and approved the final version of the draft for publication. HA, JZ, UEW, NA, HLR and MS contributed to the design of the manuscript, interpretation of data, drafting and revising of the article and approved the final version of the draft for publication. KK contributed to the idea, concept and design of the manuscript, the analysis and interpretation of the data, drafting and revising of the article and approved the final version of the draft for publication.

Ethics Approval Statement: not applicable for this type of manuscript (systematic review).

Figure 1. PRISMA Flow diagram of study selection



296 **Table 1. Study characteristics – Setting and implementing agencies**

Author (year)	Years the study was conducted	Country	Type of laboratory(ies), centres, setting	Number of laboratories	Implementing agency
Addo (2006)	2000-2002	Ghana	District laboratories from the Greater Accra Region	12	NRL
Audu (2014)	2009-2011	Nigeria	Local laboratories from different regions, national coverage	44	National Institute of Medical Research
Aziz (2002)	1997-1998	Uganda	Microscopy centers from six pilot districts, regional	48	NTP, international partner
Fattorini (2008)	2002-2006	Albania, Bahrain, Kosovo, Mozambique, Oman, Qatar, Turkey	NRLs	7	SRL
Frean (2012)	2005-2009	48 African countries	NRLs, laboratories at tertiary hospital, research laboratories	68	WHO
Kumar (2009)	2005-2008	India	RRL from nine states	9	NRL
Malik (2011)	2006-2007	India	Microscopy centers from one state in India	183	RRL
Marinucci (2013)	2009-2011	Ethiopia	Microscopy centers, regional	6	International partner
Melese (2016)	2011-2015	Ethiopia	Microscopy centers, regional	956	NRL, international partner
Misganaw (2016)	2012-2013	Ethiopia	Microscopy centers and hospital	33	NTP

			laboratories from Addis Ababa		
Mundy (2002)	1997-1999	Malawi	District laboratory	1	Self-implemented/ international organizations for EQA
Musau (2015)	2011-2013	Kenya	Research laboratory	1	Self-implemented, National Medical Research Center, international partner
Paramasivan (2003)	1998-2000	India	RRL from seven states	8	NRL
Patel (2012)	2005-2010	India	District laboratories from one state	29	RRL
Sarkinfada (2009)	2005-2006	Nigeria	Microscopy centers from one state	5	Laboratories at secondary and tertiary hospitals
Selvakumar (2003)	1999-2001	India	Microscopy centers, regional	12	District laboratory
Shargie (2005)	2000-2002	Ethiopia	Microscopy centers from one state	167	RRL, NRL
Skaggs (2016)	2011-2012	Mozambique	NRL	1	National Ministry of Health, international partner
Ssengooba (2015)	2010-2012	Uganda	University hospital research laboratory	1	National TB Reference Laboratory/ self-implemented
Sticht-Groh (1993)	1990-1992	Sierra-Leone	District laboratories	10	SRL
Van Rie (2008)	NR	Democratic Republic of Congo	Microscopy centers from Kinshasa	13	NRL

297 NRL=National Reference Laboratory, NTP= National TB Program, RRL= Regional Reference Laboratory, SRL=Supranational Reference Laboratory, WHO=

298 World Health Organization

299

300 **Table 2 – Interventions and outcomes of quality improvement measures**

Author (year)	Intervention	Procedures targeted	Methods to assess outcomes	Number, periodicity, approach	Outcome measurements	Results	Overall impact of intervention
Addo (2006)	1. EQA with feedback loop 2. Supervisory visits 3. Training 4. IQA 5. SOPs	Equipment Consumables Procedures Training	On-site evaluation: laboratory checklist Direct observation of procedures	7 EQA rounds Quarterly SVs Prompt feedback provided	Documentation	Improved documentation practices	Positive
		Microscopy	Random blinded re-checking of slides Direct observation of staining	Results of blinded-rechecking discussed with staff	Error rates Slide labelling and storage Slide preparation Quality of slides	Decrease in error rates (false positives 15% to 0%, false negatives 21% to 0%) Improved slide labelling, cleaning and storage Improved smear preparation (10-20% increase across all quality parameters)	Positive
Audu (2014)	1. EQA with feedback loop 2. Training 3. Provision of procedural	Microscopy	Panel testing	4 quarterly rounds of 5 unstained slides	Identification of slide status (positive/ negative) and quantification	Initial improvement of overall scores (from 42% to 78%), decrease in false negatives (from 28% to 4%) and increase in incorrect grading of smears (from 64% to 96%) in the second round followed by decrease in overall scores in the subsequent rounds (to 55% and	Mixed

	instructions					34% in the third and fourth rounds).	
Aziz (2002)	4. Supervisory visits	Equipment, Consumables, Procedures	On-site evaluation: laboratory **c**hecklist Direct observation of procedures	5 EQA rounds Quarterly SVs (5 rounds)	Checklist score	Improvement in all checklist items	Positive
		Microscopy	Direct observation of microscopy procedures and reading		Slide preparation and reading	Not reported	Uncertain
Fattorini (2008)	1. EQA with feedback loop 2. Supervisory visits	Drug susceptibility testing	EQA results	4 EQA rounds Results discussed with laboratory director SVS conducted when required	Performance and reproducibility of drug susceptibility testing.	Improvement of all performance parameters including efficiency and reproducibility	Positive
Frean (2012)	1. EQA with feedback loop 2. Supervisory	Smear staining and microscopy	EQA results (panel testing)	3 EQA rounds per year over 5 years Implementation of corrective measures	Performance of smear microscopy	Stable 85% acceptable scores, no improvement during the evaluation period.	No change

	visits 3. Training			sole responsibility of laboratory staff			
Kumar (2009)	1. EQA with feedback loop 2. Supervisory visits 3. Training	Equipment, Consumables, Procedures Training	On-site evaluation using a checklist	2 EQA rounds 2 SVs	Number of recommended actions Evaluation of checklist items	Improvement of facilities, infrastructures and human resources. Increase in the number of staff trained in EQA (from 42% to 55%). Fewer recommended actions recommended during follow-up visits Overall improvement of checklist items	Positive
		Microscopy	EQA results (on-site panel testing)		Number and type of errors	Improved performance (no high-grade false results during the follow-up visit) Decrease in number of low-grade false results.	Positive
Malik (2011)	1. EQA with feedback loop	Microscopy	Random blinded rechecking of slides	monthly EQA rounds Monthly SVs over 2 years Feedback of number and type of errors and suggestions for improvement	Number and type of errors	Decrease in the number of major errors by 29%. Decrease in the number of high false-positive results by 64%. Slight increase in the number of high false negative errors (by 20%)	Positive
Marinuc	1. EQA with	Microscopy	On-site evaluation	4-6 EQA rounds	Questionnaire	Decrease in centers with inadequate	Positive

ci (2013)	feedback loop 2. Supervisory visits 3. Training	for TB and malaria	using questionnaire	Quarterly SVs High turnaround time for feedback	score	performance from 5/6 at baseline to 0/6. Improvement in score for all sections of the questionnaire	
Melese (2016)	1. EQA with feedback loop 2. Supervisory visits 3. Training 4. IQA	Equipment, Consumables, Procedures Training	On-site evaluation: direct observation of procedures, consumables, data documentation	Quarterly SVs	NR	NR	Uncertain
		Microscopy	Random blinded rechecking of slides	11 EQA rounds	Number of errors. Smear and staining quality	Decrease in false positive rates from 0.6% to 0.2% Decrease in false negative results from 7.6% to 1.6% Increase in the proportion of centers with no errors from 78% to 91% Increase in quality of staining from 71% to 81% Improvement in other smear quality parameters	Positive
Misganaw	1. EQA with feedback	Microscopy	Random blinded rechecking of	7 EQA rounds Quarterly SV	Evaluation of smear quality	Increase in smear quality Decrease in the number of discordant results	Positive

(2016)	loop 2. Training		slides	Regular feedback provided and corrective measures discussed	Discordant results Number of errors		
Mundy (2002)	3. IQA 4. EQA with feedback loop	Microscopy	Random blinded re-checking as part of IQA Evaluation of specimen suitability, smear preparation, staining and reading. Specimen labeling	NR	Sample labelling and staining Proportion of discordant results (not reported as before and after)	Increase in the number of samples labelled correctly from 31% collected at health centers and -80% collected at the hospital to 100%. Improvement in staining techniques	Positive
Musau (2015)	1. IQA 2. EQA with feedback loop 3. Training 4. SOPs	Consumables, Procedures Training	Calculation of costs for expired products Electronic inventory system issuing alerts for	NR	Waste from product expiry Client satisfaction Accreditation	Decrease in expenditures due to product expiry from 6.1% to 1.3% Client satisfaction of 98% Accreditation of laboratory High EQA pass results (90-100%) for microscopy, culture, DST and Xpert.	Positive

	5. Electronic inventory		expired products and items requiring re-ordering				
		Culture	Evaluation of culture contamination		Culture contamination rates for solid and liquid media	Decrease in contamination rates for solid media from 15% to 5% and for liquid media from 15% to 9%	Positive
Paramasivan (2003)	1. EQA with feedback loop	Microscopy	Panel testing of slides	5 EQA rounds	Proportion and type of errors Concordance between technicians	Variable levels of performance and consistency during the evaluation rounds	Uncertain
Patel (2012)	1. EQA with feedback loop 2. Supervisory visits 3. IQA 4. SOPs	Infrastructure, Equipment, Consumables, Procedures. Training	On-site evaluation: checklist-based	3 EQA rounds 3 SVs	Checklist scores	Improvement in scores for all categories. Overall increase in scores from 86% to 92%. Increase in internal quality control parameters from 66% to 93%.	Positive
Sarkinfa	1. EQA with	Microscopy	Random blinded	6 EQA rounds	Concordance of	Increase in concordance of results from 81%	Positive

da (2009)	feedback loop 2. Staff training	for TB and malaria	re-checking of slides	(comparison between baseline and final visits only)	results, Reading errors, Quality of smear preparation and staining	to 91%. Decrease in false positive results from 19% to 1.8%. Slight increase in false negative results from 0% to 3.6% Increase in specificity from 80% to 97.9% Decrease in sensitivity from 100% to 77.8% Increase in the proportion of good smears from 38 to 57% and good staining from 48% to 59%	
Selvakumar (2003)	1. EQA with feedback loop 2. Training	Microscopy	Blinded rechecking of slides	12 EQA rounds Monthly SVs	Reading errors	Low proportion of false positive results of 0-1.2% and false negative results of 1.7%-4.7%. No clear trend over time.	Uncertain
Shargie et al.	1. EQA with feedback loop	Microscopy	Random blinded rechecking of slides	10 EQA rounds Quarterly SVs Regular feedback provided	Reading errors	Decrease in false positive slides from 4.4% to 1.5%. Decrease in false negative slides from 3.9% to 2.6%.	Positive
Skaggs et al (2016)	1. QMS 2. Staff training and	Equipment Consumables Procedures Training	On site-evaluation, checklist (SLIPTA)	2 EQA rounds	Checklist scores	Increase in checklist score from 59 to 196 points (maximum of 250 points). Achieved a 3-star grading	Positive

	mentoring 3. External and internal audits						
Ssengooba (2015)	1. EQA with feed-back loop 2. Monitoring of performance indicators 3. QMS	Microscopy Culture Drug susceptibility testing	EQA results (participation in two EQA schemes) Panel testing Evaluation of culture contamination	9 EQA rounds	Performance for microscopy and drug susceptibility testing EQAs Culture contamination rates for solid and liquid media (yearly reports)	High performance for microscopy EQA of 100% with a decrease to 83% at the end of the evaluation period Increase in performance of drug susceptibility testing from 89% to 100% for isoniazid, from 78% to 100% for rifampicin and from 78%% to 90% for ethambutol. Decrease for streptomycin from 100% to 90% Variable contamination rates between 1.8-5.5% for LJ and 8.2-26.1% for MGIT	Positive
Sticht-Groh (1993)	1. EQA	Microscopy	Blinded rechecking of slides Evaluation of smear quality and staining	8 EQA rounds	Reading errors Quality of smear preparation and staining	No improvement in smear quality or staining. No improvement in the performance of slide reading (training of local staff was initiated following results)	No change

Van Rie (2008)	1. EQA with feedback loop 2. Supervisory visits 3. Training 4. Provision of equipment (microscopes)	Equipment Consumables Procedures Training	On-site evaluation using a checklist	2 SVs (9 months apart) Outline of corrective actions Delayed feedback to lower-tier centers	Checklist score Evaluation of knowledge and skills of technicians	Improvement of practical skills in smear preparation, staining and reading following training (increase in score from 70% to 86%). Increase in knowledge of technicians of theoretical aspects of TB diagnosis (increased score from 89% to 92%).	Positive
		Microscopy	Random blinded rechecking		Reading errors	No improvement in the number of errors (major errors were present in 8/13 laboratories before the intervention and in 10/13 centers after the intervention). No change in the proportion of laboratories with minor errors	No change

301 EQA= external quality assessment; IQA= internal quality assessment; NR= not reported; SV = supervisory visits, SOP= standard operating procedures.

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304 **Table 3: Summary of quality assessment of included studies**

Author (year)	Selection		Comparability*	Outcome			Total	Quality of evidence
	1	2	1	1	2	3		
Addo (2006)	1	2	0	1	1	0	5	Low
Audu (2014)	1	2	0	2	0.5	1	6.5	Moderate
Aziz (2002)	1	2	0	1	0.5	0	4.5	Low
Fattorini (2008)	2	2	0	2	1	1	8	Moderate
Frean (2012)	2	2	0	1.5	1	0	6.5	Moderate
Kumar (2009)	2	1	0	0.5	0	0	3.5	Low
Malik (2011)	2	2	0	2	2	0	8	Moderate
Marinucci (2013)	1	2	0	1	1	1	6	Low
Melese (2016)	2	1	0	1	2	0	6	Low
Misganaw (2016)	1	2	0	2	1	0	6	Low
Mundy (2002)	1	2	0	1	0	2	6	Low
Musau (2015)	1	2	0	1	2	2	8	Moderate
Paramasivan (2003)	2	2	0	1.5	1	2	8.5	Moderate
Patel (2012)	2	2	0	2	1	0	7	Moderate
Sarkinfada (2009)	1	2	0	2	1	2	8	Moderate

Selvakumar (2003)	1	2	0	2	1	0	6	Low
Shargie (2005)	1	2	0	2	1	0	6	Low
Skaggs (2016)	2	2	0	2	0	2	8	Moderate
Ssengooba (2015)	1	1	0	2	2	0	6	Low
Sticht-Groh (1993)	1	1	0	1.5	1	0	4.5	Low
Van Rie (2008)	1	1	0	1	0	2	5	Low

*None of the studies reported on trends prior to intervention. Quality of evidence: 0-6 points: low; 7-9 points: moderate; 10-12 points: high.

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