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

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24 **Summary**

25 **Objective:**

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

29 **Methods:**

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

32 **Results:**

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

41 **Conclusion:**

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

46

47 **Introduction**

48 Worldwide, an estimated 10.4 million new tuberculosis cases occurred in 2015; a third remained
49 undiagnosed.¹ Accurate, rapid diagnosis is critical for timely initiation of treatment and,
50 ultimately, disease control. Today quality assurance (QA) is an essential for the diagnostic
51 process. It comprises activities that enable the achievement and maintenance of high levels of
52 proficiency and accuracy in laboratory testing² and includes staff training, quality control (QC),
53 external and internal quality assessment (EQA and IQA) of laboratory proficiency, quality
54 performance indicator monitoring and continuous quality improvement. Continuous quality
55 improvement is a comprehensive management philosophy which employs scientific methods to
56 increase knowledge and control on work processes variability³ with the goal of customer
57 satisfaction. EQA and IQA comprise systems aiming to continuously improve reliability and
58 efficiency of laboratory processes.⁴ Generally QA is the process of managing for quality, a
59 strategy of prevention with focus on planning and documenting. QC on the other side is aimed at
60 verifying the quality of the output, a strategy of detection including all activities designed to
61 determine the level of quality. All these elements are managed by the quality management
62 system (QMS) that documents processes, procedures and responsibilities for achieving quality
63 policies and objectives that is critical for guiding laboratories towards international
64 accreditation.⁵

65 In 2008, the need to expand and strengthen laboratory capacity was acknowledged by the World
66 Health Organization (WHO) together with multiple international partners.⁶ This was swiftly
67 followed by Strengthening Laboratory Management Toward Accreditation (SLMTA) launched
68 in 2009.⁷⁻⁹ SLMTA is a large-scale effort aimed at improving the quality of laboratory services
69 and patient care in resource-limited settings by developing a cadre of competent laboratory

70 managers. The program seeks to engage laboratories in continuous quality improvement and
71 accelerate their preparations toward accreditation to international standards. WHO has also
72 developed a framework for targets and indicators for laboratory strengthening as part of the “End
73 TB Strategy”, which includes indicators for EQA and implementation of QMS.¹⁰ Although there
74 has been progress towards the implementation of QMS in the African Region, more than 90% of
75 National Tuberculosis Reference Laboratories (NRLs) are not yet accredited.¹¹
76 However, whether quality improvement measures impact on quality outputs of tuberculosis
77 laboratories in low- and lower-middle income countries¹² is currently unknown and subject of
78 this review.

79

80 **Methods**

81 Studies were selected if they were conducted in tuberculosis laboratories or microscopy centers
82 from low- and lower-middle income countries¹² and evaluated the implementation of QMS, their
83 components, or more general interventions (such as training, competency checks, EQA with
84 feed-back loops, etc.) using a comparator (either the same laboratory in a before/after
85 comparison or other laboratories). Outcomes were extracted as defined by the authors.

86 MEDLINE, EMBASE and Web of Science were searched up to the 27th week of 2017 using a
87 compound search strategy (Table S2). The results were cross-referenced with the list of low and
88 lower-middle income countries from the World Bank from 2016.¹² No language restriction was
89 applied.

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

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

97

98 **Results**

99 **Characteristics of the identified studies**

100 971 unique citations were identified and screened, 78 were selected for full-text review and 21
101 were retained for further analysis (Figure 1). The majority of studies were conducted in India
102 (n=5)¹⁴⁻¹⁸ and Ethiopia (n=4),¹⁹⁻²² the remaining were from the Democratic Republic of the
103 Congo,²³ Ghana,²⁴ Kenya,²⁵ Malawi,²⁶ Mozambique,²⁷ Nigeria (n=2),^{28, 29} Sierra-Leone,³⁰ and
104 Uganda (n=2) (Table 2).^{31, 32} Two studies reported data from multiple countries including 48
105 African countries³³ and 7 countries and regions from Europe, Africa, and the Middle East.³⁴ The
106 number of participating laboratories ranged from one to 956.
107 Settings ranged from microscopy centers, hospitals, district, regional laboratories and NRLs. The
108 implementing agency in most studies was an external organization, usually the national or
109 regional reference laboratory. International partner organizations were often involved and
110 supported the national implementing authority^{21, 25, 27, 31} or were the sole implementers.¹⁹ Three
111 studies described quality improvement interventions implemented by laboratories themselves.^{25,}
112 ^{26, 32} Two multisite, multinational studies investigated the effect of EQA schemes with feedback
113 loops and troubleshooting on subsequent EQA results. Participants were NRLS and research
114 laboratories.^{33, 34}

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

128

129 **Interventions targeting microscopy**

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

138 errors. Smear quality was assessed across the following categories: staining, cleanliness,
139 thickness, size and evenness. Most studies 10/17 reported an improvement in performance,^{14, 15,}
140 ^{19-22, 24, 26, 28, 32} while the rest showed either no change or the results were difficult to interpret due
141 to variability.^{16, 18, 23, 29-31, 33} Although difficult to assess, studies of interventions showing no
142 improvement had infrequent evaluation visits²³, did not provide timely feed-back³⁰, or were
143 implemented in laboratories with a good baseline performance.^{18, 33}

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

156 Nine studies provided data investigating the effect of random blinded rechecking of microscopy
157 slides. At baseline, the proportion of false positive (0.1%-19%) and false negative errors (0%-
158 21%) varied widely across studies. Post intervention, the proportion of false positive and false
159 negative errors ranged between 0% to 1.8% and 0% to 3.6%. Six of the nine studies reported an
160 overall improvement with a decrease in the proportion of false positives ^{15, 20, 21, 24, 28} and false

161 negatives.^{20, 21, 24} Other studies reported a decrease in major errors¹⁵, an increase in laboratories
162 without any errors²¹ and increased concordance between laboratory staff and supervisors
163 performing the rechecking was reported.^{22, 28} Two studies conducted in India and Nigeria showed
164 a non-significant increase in the proportion of false negative errors.^{15, 28} Three studies failed to
165 show any impact.^{18, 23, 30} Those studies were conducted in India, Sierra-Leone and the
166 Democratic Republic of Congo and performed 2-12 rounds of random blinded rechecking.
167 Six studies reported on the effects of random blinded rechecking or slide reevaluation within an
168 EQA scheme on the quality of AFB smear preparation and staining.^{21, 22, 24, 26, 28, 30} Quality of
169 staining improved in five studies^{21, 22, 24, 26, 28} with 10-20% improvement on quantifiable effect.^{21,}
170 ^{24, 28} One study from Sierra-Leone failed to show improvement in AFB smear quality, staining
171 and reading. However, there was delayed feedback of findings to the submitting laboratory.
172 These results lead to on-site training of staff.³⁰

173

174 **Interventions targeting culture and antimicrobial susceptibility testing**

175 A study from Kenya conducted in a district laboratory reported on the implementation of quality
176 improvement measures initiated by the laboratory management aiming for accreditation.

177 Analytical SOPs, laboratory policies and a quality manual were developed. Regular analyses of
178 quality indicators such as contamination frequency were implemented and optimization of
179 processes was initiated when required. Culture contamination decreased from 15.4% to 5.3% on
180 solid media and 15.2% to 9.3% in liquid media. External support was provided for conducting
181 quality audits, implementing the QMS and gaining accreditation.²⁵

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

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

192

193 **Comprehensive quality improvement interventions**

194 Studies implementing comprehensive quality improvement measures included on-site
195 evaluations as part of EQA schemes, supervisory visits, staff training and development and
196 implementation of SOPs and electronic inventories. Eight studies described on-site evaluation of
197 laboratories assessing equipment, consumables, procedures, and levels of staff training.^{14, 17, 19, 21,}
198 ^{23, 24, 27, 31} Results of evaluation visits were systematically reported back. Additionally,
199 laboratories were supported to address shortcomings. Site visits were documented using
200 standardized checklists and questionnaires in six studies.^{14, 17, 19, 23, 27, 31} One study assessed the
201 extent and accuracy of data documentation during site visits²⁴, while one study assessed the levels
202 of theoretical and practical knowledge of staff.²³ All studies reported improvement in the
203 checklist scores, decreased number of recommendations made over time and enhanced
204 documentation practices.^{14, 17, 19, 24, 27, 31} One study implemented an electronic inventory system to
205 enable real-time control of stock, facilitate procurement and check product expiry dates.²⁵ This
206 decreased expenses due to product expiry from 6% to 1%. Another study reported on the

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

212

213 **Quality of included studies**

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

217

218 **Discussion**

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

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

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

241 Until recently AFB smear microscopy was the main tuberculosis diagnostic in low- and lower-
242 middle income countries. Thus, quality improvement has largely focused on microscopy.
243 National EQA schemes for microscopy as recommended by WHO³⁷ have been rolled out across
244 many countries. It is therefore not surprising that the majority of studies included in this review
245 investigated the effect of microscopy EQA schemes. Reassuringly these schemes had a positive
246 effect. However, more comprehensive quality improvement measures are needed if broader
247 culture and molecular diagnostic coverage is to succeed at least in regions with high MDR-
248 tuberculosis prevalence, ultimately aiming to attain the indicators for laboratory strengthening
249 proposed by the WHO.¹⁰ This could include comprehensive interventions targeted at analytic
250 tests other than microscopy, such as mycobacterial culture, drug susceptibility testing and
251 molecular techniques. In addition, rather than focusing on individual diagnostic assays,

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

254 The review highlights high heterogeneity of outcome measures. Ideally, outcome measures
255 should be standardized to enable comparison across studies. The SLMTA checklist score
256 provides such a standardized tool. However, completing the comprehensive checklist is time-
257 consuming and requires expertise. This might impede its widespread use in future studies. A
258 simpler and user-friendlier tool might be more appropriate. Alternatively, independent external
259 assessors trained in tuberculosis diagnostics, QMS and ISO 15189 and 17043 standards should
260 be considered to assess outcomes comprehensively. Other important outcome measures and
261 quality performance indicators such as turn-around times, service interruptions, specimen
262 rejection rates, QC results, cost-effectiveness and laboratory staff productivity⁵ were not reported
263 in any of the studies included in this review. Furthermore, the cost-effectiveness of implementing
264 the additional step for attaining accreditation needs to be investigated. Additionally, standardized
265 reporting on results of quality improvement projects should be attempted.³⁸

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

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

282

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

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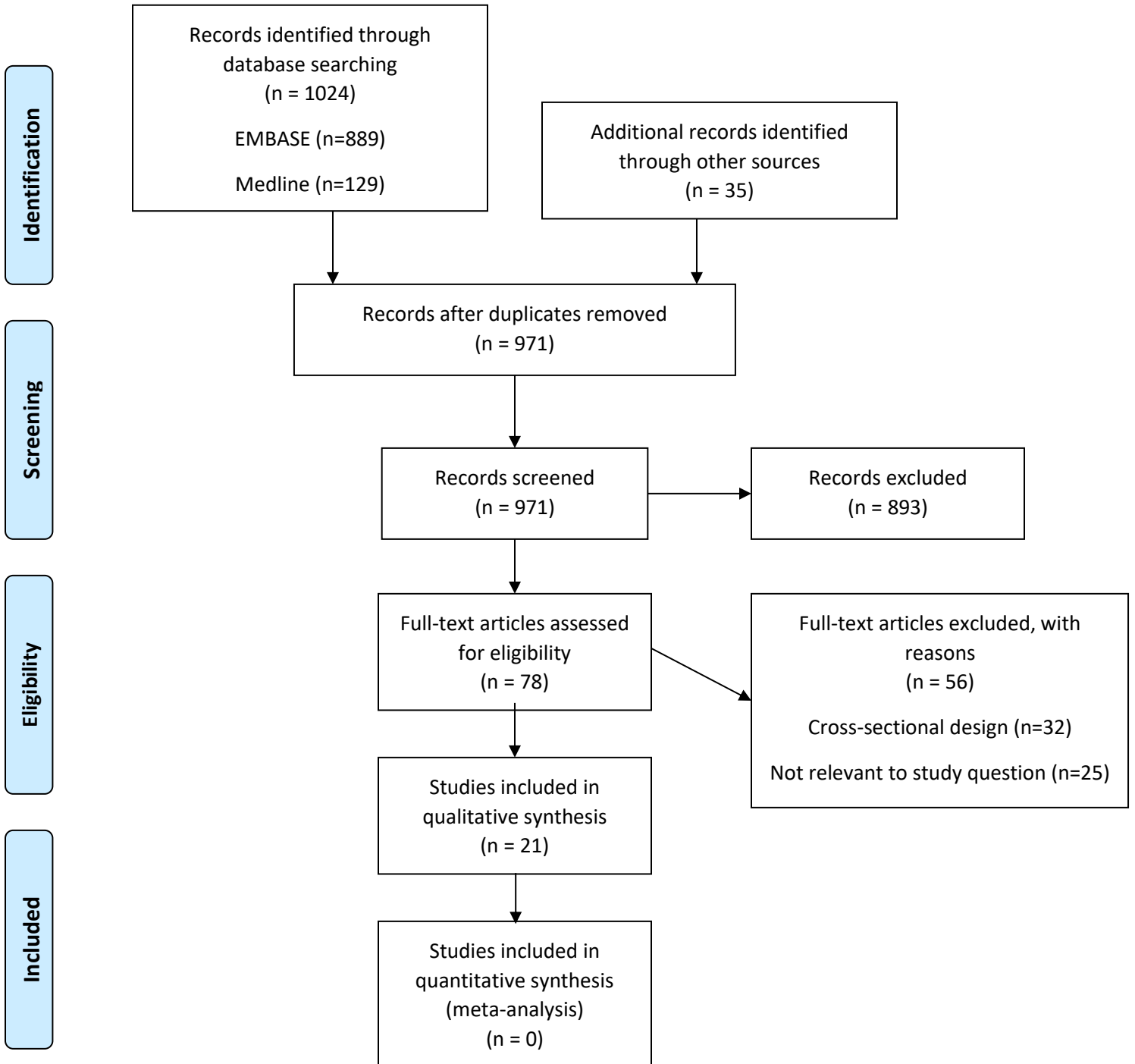
285 **Author contributions:** IDO contributed to the concept and design of the manuscript,
286 acquisition, analysis and interpretation of the data, drafting and revising of the article and
287 approved the final version of the draft for publication. HA, JZ, UEW, NA, HLR and MS
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289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

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

293



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	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 checklist 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)				
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 Microscopy	On-site evaluation: direct observation of procedures, consumables, data documentation Random blinded rechecking of slides	Quarterly SVs 11 EQA rounds	NR Number of errors. Smear and staining quality	NR 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	Uncertain Positive
Misgan aw	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. Supervisor 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%	
Selvaku mar (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 Consumable s 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						
Ssengoba (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	Equipment Consumables	On-site evaluation using a checklist	2 SVs (9 months apart) Outline of corrective actions	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
	2. Supervisory visits 3. Training	Procedures Training		Delayed feedback to lower-tier centers			
	4. Provision of equipment (microscopes)	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	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
Sarkinfaada (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

305 *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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