**Additional file 1** PRISMA checklist.

**PRISMA 2009 Checklist**

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| --- | --- | --- | --- |
| **Section/topic**  | **#** | **Checklist item**  | **Reported on page #**  |
| **TITLE**  |  |
| Title  | 1 | Identify the report as a systematic review, meta-analysis, or both.  | 2-3 |
| **ABSTRACT**  |  |
| Structured summary  | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.  | 21-71 |
| **INTRODUCTION**  |  |
| Rationale  | 3 | Describe the rationale for the review in the context of what is already known.  | 74-159 |
| Objectives  | 4 | Provide an explicit statement of questions being addressed with reference to participants, index test, comparisons, outcomes, and study design (PICOS).  | 148-159 |
| **METHODS**  |  |
| Protocol and registration  | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.  | 180-186 |
| Eligibility criteria  | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.  | 225-241 |
| Information sources  | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.  | 190-224 |
| Search  | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.  | Attached |
| Study selection  | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).  | 242-246 |
| Data collection process  | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.  | 248-250 |
| Data items  | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.  | 255-264 |
| Risk of bias in individual studies  | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.  | 265-269 |
| Summary measures  | 13 | State the principal summary measures (e.g., risk ratio, difference in means).  | 270-298 |
| Synthesis of results  | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.  | 299-326 |

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| --- | --- | --- | --- |
| **Section/topic**  | **#** | **Checklist item**  | **Reported on page #**  |
| Risk of bias across studies  | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).  | 382-396 |
| Additional analyses  | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.  | 463-488 |
| **RESULTS**  |  |
| Study selection  | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.  | 242-246 and 895-943 |
| Study characteristics  | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.  | 255-256 and 889-894 |
| Risk of bias within studies  | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).  | 265-269 and 463-488 |
| Results of individual studies  | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.  | 292-452 and 998-1026 |
| Synthesis of results  | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.  | 270-298 |
| Risk of bias across studies  | 22 | Present results of any assessment of risk of bias across studies (see Item 15).  | 382-396 |
| Additional analysis  | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).  | 463-488 |
| **DISCUSSION**  |  |
| Summary of evidence  | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).  | 487-540 |
| Limitations  | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).  | 541-575 |
| Conclusions  | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.  | 576-600 |
| **FUNDING**  |  |
| Funding  | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data), role of funders for the systematic review.  | 617-618 |

*From:*  Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

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**Additional file 2:**

**ADDITIONAL FILE 2: Search strategy**

The following Medline via PubMed search algorithm will be translated to EMBASE**:**

1. ("tuberculosis") ti,ab

2. (mycobacterium tuberculosis) ti,ab

3. (extrapulmonary tuberculosis) ti,ab

4. (pulmonary tuberculosis) ti,ab

5. (paediatric tuberculosis) ti,ab

6. 1 OR 2 OR 3 OR 4 OR 5

7. ("Real-time polymerase chain reaction") ti,ab

8. (real-time pcr) ti,ab

9. (real-time pcr assay) ti,ab

10. ("rt-pcr") ti,ab

11. ("Nucleic Acid Amplification Test") ti,ab

12. ("NAAT") ti,ab

13. 7 OR 8 OR 9 OR 10 OR 11 OR 12

14. ("culture-based media") ti,ab

15. (culture-based assay) ti,ab

16. ("liquid media") ti,ab

17. ("solid media") ti,ab

18. 14 OR 15 OR 16 OR 17

19. (“paediatric”) ti,ab

20. (“paediatrics”) ti,ab

21. (“children”) ti,ab

22. 19 OR 20 OR 21

23. 6 AND 13

24. 18 AND 22

25. 23 AND 24

 **Additional file 3:**

**Additional file 3**: Quality assessment of diagnostic accuracy

studies-2 tool

QUADAS-2 tool: Risk of bias and applicability judgments

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| --- |
| Domain 1: Patient selection |
| 1. Risk of bias
 |  |
| Describe methods of patient selection: |
| * Was a consecutive or random sample of patients enrolled?
 | Yes/No/Unclear |
| * Was a case-control design avoided?
 | Yes/No/Unclear |
| * Did the study avoid inappropriate exclusions?
 | Yes/No/Unclear |
| Could the selection of patients have introduced bias? | RISK: LOW/HIGH/UNCLEAR |
| 1. Concerns regarding applicability
 |  |
| Describe included patients (prior testing, presentation, intended use of index test and setting): |
| Is there concern that the included patients do not match the review question? | CONCERN: LOW/HIGH/UNCLEAR |
| Domain 2: Index test(s) *(if more than 1 index test was used, please complete for each test)* |
| 1. Risk of bias
 |  |
| Describe the index test and how it was conducted and interpreted: |
| * Were the index test results interpreted without knowledge of the results of the reference standard?
 | Yes/No/Unclear |
| * If a threshold was used, was it pre-specified?
 | Yes/No/Unclear |
| Could the conduct or interpretation of the index test have introduced bias? | RISK: LOW/HIGH/UNCLEAR |
| 1. Concerns regarding applicability
 |  |
| Is there concern that the index test, its conduct, or interpretation differ from the review question? | CONCERN: LOW/HIGH/UNCLEAR |
| Domain 3: Reference standard |
| 1. Risk of bias
 |  |
| Describe the reference standard and how it was conducted and interpreted: |
| * Is the reference standard likely to correctly classify the target condition?
 | Yes/No/Unclear |
| * Were the reference standard results interpreted without knowledge of the results of the index test?
 | Yes/No/Unclear |
| Could the reference standard, its conduct, or its interpretation have introduced bias? | RISK: LOW/HIGH/UNCLEAR |
| 1. Concerns regarding applicability
 |  |
| Is there concern that the target condition as defined by the reference standard does not match the review question? | CONCERN: LOW/HIGH/UNCLEAR |
| Domain 4: Flow and timing |
| 1. Risk of bias
 |  |
| Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram):Describe the time interval and any interventions between index test(s) and reference standard: |
| * Was there an appropriate interval between index test(s) and reference standard?
 | Yes/No/Unclear |
| * Did all patients receive a reference standard?
 | Yes/No/Unclear |
| * Did patients receive the same reference standard?
 | Yes/No/Unclear |
| * Were all patients included in the analysis?
 | Yes/No/Unclear |
| Could the patient flow have introduced bias? | RISK: LOW/HIGH/UNCLEAR |

**Additional file 4** Figures of Subgroup analyses (LMICs)



**Figure S1** Forest plot estimates of the pooled sensitivity for LMICs

 **Figure S2** Forest plot estimates of the pooled specificity for LMICs



**Figure S3** Forest plot estimates of the pooled PLR for LMICs



**Figure S4** Forest plot estimates of the pooled NLR for LMICs



**Figure S5** Forest plot estimates of the pooled DOR for LMICs



**Figure S6** Forest plot estimates of the pooled SROC for LMICs

**Additional file 5: Figures of Sub-group analyses (UMICs)**



**Figure S1** Forest plot estimates of the pooled sensitivity for UMICs

 **Figure S2** Forest plot estimates of the pooled specificity for UMICs

 **Figure S3** Forest plot estimates of the pooled PLR for UMICs

 **Figure S4** Forest plot estimates of the pooled NLR for UMICs

 **Figure S5** Forest plot estimates of the pooled DOR for UMICs

 **Figure S6** Forest plot estimates of the pooled SROC for UMICs

**Additional file 6:** Definition of statistical parameters

**AUC**: The area under the (regression) curve also measures the overall accuracy of diagnostic tests. If the AUC is 100%, then the test differentiates perfectly between diseased and non-diseased individuals. An AUC of 50% indicates a poor diagnostic accuracy.

**DOR**: This was calculated by positive likelihood ratio/negative likelihood ratio or *[sensitivity/ (1-specificity)]/ [(1-sensit​ivity)/ specificity].* DOR is a measure of the overall diagnostic power of a test. A high DOR implies that the test shows good diagnostic accuracy in all patients; whereas a DOR of 1 would indicate that the test cannot discriminate between people with and without disease.

**I2**: A statistic describing the proportion of total variation in study estimates that is due to heterogeneity. Values greater than 50% suggest greater heterogeneity between the studies. If the I2 statistic suggests significant heterogeneity between the studies then the reasons for such differences can be examined by relating study level co-variates i.e. type of reference test, prevalence, type of PCR or other methodological features.

**Negative likelihood ratio*:*** ratio of the proportion that test negative amongst those that have the target condition compared to the proportion that test negative amongst those who do not have the target condition.

**Positive likelihood ratio*:*** ratio of the proportion that test positive amongst those that have the target condition compared to the proportion that test positive amongst those who do not have the target condition.

**Q**: Is the intercept of the SROC and the anti-diagonal line through the unit square i.e. the point of the curve in which sensitivity equals specificity. Q estimates the overall accuracy by finding where sensitivity and specificity are the same. If the curve is closer to the top left corner, the better the accuracy. The higher the Q, the more accurate is the test. However, a high Q is desirable in tests where high sensitivity and high specificity are equally important. If, however, when either the sensitivity or the specificity is more important than one of them, then Q does not address the clinical usefulness of the test.

**Receiver characteristic operating curve (ROC)*:*** the sensitivity and specificity of a test vary depending on the threshold value chosen. The ROC curve describes the trade-off between sensitivity and specificity as the threshold changes.

**Sensitivity*:*** proportion that test positive amongst those having the target condition.

**Specificity*:*** proportion that test negative amongst those without the target condition.

**Summary receiver characteristic operating curve (SROC)**: This displays each study's sensitivity and specificity estimates within the ROC space. A regression curve is fitted through the distribution of pairs of sensitivity and specificity. A shoulder-like curve indicates that the variability between studies may be due to the threshold effect (i.e. variation in cut-off values used across studies) and that an underlying common DOR exists that does not change with the threshold. A non-shoulder-like curve shows that sensitivity and specificity are not correlated.

**Threshold*:*** A value above or below which a test result is considered positive.

**Moses-Littenberg statistical modelling of ROC curves**

