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Stool specimen for diagnosis of pulmonary tuberculosis in adults: protocol for a systematic review and meta-analysis

Saima Sultana 1, Adnan Ansar 2, K M Saif-Ur-Rahman 3,4

ABSTRACT

Introduction Tuberculosis (TB) continues to be a significant health burden, most commonly affecting the lungs and referred to as pulmonary TB (PTB). Diagnostic techniques of PTB primarily rely on expectorated sputum samples. However, the diagnostic yields are often hindered due to insufficient volume and quality of the sputum specimens. Moreover, some individuals are unable to provide sputum samples due to scanty sputum production or difficulty in coughing up and require an invasive procedure to obtain a respiratory sample, such as bronchoscopic or gastric aspiration. Thus, challenges in the acquisition of respiratory specimens warrant an alternate specimen. Therefore, this systematic review aims to evaluate the diagnostic accuracy of a stool specimen for the diagnosis of PTB in adults.

Methods and analysis We will search MEDLINE (Ovid), Embase (Ovid), Web of Science and Cochrane database from inception to April 2021 using a comprehensive search strategy. Two reviewers will independently perform screening, data extraction and quality assessment. The risk of bias assessment and applicability of results of eligible studies will be performed using the Quality of Diagnostic Accuracy Studies-2 tool. Bivariate random-effects models will be performed to calculate pooled sensitivity, specificity, positive likelihood ratio and negative likelihood ratio and diagnostic odds ratio along with 95% CI of stool specimen for each reported diagnostic method against any of the reference standard test (ie, mycobacterial culture or smear microscopy or Xpert assay using respiratory specimens). Heterogeneity between studies will be assessed by I² statistics and Q statistic of the χ² test.

Ethics and dissemination The results will be disseminated through publishing in a peer-reviewed medical journal and public presentations in relevant national and international conferences. As this is a systematic review of publicly available data, ethics approval is not required.

PROSPERO registration number CRD42021245203.

INTRODUCTION

Tuberculosis (TB) is an infectious bacterial disease caused by Mycobacterium tuberculosis (MTB). It remains one of the top 10 causes of death in lower-income and lower-middle-income countries. According to the 2020 Global Tuberculosis Report, in 2019, there was an estimated 10 million new TB cases, with approximately 1.4 million deaths due to TB. TB is an airborne disease that is mainly transmitted between humans through respiratory droplets generated during coughing, sneezing or speaking. It most commonly affects the lungs, known as pulmonary TB (PTB) but can also involve extrapulmonary sites in the body, including—lymph nodes, pleura, abdomen, urogenital tract, skin, joints and bones and meninges. Bacteriological confirmation of PTB usually depends on microscopy, culture and PCR-based assay, including Xpert assay using sputum specimens. However, the diagnostic performance of these tests depends on the concentration of MTB in sputum samples. Poor quality and inadequate volume of sputum samples can lead to missed diagnoses, delays in initiating treatment and increased risk of transmission to others from undiagnosed or untreated individuals. In addition, at least two sputum specimens (one spot specimen at the time of initial consultation followed by one early morning specimen on the next day) are recommended, which can entail additional
costs and inconvenience to individuals due to repeated visits to a healthcare facility. Furthermore, some individuals may have found it challenging to provide an expectorated sputum sample, especially young children, the elderly, severely ill, people living with human immunodeficiency virus or pregnant women. In these situations, induced sputum, bronchoalveolar lavage fluid or gastric lavage fluid are used as alternative diagnostic specimens. However, procedures for obtaining these specimens are invasive and impose additional costs; they also require technical expertise that may not be readily available in resource-constrained settings.

Diagnostic testing of stool samples is an alternative to respiratory specimens for diagnosis of PTB. As sputum is swallowed and MTB passes through the digestive tract, it can be detected in stool through microscopy, culture and PCR tests, including Xpert assay. Recent studies on PTB diagnosis using the Xpert platform on stool samples have shown promising results, and this approach has been increasingly used in the paediatric population for PTB diagnosis. While some studies on the use of stool samples for PTB diagnosis in adults have been published, its accuracy and utility compared with standard diagnostic approaches have not yet been evaluated through a systematic review. It is also important to recognise the best method that would provide maximum diagnostic accuracy to detect PTB using the stool samples. Therefore, this systematic review aims to evaluate the diagnostic accuracy of stool specimens in microscopy, culture and PCR assays to diagnose PTB in adults against any microbiological reference standard tests, that is, smear microscopy or culture or Xpert assays using respiratory specimens. The results would provide crucial evidence in the TB diagnostic landscape in adults, particularly those who cannot expectorate sputum or produce inadequate sputum.

METHODS AND ANALYSIS
This systematic review will be conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy (PRISMA-DTA) criteria (see online supplemental files S1 and S2 for PRISMA-DTA checklists). In addition, the results of the literature search and screening will be presented in a PRISMA flow diagram.

Search strategy and information sources
A comprehensive search strategy will be developed to search relevant studies in the following electronic bibliographical databases; MEDLINE (Ovid) (1946–April 2021), Embase (Ovid) (1947–April 2021), Web of Science (1950–April 2021) and Cochrane database (inception–April 2021). To develop the database search strategies, we will use Medical subject headings (MeSH) as well as terms, keywords, and synonyms such as “Mycobacterium tuberculosis” or “MTB,” “pulmonary tuberculosis” or “PTB,” “tuberculosis,” or “TB,” “adults” or “elderly,” “stool” or “faeces” or “faecal,” and “diagnosis” or “diagnostic” (Table 1; see online supplemental file S3 for the search strategy). In addition, we will search references cited in the included articles to avoid missing relevant studies. When required, we will also communicate with study authors for further information. No restrictions will be applied on the publication dates, publication status and study designs. We will not search for unpublished studies or grey literature.

Table 1 presents the search strategy for MEDLINE (Ovid) and Embase (Ovid).

Selection criteria
Studies will be identified based on the following inclusion criteria: (1) evaluated stool specimen in adults (aged 18 years and older) with presumptive/active PTB using microscopy or culture or PCR assay, including Xpert (index test); (2) diagnosis of PTB in study participants was accompanied by bacteriological confirmation of MTB in the respiratory specimen by culture and/or microscopic examination, and/or Xpert assay (reference test); (3) type of studies: both retrospective and prospective cross-sectional and cohort studies, randomised controlled trials and case–control studies that used stool samples for PTB diagnosis; (4) studies that assessed diagnostic accuracy and/or provided sufficient data to compute diagnostic accuracy measures (true positive (TP), false positive (FP), true negative (TN), false negative (FN)); (5) studies that used stored/banked sputum and stool specimen for analysis will also be eligible; (6) studies that included both adults and children provided that disaggregated adult data is available.

Studies are not eligible if (1) no study participants 18 years of age or older; (2) stool specimen was not tested for PTB diagnosis; (3) reviews, conference proceedings and abstracts, case reports, editorials and commentaries and (4) articles in languages other than English.

Data management
Results from the search of the bibliographic databases will be managed using Covidence, a web-based platform developed by the Cochrane Collaboration that supports the synthesis of evidence for systematic reviews. All articles will be imported into Covidence, and duplicate articles will be identified and removed accordingly.

Study screening and data abstraction
Initially, screening of the title and abstract of the retrieved articles will be conducted by two reviewers independently according to the predetermined study selection criteria using the Covidence platform. After initial screening, the full-text articles will be sought for potentially eligible studies, with the assessment of eligibility conducted by two reviewers independently. Any inconsistencies between two reviewers at any stage of the review process will be resolved through discussion or consultation with a third reviewer.

A data extraction form will be created using an Excel spreadsheet and piloted on three eligible studies. Two reviewers will independently extract data from each selected article and complete the data extraction form that will consist of the following data items:

- General information: study title, author(s), year of publication, study country, including the WHO classification for TB burden country (i.e., high TB burden or low TB burden countries), study settings, study design.
- Summary statistics on age, gender, HIV status, other comorbid conditions
- Sample size.
- Case definitions and reference standard test/s for PTB diagnosis.
- Index test/s (i.e., microscopy or culture or PCR assays, including Xpert on stool samples).
- Type of specimen (e.g., stool, sputum, induced sputum, bronchoalveolar lavage, gastric aspirate).
- Volume of specimen.
- Specimen condition (fresh vs stored/frozen).
- Specimen processing method.
- Timing of tests (i.e., the interval between the index and reference standard test/s).
- Outcome measures: numbers of TP, FP, FN and TN against the reference standard tests.

In the case of multiple reference standard tests within the same study, the results will be recorded separately.

### Quality assessment

Risk of bias assessment and applicability of results of included studies will be performed using the Quality of Diagnostic Accuracy Studies-2 (QUADAS-2), a recommended tool for appraising studies in systematic reviews for diagnostic accuracy. As per QUADAS-2 guideline, two reviewers will independently assess the risk of bias of each included study in four key domains: (a) patient selection, (b) index test, (c) reference standard, and (d) flow of patients and timing of index and reference standard tests. The risk of bias or applicability concerns will be qualified as ‘low,’ ‘high’ or ‘unclear.’ Similar to article selection phases, disagreement between reviewers will be solved by discussion or consultation with a third reviewer.
Data analysis
Initially, we will perform a narrative synthesis of all included studies and summarise the results, including characteristics of included studies and participants, sample type for reference standard test/s, and details of sample processing and storage methods.

Meta-analysis will be performed using the MIDAS module in STATA statistical software (V.16.0, Stata). We will construct 2×2 tables for all included studies and enter TP, FP, FN and TN for all index test/s against the reference standard test/s. If necessary, additional data may be sought from the study corresponding author through email to support meta-analysis. If this is unsuccessful, studies will be omitted from the pooled meta-analysis. We will use bivariate random-effects models to calculate pooled sensitivity, specificity, positive likelihood ratio and negative likelihood ratio and diagnostic odds ratio along with 95% CI of stool specimen for each reported diagnostic method (ie, microscopy, culture or PCR assay) for diagnosis of PTB against smear microscopy or culture or Xpert assay on a respiratory specimen. We will also report the sensitivity and specificity of each study in forest plots and analyse the areas under the summary receiver operating characteristic curves. If there is adequate data, subgroup analysis (eg, HIV status, stool processing method, conditions of the specimen (fresh or frozen/stored)) and meta-regression analysis will be performed. If deemed appropriate, sensitivity analysis will be done to evaluate the effect of risk of bias by excluding the studies of lower methodological quality (ie, high or uncertain risk of bias).

We will summarise the key results in the ‘Summary of Findings’ tables and assess the certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guideline for diagnostic tests.17

Assessment of heterogeneity and publication bias
We will estimate the heterogeneity between the studies by using I² statistics and Q statistic of the χ² test. If possible, the source of heterogeneity will be examined by conducting subgroup analysis or meta-regression. Potential publication bias will be assessed using Deeks test.18

Patient and public involvement
The patient and the public were not involved during the conceptualisation and development of the review protocol. However, we intend to involve the patients during the dissemination of findings in national conferences.

Start date
15 April 2021.

Anticipated completion date
31 October 2021.

ETHICS AND DISSEMINATION
Ethics approval will not be required for this study protocol as this systematic review focuses on the analysis of published data. On completing the review, we will disseminate the results in a peer-reviewed medical journal and present them at relevant conferences.

DISCUSSION
Rapid and accurate diagnosis of PTB is crucial for timely initiation of treatment, preventing transmission and improving the prognosis of individuals with PTB. However, diagnosing PTB can be challenging due to difficulty in obtaining sputum specimens, especially those who are unable to produce sputum. Thus, there is a need for an alternative, non-sputum-based sample for PTB diagnosis. To the best of our knowledge, this will be the first systematic review that will evaluate the diagnostic accuracy of the stool specimens for PTB diagnosis in adults. We anticipate that the results of this review will support clinicians and policymakers to provide guidance in clinical laboratory practice for the diagnosis of PTB in adults. It will also guide future research needs based on identified gaps and alleviate the pathway to end TB endemic across the globe.

The strength and limitations of the included studies will be discussed. We will assess the strength of the body of evidence and highlight the gaps in the evidence for future research, using the GRADE approach for diagnostic accuracy studies.

Acknowledgements
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Contributors
SS conceptualised, designed and drafted the initial manuscript. SS and KMS-U-R developed the search strategy. AA and KMS-U-R critically appraised and edited the manuscript. All authors reviewed the manuscript and have approved the final manuscript before submission. SS is the guarantor of this review.

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Competing interests
None declared.

Patient consent for publication
Not required.

Provenance and peer review
Not commissioned; externally peer reviewed.

Supplemental material
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REFERENCES
## PRISMA-DTA for Abstracts Checklist

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<th>PRISMA-DTA for Abstracts Checklist item</th>
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<tr>
<td><strong>TITLE and PURPOSE</strong></td>
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<tr>
<td>Title</td>
<td>1</td>
<td>Identify the report as a systematic review (+/- meta-analysis) of diagnostic test accuracy (DTA) studies.</td>
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<tr>
<td>Objectives</td>
<td>2</td>
<td>Indicate the research question, including components such as participants, index test, and target conditions.</td>
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<tr>
<td><strong>METHODS</strong></td>
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<tr>
<td>Eligibility criteria</td>
<td>3</td>
<td>Include study characteristics used as criteria for eligibility.</td>
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<tr>
<td>Information sources</td>
<td>4</td>
<td>List the key databases searched and the search dates.</td>
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<tr>
<td>Risk of bias &amp; applicability</td>
<td>5</td>
<td>Indicate the methods of assessing risk of bias and applicability.</td>
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<tr>
<td>Synthesis of results</td>
<td>A1</td>
<td>Indicate the methods for the data synthesis.</td>
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<tr>
<td><strong>RESULTS</strong></td>
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<tr>
<td>Included studies</td>
<td>6</td>
<td>Indicate the number and type of included studies and the participants and relevant characteristics of the studies (including the reference standard).</td>
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<tr>
<td>Synthesis of results</td>
<td>7</td>
<td>Include the results for the analysis of diagnostic accuracy, preferably indicating the number of studies and participants. Describe test accuracy including variability; if meta-analysis was done, include summary results and confidence intervals.</td>
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<tr>
<td><strong>DISCUSSION</strong></td>
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<tr>
<td>Strengths and limitations</td>
<td>9</td>
<td>Provide a brief summary of the strengths and limitations of the evidence</td>
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<tr>
<td>Interpretation</td>
<td>10</td>
<td>Provide a general interpretation of the results and the important implications.</td>
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<tr>
<td><strong>OTHER</strong></td>
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<td>Funding</td>
<td>11</td>
<td>Indicate the primary source of funding for the review.</td>
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<tr>
<td>Registration</td>
<td>12</td>
<td>Provide the registration number and the registry name.</td>
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For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).
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<td>Abstract</td>
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<td>Abstract: See PRISMA-DTA for abstracts.</td>
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<tr>
<td><strong>INTRODUCTION</strong></td>
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<tr>
<td>Rationale</td>
<td>3</td>
<td>Describe the rationale for the review in the context of what is already known.</td>
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<tr>
<td>Clinical role of index test</td>
<td>D1</td>
<td>State the scientific and clinical background, including the intended use and clinical role of the index test, and if applicable, the rationale for minimally acceptable test accuracy (or minimum difference in accuracy for comparative design).</td>
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<tr>
<td>Objectives</td>
<td>4</td>
<td>Provide an explicit statement of question(s) being addressed in terms of participants, index test(s), and target condition(s).</td>
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<tr>
<td><strong>METHODS</strong></td>
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<tr>
<td>Protocol and registration</td>
<td>5</td>
<td>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.</td>
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<tr>
<td>Eligibility criteria</td>
<td>6</td>
<td>Specify study characteristics (participants, setting, index test(s), reference standard(s), target condition(s), and study design) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.</td>
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<tr>
<td>Information sources</td>
<td>7</td>
<td>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.</td>
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<tr>
<td>Search</td>
<td>8</td>
<td>Present full search strategies for all electronic databases and other sources searched, including any limits used, such that they could be repeated.</td>
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<tr>
<td>Study selection</td>
<td>9</td>
<td>State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).</td>
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<tr>
<td>Data collection process</td>
<td>10</td>
<td>Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.</td>
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<tr>
<td>Definitions for data extraction</td>
<td>11</td>
<td>Provide definitions used in data extraction and classifications of target condition(s), index test(s), reference standard(s) and other characteristics (e.g. study design, clinical setting).</td>
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<tr>
<td>Risk of bias and applicability</td>
<td>12</td>
<td>Describe methods used for assessing risk of bias in individual studies and concerns regarding the applicability to the review question.</td>
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<tr>
<td>Diagnostic accuracy measures</td>
<td>13</td>
<td>State the principal diagnostic accuracy measure(s) reported (e.g. sensitivity, specificity) and state the unit of assessment (e.g. per-patient, per-lesion).</td>
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<tr>
<td>Synthesis of results</td>
<td>14</td>
<td>Describe methods of handling data, combining results of studies and describing variability between studies. This could include, but is not limited to: a) handling of multiple definitions of target condition. b) handling of multiple thresholds of test positivity, c) handling multiple index test readers, d) handling of indeterminate test results, e) grouping and comparing tests, f) handling of different reference standards</td>
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<tr>
<td>Meta-analysis</td>
<td>D2</td>
<td>Report the statistical methods used for meta-analyses, if performed.</td>
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<tr>
<td>Additional analyses</td>
<td>16</td>
<td>Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.</td>
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</tbody>
</table>

## RESULTS

| Study selection        | 17 | Provide numbers of studies screened, assessed for eligibility, included in the review (and included in meta-analysis, if applicable) with reasons for exclusions at each stage, ideally with a flow diagram. |                    |
| Study characteristics   | 18 | For each included study provide citations and present key characteristics including: a) participant characteristics (presentation, prior testing), b) clinical setting, c) study design, d) target condition definition, e) index test, f) reference standard, g) sample size, h) funding sources. |                    |
| Risk of bias and applicability | 19 | Present evaluation of risk of bias and concerns regarding applicability for each study. |                    |
| Results of individual studies | 20 | For each analysis in each study (e.g. unique combination of index test, reference standard, and positivity threshold) report 2x2 data (TP, FP, FN, TN) with estimates of diagnostic accuracy and confidence intervals, ideally with a forest or receiver operator characteristic (ROC) plot. |                    |
| Synthesis of results   | 21 | Describe test accuracy, including variability; if meta-analysis was done, include results and confidence intervals. |                    |
| Additional analysis    | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression; analysis of index test: failure rates, proportion of inconclusive results, adverse events). |                    |

## DISCUSSION

| Summary of evidence    | 24 | Summarize the main findings including the strength of evidence. |                    |
| Limitations            | 25 | Discuss limitations from included studies (e.g. risk of bias and concerns regarding applicability) and from the review process (e.g. incomplete retrieval of identified research). |                    |
| Conclusions            | 26 | Provide a general interpretation of the results in the context of other evidence. Discuss implications for future research and clinical practice (e.g. the intended use and clinical role of the index test). |                    |

## FUNDING

| Funding                | 27 | For the systematic review, describe the sources of funding and other support and the role of the funders. |                    |

Supplementary file 3: Search strategy

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily

# Searches

1 exp Mycobacterium tuberculosis/

2 (Mycobacterium tuberculosis or MTB or mycobacterium tuberculosis complex).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

3 exp Tuberculosis/

4 exp Tuberculosis, Pulmonary/

5 (TB or PTB or pulmonary tuberculosis or lung tuberculosis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

6 1 or 2 or 3 or 4 or 5

7 exp Adult/

8 exp Aged/

9 exp "Aged, 80 and over"/

10 exp Middle Aged/

11 (aged or elder* or adult*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

12 7 or 8 or 9 or 10 or 11

13 exp Feces/
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Supplemental material

BMJ Open
doi: 10.1136/bmjopen-2021-052212

Database: Embase (Ovid)

# Searches

1 exp Mycobacterium tuberculosis/

2 (Mycobacterium tuberculosis or MTB or mycobacterium tuberculosis complex).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

3 exp Tuberculosis/

4 exp Tuberculosis, Pulmonary/

5 (TB or PTB or pulmonary tuberculosis or lung tuberculosis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

6 1 or 2 or 3 or 4 or 5

7 exp Adult/

8 exp Aged/

9 exp "Aged, 80 and over"/

10 exp Middle Aged/

11 (aged or elder* or adult*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

12 7 or 8 or 9 or 10 or 11

13 exp Feces/

14 (stool or f?eces or f?ecal).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
supplementary concept word, protocol supplementary concept word, rare disease
supplementary concept word, unique identifier, synonyms

15  ((stool or f?eces or f?ecal) adj3 (analysis or sample* or specimen*)).mp. [mp=title,
abstract, original title, name of substance word, subject heading word, floating sub-heading
word, keyword heading word, organism supplementary concept word, protocol
supplementary concept word, rare disease supplementary concept word, unique identifier,
synonyms]

16  13 or 14 or 15

17  exp Diagnosis/

18  exp "Diagnostic Techniques and Procedures"/

19  exp "Sensitivity and Specificity"/

20  diagnos*.mp.

21  (diagnos* adj3 (accuracy or performance)).mp. [mp=title, abstract, original title, name
of substance word, subject heading word, floating sub-heading word, keyword heading word,
organism supplementary concept word, protocol supplementary concept word, rare disease
supplementary concept word, unique identifier, synonyms]

22  17 or 18 or 19 or 20 or 21

23  6 and 12 and 16 and 22
# Searches

1. TS=(Mycobacterium tuberculosis or MTB or mycobacterium tuberculosis complex)
2. TS=(TB or PTB or pulmonary tuberculosis or lung tuberculosis)
3. #2 OR #1
4. TS=(aged or elder* or adult*)
5. TS=(stool or f$eces or f$ecal)
6. TS=((stool or f$eces or f$ecal) NEAR/3 (analysis or sample* or specimen*))
7. #6 OR #5
8. TS=diagnos*
9. TS=(diagnos* NEAR/3 (accuracy or performance))
10. #9 OR #8
11. #10 AND #7 AND #4 AND #3