APPENDICES

Appendix A. Index Tests included in this Systematic Review

GenoType® MTBDR, introduced by Hain Lifescience in 2004, was among the first commercially available LPAs for molecular TB drug resistance. This was replaced by the GenoType® MTBDRplus (subsequently referred to as Hain V1), which was endorsed by WHO in 2008. This assay includes rpoB probes to determine RIF resistance, katG probes to determine high-level INH resistance, and inhA probes (not included in the initial GenoType® MTBDR assay) to determine low-level INH resistance. Hain developed an updated version of the MTBDRplus line probe assay in 2011 (subsequently referred to as Hain V2) to replace Hain V1. Hain V2 has an improved sample preparation that showed increased sensitivity for TB detection in the 2 studies published so far. Hain V2 was officially launched in February 2012 and Hain V1 has only remained on the market in countries until registration for Hain V2 was completed. At the current time, China remains the only country where Hain V1 is available. In 2011, Nipro Corporation has a line probe assay called NTM+MDRTB Detection Kit 2 (subsequently referred to as Nipro) on the market. This assay underwent Japanese registration in 2012 and allows for identification of M. tuberculosis complex (MTB) and resistance to RIF and INH and also differentiates M. avium, M. intracellulare and M. kansasii.

The rpoB, katG and inhA mutation probes are the same for the three assays aside from the katG S315N mutation, which is included in the Nipro assay but not Hain V1/V2. In addition there are some minor variations in the codon regions covered for the wild type between Hain V1/V2 and Nipro (see Figure S2a-d).

Figure S1. Index LPAs
Example of a) Hain GenoType MTBDRplus V1 and V2 strip readout and b) Nipro NTM+MDR Detection Kit 2 strip readout
Figure S2. Wild-type and mutation probes in index LPAs

Figure S2a. Hain V1/2 mutations in the \( \text{rpoB} \) gene and the corresponding wild type and mutation bands

| Sequence | Codons Analyzed | Mutation |
|----------|-----------------|----------|
| \( \text{rpoB} \text{ WT1} \) | 505-509 | F508L, T508A, S509T |
| \( \text{rpoB} \text{ WT2} \) | 510-513 | L511P* |
| \( \text{rpoB} \text{ WT2/WT3} \) | 510-517 | Q513L*, Q513P, del516-516 |
| \( \text{rpoB} \text{ WT3/WT4} \) | 513-519 | rpoB MUT1, D516Y, D516Y, del515 |
| \( \text{rpoB} \text{ WT4/WT5} \) | 516-522 | del518*, N521i |
| \( \text{rpoB} \text{ WT5/WT6} \) | 518-525 | S522L, S522Q |
| \( \text{rpoB} \text{ WT7} \) | 526-529 | rpoB MUT2A, H526Y, H526D |
| \( \text{rpoB} \text{ WT8} \) | 530-533 | rpoB MUT3 |

* This rare mutation has only been detected theoretically (in silico) yet. It is therefore possible that it cannot be detected in vitro.
Figure S2b. Hain V1/2 mutations in the *katG* gene and the corresponding wild type and mutation bands

| Failing wild type band | Codon analyzed | Developing mutation band | Mutation |
|------------------------|----------------|--------------------------|----------|
| *katG* WT              | 315            | *katG* MUT1              | S315T1   |
|                        |                | *katG* MUT2              | S315T2   |

Figure S2c. Hain V1/2 mutations in the *inhA* promoter region and the corresponding wild type and mutation bands

| Failing wild type band | Analyzed nucleic acid position | Developing mutation band | Mutation |
|------------------------|--------------------------------|--------------------------|----------|
| *inhA* WT1             | -15                            | *inhA* MUT1              | C-15T    |
|                        | -16                            | *inhA* MUT2              | A-16G    |
| *inhA* WT2             | -8                             | *inhA* MUT3A             | T-8C     |
|                        |                                | *inhA* MUT3B             | T-8A     |

Figure S2d. Nipro mutations in the *rpoB*, *katG* and *inhA* genes and the corresponding mutation bands

| NTM-MDR- TB2 strip | Probe | Amino acid (nucleotide) region covered by probe |
|--------------------|-------|-----------------------------------------------|
|                    | *rpoB* | 509-514                                       |
|                    | *rpoB* | 515-520                                       |
|                    | *rpoB* | 520-525                                       |
|                    | *rpoB* | 525-530                                       |
|                    | *rpoB* | 530-535                                       |
|                    | *rpoB* | D316V                                         |
|                    | *rpoB* | H526Y                                         |
|                    | *rpoB* | H526D                                         |
|                    | *rpoB* | S531L                                         |
|                    | *inhA* | (–17 to –3)                                   |
|                    | *inhA* | (a-16g)                                       |
|                    | *inhA* | (c-159)                                       |
|                    | *inhA* | (t-8c)                                        |
|                    | *inhA* | (t-8a)                                        |
|                    | *katG* | 294-299                                       |
|                    | *katG* | 313-317                                       |
|                    | *katG* | 323-327                                       |
|                    | *katG* | 325-330                                       |
|                    | *katG* | S315T                                         |
|                    | *katG* | S315N                                         |
Appendix B. Outcome Measures

Composite Reference Standard

The composite reference standard took into account the results from phenotypic DST and sequencing. If results were discrepant between phenotypic DST and sequencing, the final determination was based on whether the sequencing mutations detected are thought to be clinically significant (i.e. associated with resistance) using the TB dream database as a reference[22] and ReSeqTB (David Dolinger, personal communication) and additional clinical outcomes data[23]. The composite reference standard was constructed without knowledge of LPA results. If conventional DST showed sensitivity but sequencing identified mutations recognized to be associated with resistance, the composite reference standard was considered resistant. If conventional DST shows resistance but sequencing does not identify mutations to be associated with resistance, the composite reference standard was considered resistant (as mutations will be assumed outside of the region sequenced or alternatively there may be low-level heteroresistance below the limit of detection of the some sequencing technologies used; e.g. Sanger). The composite reference standard was constructed without knowledge of LPA results.

Indeterminate or invalid results

Test results were defined as ‘indeterminate’ if test results were valid but readers were unable to draw conclusions on the presence or absence of RIF/INH-resistance based on the visible banding pattern. This may be due to weak or completely absent bands for RIF or INH for a sample that tested positive for MTB on the LPA. Per manufacturers’ instructions, test results were regarded invalid if either the conjugate/colour control or the amplification control was negative. Of note, the only exception is that if the LPA result is positive for MTB, the amplification control may be weak or negative due to competition of the amplification reaction and thus this constitutes a valid test result. Since studies often do not differentiate between indeterminate and invalid results, we reported them together and described these as indeterminate.
Appendix C. Search Strategy

Date of search = 25th September 2015.

| Source                           | Date Range Searched | Hits Retrieved |
|----------------------------------|---------------------|----------------|
| ELECTRONIC DATABASES             |                     |                |
| Medline (PubMed)                 | 2004-present        | 328            |
| EMBASE                           | 2004-present        | 468            |
| EMBASE meeting papers            | 2004-present        | 145            |
| Web of Science                   | 2004-present        | 533            |
| BIOSIS                           | 2004-present        | 165            |
| Cochrane                         | 2004-present        | 6              |
| LILACS                           | 2004-present        | 5              |
| Final number of records in       |                     | 1650           |
| Endnote database after deleting  |                     |                |
| duplicates                       |                     | 916            |

Individual Database Search Strategies

PubMed

''("Tuberculosis"[Mesh] OR tuberculosis[tw] OR TB[tw] OR antitubercular[tw] OR "Mycobacterium tuberculosis"[Mesh]) AND (LPA[tw] OR LiPA[tw] OR "GenoType MTBDR"[tw] OR Nipro[tw] OR Hain[tw] OR MTBDRsl[tw] OR MTBDRplus[tw] OR "line probe assay"[tw] OR "line probe assays"[tw] OR "molecular diagnostic technique"[tw] OR "line probe assay"[tw] OR "line probe assays"[tw]) AND ("2004/01/01"[PDAT] : "2015/09/31"[PDAT])

Results 328

EMBASE

''mycobacterium tuberculosis'/exp OR tuberculosis:ab,ti OR tb:ab,ti OR tuberculosis*:ab,ti AND 'drug resistance'/exp OR 'tuberculosis'/exp OR tuberculosis:ab,ti OR tb:ab,ti OR tuberculosis*:ab,ti AND ('line probe assay?' OR (genotype* AND mtbdplus) OR lpa OR lipa OR 'genotype'/dn OR 'genotype mtbdrplus'/dn OR 'genotype mtbdrplus':ab,ti OR 'lipa'/dn OR 'mtbdrplus'/dn OR 'hain lifescience'/df OR nipro OR mtbdr OR mdrtb) AND ((article)/lim OR [article in press]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim) AND [2004-2015]/py

Results = 468

Meeting and Conference Papers added to EMBASE Meeting Conference folder ''mycobacterium tuberculosis'/exp OR tuberculosis:ab,ti OR tb:ab,ti OR tuberculosis*:ab,ti AND 'drug resistance'/exp OR 'tuberculosis'/exp OR tuberculosis:ab,ti OR tb:ab,ti OR tuberculosis*:ab,ti AND ('line probe assay?' OR (genotype* AND mtbdplus) OR lpa OR lipa OR 'genotype'/dn OR 'genotype mtbdrplus'/dn OR 'genotype mtbdrplus':ab,ti OR 'lipa'/dn OR 'mtbdrplus'/dn OR 'hain lifescience'/df OR nipro OR mtbdr OR mdrtb) AND ('conference abstract'/it OR 'conference paper'/it) AND [2004-2015]/py

Results 145
Web of Science

(((TS=((tuberculosis OR (TB)) OR ('MDR) (TB'))))) AND (TS=(((((((MTBDR*) OR ('line) (probe) (assay')))) OR ('line) (probe) (assay*'))))) OR (lpa)) OR (lipa)) OR (('genotype) (mtbdrplus'))) OR ('lipa')) OR ('mtbdrplus')) OR (('hain) (lifescience')))) OR (nipro)) OR (mdrtb)))) NOT (DT=( MEETING ABSTRACT OR PROCEEDINGS PAPER ))) AND DOCUMENT TYPES: (Article OR Abstract of Published Item OR Book OR Book Chapter OR Correction OR Correction, Addition OR Discussion OR Editorial Material OR Letter OR Review OR (DT=( MEETING ABSTRACT OR PROCEEDINGS PAPER )))
Indexes=SCI-EXPANDED Timespan=2004-2015

535 results

BIOSIS

You searched for: ((TS=(line probe assay OR LPA OR liPA OR MTBDRplus OR MTBDR plus OR Hain OR Nipro) AND TS=(tuberculosis OR TB)) AND DOCUMENT TYPES: (Article OR Book Chapter OR Letter OR Meeting OR Meeting Paper) OR Meeting Abstract OR Meeting Address OR Meeting Paper))
Refined by: PUBLICATION YEARS: (2013 OR 2009 OR 2012 OR 2008 OR 2014 OR 2006 OR 2007 OR 2011 OR 2005 OR 2015 OR 2004 OR 2010 )

Results 164

Cochrane
("line probe assay" OR lipa OR lpa OR 'genotype mtbdrplus' OR 'mtbdrplus' OR 'hain lifescience' OR nipro OR mdrtb ) AND ( Tuberculosis OR TB )

6 results

Lilacs
MTBDRplus [Words] or MTBDR [Words] AND tuberculosis

5 results
Appendix D. QUADAS-2 Protocol

Domain 1: Patient Selection:

Risk of Bias: Could the selection of patients have introduced bias?

- Signaling question 1: Was a consecutive or random sample of patients or specimens enrolled? We scored ‘yes’ if the study enrolled a consecutive or random sample of eligible patients; ‘no’ if the study selected patients by convenience, and ‘unclear’ if the study did not report the manner of patient selection or this could not be discerned.
- Signaling question 2: Was a case-control design avoided? We scored ‘yes’ if the study enrolled only patients suspected of drug-resistant TB, including patients with confirmed TB. We scored ‘no’ if the study enrolled patients for whom resistance status was already known, and ‘unclear’ if the study did not report the design or this could be discerned.
- Signaling question 3: Did the study avoid inappropriate exclusions? We scored ‘yes’ if no inappropriate exclusions were noted. We scored ‘no’ if studies noted specific exclusions. Inappropriate exclusions could potentially occur if patients were excluded based on prior knowledge about them or if the technician did not record performed test results but this was not anticipated for research studies in this review.

Risk of Bias was scored as ‘low risk’ if selection was done in a random or consecutive manner, avoided a case-control design and there were no inappropriate exclusions. Risk of Bias was scored as ‘high risk’ if selection was by convenience or based on a case-control design; and ‘unclear risk’ if the manner of participant selection was unclear or information on patient or specimen selection was not provided.

Applicability: Are there concerns that the included patients and setting do not match the review question?

We are interested in how LPA performed in patients suspected of having PTB who were evaluated as they would be in settings of intended use, based on the description of the clinical and laboratory settings in which the test was evaluated. Per current guidelines, LPA should be performed in laboratories at the district level and above. If study setting was below the district level, this raised the concern that the included patients and setting did not match the review question, given the infrastructure and quality control measures needed for a laboratory to perform LPA testing. We judged ‘low’ concern if the selected specimens match the review question, which reflects the way the test will be used in practice. We judged ‘high’ concern if the selected specimens or isolates did not represent those for which the test will be used in practice, such as extrapulmonary samples. We judged ‘unclear’ concern if we cannot tell.

Domain 2: Index Test

Risk of Bias: Could the conduct or interpretation of the index test have introduced bias?

- Signaling question 1: Were the index test results interpreted without knowledge of the results of the reference standard? We will score ‘yes’ if the resistance pattern of the specimen for LPA testing was interpreted without knowledge of the reference standard. We scored ‘no’ for all studies where LPA was performed without blinding to the results of reference specimens (blinding was more likely for fresh rather than frozen specimens). It is possible that bias could have been introduced when LPA is performed on culture specimens since interpretation of the test requires subjective analysis of the pattern of strips detected. If the index test is interpreted with an automated reader there should be no bias, however if it is hand interpreted or if the reader can be modified, this is subjective and could introduce bias. End users should be provided with a printed result that is not subject to interpretation. We scored ‘unclear’ if this is not stated.
- Signaling question 2: If a threshold was used, was it prespecified? The threshold was prespecified in all versions of LPA i.e. we score ‘yes’ for all studies.

For risk of bias, we judged ‘low risk’ for studies that were blinded or where LPA was clearly performed and recorded prior to culture results being available, ‘high risk’ for unblinded studies, and ‘unclear
risk’ for studies where blinding status was unclear or unspecified. Although sample processing was likely to be different between studies, this is unlikely to introduce systematic bias.

Applicability: Are there concerns that the index test, its conduct, or its interpretation differ from the review question? Variations in test technology, execution, or interpretation may affect estimates of the diagnostic accuracy of a test.

We judged ‘low concern’ if the test was done as per recommendation of the manufacturer for LPA samples and if blinding was stated. We judged ‘high concern’ if the lack of blinding was stated and/or if additional steps were used for sample preparation and ‘unclear concern’ if the blinding status of the study was unclear or unspecified.

Domain 3: Reference Standard

Risk of Bias: Could the reference standard, its conduct, or its interpretation have introduced bias?

- Signaling question 1: Is the reference standard likely to correctly classify the target condition? We scored ‘yes’ if either culture/DST with WHO critical concentrations, sequencing (with noted caveats below) or a composite reference standard with culture and sequencing were used. Since we excluded studies that did not have an adequate reference standard, we did not score ‘no’ for any included studies but scored ‘unclear’ if the conduct of performing the reference standard was unclear. Culture is the test currently endorsed by WHO for the detection of MTB and for DST. Sequencing may be used as a reference standard for DST in some studies. The accuracy of genetic sequencing for the detection of drug resistance varies according to the drug in question. For H-resistance detection, about 10-15% of phenotypically resistant strains do not have mutations in target genes. Therefore a sequencing reference standard alone is likely to misclassify a subset of isolates. However for R-resistance detection, a subset of clinically significant resistance mutations in rpoB will appear sensitive on phenotypic DST (Van Deun 2012, 2015). A composite reference standard would therefore be used ideally but we anticipated that most included studies would employ one of the other reference standards that are WHO endorsed and will thus still be scored as ‘yes’.

- Signaling question 2: Were the reference standard results interpreted without knowledge of the results of the index test? We scored ‘yes’ if the reference test provided was culture e.g. MGIT 960 DST if it is known that an automated result was generated (except for LJ with confirmation of MTB by a NAAT-based test), if blinding was explicitly stated, or if it was clear that the reference standard was performed at a separate laboratory and/or performed by different people. We scored ‘no’ if the study stated that the reference standard was interpreted with knowledge of the index LPA result. We will score ‘unclear’ if this was not stated or answered inadequately.

For risk of bias, we judged ‘low risk’ if the reference standard used is WHO-endorsed and performed as per WHO recommendations or if a composite reference standard was used and if the reference standard was interpreted without knowledge of the index LPA result. We judged ‘high risk’ if the reference standard was interpreted with knowledge of the index LPA test and ‘unclear risk’ if the standards under which the reference standard were performed were unclear.

Applicability: Are there concerns that the target condition as defined by the reference standard does not match the question?

We judge applicability to be of ‘low concern’ for all studies.

Domain 4: Flow and Timing

Risk of Bias: Could the patient flow have introduced bias?

- Signaling question 1: Was there an appropriate interval between the index test and reference standard? We scored ‘yes’ if the tests were paired or separated by less than 48 hours after treatment initiation. We scored ‘no’ if the reference and index tests were not performed on paired samples or were separated by more than a week. We scored ‘unclear’ if this was not stated in the paper or answered inadequately. In the majority of included studies, we expected specimens for LPA and culture to be
obtained at the same time (i.e. to be performed on paired samples for the majority of studies), when patients are suspected of having TB or MDR-TB. Although TB is often a chronic infection thus making misclassification of disease status unlikely, being on treatment could alter the microbial population of specimens collected more than 48 hours after treatment initiation.

- Signaling question 2: Did all patients receive the same reference standard? We scored ‘yes’ if all studies used the same reference standard (acceptable reference standard as specified above, i.e. either phenotypic, genotypic or composite reference standard, as a criterion for inclusion in the review). We scored ‘no’ if different reference standards were used or if the reference standard was only applied to a selective group of patients or if culture was followed by sequencing of only the discrepant results because this could introduce potential verification bias if the same reference standard was not used to confirm all index test results. We scored ‘unclear’ if this was not stated in the paper or answered inadequately.

- Signaling question 3: Were all patients included in the analysis? The answer to this question was determined by comparing the number of patients enrolled with the number of patients included in the two-by-two tables. We noted if authors recorded the number of indeterminate results. We scored ‘yes’ if the number of participants enrolled was clearly stated and corresponded to the number presented in the analysis or if exclusions were adequately described. We scored ‘no’ if there were participants missing or excluded from the analysis and there was no explanation given; and ‘unclear’ if not enough information was given to assess whether participants were excluded from the analysis e.g. if the number of participants originally enrolled in the study was not explicitly stated.

For risk of bias, we judged ‘low risk’ if the index and reference tests were performed on paired specimens or performed within less than 48 hours of treatment, if the same reference standard was applied to all patients or specimens and if all patients or specimens were included. We judged ‘high risk’ if the interval between the index and reference test was >48 hours after treatment initiation or if different reference standards were applied to different groups included in the study or if patients or specimens were inappropriately excluded. We judged ‘unclear risk’ if the interval between reference and index tests was unclear or if it was unclear that the same reference standard was not applied to all participants or specimens or if it is unclear whether patients or specimens were excluded from the analysis inappropriately.
Appendix D.2. Characteristics related to Methodological Quality (QUADAS-2) for included studies.

Patient Selection

Rifampicin Resistance

17 datasets were judged to have a ‘high risk of bias’. In 2 datasets, this was due to the lack of consecutive or random sampling of patients or specimens and in 14 datasets this was due to the use of a case-control design. 21 datasets were judged to have a ‘low risk of bias’. In 56 datasets, the risk of bias was ‘unclear’. In 54 of these 56 datasets, the method of sampling patients or specimens was not specified, 1 dataset had an unclear design and in 1 dataset it was unclear whether there had been inappropriate exclusions. In 15 of these 54 datasets with an unclear method of sampling, the design of the study was also unclear. In 1 of these 54 datasets, it was also unclear whether there had been inappropriate exclusions. Applicability in this domain focused on whether the patients who underwent LPA testing and whether the clinical and or laboratory settings were appropriate for their intended use. Applicability was judged to be ‘low-risk’ in 76 datasets and no datasets were ‘high-risk’. 18 datasets were judged to be of ‘unclear-risk’, 10 of which did not specify the type of patients or specimens that were tested, 7 of which did not specify the laboratory setting in which testing was performed and 1 of which did not specify either of these factors.

Isoniazid resistance detection

In the ‘patient selection’ domain, 16 datasets were judged to have a ‘high risk of bias’. In 2 datasets, this was due to the lack of consecutive or random sampling of patients or specimens and in 13 datasets this was due to the use of a case-control design. 21 datasets were judged to have a ‘low risk of bias’. In 53 studies, the risk of bias was ‘unclear’. In 50 of these 53 datasets, the method of sampling patients or specimens was not specified and in 1 dataset it was unclear whether there had been inappropriate exclusions. In 14 of these 50 datasets with an unclear method of sampling, the design of the dataset was also unclear. In 1 of these 50 datasets, it was also unclear whether there had been inappropriate exclusions. Applicability in this domain focused on whether the patients who underwent LPA testing and whether the clinical and or laboratory settings were appropriate for their intended use. Applicability was judged to be ‘low-risk’ in 72 datasets and no datasets were ‘high-risk’. 18 datasets were judged to be of ‘unclear-risk’, 10 of which did not specify the type of patients or specimens that were tested, 7 of which did not specify the laboratory setting in which testing was performed and 1 of which did not specify either of these factors.
In the ‘patient selection’ domain, 5 datasets were judged to have an ‘unclear risk of bias’ because the method of sampling patients or specimens was not specified and the other dataset had a ‘low risk of bias’. Applicability in this domain focused on whether the patients who underwent LPA testing for MTB detection and whether the clinical and or laboratory settings were appropriate for their intended use. Applicability was judged to be ‘low-risk’ in 5 datasets and no datasets were ‘high-risk’. 1 dataset was judged to be of ‘unclear-risk’ as the laboratory setting in which testing was performed was not specified.

Index Test

Rifampicin Resistance
In the ‘index test’ domain, 0 datasets were judged to have a ‘high risk of bias’. 28 datasets were judged to have a ‘low risk of bias’. In 66 datasets, the risk of bias was ‘unclear’, because datasets did not specify whether the person performing the index test was blinded to the results of the reference standard testing. Applicability in this domain focused on whether the conduct of performing and interpreting the index test was in line with the manufacturer’s recommendations. Applicability was judged to be ‘low-risk’ in 86 datasets. 8 datasets were judged to ‘high-risk’ for applicability concerns due to variations in which the test was performed that were not according to the manufacturer’s recommendations.

Isoniazid resistance detection
In the ‘index test’ domain, 0 datasets were judged to have a ‘high risk of bias’. 27 datasets were judged to have a ‘low risk of bias’. In 63 datasets, the risk of bias was ‘unclear’, because datasets did not specify whether the person performing the index test was blinded to the results of the reference standard testing. Applicability in this domain focused on whether the conduct of performing and interpreting the index test was in line with the manufacturer’s recommendations. Applicability was judged to be ‘low-risk’ in 82 datasets. 8 datasets were judged to ‘high-risk’ for applicability concerns due to variations in which the test was performed that were not according to the manufacturer’s recommendations.

MTB detection
In the ‘index test’ domain, 0 datasets were judged to have a ‘high risk of bias’. 4 datasets were judged to have a ‘low risk of bias’. In 2 datasets, the risk of bias was ‘unclear’, because datasets did not specify whether the person performing the index test was blinded to the results of the reference
standard testing. Applicability in this domain focused on whether the conduct of performing and interpreting the index test was in line with the manufacturer’s recommendations. Applicability was judged to be ‘low-risk’ in 5 datasets. 1 dataset was judged to be ‘high-risk’ for applicability concerns due to a variation in which the test was performed that were not according to the manufacturer’s recommendations.

**Reference Standard**

**Rifampicin Resistance**
In the ‘reference standard’ domain, 0 datasets were judged to have a ‘high risk of bias’. 26 datasets were judged to have a ‘low risk of bias’. In 68 datasets, the risk of bias was ‘unclear’, because datasets did not specify whether the person performing the reference test was blinded to the results of the index test. Applicability in this domain focused on whether the conduct of performing and interpreting the index test was in line with the manufacturer's recommendations. Applicability was judged to be of ‘low-concern’ in all 94 datasets.

**Isoniazid resistance detection**
In the ‘reference standard’ domain, 0 datasets were judged to have a ‘high risk of bias’. 25 datasets were judged to have a ‘low risk of bias’. In 65 datasets, the risk of bias was ‘unclear’, because datasets did not specify whether the person performing the reference test was blinded to the results of the index test. Applicability in this domain focused on whether the conduct of performing and interpreting the index test was in line with the manufacturer’s recommendations. Applicability was judged to be of ‘low-concern’ in all 90 datasets.

**MTB detection**
In the ‘reference standard’ domain, 0 datasets were judged to have a ‘high risk of bias’. 3 datasets were judged to have a ‘low risk of bias’ and 3 datasets were judged to have an ‘unclear risk of bias’ as they did not specify whether the person performing the reference test was blinded to the results of the index test. Applicability in this domain focused on whether the conduct of performing and interpreting the index test was in line with the manufacturer's recommendations. Applicability was judged to be of ‘low-concern’ in all 6 datasets.
Flow and Timing

Rifampicin Resistance
In the ‘flow and timing domain, 12 datasets were judged to have a ‘high risk of bias’ because more than one type of reference standard was used and not all patients or specimens received the same reference standard. 78 datasets were judged to have a ‘low risk of bias’. In the remaining 4 datasets, the risk of bias was ‘unclear’, because 3 datasets did not specify the type of reference standard that was used and 1 dataset did not include all patients in the 2x2 tables.

Isoniazid Resistance
In the ‘flow and timing domain, 12 datasets were judged to have a ‘high risk of bias’ because more than one type of reference standard was used and not all patients or specimens received the same reference standard. 74 datasets were judged to have a ‘low risk of bias’. In the remaining 4 datasets, the risk of bias was ‘unclear’, because 3 datasets did not specify the type of reference standard that was used and 1 dataset did not include all patients in the 2x2 tables.

MTB Detection
In the ‘flow and timing domain, all 6 datasets were judged to have a ‘low risk of bias’.
Appendix D3. Risk of bias and applicability summaries for each QUADAS-2 domain by study

Figure S3a. Risk of bias and applicability summary for RIF and INH resistance detection

### Hain MDRTBplus V1 Studies, Risk of Bias

|                       | Patient Selection | Index Test | Reference Standard | Flow and Timing |
|-----------------------|-------------------|------------|--------------------|-----------------|
| Al-Mutairi, 2011      | -                 | ?          | ?                  | +               |
| Albert, 2010          | +                 | +          | +                  | +               |
| Anek-Vorapong, 2010 (a) | ?             | +          | +                  | +               |
| Anek-Vorapong, 2010 (b) | ?             | +          | +                  | +               |
| Asante Poku, 2015     | +                 | ?          | ?                  | +               |
| Ascencios 2012 (a)    | ?                 | ?          | ?                  | +               |
| Ascencios 2012 (b)    | ?                 | ?          | ?                  | +               |
| Aung, 2015            | ?                 | ?          | ?                  | +               |
| Aurin, 2014           | ?                 | ?          | ?                  | +               |
| Banu, 2014            | ?                 | ?          | ?                  | +               |
| Barnard, 2008         | +                 | +          | ?                  | +               |
| Brossier, 2009        | ?                 | ?          | ?                  | +               |
| Bwanga, 2010          | -                 | +          | +                  | +               |
| Cabibbe, 2015 (a)     | ?                 | ?          | ?                  | +               |
| Cabibbe, 2015 (b)     | ?                 | ?          | ?                  | +               |
| Causse, 2008 (a)      | ?                 | ?          | ?                  | +               |

### Applicability Concerns

|                       | Patient Selection | Index Test | Reference Standard |
|-----------------------|-------------------|------------|--------------------|
| Al-Mutairi, 2011      | +                 | -          | +                  |
| Albert, 2010          | +                 | +          | +                  |
| Anek-Vorapong, 2010 (a) | +             | +          | +                  |
| Anek-Vorapong, 2010 (b) | +             | +          | +                  |
| Asante Poku, 2015     | +                 | +          | +                  |
| Ascencios 2012 (a)    | +                 | +          | +                  |
| Ascencios 2012 (b)    | +                 | +          | +                  |
| Aung, 2015            | +                 | +          | +                  |
| Aurin, 2014           | +                 | +          | +                  |
| Banu, 2014            | +                 | +          | +                  |
| Barnard, 2008         | +                 | +          | +                  |
| Brossier, 2009        | +                 | +          | +                  |
| Bwanga, 2010          | +                 | +          | +                  |
| Cabibbe, 2015 (a)     | +                 | +          | +                  |
| Cabibbe, 2015 (b)     | +                 | +          | +                  |
| Causse, 2008 (a)      | +                 | +          | +                  |
null
| Patient Selection | Index Test | Reference Standard | Flow and Timing |
|-------------------|------------|---------------------|-----------------|
| Huang, 2015       | +          | ?                   | +               |
| Huang, 2009       | ?          | ?                   | ?               |
| Huang, 2014       | ?          | ?                   | +               |
| Huyen, 2010       | -          | +                   | +               |
| Imperiale, 2012   | ?          | ?                   | ?               |
| Imperiale, 2012   |               |                    |                 |
| Jin, 2012         |            |                     |                 |
| Kapata, 2015      | +          | ?                   | +               |
| Khadka, 2011      | ?          | ?                   | +               |
| Kumar, 2014       | ?          | +                   | +               |
| Lacoma, 2008      | ?          | +                   | +               |
| Lacoma, 2008      | ?          | +                   | +               |
| Li, 2015          | +          | ?                   | +               |
| Luetkemeyer, 2014 |            |                     |                 |
| Lyu, 2013         |            |                     |                 |
| Macedo 2009       | ?          | +                   | +               |
| Maschmann Rde, 2013|          |                     |                 |

Figure S3a (cont.)
|                              | Patient Selection | Index Test | Reference Standard | Flow and Timing |
|------------------------------|-------------------|------------|--------------------|-----------------|
| Miotto, 2008 (a)             | -                 | ?          | ?                  | +               |
| Miotto, 2008 (b)             | ?                 | ?          | ?                  | +               |
| Miotto, 2009 (a)             | ?                 | ?          | ?                  | +               |
| Miotto, 2009 (b)             | ?                 | ?          | ?                  | +               |
| Mironova, 2012 (a)           | ?                 | ?          | ?                  | +               |
| Mironova, 2012 (b)           | ?                 | ?          | ?                  | +               |
| N’Guessan, 2014              | ?                 | ?          | ?                  | +               |
| Nathavitharana, 2016 (a)     | -                 | +          | +                  | -               |
| Nathavitharana, 2016 (b)     | +                 | +          | +                  | -               |
| Niehaus, 2015                | +                 | ?          | ?                  | +               |
| Nikolayevskyy, 2009          | +                 | +          | +                  | +               |
| Nwofor, 2015                 | ?                 | ?          | ?                  | +               |
| *Ocheretina, 2014            | ?                 | ?          | ?                  | +               |
| Raizada, 2014                | +                 | ?          | ?                  | +               |
| Raveedran, 2012 (a)          | ?                 | ?          | ?                  | +               |
| Raveedran, 2012 (b)          | ?                 | ?          | ?                  | +               |
| Patient Selection | Index Test | Reference Standard | Flow and Timing |
|-------------------|------------|--------------------|-----------------|
| Rigouts, 2011     | +          | +                  | +               |
| *Rufai, 2014      | ?          | +                  | +               |
| Sangsayunh, 2014  | ?          | ?                  | +               |
| *Schon, 2013      | -          | ?                  | +               |
| Scott, 2011       | +          | +                  | +               |
| Shubladze, 2013   | +          | ?                  | +               |
| Simons, 2015      | +          | ?                  | +               |
| Singhal, 2012     | ?          | ?                  | +               |
| Tessema 2012      | ?          | ?                  | +               |
| Tho, 2011         | -          | ?                  | +               |
| Tolani, 2012 (i)  | -          | ?                  | +               |
| Tolani, 2012 (ii) | -          | ?                  | +               |
| Tukvadze, 2012    | +          | ?                  | +               |
| Vijdea, 2008      | -          | ?                  | +               |
| Yadav, 2013       | ?          | +                  | +               |
| Yordanova, 2013   | -          | ?                  | +               |

- Green indicates 'Yes', red indicates 'No', and yellow indicates 'Questionable'.

- Rigouts, 2011
- *Rufai, 2014
- Sangsayunh, 2014
- *Schon, 2013
- Scott, 2011
- Shubladze, 2013
- Simons, 2015
- Singhal, 2012
- Tessema 2012
- Tho, 2011
- Tolani, 2012 (i)
- Tolani, 2012 (ii)
- Tukvadze, 2012
- Vijdea, 2008
- Yadav, 2013
- Yordanova, 2013
Figure S3a (cont.)

### Hain MDRTBplus V2 Studies, Risk of Bias

| Patient Selection | Index Test | Reference Standard | Flow and Timing |
|-------------------|------------|--------------------|-----------------|
| Babishvili, 2015  | +          | -                  | +               |
| Catanzaro, 2015   | ?          | -                  | +               |
| Crudu, 2012       | ?          | +                  | +               |
| Nathavitharana, 2016 (c) | - | + | + |
| Nathavitharana, 2016 (d) | + | + | + |

### Applicability Concerns

| Patient Selection | Index Test | Reference Standard |
|-------------------|------------|--------------------|
| Babishvili, 2015  | +          | +                  |
| Catanzaro, 2015   | ?          | +                  |
| Crudu, 2012       | +          | +                  |
| Nathavitharana, 2016 (c) | + | + | + |
| Nathavitharana, 2016 (d) | + | + | + |

### Nipro NTM+/MDR Detection Kit 2 Studies, Risk of Bias

| Patient Selection | Index Test | Reference Standard | Flow and Timing |
|-------------------|------------|--------------------|-----------------|
| Mitarai, 2012 (a) | ?          | ?                  | -               |
| Mitarai, 2012 (b) | ?          | ?                  | -               |
| Rienthong, 2015 (a) | - | + | + |
| Rienthong, 2015 (b) | + | + | + |
| Nathavitharana, 2016 (e) | - | + | + |
| Nathavitharana, 2016 (f) | + | + | + |

### Applicability Concerns

| Patient Selection | Index Test | Reference Standard |
|-------------------|------------|--------------------|
| Mitarai, 2012 (a) | ?          | +                  |
| Mitarai, 2012 (b) | ?          | +                  |
| Rienthong, 2015 (a) | ? | + | + |
| Rienthong, 2015 (b) | ? | + | + |
| Nathavitharana, 2016 (e) | + | + | + |
| Nathavitharana, 2016 (f) | + | + | + |

* These 4 studies only contributed data to RIF resistance detection (but not INH)
Figure S3b. Risk of bias and applicability summary for each QUADAS domain for each study for MTB detection.

| Hain MDRTBplus V1 Studies, Risk of Bias | Applicability Concerns |
|----------------------------------------|------------------------|
| **Patient Selection** | **Index Test** | **Reference Standard** | **Flow and Timing** |
| Dorman, 2012 | ? | + | + | + |
| Felkel, 2013 | ? | ? | + | + |
| Friedrich, 2011 | ? | ? | + | + |
| Luetkemeyer, 2014 | ? | + | + | + |
| Scott, 2011 | + | + | + | + |

| Hain MDRTBplus V2 Studies, Risk of Bias | Applicability Concerns |
|----------------------------------------|------------------------|
| **Patient Selection** | **Index Test** | **Reference Standard** |
| Crudu, 2012 | ? | + | + | + |

| Dorman, 2012 | + | + | + |
| Felkel, 2013 | + | + | + |
| Friedrich, 2011 | + | + | + |
| Luetkemeyer, 2014 | + | + | + |
| Scott, 2011 | ? | - | + |
Appendix E. List of Excluded Studies.

(Total 130)

Not Pulmonary TB

1. Folkvardsen DB, Svensson E, Thomsen VO, Rasmussen EM, Bang D, et al. (2013) Can molecular methods detect 1% isoniazid resistance in Mycobacterium tuberculosis? J Clin Microbiol 51: 1596-1599.

2. Folkvardsen DB, Thomsen VO, Rigouts L, Rasmussen EM, Bang D, et al. (2013) Rifampin heteroresistance in Mycobacterium tuberculosis cultures as detected by phenotypic and genotypic drug susceptibility test methods. J Clin Microbiol 51: 4220-4222.

Other LPA

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2. Bang H, Park S, Hwang J, Jin H, Cho E, et al. (2011) Improved rapid molecular diagnosis of multidrug-resistant tuberculosis using a new reverse hybridization assay, REBA MTB-MDR. Journal of Medical Microbiology 60: 1447-1454.

3. Ben Kahla I, Ben Selma W, Marzouk M, Ferjeni A, Ghezal S, et al. (2011) Evaluation of a simplified IS6110 PCR for the rapid diagnosis of Mycobacterium tuberculosis in an area with high tuberculosis incidence. Pathol Biol (Paris) 59: 161-165.

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9. Negi SS, Anand R, Pasha ST, Gupta S, Basir SF, et al. (2006) Molecular characterization of mutation associated with rifampicin and isoniazid resistance in Mycobacterium tuberculosis isolates. Indian J Exp Biol 44: 547-553.

10. O'Donnell N, Corcoran D, Lucey B, Barrett A (2012) Molecular-based mycobacterial identification in a clinical laboratory setting: a comparison of two methods. Br J Biomed Sci 69: 164-168.

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13. Shah NS, Lan NT, Huyen MN, Laserson K, Iademarco MF, et al. (2009) Validation of the line-probe assay for rapid detection of rifampicin-resistant Mycobacterium tuberculosis in Vietnam. Int J Tuberc Lung Dis 13: 247-252.

14. Skenders G, Fry AM, Prokopovic a I, Greckoseja S, Broka L, et al. (2005) Multidrug-resistant tuberculosis detection, Latvia. Emerg Infect Dis 11: 1461-1463.

15. Viveiros M, Martins M, Couto I, Rodrigues L, MacHado D, et al. (2010) Molecular tools for rapid identification and novel effective therapy against MDRTB/XDRRTB infections. Expert Review of Anti-Infective Therapy 8: 465-480.

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Other LPA - MTBDR

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9. Makinen J, Marttila HJ, Marjamaki M, Viljanen MK, Soini H (2006) Comparison of two commercially available DNA line probe assays for detection of multidrug-resistant Mycobacterium tuberculosis. J Clin Microbiol 44: 350-352.

10. Miotto P, Piana F, Penati V, Canducci F, Migliori GB, et al. (2006) Use of genotype MTBDR assay for molecular detection of rifampin and isoniazid resistance in Mycobacterium tuberculosis clinical strains isolated in Italy. J Clin Microbiol 44: 2485-2491.

11. Saglik I, Oz Y, Kiraz N (2014) Evaluation of the GenoType MTBDR assay for detection of rifampicin and isoniazid resistance in Mycobacterium tuberculosis complex isolates. Indian J Med Microbiol 32: 318-322.

12. Somoskovi A, Dormandy J, Mitsani D, Rivenburg J, Salfinger M (2006) Use of smear-positive samples to assess the PCR-based genotype MTBDR assay for rapid, direct detection of the Mycobacterium tuberculosis complex as well as its resistance to isoniazid and rifampin. J Clin Microbiol 44: 4459-4463.

13. Tho DQ, Ha DT, Duy PM, Lan NT, Hoa DV, et al. (2008) Comparison of MAS-PCR and GenoType MTBDR assay for the detection of rifampicin-resistant Mycobacterium tuberculosis. Int J Tuberc Lung Dis 12: 1306-1312.

No primary data

1. Singh S (2014) Early detection of multi-drug resistant tuberculosis in India using GenoType MTBDRplus assay & profile of resistance mutations in Mycobacterium tuberculosis. Indian J Med Res 140: 477-479.

2. Wiwanitkit V (2015) GenoType MTBDR assay for detection of rifampicin and isoniazid resistance. Indian J Med Microbiol 33: 147.

Abstract only

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3. Barreales-Fonseca A, Garcia-Martinez De Artola D, Hernandez-Caceres I, Alcoba-Florez J (2012) GeneXpert MTB/RIF system in pulmonary and extrapulmonary specimens: Comparison with other nucleic acid technologies. Clinical Microbiology and Infection 18: 773.

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7. Galkina K, Nosova E, Krasnova M (2012) Modern molecular direct tests for rapid identification and drug susceptibility testing of Mycobacterium tuberculosis. European Respiratory Journal 40.

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12. Hernández-Cáceres I, Díez-Gil Ó, Alcoba-Flórez J (2011) Genotypic detection of rifampicin- and isoniazid-resistant Mycobacterium tuberculosis strains by the pyrosequencing method. Clinical Microbiology and Infection 17: S483.

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14. Ioannidis P, Papaventsis D, Karabela S, Marinou I, Konstantinidou E, et al. (2012) Evaluation of Genotype® MTBDRplus for the rapid detection of Mycobacterium tuberculosis resistance to rifampicin and isoniazid in clinical samples. Clinical Microbiology and Infection 18: 545.

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20. Matabane MMZ, Ismail F, Strydom KA, Onwuegbuna O, Vally Omar S, et al. (2014) Evaluation of three molecular assays for the detection of M. tuberculosis from direct clinical specimens. International Journal of Infectious Diseases 21: 371.

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Unable to translate

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No diagnostic accuracy data

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No extractable data, no response from authors

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Appendix F. Explanation of the 94 datasets

Thirteen studies used different populations of patients or specimens to perform indirect and direct testing separately and were thus included as two separate datasets[19,29-40]. Only one of these studies performed head-to-head testing of all three target LPAs on directly tested clinical specimens and indirectly tested isolates and was included as 6 separate datasets[19]. One study performed indirect testing on two different populations with two different phenotypic reference standards and was included as two separate data sets[41]. Two studies (excluded from MTB analysis due to patient treatment history) examined two different populations of TB patients and were included as four separate datasets. One of these studies recruited ‘chronic’ TB patients failing first line therapies and had two populations: one enrolled prior to starting second line treatment and one population who were enrolled within the first month of treatment[42]. The second study enrolled patients with no prior history of TB and tested them at the beginning of treatment and then again in the 5th month of treatment[43]. Of the total 94 unique datasets, 74 (79%) evaluated patients from low- or middle-income countries. In 57 (61%) datasets, the laboratory setting where LPA was performed was in a low- or middle-income country.
Table S1. Indeterminate results
These are grouped by index test, type of testing and PICO question. The median and range are given followed by the number of datasets that reported this data in parentheses.

|                      | Hain V1 Direct | Hain V1 Indirect | Hain V2 Direct | Hain V2 Indirect | Nipro Direct | Nipro Indirect |
|----------------------|----------------|------------------|----------------|------------------|--------------|----------------|
| Rifampicin resistance| 5.1%, 0.9-14.5% (26) | 1.0%, 0.5-2.1% (3) | 6.0%, 1.3-10.8% (3) | 0.5% (1) | 6.1% (1) | 1.1% (1) |
| Isoniazid resistance  | 5.3%, 0.9-14.5% (24) | 0.9%, 0.5-1.0% (3) | 5.7%, 1.3-12.9% (3) | 0.5% (1) | 5.9% (1) | 0.5% (1) |
| MTB detection        | 0.7-1.7% (3) | N/R              | N/R            | N/R             | N/R          | N/R            |

N/R: none reported

Table S2. Diagnostic accuracy of LPA for all three assays, stratified by LPA type.

| Reference standard | LPA    | Test | Direct or Indirect | # Studies (# Samples) | Sensitivity 95% C.I. | Specificity 95% C.I. | Positive LR 95% C.I. | Negative LR 95% C.I. |
|--------------------|--------|------|--------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Phenotypic         | Hain V1| RIF  | All                | 80 (17 375)           | 97.1% (95.9 - 97.9)  | 98.9% (98.3 - 99.3)  | 89.2 (56.4 – 141.1)   | 0.03 (0.02 – 0.04)   |
|                    | Hain V2| RIF  | All                | 5 (2 241)             | 95.0% (91.6 - 97.0)  | 98.3% (97.2 - 99.0)  | 56.2 (33.8 – 93.5)    | 0.05 (0.03 – 0.09)   |
|                    | Nipro  | RIF  | All                | 6 (1 609)             | 94.3% (89.4 - 97.1)  | 98.1% (96.8 - 98.9)  | 50.9 (29.5 – 88.0)    | 0.06 (0.03 – 0.11)   |
| Phenotypic         | Hain V1| INH  | All                | 76 (17 106)           | 90.2% (88.0 - 92.1)  | 99.2% (98.9 - 99.5)  | 112.2 (68.3 – 184.3)  | 0.09 (0.08 – 0.12)   |
|                    | Hain V2| INH  | All                | 5 (2 243)             | 93.6% (90.4 - 95.8)  | 99.1% (95.6 - 99.8)  | 102.3 (21.4 – 487.9)  | 0.06 (0.04 – 0.10)   |
|                    | Nipro  | INH  | All                | 6 (1 605)             | 86.9% (72.5 - 94.3)  | 99.1% (97.2 - 99.7)  | 99.1 (32.2 – 305.3)   | 0.13 (0.06 – 0.29)   |
| Author, year            | LPA (Direct vs Indirect) | Country or Region | Composite standard | Targeted regions sequenced | Samples sequenced | Mutations in phenotypic resistant, LPA sensitive strains (n)* | Mutations in phenotypic sensitive, LPA resistant strains (n)* | Composite standard leads to different test performance |
|-------------------------|--------------------------|-------------------|--------------------|-----------------------------|------------------|---------------------------------------------------------------|---------------------------------------------------------------|----------------------------------------------------------|
| Al-Mutairi, 2011        | Hain V1 (Indirect)       | Kuwait            | BacTec plus targeted sequencing | rpoB†                        | All 125 strains (82 MDR and 43 pan-susceptible) | 4 total: • L533P (1) • I572F (2) • Wild type (1) | None | No |
| Asante-Poku 2015        | Hain V1 (Indirect)       | Ghana             | Proportion method plus sequencing | rpoB‡                        | 51 phenotypically resistant isolates | None | None | No |
| Dorman 2012             | Hain V1 (Direct)         | South Africa      | MGIT plus targeted sequencing | rpoB (primers not specified) | 4 phenotypic / LPA discordant isolates | 2 total: • Wild type (2) | 2 total: • S531L (2) | Yes |
| Fabre 2011              | Hain V1 (Indirect)       | 15 countries      | BacTec plus targeted sequencing | rpoB§                        | All 144 strains (129 RIF-R) | 1 total: • double mutation E562G/P564L (1) | None | No |
| Farooqi 2012            | Hain V1 (Direct)         | Pakistan          | Proportion method plus targeted sequencing | rpoB**                       | 5 phenotypic / LPA discordant isolates | 4 total: • del518 (1) • S531W (1) • Wild type (2) | 2 total (only 1 sequenced) • H526N (1) | Yes |
| Felkel 2013             | Hain V1 (Direct)         | Nigeria           | BacTec plus targeted sequencing | rpoB (primers not specified) | 1 phenotypic / LPA discordant isolate | 1 total: • Wild type (1) | None | No |

* Bold indicates a known resistance conferring mutation
† rpoB HSR, N-terminal and cluster II regions
‡ rpoB Ko1 and Ko2
§ rpoB RPOB-TR1 and RPOB-3R
** rpoB 81bp hypervariable region
| Study Year | Hain V1 Type | Country | Methodology | Gene | Number of Strains | Discordant Results | Wild Type | Susceptibility |
|------------|--------------|---------|-------------|------|-------------------|-------------------|-----------|---------------|
| 2007       | Indirect     | Germany | Mixed: MGIT and proportion method plus targeted sequencing | rpoB (primers not specified) | All 125 previously characterized strains (75 MDR, 50 pan-susceptible) | 1 total - V176F (1) | None | No            |
| 2007       | Direct       | Germany | Mixed: MGIT and proportion method plus targeted sequencing | rpoB (primers not specified) | 11 phenotypic / LPA discordant isolates or deltaWT bands only on LPA | 1 total - Wild type (1) | None | No            |
| 2015       | Indirect     | China   | Proportion method plus targeted sequencing | rpoB (primers not specified) | All 430 strains | None | None | No            |
| 2009       | Indirect     | Taiwan  | Mixed: MGIT or proportion method plus targeted sequencing | rpoB†† | All 272 isolates (242 MDR and 30 pan-susceptible) | 11 total - L533P (8) - Wild type (3) | None | No            |
| 2014       | Indirect     | Taiwan  | Proportion method plus targeted sequencing | rpoB†† | 4 LPA / oligonucleotide array discordant isolates | 3 total - V176F (1) - Wild type (2) | None | No            |
| 2010       | Indirect     | Vietnam | Proportion method plus targeted sequencing | rpoB†† | 4 phenotypic LPA discordant isolates | 4 total - H526L (1) - Wild type (3) | None | No            |
| 2012       | Direct       | Argentina | Mixed: proportion, MGIT and microplate colorimetric plus targeted sequencing | rpoB§§ | 84 out of 100 samples tested with LPA | 1 total - D516V (1) | None | No            |

†† rpoB-F and rpoB-R  
‡‡ rpoBF and rpoBR  
§§ 250 bp of the flanking region of the “hot spot” of rpoB
| Study          | Kit Type | Region | Methodology                      | rpoB Primers Specified | Total Strains | Mutations                            | Resistance Association |
|---------------|----------|--------|----------------------------------|------------------------|---------------|--------------------------------------|------------------------|
| Jin 2012      | Hain V1  | China  | Absolute concentration plus targeted sequencing | rpoB (primers not specified) | All 149 strains | 11 total: H526R (1), Wild type (10) | None |
| Lacoma 2008   | Hain V1  | Spain  | BacTec plus targeted sequencing  | rpoB (primers not specified) | 48 drug resistant strains | 1 total: D516Y (1) | None |
| Li 2015       | Hain V1  | China  | Proportion method plus targeted sequencing | rpoB (primers not specified) | 49 phenotypic / LPA discordant samples | 16 total: D531V (6), Wild type (10) | Yes (rpoB mutations detected on sequencing were presumed to be associated with resistance) |
| Maschmann 2013| Hain V1  | Brazil | Proportion method plus targeted sequencing | rpoB (primers not specified) | 68 culture positive strains | 5 total: Insertion between codon 516 and 517 (2), Wild type (3) | Yes |
| Mitarai 2012 (a)| Nipro   | Japan  | Mixed: MGIT, broth microdilution, proportion plus targeted sequencing | rpoB (primers not specified) | 40 phenotypic / LPA discordant isolates | 1 total: I572F (1) | 6 total: H526S (3), L511P (1), D516Y (1), D516D (1) | Yes |
| Nathavitharana 2016 | Hain V1 | Mixed: proportion method and MGIT plus targeted sequencing | rpoB (codons 209–694) | All discordant strains and subset of non-discordant strains | 15 total: L533P (5), Mixed: S531L plus wild type (1), V251P (4), I572P (2), 569Val (1), Wild type (2) | 4 total: L553P (1) | Yes |
| Nathavitharana 2016 | Hain V2 | Mixed: proportion | rpoB (codons) | All discordant strains and subset of non-discordant strains | 15 total: L533P (5) | 4 total: L553P (1) | Yes |
| Study                        | Method                        | Country       | rpoB Region       | Genotypes                                                                 | Discordant Strains |
|------------------------------|-------------------------------|---------------|-------------------|---------------------------------------------------------------------------|-------------------|
| Nathavitharana 2016          | Method and MGIT plus targeted sequencing | Thailand      | rpoB (codons 209–694) | subset of non-discordant strains                                           | 13 total          |
|                              |                               |               |                   | All discordant strains and subset of non-discordant strains               |                   |
|                              |                               |               |                   | • Mixed: S531L plus wild type (1)                                          |                   |
|                              |                               |               |                   | • V251P (4)                                                                |                   |
|                              |                               |               |                   | • I572P (2)                                                                |                   |
|                              |                               |               |                   | • 569Val (1)                                                              |                   |
|                              |                               |               |                   | • Wild type (2)                                                            |                   |
|                              |                               |               |                   | Wild type (3)                                                             |                   |
|                              |                               |               |                   | Mixed isolate of wild type and H526R (1)                                  |                   |
|                              |                               |               |                   | • Wild type (6)                                                            |                   |
|                              |                               |               |                   | 5 total                                                                    |                   |
| Ocheretina 2014              | Hain V1 (Indirect)            | Haiti         | rpoB***            | 153 rifampin resistant strains                                            | 16 total          |
|                              |                               |               |                   | All discordant strains                                                    |                   |
|                              |                               |               |                   | • H526L (4)                                                               |                   |
|                              |                               |               |                   | • H526C (1)                                                               |                   |
|                              |                               |               |                   | • T508A (2)                                                               |                   |
|                              |                               |               |                   | • L511P (5)                                                               |                   |
|                              |                               |               |                   | • L511P and M515T (2)                                                     |                   |
|                              |                               |               |                   | • T508T (2)                                                               |                   |
| Rienthong 2015a              | Nipro (Indirect)              | Thailand      | rpoB (primers not specified) | 10 phenotypic / LPA discordant isolates                                  | 7 total          |
|                              |                               |               |                   | All discordant isolates                                                   |                   |
|                              |                               |               |                   | • Mixed isolate of wild type and H526R (1)                                |                   |
|                              |                               |               |                   | • Wild type (6)                                                            |                   |
|                              |                               |               |                   | 3 total                                                                   |                   |
|                               |                               |               |                   | • S531L (1)                                                               |                   |
|                               |                               |               |                   | • L533P (1)                                                               |                   |
|                               |                               |               |                   | • H526N (1)                                                               |                   |
|                               |                               |               |                   | Wild type (3)                                                             |                   |
| Vijdea 2008 a                | Hain V1 (Indirect)            | Denmark and Lithuania | rpoB (primers not specified) | 1 phenotypic / LPA discordant isolate                                    | None              |
|                              |                               |               |                   | All discordant isolates                                                   |                   |
|                              |                               |               |                   | • S531L (1)                                                               |                   |
|                              |                               |               |                   | • L533P (1)                                                               |                   |
|                              |                               |               |                   | • H526N (1)                                                               |                   |
|                              |                               |               |                   | 1 total                                                                   |                   |
|                               |                               |               |                   | • L533M (1)                                                               |                   |

**rpoB_F and rpoB_R**
### b) INH resistance detection

| Author, year | LPA (Direct vs Indirect) | Country of Data Origin | Composite standard | Targeted regions sequenced | Samples sequenced | Mutations in phenotypic resistant, LPA sensitive strains (n)<sup>10</sup> | Mutations in phenotypic sensitive, LPA resistant strains (n)<sup>10</sup> | Composite standard leads to different test performance |
|--------------|--------------------------|------------------------|--------------------|---------------------------|------------------|-------------------------------------------------|-------------------------------------------------|----------------------------------------------------------|
| Al-Mutairi, 2011 | Hain V1 (Indirect) | Kuwait | BacTec plus, RFLP<sup>11</sup> and targeted sequencing | *katG*315 by RFLP, *katG* and *inhA*-RR targeted sequencing<sup>12</sup> | All 125 strains | 6 total | None | No |
| Anek-Vorapong 2010 | Hain V1 (Direct) | Thailand | MGIT plus targeted sequencing | *katG* and *inhA*<sup>13</sup> | 1 phenotypic / LPA discordant strain | 2 total (only 1 sequenced) | None | No |
| Asante-Poku 2015 | Hain V1 (Indirect) | Ghana | Proportion method plus targeted sequencing | *katG*, *inhA* and *oxyR*-ahpC<sup>14</sup> | 51 phenotypically resistant isolates | 2 total | Wild type (2) | No |
| Aung 2015 | Hain V1 (Indirect) | Myanmar | Proportion method plus targeted sequencing | *katG*, *inhA* (primers not specified) | 13/17 initially phenotypic / LPA discordant isolates | 1 total | Wild type (1) | None |
| Brossier 2009 | Hain V1 (Indirect) | France and WHO | Proportion method plus sequencing | *katG*, *inhA*, *fabG*-inhA (primers not specified) | 95 INH resistant strains | 13 total | S94A in *inhA* (3) | No |
| Dorman 2012 | Hain V1 (Direct) | South Africa | MGIT plus targeted sequencing | *katG*, *inhA* (primers not specified) | 10 phenotypic / LPA discordant isolates | 11 total (9 sequenced) | 1C15T in | Yes |

<sup>10</sup> Bold indicates a known resistance conferring mutation  
<sup>11</sup> Restriction fragment length polymorphism  
<sup>12</sup> INHAF and INHAR, INHAFS and INHARS  
<sup>13</sup> codon 315 of *katG*, nucleic acid positions -15, -16 and -8 in the *inhA* promoter region  
<sup>14</sup> *kat G* primers Ko11 and Ko12, *inhA* promoter primers Ko3 and Ko4, *oxyR*-ahpC primers Ko56 and Ko57
| Study          | Method/Primer Location | Country | Methodology | Genes Assessed | Assay results | Additional Information |
|---------------|------------------------|---------|-------------|----------------|---------------|-------------------------|
| Farooqi 2012  | Hain V1 (Direct)       | Pakistan | Proportion method plus targeted sequencing | *katG*<sup>15</sup> | 14 total phenotypic / LPA discordant isolates | 14 total: Wild type (8) C15T in *inhA* (1) |
| Felkel 2013   | Hain V1 (Direct)       | Nigeria  | BacTec plus targeted sequencing | *katG*, *inhA*<sup>15</sup> | 1 discordant strain | Wild type |
| Hilleman 2007a| Hain V1 (Indirect)     | Germany  | Mixed: MGIT and proportion method plus targeted sequencing | *katG*, *inhA*, and *ahpC*<sup>17</sup> | All 125 strains | 6 total: C52T in *ahpC* (1) K152T in *katG* G48A in *ahpC* (1) Wild type (4) |
| Hilleman 2007b| Hain V1 (Direct)       | Germany  | Mixed: MGIT and proportion method plus targeted sequencing | *katG*, *inhA*, and *ahpC*<sup>17</sup> | 41 MDR or INH resistant strains | 4 total: Wild type (4) |
| Huang 2015    | Hain V1 (Indirect)     | China    | Proportion method plus targeted sequencing | *katG*, *inhA* (primers not specified) | All 430 strains | 5 total: Wild type (5) 2 total: S315T in *katG* (2) |
| Huang 2009    | Hain V1 (Indirect)     | Taiwan   | Mixed: MGIT or proportion | *katG*, *inhA* and *ahpC*<sup>18</sup> | All 272 isolates | 44 total: C-10T in | No |

<sup>15</sup> Codon 315 of *katG*  
<sup>16</sup> *inhA* primers 3F and 4R, *katG* primers 290F and 583R  
<sup>17</sup> *inhA* primers 3F and 4R, *katG* primers 290F and 583R  
<sup>18</sup> *inhA* primers 3F and 4R, *katG* primers 290F and 583R
| Method plus targeted sequencing | ahpC (6) |  |
|--------------------------------|---------|---|
|                                | - G-66A in *ahpC* (2) |  |
|                                | - G-9A in *ahpC* (2) |  |
|                                | - C-39T in *ahpC* (1) |  |
|                                | - -4/-5 insert A in *ahpC* (1) |  |
|                                | - G-5A and G-6A in *ahpC* (1) |  |
|                                | - C-15T in *ahpC* (1) |  |
|                                | - C-32T in *ahpC* (1) |  |
|                                | - Y337C in *katG* (2) |  |
|                                | - D419H in *katG* (1) |  |
|                                | - Y413H in *katG* (1) |  |
|                                | - del401C in *katG*(1) |  |
|                                | - A379V in *katG*(1) |  |
|                                | - L378P in *katG* and E217D in *inhA* (1) |  |
|                                | - del364T in *katG* and C-12T in *ahpC* (1) |  |
|                                | - A362D in *katG*(1) |  |
|                                | - del310A in *katG* and C-10T in *ahpC* (1) |  |

18 *inhA* primers *inhA* 1713F and *inhA* 1713R, *inhA* 2194F and *inhA* 2194R, *inhA* locus-F and *inhA* locus-R, *katG* primers *katG*-F and *katG*-R, *ahpC* primers *ahpC*-f and *ahpC*-R
| Study          | Strain | Country | Methodology                                                                 | Genotypes                                                                 | Total strains | Sequenced strains |
|----------------|--------|---------|----------------------------------------------------------------------------|---------------------------------------------------------------------------|---------------|-------------------|
| Huang 2014     | Hain V1 (Indirect) | Taiwan | Proportion method plus targeted sequencing | katG, inhA and ahpC***                                                  | 27 total (26 sequenced) | None              |
|                |        |         |                                                                               | 2 LPA / oligonucleotide array discordant results                          |               |                   |
| Jin 2012       | Hain V1 (Indirect) | China | Absolute concentration plus targeted sequencing | katG, inhA (primers not specified)                                       | 42 total: S315N in katG (10), S315R in katG (1), S315I in katG (1), Wild type (30) | None              |
| Lacoma 2008    | Hain V1 (Indirect) | Spain | BacTec plus targeted sequencing | katG, mabA-inhA-RR, oxyR-ahpC (primers not specified)                     | 48 drug resistant strains | None              |

- G299A in katG and C-10T in ahpC (1)
- R202G in inhA (1)
- E217D in inhA (1)
- Wild type (16)
- W321S in katG (1)
- R463L in katG (11)
- Wild type (14)
- S315N in katG (10)
- S315R in katG (1)
- S315I in katG (1)
- Wild type (30)
- del234, del155-158 in katG (1)
- 204W -> stop in katG (1)
- S315T and G463T in katG (1)
- del640 in katG (1)
- D94N in katG (1)
- W728Y in katG
| Study          | Method          | Country  | Primers/Method Details                                           | Strains Details                                                                 | Wild type | WT discordant |
|---------------|-----------------|----------|-----------------------------------------------------------------|---------------------------------------------------------------------------------|-----------|---------------|
| Maschmann 2013| Direct          | Brazil   | Proportion method on LJ plus targeted sequencing; *katG, inhA* (primers not specified) | *katG*, inhA *aphxC-oxyR* (1) • C-15T in *inhA* (1) • Wild type (6)            | 19 total  | None          |
| Miotto 2008a  | Indirect        | Italy    | MGIT plus targeted sequencing; *katG, inhA* and *mabAF-inha operon* | 173 INH resistant isolates • Wild type (36)                                        | None      | No            |
| Mitarai 2012a | Indirect        | Japan    | Mix of MGIT, ogawa, broth microdilution, proportion plus sequencing; *inhA, fabG1, furA and katG* | 53 phenotypic / LPA discordant isolates • *katG* S17N (1) • G206S (1) • E340Q (1) • T152A (1) • Y113S (1) • T367G (2) • N138Y (1) • D142G (1) • K152Q (1) • D163N (1) • W191G (1) • Q461P (1) • G599Stop (1) • F698S (1) • T308P and S346T (2) • D419H (6) • L203L in *fabG1* and M126I in *katG* (1) • L203L in *katG* | None      | no            |

19 *katG* primers *katG* r and *katG* F, *inhA* primers *inhA* 301Rev and *MabAF*
| Study            | Method                  | Country | Sample Description                                      | Methods                                | Phenotype/LPA Discordant Isolates | Total Cases | Additional Phenotypes |
|------------------|-------------------------|---------|----------------------------------------------------------|----------------------------------------|-----------------------------------|-------------|-----------------------|
| Mitarai 2012 b   | Nipro (Direct)          | Japan   | MGIT 960 plus targeted sequencing                        | *inhA, fabG1, furA* and *katG*         | 4 phenotypic / LPA discordant isolates | 3 total     | G1795T (G599stop) (1) |
|                  |                         |         |                                                          |                                        |                                   |             | T2093C (F698S) in *katG* (1)    |
|                  |                         |         |                                                          |                                        |                                   |             | T571C (W191R) and G1079A (G360D) in *katG* (1) |
| Nathavitharana 2016 | Hain V1 (Indirect)     |         | Mixed: proportion method and MGIT plus targeted sequencing | *katG* (codons 268–328), *inhA* (position −148 to +60) for INH | All discordant strains and subset of non-discordant strains | 21 total (20 sequenced) | Wild type (15) |
|                  |                         |         |                                                          |                                        |                                   |             | C15T in *inhA* (2)              |
|                  |                         |         |                                                          |                                        |                                   |             | S315T in *katG* and G47C in *inhA* (1) |
|                  |                         |         |                                                          |                                        |                                   |             | T324P in *katG* (2)              |
| Nathavitharana 2016 | Hain V2 (Indirect)     |         | Mixed: proportion method and MGIT plus targeted sequencing | *katG* (codons 268–328), *inhA* (position −148 to +60) for INH | All discordant strains and subset of non-discordant strains | 21 total (20 sequenced) | Wild type (15) |
|                  |                         |         |                                                          |                                        |                                   |             | C15T in *inhA* (2)              |
|                  |                         |         |                                                          |                                        |                                   |             | S315T in *katG* and G47C in *inhA* (1) |
|                  |                         |         |                                                          |                                        |                                   |             | T324P in *katG* (2)              |

Yes
| Study          | Methodology               | Country                  | Method                          | Strain Type                                                                 | Discordant Strains                                                                 |
|---------------|---------------------------|--------------------------|--------------------------------|------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Nathavitharana 2016 | Mixed: proportion method and MGIT plus targeted sequencing | Thailand                  | *katG* (codons 268–328), *inhA* (position −148 to +60) for INH | All discordant strains and subset of non-discordant strains | 20 total (19 sequenced)  
• Wild type (15)  
• C15T in *inhA* (3)  
• S315T in *katG* and G47C in *inhA* (1) |
| Rienthong 2015a | Nipro (Indirect)          | Thailand                  | MGIT 960 plus targeted sequencing | *katG*, *fabG1* and *inhA* (primers not specified) | 10 phenotypic / LPA discordant isolates | 9 total  
• F565F in *katG* (1)  
• D189H in *katG* (1)  
• T618M in *katG* (1)  
• **G279D** and A379D in *katG* (1)  
• G699R in *katG* (1)  
• G690A in *fabG1* (1)  
• Wild type (3) |
| Vijdea 2008a  | Hain V1 (Indirect)        | Denmark and Lithuania    | Bactec 460 plus targeted sequencing | *katG*, *inhA* and oxy-R-aphC<sup>20</sup> (primers not specified) | 4 phenotypic / LPA discordant isolates | 4 total  
• G49A at *oxyR-aphC* (3)  
• No amplification at *katG* 463 (1) |

<sup>20</sup> *katG* primers *katG1F* and *katG4F*, *inhA* primers fabG1-*inhA*, oxyR-aphC primers 519 and 520 (*fabG1-*inhA) and tomap1 and tomap2 (oxyR–aphC)
SENSITIVITY ANALYSES

Table S4. Sensitivity analysis to exclude studies selecting for MDR risk.

| Reference standard | Test | Direct or Indirect | Smear status | # Datasets (# Samples) | Sensitivity 95% CI | Specificity 95% C.I. | Positive LR 95% C.I. | Negative LR 95% C.I. |
|-------------------|------|-------------------|--------------|-----------------------|-------------------|----------------------|----------------------|----------------------|
| Phenotypic DST    | RIF  | Both              | All          | 91 (21 225)           | 96.7% (95.6 - 97.5) | 98.8% (98.2 - 99.2) | 79.3 (54.5 – 115.5) | 0.03 (0.03 - 0.04)  |
| Phenotypic DST    | RIF  | Both              | All          | 52 (13 460)           | 96.7% (94.8-97.9)  | 99.0 (98.4-99.4)    | 99.6 (60.6-163.8)   | 0.03 (0.02-0.05)   |
| Phenotypic DST    | INH  | Both              | All          | 87 (20 954)           | 90.2% (88.2 - 91.9)| 99.2% (98.7 - 99.5)| 109.5 (70.3 - 170.4)| 0.10 (0.08 - 0.12) |
| Phenotypic DST    | INH  | Both              | All          | 52 (13 460)           | 88.4% (85.4-90.9)  | 99.2% (98.6-99.5)   | 109.1 (62.5-190.3)  | 0.12 (0.09-0.15)   |
| Phenotypic DST    | MDR  | Both              | All          | 57 (13 033)           | 92.9% (90.2 - 94.7)| 99.3% (98.7 - 99.6)| 127.2 (72.1- 224.5)| 0.07 (0.05 - 0.10) |
| Phenotypic DST    | MDR  | Both              | All          | 30 (7 680)            | 94.1% (89.8-96.7)  | 99.6% (98.9-99.9)   | 253.6 (87.1-738.0)  | 0.06 (0.03-0.10)   |
Table S5. Other pre-specified sensitivity analyses.

| LPA | Test | Direct or Indirect | Smear status | # Studies (# Samples) | Sensitivity 95% CI | Specificity 95% CI | # Studies (# Samples) | Sensitivity 95% CI | Specificity 95% CI |
|-----|------|--------------------|--------------|-----------------------|-------------------|-------------------|-----------------------|-------------------|-------------------|
|     |      |                    |              |                       |                   |                   |                       |                   |                   |
|     |      |                    |              | OVERALL               |                   |                   | OVERALL               |                   |                   |
|     |      |                    |              |                       |                   |                   |                       |                   |                   |

Excluding studies that did not enroll (or report enrolling) a consecutive or random sample of patients/specimens:

| Phenotypic DST | Test | Direct or Indirect | Smear status | # Studies (# Samples) | Sensitivity 95% CI | Specificity 95% CI | # Studies (# Samples) | Sensitivity 95% CI | Specificity 95% CI |
|----------------|------|--------------------|--------------|-----------------------|-------------------|-------------------|-----------------------|-------------------|-------------------|
| Phenotypic DST | RIF  | All                | All          | 23 (10 484)           | 95.5% (92.9-97.2) | 98.6% (97.6-99.2) | 91 (21 225)           | 96.7% (95.6 - 97.5) | 98.8% (97.0 - 99.9) |
| Phenotypic DST | INH  | All                | All          | 23 (10 484)           | 90.6% (87.0-93.2) | 98.9% (97.9-99.4) | 87 (20 954)           | 90.2% (88.2 - 91.9) | 99.2% (97.0 - 99.9) |
| Phenotypic DST | MDR  | All                | All          | 15 (6 363)            | 93.9% (88.3-97.0) | 98.8% (97.9-99.3) | 57 (13 033)           | 92.9% (90.2 - 94.7) | 99.3% (97.0 - 99.9) |
| Phenotypic DST | MTB  | All                | All          | 1 (177)               | 76.1 (N/A)        | 97.2 (N/A)        | 6 (3 451)             | 85.0% (70.0 - 93.3) | 98.0% (96.2 - 99.0) |

Excluding studies that used a case-control design or that did not specify the study design:

| Phenotypic DST | Test | Direct or Indirect | Smear status | # Studies (# Samples) | Sensitivity 95% CI | Specificity 95% CI | # Studies (# Samples) | Sensitivity 95% CI | Specificity 95% CI |
|----------------|------|--------------------|--------------|-----------------------|-------------------|-------------------|-----------------------|-------------------|-------------------|
| Phenotypic DST | RIF  | All                | All          | 62 (16 668)           | 97.0% (93.4-96.6) | 98.6% (97.8-99.1) | 91 (21 225)           | 96.7% (95.6 - 97.5) | 98.8% (97.0 - 99.9) |
| Phenotypic DST | INH  | All                | All          | 60 (16 634)           | 90.3% (87.5-92.5) | 99.0 (98.3-99.4)  | 87 (20 954)           | 90.2% (88.2 - 91.9) | 99.2% (97.0 - 99.9) |
| Phenotypic DST | MDR  | All                | All          | 38 (10 006)           | 94.8% (91.8-96.8) | 99.1% (98.3-99.5) | 57 (13 033)           | 92.9% (90.2 - 94.7) | 99.3% (97.0 - 99.9) |
| Phenotypic DST | MTB  | All                | All          | 6 (3 451)             | 83.4 (69.3-91.8)  | 97.3 (89.9-99.3)  | 6 (3 451)             | 85.0% (70.0 - 93.3) | 98.0% (96.2 - 99.0) |

Excluding studies where operators performing index test results were blinded to the results of the reference standard:

| Phenotypic DST | Test | Direct or Indirect | Smear status | # Studies (# Samples) | Sensitivity 95% CI | Specificity 95% CI | # Studies (# Samples) | Sensitivity 95% CI | Specificity 95% CI |
|----------------|------|--------------------|--------------|-----------------------|-------------------|-------------------|-----------------------|-------------------|-------------------|
| Phenotypic DST | RIF  | All                | All          | 28 (5 858)            | 95.8% (93.8-97.2) | 98.3% (97.4-98.9) | 91 (21 225)           | 96.7% (95.6 - 97.5) | 98.8% (97.0 - 99.9) |
| Phenotypic DST | INH  | All                | All          | 27 (5 835)            | 91.1% (87.8-93.6) | 99.0 (98.0-99.5)  | 87 (20 954)           | 90.2% (88.2 - 91.9) | 99.2% (97.0 - 99.9) |
| Phenotypic DST | MDR  | All                | All          | 23 (5 129)            | 92.8% (87.7-95.0) | 99.4% (98.6-99.8) | 57 (13 033)           | 92.9% (90.2 - 94.7) | 99.3% (97.0 - 99.9) |
| Phenotypic DST | MTB  | All                | All          | 4 (3 249)             | 75.5 (59.8-86.4)  | 98.3 (91.3-99.7)  | 6 (3 451)             | 85.0% (70.0 - 93.3) | 98.0% (96.2 - 99.0) |
Figure S4. Forest plots demonstrating the sensitivity and specificity of all the LPAs evaluated for the diagnosis of rifampicin resistance for culture isolates that were tested indirectly compared to phenotypic DST.
Figure S5. Forest plots demonstrating sensitivity and specificity of all the LPAs evaluated for the diagnosis of rifampicin resistance compared against a composite reference standard for all samples regardless of specimen type.

| Author               | Sensitivity (95% CI) | Specificity (95% CI) | TP  | FP  | FN  | TN  |
|----------------------|----------------------|----------------------|-----|-----|-----|-----|
| MTBDRplus V1         |                      |                      |     |     |     |     |
| Maschmann 2013       | 82.76 (64.23, 94.15) | 96.97 (84.24, 99.32) | 24  | 1   | 5   | 32  |
| Felkel 2013          | 83.33 (35.88, 99.58) | 100.00 (60.77, 100.00) | 5   | 0   | 1   | 26  |
| Dorman 2012          | 87.50 (61.65, 98.45) | 100.00 (98.17, 100.00) | 14  | 0   | 2   | 200 |
| Li 2015              | 89.87 (84.08, 94.10) | 98.78 (97.96, 99.33) | 142 | 16  | 1135|
| Nathavitharan 2016   | 91.33 (86.10, 95.07) | 98.51 (95.70, 99.69) | 158 | 3   | 15  | 198 |
| Lacoma 2008          | 91.67 (61.52, 99.79) | 100.00 (92.89, 100.00) | 11  | 0   | 1   | 50  |
| Farooqi 2012         | 92.59 (82.11, 97.94) | 100.00 (92.75, 100.00) | 50  | 0   | 4   | 49  |
| Huyen 2010           | 93.10 (83.27, 98.09) | 100.00 (93.15, 100.00) | 54  | 0   | 4   | 52  |
| Jin 2012             | 93.45 (88.59, 96.69) | 100.00 (94.79, 100.00) | 157 | 0   | 11  | 69  |
| Al-Mutairi 2011      | 95.12 (87.98, 98.66) | 100.00 (91.78, 100.00) | 78  | 0   | 4   | 43  |
| Huang 2009           | 95.45 (92.01, 97.71) | 100.00 (88.43, 100.00) | 231 | 0   | 11  | 30  |
| Imperiale 2012       | 96.15 (80.36, 99.90) | 100.00 (90.75, 100.00) | 25  | 0   | 1   | 38  |
| Hilleman 2007        | 96.77 (83.30, 99.92) | 100.00 (91.19, 100.00) | 30  | 0   | 1   | 40  |
| Hilleman 2007        | 98.67 (92.79, 99.97) | 100.00 (92.89, 100.00) | 74  | 0   | 1   | 50  |
| Huang 2014           | 98.80 (96.55, 99.75) | 100.00 (95.07, 100.00) | 248 | 0   | 3   | 73  |
| Fabre 2011           | 99.22 (95.76, 99.98) | 100.00 (81.47, 100.00) | 128 | 0   | 1   | 18  |
| Asante Poku 2015     | 100.00 (39.76, 100.00) | 100.00 (96.67, 100.00) | 4   | 0   | 0   | 109 |
| Huang 2015           | 100.00 (81.47, 100.00) | 100.00 (98.14, 100.00) | 18  | 0   | 0   | 197 |
| Vijdea 2008a         | 100.00 (84.56, 100.00) | 100.00 (96.11, 100.00) | 22  | 0   | 0   | 93  |
| Nipro                |                      |                      |     |     |     |     |
| Nathavitharan 2016   | 92.53 (87.56, 95.98) | 98.50 (95.68, 99.69) | 161 | 3   | 13  | 197 |
| Rienthong 2015a      | 93.00 (86.11, 97.14) | 100.00 (97.72, 100.00) | 93  | 0   | 7   | 160 |
| Mitarai 2012a        | 98.89 (93.96, 99.97) | 98.21 (95.49, 99.51) | 89  | 4   | 1   | 220 |
| MTBDRplus V2         |                      |                      |     |     |     |     |
| Nathavitharan 2016   | 91.33 (86.10, 95.07) | 98.51 (95.70, 99.69) | 158 | 3   | 15  | 198 |
Figure S6. Forest plots demonstrating the sensitivity and specificity of all the LPAs evaluated for the diagnosis of isoniazid resistance for culture isolates that were tested indirectly against phenotypic DST.
Figure S7. Forest plots demonstrating the sensitivity and specificity of all the LPAs evaluated for the diagnosis of isoniazid resistance compared against a composite reference standard for all samples regardless of specimen type.
Figure S8. HSROC graphs of summary estimates for all specimens for RIF and INH resistance (indirect)

Bivariate analysis of the sensitivity and specificity for all LPAs for the diagnosis of drug resistance compared to a phenotypic reference standard in specimens tested indirectly for a) RIF resistance b) INH resistance. In the plots below, the red squares represent the pooled summary estimates, the dashed red lines represent the 95% confidence region and the dashed green lines represent the 95% prediction region. The individual circles represent each study and the size of the circle is proportional to the total sample size.