Xpert MTB/RIF assay for the diagnosis of rifampicin resistance in different regions: a meta-analysis

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Abstract

Background: To estimate the diagnostic accuracy of Xpert MTB/RIF for rifampicin resistance in different regions, a meta-analysis was carried out.

Methods: Several databases were searched for relevant studies up to March 3, 2019. A bivariate random-effects model was used to estimate the diagnostic accuracy.

Results: We identified 97 studies involving 26,037 samples for the diagnosis of rifampicin resistance. The pooled sensitivity, specificity and AUC of Xpert MTB/RIF for rifampicin resistance detection were 0.93 (95% CI 0.90–0.95), 0.98 (95% CI 0.96–0.98) and 0.99 (95% CI 0.97–0.99), respectively. For different regions, the pooled sensitivity were 0.94(95% CI 0.89–0.97) and 0.92 (95% CI 0.88–0.94), the pooled specificity were 0.98 (95% CI 0.94–1.00) and 0.98 (95% CI 0.96–0.99), and the AUC were 0.99 (95% CI 0.98–1.00) and 0.99 (95% CI 0.97–0.99) in high and middle/lower income countries, respectively. The pooled sensitivity were 0.91 (95% CI 0.87–0.94) and 0.91 (95% CI 0.86–0.94), the pooled specificity were 0.98 (95% CI 0.96–0.99) and 0.98 (95% CI 0.96–0.99), and the AUC were 0.98 (95% CI 0.97–0.99) and 0.99 (95% CI 0.97–0.99) in high TB burden and middle/lower prevalence countries, respectively.

Conclusions: The diagnostic accuracy of Xpert MTB/RIF for rifampicin resistance detection was excellent.

Keywords: Xpert MTB/RIF, Rifampicin resistance, Prevalence, Income, Meta-analysis

Background

Tuberculosis (TB) remains a major global health problem and ranks as the leading cause of death from an infectious disease worldwide. In 2017, TB infected about 10.0 million people and approximately 16% (1.6 million) of infected patients died from the disease, which was a higher global total for new TB cases and deaths than previous one. Of the 1.6 million died cases, 300,000 occurred among people infected with human immunodeficiency virus (HIV) [1].

Drug-resistant TB, including multidrug-resistant TB (MDR-TB, defined as resistance to at least isoniazid and rifampicin, the two most important first-line anti-TB drugs) and extensively drug-resistant TB (XDR-TB, defined as MDR-TB plus resistance to any fluoroquinolone, such as ofloxacin or moxifloxacin, and to at least one of three injectable second-line drugs, amikacin, capreomycin, or kanamycin) has become a serious threat to global health [2]. In 2017, approximately 460,000 people, which means 3.5% of new and 18% of previously treated TB cases, were estimated to have had MDR-TB globally. And 9.0% of them had developed to XDR-TB. Rifampicin resistance (RR) was the most common resistance drug, affected approximately 558,000 people [1].

When TB is detected and effectively treated, the disease is largely curable. However, accurate and rapid detection of TB can be difficult, as challenging sample collection from deep-seated tissues and the paucibacillary characteristics of the disease [3]. Worldwide, approximately 35% of all forms of TB and 75% of patients with MDR-TB remain undiagnosed [4]. Notably,
under 3% of people who diagnosed with TB are tested to have certain pattern of drug resistance [5]. Xpert MTB/RIF was an effective, rapid, new method to diagnose TB and RR-TB, which was recommended by WHO [1].

Traditionally, the best available reference standard for TB diagnosis is solid and/or liquid culture. However, in clinical practice, prolonged turnaround times and limited laboratory infrastructure in resource-limited settings undermine the utility of culture-based diagnosis [6]. Histology is widely used for the diagnosis of TB where the technical pathologists are available. However, it is time-consuming, technically demanding, and lacks specificity [7]. In early 2011, the World Health Organization (WHO) endorsed the Xpert® MTB/RIF assay (Cepheid, Sunnyvale, USA) [8], a novel, rapid, automated, cartridge-based nucleic acid amplification test (NAAT), for the initial diagnosis in patients with suspected pulmonary MDR-TB or HIV-associated pulmonary TB [9, 10]. It can simultaneously detect TB through detection of the DNA of Mycobacterium tuberculosis and simultaneously identify a majority of the mutations that confer rifampicin resistance (which is highly predictive of MDR-TB). A high accuracy for pulmonary TB detection (sensitivity 89%, specificity 99%) was obtained [11]. In late 2013, WHO expanded its recommendations to include the diagnosis of TB in children and some forms of extrapulmonary TB (EPTB) [1].

A series of meta-analyses were carried out to determine the diagnostic accuracy of Xpert MTB/RIF in different forms of TB [12–14], however, evaluation of its accuracy in rifampicin resistance is rare [11]. More importantly, no study estimated the diagnostic accuracy of Xpert MTB/RIF for rifampicin resistance in countries with different TB prevalence and income till now. To replenish this, in this review, we synthesized the available data, taking into account the accuracy of Xpert MTB/RIF in diagnosing rifampicin resistance.

Methods

Literature search strategy
We searched the MEDLINE, Cochrane library, EMBASE, and Web of Knowledge for published works without language restrictions. The key searching words were used were: “Xpert MTB/RIF”, “Xpert”, “Gene Xpert”, plus “rifampicin resistance”. Our last search was accomplished on March 3, 2019.

Study selection and data extraction
The study selection and data extraction procedures were performed by two researchers (Kaican Zong and Hui Zhou) independently. Any differences in the process were solved by discussing with a third author (Shiying Li).

Inclusion criteria and exclusion criteria
Studies included in our meta-analysis should meet the following criteria: (i) clinical trials that used Xpert MTB/RIF for the detection of rifampicin resistance; (ii) samples were body tissues or fluid from suspected TB patients; (iii) the number of cases were more than 10; (iv) original data were sufficient to calculate the true positive (TP), true negative (TN), false positive (FP), and false negative (FN); (v) drug-susceptibility testing (DST) was used as the gold standard. Studies were excluded from our meta-analysis if they were: (i)
| Study | First author [ref.] | Year | Country | Study setting | Male (%) | HIV (%) | Age (year) (Median, IQR) | Patient selecting method | Total samples n (included n) | Specimen type (samples n) | Gold standard |
|-------|----------------------|------|---------|---------------|----------|---------|--------------------------|-------------------------|----------------------------|--------------------------|--------------|
| 1     | Al-Atiha SM [15]     | 2012 | Saudi Arabia | Laboratory | 126 (53.8) | 1 (0.4) | NR | Cross-sectional Unspecified | 234 (239) | Sputum (56), BAL (116); tissue (16), CSF (14), FNA (5), body fluid (22), abscess (10) | DST |
| 2     | Antonenka U [16]     | 2013 | Germany | Clinical | NR | NR | NR | Retrospective Unspecified | 121 (121) | Respiratory specimens (121) | Solid or liquid media DST |
| 3     | Balkells ME [17]     | 2012 | Chile | Clinical | 127 (79.4) | 160 (100) | Adults > 18 (37.4, 19–65) | Cross-sectional Prospective Consecutive | 160 (12) | Sputum (160) | Solid and liquid media DST |
| 4     | Barmankulova A [18]  | 2015 | Kyrgyzstan | Laboratory | 172 (57.3) | NR | Median 34, IQR 25–45 | Cross-sectional Unspecified | 300 (191) | Sputum (300) | Solid and liquid media DST |
| 5     | Barnard M [19]       | 2012 | South Africa | Laboratory | NR | NR | NR | Unspecified Consecutive | 282 (68) | Sputum (282) | DST |
| 6     | Bates M [20]         | 2013 | Zambia | Clinical | NR | 22 (2.4) | Children ≤ 15 | Prospective Unspecified | 930 (930) | Sputum, gastric lavage aspirate (930) | Liquid culture |
| 7     | Biadglegne F [21]    | 2014 | Ethiopia | Clinical | 99 (42.9) | NR | 14.7% ≤ 14, 85.3% > 14 | Cross-sectional Unspecified | 231 (32) | Lymph node aspirates (231) | DST |
| 8     | Blakemore R [22]     | 2010 | America | Clinical | NR | NR | NR | Unspecified Unspecified | 168 (79) | Sputum (168) | DST |
| 9     | Boehme CC [23]       | 2010 | Peru | Clinical | 929 (53.7) | 392 (22.7) | Adults ≥ 18 (34, 17–88) | Prospective Consecutive | 1730 (720) | Sputum (1730) | Solid media DST |
|       |                      |      | Azerbaijan |            | 181 (53.1) | 3 (0.9) | Adults ≥ 18 (31, 18–79) |            | 341 (209) | Sputum (341) | Solid media DST |
|       |                      |      | South Africa |            | 251 (71.1) | 9 (2.6) | Adults ≥ 18 (37, 20–69) |            | 353 (143) | Sputum (353) | Solid or liquid media DST |
|       |                      |      | India |            | 357 (49.2) | 376 (51.8) | Adults ≥ 18 (34, 18–74) |            | 726 (183) | Sputum (726) | Liquid media DST |
|       |                      |      |         |            | 140 (45.2) | 4 (12.9) | Adults ≥ 18 (30, 17–88) |            | 310 (185) | Sputum (310) | Liquid media |
| Study | First author [ref.] | Year | Country | Study setting | Male (%) | HIV (%) | Age (year) (Median, IQR) | Patient selecting method | Total samples n (included n) | Specimen type (samples n) | Gold standard |
|-------|----------------------|------|----------|---------------|----------|---------|--------------------------|-------------------------|-----------------------------|--------------------------|---------------|
| 10    | Boehme CC [24]       | 2011 | Peru     | Clinical      | 60.8     | 18.9    | Adults ≥18 (38, 29–50)   | Unspecified Conssecutive | 6648 (1060) Sputum (6648) | DST                      |
|       |                      |      |          |               | 31.2     | 0.4     | Adults ≥18 (37, 26–53)   |                         |                             |                          |                       |
|       |                      |      | Azerbaijan|              | 99.9     | 0.1     | Adults ≥18 (36, 30–44)   |                         | 749 (211) Sputum (749)   |                          |                       |
|       |                      |      | South Africa|             | 50.6     |         | Adults ≥18 (36, 29–46)   |                         | 2522 (188) Sputum (2522) |                          |                       |
|       |                      |      | Uganda    |              | 54.3     |         | Adults ≥18 (32, 26–38)   |                         | 372 (116) Sputum (372)   |                          |                       |
|       |                      |      | India     |              | 69.6     |         | Adults ≥18 (45, 32–58)   |                         | 902 (103) Sputum (902)   |                          |                       |
|       |                      |      | Philippines|            | 60.5     |         | Adults ≥18 (47, 34–58)   |                         | 918 (257) Sputum (918)   |                          |                       |
| 11    | Bowles EC [25]       | 2011 | Netherlands | Clinical | NR       | NR      | NR                       | Unspecified              | 89 (60) Sputum (86), pleural fluid (1), gastric fluid (1), bronchial washing (1) | DST                      |
| 12    | Carriquiry G [26]    | 2012 | Peru      | Clinical     | 73%      | 0%      | Adults ≥18 (35, 29–42)   | Cross-sectional          | 131 (39) Sputum (131)   |                          |                       |
| 13    | Cayci YT [27]        | 2017 | Turkey    | Laboratory   | NR       | NR      | NR                       | Unspecified              | 34 (34) Respiratory (19) and Non-respirator specimens (15) | Liquid media DST |
| 14    | Chakravorty S [28]   | 2017 | South, Africa, India | Laboratory | NR       | NR      | NR                       | Prospective               | 139 (139) Sputum (139)   |                          |                       |
| 15    | Chiang TY [29]       | 2018 | China     | Clinical     | 55%      | 0%      | Median 55, IQR 35.8–700  | Prospective               | 2957 (697) Sputum (697)  |                          |                       |
| 16    | Chikaonda T [30]     | 2017 | Malawi    | Clinical     | 50%      | 0%      | Adults ≥18 (36, 29–50)   | Retrospective Random      | 351 (188) Sputum (60)    |                          |                       |
| Study | First author [ref.] | Year | Country | Study setting | Male (% | HIV (%) | Age (year) (Median, IQR) | Patient selecting method | Total samples n (included n) | Specimen type (samples n)                  | Gold standard |
|-------|---------------------|------|---------|---------------|---------|---------|--------------------------|--------------------------|-----------------------------|------------------------------------------|--------------|
| 17    | Çiftçi IH [31]      | 2011 | Turkey  | Clinical      | NR      | NR      | NR                       | Unspecified              | 85 (24)                     | Sputum (50), BAL (25), thorascopy fluid (5), urine (5) | Liquid media DST |
| 18    | Deggim V [32]       | 2013 | Switzerland | Clinical     | NR      | NR      | NR                       | Prospective              | 79 (10)                     | Respiratory and Non-respirator specimens (79) | DST          |
| 19    | Dharan NJ [33]      | 2016 | Russia, Peru, Hong Kong, Haiti, USA | Clinical | 358 (66.8) | 536 (98.5) | Median 54.2, IQR 19–88 | Unspecified              | 544 (185)                   | Sputum (185)                  | DST          |
| 20    | Dorman SE [34]      | 2012 | South Africa | Laboratory | 6499 (98.8) | 602 (8.7) | Median 43, IQR 34–49 | Cross-sectional           | 6893 (144)                  | Sputum (6893)                | Liquid media DST |
| 21    | Dorman SE [35]      | 2018 | South Africa, Uganda, Kenya, India, China, Georgia, Belarus, Brazil | Clinical | 1059 (60.4) | 441 (25.2) | Median 38, IQR 28–50 | Prospective              | 1753 (551)                 | Sputum (551)                  | Liquid media DST |
| 22    | Du J [36]           | 2015 | China   | Clinical      | 70 (55.6) | 5 (40)  | Adults> 16 (38.6, 254–518) | Unspecified              | 126 (126)                   | Pleural biopsy (126), pleural fluid specimens (126) | Liquid media DST |
| 23    | Feliciano CS [37]   | 2018 | Brazil, Mozambique | Clinical | 22 (75.9) | 6 (20.7) | NR                       | Cross-sectional           | 29 (29)                     | NR (29)                    | Solid media DST |
| 24    | Giang do C [38]     | 2015 | Vietnam | Clinical      | 98 (65.3) | 0 (0)   | Children< 15 (18.5 months, 5–170 months) | Prospective              | 150 (29)                   | Sputum (79), Gastric fluid (215), CSF (3), Pleural fluid (4), Cervical lymphadenopathic pus (1) | Liquid media DST |
| 25    | Gu Y [39]           | 2015 | China   | Clinical      | 28 (46.7) | NR      | Median 39.7, IQR 19.5–746 | Prospective              | 60 (24)                     | Pus specimens (60)            | Liquid media DST |
| 26    | Guenaoui K [40]     | 2016 | France  | Laboratory    | 35 (0.7) | NR      | NR                       | Prospective              | 50 (50)                     | Sputum (50)                 | Liquid DST |
| 27    | Helb D [41]         | 2010 | Uganda  | Clinical      | 38 (59.3) | 20 (313) | Median 34, IQR 18–60    | Retrospective            | 64 (64)                     | Sputum (64)                 | DST          |
| 28    | Hillemann D [42]    | 2011 | Germany | Laboratory    | NR       | NR      | NR                       | Unspecified              | 521 (29)                    | Urine (91), gastric aspirate (30), tissue (245), pleural fluid (113), CSF (19), stool (23) | Liquid media DST |
| 29    | Huang H [43]        | 2018 | China   | Laboratory    | NR       | NR      | NR                       | Retrospective            | 2910 (1066)                 | NR                        | Liquid media DST |
| Study | First author [ref.] | Year | Country | Study setting | Male (%) | HIV (%) | Age (year) (Median, IQR) | Patient selecting method | Total samples n (included n) | Specimen type (samples n) | Gold standard |
|-------|---------------------|------|---------|---------------|----------|---------|--------------------------|--------------------------|---------------------------|--------------------------|---------------|
| 30    | Huh HJ [44]         | 2014 | South Korea | Clinical     | 197 (65.7) | 1 (0.3) | Median 58, IQR 18–93     | Retrospective Unspecified | 300 (98) Sputum (264), Bronchial washing or BAL (39) | Solid and liquid media DST |
| 31    | Hu P [45]           | 2014 | China    | Laboratory   | 1037 (76.7) | NR      | 3.2% < 20, 96.8% ≥ 20    | Unspecified Consecutive  | 1352 (332) Sputum (1352) | Solid media DST |
| 32    | Jin YH [46]         | 2017 | China    | Clinical     | 59 (54.1)  | NR      | Median 48.6, IQR 24.0–73.1 | Unspecified Unspecified | 109 (48) Pus (48) | Liquid media DST |
| 33    | Kawkitinarong K [47] | 2017 | Thailand | Clinical     | 284 (58.6) | 128 (25.9) | Median 41, IQR 30.8–54.3 | Prospective Unspecified | 521 (228) Pulmonary specimens (228) | DST |
| 34    | Khalil KF [48]      | 2015 | Pakistan | Clinical     | 36 (38.7)  | 0 (0)   | > 16, 19.5–576            | Unspecified Consecutive  | 93 (93) BAL (93) | Solid media DST |
| 35    | Kim CH [49]         | 2014 | South Korea | Clinical     | 104 (60.8) | 1 (0.6) | Median 58.6, IQR 41.02–76.18 | Retrospective Unspecified | 171 (26) Pulmonary (160), Non-pulmonary (38) specimens | Solid media DST |
| 36    | Kim CH [50]         | 2015 | South Korea | Clinical     | 217 (56.7) | 1 (0.3) | Median 56.3, IQR 38.43–74.18 | Retrospective Convenience | 383 (444) | Solid media DST |
| 37    | Kim MJ [51]         | 2015 | South Korea | Laboratory   | NR         | NR      | NR                        | Unspecified Convenience | 52 (45) Sputum (36), bronchial washing (10), pleural fluid (3), pleural mass (1), urine (2) | Liquid media DST |
| 38    | Kim SY [52]         | 2012 | South Korea | Clinical     | NR         | NR      | NR                        | Unspecified Convenience | 71 (62) Sputum (71) | Liquid media DST |
| 39    | Kim YW [53]         | 2015 | South Korea | Clinical     | 761 (53.3) | 12 (0.8) | Median 59, IQR 0–99       | Retrospective Convenience | 1429 (1540) LN and tissue/pus (397), body fluid (469), CSF (254), joint fluid (283), urine (106), others (31) | Solid media DST |
| 40    | Kim YW [54]         | 2015 | South Korea | Clinical     | 196 (61.1) | NR      | Median 36, IQR 38–71      | Retrospective Convenience | 321 (321) Sputum (321) | DST |
| 41    | Kokuto H [55]       | 2015 | Japan    | Clinical     | 51 (54.8)  | 0 (0)   | Adult≥20 (59.6, 450–75.0) | Retrospective Convenience | 93 (56) fecal specimens (93) | DST |
| 42    | Kostera J [56]      | 2018 | Bangladesh | Clinical     | NR         | NR      | NR                        | Unspecified Unspecified | 132 (122) Sputum (122) | Liquid media DST |
| Study | First author [ref.] | Year | Country | Study setting | Male (% | HIV (%) | Age (year) (Median, IQR) | Patient selecting method | Total samples n (included n) | Specimen type (samples n) | Gold standard |
|-------|----------------------|------|---------|---------------|---------|---------|--------------------------|---------------------------|---------------------------|-----------------------------|---------------|
| 43    | Kurbaniyazova G [57] | 2017 | Kyrgyzstan | Laboratory | NR | NR | Adult≥18 | Retrospective, Unspecified | 2734 (364) (414) | NR | Solid and liquid media DST |
| 44    | Kurbatova EV [58]   | 2013 | Russia   | Clinical     | NR | NR | Adults≥18 | Unspecified, Consecutive | 201 (99) | Sputum (201) | Solid and liquid media DST |
| 45    | Kwak N [59]         | 2013 | South Korea | Clinical | 426 (62.5) | 5 (0.7) | Median 61, IQR 47.5–73.0 | Retrospective, Unspecified | 681 (127) | Sputum (127) | Liquid media DST |
| 46    | Lawn SD [60]        | 2011 | South Africa | Clinical | 162 (34.6) | 468 (100) | Adults≥18 | Prospective, Consecutive | 468 (55) | Sputum (468) | Liquid media DST |
| 47    | Lee HY [61]         | 2013 | South Korea | Clinical | 78 (59.1) | 1 (0.8) | Median 54.0, IQR 18–90 | Retrospective, Unspecified | 132 (132) | Bronchoscopy specimens (132) | Ogawa media DST |
| 48    | Li Q [62]           | 2016 | China    | Laboratory | NR | NR | NR | Unspecified, Consecutive | 1973 (449) | Sputum (449) | Liquid media DST |
| 49    | Li Y [63]           | 2017 | China    | Laboratory | 251 (60.6) | NR | Median 48.5, IQR 38.3–58.7 | Unsimplified, Consecutive | 420 (59) | Extra-pulmonary specimens (59) | Solid media DST |
| 50    | Liu X [64]          | 2015 | China    | Clinical | NR | NR | NR | Unsimplified, Consecutive | 134 (44) | Pleural biopsy and pleural fluid specimens (100) | Liquid media DST |
| 51    | Lorent N [65]       | 2015 | Cambodia | Clinical | 160 (33.5) | 189 (64.5) | Median 43, IQR 34–52 | Prospective, Consecutive | 299 (102) | Sputum (102) | Solid media DST |
| 52    | Luetkemeyer AF [66] | 2016 | USA South Africa, Brazil | Laboratory | 446 (45.0) | 617 (62.2) | Median 46, IQR 35–64 | Unsimplified, Consecutive | 992 (194) | Sputum (2) | DST |
| 53    | Metcalfe IZ [67]    | 2016 | Zimbabwe | Clinical | 216 (61.4) | 238 (67.6) | Median 36.3, IQR 29.0–44.4 | Prospective, Consecutive | 352 (161) | Sputum (161) | Solid and liquid media DST |
| 54    | Mokaddas E [68]     | 2015 | Kuwait   | Laboratory | NR | NR | NR | Unsimplified, Consecutive | 452 (452) | Sputum (287), FNA (66), pus (58), pleural fluid (14), tissue (10), other sterile fluids (8), urine (5), CSF (2), stool (2). | Liquid media DST |
| Study | First author [ref.] | Year | Country | Study setting | Male (%) | HIV (%) | Age (year) (Median, IQR) | Patient selecting method | Total samples n (included n) | Specimen type (samples n) | Gold standard |
|-------|---------------------|------|---------|---------------|----------|---------|--------------------------|--------------------------|----------------------------|--------------------------|---------------|
| 55    | Moon HW [69]        | 2015 | South Korea | Clinical | NR       | NR      | NR                       | Unspecified Unspecified | 100 (100) | Respiratory specimens (100) | DST          |
| 56    | Moure R [70]        | 2011 | Spain    | Clinical   | NR       | NR      | NR                       | Retrospective Unspecified | 122 (85)  | Sputum (92), BA (12), pulmonary biopsy (1); pleural fluid (4), gastric aspirate (5), urine (2), stool (1); cerebrospinal fluid (3), ascitic fluid (2), lymph node aspirate (1), skin biopsy (1), mammary abscess (1) | DST          |
| 57    | Mwanza W [71]       | 2018 | Zambia   | Laboratory | NR       | NR      | NR                       | Unspecified Consecutive | 1070 (24) | NR (24)                  | Liquid media DST | Liquid media DST |
| 58    | Myneedu VP [72]     | 2014 | India    | Laboratory | NR       | NR      | NR                       | Unspecified Unspecified | 134 (88)  | Sputum (134)             | Liquid media DST | Liquid media DST |
| 59    | Nguessan K [73]     | 2014 | Côte d’Ivoire | Clinical | 91 (75.8) | NR      | Median 34.2, IQR 24.1–44.3 | Unspecified Unspecified | 120 (29)  | Sputum (120)             | Liquid media DST | Liquid media DST |
| 60    | Nguessan K [74]     | 2018 | Côte d’Ivoire | Clinical | 715 (65.3) | 130 (12) | Median 33, IQR 18–80     | Cross-sectional Consecutive | 1095 (162) | Sputum (162)             | Liquid media DST | Liquid media DST |
| 61    | Nikolayevsky V [75] | 2018 | Ukraine  | Clinical   | 2393 (68.8) | 1265 (364) | Median 38.3, IQR 27–51.6 | Retrospective Unspecified | 3478 (3167) | Pulmonary specimens (3167) | Solid and liquid media DST | DST          |
| 62    | Nicoll MP [76]      | 2011 | South Africa | Clinical | 250 (55.3) | 108 (239) | Children ≤ 15 (19.4 months, 11.1–46.2 months) | Prospective Consecutive | 452 (77)  | Sputum (452)             | DST          |
| 63    | O’Grady J [77]      | 2012 | Zambia   | Clinical   | 446 (50.6) | 595 (67.5) | Adults > 15 (35, 28–43) | Prospective Unspecified | 881 (96)  | Sputum (881)             | Liquid media DST | Liquid media DST |
| 64    | Ou X [78]           | 2014 | China    | Laboratory | 1741 (70.9) | NR      | NR                       | Unspecified Consecutive | 2454 (616) | Sputum (2454)            | Solid media DST | Liquid media DST |
| 65    | Ozkutuk N [79]      | 2014 | Turkey   | Laboratory | NR       | NR      | NR                       | Unspecified Unspecified | 2639 (133) | Sputum (721), BAL (757), gastric fluid (94), endotracheal aspirates (30), transtracheal aspirate (9); urine (341), pleural fluid (232), tissue (176), CSF (111), abscesses (94), peritoneal fluid (42), pericardial fluid (18), joint fluid (7), other (7) | Liquid media DST | Liquid media DST |
| 66    | Pan X [80]          | 2018 | China    | Clinical   | 120 (68.2) | NR      | Median 46.7, IQR 16–84  | Prospective Unspecified | 190 (62)  | Sputum, BAL (62)         | DST          |
| 67    | Pang Y [81]         | 2014 | China    | Clinical   | 128 (NR) | 14 (Children ≤ 14) | Prospective Consecutive | 211 (10)  | Gastric lavage aspirates (211) | Liquid media |
| Study  | First author [ref.] | Year | Country | Study setting | Male (%) | HIV (%) | Age (year) (Median, IQR) | Patient selecting method | Total samples n (included n) | Specimen type (samples n) | Gold standard |
|--------|----------------------|------|---------|---------------|----------|---------|---------------------------|--------------------------|---------------------------|-----------------------------|---------------|
| 68     | Park KS [82]         | 2013 | South Korea | Clinical      | NR       | NR      | NR                        | Prospective Consecutive | 320 (19)                   | Respiratory specimens (320) | Liquid media DST |
| 69     | Pimkina E [83]       | 2015 | Lithuania | Laboratory    | 559 (70.6) | NR      | Age ≥ 15                  | Retrospective Unspecified | 791 (264)                   | Respiratory specimens (264) | Solid or liquid media DST |
| 70     | Pinyopoompanish K [84]| 2015 | Thailand | Clinical      | 34 (59.6)  | 15 (26.3) | ≥15 (55.6, 35.5–75.7)    | Cross-sectional Consecutive | 57 (43)                    | Sputum (57)                 | Liquid media DST |
| 71     | Rachow A [85]        | 2011 | Tanzania | Clinical      | 141 (48.3) | 172 (58.9) | Median 39.2              | Unspecified Consecutive  | 292 (61)                    | Sputum (292)                | Liquid media DST |
| 72     | Rahman A [86]        | 2016 | Bangladesh | Clinical     | NR       | NR      | NR                        | Unspecified Unspecified     | 92 (92)                     | Sputum (92)                | Liquid media DST |
| 73     | Raizada N [87]       | 2014 | India    | Clinical      | 2339 (50.8) | NR      | Children < 14            | Prospective Consecutive    | 4600 (48)                   | Sputum (4600)              | Liquid media DST |
| 74     | Reither K [88]       | 2015 | Tanzania Uganda | Clinical  | 219 (46.8)  | 197 (43.7) | Children < 16 (5.6, 20–58) | Prospective Consecutive    | 451 (25)                    | Sputum (451)                 | Liquid media DST |
| 75     | Rice JP [89]         | 2017 | America  | Laboratory    | NR       | NR      | Median 30, IQR 35–60     | Retrospective Unspecified  | 637 (120)                   | Sputum (120)                | Liquid media DST |
| 76     | Sharma SK [90]       | 2015 | India    | Laboratory    | 909 (64.7) | NR      | Median 37.5, IQR 19.4–55.6 | Unspecified Consecutive    | 1406 (422)                  | Respiratory specimens (422) | Solid and liquid media DST |
| 77     | Sharma SK [91]       | 2017 | India    | Laboratory    | 1405 (55.6) | NR      | Median 35.29, IQR 20–50  | Unspecified Convenient     | 2468 (328)                  | Extra-pulmonary specimens (328) | Liquid media DST |
| 78     | Singh UB [92]        | 2016 | India    | Clinical      | 589 (51.4) | NR      | NR                        | Prospective Unspecified    | 1145 (72)                   | Pulmonary and Extra-pulmonary specimens (132) | Liquid media DST |
| 79     | Soeroto AY [93]      | 2019 | Indonesia | Clinical     | 193 (56.9)  | 5 (1.5)    | Median 38.2, IQR 25.7–50.7 | Retrospective Unspecified | 339 (158)                   | NR (158)                   | DST |
| 80     | Ssengooba W [84]     | 2014 | Uganda   | Clinical      | 155 (36.6) | 424 (100) | Median 32, IQR 32–34     | Prospective Unspecified    | 424 (9)                     | Sputum (424)                | Liquid media |

Table 1 Characteristics of studies included in the meta-analysis for rifampicin-resistance tuberculosis detection (Continued)
| Study | First author [ref.] | Year | Country | Study setting | Male (%) | HIV (%) | Age (year) (Median, IQR) | Patient selecting method | Total samples n (included n) | Specimen type (samples n) | Gold standard |
|-------|---------------------|------|---------|---------------|----------|---------|-------------------------|-------------------------|-----------------------------|---------------------------|----------------|
| 81    | Strydom K [95]      | 2015 | South Africa | Laboratory | NR       | NR      | NR                      | Retrospective Consecutive | 120 (115)                  | Sputum (120)              | DST |
| 82    | Tahseen S [96]      | 2016 | Pakistan | Clinical    | 1078 (54.3) | NR      | Median 33               | Cross-sectional Consecutive | 1984 (1533)               | Sputum (1533)              | Solid media DST |
| 83    | Theron G [97]       | 2011 | South Africa | Clinical    | 325 (67.7) | 130 (27.1) | Adults≥18 (96, 18–83)   | Unspecified Consecutive  | 480 (157)                  | Sputum (480)              | Liquid media DST |
| 84    | Tsuyuguchi K [88]   | 2017 | Japan    | Clinical    | 146 (61.6) | NR      | Median 65.2, IQR 23–94 | Prospective Consecutive | 237 (201)                  | Sputum (201)              | Solid media DST |
| 85    | Ullah I [99]        | 2017 | Pakistan | Clinical    | 130 (48.9) | 0 (0)    | Median 34, IQR 3–80     | Unspecified Unspecified   | 266 (88)                   | Extra-pulmonary specimens (88) | DST |
| 86    | Vadwai V [100]      | 2011 | India    | Clinical    | 251 (45.9) | 16 (29)  | Median 37, IQR 8–months–94 | Unspecified Consecutive | 547 (125)                  | Biopsy (284), pus (147), body fluids (93), CSF (23) | Solid and liquid media DST |
| 87    | van Kampen SC [101] | 2015 | Kazakhstan | Laboratory | NR       | 52 (0.9) | NR                      | Prospective Consecutive | 5611 (1054)                | Sputum (5611)              | Solid or liquid media DST |
| 88    | van Kampen SC [102] | 2015 | Indonesia | Clinical    | 872 (60.5), missing 15 (1.0) | 35 (24) | 0.5% < 15, 97.7% ≥ 16, 18% missing | Unspecified Consecutive | 1442 (339)                | Sputum (1442)              | DST |
| 89    | Wang G [103]        | 2017 | China    | Clinical    | NR        | NR      | NR                      | Prospective Undefined    | 1461 (538)                 | Pulmonary specimens (1063), extra-pulmonary specimens (398) | Solid media DST |
| 90    | Wang G [104]        | 2019 | China    | Clinical    | 192 (65.75) | 0 (0)  | Median 42, IQR 14–89   | Prospective Consecutive | 292 (119)                  | Sputum (90), pleural fluid (29) | Solid or liquid media DST |
| 91    | Williamson DA [105] | 2012 | New Zealand | Clinical    | NR        | NR      | NR                      | Unspecified Unspecified | 169 (14)                   | Respiratory specimens (89); extra-pulmonary specimens (9), MGIT liquid culture vials (71) | Liquid media DST |
| 92    | Yin QQ [106]        | 2014 | China    | Clinical    | 141 (55.3) | NR      | Children≤18 (6.1, 0.3–15.3) | Unspecified Unspecified | 255 (21)                   | BALF (255)                | Liquid media DST |
Table 1: Characteristics of studies included in the meta-analysis for rifampicin-resistance tuberculosis detection (Continued)

| Study | First author [ref.] | Year | Country | Study setting | Male (%) | HIV (%) | Age (year) (Median, IQR) | Patient selecting method | Total samples n (included n) | Specimen type (samples n) | Gold standard |
|-------|----------------------|------|---------|---------------|----------|---------|--------------------------|--------------------------|-----------------------------|---------------------------|---------------|
| 93    | Yuan M [107]         | 2016 | China   | Clinical     | NR       | 0 (0)   | NR                      | Retrospective Unspecified | 328 (90)                    | Extra-pulmonary specimens (90) | DST           |
| 94    | Zar HJ [108]         | 2012 | South Africa | Clinical   | 294 (55.0) | 117 (219) | Children<15 (19.0 months, 112–38.3 months) | Unspecified Consecutive | 535 (125)                    | Nasopharyngeal specimens, sputum (535) | Liquid culture |
| 95    | Zar HJ [109]         | 2014 | South Africa | Clinical   | 181 (47) | 31 (8)   | Children<15 (38.3 months, 212–56.5 months) | Prospective Consecutive | 384 (18)                    | Sputum (309), Nasopharyngeal aspirate specimens (309) | DST           |
| 96    | Zetola NM [110]      | 2014 | Botswana | Clinical     | 221 (59.7) | 279 (594) | Adult≥18 (37, 31–44) | Retrospective Consecutive | 370 (370)                   | Sputum (370)              | DST           |
| 97    | Zhang AM [111]       | 2016 | China   | Clinical     | 65 (95.6) | 0 (0)    | Children≤14 (Unspecified) | Unspecified              | 109 (21)                    | Pulmonary and Extra-pulmonary specimens (21) | Liquid media DST |

Sample selection: Study units selected prospectively, or retrospectively from existing samples. Consecutive, random or convenience sampling method. ‘Unspecified’ refers to studies where there was no clear indication how the study participants were chosen. Solid media culture (Löwenstein-Jensen), liquid media culture (Bactec MGIT 960).
### Table 2: Data of diagnostic accuracy of studies included in the meta-analysis for rifampicin resistance tuberculosis detection

| Study   | First author [ref.] | Year | Total samples n (included n) | True positive | False positive | False negative | True negative | Specimen type                                      |
|---------|---------------------|------|------------------------------|--------------|----------------|---------------|--------------|---------------------------------|
| 1       | Al-Ateah SM [15]    | 2012 | 234 (59)                    | 2            | 0              | 0             | 57           | Respiratory and non-respiratory specimens |
| 2       | Antonenka U [16]    | 2013 | 121 (50)                    | 2            | 0              | 0             | 48           | Respiratory specimens             |
| 3       | Balcells ME [17]    | 2012 | 160 (12)                    | 0            | 2              | 0             | 10           | Sputum                           |
| 4       | Barak M [19]        | 2012 | 282 (36)                    | 3            | 0              | 0             | 33           | Sputum                           |
| 5       | Bates M [20]        | 2013 | 930 (41)                    | 2            | 1              | 0             | 38           | Sputum, gastric lavage aspirate   |
| 6       | Bladegne F [21]     | 2014 | 231 (32)                    | 2            | 1              | 0             | 29           | Lymph node aspirates             |
| 7       | Blakemore R [22]    | 2010 | 168 (79)                    | 37           | 0              | 0             | 42           | Sputum                           |
| 8       | Boehme CC [23]      | 2010 | 1730 (720)                  | 200          | 10             | 5             | 505          | Sputum                           |
| 9       | Peru                |      | 341 (209)                   | 16           | 3              | 0             | 190          |                                  |
| 10      | Boehme CC [24]      | 2011 | 6648 (1060)                 | 236          | 14             | 14            | 796          | Sputum                           |
| 11      | Carriquiry G [26]   | 2012 | 131 (39)                    | 6            | 3              | 0             | 30           | Sputum                           |
| 12      | Cayci YT [27]       | 2017 | 34 (34)                     | 3            | 1              | 0             | 30           | Respiratory and none-respiratory specimens |
| 13      | Chakravorty S [28]  | 2017 | 139 (139)                   | 38           | 1              | 3             | 97           | Sputum                           |
| 14      | Chiang TY [29]      | 2018 | 2957 (697)                  | 36           | 9              | 0             | 652          | Sputum                           |
| 15      | Chikanda T [30]     | 2017 | 351 (200)                   | 2            | 1              | 0             | 185          | Sputum                           |
| 16      | Ciftçi IH [31]      | 2011 | 85 (24)                     | 0            | 0              | 0             | 24           | Sputum, BAL, thorasynthesis fluid, urine |
| 17      | Deggim V [32]       | 2013 | 79 (10)                     | 0            | 3              | 0             | 7            | Respiratory and None-respiratory |
| 18      | Dharan NJ [33]      | 2016 | 544 (185)                   | 85           | 9              | 2             | 89           | Sputum                           |
| 19      | Dorman SE [34]      | 2012 | 6893 (144)                  | 5            | 5              | 0             | 134          | Sputum                           |
| 20      | Dorman SE [35]      | 2018 | 1753 (511)                  | 167          | 7              | 8             | 369          | Sputum                           |
| 21      | Du J [36]           | 2015 | 126 (43)                    | 9            | 2              | 1             | 31           | Pleural biopsy specimen           |
| 22      | Feliciano CS [37]   | 2018 | 29 (29)                     | 12           | 3              | 4             | 10           | NR                               |
| 23      | Giang do C [38]     | 2015 | 150 (29)                    | 1            | 0              | 0             | 28           | Respiratory and non-respiratory specimens |
| 24      | Gu Y [39]           | 2015 | 60 (24)                     | 6            | 0              | 0             | 18           | Pus specimens                     |
| 25      | Guenavoi K [40]     | 2016 | 50 (50)                     | 21           | 0              | 0             | 29           | Sputum                           |
| 26      | Helb D [41]         | 2010 | 64 (64)                     | 9            | 1              | 0             | 54           | Sputum                           |
| 27      | Hilleman D [42]     | 2011 | 521 (29)                    | 0            | 4              | 0             | 25           | Non-respiratory specimens        |
| 28      | Huang H [43]        | 2018 | 2910 (1066)                 | 147          | 16             | 5             | 898          | NR                               |
Table 2 Data of diagnostic accuracy of studies included in the meta-analysis for rifampicin resistance tuberculosis detection (Continued)

| Study | First author [ref.] | Year | Total samples n (included n) | True positive | False positive | False negative | True negative | Specimen type |
|-------|----------------------|------|-----------------------------|---------------|----------------|----------------|---------------|---------------|
| 29 Huh HJ [44] | 2014 | 300 (98) | 6 | 1 | 1 | 90 | Respiratory specimens |
| 30 Hu P [45] | 2014 | 1352 (332) | 26 | 4 | 2 | 300 | Sputum |
| 31 Jin YH [46] | 2017 | 109 (48) | 4 | 4 | 1 | 39 | Pus |
| 32 Kawkitinarong K [47] | 2017 | 521 (228) | 15 | 0 | 1 | 212 | Pulmonary specimens |
| 33 Khalil KF [48] | 2015 | 93 (93) | 5 | 0 | 1 | 87 | BAL |
| 34 Kim CH [49] | 2014 | 171 (26) | 2 | 0 | 0 | 24 | Respiratory and non-respiratory specimens |
| 35 Kim CH [50] | 2015 | 383 (36) | 4 | 1 | 0 | 31 | Respiratory and Non Respiratory specimens |
| 36 Kim MJ [51] | 2015 | 52 (45) | 1 | 0 | 1 | 43 | Respiratory and non-respiratory specimens |
| 37 Kim SY [52] | 2012 | 71 (62) | 21 | 0 | 0 | 41 | Sputum |
| 38 Kim YW [53] | 2015 | 1429 (47) | 4 | 0 | 1 | 42 | Non-respiratory specimens |
| 39 Kim YW [54] | 2015 | 321 (321) | 25 | 4 | 0 | 292 | Sputum |
| 40 Kokuto H [55] | 2015 | 93 (56) | 4 | 0 | 2 | 50 | Fecal specimens |
| 41 Kostera J [56] | 2018 | 132 (122) | 28 | 0 | 4 | 90 | Sputum |
| 42 Kurbaniyazova G [57] | 2017 | 2734 (364, solid media DST) | 120 | 20 | 12 | 212 | NR |
| 43 Kurbatova EV [58] | 2013 | 201 (99) | 57 | 1 | 5 | 36 | Sputum |
| 44 Kwak N [59] | 2013 | 681 (127) | 8 | 6 | 0 | 113 | Sputum |
| 45 Lawn SD [60] | 2011 | 468 (55) | 4 | 3 | 0 | 48 | Sputum |
| 46 Lee HY [61] | 2013 | 132 (35) | 2 | 0 | 0 | 33 | Bronchscopy specimens |
| 47 Li Q [62] | 2016 | 1973 (449) | 47 | 16 | 6 | 380 | Sputum |
| 48 Li Y [63] | 2017 | 420 (59) | 11 | 0 | 1 | 47 | Extra-pulmonary specimens |
| 49 Liu X [64] | 2015 | 134 (44) | 10 | 2 | 1 | 31 | Pleural biopsy and pleural fluid specimens |
| 50 Lorent N [65] | 2015 | 299 (102) | 24 | 6 | 3 | 69 | Sputum |
| 51 Luetkemeyer AF [66] | 2016 | 992 (194) | 5 | 1 | 2 | 186 | Sputum |
| 52 Metcalf JZ [67] | 2016 | 352 (161) | 54 | 8 | 9 | 90 | Sputum |
| 53 Mokaddas E [68] | 2015 | 452 (452) | 10 | 2 | 0 | 440 | Respiratory and non-respiratory specimens |
| 54 Moon HW [69] | 2015 | 100 (100) | 47 | 0 | 3 | 50 | Respiratory specimens |
| 55 Muñoz L [70] | 2011 | 122 (85) | 6 | 0 | 1 | 78 | Respiratory and non-respiratory specimens |
| 56 Mwanza W [71] | 2018 | 1070 (24) | 13 | 3 | 0 | 8 | NR |
| 57 Mynedd M [72] | 2014 | 134 (88) | 54 | 1 | 1 | 32 | Sputum |
| 58 Nguessan K [73] | 2014 | 120 (29) | 14 | 4 | 0 | 11 | Sputum |
| 59 NGuessan K [74] | 2018 | 1095 (162) | 112 | 8 | 0 | 42 | Sputum |
| 60 Nikolayevskyy V [75] | 2018 | 3478 (3167) | 1212 | 77 | 86 | 1792 | Pulmonary specimens |
| 61 Nicol MP [76] | 2011 | 452 (77) | 3 | 4 | 0 | 70 | Sputum |
| 62 O’Grady J [77] | 2012 | 881 (96) | 13 | 2 | 3 | 78 | Sputum |
Table 2  Data of diagnostic accuracy of studies included in the meta-analysis for rifampicin resistance tuberculosis detection
(Continued)

| Study | First author [ref.] | Year | Total samples n (included n) | True positive | False positive | False negative | True negative | Specimen type |
|-------|----------------------|------|------------------------------|---------------|----------------|---------------|---------------|---------------|
| 63    | Ou X [78]            | 2014 | 2454 (616)                  | 54            | 16             | 8             | 538           | Sputum        |
| 64    | Ozkutuk N [79]       | 2014 | 2639 (133)                  | 1             | 1              | 0             | 131           | Respiratory and non-respiratory specimens |
| 65    | Pan X [80]           | 2018 | 190 (62)                    | 2             | 2              | 0             | 58            | Sputum and BAL |
| 66    | Pang Y [81]          | 2014 | 211 (10)                    | 1             | 0              | 0             | 9             | Gastric lavage aspirates |
| 67    | Park KS [82]         | 2013 | 320 (19)                    | 2             | 0              | 0             | 17            | Respiratory specimens |
| 68    | Pimkina E [83]       | 2015 | 791 (264)                   | 39            | 4              | 0             | 221           | Sputum        |
| 69    | Pinyopornpanish K [84] | 2015 | 57 (43)                     | 0             | 0              | 3             | 40            | Sputum        |
| 70    | Rachow A [85]        | 2011 | 292 (61)                    | 0             | 0              | 0             | 61            | Sputum        |
| 71    | Rahman A [86]        | 2016 | 92 (92)                     | 85            | 6              | 0             | 1             | Sputum        |
| 72    | Raizada N [87]       | 2014 | 4600 (48)                   | 47            | 1              | 0             | 0             | Sputum        |
| 73    | Reither K [88]       | 2015 | 451 (25)                    | 0             | 0              | 0             | 25            | Sputum        |
| 74    | Rice JP [89]         | 2017 | 637 (120)                   | 2             | 2              | 0             | 116           | Sputum        |
| 75    | Sharma SK [90]       | 2015 | 1406 (422)                  | 104           | 7              | 6             | 305           | Respiratory specimens |
| 76    | Sharma SK [91]       | 2017 | 2468 (328)                  | 38            | 2              | 3             | 285           | Extra-pulmonary specimens |
| 77    | Singh UB [92]        | 2016 | 1145 (72)                   | 14            | 0              | 2             | 56            | Pulmonary and extra-pulmonary specimens |
| 78    | Soeroto AY [93]      | 2019 | 339 (158)                   | 141           | 17             | 0             | 0             | NR            |
| 79    | Sengooba W [94]      | 2014 | 424 (94)                    | 4             | 0              | 0             | 9             | Sputum        |
| 80    | Strydom K [95]       | 2015 | 120 (115)                   | 59            | 1              | 2             | 53            | Sputum        |
| 81    | Taheen S [96]        | 2016 | 1984 (1533)                 | 85            | 17             | 15            | 1416          | Sputum        |
| 82    | Theron G [97]        | 2011 | 480 (157)                   | 5             | 1              | 0             | 151           | Sputum        |
| 83    | Tsuyuguchi K [98]    | 2017 | 237 (201)                   | 22            | 3              | 0             | 176           | Sputum        |
| 84    | Ullah I [99]         | 2017 | 266 (88)                    | 24            | 2              | 0             | 62            | Extra-pulmonary specimens |
| 85    | Vadwai V [100]       | 2011 | 547 (125)                   | 39            | 5              | 1             | 80            | Non-respiratory specimens |
| 86    | van Kampen SC [101]  | 2015 | 5611 (1054)                 | 522           | 31             | 33            | 468           | Sputum        |
| 87    | van Kampen SC [102]  | 2015 | 1442 (339)                  | 158           | 18             | 21            | 142           | Sputum        |
| 88    | Wang G [103]         | 2017 | 1461 (538)                  | 145           | 0              | 3             | 390           | Pulmonary and extra-pulmonary specimens |
| 89    | Wang G [104]         | 2019 | 229 (119)                   | 21            | 0              | 1             | 97            | Sputum, pleural fluid |
|       |                      |      | 90                         | 15            | 0              | 1             | 74            | Sputum        |
|       |                      |      | 29                         | 6             | 0              | 0             | 23            | Pleural fluid |
| 90    | Williamson DA [105]  | 2012 | 169 (14)                    | 7             | 6              | 0             | 1             | Respiratory; extra-pulmonary specimens, positive MGIT liquid culture vials |
| 91    | Yin QQ [106]         | 2014 | 255 (21)                    | 1             | 0              | 0             | 20            | BALF          |
| 92    | Yuan M [107]         | 2016 | 328 (900)                   | 12            | 0              | 3             | 75            | Extra-pulmonary specimens |
| 93    | Zar HJ [108]         | 2012 | 535 (125)                   | 5             | 5              | 1             | 114           | Nasopharyngeal specimens, sputum |
| 94    | Zar HJ [109]         | 2014 | 384 (18)                    | 0             | 0              | 0             | 18            | Sputum, Nasopharyngeal aspirate specimens |
| 95    | Zetola NM [110]      | 2014 | 370 (370)                   | 51            | 1              | 4             | 314           | Sputum        |
| 96    | Zhang AM [111]       | 2016 | 109 (21)                    | 6             | 0              | 0             | 15            | Pulmonary and extra-pulmonary specimens |

IQR Interquartile range, TA Tracheal aspirate, BA Bronchial aspirate; BAL Bronchoalveolar lavage, LN Lymph node, CSF Cerebrospinal fluid, EPTB Extra-pulmonary tuberculosis, CCRS Composite clinical reference standard, FNA Fine needle aspirate; DST: drug-susceptibility testing
case report; (ii) abstract of any conference; (iii) non-clinical research; (iv) review.

Data extraction
The following data were extracted from each included study: first author, year of publication, country, study settings, gender, the number of patients, the number and type of samples, diagnostic characteristics of Xpert MTB/RIF such as TP, TN, FP and FN. We sent e-mails to the authors for more details when data of individual studies were insufficient for a meta-analysis. In the case of inability to obtain data from the authors, the studies were excluded.

Statistical analysis
MIDAS modules in the STATA statistical software (version 12.0; STATA Corporation, College Station, TX, USA) was used to perform the meta-analyses. The summary receiver operating characteristic (SROC) model and the bivariate random-effects model were used in our study to evaluate the diagnostic accuracy of Xpert MTB/RIF for rifampicin resistance detection. For each study, we calculated the sensitivity and specificity of Xpert MTB/RIF to diagnose rifampicin resistance along with 95% confidence intervals.

Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool was introduced to assess the quality of each included study. The Review Manager software (version 5.3, The Nordic Cochrane Centre, Copenhagen, Denmark) was used to present the result of QUADAS assessment.

We assessed the heterogeneity between included studies by using a bivariate boxplot, which can describe the degree of interdependence including the central location and identification of any outliers with an inner oval representing the median distribution of the data points and an outer oval representing the 95% confidence bound (by visually examining the position of each individual study, within the range of boxplot suggesting more heterogeneity).

![Fig. 2 Risk of bias and applicability concerns as percentages across the included studies for rifampicin resistance detection](image)

![Fig. 3 Heterogeneity test of included studies in this meta-analysis: a bivariate boxplot (a) and a Deek's funnel plot (b)](image)
Results
Description of included studies
Finally, we included 97 studies in this meta-analysis [15–111] (Fig. 1), including 26,037 samples for the diagnosis of rifampicin resistance. All studies were in English except five (three in Chinese [46, 64, 111] and two in Turkish [31, 79]). Twenty-six studies (26.8%) were conducted in high income countries (the World Bank income classification 2018) and 52 studies (53.6%) were in the 22 countries with a high burden of TB [1].

The median number of samples per study was 268 for rifampicin resistance detection. The samples of 56 included studies were pulmonary, such as sputum and BAL. Another 15 studies were extrapulmonary samples (e.g. body fluid, FNA, stool and blood), 16 studies included samples of both pulmonary and extrapulmonary (Tables 1 and 2).

Methodological quality of included studies
The overall methodological quality of the included studies was summarized in Fig. 2. Approximately half of the included studies collected data consecutively (n = 41; 42.2%) (Table 1) and no study used a case-control design. All studies were carried out either in tertiary care centers or reference laboratories. In index tests part, 15 studies (15.5%) were considered as unclear risk of bias. In reference standard part, 11 studies (11.3%) were considered as unclear risk of bias because the results of the reference standard were interpreted with unclear blind of the results of the index tests. In flow and timing part, 14 studies (24.7%) were considered as unclear risk of bias because not all patients were included in the analysis.

The heterogeneity of the studies included in this study was tested by a bivariate boxplot (Fig. 3a) and a Deek's funnel plot (Fig. 3b). Most of the included studies were in the bivariate boxplot, and the slope of Deek's funnel was almost horizontal, which all meant a good heterogeneity.

Detection of rifampicin resistance in different prevalence and income regions
The accuracy of Xpert MTB/RIF for rifampicin resistance detection was estimated in 59 studies. The pooled sensitivity, specificity and AUC of Xpert MTB/RIF were estimated.
RIF for detecting rifampicin resistance were 0.93 (95% CI 0.90–0.95), 0.98 (95% CI 0.96–0.98) and 0.99 (95% CI 0.97–0.99), respectively (Fig. 4).

Of the 97 studies, 26 studies were of high income countries, 62 of middle and 9 were of low income. For TB prevalence, 52 studies were from the 22 high TB burden countries, and 45 were not. The pooled sensitivity were 0.94 (95% CI 0.89–0.97) and 0.92 (95% CI 0.88–0.94), the pooled specificity were 0.98 (95% CI 0.94–1.00) and 0.98 (95% CI 0.96–0.99), and the AUC were 0.99 (95% CI 0.98–1.00) and 0.99 (95% CI 0.97–0.99) in high and middle/low income countries, respectively (Fig. 5a and Fig. 5b). The pooled sensitivity were 0.91 (95% CI 0.87–0.94) and 0.91 (95% CI 0.86–0.94), the pooled specificity were 0.98 (95% CI 0.96–0.99) and 0.98 (95% CI 0.96–0.99), and the AUC were 0.98 (95% CI 0.97–0.99) and 0.99 (95% CI 0.97–0.99) in high TB burden and middle/low prevalence countries, respectively (Fig. 5c and Fig. 5d).

**Discussion**

Several meta-analyses have focused on the diagnostic accuracy of Xpert MTB/RIF for pulmonary [12] or extra-pulmonary TB [13, 14] detection either on adults or children [12]. However, to our knowledge, this is the first meta-analysis for Xpert MTB/RIF diagnostic accuracy for rifampicin resistance detection in different prevalence and income regions. Our systematic review demonstrated that Xpert MTB/RIF is high sensitive diagnostic tool for rifampicin resistance detection. Firstly, the accuracy of Xpert MTB/RIF for rifampicin resistance detection was estimated in our meta-analysis. As shown in Fig. 4, the accuracy of Xpert MTB/RIF for rifampicin resistance detection was impressive. The pooled sensitivity, specificity and AUC were 0.93 (95% CI 0.90–0.95), 0.98 (95% CI 0.96–0.98) and 0.98 (95% CI 0.96–0.98) and 0.99 (95% CI 0.97–0.99), respectively. As estimated, about 75% of multi-drug resistant TB remains undiagnosed [4]. We strongly hope Xpert
MTB/RIF, which provided a quick and accurate result, will contribute to early and accurate diagnosis of rifampicin resistance.

The overall sensitivity of Xpert MTB/RIF for rifampicin resistance detection were almost the same between high TB prevalence countries and middle/low ones (0.91, 95% CI 0.87–0.94 versus 0.91, 95% CI 0.86–0.94). And for different income levels, the sensitivities of high income ones was also similar with the ones of middle/low income (0.94, 95% CI 0.89–0.97 versus 0.92, 95% CI 0.88–0.94). We can see, taking the different levels of TB prevalence and country income into account, no significant differences were found between subgroups, either in sensitivities, specificities and AUCs.

TB remains one of the world’s deadliest communicable diseases. However, it is intensively distributed in several high burden countries. In 2017, more than half of the new TB was developed in the South-East Asia and Western Pacific Regions. To be specific, one quarter were in the African Region. India and China alone accounted for 24 and 13% of the total cases, respectively [4]. Interestingly, the tendency of TB prevalence was consisted with the economic development at some degree. The income levels of the 22 high TB burden countries all were all middle or low, except one (Russian) [4]. Therefore, it is of significant meanings to estimate the diagnostic accuracy of Xpert MTB/RIF in countries with different levels of TB prevalence and income. Some researchers discovered that the Xpert MTB/RIF showed a higher sensitivity of TB detection in lower TB prevalence countries, which could significantly help the physicians to make clinical decisions [112]. However, our result, from another aspect, showed the diagnostic accuracy of Xpert MTB/RIF for rifampicin resistance detection was not differed between countries with different TB prevalence and incomes.

Advantages of this review were the use of a standard protocol, a bivariate random-effects model used for meta-analysis, and independent reviewers. The data set involved comprehensive searching to identify studies as well as repeated correspondence with authors of study to obtain additional data on the studies.

While there were still some limitations in our analysis. We may have missed some studies despite the comprehensive search. Secondly, sample processing was highly variable across and within studies, as there was no recommendation available on how to process non-respiratory samples from the manufacturer or the WHO.

Conclusions
In conclusion, based on our meta-analysis, the diagnostic accuracy of Xpert MTB/RIF for rifampicin resistance detection was excellent. The overall sensitivity of Xpert MTB/RIF for rifampicin resistance detection in different TB prevalence and income countries were not significant different. We believe that the information obtained from this study will aid the decision making of physicians who take care of patients with possible resistant tuberculosis infection.

Abbreviations
BA: Bronchial aspirate; BAL: Bronchoalveolar lavage; CCRS: Composite clinical reference standard; CF: Cerebrospinal fluid; DST: Drug-susceptibility testing; EPTB: Extra-pulmonary tuberculosis; FN: False negative; FNA: Fine needle aspirate; FP: False positive; HIV: Human immunodeficiency virus; IQR: Interquartile range; LN: Lymph node; MDR-TB: multidrug-resistant TB; NAAT: Nucleic acid amplification test; QUADAS: Quality assessment of diagnostic accuracy studies; RR: Rifampicin resistance; SROC: Summary receiver operating characteristic; TA: Tracheal aspirate; TB: Tuberculosis; TN: True negative; TP: True positive; WHO: World Health Organization; XDR-TB: Extensively drug-resistant TB.

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Authors’ contributions
ZKC and LSY conceived the study. ZKC and JYZ carried out the literature selection, data extraction and statistical analysis. LC accomplished the manuscript draft. ZH and JYZ participated in the analysis. The final manuscript was approved by all the authors.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The protocol was established according to the ethical guidelines of the Helsinki Declaration and approved by the Human Ethics Committee of Department of Respiratory Disease, The Seventh People’s hospital of Chongqing. Written informed consent was obtained from individual participants.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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