Laboratory cross-contamination of Mycobacterium tuberculosis: a systematic review and meta-analysis

DOI:
10.1007/s00408-019-00241-4

Document Version
Accepted author manuscript

Published in:
Lung

Lung

Laboratory cross-contamination of Mycobacterium tuberculosis: a systematic review and meta-analysis

--Manuscript Draft--

Manuscript Number:	LUNG-D-19-00061R2
Full Title:	Laboratory cross-contamination of Mycobacterium tuberculosis: a systematic review and meta-analysis
Article Type:	Original Research
Keywords:	Mycobacterium tuberculosis; laboratory diagnosis; cross-contamination; false positive; systematic review; genotyping
Corresponding Author:	Alexander G. Mathioudakis, MD, MRCP(UK) Wythenshawe Hospital, University of Manchester Manchester, UNITED KINGDOM
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Wythenshawe Hospital, University of Manchester
Corresponding Author's Secondary Institution:	
First Author:	Aleksandra Barac
First Author Secondary Information:	
Order of Authors:	Aleksandra Barac
	Hannah Karimzadeh-Esfahani
	Mahya Pourostadi
	Mohammad Taghi Rahimi
	Ehsan Ahmadpour
	Jalil Rashedi
	Behroz Mahdavipoor
	Hossein Samadi Kafil
	Adel Spotin
	Kalkidan Hassen Abate
	Alexander G. Mathioudakis, MD, MRCP(UK)
	Mohammad Asgharzadeh
Order of Authors Secondary Information:	
Funding Information:	University of Tabriz (IR) (37876) — Dr Ehsan Ahmadpour
	Iranian National Sciences Foundation (843599) — Dr Ehsan Ahmadpour
	National Institute for Health Research (NIHR Manchester BRC) — Dr. Alexander G. Mathioudakis
	Ministry of Education, Science and Technology of the Republic of Serbia (III45005) — Dr Aleksandra Barac
Abstract:	Background: Microbiological cultures are the mainstay of the diagnosis of tuberculosis (TB). False positive TB results lead to significant unnecessary therapeutic and economic burden and are frequently caused by laboratory cross-contamination. The aim of this meta-analysis was to quantify the prevalence of laboratory cross-contamination.

	Methods: Through a systematic review of five electronic databases, we identified studies reporting rates of laboratory cross-contamination, confirmed by molecular techniques in TB cultures. We evaluated the quality of the identified studies using the National Institute of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, and conducted a meta-analysis using standard methodology recommended by the Cochrane Collaboration. Results: Based on 31 eligible studies evaluating 29,839 TB cultures, we found that 2% (95% confidence intervals [CI]: 1-2%) of all positive TB cultures represent false positive results secondary to laboratory cross-contamination. More importantly, we evaluated the rate of laboratory cross-contamination in cases where a single positive TB culture was available in addition to at least one negative TB culture, and we found a rate of 15% (95%CI: 6-33%). Moreover, 9.2% (91/990) of all patients with a preliminary diagnosis of TB had false-positive results and received unnecessary and potentially harmful treatments. Conclusions: Our results highlight a remarkably high prevalence of false positive TB results as a result of laboratory cross-contamination, especially in single-positive TB cultures, leading to the administration of unnecessary, harmful treatments. The need for the adoption of strict technical standards for mycobacterial cultures cannot be overstated.

Laboratory cross-contamination of *Mycobacterium tuberculosis*: a systematic review and meta-analysis

Aleksandra Barac[1,2,#], Hannah Karimzadeh-Esfahani[3,#], Mahya Pourostadi[4], Mohammad Taghi Rahimi[5], Ehsan Ahmadpour[6,7,*], Jalil Rashedi[8], Behroz Mahdavipoor[9], Hossein Samadi Kafil[10,11], Adel Spotin[11], Kalkidan Hassen Abate[12], Alexander G. Mathioudakis[3*], Mohammad Asgharzadeh[13]

# These two authors contributed equally to this work.

[1] Clinic for Infectious and Tropical Diseases, Clinical Centre of Serbia, Belgrade, Serbia.

[2] Faculty of Medicine, University of Belgrade, Belgrade, Serbia.

[3] Division of Infection, Immunity and Respiratory Medicine, The University of Manchester, Manchester, UK.

[4] Biotechnology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.

[5] School of Medicine, Shahroud University of Medical Sciences, Shahroud, Iran

[6] Infectious and Tropical Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

[7] Department of Parasitology, Tabriz University of Medical Sciences, Tabriz, Iran

[8] Tuberculosis and Lung Disease Research Center, Faculty of Paramedicine, Tabriz University of Medical Sciences, Tabriz, Iran

[9] Department of Laboratory Science, Faculty of Paramedicine, Tabriz University of Medical Sciences & Department of Medical Parasitology, School of Medical Sciences, Tarbiat Modarres University, Tehran, Iran

[10] Department of Microbiology, Tabriz University of Medical Sciences, Tabriz, Iran

[11] Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

[12] Institute of health sciences, Jimma University, Jimma, Ethiopia

[13] Hematology and Oncology Research Center, Faculty of Paramedicine, Tabriz University of Medical Sciences, Tabriz, Iran

***Corresponding authors:**

1. Ehsan Ahmadpour, Ph.D.

Email: ehsanahmadpour@gmail.com, ahmadpoure@tbzmed.ac.ir

Infectious and Tropical Diseases Research Center, Tabriz, Iran.

2. Alexander G. Mathioudakis MD, MRCP(UK).

Email: alexander.mathioudakis@manchester.ac.uk

Division of Infection, Immunity and Respiratory Medicine,

The University of Manchester,Manchester, UK.

Keywords: *Mycobacterium tuberculosis*, laboratory diagnose, cross-contamination, false positive, systematic review, genotyping

Word count:

Manuscript: 2374

Abstract: 222

Tables: 1

Figures: 4

Abbreviations:

HIV – Human Immunodeficiency Virus

MDR-TB – Multidrug Resistant Tuberculosis

NIH – National Institute of Health

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

TB – Tuberculosis

WHO – World Health Organization

Abstract

Background: Microbiological cultures are the mainstay of the diagnosis of tuberculosis (TB). False positive TB results lead to significant unnecessary therapeutic and economic burden and are frequently caused by laboratory cross-contamination. The aim of this meta-analysis was to quantify the prevalence of laboratory cross-contamination.

Methods: Through a systematic review of five electronic databases, we identified studies reporting rates of laboratory cross-contamination, confirmed by molecular techniques in TB cultures. We evaluated the quality of the identified studies using the National Institute of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, and conducted a meta-analysis using standard methodology recommended by the Cochrane Collaboration.

Results: Based on 31 eligible studies evaluating 29,839 TB cultures, we found that 2% (95% confidence intervals [CI]: 1-2%) of all positive TB cultures represent false positive results secondary to laboratory cross-contamination. More importantly, we evaluated the rate of laboratory cross-contamination in cases where a single positive TB culture was available in addition to at least one negative TB culture, and we found a rate of 15% (95%CI: 6-33%). Moreover, 9.2% (91/990) of all patients with a preliminary diagnosis of TB had false-positive results and received unnecessary and potentially harmful treatments.

Conclusions: Our results highlight a remarkably high prevalence of false positive TB results as a result of laboratory cross-contamination, especially in single-positive TB cultures, leading to the administration of unnecessary, harmful treatments. The need for the adoption of strict technical standards for mycobacterial cultures cannot be overstated.

Introduction

Despite global efforts to control tuberculosis (TB), the incidence of the condition is growing[1]. According to the World Health Organization (WHO) 2018 report, "TB is one of the top 10 causes of death worldwide, and the leading cause from a single infectious agent"[2]. In 2017, 10.4 million people were diagnosed with TB and 1.6 million died from the disease (including 0.3 million patients with concomitant HIV infection)[1,2]. Over 95% of TB deaths occur in low- and middle-income countries. Five countries account for 56% of the total number of cases, with India leading the count, followed by Indonesia, China, the Phillipines, and Pakistan. In 2016, the estimated incidence of TB in children exceeded 1 million. In 2016, an estimated 490 000 people developed multidrug-resistant TB (MDR-TB) worldwide[2]

TB diagnosis is confirmed by the isolation and identification of M. tuberculosis bacillus in microbiological cultures[3]. The accuracy of mycobacterial microbial cultures is limited by the prevalence of false positive and false negative results. Laboratory cross-contamination causing false positive results is not infrequent and has important medical and psychological implications for patients and their families, as well as financial and public health ramifications for the healthcare system[4]. Over the years, different methods have been utilized to limit the burden of laboratory cross-contamination. More than one decade ago, it was recommended to consider a result false positive if there were 5 or less colonies grown on a specific growth media[5]. Since the above method was not reliable, molecular techniques are now used for the

confirmation of TB[6-7]. IS6110-based restriction fragment length polymorphism typing (RFLP) is a standard method to assess the cross-contamination and transmission of tuberculosis. IS6110-RFLP which is based on the number and genomic site of IS6110[8-9]. In the cases that the copy number of IS6110 is less than 6 bands, the use of other methods can be helpful[13]. Approaches based on next generation sequencing (NGS) may offer a more accurate assessment[14].

However, the exact burden of false positive mycobacterial cultures resulting from laboratory cross-contamination is unknown. The aim of this systematic review and meta-analysis was to estimate this prevalence in order to facilitate planning accurate, cost-effective diagnostic strategies.

Methods

Inclusion criteria

We included studies reporting on the prevalence of TB-laboratory cross-contamination, detected by genotyping and confirmed by clinico-epidemiological analyses. We did not apply any geographical limitations. We only included studies published during the last 20 years (since 1997), as culturing methods and standards have been changing, and we considered that older studies would not reflect current practice. We excluded studies exploring non-TB mycobacteria, those that solely used genotyping to explore cross-contamination without taking into account clinic-epidemiological data, case reports, specific organ TB and those with very limited sample size (≤60). We only included studies written in the English language.

Outcome Measures

The outcomes of this meta-analysis include: The proportion of TB laboratory cross-contamination among (a) all positive TB cultures or smears, (b) single positive TB cultures or

smears, in cases where the results of at least one additional negative TB culture was available, and (c) all TB cultures or smears (positive or negative). In addition, we assessed the proportion of false-negative results in the same groups.

Search Strategy and Study Selection

We systematically reviewed the electronic databases of Medline, PubMed, Scopus, ScienceDirect and Cochrane Controlled Register of Trials (CENTRAL), using appropriate controlled vocabulary and free search terms to identify studies evaluating the prevalence of tuberculosis (use TB instead) laboratory cross-contamination, including the following terms: "tuberculosis", "mycobacterium", "mycobacterial", "cross-contamination", "laboratory diagnosis", "false positive", "culture" and "genotyping". Databases were searched from January 1997 to Jan 2019. Two authors independently screened abstracts and full texts (when appropriate), for eligibility for all identified studies. The study selection process was detailed in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.

Data extraction

Relevant data including the full reference and study identifiers, study date, study design, eligibility, predefined outcomes, number and characteristics of the participants and details on the outcomes of interest were extracted by two authors independently. Disagreement was resolved through discussion and adjudication by a third investigator.

Quality of the included studies

We used the National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies to assess the risk of bias of each included study (available

from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). Two authors evaluated risk of bias of the included studies independently. We used funnel plots to assess for publication bias when appropriate.

Analysis

We used I^2 statistic to assess statistical heterogeneity within the studies included in each analysis. We conducted prespecified subgroup analyses to explore the causes of heterogeneity in cases with substantial heterogeneity (I^2 >50%).

We expected significant heterogeneity in our analyses, due to the differences in the standards used in different laboratories and the accuracy of the methodologies used to confirm laboratory cross-contamination in the primary studies. For this reason, we conducted our meta-analyses using the random effects mode. We considered it imperative to present overall estimates, even if the heterogeneity was particularly significant and to declare the limitations. Meta-analyses were performed using R version 3.4.4 and the relevant Comprehensive R Archive Network (CRAN) packages for meta-analysis (meta and metafor).

In different prespecified sensitivity analyses for all outcomes (i) we included only studies with low risk of bias and (ii) we divided the studies according to the methodology used to identify TB laboratory cross-contamination. In an additional sensitivity analysis, we also excluded one of the identified studies that found unexpectedly high levels of cross-contamination, which , as reported by the investigators, reflected laboratory specific problems.

Results

Our search results and study selection process are summarized in a PRISMA flowchart (figure 1). Briefly, our systematic searches yielded 1,033 records of which we included 32 records

reporting on 31 studies evaluating n = 29,839 positive cultures for *Mycobacterium tuberculosis*[3,6,11-39]. Basic study characteristics are available in table 1.

Study characteristics

The study population of the included studies ranged between 61 and 8,889 participants. The proportion of positive cultures as a result of laboratory cross-contamination ranged from 0.3% to 7.84%, with the exception of one study[6], which reported significantly larger proportion (18.2%), as a result of an extensive episode of cross-contamination involving numerous samples.

Different genotyping methods were used to identify possible laboratory cross-contamination. Most studies (n = 19) used IS6110-RFLP. Others used 12 or 24-loci mycobacterial interspersed repetitive units (MIRU) typing, variable numbers of tandem repeats (VNTR), polymorphic GC-rich sequence (PGRS), direct repetitive element (DRE), spoligotyping, and direct repeat (DR)-RFLP. In the majority of studies more than one method was performed for genotyping.

Risk of Bias Assessment

We deemed all of the included studies to be of good (n = 21) or fair (n = 10) methodological quality (figure 2). Specific limitations included: (i) None of the included studies provided a sample size justification, (ii) The study population was poorly defined in 6 studies, (iii) the participation rate was less than 50% of the eligible persons in one study and (iv) four studies recruited heterogeneous populations. In addition, our funnel plots suggest the presence of publication bias (figure 3). These may have led to a slight overestimation of the prevalence of laboratory cross-contamination.

Data Synthesis

Overall effect estimates for each outcome are presented in figure 4. The proportion of positive samples secondary to laboratory cross-contamination as a proportion of all positive samples was evaluated by 30 studies, with an overall study population of n = 29,022. We found a mean proportion of 0.02 with 95% confidence intervals (95% CI) between 0.01 and 0.02 (figure 4a). There was significant heterogeneity (I^2 = 88%) which was resolved by removing the study with unexpectedly high levels of cross-contamination[6] and separating the studies according to the methods used to identify cross-contamination.

We defined single positive a TB culture or smear, in cases where the results of at least one additional TB culture were available and negative. Eight studies reported on cross-contamination as a proportion of single-positive samples. The mean proportion was 0.15 (95% CI: 0.06 – 0.33, figure 4b). The significant heterogeneity was resolved by the exclusion of two studies reporting unexpectedly high proportions of cross-contamination. The mean proportion of the remaining, homogeneous studies was 0.10 (95% CI: 0.06, 0.15, figure 4c).

Finally, 20 studies provided data on false-positive results and allowed us to assess the number of false-positive results as a proportion of all positive results. The mean proportion was 0.03 (95% CI 0.02, 0.04, figure 4d). The significant heterogeneity was resolved by removing the study with unexpectedly high levels of cross-contamination[6] and separating the studies according to different methodologies used to identify false positives and cross-contamination.

In addition, 9.2% (91/ 990) of patients with a preliminary diagnosis of TB had false-positive results and consequently received the incorrect treatment[3,11-25] (16 studies), which leaded to a fatal outcome in eight cases[17,23-25] (4 studies).

Discussion

In a meta-analysis of 31 studies evaluating 29,839 positive cultures of Mycobacterium tuberculosis, using genotyping and clinico-epidemiological analyses to identify false positive

cultures, we evaluated the global prevalence of false positive Mycobacterial cultures. Our findings point out a remarkably high prevalence of false-positive TB results secondary to laboratory cross-contamination. Specifically, 2% of all positive TB cultures and, more importantly, one in six (15%) of all single positive TB cultures, are the results of laboratory cross-contamination. False positive results lead to the unnecessary administration of anti-tubercular medications, which are associated with side effects and could result in avoidable harm to numerous patients[12]. Indeed, in our meta-analysis we found that up to 9.2% of patients with a preliminary diagnosis of TB had a false-positive result and received inappropriate treatment. This poses a significant health and economic burden and the need to impose strict standards to reduce the rate of cross-contamination in the laboratory cannot be overstated. It is repeatedly demonstrated that coherent planning; experienced technicians and preparation of the appropriate facilities will be effective in contamination prevention[3]. For this reason, the WHO has produced comprehensive technical standards for mycobacteriology laboratories (http://www.who.int/tb/laboratory/mycobacteriology-laboratory-manual.pdf).

Simple measures to limit laboratory cross-contamination include the use of separate areas for the handling of positive and negative TB smears. In addition, first time sampling of swabs from patients also should be conducted in separate room/part of the laboratory reserved for these activities[40]. Education of laboratory staff, strict conduction of epidemiological measures, external controls and follow-up of proposed guidelines could reduce rate of TB cross-contamination[11].

Additional measures are required for the identification of false-positive results and avoidance of the administration of unnecessary treatments to subjects with false-positive cultures. Our study demonstrated a remarkable 15% incidence of false-positive results among single positive TB cultures, suggesting it is a prime target for interventions aimed to reduce the unneeded administration of anti-tubercular medications. The American Thoracic Society, Infectious

Disease Society of America and Centers for Disease Control and Prevention recently issued Guidelines for the diagnosis of tuberculosis, suggesting the need of confirmatory tests following an initial positive mycobacterial culture, acknowledging that false-positive results are common[43]. Based on our findings, it appears appropriate to delay the initiation of anti-tubercular treatment until the acquisition of a second, confirmatory TB culture, especially in atypical presentations if the clinical condition of the patient allows such a delay. Moreover, when the obtained smear is negative and culture results are inconsistent with clinical symptoms, laboratory staff should perform genotyping methods aimed to distinguish if the result is a true or false-positive. Since this method is not precise for strains with less than 6 copies of IS6110, other methods including mycobacterial interspersed repetitive units (MIRU) and spoligotyping could be helpful[41-42]. Contaminated specimens could be detected by genotyping, as well as identification of the source of contamination and detection of re-infection with same strain[15]. Although NGS remains cost prohibitive for resource-challenged countries, this approach overcomes many of the significant challenges associated with limitations of other less comprehensive molecular tests by providing rapid, detailed sequence information for multiple gene regions or whole genomes of interest. However, the uptake of these technologies for DR-TB diagnosis has been hindered by concerns regarding costs, integration into existing laboratory workflows, technical training and skill requirements for utilization of the technology and clinical interpretation of sequencing data[14,44]. The genetic analysis using NGS has enabled rapid genome analysis with minimal sample preparation time (1 to 2 days) at relatively moderate costs when multiple samples are analyzed per run. Reagent expenses can be marginally decreased by combining 24 to 48 samples per sequencing run. Additionally, a qPCR specific for *M. tuberculosis* and used prior to NGS can be employed for the prediction of genomic sequencing success, a helpful strategy for reducing costs[44].

Obtaining false-positive results causes a delay in the correct diagnosis being reached, which further delays starting the appropriate treatment, or not receiving the necessary management. It also leads to increased costs due to hospitalization length, nursing expenses and non-medical costs[3]. By including the false-positive TB cases in the overall number of positive cases, the prevalence of TB is falsely elevated. In addition, published results with false-positive TB cases contribute to incorrect interpretation of epidemiological data. Consequently, there is no proper estimation of TB risk in many countries.

An additional complication is drug resistant TB, especially if such strains are present in the body of the "contaminator". In this case, the wrong patient with false-positive results, is treated with second-line TB drugs, that additionally increase financial and health costs. From 1998 to 1999 in the United States of America, every false diagnosis cost the health care system 10,873 dollars[45]. It is estimated that annually approximately 10 million dollars of excessive costs are imposed to health system, not only for incorrect TB treatment, but also for physical harm after use of anti-TB drugs and psychological pressures – this data could not be easily ignored[2].

Although complete elimination of false-positive results obtained from the culture is the main goal of every mycobacteriological laboratory, several factors still cause false-positivity of the culture plate. In the current meta-review, several factors were highlighted as the most significant for causing false-positivity of TB culture (Supplementary table). These include, error in the performance of the laboratory technician, reagent contamination and the presence of aerosols in the workplace. Aerosols containing live *M. tuberculosis* are created during the removal of samples which can survive for a long period in harsh environmental conditions and small areas. They have a major role in the contamination of reagents and instruments such as pipettes or lids of containers[5,46]. In addition, inadequately sterilized bronchoscope may lead to false positive results as well as transmission of the infection[33].

One of the included studies found unexpectedly high levels of cross-contamination (18.2%)[6]. The authors reported several large clusters of false-positive samples as a result of cross-contamination. Characteristically, they identified two clusters of 9 and 5 false-positive samples (9% of all included samples) that were contaminated in the laboratory by a single true positive culture each. This study was an outlier and the laboratory performance was below standards. For this reason, we excluded this study in a sensitivity analysis. Our findings were not changed by the omission of this study.

Our study has several strengths. Firstly, we conducted an extensive systematic review of five online databases and our findings are based on a large number of studies, evaluating almost 30,000 TB cultures. However, we did not identify any studies using NGS, which may offer a more accurate assessment to identify possible laboratory cross-contamination. This is unlikely to affect our estimates, as the identified studies implemented rigorous methods for identifying laboratory cross-contamination. The quality of the available evidence was good and all included studies adequately reported on the methodology used to identify laboratory cross-contamination. Our results are at risk of publication bias and this may have led to a slight overestimation of the prevalence of laboratory cross-contamination. Many were specifically conducted to evaluate the incidence of cross-contamination and employed exhaustive methods to identify false-positive results and cross-contamination. On the other hand, the variability in methods used among different studies led to a significant (but expected) heterogeneity in our results. When heterogeneity (I^2) is higher than 75%, the quality of the pooled estimate is very limited. However, in our sensitivity analyses, we were able to resolve the observed heterogeneity and that did not lead to significant alterations, supporting the robustness of our results. In addition, our results are at risk of publication bias, as evident by our funnel plot (figure 3). Finally, we did not prospectively register the protocol of this meta-analysis, but we

used standard methodology suggested by the Cochrane Collaboration, to prospectively address a clearly defined research question.

Conclusion

To our knowledge, this is the first comprehensive systematic review and meta-analysis evaluating the incidence of *M. tuberculosis* laboratory cross-contamination. We found a remarkably high incidence, 2% of all positive TB cultures and 15% of all single-positive TB cultures represent false-positive results due to laboratory cross-contamination. This is associated with a significant therapeutic and economic burden. Therefore, there is an urgent need for the adoption of a strict technical standard aiming to prevent or identify laboratory cross-contamination and false positive TB results.

Ethics approval and consent to publish: Not applicable (Meta review article).

Consent for publication: Not applicable.

Availability of data and material: Please contact author for data requests.

Competing interests: The authors declare that they have no conflict of interest relevant to this work.

Authors' contributions: MP, HK, MTR, EA, AB, JR, BM, HSK, AGM, MA carried out the systematic review and meta-analyses analyses and drafted the manuscript. AGM provided methodological expertise. AS, KHA, MA, EA participated in the design of the study and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Acknowledgment

This study was supported by the Iranian National Sciences Foundation (Grant No: 843599) and Tabriz University of Medical Sciences (Grant No: 37876). AGM is supported by the National

Institute for Health Research Manchester Biomedical Research Centre (NIHR Manchester BRC). Dr Aleksandra Barac's scientific work and research is supported by the Project of Ministry of Education, Science and Technology of the Republic of Serbia (No. III45005).

Figure and Table Legends:

Figure 1. PRISMA flow diagram of the systematic review process

Figure 2. Risk of Bias of the included studies using the National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. Domains: (1) Was the research question or objective in this paper clearly states? (2) Was the study population clearly specified and defined? (3) Was the participation rate of eligible persons at least 50%? (4) Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? (5) Was a sample size justification, power description or variance and effect estimates provided? (6) For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured? (7) Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? (8) For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)? (9) Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? (10) Was the exposure(s) assessed more than once over time? (11) Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? (12) Were the outcome assessors blinded to the exposure status of participants? (13) Was loss to follow-up after baseline 20% or less? (14)

Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

Figure 3. Funnel plots evaluating the publication bias of the included studies

Figure 4. Forest plot diagram of the meta-analyses: (a) Incidence of laboratory cross-contamination among all positive cultures, (b) Incidence of laboratory cross-contamination among single positive culture samples, (c) Incidence of laboratory cross-contamination among single positive culture samples, after excluding two studies with unexpectedly high proportions. (d) Incidence of false-positive results among all positive results.

Table 1. Characteristics of the included studies

Table 2. Causes of *M. tuberculosis* cross-contamination that were identified in the included studies

References

1. Rashedi J, Mahdavi Poor B, Rafi A, Asgharzadeh M, Abdolalizadeh J, Moaddab SR. Multidrug-resistant tuberculosis in north-west of Iran and Republic of Azerbaijan: a major public health concern for Iranian people. Journal of research in health sciences. 2015;15(2):101-103.
2. Organization WHO. Global tuberculosis report 2018. 2018.
3. de Boer AS, Blommerde B, de Haas PE, et al. False-positive mycobacterium tuberculosis cultures in 44 laboratories in The Netherlands (1993 to 2000): incidence, risk factors, and consequences. J Clin Microbiol. 2002;40(11):4004-4009.
4. de CRM, Soini H, Roscanni GC, Jaques M, Villares MC, Musser JM. Extensive cross-contamination of specimens with Mycobacterium tuberculosis in a reference laboratory. J Clin Microbiol. 1999;37(4):916-919.
5. Burman WJ, Reves RR. Review of false-positive cultures for Mycobacterium tuberculosis and recommendations for avoiding unnecessary treatment. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2000;31(6):1390-1395.
6. Martinez M, Garcia de Viedma D, Alonso M, et al. Impact of laboratory cross-contamination on molecular epidemiology studies of tuberculosis. J Clin Microbiol. 2006;44(8):2967-2969.
7. Small PM, McClenny NB, Singh SP, Schoolnik GK, Tompkins LS, Mickelsen PA. Molecular strain typing of Mycobacterium tuberculosis to confirm cross-contamination in the mycobacteriology laboratory and modification of procedures to minimize occurrence of false-positive cultures. J Clin Microbiol. 1993;31(7):1677-1682.
8. Asgharzadeh M, Shahbabian K, Majidi J, et al. IS6110 restriction fragment length polymorphism typing of Mycobacterium tuberculosis isolates from East Azerbaijan Province of Iran. Memorias do Instituto Oswaldo Cruz. 2006;101(5):517-521.
9. van Embden JD, Cave MD, Crawford JT, et al. Strain identification of Mycobacterium tuberculosis by DNA fingerprinting: recommendations for a standardized methodology. J Clin Microbiol. 1993;31(2):406-409.
10. Asgharzadeh M, Khakpour M, Salehi TZ, Kafil HS. Use of mycobacterial interspersed repetitive unit-variable-number tandem repeat typing to study Mycobacterium tuberculosis isolates

from East Azarbaijan province of Iran. Pakistan journal of biological sciences : PJBS. 2007;10(21):3769-3777.
11. Lee MR, Chung KP, Chen WT, et al. Epidemiologic surveillance to detect false-positive Mycobacterium tuberculosis cultures. Diagnostic microbiology and infectious disease. 2012;73(4):343-349.
12. Burman WJ, Stone BL, Reves RR, et al. The incidence of false-positive cultures for Mycobacterium tuberculosis. American journal of respiratory and critical care medicine. 1997;155(1):321-326.
13. Gutierrez M, Vincent V, Aubert D, et al. Molecular fingerprinting of Mycobacterium tuberculosisand risk factors for tuberculosis transmission in Paris, France, and surrounding area. Journal of clinical microbiology. 1998;36(2):486-492.
14. Breese PE, Burman WJ, Hildred M, et al. The effect of changes in laboratory practices on the rate of false-positive cultures for Mycobacterium tuberculosis. Archives of pathology & laboratory medicine. 2001;125(9):1213-1216.
15. Bauer J, Thomsen VO, Poulsen S, et al. False-positive results from cultures of Mycobacterium tuberculosis due to laboratory cross-contamination confirmed by restriction fragment length polymporphism. J Clin Microbiol. 1997;35(4):998-991
16. Behr MA, Warren SA, Salamon H, et al. Transmission of Mycobacterium tuberculosis from patients smear-negative for acid-fast bacilli. Lancet. 1999;353:444.
17. Dahle UR, Sandven P, Heldal E, Caugant DA. Continued low rates of transmission of Mycobacterium tuberculosis in Norway. J Clin Microbiol. 2003;41(7):2968-2973.
18. Braden CR, Templeton GL, Stead WW, et al. Retrospective detection of laboratory cross-contamination of Mycobacterium tuberculosis cultures with use of DNA fingerprint analysis. Clinical Infectious Diseases. 1997;24:35-40.
19. Dahle UR, Sandven P, Heldal E, et al. Molecular epidemiology of Mycobacterium tuberculosis in Norway. J Clin Microbiol. 2001;29(5):1802-1807.
20. Fujikane T, Fujiuchi S, Yamazaki Y, et al. Molecular epidemiology of tuberculosis in the north Hokkaido district of Japan. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2004;8(1):39-44.
21. Hernandez-Garduno E, Cook V, Kunimoto D, Elwood RK, Black WA, FitzGerald JM. Transmission of tuberculosis from smear negative patients: a molecular epidemiology study. Thorax. 2004;59(4):286-290.
22. Asgharzadeh M, Kafil HS, Roudsary AA, Hanifi GR. Tuberculosis transmission in Northwest of Iran: using MIRU-VNTR, ETR-VNTR and IS6110-RFLP methods. Infection, genetics and evolution : journal of molecular epidemiology and evolutionary genetics in infectious diseases. 2011;11(1):124-131.
23. Ribeiro FK, Lemos EM, Hadad DJ, et al. Evaluation of low-colony-number counts of Mycobacterium tuberculosis on solid media as a microbiological marker of cross-contamination. J Clin Microbiol. 2009;47(6):1950-1952.
24. Allix-Beguec C, Fauville-Dufaux M, Supply P. Three-year population-based evaluation of standardized mycobacterial interspersed repetitive-unit-variable-number tandem-repeat typing of Mycobacterium tuberculosis. J Clin Microbiol. 2008;46(4):1398-1406.
25. Yan JJ, Jou R, Ko WC, Wu JJ, Yang ML, Chen HM. The use of variable-number tandem-repeat mycobacterial interspersed repetitive unit typing to identify laboratory cross-contamination with Mycobacterium tuberculosis. Diagnostic microbiology and infectious disease. 2005;52(1):21-28.
26. Drobniewski FA, Gibson A, Ruddy M, et al. Evaluation and utilization as a public health tool of a national molecular epidemiological Tuberculosis outbreak database within the United Kingdom from 1997 to 2001. J Clin Microbiol. 2003;41(5):1861-1868.
27. Gascoyne-Binzi DM, Barlow REL, Frothingham R, et al. Rapid identification of laboratory contamination with Mycobacterium tuberculosis using variable number tandem repeat analysis. J Clin Microbiol. 2001;39(1):69-74.
28. Globan M, Lavender C, Leslie D, et al. Molecular epidemiology of tuberculosis in Victoria, Australia, reveals low level of transmission. Int J Tuberc Lung Dis. 2016;20(5):652-658.

29. Glynn Jr, Yates MD, Crampin AC, et al. DNA fingerprint changes in Tuberculosis: Reinfection, evolution or laboratory error? J Infect Dis. 2004;190:1158-1166.
30. Godfrey-FAussett P, Sonnenberg P, Shearer SC, et al. Tuberculosis control and molecular epidemiology in a South African gold-mining community. Lancet. 2000;356:1066.
31. Hayward AC, Goss S, Drobniewski F, et al. The molecular epidemiology of tuberculosis in inner London. Epidemiol Infect. 2002;128:175-184.
32. Jasmer RM, Roemer M, Hamilton J, et al. A prospective multicenter study of laboratory cross0contamination of Mycobacterium tuberculosis cultures. Emerg Infect Dis. 2002;8(11):1260-1263.
33. Jasmer RM, Bozeman L, Schwartzman K, et al. Recurrent Tuberculosis in United States and Canada: Relapse or Reinfection? Am J Respir Crit Care Med. 2004;170(12):1360-1366.
34. Lai CC, Tan CK, Lin SH, et al. Molecular evidence of false-positive cultures of Mycobacterium tuberculosis in a Taiwanese hospital with a high incidence of TB. Chest. 2010;137(5):1065-1070.
35. McConkey SJ, Williams M, Weiss D, et al. Prospective use of molecular typing of Mycobacterium tuberculosis by use of restriction fragment-length polymporphism in a public tuberculosis-control program. Clinical Infectious Diseases. 2002;34:612-619.
36. Nitta AT, Knowles LA, Kim J, et al. Limited transmission of multidrug-resistant Tuberculosis despite a high proportion of infectious cases in Los Angeles County, California. Am J Respir Crit Care Med. 2002;165:812-817.
37. Maguire H, Dale JW, McHugh TD, et al. Molecular epidemiology of tuberculosis in London 1995-7 showing low rate of active transmission. Thorax. 2002;57:617-622
38. Ruddy M, McHugh TD, Dale JW, et al. Estimation of the rate of unrecognized cross-contamination with Mycobacterium tuberculosis in London Microbiology Laboratories. J Clin Microbiol. 2002;40(11):4100-4104.
39. Thumamo BP, Asuquo AE, Abia-Bassey LN, et al. Molecular epidemiology and genetic diversity of Mycobacterium tuberculosis complex in the Cross River State, Nigeria. Infect Genet Evol. 2012;12(4):671-677.
40. Carroll NM, Richardson M, Engelke E, de Kock M, Lombard C, van Helden PD. Reduction of the rate of false-positive cultures of Mycobacterium tuberculosis in a laboratory with a high culture positivity rate. Clinical chemistry and laboratory medicine. 2002;40(9):888-892.
41. Jonsson J, Hoffner S, Berggren I, et al. Comparison between RFLP and MIRU-VNTR genotyping of Mycobacterium tuberculosis strains isolated in Stockholm 2009 to 2011. PloS one. 2014;9(4):e95159.
42. Kamerbeek J, Schouls L, Kolk A, et al. Simultaneous detection and strain differentiation of Mycobacterium tuberculosis for diagnosis and epidemiology. J Clin Microbiol. 1997;35(4):907-914.
43. Lewinsohn DM, Leonard MK, LoBue PA, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. Clin Infect Dis. 2017;64(2):111-115.
44. Daum LT, Konstantynovska OS, Solodiankin OS, et al. Next-Generation Sequencing for Characterizing Drug Resistance-Conferring Mycobacterium tuberculosis Genes from Clinical Isolates in the Ukraine.J Clin Microbiol. 2018;56(6).
45. Northrup JM, Miller AC, Nardell E, et al. Estimated costs of false laboratory diagnoses of tuberculosis in three patients. *Emerging infectious diseases.* 2002;8(11):1264-1270.
46. Larson JL, Lambert L, Stricof RL, Driscoll J, McGarry MA, Ridzon R. Potential nosocomial exposure to Mycobacterium tuberculosis from a bronchoscope. *Infection control and hospital epidemiology.* 2003;24(11):825-830.

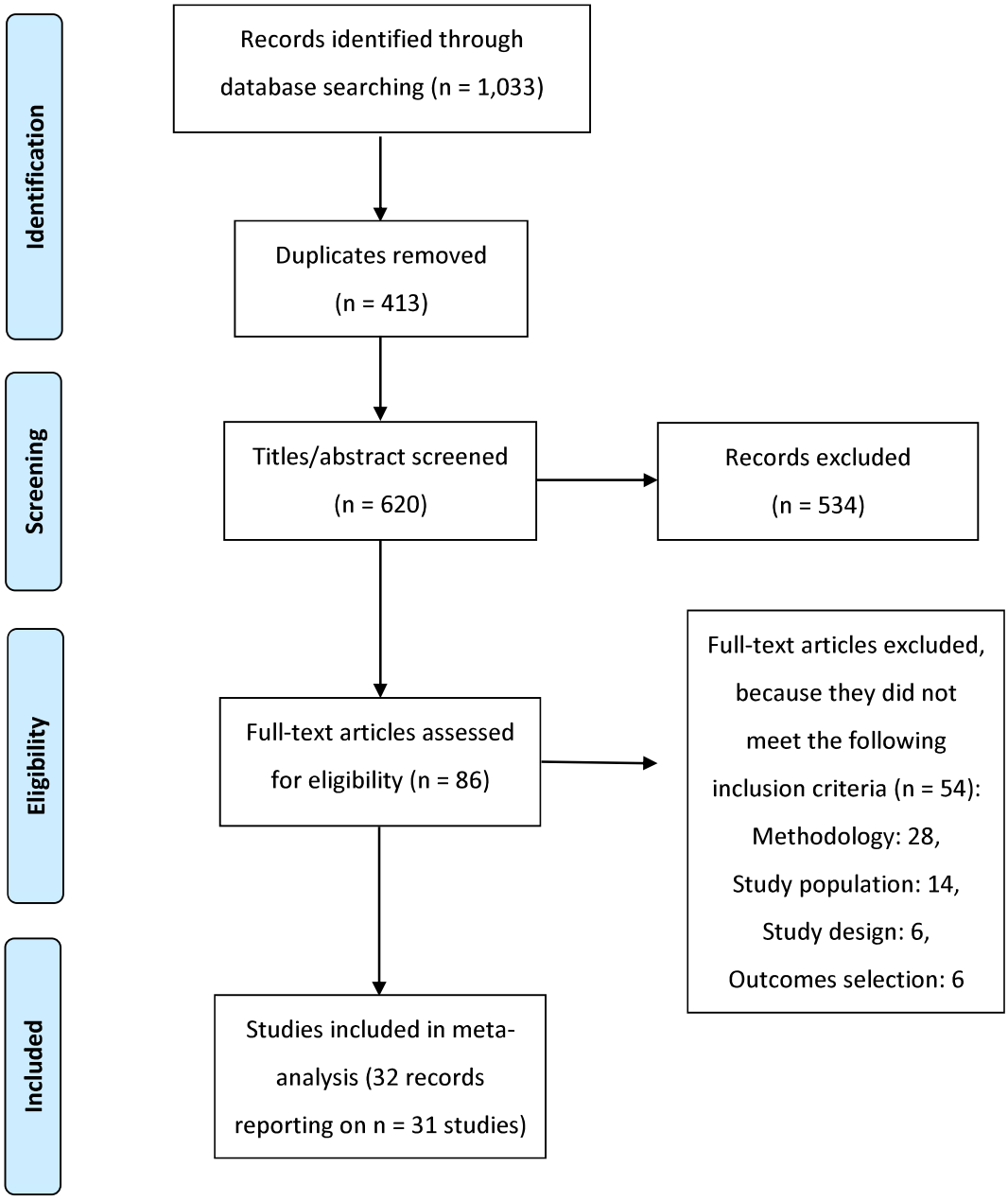

Figure 3

Click here to access/download;Figure;figure_3.png

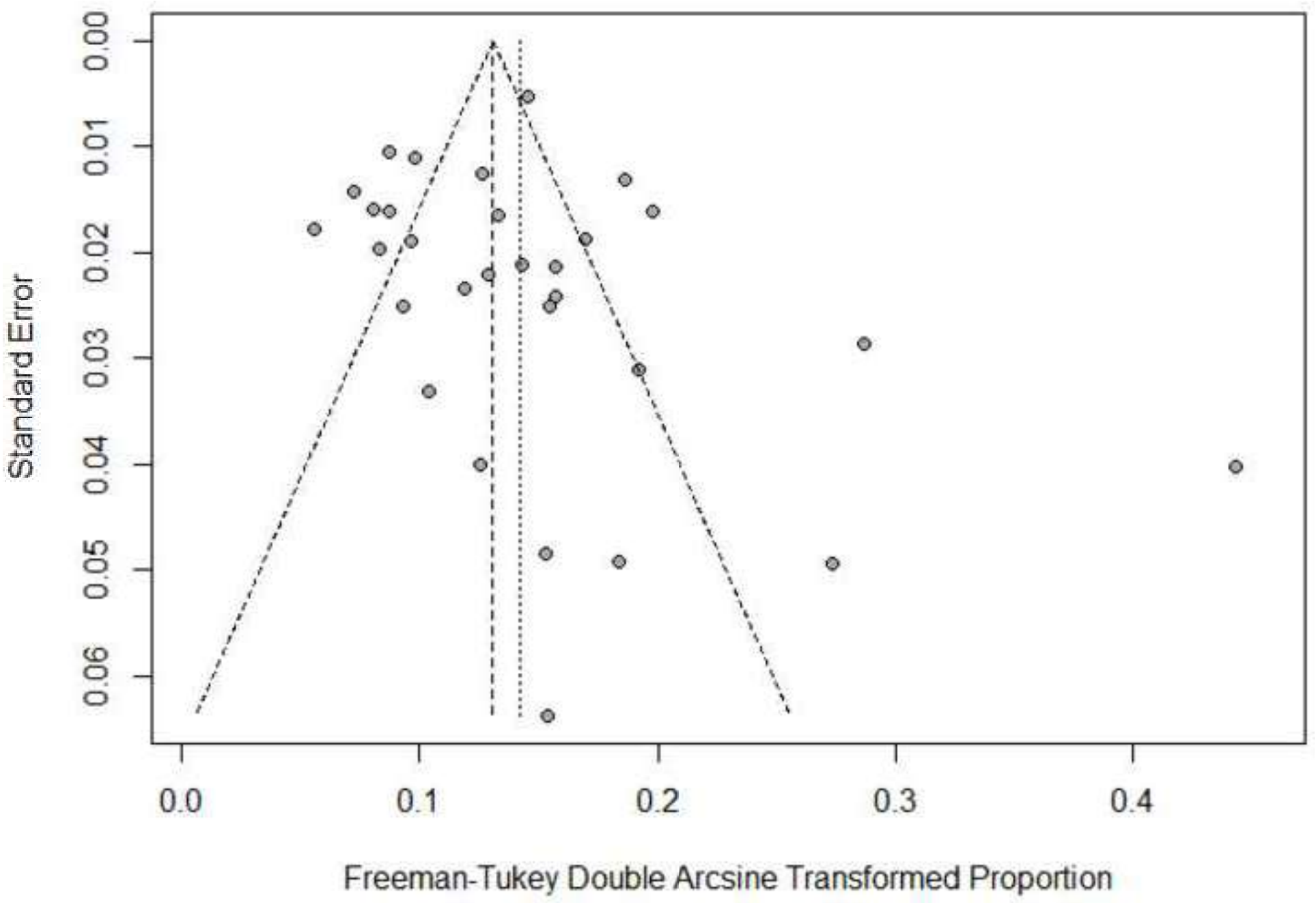

Figure 4a

Click here to access/download;Figure;figure_4a.png

Study	Events	Total	Weight (fixed)	Weight (random)	IV, Fixed + Random, 95% CI
Allix-Beguec 2008	7	974	3.4%	3.8%	0.01 [0.00; 0.01]
Asgharzadeh 2010	2	156	0.5%	2.5%	0.01 [0.00; 0.05]
Bauer 1997	49	1439	5.0%	4.0%	0.03 [0.03; 0.04]
Behr 1999	25	1599	5.5%	4.0%	0.02 [0.01; 0.02]
Braden 1997	9	259	0.9%	3.0%	0.03 [0.02; 0.06]
Bresse 1999	4	652	2.2%	3.7%	0.01 [0.00; 0.02]
Burrman 1997	6	696	2.4%	3.7%	0.01 [0.00; 0.02]
Dahle 2001	20	718	2.5%	3.7%	0.03 [0.02; 0.04]
Dahle 2003	13	552	1.9%	3.6%	0.02 [0.01; 0.04]
De Boer 2002	187	8889	30.6%	4.3%	0.02 [0.02; 0.02]
Drobniewski 2003	37	972	3.3%	3.8%	0.04 [0.03; 0.05]
Fujikane 2004	2	227	0.8%	2.8%	0.01 [0.00; 0.03]
Gascoyne Binzi 2001	9	397	1.4%	3.3%	0.02 [0.01; 0.04]
Globan 2016	17	2298	7.9%	4.1%	0.01 [0.00; 0.01]
Glynn 2004	16	930	3.2%	3.8%	0.02 [0.01; 0.03]
Godfrey fausett 2000	10	429	1.5%	3.4%	0.02 [0.01; 0.04]
Gutierrez 1998	24	306	1.1%	3.1%	0.08 [0.05; 0.11]
Hayward 2001	11	563	1.9%	3.6%	0.02 [0.01; 0.03]
Hernandez 2004	2	793	2.7%	3.8%	0.00 [0.00; 0.01]
Jasmer 2002	6	988	3.4%	3.9%	0.01 [0.00; 0.01]
Jasmer 2004	6	1244	4.3%	3.9%	0.00 [0.00; 0.01]
Lai 2010	3	400	1.4%	3.3%	0.01 [0.00; 0.02]
Lee 2012	6	458	1.6%	3.4%	0.01 [0.00; 0.03]
Martinez 2006	28	154	0.5%	2.4%	0.18 [0.12; 0.25]
McConkey 2002	1	61	0.2%	1.5%	0.02 [0.00; 0.09]
Nitta 2002	7	102	0.4%	2.0%	0.07 [0.03; 0.14]
Ribeiro 2009	2	106	0.4%	2.0%	0.02 [0.00; 0.07]
Ruddy 2002	19	2042	7.0%	4.1%	0.01 [0.01; 0.01]
Thumamo 2012	3	103	0.4%	2.0%	0.03 [0.01; 0.08]
Yan 2005	8	515	1.8%	3.5%	0.02 [0.01; 0.03]
Total (fixed effect, 95% CI)		**29022**	**100.0%**	--	**0.02 [0.01; 0.02]**
Total (random effects, 95% CI)			--	**100.0%**	**0.02 [0.01; 0.02]**

Heterogeneity: $Tau^2 = 0.0021$; $Chi^2 = 245.75$, df = 29 ($P < 0.01$); $I^2 = 88\%$

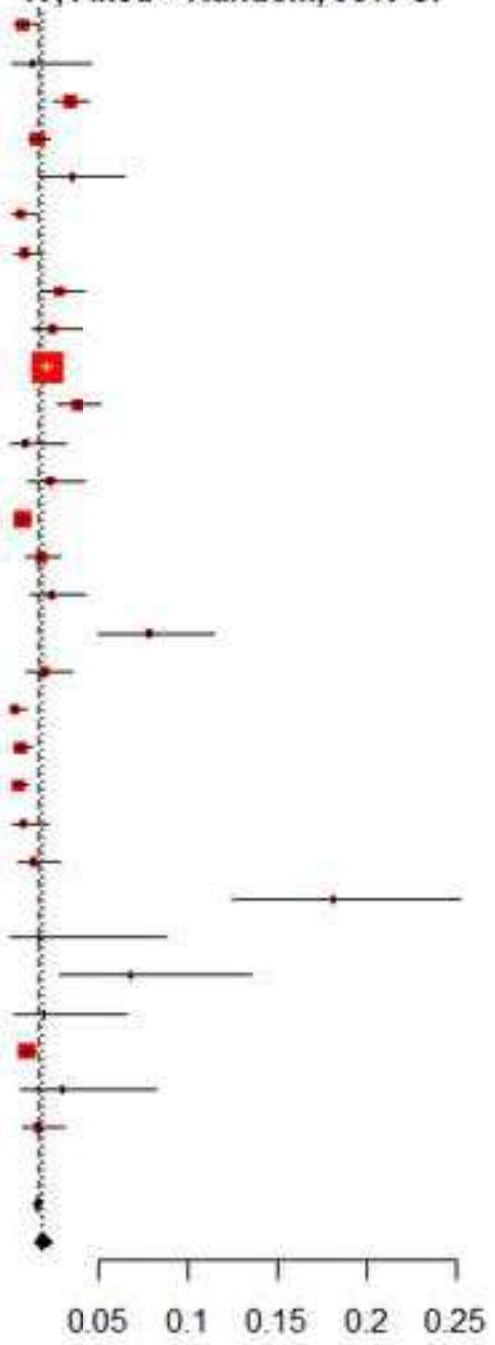

Figure 4b

Click here to access/download;Figure;figure_4b.png

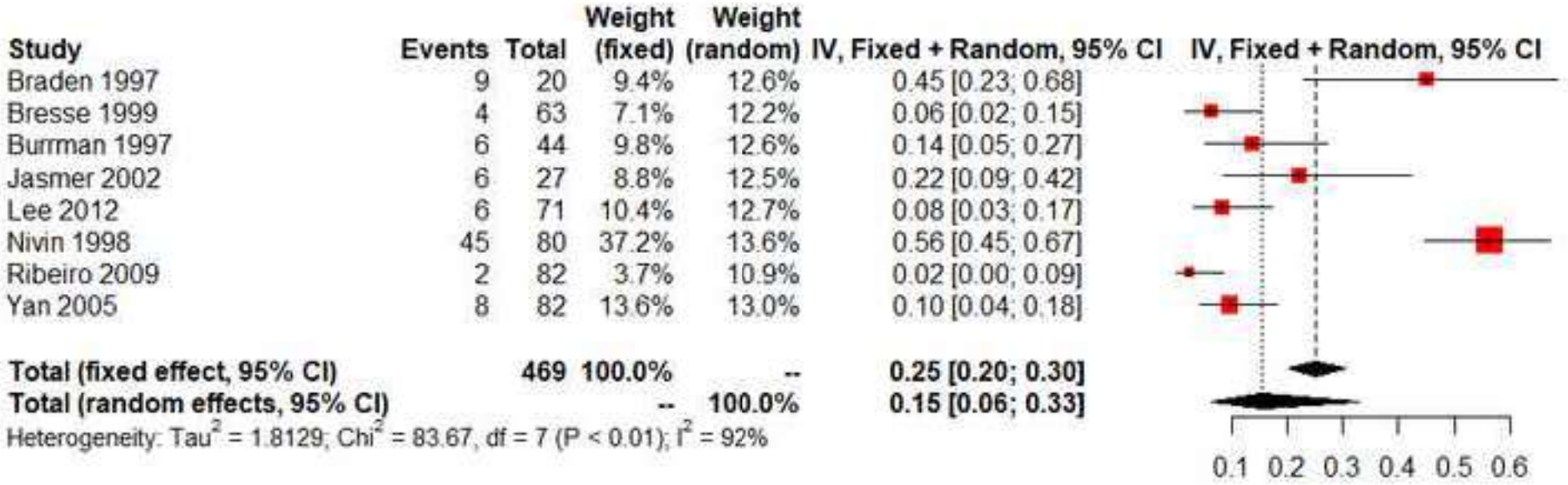

Figure 4c

Study	Events	Total	Weight (fixed)	Weight (random)	IV, Fixed + Random, 95% CI
Bresse 1999	4	63	13.3%	15.3%	0.06 [0.02; 0.15]
Burrman 1997	6	44	18.3%	18.0%	0.14 [0.05; 0.27]
Jasmer 2002	6	27	16.5%	17.2%	0.22 [0.09; 0.42]
Lee 2012	6	71	19.4%	18.5%	0.08 [0.03; 0.17]
Ribeiro 2009	2	82	6.9%	10.3%	0.02 [0.00; 0.09]
Yan 2005	8	82	25.5%	20.7%	0.10 [0.04; 0.18]
Total (fixed effect, 95% CI)		**369**	**100.0%**	--	**0.10 [0.07; 0.14]**
Total (random effects, 95% CI)			--	**100.0%**	**0.10 [0.06; 0.15]**

Heterogeneity: $Tau^2 = 0.2283$; $Chi^2 = 10.25$, df = 5 (P = 0.07); $I^2 = 51\%$

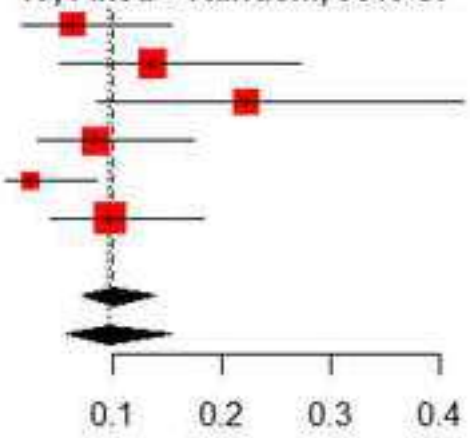

Figure 4d

Study	Events	Total	Weight (fixed)	Weight (random)	IV, Fixed + Random, 95% CI
Asgharzadeh 2010	3	156	0.8%	4.2%	0.02 [0.00; 0.06]
Braden 1997	9	259	1.3%	4.8%	0.03 [0.02; 0.06]
Bresse 1999	4	652	3.3%	5.4%	0.01 [0.00; 0.02]
Burrman 1997	13	696	3.6%	5.5%	0.02 [0.01; 0.03]
Dahle 2001	20	718	3.7%	5.5%	0.03 [0.02; 0.04]
De Boer 2002	213	8889	45.4%	5.9%	0.02 [0.02; 0.03]
Drobniewski 2003	40	972	5.0%	5.6%	0.04 [0.03; 0.06]
Gascoyne Binzi 2001	34	397	2.0%	5.1%	0.09 [0.06; 0.12]
Godfrey fausett 2000	10	429	2.2%	5.2%	0.02 [0.01; 0.04]
Gutierrez 1998	24	306	1.6%	4.9%	0.08 [0.05; 0.11]
Jasmer 2002	10	988	5.0%	5.6%	0.01 [0.00; 0.02]
Jasmer 2004	6	1244	6.4%	5.7%	0.00 [0.00; 0.01]
Lai 2010	5	400	2.0%	5.1%	0.01 [0.00; 0.03]
Lee 2012	11	458	2.3%	5.2%	0.02 [0.01; 0.04]
Martinez 2006	28	154	0.8%	4.2%	0.18 [0.12; 0.25]
Nitta 2002	8	102	0.5%	3.6%	0.08 [0.03; 0.15]
Ribeiro 2009	3	106	0.5%	3.7%	0.03 [0.01; 0.08]
Ruddy 2002	11	2042	10.4%	5.8%	0.01 [0.00; 0.01]
Thumamo 2012	10	103	0.5%	3.7%	0.10 [0.05; 0.17]
Yan 2005	15	515	2.6%	5.3%	0.03 [0.02; 0.05]
Total (fixed effect, 95% CI)		**19586**	**100.0%**	--	**0.02 [0.02; 0.02]**
Total (random effects, 95% CI)			--	**100.0%**	**0.03 [0.02; 0.04]**

Heterogeneity: $Tau^2 = 0.0038$; $Chi^2 = 247.80$, df = 19 ($P < 0.01$); $I^2 = 92\%$

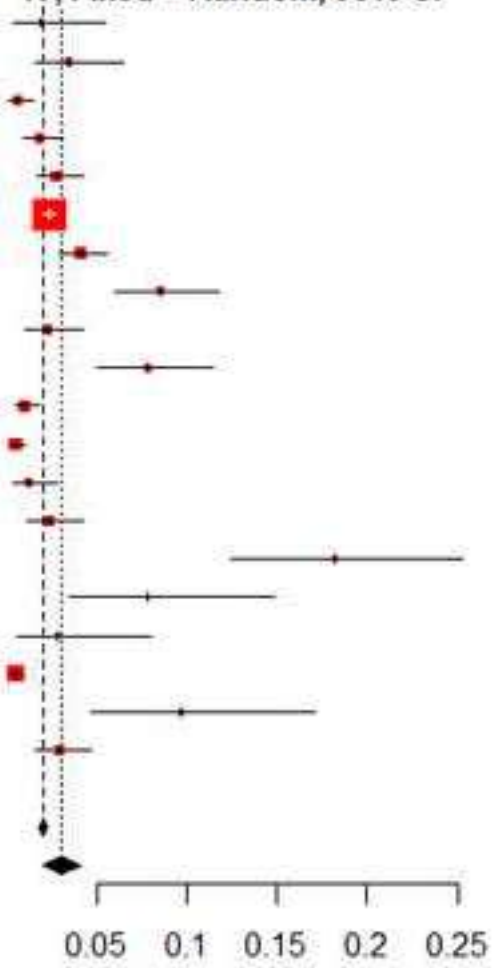

Figure 2

Click here to access/download;Table;figure2.docx

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Allix-Beguec 2008	Yes	Yes	Yes	Yes	No	Yes	Yes	N/A	Yes	N/A	Yes	N/A	N/A	N/A
Asgharzadeh 2010	Yes	Yes	Yes	Yes	No	Yes	Yes	N/A	Yes	N/A	Yes	N/A	N/A	N/A
Bauer 1997	Yes	Yes	Yes	Yes	No	Yes	Yes	N/A	Yes	N/A	Yes	N/A	N/A	N/A
Behr 1999	Yes	Yes	Yes	Yes	No	Yes	Yes	N/A	Yes	N/A	Yes	N/A	N/A	N/A
Braden 1997	Yes	Yes	Yes	Yes	No	Yes	Yes	N/A	Yes	N/A	Yes	N/A	N/A	N/A
Bresse 2001	Yes	No	Yes	Yes	No	Yes	Yes	N/A	Yes	N/A	Yes	N/A	N/A	N/A
Burrman 1997	Yes	Yes	Yes	Yes	No	Yes	Yes	N/A	Yes	N/A	Yes	N/A	N/A	N/A
Dahle 2001	Yes	Yes	Yes	Yes	No	Yes	Yes	N/A	Yes	N/A	Yes	N/A	N/A	N/A
Dahle 2003	Yes	Yes	Yes	Yes	No	Yes	Yes	N/A	Yes	N/A	Yes	N/A	N/A	N/A
De Boer 2002	Yes	No	Yes	Yes	No	Yes	Yes	N/A	Yes	N/A	Yes	N/A	N/A	N/A
Drobniewski 2003	Yes	No	Yes	Yes	No	Yes	Yes	N/A	Yes	N/A	No	N/A	N/A	N/A
Fujikane 2004	Yes	Yes	Yes	Yes	No	Yes	Yes	N/A	Yes	N/A	No	N/A	N/A	N/A
Gascoyne Binzi 2001	Yes	Yes	Yes	Yes	No	Yes	Yes	N/A	Yes	N/A	Yes	N/A	N/A	N/A
Globan 2016	Yes	Yes	Yes	Yes	No	Yes	Yes	N/A	Yes	N/A	Yes	N/A	N/A	N/A
Glynn 2004	Yes	Yes	Yes	Yes	No	Yes	Yes	N/A	Yes	N/A	Yes	N/A	N/A	N/A
Godfrey fausett 2000	Yes	Yes	Yes	Yes	No	Yes	Yes	N/A	Yes	N/A	Yes	N/A	N/A	N/A
Gutierrez 1998	Yes	Yes	Yes	Yes	No	Yes	Yes	N/A	Yes	N/A	Yes	N/A	N/A	N/A
Hayward 2001	Yes	Yes	Yes	Yes	No	Yes	Yes	N/A	Yes	N/A	Yes	N/A	N/A	N/A
Hernandez 2004	Yes	Yes	Yes	Yes	No	Yes	Yes	N/A	Yes	N/A	Yes	N/A	N/A	N/A
Jasmer 2002	Yes	No	Yes	Yes	No	Yes	Yes	N/A	Yes	N/A	Yes	N/A	N/A	N/A
Jasmer 2004	No	Yes	Yes	Yes	No	Yes	Yes	N/A	Yes	N/A	No	N/A	N/A	N/A
Lai 2010	No	Yes	Yes	Yes	No	Yes	Yes	N/A	Yes	N/A	Yes	N/A	N/A	N/A
Lee 2012	Yes	Yes	Yes	Yes	No	Yes	Yes	N/A	Yes	N/A	Yes	N/A	N/A	N/A
Martinez 2006	Yes	No	No	Yes	No	Yes	Yes	N/A	Yes	N/A	No	N/A	N/A	N/A
McConkey 2002	Yes	Yes	Yes	Yes	No	Yes	Yes	N/A	Yes	N/A	Yes	N/A	N/A	N/A
Nitta 2002	Yes	No	Yes	Yes	No	Yes	Yes	N/A	Yes	N/A	No	N/A	N/A	N/A
Nivin 1998	Yes	Yes	Yes	Yes	No	Yes	Yes	N/A	Yes	N/A	Yes	N/A	N/A	N/A
Ribeiro 2009	Yes	Yes	Yes	Yes	No	Yes	Yes	N/A	Yes	N/A	Yes	N/A	N/A	N/A

Ruddy 2002	Yes	Yes	Yes	Yes	No	Yes	Yes	N/A	Yes	N/A	Yes	N/A	N/A	N/A
Thumamo 2012	No	Yes	Yes	Yes	No	Yes	Yes	N/A	Yes	N/A	No	N/A	N/A	N/A
Yan 2005	Yes	Yes	Yes	Yes	No	Yes	Yes	N/A	Yes	N/A	Yes	N/A	N/A	N/A

Table 1

Study	Typing method	total tested	Total positives	Single positive culture	Cross-contamination	Total number of false positives
Globan 2016	24-locus MIRU VNTR		2298		17	
Lee 2012	100% identical DRE-PRCR	14462	458	71	6	5
Thumamo 2012	Spoligotyping and 12-loci MIRU		103		3	10
Asgharzadeh 2010	12-locus MIRU VNTR		156		2	1
Lai 2010	24-loci MIRU VNTR		400		3	5
Ribeiro 2009	RAPET (Rapid PCR based epidemiological typing)	2399	106	82	2	1
Allix-Beguec 2008	24-loci MIRU VNTR and Spoligotyping		974		7	
Martinez 2006	IS6110- RFLP and spoligotyping		154		28	28
Yan 2005	VNTR and MIRU		515	82	8	15
Fujikane 2004	IS6110- RFLP		227		2	
Hernandez 2004	IS6110- RFLP		793		2	
Glynn 2004	IS6110- RFLP		930		16	

Jasmer 2004	IS6110- RFLP		1244		6	6
Drobniewski 2003	IS6110- RFLP		972		37	40
Dahle 2003	IS6110- RFLP and Spoligotyping		552		13	
Hayward 2001	Spoligotyping HIPCR		563		11	
McConkey 2002	IS6110- RFLP and pTBN12		61		1	
Maguire 2002	IS6110- RFLP		2779		10	
Nitta 2002	IS6110- RFLP		102		7	8
Jasmer 2002	IS6110- RFLP	21835	988	27	6	10
De Boer 2002	IS6110- RFLP and polymorphic GC-rich sequence		8889		187	213
Ruddy 2002	IS6110- RFLP		2042		19	11
Gascoyne Binzi 2001	VNTR	4751	397		9	34
Dahle 2001	IS6110- RFLP		718		20	20
Breese 2001	DNA Fingerprinting	13940	652	63	4	4
Godfrey Fausett 2000	IS6110- RFLP		429		10	10
Behr 1999	IS6110- RFLP		1599		25	
Gutierrez 1998	IS6110- RFLP		306		24	24

Braden 1997	DNA fingerpringting		259		9	9
Burrman 1997	IS6110- RFLP		696	44	6	13
Bauer 1997	IS6110- RFLP		1439		49	

1

No.	Factors	No.	Reference
1.	Inappropriate technician's laboratory work	34	15
2.	Contamination of reagents	25	15, 26, 31, 32, 27
3.	Creation of aerosols	24	3, 26
4.	Mislabeling	16	3, 5, 28, 18, 22, 26, 37, 32
5.	Contaminated equipment	11	3, 27
6.	Poor laboratory techniques	10	26
7.	Contaminated bronchoscope	4	3, 26
8.	Splashing	2	27
9.	Reprocessing of contaminated	2	32
10.	BACTEC needle carryover	2	12

2