REVIEW ARTICLE

Review of False-Positive Cultures for *Mycobacterium tuberculosis* and Recommendations for Avoiding Unnecessary Treatment

William J. Burman and Randall R. Reves

Department of Public Health, Denver Health and Hospital Authority, and Division of Infectious Diseases, Department of Medicine, University of Colorado Health Sciences Center, Denver

We reviewed reports of false-positive cultures for *Mycobacterium tuberculosis* and here propose guidelines for detecting and managing patients with possible false-positive cultures. Mechanisms of false-positive cultures included contamination of clinical devices, clerical errors, and laboratory cross-contamination. False-positive cultures were identified in 13 (93%) of the 14 studies that evaluated ⩾100 patients; the median false-positive rate was 3.1% (interquartile range, 2.2%–10.5%). Of the 236 patients with false-positive cultures reported in sufficient detail, 158 (67%) were treated, some of whom had toxicity from therapy, as well as unnecessary hospitalizations, tests, and contact investigations. Having a single positive culture was a sensitive but nonspecific criterion for detecting false-positive cultures. False-positive cultures for *M. tuberculosis* are not rare but are infrequently recognized by laboratory and clinical personnel. Laboratories and tuberculosis control programs should develop procedures to identify patients having only 1 positive culture. Such patients should be further evaluated for the possibility of a false-positive culture.

The diagnosis of tuberculosis initiates a complex series of events: respiratory isolation, initiation of multidrug therapy, and investigation of close contacts. These actions are crucial for tuberculosis control, but are expensive and carry the potential for drug toxicity, disruption of daily life, and social ostracism. Therefore, it is essential that the methods used to diagnose tuberculosis be as accurate as possible. Although there is great interest in nucleic acid amplification tests for tuberculosis, the most widely used test remains mycobacterial culture.

The occurrence of false-positive cultures is not widely recognized; indeed, this possibility is not even mentioned in the most recent national guidelines for the diagnosis of tuberculosis [1]. As a result of this lack of recognition, tuberculosis control activities are sometimes inappropriately applied to people with false-positive cultures.

We review the mechanisms of false-positive cultures and their frequency, clinical consequences, and laboratory characteristics. Although the focus of this review will be false-positive cultures for *Mycobacterium tuberculosis,* false-positive results can occur in the examination of acid-fast stained smears [2, 3], with nucleic acid amplification tests for tuberculosis [4], and in cultures for nontuberculous mycobacteria [5–7].

Methods

We searched MEDLINE from 1966 to June 1999; we searched for tuberculosis or *M. tuberculosis,* with the following key words: equipment contamination, diagnostic errors, false-positive reactions, or DNA fingerprinting. The bibliographies of all studies so selected were reviewed to identify additional references. Finally, we reviewed abstracts of the 1994–1999 American Thoracic Society and International Union against Tuberculosis and Lung Disease conferences.

Studies that used DNA fingerprinting to study tuberculosis epidemiology were included if there was a statement that the possibility of false-positive cultures was evaluated. The false-positive rate was defined as the number of patients having a false-positive culture divided by the total number of patients with a positive culture. Because small studies often include only the rate of cross-contamination during an outbreak of false-positive cultures and may not be representative of the underlying false-positive rate, only studies that evaluated ⩾100 patients were included in the section on rates of false-positive cultures.

The most commonly reported clinical consequence of false-positive cultures was unnecessary treatment; further details, such as hospitalization and medical procedures, were abstracted when available. In the few studies that compared microbiological characteristics of cross-contaminated cultures to true-positive cultures, the culture media used, the colony count on solid media, and the time to growth detection in liquid media were abstracted.

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Reprints or correspondence: Dr. William Burman, Denver Public Health, 605 Bannock St., Denver, CO 80204 (bburman@dhha.org).

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Results

Mechanisms of false-positive cultures: contamination of clinical devices. Cross-contamination of specimens in the laboratory has received the greatest attention in studies of false-positive cultures. However, events before the arrival of a specimen in the laboratory can also cause false-positive results. Contamination of clinical equipment can cause false-positive cultures. For example, fiberoptic bronchoscopy is a common procedure, and the channels of the bronchoscope may be difficult to sterilize once contaminated by mycobacteria [5, 8]. Therefore, specimens from subsequent patients who are examined with the same instrument can be contaminated [9]. A contaminated instrument can also infect patients, so bronchoscopic contamination is a cause of both false-positive cultures and tuberculosis transmission [9, 10]. Although bronchoscopic cross-contamination has been clearly documented [9], it appears to be a relatively uncommon cause of false-positive cultures for *M. tuberculosis.*

Mechanisms of false-positive cultures: clerical errors. There are limited data on the role of mislabeling or other clerical errors as causes of false-positive culture reports. The only comprehensive study of the role of clerical errors used sterile, simulated sputum samples, randomly spiked with a strain of *M. tuberculosis* having a unique pattern of drug resistance, to study false-positive cultures in clinical research laboratories [11]. Clerical errors resulted in a false-positive culture report as often as did laboratory cross-contamination (1.0% and 0.8%, respectively) [11]. Subsequent reports have documented mislabeling as a cause of false-positive culture reports [12–14], but there have been no recent comprehensive studies to determine the relative frequency of clerical errors and laboratory cross-contamination.

Mechanisms of false-positive cultures: laboratory cross-contamination. Three factors underlie the occurrence of laboratory cross-contamination of *M. tuberculosis:* the ability of the organisms to remain viable despite harsh environmental conditions, the complexity of mycobacterial laboratory techniques, particularly batch processing, and the use of radiometric growth detection methods having the potential for cross-contamination. There is no environmental reservoir of *M. tuberculosis,* but it is a remarkably hardy organism in the laboratory. For example, *M. tuberculosis* can be recovered from specimens that have been heated for acid-fast staining [15] or allowed to dry in the sun [16]. An organism that can survive in the laboratory can contaminate specimens that are subsequently placed in that same environment.

Several large outbreaks of false-positive cultures have been attributed to defects in the exhaust systems of the biological safety cabinets used for specimen processing [17]. The mechanism for these outbreaks is presumably the creation of an aerosol when samples are mixed with reagents, such as the neutralizing solution. Unless promptly cleared, these airborne particles may settle in subsequent specimens (a process analogous to the transmission of *M. tuberculosis* from one person to another).

The initial processing of nonsterile specimens for mycobacterial culture is a complex process. Bacteria and yeast are commonly present in such specimens and can easily overgrow the slowly dividing tubercle bacillus. Therefore, decontamination (i.e., the use of severe alkaline conditions to kill bacteria and yeast while allowing *M. tuberculosis* to survive) is a standard step in the processing of nonsterile specimens for mycobacterial culture. Decontamination is a multistep process involving addition of the alkaline solution, neutralization, and then centrifugation to concentrate the remaining mycobacteria. This process must be carefully timed, because the survival advantage of mycobacteria under alkaline conditions is relative, not absolute. Because of the need for multiple, carefully timed steps, the decontamination process is almost always performed on batches of specimens, rather than on individual specimens. Although batch processing is more efficient, it clearly carries the potential for cross-contamination.

Cross-contamination during batch processing can be an isolated event (via a contaminated splash, lid, or pipette) or an event that contaminates multiple specimens. Contamination of one of the reagents used in batch processing, most commonly the neutralizing buffer, can result in the inoculation of *M. tuberculosis* into subsequent specimens to which the buffer is added. Large volumes of reagent can be contaminated and then cause large outbreaks of false-positive cultures [18, 19], including a recent outbreak of 60 false-positive cultures [20].

Cross-contamination during batch processing is suggested by matching DNA fingerprints of 2 specimens that underwent initial processing on the same day. However, this is not always the case. Broth culture vials having fungal or bacterial overgrowth are sometimes reprocessed by withdrawing the contents of the broth culture into a tube and repeating the decontamination process. If this reprocessing step is done in a batch with fresh clinical specimens, cross-contamination can occur [13, 21]. Specimens cross-contaminated in this manner may be difficult to recognize because the 2 specimens would have undergone initial processing on different days.

A widely used broth culture system (Bactec 460; Becton-Dickinson, Sparks, MD) uses changes in the concentration of a radioactive tracer to detect microbial metabolism and, hence, growth. Measurement of the radioactive tracer requires the insertion of a needle through a rubber diaphragm in the vial to sample the gas above the broth culture. After sampling a culture vial, the needle is withdrawn into a heating unit and sterilized before insertion into the next vial. Malfunction of the heating element can allow the transfer of viable bacilli from a culture-positive vial to subsequently sampled culture vials [22, 23]. However, this mechanism appears to be a less common cause of cross-contamination than the initial processing of nonsterile specimens [13, 24]. Furthermore, broth culture systems are now available that detect growth noninvasively, so cross-contamination cannot occur during monitoring of culture vials.

Rates of false-positive cultures. False-positive cultures were

identified in 13 (93%) of 14 large studies (≥100 patients) reported to date (table 1). The median false-positive rate was 3.1% (interquartile range, 2.2%–10.5%). However, much higher rates have been seen when there has been a major error in laboratory techniques or conditions. For example, a hospital laboratory that used a positive growth control and a sensitive broth culture technique (Mycobacterial Growth Indicator Tube system, Becton-Dickinson) had a false-positive rate of 33% (45 of 138 patients) [35]. In addition, a few studies of laboratories processing low numbers of specimens for mycobacterial culture (and, hence, not shown in table 1) reported very high rates of false-positive cultures [13], to the extreme of a laboratory in which the false-positive rate over a 4-month period was 81% (9 of 11 patients) [36].

Studies of false-positive cultures can be categorized by the method used to identify possible cross-contamination (table 1). Until 1990, there were no highly specific markers of identical strains of *M. tuberculosis.* In a study that used low colony count on solid media (<5 colonies) as a marker of possible false-positive cultures, 12 (5%) of 239 patients were thought to have had a false-positive culture when clinical and radiographic criteria were used [25]. Several recent studies evaluated false-positive cultures during outbreaks of multidrug-resistant (MDR) tuberculosis and found that 1%–26% of patients having an MDR isolate did not meet clinical criteria for a diagnosis of drug-resistant tuberculosis [23, 26, 37].

The availability of DNA fingerprinting methods in the past decade for strain identification of *M. tuberculosis* markedly improved the number and quality of studies of false-positive cultures. It is difficult to compare directly the false-positive rates in these studies because of differences in the definition of a false-positive culture, the marker used for strain identification, and the selection criteria of isolates to be evaluated (see comments in table 1). In addition, the relatively small number of studies hinders comparisons of factors that may be associated with cross-contamination. For example, as described in table 1, there is a trend toward higher false-positive rates in laboratories that used liquid media, with or without solid media, than in those that used solid media alone (median false positive rates of 10% and 2.9%, respectively), but this difference was not statistically significant ($P = .21$, Wilcoxon rank sum test). Frieden et al. [30] found an association between the use of liquid media and the occurrence of false-positive cultures in their study involving multiple laboratories in New York City.

Clinical consequences of false-positive cultures. The clinical follow-up of patients having false-positive cultures is not detailed in all published reports. However, in those reports providing clinical follow-up, 158 (67%) of 236 patients with false-positive cultures were treated for active tuberculosis [13, 14, 18–20, 22, 24, 29, 35, 36, 38, 39], some of whom experienced toxicity from multidrug tuberculosis treatment [13, 22, 39]. In addition, false-positive cultures resulted in unnecessary diagnostic tests, including bronchoscopy, and hospitalizations [13, 39]. Among people with proven tuberculosis, the occurrence of false-positive cultures during and after treatment can result in an inappropriate diagnosis of treatment failure or relapse. The vast majority of such isolated positive cultures during follow-up have been shown to be due to cross-contamination [40]. Large contact investigations have been performed as a result of false-positive cultures, resulting in unnecessary isoniazid preventive therapy [39, 41].

False-positive cultures may also result in an overestimation of the tuberculosis case rate, an important parameter in assessing tuberculosis control efforts. For example, in a recent

Table 1. Rates of false-positive cultures from studies evaluating ≥100 patients.[a]

False-positive rate, % (no. of false positives/total)	Culture techniques	Comments	Reference
Studies not using DNA fingerprinting			
5 (12 of 239)	Solid media	Reviewed single-positive sputum specimens with <5 colonies	[25]
16 (23 of 140)	Liquid media (Bactec 460)[b]	Used clinical definition, no laboratory marker of clonality	[26]
Studies using DNA fingerprinting			
2.6 (3 of 114)	Not reported	Required initial processing on the same day	[27]
1.8 (9 of 496)	Various	Required initial processing on the same day and that the source specimen be smear positive	[28]
3.5 (9 of 259)	Various	Isolates from multiple laboratories	[29]
2.7 (12 of 441)	Various	Cross-sectional sample of isolates from many laboratories	[30]
0.9 (4 of 463)	Not reported	Isolates from multiple laboratories	[31]
7.8 (24 of 306)	Various	Required initial processing on the same day	[32]
2.9 (5 of 173)	Not reported	Required initial processing on the same day	[21]
2.9 (3 of 105)	Solid media	Isolates from multiple laboratories	[33]
0 (0 of 210)	Solid media	All isolates were fingerprinted	[34]
4 (8 of 199)	Liquid (Bactec 460) and solid media	Did not require same-day processing	[11]
3.2 (46 of 1439)	Liquid (Bactec 460) and solid media	Only isolates from suspected cross-contamination episodes were fingerprinted	[12]
33 (45 of 138)	Liquid (MGIT)[c] and solid media	Used a positive growth control	[35]

[a] The study by Aber et al. [11] used simulated specimens, and the resultant "contamination rate" is not directly comparable to the false-positive rates reported from the studies included here.

[b] Becton-Dickinson, Sparks, MD.

[c] Mycobacterial Growth Indicator Tube (Becton-Dickinson).

report, 9% of those initially reported to have tuberculosis in Wisconsin were found to have had false-positive cultures [39]. Finally, cross-contamination can cause a misdiagnosis of drug-resistant tuberculosis in a patient with drug-susceptible disease. A specimen containing drug-susceptible *M. tuberculosis* may be contaminated with a drug-resistant strain [38] or a nontuberculous mycobacterial species [12], thereby altering the results of drug susceptibility testing. Such patients may receive lengthy treatment with more toxic second-line drugs, rather than receiving short-course therapy [38].

Laboratory features of false-positive cultures. The most commonly reported laboratory characteristic of false-positive cultures was that the false-positive culture was the only positive culture from that patient (termed single-positive culture; contamination of multiple specimens from the same patient has been reported, but is probably rare: <0.1% in the only study that detected this event [24]). For example, 44% of the patients with single-positive cultures in one study were judged to have false-positive cultures [30]. However, single-positive cultures also occur among patients who meet clinical criteria for a diagnosis of tuberculosis and for whom there is no evidence of cross-contamination. Therefore, the laboratory criterion of a single-positive culture appears to be sensitive, but relatively nonspecific, in detecting false-positive cultures. Nevertheless, prospective monitoring of the rate of single-positive cultures detected 2 outbreaks of laboratory cross-contamination that had not been recognized by clinicians or laboratory personnel [35, 42].

Because the inoculum of material that contaminates another specimen is generally small (e.g., a droplet) and therefore contains few bacilli, most false-positive cultures require prolonged incubation before detection of growth in liquid media, have low colony counts on solid media, or both [11, 13, 24, 29]. If the Bactec 460 system is used, growth in only the broth culture raises the question of cross-contamination via the sampling needle [22]. However, cultures of specimens from patients with active tuberculosis—that is, true-positive cultures—can have the characteristics outlined above [13, 30], and no studies have systematically evaluated the predictive value of microbiological indexes such as a low colony count on solid media or prolonged time to detection of growth in liquid media. In addition, clerical errors may not be detected as potentially false-positive by the criterion of low colony count.

Discussion

False-positive cultures for *M. tuberculosis* are not rare, being detected in nearly all studies that included a rigorous evaluation for this event. False-positive rates may actually be higher than those summarized here. In some studies, isolates were DNA fingerprinted only when cross-contamination was suspected by clinical or laboratory personnel [21, 24], but ⩾50% of the episodes of cross-contamination in other studies were not suspected without DNA fingerprinting data [13, 32]. Studies requiring a DNA fingerprint match between clinical isolates may have underestimated cross-contamination; the processing of laboratory strains of *M. tuberculosis* as controls or proficiency test specimens has resulted in isolated or widespread cross-contamination [13, 35, 39, 41]. Finally, some studies used overly restrictive criteria to define false-positive cultures: requiring that source specimens be smear-positive, that the contaminated specimen be smear-negative, or that the 2 specimens must have undergone initial processing on the same day. Exceptions to these criteria have been clearly documented [13, 19]. Therefore, the actual rates of false-positive cultures are probably somewhat higher than those in table 1.

False-positive cultures have important clinical consequences. That two-thirds of the patients having false-positive cultures were treated for tuberculosis demonstrates a lack of awareness among clinicians and laboratory personnel of the possibility of false-positive cultures. Even in large outbreaks of laboratory cross-contamination, when recognition of the possibility of false-positive cultures should be easiest, most patients were treated [20, 35]. Not detailed in these reports, although surely a part of the clinical consequences of false-positive cultures, are interruptions in the daily activities of those with false-positive cultures and social ostracism due to the misdiagnosis of a contagious disease [43].

Recommendations

How should clinicians and health departments prevent the consequences of false-positive cultures? First, clinicians should evaluate positive cultures critically; false-positive cultures are not rare. Second, patients having only 1 positive culture should be evaluated for the possibility of a false-positive culture. Table 2 suggests specific strategies to decrease inappropriate treatment of patients with false-positive cultures. If at all possible, treatment should not be based on the results of a single culture, even if it is smear positive. When only one culture is positive, additional specimens should be obtained, if possible, and a final decision about therapy might reasonably be deferred pending the results of additional cultures, if an alternative diagnosis seems likely. If a false-positive culture is suspected, the laboratory should be instructed to retain all isolates manipulated that day, so that DNA fingerprinting can be used to try to confirm cross-contamination. We recommend that laboratories save the initial isolate from all culture-positive patients for 12 months, to allow evaluation for cross-contamination, as well as for use in suspected outbreaks of tuberculosis.

It may not be feasible to completely eliminate false-positive cultures for *M. tuberculosis.* It would be very difficult to eliminate batch processing in a busy mycobacteriology laboratory. Furthermore, *M. tuberculosis* is present in high concentrations in some clinical specimens [44] and can survive for a long time in the laboratory environment [45]. Thus, minor errors in tech-

Table 2. Suggested clinical approaches for reducing the likelihood of treating patients with false-positive cultures for *Mycobacterium tuberculosis.*

Scenario	Approach	Comment[a]
Single smear-positive specimen		
Treatment not started	Obtain ⩾1 more specimen	Single smear-positive specimen could have been mislabeled or misread
Treatment well underway	If clinically compatible and responding, complete therapy	Consider stopping therapy and evaluating further if tuberculosis seems unlikely
Single positive culture, untreated patient		
Low suspicion for active tuberculosis	Collect 3 additional specimens, withhold therapy and observe pending cultures	Treatment without repeat cultures may complicate distinguishing false-positive versus active tuberculosis
Remains suspicious for tuberculosis	Collect 3 specimens, begin therapy	New specimens may be culture positive; confirming the diagnosis eliminates concerns about false positive findings

[a] If a false-positive culture appears likely, consider confirmation with DNA fingerprinting studies.

nique or laboratory conditions can result in cross-contamination. However, the large variation in false-positive rates demonstrates that cross-contamination can be minimized.

Previous reports suggested specific changes in laboratory techniques to minimize cross-contamination [22, 46]. It is not our purpose to review laboratory techniques, but some general comments are relevant for clinicians. Several studies found that 1–2 technicians appeared to be responsible for most episodes of cross-contamination [11, 24]. This suggests that in-depth training and experience in mycobacteriology laboratory techniques are crucial in decreasing cross-contamination. The high rates of false-positive cultures reported from laboratories processing a low volume of mycobacterial cultures [13, 36] suggest that using general laboratory technicians may result in higher rates of cross-contamination than those that occur with technicians who are dedicated to mycobacteriology. Facilities with a low demand for mycobacterial cultures should consider sending such specimens to a laboratory that has full-time mycobacteriology personnel.

Despite the frequency and importance of cross-contamination, there has been little formal research about the factors affecting it. Research in clinical mycobacteriology has emphasized the development of culture systems that are highly sensitive and that can detect growth as soon as possible. However, this review suggests that the attempt to maximize sensitivity by broth culture and by radiometric growth detection may have increased the rate of cross-contamination.

Existing laboratory proficiency programs test the ability to read acid-fast smears, to identify mycobacterial species, and to perform drug susceptibility testing, but do not include an assessment of cross-contamination. The study of Aber et al. [11] suggests a convenient way to assess cross-contamination: include sterile specimens in a group to be batch-processed with culture-positive specimens and evaluate the frequency with which positive cultures are reported from the sterile specimens. Laboratory testing programs should consider adding such testing to their current proficiency screens.

The quality assurance program for mycobacteriology laboratories should include a plan for identification and review of possible false-positive cultures. From the available studies, criteria that might prompt such a review include patients having only a single culture-positive specimen, cultures with a low colony count on solid media, or isolates with unexpected drug resistance. Finally, tuberculosis control programs should have a system for the timely review of patients with single-positive cultures [35].

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