Mycobacterial culture results of smear-positive patients with suspected pulmonary tuberculosis in Liverpool

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Mycobacterial culture results of smear-positive patients with suspected pulmonary tuberculosis in Liverpool. J.A. Corless, P.A. Stockton, P.D.O. Davies. ©ERS Journals Ltd 2000.
ABSTRACT: The aim of this study was to assess the final mycobacterial culture results of patients with smear-positive sputum or bronchial washings and to investigate the efficiency of local tuberculosis (TB) contact-tracing.

Retrospective analysis of mycobacterial cultures and contact-tracing was performed in every patient with smear-positive sputum or bronchoalveolar lavage (BAL) in two Liverpool teaching hospitals (1996-1998). Of these patients 116 with smear-positive sputum or BAL were identified. *Mycobacterium tuberculosis (M. tuberculosis)* was cultured in 57 (49%), environmental mycobacteria in 37 (32%) and cultures were negative in 22 (19%) of the patients. Contact-tracing information was available in 107 of the 116 (92%) patients. A total number of 1,357 contacts were screened for possible tuberculosis. Of these, 420 (31%) were contacts of patients who cultured environmental organisms or had negative cultures.

In this study, 51% of smear-positive patients in Liverpool did not have tuberculosis. Inefficiencies in current contact-tracing procedures have been identified which result from screening contacts of index cases that are subsequently found not to have cultured *Mycobacterium tuberculosis*. The authors believe that there are clear grounds for using rapid tests to identify and type mycobacteria more quickly than current solid or liquid media methods. It is also suggested that regional variations in the frequency of infection with environmental mycobacteria should be considered when formulating tuberculosis contact-tracing procedures.
Eur Respir J 2000; 16: 976–979.

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The aim of contact-tracing is to prevent the spread of tuberculosis. Current contact-tracing procedures in the UK [1–3] rely on early notification of patients with suspected tuberculosis, usually on the basis of a positive sputum smear or bronchoalveolar lavage (BAL) fluid. Following notification of a case of suspected tuberculosis to the "Proper Officer" of the local authority, a program of screening close contacts of the index case is implemented. The tuberculosis (TB) health visitor responsible for the locality in which the index case lives is notified and the index case is then interviewed. The health visitor will then approach each potential contact who will usually be seen in the TB screening clinic at a local hospital. Typically the contact has a chest radiograph and if indicated, a Heaf test. As standard mycobacterial culture techniques may take more than six weeks [4], contact-tracing procedures may be undertaken before mycobacterial species and antibiotic sensitivities in the index case are known.

Environmental mycobacteria, unlike *Mycobacterium tuberculosis* (*M. tuberculosis*) are ubiquitous organisms that live in media such as water and soil and except in very rare cases do not spread from person to person. Screening of contacts of patients with pulmonary infection from environmental mycobacteria is therefore, unnecessary. In regions with a high incidence of lung disease caused by environmental mycobacteria, the tuberculosis contact-tracing service may theoretically become inefficient as contacts are screened of "index cases" who are later found not to have cultured *M. tuberculosis*.

No recently published data on the national incidence of respiratory disease due to environmental mycobacteria is available. The authors subjective experience was that despite Liverpool having a similar incidence of tuberculosis to the national average (10.3 notifications·100,000 cases[-1] in North West England in 1998. The national average for England and Wales being 11.6·100,000 cases[-1]; source: Public Health Laboratory Service), there also seemed to be a high incidence of environmental mycobacteria. In this study the frequency of pulmonary infections with environmental mycobacteria was investigated in two Liverpool hospitals and the efficiency of the tuberculosis contact-tracing service assessed.

Materials and methods

The study was carried out at two large teaching hospitals in Liverpool, each with its own independent Microbiology laboratory. Data was collected retrospectively, over a two-year period, on all patients who had positive smears of sputum or bronchoalveolar lavage fluid using an auramine-phenol stain. The final mycobacterial culture results for each patient were then obtained. The first hospital studied, "Hospital A" (Royal Liverpool University

Hospital, Liverpool, UK) has approximately 800 beds and serves a population of 300,000 people. Data were collected April 1996–April 1998. The second hospital studied, "Hospital B" (University Hospital Aintree, Liverpool, UK) has approximately 900 beds and serves a population of 400,000 people. Data at hospital B were collected February 1996–March 1999. Patients with smear-negative culture-positive tuberculosis or suspected nonpulmonary tuberculosis were not considered. The catchment area of the two hospitals covered central Liverpool and some of its suburbs.

The aim of the second phase of this study was to establish what had happened, in terms of contact-tracing in each case of suspected pulmonary tuberculosis. This was achieved by liaising with every local TB health visitor. A list of names of all the smear-positive patients was provided and the TB health visitors were asked to provide details of the numbers and names of contacts that they had seen in the TB contact clinic.

As the authors source of patient data was the Microbiology databases, only details entered on the initial laboratory request form concerning age, sex and ethnicity were available.

Statistical methods used

Results of the mycobacterial cultures at the two hospital sites and differences in the mycobacterial cultures between sputum and BAL were analysed using the chi-squared test. Differences between the number of contacts screened for index cases who cultured *M. tuberculosis* and the group who either cultured environmental mycobacteria or had negative cultures were assessed using the Mann-Whitney U-test.

Results

A total of 116 "smear-positive" patients were identified, 95 from sputum samples and 21 from BAL fluid. Many patients had multiple samples sent to the laboratory. Fourty-nine patients were from hospital A and 67 patients were from hospital B. A complete breakdown of the final mycobacterial culture results is given in table 1. This data is summarized in figure 1 which shows that *M. tuberculosis* was cultured in 57 patients (49%), environmental mycobacteria were cultured in 37 (32%) and cultures were negative in 22 (19%) patients. The proportion of patients in each of the three groups was similar at both hospitals with no statistically significant difference seen. Of the group from whom *M. tuberculosis* was cultured, 42 (74%) were male, 11 (19%) were female and the authors were unable to confirm the sex in 4 (7%) of the cases. In the group from whom environmental mycobacteria was cultured, 23 (62%) were male and 14 (38%) were female. In the smear-positive culture-negative group 14 (64%) were male, seven (32%) were female and one (4%) was of unknown sex. Details of age were obtained in 62 of 116 patients. Median age for the *M. tuberculosis* group was 47 (range 16–86, n=34) and for the non-*M. tuberculosis* group was 61.5 (range 35–87, n=28). Analysis of the patients names suggested that 105 of 116 were of Western European ethnic origin and 11 of 116 were of other ethnic origin.

Table 1. – Final mycobacterial cuture results in 116 patients with positive smears

Culture result	All	Hospital A	Hospital B
Subjects n	116	49	67
MTB	57	24	33
Environmental			
All species	37	13	24
Mycobacteria			
M. Avium intracellulare	17	8	9
M. malmoense	10	2	8
M. kansasii	7	3	4
M. xenopi	1	0	1
M. gordonae	1	0	1
M. chelonae	1	0	1
Negative	22	12	10

MTB: Mycobacterium tuberculosis.

The breakdown of the different environmental mycobacteria that were cultured is given in table 1. Only one of the patients who cultured *M. avium-intracellulare* was known to be HIV-positive.

Statistically significant differences were found in the culture results from BAL compared with sputum (p= 0.042). Mycobacterial cultures from the sputum samples (n=95) grew *M. tuberculosis* in 50 (53%), environmental mycobacteria in 31 (33%) and were negative in 14 (14%) cases. Cultures from BAL samples (n=21) grew *M. tuberculosis* in 7 (33%), environmental organisms in 6 (29%) and were negative in 8 (38%) cases. The BAL samples included a case of *M. gordonae* and *M. chelonae* which are usually regarded as contaminants.

The details of the 22 patients who were smear-positive and culture-negative were analysed. In 11 of them only a single sputum sample and in nine only a single BAL sample was received by the laboratory (this contrasted with culture-positive patients in whom multiple samples were typically received). In two of the patients multiple sputum samples sent on different days were all smear-positive culture-negative. There was no clustering of the occurrence of smear-positive culture-negative samples around any particular date in either laboratory. Twenty of the patients had not received recent antituberculous therapy. Two patients had previously completed chemotherapy for *M. tuberculosis* and when they represented were found not to have active tuberculosis.
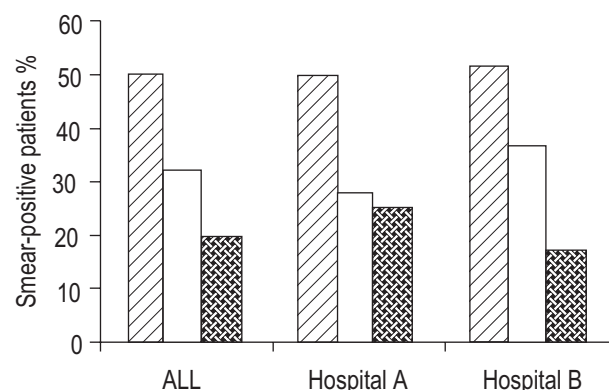

Fig. 1. – Percentage of smear-positive patients culturing *Mycobacterium tuberculosis* environmental mycobacteria and negative cultures with a breakdown of figures for the two hospitals. (▨): MTB (*Mycobacterium tuberculosis*); (▢) : environmental; (▦) : culture-negative.

The authors were able to establish what had happened with regards to contact-tracing in 107 of 116 cases (92%). The remaining nine cases were either patients with incomplete demographic data on the initial laboratory request form or patients who lived outside Liverpool and were dealt with by TB health visitors from outside the region. A total of 97 of the remaining 107 patients were initially notified as having suspected tuberculosis. The remaining ten were never notified. Specimens from one of these patients subsequently cultured *M. tuberculosis* with the other nine culturing either environmental organisms or having negative cultures.

A total of 1,357 contacts of 97 patients were screened for possible tuberculosis. Of these 937 (69%) were contacts of patients who subsequently cultured *M. tuberculosis* and 420 (31%) were contacts of patients who either cultured environmental organisms or who had negative cultures. Therefore, 31% of all contact-tracing work was unnecessary. A comparison of the number of contacts screened for each index case showed statistically significant differences (p=0.004) when comparing the patient from whom *M. tuberculosis* was cultured with the group culturing environmental organisms or with negative cultures. The median number of contacts traced·index case^{-1} was 11 (range 0–124) for patients culturing *M. tuberculosis* and 4 (range 0–47) for patients culturing environmental organisms or with negative cultures. No contact in this study developed tuberculosis while under surveillance.

Discussion

More than half of all patients in this study who had a positive smear of sputum or BAL did not in fact have tuberculosis. The relatively high frequency of both environmental mycobacteria and negative cultures also resulted in a large amount of unnecessary work for the tuberculosis contact-tracing service. It has been demonstrated that nearly one-third of all contact-tracing work studied in this survey was unnecessary.

The relative fraction of false-positive smear results is defined as the proportion of positive smear results that are culture-negative. It is generally regarded that this figure should be nearer to 5% than the 19% and 24% that is reported in this study, however, there is no recently published data from the UK to support this assumption. A number of older studies exist which demonstrate a wide variation in the relative fraction of smear-positive culture-negative results as outlined in table 2, although not all were limited to respiratory specimens. Potential causes

Table 2. – Percentages of smear-positive culture-negative specimens in previous studies

Investigators	Total false-positive smears %
Boyd and Marr [5]	55
Narain *et al.* [6]	40
Truant *et al.* [7]	31
Messa *et al.* [8]	11
Mitchison *et al.* [9]	8
Dominguez *et al.* [10]	6.5
Chan *et al.* [11]	6
Gordin *et al.* [12]	0.7
Borchardt *et al.* [13]	0.3

for smear-positive culture-negative specimens include contamination at the time of bronchoscopy, contamination of specimens [14] or inadvertent killing of live mycobacteria in the laboratory [15] and samples sent from patients already started on antituberculous therapy, (two patients with false-positive smears in the present study had previously completed antituberculosis chemotherapy. It was presumed that they were still shedding dead mycobacteria at the time the samples were taken). The fact that the results from two independent hospital laboratories were similar does suggest that this situation is not unique and the causes are probably multifactorial.

The current system of tuberculosis contact-tracing in the UK was developed at a time when the prevalence of tuberculosis was higher than it is today and when environmental organisms were either less common or less well recognized. Even the current UK guidelines for control and prevention of tuberculosis [16, 17] do not mention the potential pitfall caused by notification of suspected tuberculosis, which is subsequently found to be nontuberculous disease. Separate guidelines for notification and management of opportunistic mycobacterial infection [3, 18] discuss "denotification" of patients on the basis of culture results.

The results of the present study suggest that a re-evaluation of contact-tracing procedures should be considered. A number of new diagnostic tests are commercially available that can identify and type mycobacteria more quickly than standard solid or liquid culture methods [19–24]. It is now possible to determine whether or not a smear-positive sample of sputum or BAL results from infection with *M. tuberculosis* in as little as 24 h. Although these tests have not yet been proven to be totally reliable, they may in the very near future allow for a significant reduction in the standard six week delay for mycobacterial culture results and therefore, eliminate the unnecessary contact-tracing work that results. The extra costs of testing would certainly be offset by, savings in the tuberculosis health visitors and doctors time, a reduction in unnecessary chest radiography and in some cases unnecessary tuberculosis treatment. The psychosocial impact of a false diagnosis of tuberculosis is also an important factor.

To conclude, the authors believe that they have identified local inefficiencies in current contact-tracing procedures, mainly due to an increase in the number of respiratory infections recognized as being caused by environmental mycobacteria. It is suggested that regional variations in the incidence of infection with environmental mycobacteria should be considered when formulating tuberculosis contact-tracing procedures.

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