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Risk factors for drug resistant tuberculosis in Leicestershire – poor adherence to treatment remains an important cause of resistance

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SUMMARY

In the light of rising numbers of tuberculosis (TB) cases in the United Kingdom, the problem of anti-tubercular drug resistance remains a significant concern. Drug resistant TB cases are more difficult and costly to treat, and require appropriate treatment and control mechanisms. This matched case control study aimed to investigate risk factors for resistance in Leicestershire, using data for laboratory isolates of *Mycobacterium tuberculosis* identified from 1993 to 1998. Each case, defined as culture positive laboratory isolates resistant to at least one first-line drug, was matched to four fully sensitive controls on age, sex and ethnic group. Twenty-three cases and 81 controls were included in the analysis. Drug resistance in Leicestershire was found to be associated with poor adherence to treatment (OR 4·8, 95% CI 1·6–14·4, $P=0·005$) and with previous TB (OR 3·7, 95% CI 1·2–11·8, $P=0·022$). These findings emphasize the need to provide support to patients taking treatment in order to maximize adherence.

In 2000 there were 7000 tuberculosis notifications in the United Kingdom, a rise of 34% since 1987 [1]. This equates to a national incidence rate of 13/100000 population per year. The incidence in Leicestershire is twice this (25/100000 per year), mainly because of the fact that a high proportion of Leicester residents are of Indian Subcontinent (ISC) ethnic origin.

Nationally 6% of *Mycobacterium tuberculosis* isolates are resistant to isoniazid and 1% are multidrug resistant [2]. Although the problem of resistance is currently relatively minor in the United Kingdom, drug resistance (especially multidrug resistance) makes tuberculosis more difficult and costly to treat and there have been worrying outbreaks of drug resistant tuberculosis. In the United Kingdom risk factors for resistance in patients with tuberculosis include being of ISC or Black-African origin, HIV status, foreign birth, recent immigration and previous treatment [3]. We sought to further explore risk factors for resistance in a matched case control study of patients with tuberculosis in Leicestershire.

METHODS

Patients with culture confirmed tuberculosis which was resistant to any first line drug were compared to patients with fully sensitive disease. All cases and controls lived in Leicestershire and had culture confirmed tuberculosis between 1993 and 1998. Cases and controls were identified using laboratory reports and matched on ethnic group, gender and age group. To maximize the power of the study four controls were

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Table 1. *Matched case-control analysis. Unadjusted odds ratios for laboratory isolates resistant to at least one first line drug, matched for age, sex and ethnic group* (*missing data excluded*)

Risk factor	Resistant $n=23$ (%)	Sensitive $n=81$ (%)	Unadjusted OR (95% CI)	P
Poor adherence* recorded in notes	11 (47·8)	12 (14·8)	4·8 (1·7–13·7)	0·004
No evidence of poor adherence in notes	12 (52·2)	69 (85·2)	1	
Previous TB recorded in notes	8 (34·8)	10 (12·3)	3·6 (1·2–10·6)	0·021
No evidence of previous TB in notes	15 (65·2)	71 (87·7)	1	
Non-pulmonary	10 (45·5)	47 (58·0)	1·4 (0·6–3·6)	0·475
Pulmonary	12 (54·5)	34 (42·0)	1	
Foreign birth recorded in notes	13 (56·5)	53 (65·4)	0·6 (0·2–1·7)	0·357
No evidence of foreign birth in notes	10 (43·5)	28 (34·6)	1	
Foreign travel† recorded in notes	13 (56·5)	35 (43·2)	1·7 (0·7–4·3)	0·268
No evidence of foreign travel in notes	10 (43·5)	46 (56·8)	1	
Recent immigration‡ recorded in notes	2 (8·7)	6 (7·4)	1·2 (0·2–6·4)	0·838
No evidence of recent immigration in notes	21 (91·3)	75 (92·6)	1	

* This includes any mention of poor adherence in the notes whether it be based on clinician suspicion, urine tests or patient self report.

† Travel to high prevalence country in the last 10 years.

‡ Immigration within 2 years prior to diagnosis.

chosen for each case. Epidemiological data were extracted from medical and nursing records using a standard data extraction form which included information on ethnic group, age, gender, country of origin, year of immigration, previous tuberculosis, travel abroad to a high prevalence area in the last 10 years and any mention of suspected or proven poor adherence to prescribed treatment. As clinicians tended to record presence of risk factors more reliably than absence of risk factors (e.g. they were more likely to make a note of the fact that a patient had a previous history of tuberculosis than they were to record that a patient had no previous history of tuberculosis) the potential risk factors are categorized into two groups: 'presence of the risk factor recorded in the notes' and 'no evidence of the risk factor in notes'. For example in the case of previous treatment this latter category would include both patients where the clinician had made no mention of previous treatment and patients where they had specifically recorded that the patient did not have a previous history of tuberculosis. Conditional logistic regression (using Egret V2.0.3 for Windows) was used to investigate the relationship between drug resistance and potential risk factors.

RESULTS

Twenty-three cases and 81 controls were included in the analysis (11 controls were excluded because of missing notes). Table 1 shows the results of the univariate analysis. It can be seen that nearly 50% of cases had a history of poor adherence to treatment compared to only 15% of controls; 35% of cases had a previous history of tuberculosis compared to only 12% of controls. In the multivariate analysis poor adherence (OR 4·8, 95% CI 1·6–14·4, $P=0·005$) and a previous history of tuberculosis (OR 3·7, 95% CI 1·2–11·8, $P=0·022$) remained significantly associated with resistance but there were no significant associations with site of tuberculosis, foreign birth, foreign travel or recent immigration.

DISCUSSION

This study has identified poor adherence to treatment and a previous history of tuberculosis as important independent risk factors for drug resistant tuberculosis. The study was matched on ethnicity, age and gender so it was not possible to analyse these factors in the matched study. However, a separate unmatched analysis showed no evidence for association with these factors. Since almost all of the patients in this unmatched analysis were of ISC ethnicity the failure to find an association with ethnicity does not rule out an association. The matched study also found no evidence of association with site of tuberculosis, foreign birth, travel to a high incidence country or recent

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immigration (<2 years). As the study was relatively small it is possible that it may have missed moderate associations with these variables but the matched design and the use of four controls per case will have increased the power.

Both differential and non-differential misclassification of risk factors for resistance may have occurred in this study. Non-differential misclassification bias tends to lead to a reduction in power to detect associations between risk factors and outcomes. Misclassification of risk factors may have arisen because we cannot be absolutely certain that failure to record risk factors in the notes means that the risk factors were not present. For most potential risk factors (foreign birth, recent immigration and travel abroad) this misclassification is likely to be the same in cases and controls and may therefore have contributed to the failure to identify associations between these risk factors and drug resistance. For previous treatment and poor adherence the misclassification may be differential (clinicians may be more likely to enquire about these factors in patients with known resistance). This is of more concern as differential misclassification bias (where the misclassification is different in cases and controls) can lead to false associations between risk factors and outcomes. This potential bias would tend to lead to exaggerated associations between resistance and previous treatment and poor adherence. However, given the strength of the observed associations we do not consider it likely that they are simply the results of this potential bias.

The study emphasizes the need to ensure that those with a previous history of tuberculosis are treated with initial regimes that include at least four drugs so that isoniazid resistance is covered [4]. In this study poor adherence was commonly reported (15% of the control group with fully sensitive disease were poorly adherent). Studies elsewhere in the United Kingdom have shown similar levels of poor adherence to treatment regimes [5]. In order to avoid the emergence of further resistance tuberculosis services need to have sufficient resources to maximize patient adherence through high levels of support and if necessary through the provision of Directly Observed Therapy.

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