# Recurrence of tuberculosis at a Sydney chest clinic between 1994 and 2006: reactivation or reinfection?

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## ABSTRACT

**Objective:** To estimate the incidence of recurrence of culture-positive tuberculosis (TB) and the relative contributions of reinfection and reactivation (based on DNA fingerprinting).

**Design, setting and participants:** Retrospective analysis of all culture-positive TB notifications between 1994 and 2006 from Liverpool Chest Clinic in the south-west of Sydney. Patients with more than one notification of culture-positive TB during this period were identified. Genotyping of *Mycobacterium tuberculosis* was used to determine whether recurrence was due to reinfection or reactivation.

**Main outcome measures:** Estimation of the incidence of recurrence of culture-positive TB (cases per 100 000 person-years of follow-up), and the proportions of reinfection and reactivation.

**Results:** Three cases of recurrent culture-positive disease were identified (incidence of recurrence: 57.7 per 100 000 person-years of follow-up). All three patients were treated with directly observed therapy. Two of these patients had evidence of reinfection with different strains; both were natives of a country with a high incidence of TB and had returned to that country after the initial episode. The other patient had evidence of reactivation of the initial strain, indicating secondary failure of treatment. This patient had poor adherence to treatment.

**Conclusions:** Our observations suggest there is a very low rate of reactivation of tuberculosis. The low incidence of recurrence due to reinfection reflects the low incidence of tuberculosis in Australia. When reinfection does occur, this probably has been sustained during residence in a country with a high incidence of tuberculosis.


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After a long period of decline, the incidence of tuberculosis (TB) in Australia has been stable since the late 1980s.[1] In 2005, there were 1072 TB notifications nationwide (5.3 per 100 000 population), with the largest number in New South Wales (442) and the highest rate in the Northern Territory (13.3 cases per 100 000 population).[1] The incidence of TB in south-western Sydney is around 11 per 100 000 population.

Active TB in patients who have recovered from a prior episode of active disease can be caused by endogenous reactivation of the same strain of *Mycobacterium tuberculosis* (MTB) or by exogenous reinfection with a different strain. These may be distinguished by DNA fingerprinting. In a country with a low incidence of TB, such as Australia, recurrent TB is usually suspected to be due to reactivation rather than reinfection. However, this has not been systematically examined in Australia.

We estimated the incidence of recurrence of culture-positive TB at Liverpool Chest Clinic from all culture-positive TB notifications between 1994 and 2006 and the relative contributions of reinfection and reactivation. Liverpool Chest Clinic is the principal centre for the management of TB in south-western Sydney. Its average of about 90 TB notifications per year between 1994 and 2006 made up about 10% of all TB notifications in Australia.

## METHODS

### Setting and study population

By manual review of the notification records, we identified all patients who had more than one episode of TB notified by Liverpool Chest Clinic between 1 January 1994 and 31 December 2006, had positive cultures for both episodes, and who had completed treatment for the first episode. We verified the patients of recurrent TB from the chest clinic by comparing these records with the NSW Department of Health TB notifications database. Data linkage was used to identify patients with more than one TB notification in that period. The minimum required interval between the end of treatment for the first episode and diagnosis of recurrence has ranged from 0 to 6 months, or 12 months between positive cultures, in published studies.[2-5] We defined a second episode of TB as a recurrence if the interval between the end of treatment and another disease episode was at least 6 months.

The study included patients with pulmonary and extrapulmonary TB. Patients with multiple-drug resistant TB (MDR-TB) in any disease episode were also included.

All patients were treated with directly observed therapy (DOT) for a minimum of 6 months, initially with four first-line agents (isoniazid, rifampicin, pyrazinamide and ethambutol) for a minimum of 2 months and, in fully sensitive disease, rifampicin and isoniazid for the subsequent 4 months. In the presence of isoniazid resistance, all four drugs were continued for 6 to 9 months. When no supervision was possible (eg, the patient went abroad), the treatment would often be extended, so that the patient did receive 6 months of supervised treatment. In cases of miliary TB or tuberculous meningitis, treatment was extended to 12 months. Patients with MDR-TB were treated with second-line DOT over 12 to 24 months.

### Follow-up period

The average follow-up period was 6.2 years, and active radiological surveillance continued for at least 2 years after treatment cessation.

### MTB isolates

Isolates of MTB for genotyping were obtained from patients with culture-positive recurrent TB during both disease episodes. DNA fingerprinting used any or all of:

- direct repeat based spacer oligonucleotide typing (spoligotyping);
- mycobacterial interspersed repetitive unit (MIRU) typing, a polymerase chain reaction-based method that targets 12 separate loci containing variable numbers of MIRUs;
- IS*6110*-based restriction fragment length polymorphism (RFLP).

**Profiles of the three cases of recurrent culture-positive tuberculosis**

| Case | Type of recurrence | HIV status | Months to recurrence | Diagnostic site | | Smear results | | Sensitivities | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Episode 1 | Episode 2 | Episode 1 | Episode 2 | Episode 1 | Episode 2 |
| 1 | Reinfection with different strain | Negative | 16 | Lung only | Lung only | Bronchial washings + Sputum + | Sputum + | Sensitive to H, R, Z, E | Resistant to R, Z; moderately resistant to H |
| 2 | Reinfection with different strain | Unknown | 8 | Lung plus lymphatic site | Lung only | Lymph node +* Sputum – | Sputum – | Resistant to H, R, Z, E, S | Sensitive to R, Z, E; moderately resistant to H |
| 3 | Reactivation of initial strain | Negative | 9 | Lung only | Lung only | Sputum + | Sputum + | Sensitive to H, R, Z, E | Sensitive to H, R, Z, E |

+ = positive result. – = negative result. H = isoniazid. R = rifampicin. Z = pyrazinamide. E = ethambutol. S = streptomycin. * By fine-needle aspiration. ◆

Genotyping was done at the time of the second episode at the Institute of Clinical Pathology and Medical Research (Westmead Hospital, Sydney, NSW).

### Definitions

In this article we use the term "recurrent TB" to refer to a second episode of culture-positive TB occurring after completion of treatment for the initial episode. The term "reactivation" refers to a recurrent episode of TB with the same strain, and "reinfection" refers to a recurrent episode of TB with a different strain.

### Ethical approval

Ethical approval was obtained from the NSW Population and Health Services Research Ethics Committee.

## RESULTS

Of the 1161 TB notifications between 1994 and 2006, 848 (73%) were culture positive. Among the latter, three cases of recurrent culture-positive disease were identified (incidence of recurrence: 57.7 per 100 000 person-years of follow-up) (Box). No recurrences occurred in the first 6 months after completion of treatment for the initial disease episode.

Of the three recurrent cases, two were reinfections with different strains. The other patient had evidence of reactivation of the initial strain, indicating secondary failure of treatment.

The first case of reinfection was in a woman born in a country with a high incidence of TB, whose initial disease was with an organism fully sensitive to first-line treatment. In her recurrent episode, the organism was multiple-drug resistant. Her supervised treatment for the first disease episode had been extended to 8 months rather than the usual 6 months because of an unsupervised period of 2 months during a trip to her home country (for which a 2-month supply of daily isoniazid and rifampicin had been provided). The isolates had unrelated spoligotypes.

In the second case of reinfection, in a woman who came from a high-incidence country, the primary infection was with MDR-TB and reinfection occurred with an organism sensitive to rifampicin, ethambutol and pyrazinamide and moderately resistant to isoniazid. Both spoligotype profiles were from the Beijing family, but the MIRU profiles for the two isolates differed at seven loci.

Both patients had prolonged stays (9 and 2 months, respectively) in a high-incidence country after their initial treatment in Australia. It is assumed that reinfection occurred during these visits.

The third patient, with TB reactivation, had evidence of poor adherence to treatment. He had two periods of attempted treatment, each for about 3 months. On both occasions, treatment was not completed because the patient was lost to follow-up. At the third attempt, he finally completed treatment over 9 months. On most occasions, it was appropriately supervised (at least 7 months of supervised appropriate treatment), and his sputum cultures turned negative. The treating chest physician accepted the patient as having completed his treatment, rather than as a defaulter. Nine months later he re-presented with cough and increased shadowing on chest x-ray. At this time, sputum cultures were positive for MTB. DNA fingerprinting by IS*6110* RFLP showed indistinguishable isolates for the two different episodes, indicating reactivation. After completing about 3 months of treatment, he disappeared again. When he presented again to the clinic 4 months later, his sputum samples were negative, by smear and culture. He was recommenced on treatment for 4 weeks, before again becoming unlocatable. He never did complete the treatment for the second episode of TB, but sputum smears and cultures remained negative, and he was well at the last follow-up 10 years after the episode of recurrence.

## DISCUSSION

The principal observation of this study is that, in a population with a low incidence of tuberculous disease, treatment of active TB with DOT results in an extremely low rate of recurrence. Our observed rate was so low that, despite a substantial number of initial culture-proven cases (848), we were able to subsequently identify only three cases of disease recurrence over an observation period of 13 years. Therefore, we are unable to definitively conclude whether reinfection or reactivation is more likely to cause TB recurrence in this population.

Our recurrence rate (0.4%) appears to be substantially lower than the recurrence rates reported in comparable studies of treatment outcomes in similar low-incidence populations (ranging from 1.2% to 7%),[2,5-7] most of which did not use DOT. The fact that two of our three identified recurrences were due to reinfection rather than reactivation emphasises the effectiveness of treatment. We postulate that these results are a consequence of optimal anti-TB treatment being administered by a unit specialising in the management and treatment of tuberculous disease under DOT. Since the early 1980s, it has been the policy of the NSW Department of Health that all cases of TB in NSW should be treated by DOT.[8] Our results, represent-

ing 10% of Australian TB cases, validate the policy, which requires considerable resources for proper implementation. The World Health Organization also strongly advocates the use of DOT in treatment programs for active TB. Nevertheless, some prospective randomised trials in high-incidence populations have failed to show that DOT, per se, improves the outcomes of treatment of active TB.[9,10]

We are unable to account for patients who left NSW, so our recurrence rate may have been underestimated. However, we used two independent methods in determining the rate of recurrence, with 100% concordance. It is unlikely we missed any significant cases of disease recurrence, as every TB notification over the specified period was included, regardless of whether treatment had been completed. Because of good communication among the clinics, we are reasonably confident that any case initially treated at Liverpool Chest Clinic that recurred and was diagnosed in another state would have been notified to us.

Unfortunately, we are unable to report the exact proportion of HIV-positive patients in our study population, as HIV testing was not done routinely. However, dual infection seems to be rare in Australia. Among 393 patients in whom HIV status was assessed (37% of all notified cases in 2005), only 9 (2.3%) were HIV positive.[1]

As illustrated by this report, genotyping techniques are a means of distinguishing between reinfection and reactivation of TB. With the use of such techniques, recurrent TB due to reinfection in low-incidence countries ranging from 4% to 33% has been reported.[2,5-7,11-13] In contrast, in high-incidence countries (> 200 cases/100 000 population per year), reinfection may account for up to 77% of cases of recurrent disease.[14,15] The variability of such reported rates, both in low- and high-incidence populations, is probably a consequence of the variability of treatment efficacy, in terms of optimal drug therapy and patient compliance, as well as the duration of observation after the initial disease episode. The paucity of recurrent cases in this study prevents quantitative analysis. Nevertheless, we have been able to show that two of the three identified cases of recurrence were due to reinfection. There is a theoretical possibility that the patients classified as having reinfection had a simultaneous infection with different strains in the first episode, with one genotype detected initially and the other genotype detected at the time of recurrence.[16] Cases that are attributable to reactivation could therefore be misclassified as reinfection. However, the likelihood of this is very low. The rate of TB transmission has recently been documented to be low in the population of NSW,[17] so it would seem unlikely that the reinfections occurred in NSW.

## CONCLUSIONS

Recurrent TB due to reinfection in patients who have previously received an optimal course of treatment for TB is likely to be a consequence of visits to countries with high incidences of TB.[18] Therefore, in the assessment of patients presenting with recurrent TB in a low-incidence country such as Australia, taking a travel history is essential.

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## COMPETING INTERESTS

None identified.

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