Tuberculosis (2007) **87**, 176–184

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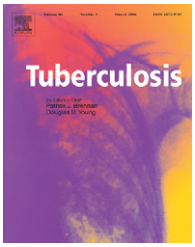

Utility of genotyping of *Mycobacterium tuberculosis* in the contact investigation: A decision analysis

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Received 3 January 2006; received in revised form 18 October 2006; accepted 25 October 2006

KEYWORDS
Tuberculosis;
Decision analysis;
Contact investigation;
Molecular epidemiology;
Markov models

Summary
The objective of this study was to compare the traditional tuberculosis contact-tracing strategy with a two-stage strategy, in low prevalence countries. We compared the utility of contact tracing of pulmonary tuberculosis patients using a single interview (Strategy I) with that of two-stage strategies, namely traditional 'stone-in the pond' contact tracing (strategy II) and a strategy involving second interviews of patients whose *Mycobacterium tuberculosis* isolates are genotypically clustered (Strategy III). Factors affecting the utility and impact of each were explored using sensitivity analysis of probabilistic decision trees and a quantitative Markov simulation. Contact tracing using Strategy III demonstrated a higher utility and a 12% lower probability of secondary infection being missed compared with Strategy II. The threshold level, at which a change, from a traditional to a two-stage contact tracing strategy is indicated, is when the rate of clustering is 4% or more. The utility of Strategy III is optimal when the probability of detecting new epidemiological links is more than 10%. Strategy III allows detection of 58% of infected patients within 2 years after exposure compared with Strategy II and Strategy I which will detect 47% and 32% of infected contacts within 2 years, respectively. Strategy III allows detection of 58% of infected patients within 2 years after exposure, compared with 32% and 47% for Strategies I and II, respectively. There is a linear relationship between the rate of clustering of isolates and the probability of secondary cases being prevented by the use of Strategy III. A two-stage tuberculosis contact tracing strategy, based on clustering of genetically related *M. tuberculosis* isolates, should improve identification of epidemiologic links and prevent more cases of secondary infections in low prevalence settings and so augment traditional contact tracing. The main factors affecting utilities were the likelihood of new epidemiological links being identified after the second interview and the local rate of clustering of *M. tuberculosis* isolates.

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1472-9792/$ - see front matter
doi:10.1016/j.tube.2006.10.003

Introduction

Genotyping of *Mycobacterium tuberculosis* isolates allows recognition of case relatedness and has revolutionized the ability to monitor recent transmission rates and track the spread of infection.[1–4] When applied to large cohorts of patients with tuberculosis in urban, industrialized settings, routine genotyping has shown that between 14% and 40% of cases result from recent transmission and a substantial proportion (20–72%) occur in clusters.[5–8] Molecular epidemiological studies have highlighted deficiencies in the completeness and timeliness of conventional tuberculosis control strategies by demonstrating that as few as 5–10% of clustered cases are identified through routine investigation of close contacts.[5,9–11] These studies suggest the importance of casual contact in transmission, but their conclusions are potentially biased because of their relatively short duration, inclusion of only culture-proven cases and the possible concentration of local *M. tuberculosis* clones in certain ethnic groups.

In low incidence countries, the number of secondary cases, ideally, should be controlled by rapid and complete contact investigations. However, in practice, this is limited by diagnostic delays and the occurrence of cases in hard-to-reach, itinerant groups,[12] in which transmission often occurs beyond recognized "concentric circles" of close contacts. Therefore, it has been suggested that clustering of genetically related *M. tuberculosis* isolates be used as a trigger for a second targeted interview, designed to uncover otherwise unrecognized routes of transmission.[13] A strategy involving a two-stage contact investigation would complement traditional contact tracing and, potentially, add "epidemiologic value".[14] While some infected contacts may have already progressed to active disease by the time of the contact investigation, most have latent infection identified by skin testing. Identification and prophylaxis of latently infected contacts reduces the risk of progression to clinical disease and prevents secondary cases of tuberculosis.[15]

Currently, contact tracing is often limited to household contacts. Previous studies have shown that the second targeted interview increases the likelihood of identification of epidemiologic links and infected contacts.[12,16,17] For example, in one study epidemiologic links were established among 45% of clustered cases: 31% were identified among close contacts, at an initial interview, and the rest only after genotyping and follow-up interviews.[18] In other studies, cluster feedback has resulted in 21–45% increases in epidemiological links detected.[13,16,18] Both strategies have been used in public health practice in countries with a low prevalence of tuberculosis.

The objective of this study was to compare and contrast traditional and two-stage tuberculosis contact tracing strategies, in low prevalence countries, by exploring factors affecting the utility and expected impact of each, using sensitivity analysis of probabilistic decision trees and a quantitative Markov model, respectively.

Methods

Alternative strategies

In the model, we considered only immunocompetent adult patients with pulmonary tuberculosis. The alternative strategies were (a) traditional investigation of patients with pulmonary tuberculosis, with a single interview by a public health or chest clinic nurse, to identify (investigate and treat, if indicated) close contacts and persons who share the same airspace (Strategy I); (b) as for Strategy I, with second interview to identify more distant contacts, if any close contacts has evidence of infection-known as the 'stone in the pond'' approach (Strategy II) and (c) two-stage contact tracing comprising an initial interview, as in Strategy I, followed by second, targeted interviews of patients whose *M. tuberculosis* isolates are apparently clustered, based on genotyping results (Strategy III). Contacts identified by either strategy are traced, evaluated for tuberculosis infection or disease and managed accordingly. Strategy III includes cluster investigations, when epidemiologic links or a common source cannot be identified between two or more cases, with genotypically matched *M. tuberculosis* isolates.[11,12]

Decision tree construction

Decision analysis offers a way to balance the benefits and costs of competing strategies in a systematic, structured way and to identify the main determinants of management choice.[19,20] It employs Bayesian probabilities together with values assigned to different outcomes to determine the optimal course of action. We chose a decision analytic approach[21] for initial comparison of the values of three tuberculosis contact tracing strategies described above.

A decision tree, with three branches representing alternative strategies was created (Fig. 1). The allocated probabilities at each chance node are derived from published data (see Table 1). Utilities, or subjective numeric values given to a health state or a decision outcome, represent preferences of public health practitioners for one type of outcome over others. They are quantified on a scale from 0 to 1 to allow comparison of alternative outcomes. According to the threshold model, the strategy selected should be the one with the highest expected utility, which should, on average, produce the optimal outcomes.[20,21]

Markov model

To assess the impact of each strategy on the number of cases of infection prevented, we developed a state-transition Markov model to follow individuals infected with *M. tuberculosis* strains belonging to a genotypic cluster. The course of infection was represented as a sequence of transitions between mutually exclusive health states, each of which describes the individual's diagnostic and treatment status. Five possible states were defined (Fig. 2), which were either transient (*asymptomatic not detected, asymptomatic detected* or *symptomatic untreated*) or terminal (*symptomatic treated* or *symptomatic prevented*).[22] A hypothetical cohort of immunocompetent adult patients infected from a single source and comprising one epidemiological and genotypic cluster moves yearly between health states according to the transition probabilities, based on published evidence (see Table 1). The time horizon of the