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Risk of Active Tuberculosis in the Five Years Following Infection . . . 15%?

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BACKGROUND: It is often stated that the lifetime risk of developing active TB after an index infection is 5% to 10%, one-half of which accrues in the 2 to 5 years following infection. The goal of this study was to determine whether such estimates are consistent with local programmatic data.

METHODS: This study included close contacts of individuals with active pulmonary TB notified in the Australian state of Victoria from January 1, 2005, to December 31, 2013, who we deemed to have been infected as a result of their exposure. Survival analysis was first performed on the assumption of complete follow-up through to the end of the study period. The analysis was then repeated with imputation of censorship for migration, death, and preventive treatment, using local mortality and migration data combined with programmatic data on the administration of preventive therapy.

RESULTS: Of 613 infected close contacts, 67 (10.9%) developed active TB during the study period. Assuming complete follow-up, the 1,650-day cumulative hazard was 11.5% (95% CI, 8.9-14.1). With imputation of censorship for death, migration, and preventive therapy, the median 1,650-day cumulative hazard over 10,000 simulations was 14.5% (95% CI, 11.1-17.9). Most risk accrued in the first 5 months after infection, and risk was greatest in the group aged < 5 years, reaching 56.0% with imputation, but it was also elevated in older children (27.6% in the group aged 5-14 years).

CONCLUSIONS: The risk of active TB following infection is several-fold higher than traditionally accepted estimates, and it is particularly high immediately following infection and in children.   CHEST 2016; 149(2):516-525

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Accurate determination of the risk of future disease in subjects with latent TB infection (LTBI) is critical to understanding this disease.[1] It has been estimated that approximately one-third of the world's population is infected,[2] and close contacts are at particularly high risk.[3] Latency dynamics have implications for the individual[4] and are crucial to transmission models.[5] Much research has been conducted on the assumption that the annual risk of active disease is < 0.3%,[6,7] and current information from groups such as the World Health Organization states that 5% to 10% of infected subjects will develop TB, one-half of whom will do so within 2 to 5 years.[8,9]

These estimates are based on empirical research (reviewed in more detail in the following text). However, we are unaware of modern estimates that rigorously adopt the principles of a survival analysis[10] to allow for the incomplete detection of all individuals developing active disease inherent in any surveillance system. We thus believe it is unsafe to assume that all members of a cohort of subjects who go on to develop active TB will be reliably detected through surveillance; even in settings in which case detection is very high, loss to follow-up will occur through migration, death, and preventive therapy.[11,12]

The goal of the present study was therefore to determine whether commonly accepted risk estimates are consistent with modern epidemiologic observations. Using notification data from Victoria, Australia, a subgroup of close contacts of TB cases were identified who could be determined (with a high degree of confidence) to have been infected as a result of their exposure. Survival analyses were then performed to determine risk of progression to active disease.

Materials and Methods

The full methods are described in e-Appendix 1 and are summarized as follows.

Data Source

Records for all close contacts of bacteriologically confirmed pulmonary cases prospectively identified by the Victorian Tuberculosis Program from January 1, 2005, to December 31, 2013, were extracted from an existing programmatic database obtained from surveillance records. The database contains demographic information, laboratory results, and case notes and has been previously described.[13] Analysis was performed by using Matlab Version R2015a (MathWorks). The project was approved by the Victorian Department of Health and Human Services Human Research Ethics Committee.

Definitions

The exposure date was defined as the collection date of the first specimen from the index case or estimated as 6 days prior to notification, when this information was unavailable (2.9% of contacts). LTBI was defined as results of a tuberculin skin test (TST) ≥ 10 mm or a positive result on the interferon-gamma release assay (IGRA), rather than the more commonly used ≥ 5 mm for close contacts.[14,15] LTBI conversion was defined as: a first LTBI assessment consisting of either a TST result < 10 mm or a negative IGRA and an assessment performed at least 14 days later that was either a TST result ≥ 10 mm that had increased by ≥ 6 mm from baseline[16] or a positive IGRA. Low-endemic countries were defined by an incidence < 15 per 100,000 per year.[17]

In Victoria, close contacts are defined as "people who have had frequent, prolonged and close contact in an enclosed environment with an infectious case such as: all people living in the same dwelling; relatives and friends who have frequent, prolonged and close contact; and work colleagues who share the same indoor work areas on a daily basis, following an individual risk assessment."[18]

Survival Analyses

Close contacts of bacteriologically confirmed index pulmonary cases were included in the analysis if they either demonstrated conversion or were born in a low-endemic country and had a positive LTBI assessment recorded during contact investigations. This definition was intended to be highly specific, ensuring with a high degree of confidence that the study cohort consisted only of individuals determined to be infected. However, several alternative definitions are also considered (Table 1).

Survival analyses were first performed on raw data with universal censorship at December 31, 2013. Survival analyses were then performed with imputation of censorship due to death, migration, or treatment-related protection from reactivation. Imputed analysis was performed 10,000 times, with the individual-level probability of censorship due to each cause drawn from plausible ranges and then randomly imputed at the individual level (Fig 1).

Censorship Imputation

Case notes of all 776 infected contacts included in any of the alternative analyses presented were reviewed to determine whether and when preventive therapy was commenced. In the main analysis cohort of 613, a total of 44 contacts infected by isoniazid-resistant strains were presumed not to have received effective preventive therapy, as were 121 contacts for whom case records suggested they had not completed treatment and the 67 contacts who developed active TB. Of the remaining 381 contacts, 65 were known to have completed a full course of preventive treatment; 134 started treatment, but their completion status was uncertain; and the treatment status of 182 contacts could not be determined. Treatment efficacy was estimated at 87.5% (ie, approximately 85%-90%)[11,19,20] and compliance at 85%.[21] Therefore, the 65 contacts known to have completed treatment were conferred a 87.5% chance of censorship due to preventive therapy, whereas the 134 contacts with uncertain completion status were conferred a 74.4% chance of censorship (87.5% × 85%). The 182 contacts for whom information was unavailable were conferred a probability of treatment by using a β-cumulative distribution function with parameters 3.81 and 2 (e-Fig 1), multiplied by 74.4% to incorporate compliance and efficacy. Of the 199 contacts known to have commenced treatment, the start date was known in 169 (84.9%). For the remainder and for the 182 contacts with no data, start dates were estimated at approximately 100 days from infection.