Spatial and Spatio-temporal Epidemiology 8 (2014) 47–54

Contents lists available at ScienceDirect

Spatial and Spatio-temporal Epidemiology

journal homepage: www.elsevier.com/locate/sste

Accuracy of prospective space–time surveillance in detecting tuberculosis transmission

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ARTICLE INFO

Article history:
Received 20 September 2013
Revised 11 January 2014
Accepted 14 January 2014
Available online 23 January 2014

Keywords:
Prospective surveillance
Space–time clustering
Tuberculosis

ABSTRACT

To improve detection of tuberculosis transmission, public health can supplement contact tracing with space–time surveillance. However, investigation of space–time clusters not due to transmission (false alarms), may lead to costly, unnecessary interventions. We measured the accuracy of prospective space–time surveillance in detecting tuberculosis transmission, assessing the number of clusters containing transmission and the false alarm rate. We simulated monthly prospective applications of a scan statistic using the home addresses and diagnosis dates of all 1566 culture-positive TB cases reported in Montreal during 1996–2007. We verified transmission within the space–time clusters by analyzing the TB genotype. Over 11.5 years, at 1.3 false alarms per month, we detected 89 transmission chains; at 0.05 false alarms per month we detected 5 transmission chains. We found evidence that prospective space–time surveillance for TB leads to a high false alarm rate, limiting its practical utility in settings with TB epidemiology similar to Montreal.

1. Introduction

Tuberculosis (TB) remains a public health concern in developed countries, despite a decline in incidence (Public Health Agency of Canada 2008). Although developed countries have implemented effective TB control programs, outbreaks continue to occur, especially within urban settings (Lofy et al. 2006). Rapid detection techniques to find ongoing transmission remain a priority for TB control.

In most jurisdictions, TB is a notifiable disease; clinicians and laboratories must report newly diagnosed cases of TB to public health officials. To prevent further transmission, public health officials interview newly reported cases to identify others that they may have infected (or been infected by), a technique known as contact tracing.

Contact tracing effectively identifies known contacts (family, friends and coworkers), but casual contacts (those who cases cannot identify sufficiently for public health to contact) may be missed. In public places, such as bars, on

Abbreviations: FSA, forward sortation address; IS, insertion sequence; RFLP, restriction fragment length polymorphism; ROC, receiver-operating characteristic; SaTScan, software for spatial temporal and space–time scan statistics; SD, standard deviation; TB, tuberculosis.

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http://dx.doi.org/10.1016/j.sste.2014.01.003
1877-5845/

public transit, or at sporting events, transmission can occur between casual contacts, and contact tracing will be unable to identify these cases.

When ongoing transmission occurs between casual contacts in a neighbourhood, the chain of transmission may result in an unusual number of cases over a short time period in a small region: a space–time cluster. If public health monitored the TB cases for space–time clusters, they may identify transmission that contact tracing would miss (Nunes, 2007; Onozuka and Hagihara, 2007; Tiwari et al., 2006).

But space–time clusters of TB cases are not always due to recent ongoing transmission. Unlike some other infectious diseases, a person can be infected with TB but not have TB disease, known as a latent infection. A latent infection can be reactivated (cause TB disease) decades after the original infection. Since some risk factors for latent infections cluster in space and time, reactivated cases can also form space–time clusters. For example, if migrants from TB-endemic countries live in the same neighbourhood, it could lead to space–time clusters of latent reactivation (Haase et al., 2007). If public health investigated space–time clusters due to reactivation, the investigation would not reveal any new transmission, or worse, lead to identification of spurious links between the unrelated cases, leading to unnecessary interventions.

It is possible to distinguish between reactivation and recent transmission by culturing and genotyping the TB bacteria from people with TB disease. When cases are involved in a chain of transmission, the TB organisms will share a similar genotype. Some researchers (Moonan et al., 2004; Haase et al., 2007; Stone 2001; Kammerer et al., 2013) have retrospectively identified space–time clusters of TB, and, using the genotype, found that some (but not all) of these clusters contained chains of transmission.

Public health authorities need to identify ongoing transmission quickly, before more infections arise; they cannot wait for the bacteria cultures and genotype analysis to verify that a space–time cluster is due to transmission. However, investigation of a "false alarm" (a space–time cluster not due to transmission) is costly, and may lead to harmful, unnecessary interventions, such as school closures. We are not aware of any published evidence that has compared the potential benefit (detected clusters containing transmission) to the false alarm rate, a critical metric for practical, prospective use. In this study, we sought to measure the accuracy of prospective space–time surveillance in detecting chains of tuberculosis transmission. We simulated prospective surveillance for space–time clusters of TB cases, and verified if the cases in the detected space–time clusters were involved in a chain of transmission by examining the genotypes of the TB organisms.

2. Methods

2.1. Case data

From Montreal Public Health records, we obtained data for all TB cases on the island of Montreal reported during 1996–2007 (inclusive). We extracted TB case data from paper charts into a database, removing personal identifiers to protect patient privacy. We used the residential postal code to assign each TB case to a geographic region called a Forward Sortation Area (FSA), corresponding to the first 3 digits of the Canadian postal code. The island of Montreal (511.3 km^2) contains 102 FSAs with an average area of 5.2 km^2. We summed the reported cases by month and FSA for analysis. The Institutional Review Board of the McGill University Faculty of Medicine approved this study.

We excluded cases with addresses at institutional facilities with relatively "closed" populations, such as prisons and long-term care facilities, because their inclusion would distort space–time analyses by creating links between populations unlikely to contract TB from each other. We also excluded cases with a missing address or TB diagnosis date.

We extracted 1588 unique cases of TB, confirmed by positive culture, from the Montreal Public Health database. Of these cases, 22/1588 (1.4%) were excluded: nine were homeless, three were in prison, one was in a health facility, two had a missing address, and seven had a missing date of diagnosis. We analyzed the remaining 1566 cases.

2.2. Tuberculosis cluster detection

Prospective space–time surveillance finds space–time clusters of high rates of disease, potentially highlighting areas of person-to-person transmission. We scanned for TB clusters by using a space–time scan statistic (Kulldorff et al., 2005) with a Poisson model, which is used routinely in some public health settings (Heffernan et al., 2004). We linearly interpolated the 1996, 2000 and 2006 Canadian censuses to estimate the population in each FSA (a requirement for the Poisson model) every month.

We simulated prospective space–time surveillance by scanning for geographic clusters at monthly intervals. Each scan used data from the 12 previous months. We began scanning at the end of 1996, to start with a full 12 months of data. The final scan occurred at the end of 2007, resulting in 132 scans in total. Clusters were limited spatially in that the area covered must have included less than half of the population of Montreal, and temporally in that they must have been 12 months long or less. In essence, we determined which space–time clusters public health staff would find if they looked for them every month, with reference to the preceding 12-month period. In a sensitivity analysis, we varied the length of the reference time period to 24, 36 and 48 months. Every prospective scan resulted in a set of detected clusters, each with a statistical significance.

2.3. Genotyping

We verified that the detected clusters contained possible person-to-person transmission chains by reviewing the genotypes of the *Mycobacterium tuberculosis* organism for each case. For the island of Montreal, more than 95% of all isolates were genotyped using insertion sequence (IS) 6110-based restriction fragment length polymorphism (RFLP) analysis (van Embden et al., 1993). We assumed that groups of cases with similar TB genotypes (genotype groups) reflect recent transmission events, an assumption consistent with the substantial background genetic