Surveillance and outbreak reports

Tuberculosis in a shopping centre, Portugal, 2004-5

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Genotyping enables to confirm or exclude a tuberculosis (TB) cluster. Excluding the link between cases is particularly important in countries with intermediate/high incidence of TB where the emergence of several TB cases in a particular location in space or time (higher than the expected) could be explained by chance alone.

During 2004 and 2005, five TB cases occurred in five shops of a Portuguese shopping centre which employed a total of about 1000 workers. After an epidemiological survey, 52 close contacts were identified and screened. Latent tuberculosis infection was diagnosed in 10 contacts (eight family members and two work colleagues of cases). Genotyping of the *Mycobacterium tuberculosis* isolates revealed no link between the cases. For this reason no screening of all staff of the shopping centre was carried out. However, close contacts (52) and all fellow workers (1000) were kept under surveillance for two years, and no additional cases were diagnosed.

The present analysis demonstrates that the exclusion of a chain of ongoing transmission by genotyping for the investigation of a cluster is cost-effective from the perspective of the public health service, because it allows to avoid unnecessary large scale screening operation and instead to direct resources to more effective measures of TB control.

Introduction

Tuberculosis (TB) remains a serious problem worldwide. In Portugal, the incidence of TB is 29.4 per 100,000 inhabitants per year [1], higher than the European Union average of 17 per 100,000 [2]. Contact screening is mostly aimed at identifying family, social and work contacts of cases [3,4]. It is often difficult to decide how far to proceed with screening, particularly if several cases coincide in time and space, which in intermediate/high incidence countries can be due to chance only. A good understanding of the factors affecting the transmission of the disease in the community may result in avoiding the diagnosis of false clusters and directing the resources to more effective measures of TB control.

Molecular typing can help clinicians and public health practitioners to identify or exclude clusters of recently acquired tuberculosis [5,6]. *Mycobacterium tuberculosis* isolates from space or time clusters are expected to show identical or very closely related genotypic patterns [7]. IS6110 restriction fragment length polymorphism (RFLP) has been used as the "gold standard" method for more than a decade [7]. This method provides the highest discriminatory power among *M. tuberculosis* typing techniques, showing sufficient variability to distinguish unrelated strains.

This paper is based on a retrospective review of the investigation of a suspected time–space cluster of cases of TB. During 2004 and 2005, five cases of active tuberculosis were identified among employees of a shopping centre with 172 shops and a total of approximately 1000 workers in Vila Nova de Gaia, south of Porto in north-west of Portugal. The TB diagnosis was based on culture and identification of *M. tuberculosis*. The isolates were confirmed to be fully sensitive. The patients were voluntarily tested for human immunodeficiency virus (HIV) infection and all were negative. All five patients were started on directly observed therapy short-course (DOTS) and all have completed the treatment.

A number of common features were found in the five patients. They all lived in neighbouring districts near the shopping centre and frequented the same food and leisure places. This raised the question of what size of population should be subject to screening.

Material and methods

An epidemiological survey was performed in order to identify the daily activities of all TB patients. Home, transport, workplace and social settings of the TB cases were described (size of place, ventilation, time and length of exposure, etc.) and contacts were identified. This information was put together to disclose all possible links between the five cases, taking into account the presumed infectious period of the cases, known contacts between the cases, residence, transport used, spatial distribution of the shopping centre and social activities.

Close contacts were defined as household members, co-workers (of the same shop), and persons who had spent more than a cumulative contact time of eight hours in a confined environment with the case during the symptomatic phase (before the diagnosis and the beginning of treatment). All close contacts of TB patients were offered the screening programme, including symptom questionnaire, tuberculin skin testing (TST) and chest X-ray (CXR).

Distant contacts were defined as employees of other shops of the same shopping centre with no known contact with the TB patients or other persons who had only had sporadic contact lasting less than 8 hours with the cases during the symptomatic phase.

All identified contacts (both close and distant) were followed for a two-year period and special attention was given to the identification

of all new cases in the area covering the districts of residence of the cases and the shopping centre to discard possible links with these five cases. The follow-up included clinical examination of all the close contacts screened (52 close contacts) and surveillance of all employees of the shopping centre, including those not considered to be close contacts and therefore not screened. The period of follow-up was two years, as it is known that 10% of cases of latent TB infection develop active tuberculosis, and 5% do so two years after infection [7].

In order to identify the link between the cases and thus provide evidence for further public health decisions, genotyping techniques were used to analyse the clinical strains. Molecular strain typing was performed using the standard method IS6110 RFLP [7]. We used a combination of external and internal standards as positive controls, including a reference strain of *M. tuberculosis* named Mt14323. The latter gives 10 approximately evenly spaced bands of known size. This combination of markers allows extremely precise band molecular size determinations and permits computerised comparisons between strains.

The costs of the screening programme were calculated based on the values published in the Portuguese official journal of legal acts – Diário da República (Republic Diary) 113 1ª série/B published 12 June 2006. All costs are reported in euros and presented in Table 1. TST licensed for Portugal is PPD RT 23, 2 T.U. from the Danish Statens Serum Institute. The delivered price for 10 glass vials, each containing 1.5 ml RT 23, is 149.99 euros. From the 1.5 ml vials, we withdraw 10 test doses of 2 T.U. The charge for the RFLP analysis made by the reference laboratory (Instituto Nacional de Saúde, Laboratório de Tuberculose, Porto) is 149.64 euros.

Table 1

Base-case estimates used in cost analysis of the investigation of tuberculosis cases in a shopping centre in Vila Nova de Gaia, Portugal, 2004-5

Public health service (PHS) procedures and other costs (in euros)	Base-case cost estimate (in euros)	Source
Tuberculin skin test	15	PHS*
Chest radiography	9.80	PHS*
Medical consultation (doctor, 25 minutes)	30	PHS*
Restriction fragment length polymorphism (RFLP)	149.64	Laboratory provider

PHS* Costs of public health service procedures are per test/procedure as listed in Diário da República (Republic Diary) 113 1ª série/B published 12 June 2006

Results

The five cases' mean age was 31 years (range 28 to 36 years). They all had pulmonary active tuberculosis, based on microbiologic identification. The median time between the onset of symptoms and diagnosis was four months (range 2-9 months). In practice, there was no delay between diagnosis and treatment initiation (diagnoses took one day).

The cases lived in neighbouring boroughs around the shopping centre but did not have any social contact outside the workplace, not even in public transport. They all worked in different shops within the shopping centre but two pairs of cases worked on the same floor. Three cases frequented the same restaurant regularly and four cases went to the same leisure place once a week, but they never met on those occasions.

Fifty-two close contacts (mean 10 per case, range 7-16 contacts) were identified and examined. Close contacts were identified among family (20), close friends (15) and work colleagues (17). Latent tuberculosis infection was diagnosed in 10 contacts (eight among family members and two among work colleagues) and treatment was provided (OR=2.2, 95% CI: 0.4-22, p=0.466). No additional cases of TB infection were diagnosed.

All cultures obtained from cases were regrown on Lowenstein Jensen culture medium slants but only four out of five produced colonies, resulting in the loss of one strain. When growth was considered to have attained an optimal biomass, cells were harvested and inactivated. IS6110 RFLP results revealed that at least four of the five TB cases were caused by strains with different hybridisation patterns thus discarding the possibility of transmission of the disease inside the shopping centre. The fingerprints of the four *M. tuberculosis* isolates investigated are shown in the Figure. Taking into consideration the definition of cluster as two or more strains sharing the same IS6110 RFLP pattern, none of the strains included in this study were clustered, because all patterns were different as demonstrated in Figure.

Therefore, we concluded that the TB cases were not linked and decided not to extend the screening programme beyond the close contacts.

The cost of TB screening in our public health service is 54.8 euros per patient. The total cost of screening of the 17 close contacts identified among the shopping centre employees was 931.6 euros. The additional cost of genotyping of the four *M. tuberculosis* isolates was 598.56 euros. Had we screened all workers of the shopping centre (about 1000 people) we would have spent 54,800 euros.

No additional cases of TB were diagnosed during the two years of follow-up, either among the close contacts who had been screened or other employees of the shopping centre.

Table 2

Characteristics of cases of tuberculosis identified among employees of a shopping centre in Vila Nova de Gaia, Portugal, 2004-5 (n=5)

Case	Date of diagnosis	Age at time of diagnosis(years)	Sex	TB site	AFB sputum smears	PCR result	Symptoms
1	May 2004	29	Female	Pulmonary	Positive	Positive	Yes
2	July 2004	33	Female	Pulmonary	Positive	Positive	Yes
3	Sep 2005	28	Female	Pulmonary	Positive	Positive	Yes
4	Oct 2005	36	Female	Pulmonary	Positive	Positive	Yes
5	Dec 2005	31	Male	Pulmonary	Positive	Positive	Yes

Discussion

A disease cluster is a local anomaly in the data where the observed incidence for a particular location in space and/or particular time interval appears to be different (higher) from the expected, based on the assumption of a uniform disease distribution among persons at risk, irrespective of time or location [9].

When the possibility of a TB cluster arises, particularly in a public space, screening procedures must be extended to a larger population. However, when making decisions about the extent of contact tracing and screening we need to weigh the chance of missing potentially exposed individuals against causing unnecessary anxiety in a large number of people involved.

Of the 17 work colleagues screened, two (12%) had latent TB infection (LTBI). Among family and close friends, LTBI was detected in eight out of 35 contacts (23%). In the general Portuguese population, LTBI prevalence has been estimated at 15% [1], which is higher than the rate observed in the co-workers but lower than that found among family and close friends. Thus the number of LTBI cases detected among work colleagues was not higher than expected in the general population. Family contacts, on the other hand, were found to be at increased risk for LTBI.

Extending the screening procedures beyond close contacts raises questions regarding the efficacy and the real benefit especially in a population with intermediate/high incidence of tuberculosis. Universal screening is no longer advised. We must therefore direct our efforts at identifying the individuals at risk and understanding the local mechanisms of tuberculosis transmission in order to define the best strategy to control the disease.

The investigation described in this paper benefited from evolving technologic solutions in the field of genotyping. IS6110 RFLP revealed that none of the four isolates obtained shared the same genotype, which ruled out the hypothesis of an outbreak.

With the exclusion of a link between the cases and a prevalence of LTBI lower than expected among the other workers of the same shop, we decided not to extend the screening procedures to the rest of the staff. Thus we managed to save about 1000 screenings.

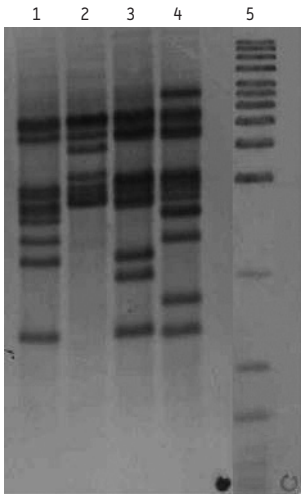
The follow-up provided evidence that our decision was right because no other TB case was diagnosed among the employees of the shopping centre or residents of the neighbouring area.

A thorough assessment based on clinical and laboratory diagnosis combined with genotyping of all *M. tuberculosis* isolates is recommended for the confirmation or exclusion of an outbreak. Usually, the literature describes the usefulness of genotyping techniques in confirming a cluster, but it is also very important when it can exclude a link between the cases. In countries with intermediate/high prevalence of TB, resources must be directed towards the optimisation of active TB treatment and the screening of contacts at risk.

The present analysis demonstrates that the combination of genotyping with the traditional TB screening procedures in the investigation of a cluster, from the perspective of the public health service, allows to save financial and human resources. In the situation presented, it allowed to exclude a link between the different cases and concentrate the resources on the individuals who were really at risk. We would therefore suggest that in countries with intermediate/high TB incidence genotyping should be performed whenever there is a suspicion of a cluster to confirm or exclude a chain of ongoing transmission and thus decide on the size of population to be screened.

FIGURE

IS6110 restriction fragment length polymorphism (RFLP) result of *M. tuberculosis* isolates obtained from four cases of tuberculosis in a shopping centre in Vila Nova de Gaia, Portugal, 2004-5



Legend: Southern blot hybridisation
Lanes 1-4: Four *M. tuberculosis* isolates.
Lane 5: molecular markers: 16.2 kb, 14.2 kb, 12.3 kb, 10.1 kb, 8.1 kb, 7.0 kb, 6.0 kb, 5.0 kb, 4.0 kb, 3.0 kb, 766 kb, 500 kb, 350 kb.

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