S. Manhattan have been described in Europe [4]. To our knowledge, the most recent *S.* Manhattan outbreak before this one occurred in France in 1982 in a hospital nursery, but the source of contamination was not identified [5].

In France, cooperation between the national agencies in charge of human health and food safety allowed us to determine the most probable source of contamination and to take appropriate control measures. To prevent community acquired salmonella infections, the greatest care should be taken in animal husbandry, to prevent contamination, and in slaughterhouses, to prevent cross contamination. Cooking meat and dairy products thoroughly before consumption should be recommended. This advice may prevent not only salmonellosis but also other potentially serious foodborne infections.

References

1. Vaillant V, De Valk H, Baron E, Ancelle T, Colin P and al. Foodborne Infections in France. Foodborne Pathog Dis. 2005;2(3):221-32.
2. Ribot EM, Fair MA, Gautom R, Cameron DN, Hunter SB, Swaminathan B, Barett TJ. Standardization of pulsed-field gel electrophoresis protocols for the subtyping of Escherichia coli O157:H7, Salmonella, and Shigella for PulseNet. Foodborne Pathog Dis. 2006;3(1):59-67.
3. Watabe M, Rao JR, Stewart TA, Xu J, Millar BC and al. Prevalence of bacterial faecal pathogens in separated and unseparated stored pig slurry. Lett Appl Microbiol. 2003;36(4):208-12 .
4. Fisher I, Hald T, Mølbak K, Riewerts Eriksen N. Outbreak of *Salmonella* manhattan infection in Denmark with international implications . Eurosurveillance Weekly. 1998;2(9) 980226. Available from: http://www.eurosurveillance.org/ew/1998/980226.asp#2 .
5. Sarlangue J, Billeaud C, Mégraud F, Martin C. [Neonatal epidemic caused by *Salmonella* Manhattan. Protective role of maternal milk]. Pediatrie. 1982;37(6):461-6. [In French]

ORIGINAL ARTICLES

Outbreak report

INVESTIGATION OF A TUBERCULOSIS CLUSTER AT A JOB CENTRE IN MANCHESTER, UK

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During the summer of 2005, four cases of active tuberculosis from the same occupational setting were investigated in Manchester, UK. The index case had been diagnosed in December of the previous year. At that stage the closest occupational contacts had been screened, all of whom were assessed as being free from active disease, and none had met nationally recommended criteria for chemoprophylaxis for latent tuberculosis infection (LTBI).

In June 2005, two work contacts developed progressive primary extrapulmonary (pleural) TB. Following a detailed risk assessment, the screening programme was widened to include 137 staff who worked at the job centre (employment agency) where the first four cases had been found. This screening programme was based on tuberculin Mantoux testing, CXR and gamma-interferon testing. Of these 137 contacts screened, one additional person was found to have active disease and six others were offered chemoprophylaxis for LTBI. The isolates from the index case and the first two secondary cases were indistinguishable on VNTR-MIRU (variable number tandem repeat - mycobacterial interspersed repetitive unit) typing at 15 loci. No samples were available for testing from the fourth case of active disease.

Management of this incident has benefited from the evolving fields of both genotyping and diagnostic testing for LTBI. However, further research into the epidemiological inferences made through genotyping, as well as the significance of a positive gamma-interferon test in assessing the risk of development of active disease, is still required.

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Introduction

In December 2004 a case of sputum smear positive tuberculosis (TB) was diagnosed in an employee of a job centre (a branch of the United Kingdom government funded employment agency) in North Manchester. The isolate was confirmed to be fully sensitive *Mycobacterium tuberculosis*. In accordance with pre-existing national guidance [1] all household and close occupational contacts were screened. None of the three household contacts had active disease but two were offered chemoprophylaxis on the basis of their tuberculin Heaf test result, age and BCG status [1]. Ten close occupational contacts were all assessed as being free from active disease and none of them met the recommended criteria [1] for chemoprophylaxis for latent tuberculosis infection (LTBI).

In June 2005, however, two of these occupational contacts developed progressive primary extrapulmonary (pleural) TB. Initial screening had revealed Grade II and IV Heaf tests (neither had had BCG vaccination) and normal chest x rays (CXRs). Gamma interferon (GIF) testing was not performed, since at this time it was not available for routine use within Greater Manchester. Given the ages of these contacts, both of whom were adults in their late fifties and early sixties, neither were offered chemoprophylaxis: this was in accordance with national guidance. An incident management team (IMT) was subsequently convened to assess the need to expand screening in the workplace setting.

Methods

In order to guide the extent of further screening, a risk assessment was undertaken. This took into account the presumed infectious period of the index case, the duration of exposure for both staff and clients, the layout of the job centre, social activities, and use of canteens and smoking rooms. The two new cases were carefully assessed and were judged to be at low risk of being infectious, on the basis of their clinical presentation and the absence of any evidence that they were smear positive on sputum microscopy.

The centre was divided into three floors. The index case worked almost exclusively on the ground floor. The exact onset of symptoms

in the index case was uncertain and it was therefore decided to assume a maximum infectious period of three months before the diagnosis.

Given the change in availability of the Heaf test and that the National Institute of Clinical Excellence (NICE)'s draft national guidance on tuberculosis [1] had just been published, a screening programme was undertaken based on tuberculin Mantoux testing, CXR and gamma interferon testing (QuantiFERON-TB Gold In Tube Method). GIF testing was offered to anyone who had a Mantoux positive result, defined as either an induration of 6 mm or more without prior BCG vaccination or an induration of 15 mm or greater with prior BCG vaccination. In turn, a GIF test was considered positive for M. tuberculosis infection if it had a GIF response to either of the TB specific antigens early secretory antigenic target (ESAT) 6 or culture filtrate protein (CFP) 10 that were significantly above the control value obtained using the QuantiFERON-TB Gold In Tube Method. Contacts with a positive GIF test were offered CXR. Those with radiological signs suggestive of TB were clinically assessed to exclude active disease. Those with no radiological signs of TB were diagnosed as having LTBI. The criteria for chemoprophylaxis were diagnosis of latent infection where the benefit was felt to outweigh the risks as judged by the treating physician.

At least six months elapsed between the last known exposure to the index case and further investigations being undertaken after the two secondary cases coming to light. Screening investigations were completed for all contacts over the following three-month period with the condition that anybody eligible for GIF testing was fast-tracked, so that this was undertaken within a fortnight of the tuberculin skin test (TST) being performed.

Screening was initially limited to staff on the ground floor, including repeat screening of the eight initial close contacts who remained disease free. As positive results, on the basis of the GIF tests, were subsequently found in both close and more distant ground floor contacts, screening was extended to all staff in the centre, in accordance with the 'stone in the pond' principle [3]. This principle means that those with the closest, most prolonged contact are screened first and if there is a high rate of infection in these contacts, screening is then extended to those who had a lesser degree of contact. Although it was initially judged necessary to screen only those employees who worked at the job centre during the three months before the diagnosis in the index case, because of the high degree of anxiety being expressed by staff within the centre, the pragmatic decision was taken to extend the screening period up to the time when the two subsequent (non-infective) cases were diagnosed.

All available isolates from cases in this cluster were genotyped by VNTR-MIRU (variable number tandem repeat - mycobacterial interspersed repetitive unit) at the Northern Regional Centre for Mycobacteriology, Newcastle.

Results

Following the methodology outlined above, a total of 137 staff members from all areas of the job centre were screened. Their distribution throughout the job centre is shown in the table together with the distribution of those who were subsequently found to have a positive GIF test.

All of the 30 contacts eligible for GIF testing all were offered it, and an uptake rate of 93% (28/30) was achieved. Two people did not attend for testing, despite repeated attempts to facilitate this, and their general practitioners were informed accordingly. Those testing negative for GIF were given advice about the symptoms of TB, as were the remaining 107 people who had a negative TST.

The actions taken for the eight people who had a positive GIF test are shown in the figure. One of these eight had not been present in the occupational setting during the three month infectious period and furthermore had a previous history of a positive Heaf test before receiving BCG as part of the routine childhood immunisation schedule, and was considered unlikely to benefit from chemoprophylaxis. The other seven positive GIF tests were all in workers who had no other known risk factors and who had either worked on the ground floor of the job centre or had close contact with the index case in the smoking room. One was assessed to have active disease. This person had also been investigated as part of the initial screening earlier in the year. These previous investigations had revealed a Grade II Heaf Test (in the context of no previous BCG) together with a normal CXR and therefore had not been offered chemoprophylaxis, which was at that time in line with national guidance [1]. The remaining six had not previously been investigated, were all asymptomatic and were offered chemoprophylaxis for LTBI.

The isolates from the index case and the first two secondary cases were indistinguishable on VNTR-MIRU typing at 15 loci. No samples were available for testing from the fourth case of active disease.

TABLE

Distribution of staff members screened and results, Manchester, United Kingdom, 2005

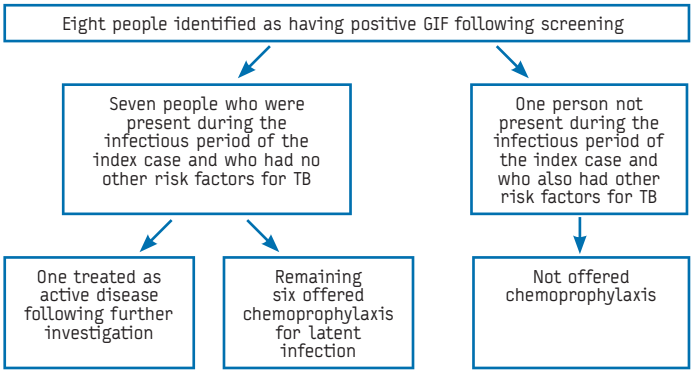
Category of contacts	Ground floor (Close contact with index case)	Ground floor (Distant contact with index case)	Other floors	Total
THOSE SCREENED USING TST				
Number screened with tuberculin Mantoux test	8	15	114	137
Number with positive tuberculin Mantoux test*	2	4	24	30
THOSE SCRENED USING GIF				
Number offered GIF testing**	2	4	24	30
Number who accepted GIF testing	2	4	22	28
Number with positive GIF test result	2	3	3	8
THOSE SCREENED USING CXR				
Number offered CXR	2	3	3	8
Number who accepted CXR	2	3	3	8
Number with abnormal CXR suggestive of active TB	1	0	0	1
FINAL RESULTS OF SCREENING				
Number diagnosed with active TB	1	0	0	1
Number diagnosed with LTBI	1	3	3	7
Number offered chemoprophylaxis	1	3	2	6

* Mantoux positive result is defined as either an induration of 6mm or greater without prior BCG vaccination or an induration of 15mm or greater with prior BCG vaccination

** GIF Testing was offered to all people with a positive Mantoux test defined as either an induration of 6mm or greater without prior BCG vaccination or an induration of 15mm or greater with prior BCG vaccination

FIGURE

Actions taken after identification of positive GIF test following screening, Manchester, United Kingdom, 2005



Discussion

Management of this incident has benefited from new technology in the evolving fields of both genotyping and diagnostic testing for LTBI.

The use of VNTR-MIRU genotyping, in preference to RFLP (restriction fragment length polymorphism), has provided more rapid laboratory evidence [4] of linkage between the cases, therefore offering the potential for real-time epidemiological investigation. However it should be remembered that studies have identified significant limitations in the operating characteristics of these newer techniques, which are likely to compromise the epidemiological inferences so derived [5] and further research is still needed in this area. Furthermore, although in this case the most likely explanation is that the three secondary cases all contracted their disease form the identified index case, it is possible that an unidentified alternative source existed.

Although tuberculin skin tests are the mainstay of the diagnosis of LTBI, they have recently been supplemented by the advent of GIF technology. The GIF test is based on short-term incubation with TB specific antigen and is therefore designed to detect cytokine secretion by primed effector T cells which are present only in true latent infection. This has resulted in improved specificity [4] in the diagnosis of LTBI. The improved specificity of these assays is based on the fact that the genes encoding the secretory proteins' early secretory antigenic target (ESAT) 6 / culture filtrate protein (CFP)10 are absent in the BCG vaccine strain and most environmental mycobacteria [6] .

GIF assays have been shown to have higher sensitivities than TSTs [6,7]. However recognising that the GIF assay is not 100% sensitive it must be recognised that even in the presence of a negative GIF test, the possibility of later developing active disease cannot be excluded. For this reason, all such patients were counselled accordingly told to should contact their general practitioner if at any stage in the future they developed symptoms suggestive of TB.

It is also important to consider the various issues that affect the optimum timing of screening investigations using GIF technology. National guidance indicates that there shold be at least six weeks between exposure and testing with GIF for TST negative contacts of smear positive pulmonary disease [2], since levels of GIF may not appear for at least two weeks after exposure. Although this would not have been an issue in this investigation, the time interval from exposure to taking the specimen for GIF may have influenced the result in another way, since GIF levels may start to wane for people who subsequently progress to active TB [8].

Nevertheless, the improvements in diagnosis of LTBI that results from the use of GIF assays offer the potential for a reduction in the number of cases inappropriately offered chemoprophylaxis, and the potentially serious side effects that this sometimes entails. It meant that chemoprophylaxis could be offered to people older than had been advocated by pre-existing guidance [1], taking into account the age-dependent hepatotoxicity profile of drugs used for chemoprophylaxis. This resulted in an additional five people being offered chemoprophylaxis in this outbreak.

However, the improved confidence that GIF technology offers needs to be treated with caution, given the absence of a gold standard for the diagnosis of LTBI. While GIF testing offers a significant step forward in terms of considering the possibility of a diagnosis of true latent infection, the evidence base for the significance of a positive GIF test in assessing the risk of development of active disease is currently lacking [9].

References

1. Joint Tuberculosis Committee of the British Thoracic Society. Control and prevention of tuberculosis in the United Kingdom: Code of Practice 2000. Thorax. 2000;55(11):887-901.
2. National Institute of Clinical Excellence. Clinical diagnosis and management of tuberculosis, and measures for its prevention and control - second consultation, June 2005. Available from http://www.nice.org.uk/page.aspx?o=271279
3. Veen J. Microepidemics of tuberculosis: the stone-in-the-pond principle. Tuber Lung Dis. 1992;73(2):73-6.
4. National TB Controllers Association/CDC Advisory Group on Tuberculosis Genotyping. Guide to the application of genotyping to tuberculosis prevention and control. Atlanta, GA: US Department of Health and Human Services, CDC; 2004. Available from http://www.cdc.gov/nchstp/tb/genotyping/toc.htm.
5. Allison N. Scott, Dick Menzies, Terry-Nan Tannenbaum, Louise Thibert, Robert Kozak, Lawrence Joseph, Kevin Schwartzman, and Marcel A. Behr. Sensitivities and Specificities of Spoligotyping and Mycobacterial Interspersed Repetitive Unit-Variable-Number Tandem Repeat Typing Methods for Studying Molecular Epidemiology of Tuberculosis. J Clin Microbiol. 2005;43(1):89-94.
6. Davies P.D.O and Drobniewski. Editorial. The use of interferon-gamma-based blood tests for the detection of latent tuberculosis infection. Eur Respir J. 2006; 28:1-3.
7. Richeldi Luca. An update on the diagnosis of tuberculosis infection. Am J Respir Crit Care Med. 2006;174(7):736-42.
8. Rothel JS, Andersen P. Diagnosis of latent *Mycobacterium tuberculosis* infection: is the demise of the Mantoux test imminent? Expert Rev Anti Infect Ther. 2005;3(6):981-93.
9. National Institute for Health and Clinical Excellence. Clinical diagnosis and management of tuberculosis, and measures for its prevention and control, March 2006. Available from http://www.nice.org.uk/page.aspx?o=CG033