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LETTERS

Assessing an outbreak of tuberculosis in an English college population

To the Editors:

In October 2008, a sixth form college student in England, UK, who had had a cough for 2 months was diagnosed with sputum smear-positive cavitatory pulmonary tuberculosis. An investigation led to the identification of 19 cases of active tuberculosis among 2,284 students. Here, we describe the outbreak and investigation into the factors associated with active tuberculosis.

The study population consisted of students enrolled at the college for daytime courses. All participants were aged >16 yrs. Members of staff who directly taught these students were also screened. Between October 2008 and December 2009, students, friends of the index case and staff at the college were interviewed. The interviews were used to collect demographic and clinical information, including symptoms suggestive of tuberculosis. At the same time, a blood sample was drawn from each participant for interferon-γ release assay (IGRA) testing [1, 2]. Following the screening of household contacts and friends of the index case, the students at the school were assessed in concentric circles of decreasing intensity of exposure in three groups (table 1) [3]. Those with a positive IGRA result from any screening round were recalled for chest radiography and clinical review at a respiratory medicine clinic. Preventative therapy was offered to all those with no evidence of active tuberculosis and a positive IGRA result who were <35 yrs of age, according to national guidelines [4]. Detailed results of the IGRA tests are described elsewhere [5].

Where relevant samples were available, following decontamination, direct microscopy and culture using a liquid culture system were performed and, where positive, subsequent testing for sensitivity to standard antituberculosis drugs, followed by 24-locus *Mycobacterium* interspersed repetitive unit–variable-number tandem repeats typing (MIRU-VNTR) [6]. In addition to a detailed clinical review, patients with suspected active tuberculosis had further tests, including computed tomography (CT) and bronchoscopy, where appropriate. Active tuberculosis was defined as any individual with culture-confirmed disease caused by *Mycobacterium tuberculosis* or a clinical presentation consistent with active tuberculosis where the clinician had decided to give a full 6 months of treatment.

Adjusted and unadjusted odd ratios were calculated using logistic regression analysis to investigate factors associated with active tuberculosis. All variables considered *a priori* to be risk factors for tuberculosis, including age, sex, place of birth, ethnicity, contact with the index case and lack of bacille Calmette–Guérin (BCG) vaccination, were modelled. We investigated interaction between risk factors for tuberculosis using the likelihood ratio test. Data were analysed using the statistical software STATA (version 11; StataCorp, College Station, TX, USA).

The median age of the students was 17.8 yrs (interquartile range (IQR) 17.3–18.5 yrs) and 1,055 (46.2%) were male. Among the students, 49.6% were BCG-vaccinated, 90.2% were of white ethnicity and 18.8% had recently travelled to a high-incidence country. The participants travelled to a number of countries, including China, Russia, India, Bangladesh and several countries in sub-Saharan Africa; 400 (17.5%) had a positive IGRA. The median age of the staff was 46.8 yrs (IQR 38.5–55.3 yrs). No active tuberculosis cases were diagnosed among staff members.

The index case attended the college for <3 weeks during September 2008. Excluding the index case, 19 cases of active tuberculosis were diagnosed and treated. Eight cases were culture confirmed as *M. tuberculosis*; seven cases were confirmed as having an indistinguishable 24-locus MIRU-VNTR genotype (42234 2742511334 422423255) as the index case; a further case had 23 identical digits with a missing 24th digit. Of the eight culture-confirmed cases, two were sputum smear and culture positive; one case was sputum smear-negative but culture positive; four cases were positive on culturing washings obtained from bronchoalveolar lavage; and one case was positive on culture of pleural biopsy material. The two sputum smear-positive cases were not symptomatic while attending the college. The diagnosis of cases who were not microbiologically confirmed was largely based on radiological findings, including CT. In total, nine cases were asymptomatic.

During the first two rounds of screening, nine cases of active tuberculosis were identified (including three who were also friends or extended family). Two cases outside the groups screened then presented clinically, prompting a third round of screening that identified a further eight cases. The yield therefore was 3, 2 and 0.5% in groups 1, 2 and 3, respectively. table 1 shows the characteristics of all cases. All isolates were fully susceptible to first-line antituberculosis drugs. The median age of the active tuberculosis cases was 17.2 yrs (IQR 17–18.3 yrs) and 12 (63.2%) out of 19 were male. In the fully adjusted model (table 2), only age was associated with the risk of active tuberculosis, with younger students being at a higher risk of tuberculosis (OR 0.23, 95 CI 0.07–0.75).

This study found that the only independent risk factor for active tuberculosis was age. Although the incidence of tuberculosis has increased in the UK over the last two decades [7], the rate of active tuberculosis identified in this college (875 cases per 100,000 persons) is several times higher than the age-equivalent rate for England (14.6 cases per 100,000). A limitation of the study was the relatively small number of active tuberculosis cases, reducing our ability to investigate the risk factors for active disease. The time taken to screen the entire college possibly contributed to the emergence of secondary cases.

TABLE 1 Clinical characteristics of active tuberculosis cases

Case	Clinical details	Group[#]
1	Symptoms started July 2008 Smear and culture positive Treatment started October 2008	Index case
2	Friend of index case No symptoms IGRA positive December 2008 CXR: right mid-zone nodules CT scan showed multiple small cavities BAL smear and culture negative Treatment started November 2009	Group 1
3	Cough and sputum December 2008 Smear and culture negative CXR and CT: small nodules right mid-zone Started treatment February 2009	Group 1
4	No symptoms Smear negative IGRA positive BAL culture positive, same genotype Treatment started April 13, 2009 Treatment completed October 2009	Group 2
5	Smear negative IGRA positive CXR in April 2009: right upper zone multiple cavities BAL culture positive, same genotype Treatment started April 2009	Group 2
6	In same tutor group as another case IGRA positive Onset of cough and weight loss in April 2009 Sputum smear negative Culture positive, same genotype CXR normal Treatment started May 2009	Group 2
7	No symptoms IGRA positive CXR February 2009 and CT scan: left hilar gland and left hilar shadow Treatment started May 2009	Group 2
8	No symptoms IGRA positive CXR and CT scan: left upper zone shadowing BAL culture negative Treatment started June 2009	Group 2
9	Cough, fever, night sweats and weight loss since December 2008 GP presentation Had indeterminate IGRA in April 2009 Pleural biopsy histology: caseating granulomata PCR negative Treatment started May 2009	Group 3
10	Cough, weight loss CXR and CT: left hilar glands Smear and culture negative Extended family of index case Treatment started April 2009	Group 3
11	Eye symptoms from June 2009 Choroid tubercles seen IGRA positive CXR normal Treatment for eye TB started July 2009	Group 3
12	No symptoms CXR parenchymal changes and CT scan showed left apex changes BAL smear negative and culture positive, same genotype Treatment started September 2009	Group 3
13	Attended school for a few hours in January and May 2009 Diagnosed through GP with cough, sputum, haemoptysis and night sweats which started in April 2009 Smear and culture positive, same genotype Treatment started August 27, 2009	Group 3
14	No respiratory symptoms Cervical node biopsy in Hong Kong, China Smear and culture not performed Histological diagnosis Treated in Hong Kong from April 2009	Group 3
15	Cough, night sweats from June 2009 IGRA positive CXR: cavities right upper lobe, sputum smear and culture negative, refused bronchoscopy Treatment started July 2009	Group 3
16	No symptoms CT: left upper zone early cavitation BAL smear negative and culture positive, same genotype Treatment started July 2009	Group 3
17	Diagnosed in July 2009 with lymph node disease CT scan: left lower lobe changes BAL: smear and culture negative Treatment started July 2009	Group 3
18	Cough, night sweats, weight loss IGRA positive, pleural biopsy Smear positive PCR negative CXR: effusion Culture positive, same genotype except last digit missing	Group 3
19	Cough, weight loss in November 2008 Attended college 2007–2008 CXR and CT: cavities and enlarged hilar nodes Sputum smear and culture positive, same genotype Treatment started April 2009	Other
20	Fever, night sweats, weight loss, no cough from January 2009 Friend of index case but attended a different college IGRA positive CXR and CT scan: hilar node and parenchymal changes; left lower lobe apical nodule Treatment started July 2009	Other

IGRA: interferon-γ release assay; CXR: chest radiography; CT: computed tomography; BAL: bronchoalveolar lavage; GP: general practitioner. [#]: group 1 included those who shared classroom groups with cumulative exposures >2 h with the index case and friends of the index case, group 2 included students who attended the same general studies group with exposure time between 1 and 2 h in a large hall setting, and group 3 included the rest of the college.

TABLE 2 Univariable and multivariable analysis of the factors associated with active tuberculosis among 2,284 students

Characteristic	Median or n/N	Univariable	Multivariable	
		OR (95% CI)	OR (95% CI)	p-value#
Age yrs	17.2	0.27 (0.11–0.67)	0.23 (0.07–0.75)	0.011
Sex				
Female	7/19	1	1	0.488
Male	12/19	0.89 (0.73–4.90)	1.50 (0.40–5.55)	
UK born¶				
No	2/19	1	1	
Yes	17/19	0.65 (0.15–2.87)		
Travel to high-burden country				
No	14/19	1	1	0.200
Yes	5/19	1.81 (0.63–5.17)	2.20 (0.55–8.84)	
White ethnicity				
No	7/19	1	1	0.055
Yes	12/19	0.20 (0.07–0.53)	0.26 (0.05–1.43)	
Group				
1		1	1	0.371
2		0.72 (0.19–2.72)	2.14 (0.23–20.04)	
3		0.18 (0.06–0.59)	0.60 (0.07–4.96)	
BCG				
No	15/19	1	1	0.780
Yes	4/19	0.38 (0.12–1.25)	1.06 (0.22–5.23)	

BCG: bacille Calmette–Guérin. #: likelihood ratio test; ¶: perfectly predicts outcome in the multivariable model.

While this may, in part, question the ''stone in the pond'' approach [8], we contend that this incident is unusual. A time-to-event analysis would have been more appropriate to account for right censoring. The lack of dates of contact with infectious cases precluded hazard analysis.

We conclude that this outbreak resulted in transmission within the college, as evidenced by indistinguishable DNA fingerprints of the *M. tuberculosis* strains. Public health services should ensure the prompt detection and management of such outbreaks.

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