

mycobacteria. Furthermore, limitations of our study include the single-centre design. Our observations may have been different if our NCFBr centre facilities were shared with our regional CF clinic. We therefore advocate further multicentre studies to delineate the cross-infection risks.



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Cross-infection with *Pseudomonas aeruginosa* is rare in non-cystic fibrosis bronchiectasis

<http://ow.ly/sjvKz>

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Received: Sept 25 2013 | Accepted: Oct 16 2013 | First published online: Oct 31 2013

Support statement: A. De Soya acknowledges a Higher Education Funding Council for England senior lectureship and funding from the National Institute for Health Research Newcastle Biomedical Resource Centre for Ageing and Chronic Disease.

Conflict of interest: Disclosures can be found alongside the online version of this article at www.erj.ersjournals.com

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Eur Respir J 2014; 43: 900–903 | DOI: 10.1183/09031936.00167813 | Copyright ©ERS 2014

Rapidly progressing tuberculosis outbreak in a very low risk group

To the Editor:

We report an unusual tuberculosis (TB) outbreak, centred on a professional basketball team in Montevideo, Uruguay, a country with a low TB incidence (21 cases per 100 000). Uruguay has a relatively high income (2010 gross domestic product USD14 338 *per capita*), a low HIV prevalence (305 cases per 100 000) and a very low rate of multidrug-resistant TB (0.24%) [1]. In August 2008, a young male member of the basketball team was diagnosed with TB, with positive microscopic examination and Ziehl-Nielsen staining of a sputum sample (graded 1). Chest radiography indicated a bilateral pulmonary form with cavities. TB was bacteriologically confirmed 20 days later, with a *Mycobacterium tuberculosis* isolate pan-susceptible to antituberculous drugs. The patient was compliant with first-line treatment (2HRZ/4H₂R₂; 2 months daily

treatment with isoniazid, rifampicin and pyrazinamide followed by 4 months of twice weekly isoniazid and rifampicin) and was cured. However, following this index case six other team members, who were living at the same basketball clubhouse during the week, the brother of the index case, a team member's girlfriend and two other friends were successively diagnosed with TB over the next 29 months (fig. 1). The diagnosis was confirmed by chest radiography indicating unilateral (n=3) or bilateral (n=1) forms without cavity, bilateral forms with cavity (n=2), and pleural forms (n=4), as well as by positive smear microscopy (n=6) and/or culture (n=8) (with a pan-susceptible isolate obtained from sputum (n=5), pleural biopsy (n=2) or bronchial lavage (n=1)) or elevated adenosine deaminase levels in pleural fluids (n=2). All patients were immunocompetent, athletic and wealthy, of Caucasian ethnicity and born in Uruguay. No drug abuse, alcoholism, HIV or other comorbidity factor was detected for any of them. They were aged between 17 and 23 years. Nine of the secondary cases were successfully cured by first-line treatment. However, the eighth consecutive secondary case to be diagnosed, more than 2 years after the index case, died of respiratory failure as a result of very advanced TB in an intensive care unit, despite starting treatment immediately.

Standard 24-locus variable-number of tandem-repeat typing [2] demonstrated identical genotypes among the 10 isolates obtained (including an additional, more recent case; see later) and, thus, fully supported the clonality of the outbreak, caused by a strain of branch II of the Latin-American Mediterranean lineage [3, 4] (fig. 1).

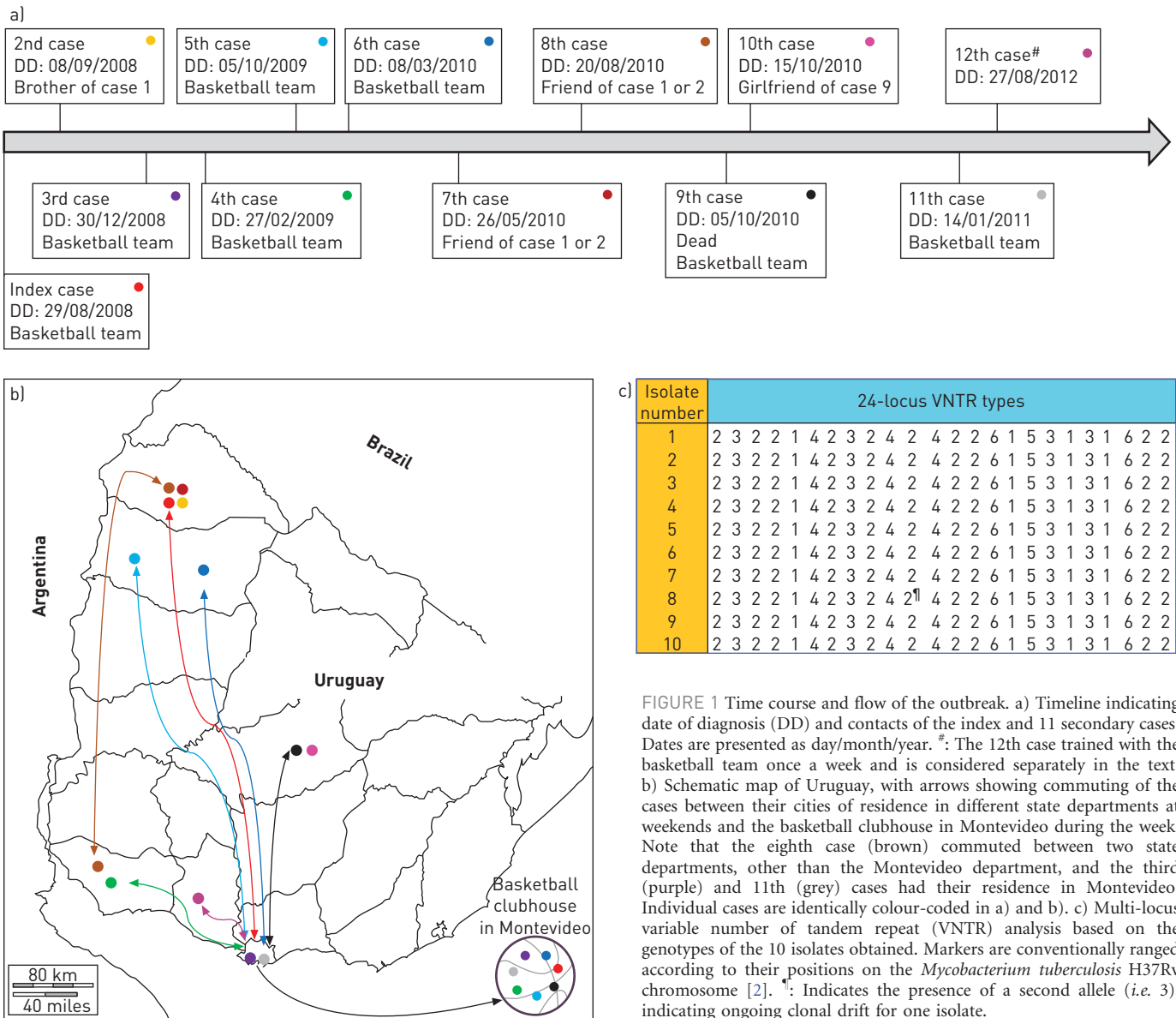


FIGURE 1 Time course and flow of the outbreak. a) Timeline indicating date of diagnosis (DD) and contacts of the index and 11 secondary cases. Dates are presented as day/month/year. #: The 12th case trained with the basketball team once a week and is considered separately in the text. b) Schematic map of Uruguay, with arrows showing commuting of the cases between their cities of residence in different state departments at weekends and the basketball clubhouse in Montevideo during the week. Note that the eighth case (brown) commuted between two state departments, other than the Montevideo department, and the third (purple) and 11th (grey) cases had their residence in Montevideo. Individual cases are identically colour-coded in a) and b). c) Multi-locus variable number of tandem repeat (VNTR) analysis based on the genotypes of the 10 isolates obtained. Markers are conventionally ranged according to their positions on the *Mycobacterium tuberculosis* H37Rv chromosome [2]. #: Indicates the presence of a second allele (i.e. 3), indicating ongoing clonal drift for one isolate.

Despite control programmes, large clonal TB outbreaks can develop even in low incidence countries, reflecting active ongoing disease transmission [5, 6]. In such settings risks of TB and large, steadily expanding TB case clusters are typically concentrated in socioeconomically underprivileged groups, with well-identified associated risk factors such as alcohol abuse, injectable drug use and homelessness [7].

Our report points to a situation of particularly rapid TB spread in an atypical population category, thought to be at very low risk for TB, without timely implementation of appropriate TB control measures. In the latter category, the rapid spread of TB was probably driven, in part, by an especially acute risk of infection due to reiterated close contacts and strong breathing during intensive daily practice of indoor basketball and to sharing dormitories at the basketball clubhouse during the week. Other factors probably include the increased chance of progression from infection to disease in young, tall, thin adults as pointed out by old reports [8, 9], on the basis of the age and athletic profile of the patients involved and the estimated proportion of infected close contacts who declared the disease within the 2–3-year period after exposure. Indeed, 18 close daily contacts (*i.e.* basketball team members and close friends) deemed to be most at risk were identified for the source case, comprising nine of the 11 secondary TB cases. Out of the nine contacts without a TB diagnosis, four had a positive TB skin test (TST) of ≥ 6 mm induration, suggestive of TB infection, and one with a negative result of 0 mm, while TST results were unavailable for the remaining four. The TB infection rate (TB cases and infected individuals) among the contacts most exposed to the index case was, thus, estimated to be between 72% (13 out of 18) and 94% (17 out of 18), depending on the assumed status of the contacts with missing data. Accordingly, the proportion of infected close contacts who progressed to disease within 2–3 years ranged between 53% (nine out of 17) and 69% (nine out of 13). This elevated disease attack rate sharply contrasts with the lifetime risk of developing active TB, estimated to be <10% among infected individuals in the general population.

Clearly and importantly, as the isolates obtained were all fully sensitive to drugs, all the secondary cases (including the fatal case) were theoretically preventable by timely application of effective contact tracing coupled with chemoprophylaxis. Most patients had their permanent residence in different cities in five different departments/provinces of the country (fig. 1). The index case was diagnosed in the capital, Montevideo, and he then immediately returned to his hometown, where his family live, to receive treatment. His familial contacts were investigated, leading to diagnosis of TB in his brother 1 month later, while the other family contacts received chemoprophylaxis.

Such measures were implemented much more belatedly for the other contacts involved, although the link with the basketball team was identified from the beginning. As these individuals were cohabiting with the index case only from Monday to Friday (*i.e.* at the basketball clubhouse) but spent their weekends with their families, they were defined as working contacts. As per the guidelines of the national TB control programme, the list of these contacts was requested from the employer (*i.e.* the professional basketball club) and not from the index case. However, this list was sent very late and, furthermore, the case was not properly made for obtaining it as quickly as possible. In addition, even after the list was received, some contacts did not respond to investigator calls and/or refused to receive chemoprophylaxis, as has been frequently seen elsewhere [10].

As a predictable consequence of this delayed implementation of control measures, a further, 11th secondary case (fig. 1) was diagnosed in August, 2012 (and has now successfully completed treatment), corresponding to a 17-year-old individual who was training with the team once a week. Strain typing data showed that this case indeed represented an extension of the same outbreak.

It is noteworthy that investigation of 23 other, more distant contacts of the source case did not reveal additional TB cases. This absence of extension beyond the circle of the basketball team (including the source case's brother and two close friends with the same low risk profiles; see earlier) tends to suggest that the outbreak characteristics are related to the specific characteristics of the host group, rather than to an increased virulence of the *M. tuberculosis* strain involved.

Knowing the specific outbreak potential in such a group, with the benefit of hindsight, we wish we had triggered more intensive contact investigation shortly after the first case, and had offered preventive therapy to all infected contacts, such as that recommended by European standards for TB care [11], by informing them about the specially increased risk of progression to active disease in this specific context. Such intensive interventions are necessary to achieve TB elimination, given the low incidence setting of this micro-epidemic [10].



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Tuberculosis can rapidly spread among individuals thought at low risk, without timely application of control measures <http://ow.ly/qvuDS>

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Received: Aug 30 2013 | Accepted after revision: Sept 29 2013 | First published online: Oct 10 2013

Conflict of interest: Disclosures can be found alongside the online version of this article at www.erj.ersjournals.com

Acknowledgements: C. Rivas (Comisión Honoraria de Lucha Antituberculosa y Enfermedades Prevalentes, Montevideo, Uruguay) is thanked for support and M. Haddad (Outbreak Investigations Team, Division of Tuberculosis Elimination, CDC, Atlanta, USA) for insightful discussion.

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Eur Respir J 2014; 43: 903–906 | DOI: 10.1183/09031936.00150413 | Copyright ©ERS 2014

Severe pulmonary embolism decreases plasma L-arginine

To the Editor:

Measurements from humans and animal models with pulmonary embolism (PE) have demonstrated increases in multiple vasoconstrictive molecules, including prostaglandins, platelet-activating factor and leukotrienes [1]. Nitric oxide (NO), produced tonically by vascular endothelial nitric oxide synthase (eNOS), plays a pivotal role in maintaining a normal pulmonary vascular resistance under these conditions [2]. These facts underlie the construct hypothesis that in different subjects, PE can obstruct the same degree of pulmonary vasculature but manifest widely different pulmonary arterial resistances.

Preliminary evidence from animal models and humans suggests that acute PE is associated with intravascular haemolysis, related to the severity of PE [3–8]. Intravascular haemolysis liberates haemoglobin and diffusible haem, both of which directly bind NO. Ruptured erythrocytes also release large amounts of the enzyme arginase-1, which cleaves the eNOS substrate L-arginine, producing urea and L-ornithine.

We hypothesised that patients with acute PE that causes significant tricuspid regurgitation (TR) will have acutely increased plasma concentrations of arginase-1, decreased L-arginine and increased asymmetric dimethylarginine (ADMA) compared with patients who have mild PE without TR as well as patients without PE.