Occupational tuberculosis transmission despite minimal nosocomial contact in a healthcare worker receiving anti-TNF therapy

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A healthcare worker (HCW) receiving anti-TNF therapy presented with a second episode of tuberculosis. The *Mycobacterium tuberculosis* isolated differed from the first episode by whole-genome sequencing, but matched a patient's isolate which, despite them having had minimal contact, proved nosocomial transmission. Careful occupational risk assessment of HCWs receiving immunosuppressants is advised.

A 37-year-old female, HIV negative HCW with a history of ankylosing spondylitis requiring the anti-TNF agent Etanercept presented with an abrupt onset of wheeze and fever. Examination and a chest radiograph suggested right upper lobe consolidation prompting antibiotic treatment for community acquired pneumonia. Seven months prior to this she recalled a self-resolving, several week history of dry cough. Eight years previously, after returning from voluntary healthcare work in Africa, she had drug sensitive tuberculosis (TB), for which she received 6 months standard treatment. She was left with residual mild lower lobe bronchiectasis.

On this presentation, a sputum sample was negative for acid-fast bacilli on smear microscopy but an Xpert MTB/RIF (Cepheid, CA, USA) molecular test was positive for *Mycobacterium tuberculosis* (M.tb), and negative for genetic mutations associated with rifampicin resistance. Antibiotics were stopped and the patient was commenced on standard anti-TB treatment of rifampicin, isoniazid, ethambutol and pyrazinamide. Drug sensitive M.tb was isolated after 14 days growth in liquid MGIT culture (Bactec MGIT™ 960, Becton Dickinson (BD) Microbiology Systems, Sparks, MD, USA).

As part of the epidemiological investigation, MIRU-VNTR (Mycobacterial Interspersed Repeat Unit-Variable Number Tandem Repeat) genotyping was performed which identified an isolate that differed in 9 loci when compared to her previous isolate, thereby excluding reactivation of her previous TB (figure 1a). However, it did match a previously unique isolate in the National Mycobacterial Reference Laboratory (NMRL) database which had been identified in a person living with HIV (PLWH) diagnosed 2 years previously with smear positive drug sensitive pulmonary TB. Whole genome sequencing (WGS), using Illumina HiSeq platform (Illumina, San Diego, USA), confirmed the findings of the routine typing with 1 single nucleotide polymorphism (SNP) difference between the PLWH and HCW isolate, and refuted any link with the HCW's previous M.tb isolate which differed by 422 SNPs (figure 1b; generated using PopART Population Analysis with Reticulate Trees, New Zealand).

At the time of his diagnosis, the PLWH had been admitted to hospital and placed in a bay on the general Infectious Diseases ward. On the day of admission, a sputum sample was smear-microscopy positive for acid fast bacilli (smear grade 1+) and respiratory infection control practices were instituted immediately, including respiratory precautions with FFP3 masks for prolonged patient contact and aerosol-generating procedures in a negative pressure isolation room. Extensive investigation was undertaken to assess exposure to staff, patients and contacts and adherence to infection control procedures.

During this patient's admission, the HCW had worked in the hospital and on the Infectious Diseases ward in a largely managerial role. The HCW was not involved in routine day-to-day patient care. There was no reported face-to-face contact with the index patient prior to, or after, patient isolation. Reviewing shift patterns and work diaries, the overlap between the two cases on the same ward was minimal and estimated to be less than 30 minutes. No other HCW developed active TB and there were no Tuberculin Skin Testing (TST)/Interferon Gamma-Release Assay (IGRA) conversions to suggest transmission to other HCW or social contacts.

Nosocomial transmission of TB has been well-documented in seminal experiments conducted by Riley et al in the 1950s, where guinea pigs in air ventilation ducts from a TB ward were frequently infected (1). HCWs are often affected, with epidemiological surveys routinely identify HCWs as being at higher risk of TB, even in low incidence settings (2, 3). Infection control measures to reduce

occupational TB transmission in the UK, including the use of isolation rooms, negative pressure ventilation and FFP3 masks for aerosol-generating procedures, are only partially effective, and healthcare workers remain at increased risk (4). The WHO (World Health Organisation) recommends four levels of infection control measures to effectively control TB, including managerial, administrative, and environmental controls and personal respiratory protection, but these are often poorly implemented in resource-limited settings (5).

There are scant data on the occupational risk of TB in HCW receiving anti-TNF therapy, although these drugs increase the relative risk of TB up to 25-fold in the general population (6). They are often used as disease modifiers in rheumatological and other inflammatory disorders, and so are frequently introduced early in the clinical pathway. The Joint Tuberculosis Committee of the British Thoracic Society provided guidance to reduce the risk of TB in patients commencing anti-TNF therapies (7). They recommended that active TB should be excluded, or treated for at least 2 months prior to commencing anti-TNF treatment. Patients with latent TB should be offered chemoprophylaxis where the risk of TB exceeded that of drug-induced hepatitis. This favours treating HCW at any age, given their higher risk of active TB. They proposed that patients such as this HCW, with a history of previous adequately treated TB, should be monitored clinically every 3 months during anti-TNF therapy; those with respiratory symptoms should have with a chest radiograph and sputum examination for TB performed.

Given the increased risk of TB during anti-TNF therapy, occupational restrictions on HCWs are sensible, though there is little evidence on which to base what may be career-limiting decisions. Prior to the advent of molecular typing, occupational transmission events were frequently misclassified using routine epidemiological investigations. One study of presumed occupationally acquired TB in Denmark, a low TB burden country, indicated that one third of these cases were in fact 'unlikely' on the basis of Restriction Fragment Length Polymorphism (RFLP) and/or MIRU typing (8). WGS offers unrivalled resolution to confirm or refute transmission events, with greater discrimination than MIRU-VNTR, and identify missing links in chains of transmission, even where people in the chain remain unknown (9). WGS may also be able to demonstrate "directionality" of transmission given the biological rarity of backward mutations (10). The technology is limited by the current lack of national and international databases of strains – such that in this case we are unable to investigate whether the unique isolate from the PLWH was part of a larger international genetic grouping.

The minimal contact between the patient and HCW that led to transmission, despite standards of infection control expected in a specialist Infectious Diseases unit in a high income country, highlights the challenge in protecting HCW with immuno-compromise and is a concern. In resource limited settings, the occupational risk of TB to HCWs is greater and TB infection control measures more challenging (5). This is compounded in areas where the prevalence of HIV co-infection is higher. A case-control study of HCWs in South Africa, a country with a very high prevalence of HIV in the general population at 17%, identified HIV as conferring a greater than 6-fold risk of occupational TB compared to non-HIV infected HCWs (11). The additional challenges of poor outcomes in HCWs managing drug resistant TB, plus the impact on the health and financial well-being of their families, raise further ethical issues surrounding the sociopolitical aspects of infection control and highlight the responsibility of the state to protect and support those HCW who place themselves at risk in the line-of-duty. Moreover, the extension of TB care to community and home-based settings is likely to further complicate infection control procedures, and should be considered in future efforts to protect HCW (12).

This case highlights the risk of occupational TB transmission in a HCW receiving anti-TNF therapy after minimal exposure, despite adherence to reasonable infection control precautions in a resource rich setting. Further data are required to quantify the occupational risk of TB in HCWs receiving anti-TNF therapies and so provide the evidence for sensible and safe infection control policies.

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Figure 1

a. MIRU-VNTR typing healthcare worker (HCW) and patient living with HIV (PLWH) *Mycobacterium tuberculosis* isolates compared to HCW previous historical isolate; differences highlighted in grey

Isolate	**MIRU-VNTR typing**																						
PLWH	2	1	4	3	3	2	4	2	2	6	1	6	3	2	1	4	3	4	4	1	5	2	-	2
HCW	2	1	4	3	3	2	4	2	2	6	1	6	3	2	1	4	3	4	4	1	5	2	7	2
HCW (2006)	2	**2**	**2**	3	**5**	2	4	2	2	6	-	**4**	3	2	**3**	4	3	4	4	**2**	**1**	**1**	**3**	2

b. Representation of *Mycobacterium tuberculosis* isolates identified by whole genome sequencing; purple circles represent patient and HCW TB isolates, numbers in brackets show single nucleotides variations (SNPs) between isolates , supporting transmission between PLWH and HCW with isolates (1 SNP) and distinct from HCW workers previous episode (422 SNPs)