Title: Investigating a tuberculosis cluster among Filipino healthcare workers in a low incidence country

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Summary

Setting

Nearly 8% of adult tuberculosis (TB) cases in England, Wales and Northern Ireland (EW&NI) occur in healthcare workers (HCWs), the majority of whom are from high TB incidence countries.

Objectives

To determine if a TB cluster containing multiple HCWs was due to nosocomial transmission.

Methods

A cluster of TB cases notified in EW&NI from 2009-2014, with indistinguishable 24-loci MIRU-VNTR profiles, was identified through routine national cluster review. Cases were investigated to identify epidemiological links and occupational health (OH) information was collected for HCW cases. To further discriminate strains typing of eight additional loci was conducted.

Results

Fifty-three cases were identified; 22 were HCWs. The majority (43), including 21 HCWs, were born in the Philippines. Additional typing split the cluster into three sub-clusters and seven unique strains. No epidemiological links were identified beyond one household and a common residential area. HCWs in this cluster received no or inadequate OH assessment.

Conclusions

The MIRU-VNTR profile of this cluster probably reflects common endemic strains circulating in the Philippines with UK reactivation. 32-loci typing showed 24-loci MIRU-VNTR failed to distinguish strain diversity. The lack of OH assessment indicates latent TB could have been identified and treated, preventing active cases occurring.

INTRODUCTION

Tuberculosis (TB) in healthcare workers (HCWs) presents the possibility of nosocomial transmission to colleagues and patients. Evidence of such transmission has been identified in many low and middle income countries[1–3] with HCWs at higher risk of TB compared with the general population in high TB incidence countries.[2–4] In low incidence countries, such as the UK, TB mainly affects non-native born HCWs who originate from high TB incidence countries.[5] Despite the considerable annual number of TB cases notified in HCWs in the UK, little evidence of transmission within healthcare settings, with only a few isolated incidents in recent years, exists.[5]

In recent decades there has been an expansion, by both the National Health Service (NHS) and private sector healthcare employers, in recruiting HCWs to the UK from abroad,[6–8] many of whom originate from high TB incidence countries.[8,9] UK guidance for HCW occupational health (OH) TB assessment sets out the requirements for pre-employment checks, including latent TB infection (LTBI) testing, in those from high TB incidence countries.[10,11]

As part of TB control strategies in England, Wales and Northern Ireland (EW&NI), the National TB Strain Typing Service (TB-STS) was established in 2010, prospectively strain typing all culture-confirmed cases[12] allowing the identification and investigation of clustered cases.[13] Clusters may occur as a result of recent transmission or reactivation of common strains. Approximately 60% of TB cases in England are in a cluster, with the majority of clusters consisting of only 2 cases.[14]

In 2010, a cluster of TB cases containing a high number of HCWs born in the Philippines (a high TB burden country with an incidence of 322 (95% CI 277-370) per 100,000 population in 2015),[15] was identified. A national cluster investigation was initiated to seek epidemiological links between cases,[13] determining whether transmission had occurred in a healthcare setting requiring public health action. It is known that 24-loci MIRU-VNTR typing may not adequately distinguish between strains,[16,17] and at the time of this cluster investigation 32-loci MIRU-VNTR typing was trialled to provide further discrimination to confirm or refute transmission.[18,19] Occupational health practises were also reviewed through case interviews to determine national guidance had been followed.

This paper presents molecular and epidemiological findings from the investigation of this cluster and reviews the public health implications associated with current OH practices for TB detection.

STUDY POPULATION AND METHODS

Data sources

TB cases in EW&NI are notified to the Enhanced Tuberculosis Surveillance System (ETS) which collects demographic and clinical information, including occupation.[14] Culture-positive

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Mycobacterium tuberculosis complex isolates from Mycobacterium Reference Laboratories in EW&NI, including data on drug susceptibilities and MIRU-VNTR strain types, are matched to notifications allowing the identification of clusters of cases with indistinguishable 24-loci MIRU-VNTR profiles in real-time. PHE has authority under the Health and Social Care Act 2012 to hold and analyse national surveillance data for public health and research purposes.

Cluster definition

Following the launch of the TB-STS, between January 2010 and December 2011, a cluster was defined as at least two cases with indistinguishable 24-loci MIRU-VNTR strains which included strains with a maximum of two missing loci and at least one strain with a full 24-loci profile.[20] From 2012 onwards, the definition was revised to include isolates with a maximum of one missing loci.[13] Prior to the TB-STS 15-loci MIRU-VNTR typing occurred at the request of a clinician or public health specialist.

Additional strain typing

In addition to the standard 24-loci MIRU-VNTR strain typing[21] the National Mycobacterium Reference Laboratory (NMRL) used an experimental panel to type eight additional loci; 1982, 2074, 2163a, 3232, 3239, 3336, 3820 and 4120.[18] The aim of which was to provide further discrimination of strains[19] within a cluster to attempt to confirm or refute transmission since 24-loci MIRU-VNTR was suspected to be insufficient.

Cluster investigation

In 2010, a MIRU-VNTR profile 4646424326223321A8323271 (designated cluster A1018 in EW&NI) was identified during routine national cluster review and investigated according to national guidance using a standard cluster investigation questionnaire to obtain additional lifestyle and social network information.[13] This included details of the cases' current and past: locations of work, worship, socialising, imprisonment, hostels/homeless shelters, and hospital stays, known exposure to TB, and travel abroad or receiving visitors from abroad. This information was used to investigate epidemiological links between cases from 2010 until 2012, after which time cluster investigation was suspended but review of the cluster continued (Figure 1). TB cases notified in 2009 with indistinguishable 15-loci MIRU-VNTR strain types were retrospectively typed to 24-loci where possible and all included in the investigation. Isolates processed at the NMRL had eight additional loci analysed to distinguish strains within the cluster (Figure 1), this was not available for those processed at Regional Reference Laboratories.

Filipino TB case comparison

All clusters containing cases born in the Philippines were described by lineage and size.

To retrospectively identify demographic and clinical characteristics associated with Filipino cases identified as part of A1018, cases notified between 2010 and 2014 with a strain type of at least 23-loci and born in the Philippines were compared to A1018 cases. Characteristics were compared using a chi-squared test with a p-value of 0.05 denoting statistical significance.

Healthcare worker occupational health assessment

HCW cases in A1018 included in the cluster investigation were also interviewed by TB service staff to elicit their history of OH assessment. This included; if the case worked in a healthcare setting in the UK, if the workplace(s) was a NHS or private healthcare establishment, the type of workplace(s) (nursing home, hospital, primary care), and if the case received OH assessment. If OH assessment had occurred, the method (BCG scar check, symptom check, LTBI testing) and the results were collected.

RESULTS

Cluster summary

Fifty-three TB cases were identified in cluster A1018 (Figure 1); the majority were born in the Philippines (82.7%, 43/52). A high proportion of cases were HCWs (48.9%, 22/45) with 95.4% (21/22) were born in the Philippines (Table 1). Of the remaining cases, 7.5% (4) were born in the UK, 5.6% (3) in India, 1.9% (1 – the only non-Filipino born HCW) in Sri Lanka and 1.9% (1) in New Zealand (Table 1). 56.6% (30) of cases were female; 77.3% (17/22) of HCWs were female, while only 41.9% (13/31) of non-HCWs were female. Although the majority of cases lived in London and South East England, cases were geographical dispersed.

BCG vaccination status was known for 69.8% (37) of the cases, of which 78.4% (29) were vaccinated. All HCWs were vaccinated where vaccination status was known (68.2%; 15/22). Overall 47.2% (25/53) of cases had only extra-pulmonary disease, and among HCWs was 54.5%.

Cluster investigation

The 39 cases which occurred between 2009 and 2012 were investigated; 27 cases had a cluster questionnaire returned to the investigation team. This included 19 HCWS, 16 of which had a questionnaire. Two cases were identified as household contacts. Four cases (three UK born and one from New Zealand) were resident and/or had socialised in the same area of North West London but no common venues were identified. Two of the UK born cases from North West London lived in the Philippines prior to their TB diagnosis. No other epidemiological links (shared geographical or social settings) were identified between cases. Specifically, none of the HCWs were identified as having worked in the same healthcare establishment.

Further typing to 32-loci was conducted on all 27 isolates from the NMRL; results were obtained for 20 isolates. This split the cluster into three sub-clusters of; four cases (sub-cluster 1), seven cases (sub-cluster 2) and two cases (sub-cluster 3) and a number of unique strains (seven cases) (Figure 2). Results showed that of the four cases with links to North West London, two had unique strains; including one with travel links to the Philippines and two were in sub-cluster 1; one with travel links to the Philippines and the other without travel links (Figure 2) suggesting it is likely community transmission occurred, although an epidemiological link was not confirmed. Eight HCWs had additional typing; four had unique strains, three were in sub-cluster 2 and one was in sub-cluster 1 (Figure 2). 32-loci typing was not carried for the household contacts.

Following no identified nosocomial transmission based on the findings of cluster investigation and 32-loci typing results, the active cluster investigation was suspended, but the cluster remained under review until the end of 2014.

Filipino TB case comparison

Between 2010 and 2014, 51.1% (164/321) of TB cases born in the Philippines clustered with at least one other TB case. Cases were in 57 different clusters, with 34 containing more than one TB case born in the Philippines of which all but one cluster (Euro-American) were of Indo-Oceanic lineage. Nineteen of these clusters contained cases only from the Philippines (all contained only a small number of cases; 16 with 2-4 cases, 3 with 5-6 cases) and in the other 15 clusters at least 60% of all cases were from the Philippines (4 with 2-4 cases, 7 with 5-9 cases, 3 with 11-14 cases and 1 with 34 cases – this was A1018).

Analysis carried out to examine if Filipino TB cases in A1018 were different to other TB cases from the Philippines showed there were no statistically significant differences in age (p=0.652), sex (female: 42% vs 37%, p=0.608) , occupation (HCW: 63% vs 59%, p=0.719), years since entry to the UK (p=0.859), site of disease (pulmonary: 44% vs 52%, p=0.370), BCG vaccination (78% vs 86%, p=0.278), or having a social risk factor (6.7% vs 2.4%, p=0.181).

Occupational health review

The 16 HCWs (all born in the Philippines) for which cluster questionnaires were obtained were also asked about OH assessment. Information on OH assessment was available for 13 HCWs (Figure 3); three had their TB identified prior to entering a workplace in the UK (two of which were identified at new entrant screening), two had been assessed for TB by OH, and nine had not received any OH check. Eight of the HCWs worked for a private sector healthcare provider, two in the NHS, and one had worked in both the private sector and the NHS. Of the two known to have received OH assessment, both had worked in the NHS. One only had a BCG scar checked and was not assessed or

tested for LTBI or active TB. The other case was referred to the TB services after TB was identified through OH, however the exact method of TB identification was not known.

DISCUSSION

The MIRU-VNTR cluster we presented here contained a high number of HCWs, prompting cluster investigation[13] with the concern that nosocomial transmission may have occurred. Despite extensive investigation, no evidence of nosocomial transmission or transmission in another setting was detected. These findings were supported by the use of 32-loci MIRU-VNTR typing which showed that the majority of cases had a unique strain, demonstrating that 24-loci MIRU-VNTR typing did not satisfactorily discriminate between the strains.

Given the lack of epidemiological links between cases in this cluster, it is likely this strain type reflects a common endemic strain circulating in the Philippines, with cases having subsequently reactivated after UK arrival. This hypothesis can be supported by the high proportion of extra-pulmonary TB cases[22] in the cluster, and the fact that Indo-Oceanic lineage is frequent in TB cases originating from the Philippines, but is rare in the UK born population;[23,24] two of the four UK born TB cases had known travel links to the Philippines, where they may have acquired TB infection. There were no statistically significant differences between the demographic or clinical characteristics of Filipino cases in A1018 and other Filipino TB cases suggesting A1018 cases are representative of all TB cases originating from the Philippines. Such factors are important to take into account when reviewing molecular clusters and determining the possibility of transmission.

Although no nosocomial transmission was identified in this investigation, the 10 HCWs in this cluster who received insufficient or no OH assessment, represent missed opportunities for detection of LTBI or active TB. OH guidance aims to prevent TB transmission in healthcare settings. As part of UK guidance it is recommended that HCWs from high TB incidence countries should be tested and treated for LTBI prior to starting in employment,[10,11] which is in keeping with the World Health Organization's guidelines recommending systematic testing and treatment of LTBI in high risk groups, including HCWs.[25] The incidence of TB in the Philippines between 2010 and 2014, when the HCWs in this cluster who originated from the Philippines were diagnosed, was approximately 300 per 100,000 population.[15] Therefore, all HCWs from the Philippines should have received OH assessment. Between 2009 and 2013, 11% of HCWs with TB in the UK were born in the Philippines[5] which means targeted OH assessment could have a significant impact on preventing development of active TB disease in this population, and other high TB incidence countries, as well as ensuring early diagnosis and treatment. Indeed a recent study in the North of England identified a high proportion of LTBI among HCWs from high TB incidence countries, including the Philippines.[26]

As current guidance is directed at NHS employers, there may be less stringent practices, including LTBI testing and treatment, by private sector healthcare employers. A survey conducted in 2008 in the South East of England identified that the majority of care homes (largely private sector) did not have OH policies and provided no assessment for TB in HCWs born abroad.[27] The finding that the majority of HCW TB cases in this cluster were employed by the private sector and did not have OH check highlights the importance of ensuring that all healthcare employers have appropriate OH provision for TB assessment. Other UK studies identified, unlike our findings, that the majority of HCWs with TB had pre-employment healthcare checks before their diagnosis with active TB.[28,29] However, these studies did note that the methods employed during these health checks fall short of testing for LTBI, similar to one of the HCWs we reported on here. Other low incidence countries including the USA, Germany and the Netherlands, place high importance on the detection of LTBI in HCWs,[30,31] as recommended by the World Health Organization for low TB burden countries.[25]

There are several limitations to the work presented here. Firstly, only 74% of cases included were typed to at least 23-loci and the subsample of cases typed to 32-loci only accounted for 51% of cases. Due to the less stringent cluster definition initially used, including strains with up to two missing loci, those with a different full 24-loci MIRU-VNTR profiles may have been included.[13,20] Secondly, the cluster questionnaire return rate was low (59%), therefore some epidemiological links between cases may have not been identified, this includes among HCWs. However, these limitations reflect that this was a real-time public health investigation rather than a pre-designed study.

CONCLUSIONS

The majority of HCWs in this cluster likely occurred due to reactivation of TB acquired prior to UK arrival, with no evidence of nosocomial transmission within EW&NI. OH assessment to test and treat LTBI would likely have reduced the number of active TB cases. It is hoped that the use of genotyping techniques with a higher discriminatory power could reduce the identification of false positive clusters.[32] The rollout of whole genome sequencing by Public Health England,[16] including its use in assessing relatedness, should provide an improved level of discrimination for identifying probable transmission chains.

ACKNOWLEDGEMENTS

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Table 1. Characteristics of TB cases in cluster A1018, 2009-2014 (n=53)

	Number of cases	Proportion of cases
Year of notification	n=53	
2009	5	9.4
2010	9	17.0
2011	14	26.4
2012	11	20.8
2013	8	15.1
2014	6	11.3
Sex	n=53	
Female	30	56.6
Age group	n=53	
0-14	3	5.7
15-24	5	9.4
25-34	16	30.2
35-44	19	35.8
45-64	8	15.1
65+	2	3.8
Occupation (cases aged 16-64 years)	n=45	
Healthcare worker	22	48.9
Other	17	37.8
None*	6	13.3
Country of birth	n=52	
UK	4	7.7
Philippines	43	82.7
India	3	5.8
Sri Lanka	1	1.9
New Zealand	1	1.9
Years since UK entry (non-UK born cases)	n=43	
<2	11	25.6
2-5	15	34.9
6-10	8	18.6
11+	9	20.9
Site of disease	n=53	
Pulmonary	28	52.8
Extra pulmonary only	25	47.2
BCG vaccination†	n=37	
Yes	29	78.4
Any social risk factor‡	n=44	
Yes	4	9.1
Strain type with at least 23 typed loci	n=53	
Yes	43	81.1
Area of residence	n=53	
London	17	32.1
South East England	14	26.4
West Midlands	6	11.3
East of England	5	9.4
South West England	4	7.6
Yorkshire and the Humber	4	7.6
North East England	1	1.9
North West England	1	1.9
Wales	1	1.9

*those of working age but not in employment or education i.e. unemployed, prisoners, asylum seekers or housewife/husband

†vaccination determined based on medical documentation or if a scar provides proof of vaccination

‡current or history of homelessness, imprisonment, drug misuse and alcohol misuse

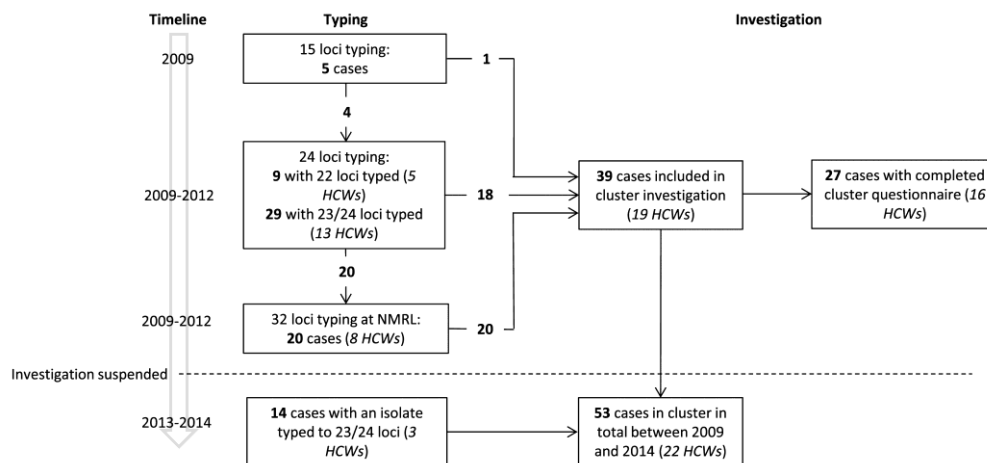## Figure 1. Flow chart of A1018 typing, review and investigation case numbers, 2009-2014
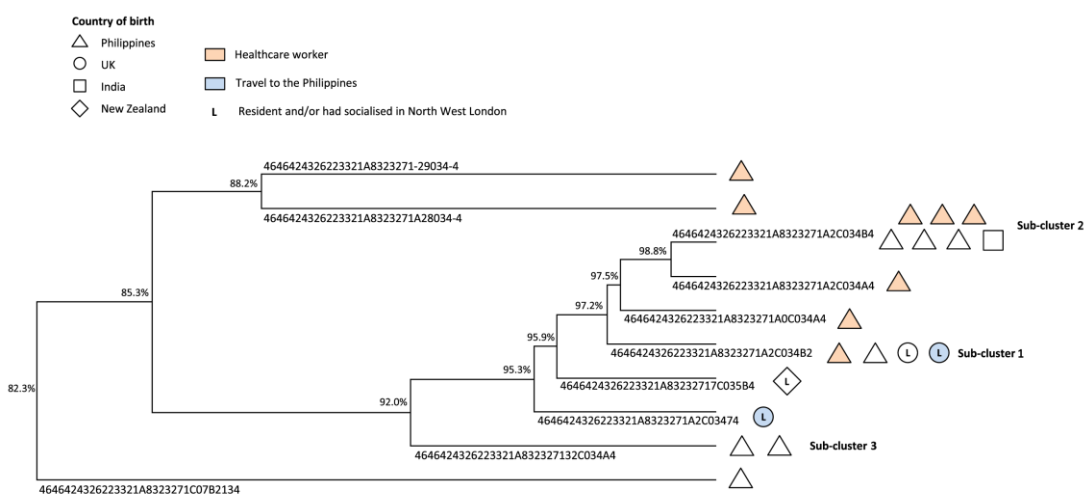

Figure 2. Sub-clusters of A1018

Figure 3. Flowchart of HCW screening and TB diagnosis