Public Health Outcome of Tuberculosis Cluster Investigations, England 2010-2013

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Running Title - A descriptive analysis of molecular strain-typed cluster investigations undertaken in England from 2010-2013

Take home message - TB molecular strain-typing and cluster investigation leads to additional public health action and saving of resources

Abstract

Objectives: Tuberculosis(TB) is a serious re-emergent public health problem in the UK. In response to rising case incidence a National TB Strain-Typing Service based on molecular strain-typing was established. This facilitates early detection and investigation of clusters, targeted public health action, and prevention of further transmission. We review the added public health value of investigating molecular TB strain-typed(ST) clusters.

Methods: A structured questionnaire for each ST cluster investigated in England between 1 January 2010 and 30 June 2013 was completed. Questions related to epidemiological links and public health action and the perceived benefits of ST cluster investigation.

Results: There were 278 ST cluster investigations(CIs) involving 1882 TB cases. Cluster size ranged from 2 to 92. CIs identified new epidemiological links in 36% of clusters; in 18% STs were discordant refuting transmission thought to have occurred. Additional public health action was taken following 23% of CI.

Conclusions: We found positive benefits of TB molecular ST and CI, in identifying new epidemiological links between cases and taking public health action and in refuting transmission and saving resources. This needs to be translated to a decrease in transmission to provide evidence of public health value in this low prevalence high resource setting.

Background

Tuberculosis (TB) is a serious re-emergent public health problem in the United Kingdom (UK). Since the late 1980s the incidence of tuberculosis in England steadily increased to a peak of 15.6 per 100,000 in 2011 (1), higher than most western European countries (2) and nearly five times greater than in the United States (3). In response to this rising incidence and the UK Chief Medical Officer's TB Action Plan of 2004 which recommended developing molecular typing as a surveillance tool (4), a national prospective molecular strain typing service was established. The Tuberculosis Strain Typing Service (TB-STS) was therefore initiated in 2010, by Public Health England (PHE), as a key component in helping to control the spread of TB.

The PHE TB-STS aims to support TB control by facilitating early detection and subsequent epidemiological cluster investigation leading to targeted public health action. Although molecular typing services exist in a number of other countries including the United States of America, the Netherlands and Denmark (5,6,7) the TB-STS in England is unique in that it was the first universal national prospective service using 24-loci mycobacterium interspersed repetitive units variable number tandem repeat (MIRU-VNTR) matched with epidemiological surveillance data for those diagnosed with TB (8).

As part of the TB-STS, clusters were investigated by PHE local public health specialists supported by National Health Service (NHS) clinical services staff. The aim of a cluster investigation was to identify epidemiological links between cases in order to prevent further transmission of that TB strain by undertaking enhanced public health action e.g. extended contact tracing to identify and treat additional cases of Latent Tuberculosis Infection (LTBI) and active TB disease (9).

We aim to describe the additional public health actions and perceived added public health value of investigating molecular TB strain-typed (ST) clusters to provide information for further development of the national TB-STS and future Whole Genome Sequencing (WGS) in England. We describe a study of TB cluster investigations (CIs) in England from January 2010 to June 2013, the reasons why they were initiated, the frequency with which epidemiological links were found and the resulting actions undertaken.

Method

Cluster Identification and Investigation

As part of the TB-STS in England molecular typing using 24-loci MIRU-VNTR was carried out on all initial TB culture-positive isolates at one of the three reference laboratories in England (8). Molecular information was matched to routinely collected case-based epidemiological information obtained from the PHE national Enhanced Tuberculosis Surveillance system (ETS) (8,9). A decision to investigate a strain-typed cluster was based on pre-agreed criteria including size, geographical spread or inclusion of cases which had risk factors suggesting potential for higher risk or recent TB transmission (e.g. children, drug resistant cases) (9). CI included review of hospital clinic records, and/or patient interviews and standardised CI questionnaires. This information was reviewed to determine potential epidemiological links and if disease transmission had occurred (9). An incident control team may be established consisting of multidisciplinary experts to advise and determine the appropriate course of public health actions required (9).

Data collection

We developed a structured questionnaire, the TB-STS Cluster Investigation Outcome Form to be completed by public health staff who investigated a cluster at local, regional or national level between 1 January 2010 and 30 June 2013. Details recorded included geography and size of the cluster, reason for beginning the investigation (reached a threshold, risk factors identified or other), whether epidemiological links were known prior to molecular cluster information, whether new epidemiological links were found following molecular cluster information, what public health actions were taken, outcome of the CI (probable or definite chain of transmission identified, or no apparent transmission, investigation ongoing or inconclusive), what factors may have contributed to the cluster, whether the molecular typing information was useful and whether it refuted previously suspected epidemiological links.

Data entry

We developed a Cluster Monitoring Database (CMD) in Microsoft Access. Data on all CIs being undertaken was entered together with data from the CI Outcome Form after conclusion of the CI.

Data management and analysis

We performed data consistency checks on key variables from the CI Outcome Form to ensure their validity. Any identified discrepancies were followed up with lead investigators. We created two new variables derived from information on the CI Outcome Form: public health action taken prior to receipt of ST information, and public health action taken as a consequence of CI. Descriptive analysis was undertaken using Microsoft Excel and Stata 13.1.

Definitions

A *ST cluster* was defined as two or more cases with indistinguishable 24-loci MIRU-VNTR in England (with at least one case with a complete 24-loci profile and others at least 23-loci typed). Local clusters were those where all members lived in a single Health Protection Team (HPT) area (there were 26 such teams in England); regional clusters were those where cases spanned two or more HPTs (though remained within a single region, of which there were nine); and national were those containing cases in more than one region.

Clusters were defined as *small* if they contained 2-4 cases, *medium* if contained 5-9 cases and *large* if contained ten or more cases.

Risk factors(RFs) suggesting potential for higher risk of or recent TB transmission included alcohol or drug misuse, history of or currently being homeless or in prison.

The *threshold for investigation* was set as five cases in a cluster in the same local HPT or ten cases across a region or nationally. Some clusters where cases had RFs may have been investigated when the cluster contained fewer than five cases.

Epidemiological links were recorded if cases were linked in time and place, and were categorised as known or possible links.

Known epidemiological links were recorded if;
-   one case volunteered the name of another case whilst either was potentially infectious (had pulmonary TB irrespective of sputum status), or
-   the cases were in the same setting at the same time when either was potentially infectious (9).

Possible links were recorded if;
-   two cases were in the same place around the same time but the timing of when they were there or when they were infectious was not definite, or
-   two cases worked in or were in the same place around the same time and shared social, occupational or behavioural characteristics that increased the chances of transmission, or
-   two cases were in the same place at the same time but both had non-pulmonary TB, or
-   one case volunteered the name of the other as a contact but both had non-pulmonary TB (9).

Probable or definite transmission was deemed to have occurred in a ST cluster if known or possible epidemiological links were identified linking members of the cluster, good evidence that they were involved in the same chain of recent transmission (9).

Public health action was defined as any action undertaken in addition to standard contact tracing, e.g. extended contact tracing and screening of new contacts in response to the cluster or any other actions undertaken that would constitute public health action such as awareness raising of TB signs and symptoms.

The timing of the knowledge of the existence of epidemiological links existing between members of the cluster was categorised as either;

- *prior to cluster investigation* if the epidemiological link was already known to the public health professionals or,
- *as a consequence of cluster investigation* if the link between two cases in a cluster was elucidated during the process of cluster investigation.

Clusters may include both epidemiological links known prior to cluster investigation and links found as a consequence of cluster investigation.

Equally the timing of public health action being undertaken was categorised as either prior to or as a consequence of molecular cluster investigation. For example, if two cases were linked in time and place during standard contact tracing which resulted in extended contact tracing being undertaken in the setting identified, this would be public health action prior to cluster investigation.

Results

Cluster Investigations
There were 278 TB ST CIs in England from 1 January 2010 to 30 June 2013 involving 1882 TB cases with cluster size ranging from 2 to 92 (median 6). A CI Outcome Form was completed for every investigation initiated, a 100% response rate.

Cluster investigations were most frequently (n=150, 54%) initiated within a local health protection team, 37% (n=104) were national and 9% (n=24) within a region. Forty percent (n=111) of CIs were initiated because the pre-determined threshold for investigation was reached. In 27% (n=76), CI were undertaken because at least one case in the cluster had RFs, with drug and/or alcohol misuse being the most commonly occurring risk factors. In 8% clusters were investigated due to the inclusion of a healthcare worker (n=21) and in 7% due to the cluster containing a child (n=20) (Table 1). There were a number of other reasons clusters were investigated below the set threshold, these included geographical proximity of cases, cluster containing individuals with resistance to one or more first line drugs and cases all having the same ethnicity or country of birth. A review meeting was held for nearly all CIs (n=275) and a meeting of the incident control team involving allied professionals for nearly a quarter (n=61). In 9% of CIs (n=25) additional typing at PHE Mycobacterial Reference Laboratories to further differentiate cases was requested, both typing of historical isolates which were only previously typed to 12 loci, or further typing of isolates to 32 loci.

Epidemiological Links Identified
Epidemiological links were identified in 66% (n=184) of clusters investigated. Of these clusters with epidemiological links established, 55% (n=101 clusters) had epidemiological links as a result of the CI (26% as a consequence of the CI and 29% both as a consequence of and prior to the CI) and 45% (n=83) were known prior to the CI (Figure 1). We estimated the added epidemiological value of CIs as 36% (101/278) in terms of identifying new epidemiological links in clusters.

In 26 (9%) CIs, epidemiological links were found to exist between all members of the cluster. The median size of these clusters were three cases.
In 18% of clusters (n=49), ST results showed cases previously determined, during routine TB contact tracing activities, to be epidemiologically linked, had strains with discordant MIRU-VNTR patterns therefore refuting transmission.

Epidemiological links were identified in 69% (n=103) of local CIs (half of which were identified as a consequence of the CI), 61% (n=63) of national investigations, (of which 62% were as a result of the CI) and 75% (n=18) of regional investigations (of which 56% were as a result of the CI) (Table 1).

In clusters investigated because the predefined threshold was reached nearly 80% had epidemiological links identified, of which 53% were as a consequence of the CI. In clusters investigated because they contained individuals with RFs for transmission, 57% had epidemiological links identified (53% of which were as a consequence of the CI). In cluster investigations initiated because they contained a healthcare worker, 43% had epidemiological links identified within the cluster but not necessarily with the healthcare worker, (56% of which were as a consequence of the CI). In those investigated because they contained a child 60% had epidemiological links identified (of which 58% were as a consequence of the CI) (Table1).

Public Health Actions Taken
Public health action was reportedly undertaken (in addition to standard contact tracing) in 91 (46%) of 200 CIs with this information. In 34 (37%) this was as a consequence of the CI; in 46 (51%) sufficient public health action had already been undertaken prior to the CI and in 11 (12%) action was taken both prior to, and as a consequence of, the CI (Figure 2). Overall we found 23% (45/200) of clusters had additional public health actions undertaken as a consequence of CIs (Table 2).

In twelve out of these 45 clusters where public health action was undertaken as a consequence of the CIs, the number of additional cases identified was reported. Overall 1517 additional contacts were identified and screened (628 from one cluster) following cluster investigation, this led to the identification of 23 active and 136 latent cases.

In CIs initiated because of reaching the predefined threshold, 43% resulted in additional public health action being undertaken as a consequence of the CI compared to 75% of those initiated because they contained individuals with RFs for transmission (Table 2).

Occurrence of Transmission
Transmission occurred more often in large compared to small clusters (82% in large clusters, 47% in small clusters) ($p < 0.05$) and additional public health action, as a consequence of CI, was more likely to be undertaken in large compared to small clusters (51% in large clusters, 30% in small clusters) ($p < 0.05$) (Table 1,2).

Probable or definite transmission was reported to have occurred in 180 (65%) CIs, no apparent transmission in 73 (26%), investigations were inconclusive in 16 (6%) and in 9 (3%) investigations were ongoing (Table 1).

Health protection staff who responded to the question (n=187) stated what factors they believed contributed to transmission; in 63% (n=117) of CIs no factors were identified, in 14% (n=27) transmission was considered to have occurred due to inadequate identification of, and screening of, contacts of early cases, in 9% (n=16) transmission was reportedly due to a lack

of co-operation with contact tracing of the early cases in the cluster, 8% (n=15) due to delayed diagnosis of early cases and 6% (n=12) for other reasons.

Utility of ST information

The ST data was deemed useful by public health staff leading the investigations in nearly 80% of investigations, where reported (207/260).

Discussion and Conclusions

We report a high level of potential benefit to local health professionals of molecular TB strain-typing in England. Our study during 2010 to 2013 showed that 278 clusters were investigated and new epidemiological links were identified in 36% of clusters, resulting in additional public health action being undertaken in 23% of clusters and in 18% of clusters, investigation refuted links previously thought to exist.

This proportion of new epidemiological links discovered is comparable to the 38-57% of epidemiological linkages identified in clusters (varying on strength of epidemiological association) across four sentinel sites in the United States of America (USA) in 1998-2000(10). Although their proportion was based on cluster pairs and a different molecular method, restriction fragment length polymorphism (RFLP), was used. Similarly in the Netherlands, also using the RFLP molecular method, researchers found that 31% of clustered cases had a new epidemiological link established after cluster feedback (11).

The proportion of clusters with true epidemiological links between cases may be higher than identified. Cases may deliberately or innocently withhold information regarding links to others, particularly those with prison history or problems with drug misuse due to the misconception of implication in potential illegal activities; this can result in ongoing transmission in specific populations and a failure to identify the connection between cases (12,13).

In 18% of clusters, investigation refuted links previously thought to exist. This is very useful since it enables limited public health resources to be targeted elsewhere. Research from the USA reports that 29% of links identified and thought to exist during standard contact tracing were disproved after molecular typing became available(10,14). Conversely the Netherlands research reported that just 5% of links identified prior to the availability of molecular information were disproved (11). The validity of comparisons remains problematic however due to the use of different molecular techniques and should be further explored with differing definitions of a cluster. Additionally the use of more sophisticated laboratory methods, such as whole genome sequencing which has been shown to have a higher discriminatory power (15), to determine clustering will be key in further understanding the evidence for transmission.

The time taken for culture diagnosis, DNA extraction, performance of and receipt of ST results inevitably leads to a delay in CI initiation and lost opportunity for any additional public health action. Early cases in a cluster are likely to have completed treatment and can be difficult to trace again to interview as part of an investigation (14). The challenge of minimising delays in diagnosis of TB cases by identifying and screening contacts was highlighted as the main factor to have contributed to cluster growth in more than one in five clusters. Following a comprehensive evaluation it has been reported that the TB-STS had no significant effect on reducing diagnostic delay (16). However this evaluation utilised data from the early part of

the service, the first three years, therefore it was less likely to find evidence. Work in the USA indicated that linkages discovered only during cluster investigation were more likely to be in non-traditional settings (defined as those not including home, school, workplace and common congregate settings such as correctional facilities, day-care centres nursing homes) and non-traditional relationships (defined as to not include household, friend and co-worker contacts) (10, 17) than during conventional contact tracing. We recommend that sufficient time is given for interviews with patients to build rapport and enable effective contact tracing to be carried out so that epidemiological links can be established and any foci for enhanced transmission identified. In addition investment should be made in epidemiological skill training and capacity building to enhance investigation skills.

If limited public health resources are to be targeted well, then clusters where there is the greatest potential for added public health value need to be prioritised for investigation. The proportion of CIs with new links identified was 42% in those investigated because the threshold for investigation was reached, which translated to additional public health action being undertaken in 21% of these. New epidemiological links were identified in 35% of clusters containing a child or children with additional public health action in 16%, and 30% in clusters containing individuals with risk factors resulting in additional public health action reportedly being undertaken in 44% of these clusters. We recommend clusters with these characteristics be prioritised for investigation on the basis of likely higher yield of previously unknown epidemiological links. The additional knowledge gained on the basis of ST CI has previously been reported as limited (7). While additional public health action being undertaken as a result of strain type cluster investigations for only 23% of clusters may initially appear low, if this additional action led to a reduction in TB transmission, it may have led to public health benefit.

Limitations
The existence of epidemiological links were locally determined. We were unable to validate epidemiological links stated to exist nor to confirm the exact timing of any public health interventions in relation to timing of receipt of ST results. Further, the unit of investigation was cluster, rather than case, therefore it was not defined who within the cluster the epidemiological links were between. Future work should investigate the nature of the epidemiological links and describe them in more detail. We were only able to establish if public health actions taken led to the identification and treatment of additional cases of latent TB infection or active TB in a limited number of clusters. This information needs to be better collected in the future as evidence for prevention of further transmission.

Quantifying the added epidemiological value in prospective strain typing cluster investigations is not straightforward. Although a standard method of investigation was recommended in England (in the national strain typing handbook) (9) we know that there were variations in intensity of investigation which could have led to a detection bias in

determining epidemiological links. Funding was not provided, as part of the TB-STS, to the NHS TB Services for any extra workload resulting from gathering additional information from patients as part of cluster investigations. There is the possibility that with additional resources further epidemiological links may have been elucidated due to the additional time an individual could spend investigating the cluster. We believe it is likely, therefore, that the estimates of clusters with true epidemiological links found as a result of cluster investigations are an under- rather than an over- estimation. We recommend that cluster investigations are carried out and actions and outcomes should continue to be recorded in a systematic manner to ensure continued public health review and quality assurance.

The usefulness of strain typing information was a personal opinion of the public health workers leading the investigation, it was subjective and therefore difficult to measure the interpretation. This has previously been reported as high (18).

Given the level of resolution of genetic relatedness provided by MIRU-VNTR, clustering does not necessarily signify recent transmission (19-21), as some MIRU-VNTR clusters investigated will have been false positive transmission clusters. The higher level of resolution provided by Whole Genome Sequencing (WGS) of TB strains should increase the utility of cluster investigation (18). In addition, it is hoped that WGS will increase the timeliness of molecular characterisation of strains from the laboratory perspective which should improve the speed with which public health action can be initiated (19).

Conclusion

We found positive benefits in both TB molecular strain typing and cluster investigation in England. Both in terms of identifying new epidemiological links between cases and taking public health action, and conversely in refuting transmission and saving limited public health resources. The public health benefit is evidenced in the reported cases identified following cluster investigations however the additional public health benefit in terms of reduced onward transmission of TB needs further quantification in order to provide convincing evidence of public health value.

Indicators of such benefit might include reduced diagnostic delay through earlier identification of active cases (shortened intervals from onset to diagnosis or treatment of those contacts who are found to have active TB), through contact investigations in strain type cluster investigations compared to other active cases detected through routine contact tracing, as well as higher rates of LTBI detection and prophylaxis.

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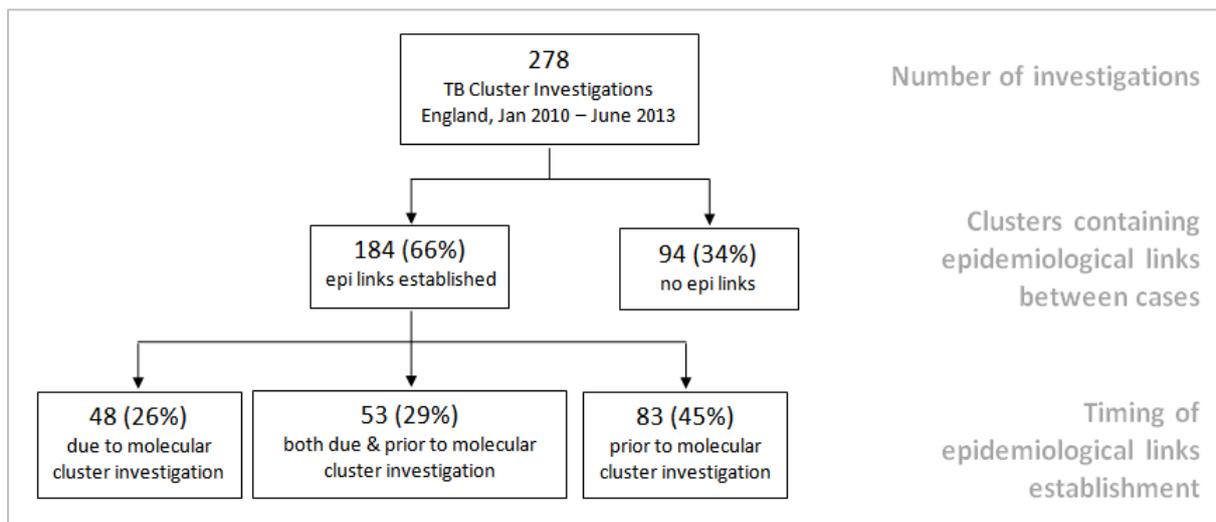
Table and Figures

Figure 1: Cluster investigations carried out, epidemiological links reportedly identified as a consequence of or prior to Strain Typed Cluster Investigations, TB Strain Typing Outcomes England January 2010- June 2013
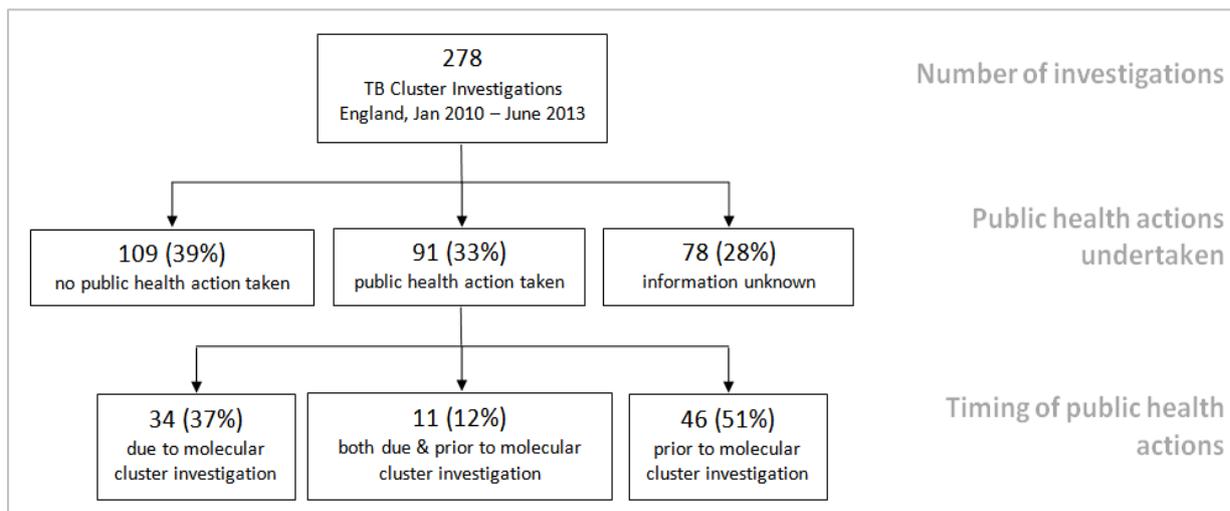

Figure 2: Cluster investigations carried out, public health action taken as a consequence of or prior to Strain Typed Cluster Investigations, TB Strain Typing Outcomes England January 2010- June 2013

Variable	Total no. of clusters	Percentage (no.) of clusters with epi links established	Percentage (no.) links found due to CI (of those with epi links)	Added epidemiological value of cluster investigations	Percentage (no.) with probable or definite transmission
All cluster investigations	*278*	*66% (184)*	*55% (101)*	*36%*	*65% (180)*
Geographical footprint of investigation					
Local	*150*	*69% (103)*	*50% (52)*	*35%*	*67% (100)*
Regional	*24*	*75% (18)*	*56% (10)*	*42%*	*75% (18)*
National	*104*	*61% (63)*	*62% (39)*	*38%*	*60% (62)*
Size of cluster investigated					
Small (2-4 cases)	*100*	*48% (48)*	*52% (25)*	*25%*	*47% (47)*
Medium (5-9 cases)	*91*	*69% (63)*	*54% (34)*	*37%*	*68% (62)*
Large (≥10 cases)	*87*	*84% (73)*	*58% (42)*	*48%*	*82% (71)*
Reason cluster investigated					
Threshold reached	*111*	*79% (88)*	*53% (47)*	*42%*	*77% (86)*
Contained individual(s) with risk factors	*76*	*57% (43)*	*53% (23)*	*30%*	*55% (42)*
Contained HCW(s)	*21*	*43% (9)*	*56% (5)*	*24%*	*43% (9)*
Contained Child(ren)	*20*	*60% (12)*	*58% (7)*	*35%*	*55% (11)*
Other	*50*	*64% (32)*	*59% (19)*	*38%*	*64% (32)*

Table 1: Number and percentage of clusters investigated, with epidemiological links identified, the resulting added epidemiological value and transmission thought to have occurred according to geographical footprint, size of cluster, and reason for the cluster investigation, TB Strain Typing Outcomes England January 2010- June 2013

Variable	Total no. of clusters	No. of clusters with information on public health actions taken*	Percentage (no.) of clusters where public health action undertaken	Percentage (no.) of clusters with additional public health action taken due to CI
All cluster investigations	*278*	*200*	*46% (91)*	*23% (45)*
Geographical footprint of investigation				
Local	*150*	*150*	*41% (61)*	*14% (21)*
Regional	*24*	*24*	*33% (8)*	*8% (2)*
National	*104*	*26*	*85% (22)*	*85% (22)*
Size of cluster investigated				
Small (2-4 cases)	*100*	*76*	*38% (29)*	*30% (12)*
Medium (5-9 cases)	*91*	*67*	*48% (32)*	*36% (14)*
Large (≥10 cases)	*87*	*57*	*53% (30)*	*51% (19)*
Reason cluster investigated				
Threshold reached	*111*	*91*	*48% (44)*	*21% (19)*
Contained individual(s) with risk factors	*76*	*34*	*59% (20)*	*44% (15)*
Contained HCW(s)	*21*	*19*	*21% (4)*	*11% (2)*
Contained Child(ren)	*20*	*19*	*47% (9)*	*16% (3)*
Other	*50*	*37*	*38% (14)*	*16% (6)*

* information unknown for 78 clusters

Table 2: Number and percentage of clusters investigated, with public health action taken and the resulting added public health value according to geographical footprint, size of cluster and reason for the cluster investigation, TB Strain Typing Outcomes England January 2010- June 2013