Institution: University of Birmingham

Unit of Assessment: A1

Title of case study: Enabling faster and more accurate treatment of Tuberculosis

1. Summary of the impact (indicative maximum 100 words)

In 2010, 8,483 cases of tuberculosis (TB) were reported in the UK, mainly in urban areas and with London and the West Midlands having the highest rates of disease (rate within Heartlands Primary Care Trust 80+ per 100,000). Research led by Professor Peter Hawkey at the University of Birmingham has resulted in the development of novel techniques for real time typing of *Mycobacterium tuberculosis* strains. The new cost effective and rapid methodology has been adopted by the three UK national reference laboratories and has resulted in significant improvements to the national TB typing scheme and TB infection management. An associated secure IT system has been developed to enable TB control teams to rapidly receive typing data together with an analysis of the local cases. This has influenced changes in clinical practice by reducing the need for contact tracing. Use of the new techniques developed at Birmingham has resulted in faster, more accurate identification of outbreaks of TB and this information has been used to significantly improve patient management.

2. Underpinning research (indicative maximum 500 words)

In the management of suspected outbreaks of TB infection it is critical to identify the specific strain of *M. tuberculosis* for all potentially linked isolates, known as typing, so that identical strains in apparently unlinked cases can be identified and treatment initiated. Previously TB typing used a slow and complex method involving cultivation of sputum samples on solid media (3-6 weeks), and a nucleic acid restriction digest assay (25% failure rate and takes 5 days). This method was expensive and was therefore only applied to a small number of cultured isolates.

An alternative and improved strain typing method was developed at the University of Birmingham by Professor Peter Hawkey, Professor of Public Health and Clinical Bacteriology with laboratory work undertaken by Dr Jason Evans, Clinician Scientist at Heart of England NHS Foundation Trust. The method is based on the amplification of previously identified variable number tandem repeat (VNTR) DNA sequences in the *M. tuberculosis* genome from liquid cultures and quantification of the number of repeat sequences using denaturing high performance chromatography (dHPLC) (≤ 14 days, first time used for mycobacterial typing) [1]. The team developed and validated novel polymerase chain reaction primers to amplify these sequences and applied them to collections of known and unknown *M. tuberculosis* strains [2].

As a result of preliminary work from 2001 to 2003 (funded by Health Protection Agency (HPA), a further £175k was secured from the Department of Health, which enabled the further development and validation of the use of the dHPLC VNTR technique for routine clinical typing of *M. tuberculosis*. The test was first implemented into clinical service at the Public Health Laboratories at Heart of England NHS Foundation Trust in 2001 and by 2004 all TB isolates going through the Heartlands service were being typed using the new technique. Data from the clinical service at Heartlands Hospital was used to further understand the worldwide evolution of *M. tuberculosis,* as well as carefully dissecting the phylogeny of strains from the Birmingham South Asian community [3, 4].

In 2007 a cluster of *Mycobacterium bovis* (normally found in cattle) infections was identified in patients in Birmingham. In collaboration with Animal Health and Veterinary Laboratories Agency, University College London, Health Protection Surveillance Units and the Welsh Zoonoses Surveillance Unit, the dHPLC VNTR technique was used to identify for the first time *M. bovis* human to human transmission in individuals using recreational steroids [5].

Using the dHPLC VNTR technique Professor Peter Hawkey's team has also been able to identify the world's largest reported cluster (≥ 400 patients) of cross infection caused by a single *M. tuberculosis* strain (Mercian Strain), which has demonstrated that this strain is associated with UK born Caribbean individuals who use recreational drugs in a highly restricted geographical location based on epidemiological work combined with DNA fingerprinting [6].

Professor Hawkey and Dr Evans have also led the development of a software platform to support the HPA's national TB typing scheme. The OriginsInfo software was originally developed by Professor Webber of UCL and utilises given and family names to predict cultural, ethnic and linguistic origins of patients. The adaptation of the software by Professor Hawkey and Dr Evans to the TB setting has enabled the identification of otherwise unsuspected social links e.g. a group of Lithuanian immigrant workers in illegal accommodation, which when combined with the new typing technique controlled this and many other outbreaks [7].

3. References to the research (indicative maximum of six references)

1. Hawkey PM, Smith EG, Evans JT, Monk P, Bryan G, Mohamed HH, Bardhan M, and Pugh RN. Mycobacterial Interspersed Repetitive Unit Typing of *Mycobacterium tuberculosis* Compared to IS*6110*-Based Restriction Fragment Length Polymorphism Analysis for Investigation of Apparently Clustered Cases of Tuberculosis. Journal of Clinical Microbiology, Aug. 2003, 41(8): 3514–3520. *doi: 10.1128/JCM.41.8.3514-3520.2003*
2. Evans JT, Hawkey PM, Smith EG, Boese KA, Warren RE, Hong G. Automated high-throughput mycobacterial interspersed repetitive unit typing of **Mycobacterium** tuberculosis strains by a combination of PCR and non-denaturing high-performance liquid chromatography. J Clin Microbiol. 2004 Sep;42(9):4175-80. *doi: 10.1128/JCM.42.9.4175-4180.2004*
3. Evans JT, Gardiner S, Smith EG, Webber R, Hawkey PM. Global Origin of Mycobacterium tuberculosis in the Midlands, UK. Emerg Infect Dis. 2010 Mar;16(3):542-5. *DOI: 10.3201/eid1603.090813*
4. Menéndez MC, Buxton RS, Evans JT, Gascoyne-Binzi D, Barlow RE, Hinds J, Hawkey PM, Colston MJ. Genome analysis shows a common evolutionary origin for the dominant strains of **Mycobacterium** tuberculosis in a UK South Asian community. Tuberculosis (Edinb). 2007 Sep;87(5):426-36. *http://dx.doi.org/10.1016%2Fj.tube.2007.05.017*
5. Evans JT, Smith EG, Banerjee A, Smith RM, Dale J, Innes JA, Hunt D, Tweddell A, Wood A, Anderson C, Hewinson RG, Smith NH, Hawkey PM, Sonnenberg P. Cluster of human tuberculosis caused by **Mycobacterium** bovis: evidence for person-to-person transmission in the UK. Lancet. 2007 Apr;369(9569):1270-6. *http://dx.doi.org/10.1016/S0140-6736(07)60598-4*
6. Evans JT, Serafino Wani RL, Anderson L, Gibson AL, Smith EG, Wood A, Olowokure B, Abubakar I, Mann JS, Gardiner S, Jones H, Sonnenberg P, Hawkey PM. A geographically-restricted but prevalent **Mycobacterium** tuberculosis strain identified in the West Midlands Region of the UK between 1995 and 2008. PLoS One. 2011 Mar 25;6(3):e17930 *doi:10.1371/journal.pone.0017930*
7. Evans et al, Global Origin of *Mycobacterium tuberculosis* in the Midlands, UK. Emerging Infectious Diseases. 2010; 16:3, 542 *DOI: 10.3201/eid1603.090813*

4. Details of the impact (indicative maximum 750 words)

The research described above resulted in the development of a real time typing method for *M. tuberculosis*, which has resulted in a nationwide change in the methodology used for typing of TB, significant improvements to the national TB typing scheme and the management of TB infections.

Delivery of a National Reference Standard

Prior to the outcomes from this research there was no prospect of real-time high volume accurate typing being provided for English isolates of *M. tuberculosis.* The UK National Reference Laboratories used a complex, slow and unreliable technique, which only provided results on 75% of strains which would then require re-typing using a second method, followed by further analysis to identify specific strain types. The research conducted by Professor Peter Hawkey at the University of Birmingham resulted in a low cost, high volume dHPLC method, with new primers and targets that provides real-time typing of *M. tuberculosis*. The new typing method was fully implemented into clinical service at the Birmingham National Reference Laboratories for *Mycobacterium tuberculosis*, based at Heart of England NHS Foundation Trust in 2004 and continues to be used until the present day. As a result of the early work completed by the National Reference Laboratory in Birmingham, where all isolates were typed and which showed that unsuspected clusters of cross-infection were occurring, the universal rapid MIRU-VNTR 24 locus typing was recognised as a key component to enable the delivery of the Chief Medical Officer's TB action plan [1], which was published in October 2004 and detailed that "molecular strain typing of all M. tuberculosis isolates and the establishment of a central database linking epidemiological data is a key component of TB control". Whilst the publication of document is outside the period of assessment it provided the necessary mandate for the other National Reference Laboratories (London and Newcastle) to adopt the rapid typing technology developed by Professor Peter Hawkey, this occurred fully in 2010.

Professor Hawkey was a member of the TB Diagnosis and Molecular Epidemiology (DAME) Group in the HPA which was responsible for producing a national strategy for TB diagnosis. The Chair of DAME, Prof Pete Borriello (Chief Executive of the Veterinary Medicines Directorate), detailed in a statement to accompany this case study that "the research undertaken at Birmingham to see if the emerging molecular strain differentiation techniques could be applied to this problem and turn molecular typing into a useful public health tool was very important" [2]. The DAME Group argued successfully for the adoption of the Midlands' TB typing model nationally. The service model for *M. tuberculosis* typing established in Birmingham was adopted by the HPA to deliver molecular typing of every isolate via the HPA National Strain typing project, which began in January 2010 and is described in the HPA question and answer sheet published in February 2011 [3] and the 2012 HPA report on TB in the UK [4]. Dr P Monk, Consultant in Health Protection from the HPA, detailed the following in a statement to accompany this case study: "as a result of the work you [Professor Peter Hawkey] have led, there has been a step change in the control of TB. The developments of strain typing which came out of the research you led have allowed us to introduce a national strain typing service" [5].

The Birmingham strategy of direct real time reporting on the VNTR targets has become the national reference standard and is currently used in the other two reference labs (London and Newcastle) for England, Cardiff for Wales and Edinburgh for Scotland, as detailed in the National Institute for Health and Clinical Excellence guidance on the clinical diagnosis and management of tubercuosis [6], which was published in November 2010. A compatible variant of the technique is also used in USA, Canada, France, Holland and Germany [7].

Impact on public health

All *M. Tuberculosis* isolates in the UK are now typed by the National Reference Laboratories which are a critical component of the national Public Health England TB typing surveillance tool used by public health physicians to delineate and recognise clusters of TB cross-infection. The new typing technology has meant that pseudo outbreaks can be rapidly identified, i.e. individuals incorrectly thought to have acquired TB can be rapidly excluded, thus reducing the time and money spent on contact tracing. The use of the rapid typing method in the TB typing project has meant that isolates indistinguishable from those in previous cases reported to Health Protection Units, regional teams and nationally could be linked and controlled as a direct result of the typing information. Possible epidemiologically linked cases are investigated to ascertain whether an epidemiological cluster or outbreak exists. Any ensuing outbreak investigation aims to identify and treat all cases of active disease to prevent further transmission.

The public health community are now provided with detailed information on the relationship of different strains of TB. The strain typing data when integrated with epidemiological and social information via Origins software provides a powerful tool for Health Protection Units to recognise and track clusters of TB. Origins is a database which assigns a cultural, ethnic and linguistic group based on personal and family name; its application to TB epidemiology was developed by Prof Hawkey. Data detailed by the HPA through their TB Strain Typing and Cluster Investigation Newsletters provides an indication of the level of clusters being investigated in the UK. In the period Jan 2011-Dec 2012, of the 144 clusters being actively investigated by Public Health teams, 40 were from London and 41 from the Midlands [8]; this disproportionate use represents the early adopter status in the Midlands. This level of investigation has only been made possible by the implementation of the rapid typing technology and associated epidemiological and social information provided via Origins. The method has also enabled the almost complete eradication of laboratory contamination being responsible for false positives; prior to typing 8% of positive results were contamination.

Impact on patients

The early identification of TB patients, which are part of previously unidentified clusters of infection, is enabling early treatment and avoidance of morbidity and mortality, as detailed in a study from the Netherlands and in the report from the HPA on Surveillance of *Mycobacterium tuberculosis* Strain Typing [7, 9].

Impact on local clinical practice

In 2006, the University of Birmingham team established a secure website (Document Gateway) so that TB teams across East and West Midlands could access the data in real-time. This was so successful that from 2008 onwards Birmingham and Black Country isolates have been managed in monthly multidisciplinary meetings with clinicians directly responsible for managing the patients, public health clinicians and TB control nurses examining typing data. In January 2010, in response to requests from users and through the continuing support from the HPA, the service was expanded in parallel with nationally agreed guidelines and increased the resolution to beyond that of the methodology originally used by the main reference lab. This work was done by Dr Evans, Dr Grace Smith (Head of Regional Reference Laboratory) and Professor Peter Hawkey working directly with clinicians.

5. Sources to corroborate the impact (indicative maximum of 10 references)

1. Chief Medical Officer’s TB Action Plan published in 2004
2. Letter from the Chief Executive of Defra’s Veterinary Medicines Directorate (VMD)
3. Q & A sheet for HPA National Tuberculosis Strain Typing project, published February 2011
4. HPA Report: Tuberculosis in the UK, published in 2012
5. Letter from the Health Protection Agency, East Midlands South Health Protection Unit, County Hall, Glenfield, Leicestershire, LE3 8TB
6. NICE Clinical Guideline. Tuberculosis: Clinical diagnosis and management of tuberculosis, and measures for its prevention and control. Published March 2011
7. de Beer et al, Comparative Study of IS6110 Restriction Fragment Length Polymorphism and Variable-Number-Tandem-Repeat Typing of Mycobacterium tuberculosis Isolates in the Netherlands, Based on a 5-Year Nationwide Survey, Journal of Clinical Microbiology. 2013, 51:1193
8. HPA TB Strain Typing & Cluster Newsletter published January 2013
9. HPA Surveillance of *Mycobacterium tuberculosis* Strain Typing