Can routine genetic testing help to end TB transmission?

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TB incidence may be finally falling in England; 6520 cases were notified in 2014 giving an estimated annual incidence of 12/100 000.[1] There has been a year-on-year decrease in notified cases since 2011, but TB incidence in England still remains unacceptably high and in excess of most European Union countries.[2] A strategy to reduce and eventually eliminate TB as a public health problem was released by Public Health England (PHE) and National Health Service England in 2015.[3] It identifies 10 areas where improvements in current practice can improve TB control, which include ensuring comprehensive contact tracing, tackling TB in underserved populations, systematic implementation of new entrant latent TB screening, strengthening surveillance and monitoring and providing universal access to high-quality diagnostics.

The introduction of routine genetic testing of cultured TB isolates in 2010 by PHE has the potential to improve our understanding of each of these challenges. In *Thorax*, Hamblion *et al* use data from 2010 to 2012 to provide some insight into TB transmission in London, the unofficial TB capital of Europe and home to approximately 40% of TB cases in England.[4]

The methodology using 24 loci mycobacterial interspersed repetitive units–variable number of tandem repeats (MIRU–VNTR) typing has been well validated.[5] TB cases were classed as clustered if they matched to another case on at least 23 typed loci. Clustered cases were compared with non-clustered cases and small clusters were compared with large clusters. The study's main findings are interesting. First, clustered cases were more likely to have been born in the UK or lived in the UK for a long time compared with non-clustered cases. Second, clustered cases were more likely to have a social risk factor namely having spent time in prison, being homeless and alcohol or drug misuse. These findings support the recommendation of the national TB strategy on strengthening services for underserved populations.[3] The majority of clusters spanned more than one area of London and would therefore have involved more than one TB service, and raises the question as to why such services are not organised as a single entity as in other cities around the UK.

When large clusters (defined as a cluster with five or more cases) were compared with smaller clusters, larger clusters were more likely to have had the first two cases notified within 90 days of the first notification. This supports the prioritisation of these rapidly expanding outbreaks for direct case finding and contact tracing resources, and experience suggests these will often be in settings such as prisons or hostels. It is also further evidence of the value of providing strain typing data in close to 'real time'. This is relevant in the context of a recent evaluation published in *Thorax*, which did not find evidence that the national strain typing service was cost-effective in its current form, when assessing its impact on diagnostic delay or increased yield from contact tracing.[6]

The imminent introduction of whole genome sequencing (WGS) in PHE reference laboratories (ultimately replacing MIRU–VNTR) is likely to alter contact-tracing practices in the near future. Although 24 loci MIRU–VNTR typing may indicate that two strains are linked (and therefore suggest transmission between two individuals) it may also simply reflect that two individuals acquired TB in the same high prevalence region and have reactivated their disease in England (a common situation where migrant/displaced populations tend to settle in one area). WGS has several advantages over MIRU–VNTR typing. First, the genetic evidence of drug resistance can be determined rapidly, and eventually may reduce costs and replace phenotypic sensitivity testing.[7] Second, there is good evidence for its use in investigation of TB transmission.[8–10] It allows linking of TB cases with greater resolution than MIRU–VNTR and also can indicate direction of spread, which has not been possible previously. A recent study in Switzerland used WGS to re-examine TB isolates clustered by identical MIRU–VNTR typing. It was found that 50% of clusters identified could not be confirmed by WGS.[11]

For the benefits of advances in molecular testing to be maximised, a greater proportion of patients on treatment need to have organisms isolated. Forty-three per cent of patients treated in the study by Hamblion *et al* did not have cultured organisms—decreasing this proportion would improve our insight into transmission and the prevalence of drug resistance. In addition, it is vital that field investigations around TB cases are adequately conducted to identify who is infecting who with TB and where this is occurring. The standard 'Stone in the pond' principle for contact tracing may not be sufficient.[12] Social network analysis shows promise but is labour intensive and time consuming[8] and innovative methods to see where TB may be acquired are needed;[13] for example, smart phones lend themselves to providing a picture of places visited which can be difficult to capture by questionnaire.

Evaluating the cost-effectiveness of molecular typing in practice is complex. The key benefits of molecular testing extend well beyond informing cluster investigations.[6 14] Its most important role may be in assessing the impact of changes in policy on patterns of transmission. Worryingly, 34% of cases in London were felt to be due to recent transmission, higher than previous estimates of around 14% from the mid-1990s.[15] Because previous estimates were based on different methodologies (restriction fragment length polymorphism), these data are not directly comparable, but being able to monitor these trends over time will be crucial as new technologies are introduced (and may require *in silico* recreation of VNTR–MIRU data from WGS data to allow comparisons over time). Currently, around 3/4 of TB cases in England occur in people born overseas.[1] Strengthening the implementation of pre-entry screening and latent TB screening in England is likely to impact on this group and the greater resolution of WGS, linked to large datasets of pathogens sequenced from countries of high prevalence, may allow greater confidence in determining the origins of infection.

TB control in England is entering exciting times and it is incumbent on clinical commissioning groups and local TB services to work together to use these new tools to best effect. As one of the first countries in the world to bring routine WGS into its TB services, it is vital that a plan is in place in advance to measure the benefits (or otherwise) of using the newly

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implemented technology. PHE have plans to conduct ongoing evaluation of the utility of WGS to end users in clinical TB services, and this will provide important information for other health systems as they consider implementing technology that will become increasingly affordable.

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