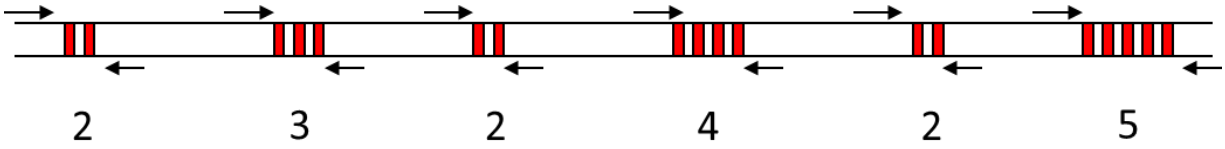
Public Health England

The National Tuberculosis Strain Typing Service

What it involves and how it affects you

24 loci MIRU-VNTR typing

The *M. tuberculosis* complex genome possesses repetitive sequences of DNA located at specific loci. Repeats are referred to as MIRU (mycobacterial interspersed repeat units) or VNTR (variable number tandem repeats) and these vary in number between different loci and between different strains. The strain typing method is PCR based, where the number of repeats at each locus is detected using locus specific primers.



This method distinguishes between *M. tuberculosis* complex strains by comparing the number of repeats present at 24 specific loci across the genome. The MIRU-VNTR profile therefore consists of a 24 digit number which represents the number of repeats at each of these loci (e.g. 232425673216524316425375.)

Advantages and disadvantages of using MIRU-VNTR over other genotyping methods

Method	Advantages	Disadvantages
Restriction Fragment Length Polymorphism (RFLP)	High discriminatory power for distinguishing between stains	Requires a viable culture and large amounts of DNA
	Highly stable with a half-life of 3.2 years (rate at which the biomarker changes)	Labour intensive and time consuming
		Requires technical expertise and specialist software for analysis
		Comparative analysis of RFLP patterns is difficult between different laboratories
Spoligotyping	Requires small amounts of DNA and does not require viable organisms Rapid and reproducible results Easy to compare results between laboratories	Low discriminatory power when used alone
MIRU-VNTR	Higher discriminatory power than spoligotyping	Lower discriminatory power than RFLP
	Rapid and reproducible results Easy to compare results between laboratories	Not always able to obtain a complete MIRU-VNTR profile Stability/mutation rate of biomarker is unclear
	Cheaper than other genotyping methods	
Next generation sequencing	Highest discriminatory power	Expensive
	Stable biomarker	Requires technical expertise and specialist software for analysis
	Can determine the direction of transmission	Interpretation of results is complicated

Where MIRU-VNTR strain typing will be carried out

MIRU-VNTR typing is performed in England at one of three reference laboratories. The National Mycobacterium Reference Laboratory (NMRL) types isolates from southern and eastern England (including London). Isolates from the Midlands and north of England are typed at the Regional Centres for Mycobacteriology (RCM) in Birmingham and Newcastle, respectively. The NMRL also carries out typing for isolates from Northern Ireland and the Cardiff reference laboratory carries out typing for Wales and the South West of England.

The goal of the reference laboratories is to type at least 95% of all initial *M. tuberculosis* isolates with the 24 loci MIRU-VNTR method as part of the routine service, with results available to clinics within 21 days of confirmation of species identification. It is not always feasible to obtain a MIRU-VNTR profile for 100% of isolates, despite repeated testing, due to sample contamination or mixed cultures. There are also some strains where a given locus is untypeable. Laboratories have identified a number of strains with an untypeable locus and these are given the letter “u” to denote that the locus is untypeable.

Information on how the results will be used

24 loci MIRU-VNTR typing results will be reported to the referring NHS hospital laboratory. Results are also received by the Centre for Infectious Disease Surveillance on a regular basis from the TB reference laboratories and these data are available in the Enhanced TB Surveillance System (ETS).

Molecular clusters of cases with 24 loci MIRU-VNTR strain types that are indistinguishable will also be reported through the Strain typing module (component of ETS. Cluster reports are available to view by Health protection Teams, regional users and national users of ETS; reports are regenerated to display the latest results on a weekly basis.

Cluster investigations at a local or national level will be conducted based on guidance available in the “TB Strain Typing and Cluster Investigation Handbook”, December 2013.

- local cluster investigations should be initiated from the local level in response to local demand
- national cluster investigation should be limited to clusters that have been identified to be of public health importance

How to interpret the results

Cases which have indistinguishable 24 MIRU-VNTRs are in the same molecular strain typing cluster and transmission may have occurred. Further information from cases may be collected as part of an investigation including information about time, place, and contacts. Epidemiological links between cases within molecular clusters provide further support for transmission events having occurred. Cases found to have different strain types (even if they are in an epidemiological cluster) should not be considered as being in the same chain of transmission.

How the results will affect my patients

The results of 24 loci MIRU-VNTR typing are unlikely to directly influence the treatment and management of patients. The aim of the National Strain Typing Service is to enable the rapid detection of potential clusters or outbreaks and identify associated transmission settings to inform targeted screening for active and latent TB. By detecting additional TB cases quickly, further onward transmission to individuals can be prevented, leading to a reduction in TB incidence over time.

The National Strain Typing Service data has been collected and is currently being analysed. This analysis should allow us to identify endemic strains circulating in particular regions or populations and strains that are associated with on-going TB transmission in the UK. This will help us to identify true TB outbreaks requiring public health action as opposed to clusters consisting of patients with common imported strains.

Further information

For further information regarding the National Strain Typing Service, please refer to the PHE “TB Strain Typing and Cluster Investigation Handbook”, or email tbsection@phe.gov.uk.

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