Policy and guidelines

Defining a tuberculosis cluster or outbreak

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Executive summary

Transmission of tuberculosis (TB) in an Australian context is a relatively uncommon event. However, episodes of transmission do occur, and may have a large significance in a low-incidence region. Defining when transmission has occurred is not straightforward in a variety of circumstances, but may have significant epidemiologic, public health and political implications. This paper, therefore, will review approaches to determining when transmission has occurred, and offer standardised Australian policy for classification of possible transmission events, including 'clusters' and 'outbreaks'.

Key definitions:

- A 'cluster' of TB cases will be any 2 or more active cases with identified epidemiological links and the same genotype of *Mycobacterium tuberculosis* as defined by the method used.
- A 'probable cluster' will be any 2 or more active cases with identified epidemiological links where genotyping is not feasible (e.g. the case is not confirmed by culture) or the genetic variability between *M. tuberculosis* isolates recovered from cases is minimal, defined as no more than 1 locus variance for mycobacterial interspersed repetitive unit-variable number tandem repeat typing or as advised by expert analysis for whole genome sequencing.
- A 'possible cluster' will be any 2 or more active cases with the same genotype as defined by the method used where temporal and geospatial association is plausible but no direct epidemiological link is identified.
- An 'outbreak' will be defined as a cluster that includes 3 or more active cases with evidence of serial transmission.

Introduction

The World Health Organization's *Framework towards TB elimination in low incidence countries* highlights the importance of detailed understanding of epidemiology and transmission in local contexts.[1] The *Framework* emphasises the need to develop tailored public health interventions in response to this information, particularly for 'containment of local outbreaks' in high-risk groups. However, no standardised inter-jurisdictional definition of an 'outbreak' is offered. Standardised definitions of terms for considering transmission within Australia is an important step towards an improved understanding of local disease epidemiology. Adopting uniform terminology across Australian state and territory jurisdictions would allow for better considerations of national epidemic descriptions, as well as comparison between and within regions. Such considerations are of considerable importance for TB service planning into the future, and in particular, allow detailed consideration of which of various approaches may be more likely to be effective in a given region or population. For example, 2 suburbs may have the same TB incidence but very different rates of transmission, and contexts with high clustering rates will benefit more from appropriately targeted strategies.

Epidemiologic contact tracing

Historically, epidemiologic and contact tracing investigations have formed the basis of the evaluation of transmission of TB in most settings. In particular, the identification of household and other close contacts of known cases of active pulmonary TB through active case finding has been key to describing patterns of risk in many contexts.[2,3] This approach, still very much in use in all Australian jurisdictions, seeks to identify individuals with a history of significant contact with infectious tuberculosis in order to both find additional cases of TB and allow for chemoprophylaxis where TB infection has occurred.[4,5] However, while a history of close contact is associated with an increased risk of TB disease, 2 cases of active TB with known contact may not conclusively establish that transmission has occurred. For example, individuals with TB may have had opportunities for contact with multiple cases of TB in the past, some unrecognised, and it may not be clear which contact has led to infection.[6,7] Conversely, 2 cases of TB without known contact may be linked, as transmission through minor or casual contact is less common but recognised.[8] Therefore, in many circumstances, additional laboratory methods can be employed to further consider the degree to which 2 TB cases may be related.

Laboratory approaches

Fundamentally, laboratory approaches to evaluating potential transmission events seek to evaluate the degree to which 2 (or more) clinical isolates of *M. tuberculosis* are related. While some methods for the identification of TB do not discriminate between isolates (such as microscopy or diagnostic polymerase chain reaction), others provide genomic detail, which may be used to demonstrate similarity or differences between isolates. As summarised in a recent comprehensive review, various methods provide a range of degrees of resolution, from pulsed-field gel electrophoresis, to spoligotyping IS6110-based approaches, mycobacterial interspersed repetitive unit-variable number tandem repeat (MIRU-VNTR) and whole genome sequencing (WGS) (in increasing order of discriminatory power).[9] A demonstration that 2 isolates are significantly different may occur using any method, but increasing confidence in concluding that isolates are clonally related can be provided with methods offering more resolution. Drug susceptibility testing result patterns may also allow isolates to be distinguished, particularly where common genomic profiles are present.

In practice, Australian mycobacterium reference laboratories (MRL) in different jurisdictions all utilise MIRU-VNTR typing and some are increasingly employing WGS. The discriminatory power of a given method can be determined not only by the method but the strain of organism, the time over which transmission has occurred, the presence of mixed strain infection and the section of genome examined. Beijing family strains are well recognised to show restricted variability with conventional MIRU-VNTR typing; increased discrimination can be achieved by examining additional hypervariable VNTR loci,[10] which are not part of the panel usually used by Australian MRLs. Even whole genome sequencing seldom covers the whole genome and certain repetitive sequences are often excluded from analysis.[11]

Review of existing published definitions

Clustering definitions from the United States Centers for Disease Control and Prevention (CDC) are based in the first instance on laboratory data; that is, questions of whether 2 cases of TB are linked are considered subsequent to the identification of genomically indistinguishable isolates.[12] Where 2 or more identical isolates are identified, they are referred to as 'clustered'. Epidemiological considerations are then employed to classify the strength of connection between 2 cases with clustered isolates, with links grouped as 'identified', 'possible' or 'none identified' based on disease characteristics and contact patterns.

Epidemiological and molecular publications on TB transmission have offered a variety of different approaches to defining related terms. In some high incidence settings, clusters may be defined on the basis of epidemiological connection alone (for instance, disease in individuals with shared membership in a household) or spatial proximity.[13] Others have adopted definitions of genomic relatedness to define clusters, sometimes with little epidemiological data beyond date and location of diagnosis.[14] Examples can also be found of laboratory evaluation of isolate similarity by non-genomic methods, such as comparison of strain drug-susceptibility test results.[15] In a review of TB outbreak investigations, the US CDC defined a TB outbreak as $\geq$ 3 epidemiologically linked and genomically matched cases,[16] but such an approach adds little further to the definition of cluster unless there is evidence of serial transmission.

Special challenges

Genomic linkage without local epidemiology

Where circulating international strains are common, cases in Australia may be identified where identical strains occur without known local contact. While connection between these cases (such as may have occurred prior to migration) is possible, the focus on these guidelines is on transmission within Australia. Therefore, definitions will concentrate on a requirement for local epidemiological contact; i.e. where local transmission is plausible based on geospatial and temporal association.

Cases without culture confirmation

While the majority of cases of TB in Australia are confirmed by culture, a proportion are not. This may be due to the site of disease (e.g. pericardial TB or TB uveitis) or related to patient characteristics, particularly young age, where a substantial proportion of paediatric cases are not culture confirmed. While epidemiologic links may be very strong in such situations, such as an Australian-born child with no other history of TB exposure other than a parent recently diagnosed, the absence of genotypic confirmation may still leave some uncertainty regarding the potential transmission event.

Evolution of genotype

The mutation rate of *M. tuberculosis* is low, but incompletely defined. It is accepted that changes in genetic composition occur with time, and it is theoretically possible for mutation to occur around the time of transmission. In such a circumstance, closely related but non-identical strains could be truly clustered. However, such events appear uncommon where MIRU-VNTR (24 loci) test-

ing is employed. Defining a genotyped cluster as sharing identical 24 loci MIRU-VNTR type has been employed in an Australian context[17] but published[18,19] and unpublished observations indicate that isolates recovered from cases with strong epidemiological links can occasionally show a single locus variance and this genomic clustering can be confirmed by use of a second typing method.

Two isolates of *M. tuberculosis* are judged to be the same by WGS if they differ by no more than 5 single nucleotide polymorphisms.[19] It is estimated that molecular evolution would anticipate 0.3–0.5 SNP differences per genome per annum,[19] but these 'molecular clocks' have broad confidence intervals and are not regular[20] and greater than 5 SNP differences to the index case may occur following sequential transmission over many years. In addition, estimates of mutational rate may differ for different phylogenetic lineages.[21] Current evidence indicates that strains with more than 12 SNP differences are very unlikely to be related; where there are 6–12 SNP differences transmission is possible.[19] Use of such definitions has recently been endorsed in a large multi-centre European/North American study.[22]

As whole genome sequencing is increasingly adopted, definitions regarding the degree of genetic change permissible within a cluster will be expected to be reassessed. For the purposes of this standardised Australian position paper, contemporary criteria as proposed by Walker[19] and supported by Pankhurst[22] shall be adopted.

Time course of tuberculosis transmission

Finally, a general issue in TB transmission evaluation is the protracted time that may occur between exposure and development of subsequent disease. This means that any evidence of transmission in a given environment will have the possibility of change over time; that is, even years following potential exposure there remains the chance of additional cases of TB becoming evident. Accordingly, it is proposed that no time considerations be included in definitions related to TB transmission.

Recommendations

Assessment of clusters defined by genomic data and possible transmission pathways within these clusters requires a close collaboration between laboratory specialists, clinicians and epidemiologists taking into account such factors as described above and new scientific information in a rapidly evolving field of study.

A 'cluster' of TB cases will be defined as any 2 or more cases with identified epidemiological links and the same laboratory (genomic and drug susceptibility) profiles. The capacity to define strains as being genetically the same is dependent on the method used and may be subject to change where a more discriminatory method is sequentially adopted. The term 'probable cluster' will be reserved for cases epidemiologically linked without genomic identification of organism (e.g. case not confirmed by culture) or where genotype is not indistinguishable but very closely related as discussed above for MIRU-VNTR typing and WGS. 'Possible cluster' will be reserved for the scenario where the genotype is the same but no epidemiological links are demonstrated but geospatial and temporal association is plausible. Where epidemiology or genomic testing demonstrates linkage is not possible, clustering is excluded. This may occur if case history is incompatible with transmission (for example, 2 cases with extra-pulmonary disease only, or cases not residing in the same state or country during a period of potential transmissibility) or if isolates are shown to be not clonally related.

The term 'outbreak' is not one typically defined in literature relating to TB, in part due to the lengthy latency periods, which may occur following exposure. However, it is felt that a working definition of an outbreak would be useful in an Australian setting, particularly given that identification of an outbreak may signal a need for increased resources applied to a given region or situation. We would suggest that the relevant features of a TB outbreak would be evidence of ongoing community transmission of a genotypic strain of TB, indicating that additional public health measures may be required for prevention of future cases. It is proposed, then, that an 'outbreak' will be defined as a cluster that includes 3 or more cases with evidence of serial transmission; that is, where at least 2 members of the cluster have transmitted disease. While a cluster may occur in a household setting, an outbreak is most unlikely.

It is important to note that these definitions are based only on active disease; cases of TB that result only in the probable acquisition of latent tuberculosis infection (LTBI) are neither clusters nor an outbreak, unless they progress to active disease in future. There are several reasons for this. Firstly, the absence of an isolate in LTBI means that acquisition from a given source is always to a degree, uncertain. Secondly, as a public health evaluation, the identification of recently acquired LTBI allows the use of chemoprophylaxis to prevent the development of active disease. Therefore,

inclusion of cases of LTBI within these definitions would not accurately reflect the public health focus of epidemiological surveillance.

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