Transmission of *Mycobacterium avium* complex in healthcare settings: from environment, person to person, or both?

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Most transmission of *Mycobacterium avium* complex occurs outside of healthcare facilities, and transmission within them is uncommon but likely through indirect means hiip://bit.ly/3ZsvZeC

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Nontuberculous mycobacteria (NTM) are found throughout our environment and infection is thought to occur through acquisition from environmental sources such as soil and water [1]. However, recent studies have reported that many people with cystic fibrosis (CF) share one of several dominant circulating clones, suggesting the possibility of transmission between individuals, perhaps in healthcare facilities [2–4]. Indeed, several studies have reported the possibility of person-to-person transmission of NTM in people with and without CF in the healthcare setting [2, 5–19]. Most of these studies have investigated healthcare-associated transmission of *Mycobacterium abscessus* and *Mycobacterium abscessus* subspecies *massiliense* in the context of CF care centres and they have reported conflicting results, although most concluded that person-to-person transmission was uncommon and does not explain how most people with CF acquire infection.

Within a healthcare facility, transmission could occur directly from person to person, indirectly through a shared source within a healthcare facility or from outside the healthcare facility [20]. In 2012, Aitken *et al.* [5] first reported likely transmission of *M. abscessus* subspecies *massiliense* in a CF care centre using pulsed field gel electrophoresis (PFGE) and rep-PCR to compare strains. The authors concluded that transmission was likely indirect from an environmental intermediate. Although no environmental source was identified, the environmental sampling occurred 8 months after the outbreak. An outbreak of *M. abscessus* subspecies *abscessus* occurred in 2012 in Hawaii, where nine of 19 people with CF harboured isolates that had identical PFGE patterns. The authors concluded that the use of a shared pulmonary function testing laboratory was the likely cause of the outbreak [19]. Both studies described likely indirect transmission and reported that the outbreak ceased after new administrative and infection control policies were implemented.

Subsequently, Bryant *et al.* [2] reported the results of an investigation using whole genome sequencing (WGS) in 168 consecutive isolates of *M. abscessus* from 31 people with CF at Papworth Hospital in the UK. The investigators identified two highly similar clusters of *M. abscessus* subspecies *massiliense*. After performing contact investigations and examining epidemiological data, the authors concluded that healthcare-related transmission, likely indirect in nature, was occurring. The same authors subsequently reported the global dissemination of "dominant clones" of *Mycobacterium abscessus* subspecies *abscessus* and subspecies *massiliense* [3], and suggested that dissemination occurred *via* global transmission networks [4].

Studies from the USA evaluating the genomic population structure of CF-related isolates of *M. abscessus*, *M. massiliense* and *M. avium* complex (MAC) suggest that transmission within CF care centres may be occurring, but that it does so infrequently [6, 12]. Hasan *et al.* [12] evaluated 364 MAC isolates from 186

people with CF from 42 CF care centres across 23 states in the USA. Genomic comparisons revealed 18 clusters of highly similar isolates based on WGS of the core genome within a threshold of ⩽20 single nucleotide polymorphisms (SNPs). In eight (44%) of the clusters, people with CF attended the same CF care centre, but this represented only 15% of the persons in the study. The results of this study, as well as those from most that have been published, suggest that most people with CF do not transmit strains from person to person or share sources of acquisition.

In this current issue of the *European Respiratory Journal*, VAN TONDER *et al.* [21] investigated the potential for person-to-person transmission of MAC by evaluating the similarity in WGS results between 996 isolates from 354 CF and non-CF individuals at the Royal Brompton Hospital in London, UK. The investigators evaluated pairwise SNP distances within patient longitudinal isolates for each species of MAC to calculate thresholds for defining transmission clusters, as has been done in other studies [12]. They used previously published genomes to characterise global population structures. In order to identify epidemiological links, the authors reviewed patient medical records but, importantly, the study was performed retrospectively so important links could have been missed, and there was no attempt to investigate potential transmission sources outside of the healthcare facility.

The authors identified putative transmission in two MAC species, *M. avium* (subspecies *avium* and *hominissuis*) and *M. intracellulare* (subspecies *intracellulare* and *chimaera*). Not surprisingly, based on the study design and the findings from previous reports, epidemiological links could not be identified. The authors concluded that people with and without CF shared transmission chains and the lack of epidemiological links suggested that most transmission is indirect and not related to person-to-person transmission. However, it is possible that unidentified opportunities of transmission were not identified given the retrospective approach and that no out of health facility epidemiological links were investigated.

One limitation of the study by VAN TONDER *et al.* [21], and one shared by most of the other studies assessing healthcare-related transmission, is the lack of environmental sampling. If transmission is occurring through indirect means (patient to environment to patient) then it would be important to document where and how this is happening in healthcare facilities. The four studies [2, 5, 9, 10] that sampled the healthcare environment did so after contact with the health facility or late in the outbreak: two studies did not isolate the putative organism from the environment [2, 5], one noted no identical isolates between patient and environmental samples [9] and one identified a possible source of infection in the healthcare facility [10]. The two studies by GROSS *et al.* [9, 10], used the Healthcare-associated Links in Transmission of NTM (HALT NTM) toolkit, which uses a standardised epidemiological instrument, combined with environmental sampling, watershed analysis and integrated pan-genome analysis for investigation of potential healthcare-associated NTM outbreaks. The authors used this approach to investigate a potential outbreak at the University of Vermont Medical Center Adult CF Program and reported that the majority of people with CF who were infected by clustered *M. chimaera* isolates had a common healthcare environmental acquisition of *M. chimaera*, possibly from or related to the genetically matched hospital water exposure (water fountain). In fact, the respiratory isolates revealed greater genetic similarity to the hospital water biofilm isolate than to each other. This study highlights the importance of environmental sampling in addition to genomic and epidemiological analyses.

An additional potential limitation in the study by VAN TONDER *et al.* [21], and again, one shared by other studies, is the focus on the core genome. Identical core genomes do not mean that the accessory genome is identical [7, 22]. This important point was highlighted in a study that examined the widely dispersed dominant circulating clones seen globally. Examination of the accessory genome demonstrated that strains from Brazil and Papworth in the UK, which shared nearly identical core genomes, had unique accessory genomes [22]. Other studies have also used pan-genome analysis to integrate the use of accessory genome comparisons with core genome SNP comparisons to further scrutinise putative matches [7, 10]. Interrogation of the accessory genome may provide additional discriminatory ability in future studies.

A notable finding of the study was the frequency of mixed NTM infections. VAN TONDER *et al.* [21] report that 45 of 354 patients (12.7%) were infected with two or more species. In a previously published study [12], 15 of 55 people with CF (27%) had multiple strains or species. As noted by the authors, single colonies from sputum cultures may be underrepresenting the underlying diversity of MAC species in patients, so to better understand transmission of MAC species, a deep sequencing approach in which plate sweeps or MGIT cultures are utilised should be considered for future studies.

The authors concluded that "transmission is occurring between CF and non-CF patients even in the presence of strict infection controls". However, that does not seem to be what is presented in the study as

epidemiological links could not be ascertained, only that the people harboured genomically similar strains. Is this enough to conclude person-to-person transmission is occurring? In order to demonstrate that person-to-person transmission is occurring, the mycobacterial isolates should be genetically similar to other patients' or environmental isolates and share epidemiological linkages consistent with shared exposures. The authors clearly demonstrated that patients in their facility have isolates of different MAC species and that subspecies are genomically similar, as has been reported previously in CF care centres with MAC [10, 12] and more commonly with *M. abscessus* and *M. massiliense* [2, 5–9, 11, 13, 15–17, 23]. However, without clear epidemiologic linkages and, ideally, environmental matches for indirect transmission, between patient transmission can only be said to be possible.

In summary, the study by VAN TONDER *et al.* [21] documented that patients in their hospital commonly share genomically nearly identical isolates, as determined by WGS of the core genome. The study has also re-demonstrated the difficulty in identifying whether transmission is occurring from person-to-person in healthcare facilities when looking retrospectively. In the future, studies should be prospective in design, use standardised tools like that used in HALT NTM, sample the clinical environment (and ideally also evaluate home and work environments) and use the pan-genome for analysis. A tall task indeed, but without such an approach it is unlikely we will uncover the answers we seek regarding person-to-person transmission. So, is transmission of MAC due to direct or indirect person-to-person transmission in healthcare facilities or through environmental acquisition outside the healthcare environment? Based on the results of this study and others, we would say that most transmission occurs outside of healthcare facilities and that transmission within them is uncommon but likely through indirect means.

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