Can mixed infection explain the high prevalence of TB in crowded areas with high strain diversity and low HIV prevalence?

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Different TB strains

Tuberculosis (TB) is an airborne disease caused by *Mycobacterium tuberculosis* that is transmitted when an infected individual coughs, sneezes, laughs, speaks, spits or talks. There are many different strains of TB. The first ones were noticed in 1944 after the discovery of the antibiotic streptomycin, as treatment with this drug alone led to resistant mutants (1). Moreover, with mutations, strains have evolved over time and there have been different strains in different regions. In fact, some strains are named according to their purported areas of origin; for example the Beijing strain, which is believed to have its origins in Beijing, China. With present day globalisation, strains have been transported all over the world and this has resulted in a great diversity of strains in some places (2, 3). If there happen to be many strains circulating in a population, then individuals could be infected with more than one strain at a time which we define as *mixed infection*. This is believed to be a rare event (4, 5) due to the preconceived idea of acquired immunity after initial infection (4, 6, 7, 8). However, most of the recurrences of TB turn out to be due to exogenous re-infection with a strain different from the one in the initial episode of disease, and this highlights the role of mixed infections (5). Moreover, there have been an increasing number of molecular epidemiological studies documenting mixed infection in TB (6, 7, 8). These studies have found individuals harbouring more than one strain in their sputum, blood or urine samples.

It is important to note that the tests and methods used for testing of mixed infection are not 100% sensitive (ability to detect all that are infected). Some tests are more sensitive than others, for example Restriction Fragment Length Polymerase (RFLP) and spoligotyping have a higher discriminatory power than mycobacteriophage typing (12). Furthermore, these tests need a certain concentration of bacilli in the sample to work well (13).

Other studies have shown that mixed infection could occur in areas with high TB incidence and where the risk of infection is high (8, 12). It has been documented in prisons (12), mines (5), and homeless shelters (14). All these places have things in common such as overcrowding, poor living and working conditions and bad housing facilities. There is thus a connection between such conditions and mixed infection in TB.

Although most of these areas have been noted to have a high HIV prevalence, it is surprising that some of them have a low HIV prevalence (3, 5) which means that HIV alone can not account for the high TB incidences there. The explanation for this high TB incidence is not known (3).

High prevalence due to mixed infection?

The question that comes to mind then is: Can mixed infection be the explanation for the high prevalence of TB in areas with low HIV prevalence?

The answer to this question one should bear in mind that having more than one strain in individuals’ sputum implies that they could spread more than one strain simultaneously. This means that individuals with mixed infections are more likely to be more infectious than individuals with one strain infections. Another important point is that in individuals with latent TB, those with more than one strain may be at a higher risk of developing active TB than those with one strain only.

The aim of the study described here was to investigate the idea that mixed infection can explain the high prevalence of TB in some areas with overcrowding, low HIV prevalence and a high diversity in TB strains. The major goal was to identify the factors that characterize mixed infection and investigate their impact on both the prevalence of TB and the proportion of mixed infection in these areas.

The parameters related to mixed infection are classified into two categories:
1. Parameters representing the pathogenesis of mixed infection in TB, that is, the risk of reactivation and the probability of transmitting more than one strain at a time.
2. Parameters related to strain diversity and their distribution as well as crowding in the area of study.

To investigate the impact of these parameters, a mathematical model was developed for TB transmission dynamics that accounts for mixed infection. The model does not consider particular strains but focuses on the number of strains that an individual is infected with. Individuals are classified according to the number and not the type of strains they are infected with.

One critical point for mixed infection is that its prevalence is not well estimated. Some studies have shown that it ranges between 2.3% and 75% in
active TB individuals (7, 11, 15) but its prevalence in the total population is unknown (16). This is because not all individuals who have mixed infection show it when they are tested. It is even possible that an individual having mixed infection may be active with one strain and latent with others, and that when tested, that individual would show the one strain only. Furthermore, the effects of mixed infection on mortality and recovery rates are still unclear (7).

Due to the lack of data and information on mixed infection, we carried out an exploratory investigation of the impact of parameters associated with mixed infection on TB dynamics. Our numerical analysis showed that the prevalence and incidence of TB as well as the proportion of mixed infection in a population increase as the values of the parameters related to mixed infection increase.

Figure 1 demonstrates that the contribution of mixed infection to TB prevalence ranges between 10% and 60%. It also shows an increase in the prevalence of one strain infection, which is due to the fact that individuals with mixed infection may transmit one strain at a time. This implies that mixed infection can explain the high TB prevalence and incidence if it does indeed increase the risk of reactivation and the probability of transmitting more than one strain at a time.

Our study suggests that in areas with high prevalence of TB, it is important to reduce the proportion of mixed infection. Since mixed infection occurs mainly in areas with overcrowding and poor living conditions (8), it is useful to determine how the parameters related to mixed infection are affected by these factors. This should take into account the social economic status of individuals, type of housing facilities, number of people per household and the number of houses per square kilometer as well as public services such as transport. It is hoped that this study will guide the collection of data on mixed infection towards better understanding of possible associations between mixed infection and high prevalence of TB. This would further inform clinicians, public health workers and policy makers about the importance of mixed infection in the fight against TB.

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References


