Published in final edited form as:

Infect Genet Evol. 2012 June ; 12(4): 678–685. doi:10.1016/j.meegid.2011.08.010.

Old and New Selective Pressures on *Mycobacterium Tuberculosis*

Daniela Brites^{a,b} and Sebastien Gagneux^{a,b,*}

^aSwiss Tropical and Public Health Institute, Basel, Switzerland ^bUniversity of Basel, Switzerland

Abstract

Tuberculosis (TB) has been affecting humans for millennia. There is increasing indication that human-adapted *Mycobacterium tuberculosis* complex (MTBC) has been co-evolving with different human populations. Some of the most important drivers of MTBC evolution have been the host immune response and human demography. These old selective forces have shaped many of the features of human TB we see today. Two new selective pressures have emerged only a few decades ago, namely HIV co-infection and the use of anti-TB drugs. Here we discuss how the emergence of HIV/TB and drug resistance could impact the long-term balance between MTBC and its human host, and how these changes might influence the future evolutionary trajectory of MTBC.

Keywords

Tuberculosis; HIV; co-infection; selection; immunity; drug resistance

1. Introduction

Tuberculosis (TB) has been known throughout human history (Daniel, 2006). Some of the key features of TB are the chronic nature of the disease, usually preceded by many years of latent infection. During latency, the infecting agent, generally a member of the *Mycobacterium tuberculosis* complex (MTBC) is effectively held in check by the host immune system. Persistent relationships between pathogens and hosts have been suggested to be the result of natural selection favouring co-evolved phenotypes (Blaser and Kirschner, 2007). During most of MTBC's evolutionary history, some of the most important selective pressures have been the host immune response and changes in human demography. Here we start by reviewing these 'old' selective forces in the light of the current evidence for host-pathogen co-evolution in human TB. We then discuss the emergence of the new selective pressures represented by HIV co-infection and the use of anti-microbials, and how these novel forces may influence the evolutionary trajectory of MTBC.

2. Old selective forces in human TB

Mounting evidence suggest that MTBC evolved as a human pathogen in Africa and has spread associated with the first migrations of modern humans out of Africa around 70 000 years ago (Gutierrez et al., 2005; Hershberg et al., 2008). Human MTBC is an obligate human pathogen whose life history traits (growth, replication and transmission) have been

* Corresponding Author: Sebastien Gagneux, Swiss Tropical and Public Health Institute, Basel, Switzerland and University of Basel, Switzerland, Address: Socinstrasse 57, 4051 Basel, Switzerland, Phone: +41 61 284 8369, Fax: +41 61 284 8101, sebastien.gagneux@unibas.ch.

shaped by a potent host immune system, which most of the times controls bacterial survival and replication, and by human demography, which determines the number of available susceptible hosts (Comas and Gagneux, 2011). During the long-term association between MTBC and its human host, the human immune response in TB has evolved into a double-edged sword (Flynn and Chan, 2005). For example, even though one of the primary roles of macrophages is to destroy intracellular pathogens, MTBC evolved mechanisms to survive and replicate inside infected lung macrophages (Flynn and Chan, 2001). Moreover, the transmission potential of MTBC is increased by the formation of lung cavitations (Rodrigo et al., 1997), which to a large extent are a product of host-dependent immunopathological phenomena (Flynn and Chan, 2005). Thus, even though host immunity to TB is essential for an efficient control of bacterial replication, it also contributes to the survival and transmission of MTBC.

Several recent studies support the notion that MTBC might benefit from the host immune responses. Work studying *Mycobacterium marinum* in zebra fish embryos showed that granuloma formation was linked to initial growth of the mycobacteria, and to new macrophages being recruited to the site of infection, hence creating new opportunities for the pathogen to infect new macrophages (Davis and Ramakrishnan, 2009). These observations challenge the usual assumption about granulomas simply being formed to contain the infecting bacteria. Another study found that the sequence variation found in MTBC antigens, which were experimentally confirmed to interact with human T-cells, is consistent with the action of purifying selection (Comas et al., 2010). In other words, natural selection acts to maintain the amino acid sequence in these antigens. One possible explanation put forward was that these antigens elicit an immune response necessary for the transmission of MTBC by, for example, contributing to the establishment of lung cavities.

Transmission in TB is further enhanced by the ability to establish latent infections, which is also dependent on host immunity, as illustrated by the fact that HIV-infected patients with low CD4 T-cell counts progress rapidly to active TB disease (Kwan and Ernst, 2011). Latency was suggested to have evolved as an adaptation to persist in host populations during times when human densities were low (Blaser and Kirschner, 2007). A long latency period followed by reactivation allows the pathogen to jump generations of already infected hosts, and to access new birth cohorts of susceptible individuals. Phylogenetic studies show that human MTBC can be divided into evolutionarily 'ancient' and 'modern' lineages (Brosch et al., 2002; Hershberg et al., 2008). Recent data suggest that ancient MTBC lineages have evolved under low human densities (Hershberg et al., 2008), whereas the more derived, evolutionarily 'modern' lineages are thought to have experienced population expansions following their migration out of Africa and the strong human demographic increases that occurred in Europe, India and China during the last few hundred years (Hershberg et al., 2008; Wirth et al., 2008). In obligate pathogens such as MTBC, in which transmission is directly linked to virulence, increases in host density are predicted to lead to higher virulence and shorter latency as access to new susceptible hosts is enhanced (further discussed below) (Levin, 1996). Of note, the 'modern' MTBC lineages are much more geographically widespread than the 'ancient' lineages (Hershberg et al., 2008), suggesting that the former have an evolutionary advantage (i.e. have a higher fitness) compared to the latter.

In summary, TB is an ancient disease, which through most of its evolutionary history has been to subject of 'old' selective pressures, including the host immune system and human demography. MTBC has evolved to take advantage of host immunity, and the changes in human population densities may have influenced the success of the different MTBC lineages (Comas and Gagneux, 2011). One important question that follows is: how has the human host responded? Clearly, the human immune system is well equipped to deal with MTBC in

most cases, given that only about 10% of latently infected individuals will develop active TB during their lifetime. Yet, two thirds of humans are believed to be latently infected, and are thus unable to completely eradicate the infection. The comparably low number of patients with active TB relative to the high number of latently infected individuals suggests that MTBC is not a very good pathogen in terms of causing disease. However, it is very good at infecting people once active disease develops. Conversely, humans are good at preventing TB disease but less well equipped to prevent infection. Let us now turn to the host and discuss how humans evolved in face of their long-term liaison with MTBC.

3. MTBC and humans, a co-evolutionary relationship?

While host-pathogen co-evolution is increasingly being invoked in human TB (Gutierrez et al., 2005; Hershberg et al., 2008; Wirth et al., 2008), formal demonstration of such a process, particularly in an infectious disease affecting humans, is not trivial. For co-evolution to occur at least three conditions have to be met (Woolhouse et al., 2002); i) genetic variation for the relevant traits of both pathogen and host (e.g. resistance and infectivity); ii) reciprocal effects of those traits on the fitness of the host and pathogen populations, and iii) that the outcome of the interaction between host and pathogen depends on the combination of their genotypes. Co-evolution of host and pathogens can lead to local adaptation when local populations of both host and their parasites adapt reciprocally (Gandon et al., 2002; Kawecki and Ebert, 2004). Hence, local adaptation can be taken as evidence for potential co-evolution.

The population structure of MTBC is highly geographically subdivided (Baker et al., 2004; Brudey et al., 2006; Filliol et al., 2006; Gagneux et al., 2006a; Gutacker et al., 2006; Reed et al., 2009), and the different genetic lineages corresponding to geographical regions seem to have adapted to their local human populations (Gagneux et al., 2006a). However, formal proof for such an adaptation is still lacking, in particular because of the difficulty of separating biological factors from the social impact (Comas and Gagneux, 2009). Nevertheless, there is increasing evidence that the genetic differences between MTBC strains are relevant to the outcome of TB infection and disease in human populations (de Jong et al., 2008; Gagneux and Small, 2007; Nicol and Wilkinson, 2008). *In vitro* experiments and studies in animal models have shown that different MTBC strains vary in immunogenicity and virulence (Coscolla and Gagneux, 2010), suggesting MTBC strains have evolved different ways to overcome host immune responses (Lasunskaja et al., 2010; Portevin et al., 2011). Have humans also evolved certain features in response to the selective pressures imposed by MTBC? It has been suggested that not even the high death toll of the TB epidemics in 19th century Europe constituted a selective pressure strong enough to lead to an increase in frequency of resistance alleles in a way that could explain the decline of TB before the antibiotic era (Lipsitch and Sousa, 2002). By contrast, another study found a positive correlation between dates of first urbanization and the frequency of an allele of the human gene SLC11A1, which has been associated with protection against intracellular pathogens, including MTBC. These findings suggest that MTBC-induced selection drove the increase in frequency of this allele (Barnes et al., 2011). Many other polymorphisms in genes involved in human immunity to TB have been reported, but as resistance to TB is a complex character determined by many genes with small effects (Moller et al., 2010), demonstrating that allele frequencies of genes involved in immunity to TB could be changing as a result of pathogen-imposed selection is not straightforward.

With respect to 'reciprocal adaptive changes' characteristic of host-pathogen co-evolution (Woolhouse et al., 2002), no data are yet available in TB. Nevertheless, a few studies have reported associations between some human polymorphisms in TB patients and particular MTBC strains, supporting the notion that the outcome of infection and disease in TB

depends on the genotype of both the pathogen and the host (Caws et al., 2008; Herb et al., 2008; Intemann et al., 2009; Thye et al., 2011; van Crevel et al., 2009). Whether or not these associations are the result of co-evolution will be difficult to demonstrate rigorously (Comas and Gagneux, 2009). However, certain associations between MTBC strains and particular human populations seem to be highly stable, and could possibly be a strong determinant of the disease and its evolution (Hirsh et al., 2004).

4. Virulence and transmission

Before discussing the effect of novel selective forces on the evolution of MTBC, we would like to review our understanding of virulence in TB. Defining ‘virulence’ is not a trivial matter because any definition will be unsatisfactory under certain circumstances (Bull, 1994; Ebert and Bull, 2008). From an evolutionary perspective, virulence can be seen as a consequence of natural selection acting to maximise parasite transmission, and it can be defined as reduction in the host fitness by pathogen infection (Anderson and May, 1982; Ewald, 1983). As mentioned previously, in pulmonary TB, there is a positive relationship between virulence and transmission, given that transmission is related to the formation of cavities (Rodrigo et al., 1997), which often lead to death of the patient (Helke et al., 2006). In that sense, pulmonary TB is a classical example of the so-called “trade-off” model of virulence (Anderson and May, 1982; Ebert and Bull, 2003; Ewald, 1983). In contrast, clinical expressions of MTBC infection such as tuberculous meningitis or extrapulmonary TB represent a dead end for the bacteria. In this case, MTBC is said to be virulent because it leads to the death of the patient, but this does not confer any survival or reproductive advantage to the pathogen. Such phenomena have been described as the “short-sighted evolution” model of virulence (Levin and Bull, 1994). More importantly for our discussion, this illustrates the importance of using the virulence definition, or the measurements of virulence components, that better reflect the reproductive success of the pathogen. In TB epidemiology, virulence is usually measured as the likelihood of disease progression, the rate of progression to fatal disease, the bacillary load in the sputum, or the presence of cavitations (Helke et al., 2006). In reality, virulence is a composite of all these aspects, and whereas the first measurements reflect the fitness reduction imposed by MTBC infection onto humans, in practice, they tell us little about the benefit to the parasite, which is best determined by the rate of spread or the number of secondary infections. The second measure of virulence can be deceptive because MTBC strains that kill their host more quickly are considered more virulent, but these strains do not necessarily transmit more efficiently (e.g. as in the case of tuberculous meningitis). In reality, an extended (i.e. chronic) duration of pulmonary disease leads to higher transmission of TB, and therefore to higher pathogen fitness (Dye and Williams, 2010).

We feel that discussing the concept of virulence and how it should be measured is particularly relevant in the context of HIV/TB co-infections. The transmission of MTBC from patients with active pulmonary disease correlates with the burden of bacilli in lung cavities as measured by positive sputum-smear (Rouillon et al., 1976). An accelerated progression of TB disease, as observed in HIV/TB co-infected individuals, could be considered a virulent expression of MTBC under some definitions. However, HIV/TB co-infection is also often associated with disseminated TB, which in turn is associated with lower transmission (Rieder et al., 1990; Shafer et al., 1991). Let us now move to the new selective forces that started to impact onto the evolution of MTBC only a few decades ago.

5. New drivers of TB epidemics: HIV and drug resistance

New selective pressure on MTBC Number 1: HIV

Of the estimated 9.4 million cases of incident TB in 2009, 1.2 million were HIV-positive (WHO, 2010). The risk of contracting TB in HIV-positive patients is up to 40-fold higher than in HIV-negative patients (Getahun et al., 2010). In 2009, one in four deaths among HIV-infected people was due to TB (WHO, 2010) and the case fatality rate of incident TB for HIV-positive people was more than two-fold higher than for HIV-negative people (Getahun et al., 2010). Because immunocompromised individuals fail to mount efficient immune responses to control the growth of MTBC, they constitute a fraction of the population which is more susceptible to TB infection, including re-infection, and reactivation (Kwan and Ernst, 2011).

The selective pressures on MTBC, both acting within and between hosts (i.e. at individual or population levels), are possibly very different in HIV-positive compared to HIV-negative patients (Table 1). Individuals co-infected with MTBC and HIV are not able to contain the TB infection, mainly because HIV depletes CD4 T-cells which are essential for macrophage activation and granuloma formation (Forte et al., 1992; Kwan and Ernst, 2011; Shen et al., 1988). Given the link between granuloma formation, cavitation, and transmission in TB, the selective pressures acting on MTBC within the immunocompromised host might have important consequences for the transmission of MTBC to the general population. The infectiousness of HIV/TB co-infected patients compared to HIV-negative individuals has been the subject of many studies, which however have yielded conflicting results. These data, both from nosocomial and community settings, have been combined in a meta-analysis by Cruciani et al. who concluded that overall, HIV co-infected patients were neither more nor less infectious than HIV-negative patients (Cruciani et al., 2001). However, the findings of the different studies were very heterogeneous. Another study not covered in this meta-analysis, suggested that more house-hold contacts from HIV-negative index-cases contracted TB in comparison with contacts from HIV/TB co-infected patients in Rio de Janeiro (Carvalho et al., 2001).

In conclusion, it seems that in some settings, HIV-infected patients with pulmonary disease might transmit MTBC less than HIV-uninfected patients. Probably, HIV-infected individuals are generally less infectious because they harbour fewer bacilli in their sputum due to reduced cavitation (Brindle et al., 1993; Telzak et al., 1998). Additionally, because of the lack of immunity, the mean rate of disease progression in HIV/TB co-infected individuals is accelerated relative to TB patients that are HIV-negative. As a consequence, HIV/TB co-infected patients die earlier (Corbett et al., 2004); i.e. they have a shorter period during which they are infectious, and MTBC has thus less opportunity to spread.

In face of this, how will MTBC evolve in the future? Could HIV patients be a breeding ground for new highly infectious MTBC strains? Or will all strains that transmit from HIV-infected patients have a lower fitness than strains from HIV-negative cases? Transmissibility varies among MTBC strains even in the absence of HIV co-infection (Newton et al., 2006; Nicol and Wilkinson, 2008; Valway et al., 1998). Could different MTBC strains also transmit differently in HIV-infected individuals? We propose three extreme scenarios for the evolution of MTBC in the context of HIV co-infection, which are likely to be too simplistic but potentially useful for generating new hypotheses (Fig. 1). For the sake of simplicity, we do not distinguish between multiple infections with different MTBC genotypes within the same host as opposed to the number of different MTBC genotypes circulating in the host population.

One possibility would be that because of the absence of an intact immune response in HIV-infected individuals, these could be infected by more MTBC genotypes than HIV-negative individuals under the rational “Anybody can make it” (Fig.1 A). This is supported by an observation from a study in San Francisco where HIV-infected individuals had a higher likelihood of becoming infected with MTBC from different genetic lineages than HIV-negative individuals (Gagneux et al., 2006a). In contrast, HIV-negative individuals were more likely to be infected with an MTBC lineage from the same geographical origin as the patient. A few studies reporting on MTBC genetic diversity in HIV-infected *versus* -uninfected patient populations found, except in one case, that the genetic diversity of MTBC isolates in both groups of patient populations was similar (Table 2). However, because of the inherent limitations of the standard molecular techniques used in these studies (Comas et al., 2009) it is not possible to ascertain the degree of relatedness between this MTBC clinical isolates, i.e. whether they belong to different lineages or whether they were different strains belonging to a same lineage.

Even when assuming that HIV-infected patients harbour the same or more MTBC genotypes than HIV-negative patients, it is possible that those genotypes that are fit enough to survive, grow in, and spread from HIV-infected hosts could never infect a HIV-uninfected host, or at least not in the presence of a genotype transmitted by another HIV-uninfected patient (Fig1. A). The implications of this would be that although HIV infections could increase the prevalence of different MTBC genotypes, this would not have any substantial impact in terms of transmission to the general population.

The other two scenarios assume that the human adaptive immune response is necessary for the growth and transmission of MTBC. This being the case, in HIV-infected patients whose adaptive immunity is severely impaired, MTBC would face very stringent conditions and perhaps only a few genotypes would survive (Fig. 1B & C). The success of such MTBC genotypes in terms of their spread to the general population would depend on whether they could transmit only to HIV-infected individuals (Fig. 1B), or whether they could transmit equally well to HIV-infected and uninfected hosts (Fig. 1C). The latter could give rise to ‘super-spreaders’ (Lloyd-Smith et al., 2005), which might be more difficult to control from a public health perspective. Some support to this idea comes from an animal study in which, 98% of infected guinea pigs exposed to ventilated air coming from a ward with HIV/TB co-infected patients, were found to be infected by only 8.5 % of the patients (Escombe et al., 2008). In this study however, transmission of MTBC by HIV-infected and -uninfected individuals were not directly compared. Another study reported that patients in an urban community in Cape Town infected with the so-called “Beijing” genotype were more likely to be HIV-infected (Middelkoop et al., 2009). This supports the idea that certain MTBC genotypes might have a competitive advantage in HIV-infected individuals. Two further studies from Cape Town showed that the Beijing lineage has been emerging over the last few decades in this region, possibly associated with the emergence of HIV (Cowley et al., 2008; van der Spuy et al., 2008).

We are only aware of one theoretical study that addressed this topic in a quantitative manner ((Basu and Galvani, 2009). Using computer simulations, the authors found that the increase in HIV/TB co-prevalence will lead to the evolution of MTBC genotypes that are more virulent to the general population. This study considered that transmission to HIV-infected and -uninfected individuals was similar, which would correspond to our third scenario (Fig. 1C).

New selective pressure on MTBC Number 2: anti-microbial drugs

The biological factors that influence the emergence and spread of drug-resistant strains are still not very well known. For example, how well do they transmit in comparison to drug-

sensitive strains? What is the role of compensatory mutations in clinical settings? Is the high burden of MDR-TB strains mainly due to *de novo* resistance acquired during treatment (secondary resistance) or to transmission of drug-resistant strains (primary resistance)? These aspects have been reviewed by (Cohen et al., 2003) and more recently by (Borrell and Gagneux, 2009). The evolutionary success of drug-resistance strains, and consequently the extent to which they will influence the TB epidemics, will to a large part depend on their ability to transmit when compared to drug-sensitive strains. Epidemiological studies in different human populations reporting active cases of TB transmission reported that MDR-TB strains vary markedly in their transmission potential (Borrell and Gagneux, 2009). *In vitro*, it has been shown that strains bearing rifampicin laboratory-derived resistance-conferring mutations grew slower than their sensitive counterparts (Billington et al., 1999; Gagneux et al., 2006b; Mariam et al., 2004). Interestingly, some clinical strains carrying these same mutations suffered no fitness reduction in relation to their drug-sensitive ancestral strain (Gagneux et al., 2006b). This suggests that compensatory mutations can occur (Andersson and Hughes, 2010), and that the selective pressures imposed by drug treatment are strong enough to select for drug-resistant strains that have small to no fitness defects (Bottger et al., 1998). How will the phenomena of compensatory mutations influence MDR in the future? Is it possible that it partially explains the high rates of MDR reported in some regions of the former Soviet Union where MDR strains have been circulating for several decades? Multidrug resistance has also been associated with the Beijing MTBC lineages in several geographical regions (reviewed in (Borrell and Gagneux, 2009)). However, the underlying basis of this association remains unknown. The Beijing lineage of MTBC represents about 50% of the strains in East Asia and around 10% of all MTBC strains worldwide (Parwati et al., 2010). Could this lead to higher MDR rates in the future? MDR-TB is a particular problem in HIV-coinfected patients (WHO, 2010). So let us now discuss how the combined effects of HIV co-infection and MDR-TB might influence the evolution of MTBC.

New selective pressures on MTBC Number 1+2: HIV and anti-microbial drugs

Theoretical studies support what is commonly assumed; the immune system can contribute to the clearance of bacteria by acting synergistically with drug treatment (Handel et al., 2009). The emergence of drug resistance results from the interplay between selection, mutation rate from the sensitive to the resistant strain, and transmission of drug resistance-conferring mutations already present in the population (Zur Wiesch et al., 2011). Once drug resistance has emerged, additional compensatory mutations might occur which can lead to an increase or stabilization of the frequency of drug resistance-conferring mutations, even in the absence of the drug (Andersson and Hughes, 2010). In HIV/TB patients under treatment, the selective pressure imposed by the immune system on drug resistance-conferring mutations is weaker than in TB patients who are not HIV co-infected. How will the prevalence of HIV/TB co-infection shape the spread of drug-resistant strains? Our previous hypothetical “Anybody can make” scenario goes along with the idea that a weaker immune pressure could lead to a higher diversity of MTBC genotypes, including different drug-resistant genotypes, within a host and/or in the host population. Here it is necessary to distinguish between these two levels, as multiple infections can have a significant impact on primary resistance levels (Sergeev et al., 2011). Patients that are not under TB treatment and carry a majority of drug-sensitive genotypes may carry small numbers of drug-resistant genotypes, which will out-compete the drug-sensitive bacteria once the patient starts treatment. Furthermore, these drug-resistant genotypes might be able to transmit while the patient is under first-line drug treatment. This has been suggested by a recent study where a relatively high frequency of mixed infections was unveiled in HIV/TB co-infected patients (Cohen et al., 2011).

But do HIV/TB co-infections increase the likelihood of generating *de novo* drug-resistant mutations? One possibility is that by reducing the selection imposed by the immune system the population sizes of the bacteria within host increases. This being true, as the probability of acquiring drug resistance-conferring and compensatory mutations increases with population size (Zur Wiesch et al., 2011), and assuming similar drug selective pressures for both HIV-infected and -uninfected patients, drug resistance would be more likely to emerge in HIV/TB co-infected individuals. Such an effect could appear in a scenario as the one described as “Anyone can make it” (Fig. A). Furthermore, this effect could be enhanced in the presence of more MTBC genetic diversity considering that the fitness effects of drug-resistant mutations can be influenced by the genetic background of MTBC (Borrell and Gagneux, 2011). If more MTBC strain genetic backgrounds are present in a single host and/or in the host population, this would increase the chances that a particular drug resistance-conferring mutations occurs in a genetic background that confers less fitness defects compared to a different genetic background. The relevance of this for the general population would be, as discussed before, dependent on the transmissibility of these drug-resistant strains compared to strains that are transmitted from HIV-uninfected patients (Fig. 1A). Another interesting aspect suggested by a theoretical study is that even drug-resistant genotypes with low transmission potential could propagate in areas with high MTBC genetic diversity due to reduced levels of host cross-immunity (Basu et al., 2008).

Turning to the two other scenarios (Fig. 1B & 1C), could HIV-infected individuals be a source of drug-resistant ‘superspreader’ genotypes? Assuming as proposed above, that components of the adaptive immune system are necessary for optimal growth and transmission of MTBC, we would argue that this situation is perhaps less likely because it would require that not only drug-resistant and compensatory mutations accumulate, but mutations allowing MTBC to grow and spread in the absence of granulomas and cavitations would also be required. Furthermore, to spread into the general population, these genotypes would have to have a competitive advantage compared to drug-sensitive genotypes and genotypes from HIV-negative individuals (Fig. 1C). Nosocomial transmission of an MDR strain from HIV-infected patients to HIV-negative patients has been documented in Buenos Aires, Argentina (Palmero et al., 2003). This shows that transmission of particular MDR strain can be successful.

6. Concluding remarks

The relationship between MTBC and humans is ancient, which has shaped many of the characteristics of TB. The expression of TB is best explained as the result of an intimate dialogue between the bacteria and the human immune system. During the last decades, this relationship has been in altered, both at the individual and at the population level, by the appearance of HIV and the use of anti-TB drugs. Here we speculated on how these new selective pressures could influence TB in the future. For our discussion, we have greatly simplified the complex relationship between the pathogen and the host population. Furthermore, we have completely ignored the many socio-economic and environmental factors likely to influence this relationship (Comas and Gagneux, 2009, 2011). Yet, despite being overly simplistic, hypothetical scenarios as the ones presented here can help generating new research questions. For example, do HIV/TB-coinfected individuals and/or populations harbour more MTBC genetic diversity than HIV-negative individuals? Do some bacterial genotypes from HIV/TB-coinfected patients transmit more efficiently than others? Does this correlate with the degree of depletion in the patient's CD4 T-cells? Or which other properties do these MTBC genotypes exhibit? Can we pinpoint mutations that explain why some of these genotypes seem to be fitter than others? Elucidating the evolutionary aspects of this host-pathogen system might help us understand the responses of MTBC to the current and future changes in selective pressures imposed by the human host and its environment.

Acknowledgments

We thank all the members of our group for comments on the manuscript. Work in our laboratory is supported by the Swiss National Science Foundation (PP00A-119205) and the National Institutes of Health (AI090928 and HHSN266200700022C). D.B. is supported by the Marie Heim-Vögtlin program of the Swiss National Science Foundation.

References

- Anderson RM, May RM. Coevolution of hosts and parasites. *Parasitology*. 1982; 85(Pt 2):411–426. [PubMed: 6755367]
- Andersson DI, Hughes D. Antibiotic resistance and its cost: is it possible to reverse resistance? *Nat Rev Microbiol*. 2010; 8:260–271. [PubMed: 20208551]
- Baker L, Brown T, Maiden MC, Drobniewski F. Silent nucleotide polymorphisms and a phylogeny for *Mycobacterium tuberculosis*. *Emerg Infect Dis*. 2004; 10:1568–1577. [PubMed: 15498158]
- Barnes I, Duda A, Pybus OG, Thomas MG. Ancient urbanization predicts genetic resistance to tuberculosis. *Evolution*. 2011; 65:842–848. [PubMed: 20840594]
- Basu S, Galvani AP. The evolution of tuberculosis virulence. *Bulletin of Mathematical Biology*. 2009; 1:1073–88. [PubMed: 19172358]
- Basu S, Orenstein E, Galvani AP. The theoretical influence of immunity between strain groups on the progression of drug-resistant tuberculosis epidemics. *J Infect Dis*. 2008; 198:1502–13. [PubMed: 18816192]
- Billington OJ, McHugh TD, Gillespie SH. Physiological cost of rifampin resistance induced in vitro in *Mycobacterium tuberculosis*. *Antimicrob Agents Chemother*. 1999; 43:1866–1869. [PubMed: 10428904]
- Blaser MJ, Kirschner D. The equilibria that allow bacterial persistence in human hosts. *Nature*. 2007; 449:843–849. [PubMed: 17943121]
- Borrell S, Gagneux S. Infectiousness, reproductive fitness and evolution of drug-resistant *Mycobacterium tuberculosis*. *Int J Tuberc Lung Dis*. 2009; 13:1456–1466. [PubMed: 19919762]
- Borrell S, Gagneux S. Strain diversity, epistasis and the evolution of drug resistance in *Mycobacterium tuberculosis*. *Clin Microbiol Infect*. 2011; 17:815–820. [PubMed: 21682802]
- Bottger EC, Springer B, Pletschette M, Sander P. Fitness of antibiotic-resistant microorganisms and compensatory mutations. *Nat Med*. 1998; 4:1343–1344. [PubMed: 9846553]
- Brindle RJ, Nunn PP, Githui W, Allen BW, Gathua S, Waiyaki P. Quantitative bacillary response to treatment in HIV-associated pulmonary tuberculosis. *Am Rev Respir Dis*. 1993; 147:958–961. [PubMed: 8466133]
- Brosch R, Gordon SV, Marmiesse M, Brodin P, Buchrieser C, Eiglmeier K, Garnier T, Gutierrez C, Hewinson G, Kremer K, Parsons LM, Pym AS, Samper S, van Soolingen D, Cole ST. A new evolutionary scenario for the *Mycobacterium tuberculosis* complex. *Proc Natl Acad Sci U S A*. 2002; 99:3684–3689. [PubMed: 11891304]
- Brudey K, Driscoll JR, Rigouts L, Prodinger WM, Gori A, Al-Hajjaj SA, Allix C, Aristimuno L, Arora J, Baumanis V, Binder L, Cafrune P, Cataldi A, Cheong S, Diel R, Ellermeyer C, Evans JT, Fauville-Dufaux M, Ferdinand S, Garcia de Viedma D, Garzelli C, Gazzola L, Gomes HM, Gutierrez MC, Hawkey PM, van Helden PD, Kadival GV, Kreiswirth BN, Kremer K, Kubin M, Kulkarni SP, Liens B, Lillebaek T, Ly HM, Martin C, Mokrousov I, Narvskaja O, Ngeow YF, Naumann L, Niemann S, Parwati I, Rahim MZ, Rasolofo-Razanamparany V, Rasolonavalona T, Rossetti ML, Rusch-Gerdes S, Sajduda A, Samper S, Shemyakin I, Singh UB, Somoskovi A, Skuce R, van Soolingen D, Streicher EM, Suffys PN, Tortoli E, Tracevska T, Vincent V, Victor TC, Warren R, Yap SF, Zaman K, Portaels F, Rastogi N, Sola C. *Mycobacterium tuberculosis* complex genetic diversity: mining the fourth international spoligotyping database (SpolDB4) for classification, population genetics and epidemiology. *BMC Microbiol*. 2006; 6:23. [PubMed: 16519816]
- Bull JJ. Perspective: virulence. *Evolution*. 1994; 48:1423–1437.

- Carvalho AC, DeRiemer K, Nunes ZB, Martins M, Comelli M, Marinoni A, Kritski AL. Transmission of *Mycobacterium tuberculosis* to contacts of HIV-infected tuberculosis patients. *Am J Respir Crit Care Med*. 2001; 164:2166–2171. [PubMed: 11751181]
- Caws M, Thwaites G, Dunstan S, Hawn TR, Thi Ngoc Lan N, Thuong NT, Stepniewska K, Huyen MN, Bang ND, Huu Loc T, Gagneux S, van Soolingen D, Kremer K, van der Sande M, Small P, Thi Hoang Anh P, Chinh NT, Thi Quy H, Thi Hong Duyen N, Quang Tho D, Hieu NT, Torok E, Hien TT, Dung NH, Thi Quynh Nhu N, Duy PM, van Vinh Chau N, Farrar J. The influence of host and bacterial genotype on the development of disseminated disease with *Mycobacterium tuberculosis*. *PLoS Pathog*. 2008; 4:e1000034. [PubMed: 18369480]
- Cohen T, Sommers B, Murray M. The effect of drug resistance on the fitness of *Mycobacterium tuberculosis*. *Lancet Infect Dis*. 2003; 3:13–21. [PubMed: 12505028]
- Cohen T, Wilson D, Wallengren K, Samuel EY, Murray M. Mixed-strain *Mycobacterium tuberculosis* infections among patients dying in a hospital in KwaZulu-Natal, South Africa. *J Clin Microbiol*. 2011; 49:385–388. [PubMed: 20980576]
- Comas I, Chakravarti J, Small PM, Galagan J, Niemann S, Kremer K, Ernst JD, Gagneux S. Human T cell epitopes of *Mycobacterium tuberculosis* are evolutionarily hyperconserved. *Nat Genet*. 2010; 42:498–503. [PubMed: 20495566]
- Comas I, Gagneux S. The past and future of tuberculosis research. *PLoS Pathog*. 2009; 5:e1000600. [PubMed: 19855821]
- Comas I, Gagneux S. A case for systems epidemiology in tuberculosis research. *Trends Microbiol*. 2011 in press.
- Comas I, Homolka S, Niemann S, Gagneux S. Genotyping of genetically monomorphic bacteria: DNA sequencing in *Mycobacterium tuberculosis* highlights the limitations of current methodologies. *PLoS ONE*. 2009; 4:e7815. [PubMed: 19915672]
- Corbett EL, Charalambous S, Moloi VM, Fielding K, Grant AD, Dye C, De Cock KM, Hayes RJ, Williams BG, Churchyard GJ. Human immunodeficiency virus and the prevalence of undiagnosed tuberculosis in African gold miners. *Am J Respir Crit Care Med*. 2004; 170:673–679. [PubMed: 15191919]
- Coscolla M, Gagneux S. Does *M. tuberculosis* genomic diversity explain disease diversity? *Drug Discov Today Dis Mech*. 2010; 7:e43–e59. [PubMed: 21076640]
- Cowley D, Govender D, February B, Wolfe M, Steyn L, Evans J, Wilkinson RJ, Nicol MP. Recent and rapid emergence of W-Beijing strains of *Mycobacterium tuberculosis* in Cape Town, South Africa. *Clin Infect Dis*. 2008; 47:1252–9. [PubMed: 18834315]
- Cruciani M, Malena M, Bosco O, Gatti G, Serpelloni G. The impact of human immunodeficiency virus type 1 on infectiousness of tuberculosis: a meta-analysis. *Clin Infect Dis*. 2001; 33:1922–1930. [PubMed: 11692305]
- Daniel TM. The history of tuberculosis. *Respir Med*. 2006; 100:1862–1870. [PubMed: 16949809]
- Davis JM, Ramakrishnan L. The role of the granuloma in expansion and dissemination of early tuberculous infection. *Cell*. 2009; 136:37–49. [PubMed: 19135887]
- de Jong BC, Hill PC, Aiken A, Awine T, Antonio M, Adetifa IM, Jackson-Sillah DJ, Fox A, Deriemer K, Gagneux S, Borgdorff MW, McAdam KP, Corrah T, Small PM, Adegbola RA. Progression to active tuberculosis, but not transmission, varies by *Mycobacterium tuberculosis* lineage in The Gambia. *J Infect Dis*. 2008; 198:1037–43. [PubMed: 18702608]
- Dye C, Williams BG. The population dynamics and control of tuberculosis. *Science*. 2010; 328:856–861. [PubMed: 20466923]
- Ebert D, Bull JJ. Challenging the trade-off model for the evolution of virulence: is virulence management feasible? *Trends Microbiol*. 2003; 11:15–20. [PubMed: 12526850]
- Ebert, D.; Bull, JJ. The evolution and expression of virulence. In: Stearns, SC.; Koella, JC., editors. *Evolution in Health and Disease*. Oxford University Press; New York: 2008. p. 153-167.
- Escombe AR, Moore DA, Gilman RH, Pan W, Navincopa M, Ticona E, Martinez C, Caviedes L, Sheen P, Gonzalez A, Noakes CJ, Friedland JS, Evans CA. The infectiousness of tuberculosis patients coinfecting with HIV. *PLoS Med*. 2008; 5:e188. [PubMed: 18798687]
- Ewald PW. Host-parasite relations, vectors, and the evolution of disease severity. *Annu Rev Ecol Syst*. 1983; 14:465–485.

- Filliol I, Motiwala AS, Cavatore M, Qi W, Hernando Hazbon M, Bobadilla Del Valle M, Fyfe J, Garcia-Garcia L, Rastogi N, Sola C, Zozio T, Guerrero MI, Leon CI, Crabtree J, Angiuoli S, Eisenach KD, Durmaz R, Joloba ML, Rendon A, Sifuentes-Osornio J, Ponce de Leon A, Cave MD, Fleischmann R, Whittam TS, Alland D. Global phylogeny of *Mycobacterium tuberculosis* based on Single Nucleotide Polymorphism (SNP) analysis: insights into tuberculosis evolution, phylogenetic accuracy of other DNA fingerprinting systems, and recommendations for a minimal standard SNP Set. *J Bacteriol.* 2006; 188:759–772. [PubMed: 16385065]
- Flynn JL, Chan J. Immunology of tuberculosis. *Annu Rev Immunol.* 2001; 19:93–129. [PubMed: 11244032]
- Flynn JL, Chan J. What's good for the host is good for the bug. *Trends Microbiol.* 2005; 13:98–102. [PubMed: 15737727]
- Forte M, Maartens G, Rahelu M, Pasi J, Ellis C, Gaston H, Kumararatne D. Cytolytic T-cell activity against mycobacterial antigens in HIV. *AIDS.* 1992; 6:407–411. [PubMed: 1377474]
- Gagneux S, Deriemer K, Van T, Kato-Maeda M, de Jong BC, Narayanan S, Nicol M, Niemann S, Kremer K, Gutierrez MC, Hilty M, Hopewell PC, Small PM. Variable host-pathogen compatibility in *Mycobacterium tuberculosis*. *Proc Natl Acad Sci U S A.* 2006a; 103:2869–2873. [PubMed: 16477032]
- Gagneux S, Long CD, Small PM, Van T, Schoolnik GK, Bohannon BJ. The competitive cost of antibiotic resistance in *Mycobacterium tuberculosis*. *Science.* 2006b; 312:1944–1946. [PubMed: 16809538]
- Gagneux S, Small PM. Global phylogeography of *Mycobacterium tuberculosis* and implications for tuberculosis product development. *Lancet Infect Dis.* 2007; 7:328–337. [PubMed: 17448936]
- Gandon S, Agnew P, Michalakis Y. Coevolution between parasite virulence and host life-history traits. *Am Nat.* 2002; 160:374–388. [PubMed: 18707446]
- Getahun H, Gunneberg C, Granich R, Nunn P. HIV infection-associated tuberculosis: the epidemiology and the response. *Clin Infect Dis.* 2010; 50(3):S201–207. [PubMed: 20397949]
- Gutacker MM, Mathema B, Soini H, Shashkina E, Kreiswirth BN, Graviss EA, Musser JM. Single-nucleotide polymorphism-based population genetic analysis of *Mycobacterium tuberculosis* strains from 4 geographic sites. *J Infect Dis.* 2006; 193:121–128. [PubMed: 16323140]
- Gutierrez C, Brisse S, Brosch R, Fabre M, Omais B, Marmiesse M, Supply P, Vincent V. Ancient origin and gene mosaicism of the progenitor of *Mycobacterium tuberculosis*. *PLoS Pathogens.* 2005; 1:1–7.
- Handel A, Margolis E, Levin BR. Exploring the role of the immune response in preventing antibiotic resistance. *J Theor Biol.* 2009; 256:655–662. [PubMed: 19056402]
- Helke KL, Mankowski JL, Manabe YC. Animal models of cavitation in pulmonary tuberculosis. *Tuberculosis (Edinb).* 2006; 86:337–348. [PubMed: 16359922]
- Herb F, Thye T, Niemann S, Browne EN, Chinbuah MA, Gyapong J, Osei I, Owusu-Dabo E, Werz O, Rusch-Gerdes S, Horstmann RD, Meyer CG. ALOX5 variants associated with susceptibility to human pulmonary tuberculosis. *Human molecular genetics.* 2008; 17:1052–1060. [PubMed: 18174194]
- Hershberg R, Lipatov M, Small PM, Sheffer H, Niemann S, Homolka S, Roach JC, Kremer K, Petrov DA, Feldman MW, Gagneux S. High functional diversity in *Mycobacterium tuberculosis* driven by genetic drift and human demography. *PLoS Biology.* 2008; 6:e311. [PubMed: 19090620]
- Hirsh AE, Tsolaki AG, DeRiemer K, Feldman MW, Small PM. Stable association between strains of *Mycobacterium tuberculosis* and their human host populations. *Proc Natl Acad Sci U S A.* 2004; 101:4871–4876. [PubMed: 15041743]
- Intemann CD, Thye T, Niemann S, Browne EN, Amanua Chinbuah M, Enimil A, Gyapong J, Osei I, Owusu-Dabo E, Helm S, Rusch-Gerdes S, Horstmann RD, Meyer CG. Autophagy gene variant IRGM -261T contributes to protection from tuberculosis caused by *Mycobacterium tuberculosis* but not by *M. africanum* strains. *PLoS Pathog.* 2009; 5:e1000577. [PubMed: 19750224]
- Kawecki TJ, Ebert D. Conceptual issues in local adaptation. *Ecol Lett.* 2004; 7:1225–1241.
- Kwan CK, Ernst JD. HIV and tuberculosis: a deadly human syndemic. *Clin Microbiol Rev.* 2011; 24:351–376. [PubMed: 21482729]

- Lasunskaja E, Ribeiro SC, Manicheva O, Gomes LL, Suffys PN, Mokrousov I, Ferrazoli L, Andrade MR, Kritski A, Otten T, Kipnis TL, da Silva WD, Vishnevsky B, Oliveira MM, Gomes HM, Baptista IF, Narvskaya O. Emerging multidrug resistant *Mycobacterium tuberculosis* strains of the Beijing genotype circulating in Russia express a pattern of biological properties associated with enhanced virulence. *Microbes Infect.* 2010; 12:467–475. [PubMed: 20215000]
- Levin BR. The evolution and maintenance of virulence in microparasites. *Emerg Infect Dis.* 1996; 2:93–102. [PubMed: 8903208]
- Levin BR, Bull JJ. Short-sighted evolution and the virulence of pathogenic microorganisms. *Trends Microbiol.* 1994; 2:76–81. [PubMed: 8156275]
- Lipsitch M, Sousa AO. Historical intensity of natural selection for resistance to tuberculosis. *Genetics.* 2002; 161:1599–1607. [PubMed: 12196403]
- Lloyd-Smith JO, Schreiber SJ, Kopp PE, Getz WM. Superspreading and the effect of individual variation on disease emergence. *Nature.* 2005; 438:355–359. [PubMed: 16292310]
- Mariam DH, Mengistu Y, Hoffner SE, Andersson DI. Effect of *rpoB* mutations conferring rifampin resistance on fitness of *Mycobacterium tuberculosis*. *Antimicrob Agents Chemother.* 2004; 48:1289–1294. [PubMed: 15047531]
- Middelkoop K, Bekker LG, Mathema B, Shashkina E, Kurepina N, Whitelaw A, Fallows D, Morrow C, Kreiswirth B, Kaplan G, Wood R. Molecular epidemiology of *Mycobacterium tuberculosis* in a South African community with high HIV prevalence. *J Infect Dis.* 2009; 200:1207–11. [PubMed: 19764885]
- Moller M, de Wit E, Hoal EG. Past, present and future directions in human genetic susceptibility to tuberculosis. *FEMS Immunol Med Microbiol.* 2010; 58:3–26. [PubMed: 19780822]
- Newton SM, Smith RJ, Wilkinson KA, Nicol MP, Garton NJ, Staples KJ, Stewart GR, Wain JR, Martineau AR, Fandrich S, Smallie T, Foxwell B, Al-Obaidi A, Shafi J, Rajakumar K, Kampmann B, Andrew PW, Ziegler-Heitbrock L, Barer MR, Wilkinson RJ. A deletion defining a common Asian lineage of *Mycobacterium tuberculosis* associates with immune subversion. *Proc Natl Acad Sci U S A.* 2006; 103:15594–8. [PubMed: 17028173]
- Nicol MP, Wilkinson RJ. The clinical consequences of strain diversity in *Mycobacterium tuberculosis*. *Trans R Soc Trop Med Hyg.* 2008; 102:955–65. [PubMed: 18513773]
- Palmero D, Ritacco V, Ambroggi M, Marcela N, Barrera L, Capone L, Dambrosi A, di Leonardo M, Isola N, Poggi S, Vescovo M, Abbate E. Multidrug-resistant tuberculosis in HIV-negative patients, Buenos Aires, Argentina. *Emerg Infect Dis.* 2003; 9:965–969. [PubMed: 12967495]
- Parwati I, van Crevel R, van Soolingen D. Possible underlying mechanisms for successful emergence of the *Mycobacterium tuberculosis* Beijing genotype strains. *Lancet Infect Dis.* 2010; 10:103–111. [PubMed: 20113979]
- Portevin D, Gagneux S, Comas I, Young D. Human macrophage responses to clinical isolates from the mycobacterium tuberculosis complex discriminate between ancient and modern lineages. *PLoS Pathog.* 2011; 7:e1001307. [PubMed: 21408618]
- Reed MB, Pichler VK, McIntosh F, Mattia A, Fallow A, Masala S, Domenech P, Zwerling A, Thibert L, Menzies D, Schwartzman K, Behr MA. Major *Mycobacterium tuberculosis* lineages associate with patient country of origin. *J Clin Microbiol.* 2009; 47:1119–28. [PubMed: 19213699]
- Rieder HL, Snider DE Jr, Cauthen GM. Extrapulmonary tuberculosis in the United States. *Am Rev Respir Dis.* 1990; 141:347–351. [PubMed: 2301852]
- Rodrigo T, Cayla JA, Garcia de Olalla P, Galdos-Tanguis H, Jansa JM, Miranda P, Brugal T. Characteristics of tuberculosis patients who generate secondary cases. *Int J Tuberc Lung Dis.* 1997; 1:352–357. [PubMed: 9432392]
- Rouillon A, Perdrizet S, Parrot R. Transmission of tubercle bacilli: The effects of chemotherapy. *Tubercle.* 1976; 57:275–299. [PubMed: 827837]
- Sergeev R, Colijn C, Cohen T. Models to understand the population-level impact of mixed strain *M. tuberculosis* infections. *J Theor Biol.* 2011; 280:88–100. [PubMed: 21514304]
- Shafer RW, Kim DS, Weiss JP, Quale JM. Extrapulmonary tuberculosis in patients with human immunodeficiency virus infection. *Medicine (Baltimore).* 1991; 70:384–397. [PubMed: 1956280]
- Shen JY, Barnes PF, Rea TH, Meyer PR. Immunohistology of tuberculous adenitis in symptomatic HIV infection. *Clin Exp Immunol.* 1988; 72:186–189. [PubMed: 3261659]

- Telzak EE, Fazal BA, Turett GS, Justman JE, Blum S. Factors influencing time to sputum conversion among patients with smear-positive pulmonary tuberculosis. *Clin Infect Dis*. 1998; 26:775–776. [PubMed: 9524873]
- Thye T, Niemann S, Walter K, Homolka S, Intemann CD, Chinbuah MA, Enimil A, Gyapong J, Osei I, Owusu-Dabo E, Rusch-Gerdes S, Horstmann RD, Ehlers S, Meyer CG. Variant G57E of Mannose Binding Lectin associated with protection against tuberculosis caused by *Mycobacterium africanum* but not by *M. tuberculosis*. *PLoS ONE*. 2011; 6:e20908. [PubMed: 21695215]
- Valway SE, Sanchez MP, Shinnick TF, Orme I, Agerton T, Hoy D, Jones JS, Westmoreland H, Onorato IM. An outbreak involving extensive transmission of a virulent strain of *Mycobacterium tuberculosis*. *N Engl J Med*. 1998; 338:633–639. [PubMed: 9486991]
- van Crevel R, Parwati I, Sahiratmadja E, Marzuki S, Ottenhoff TH, Netea MG, van der Ven A, Nelwan RH, van der Meer JW, Alisjahbana B, van de Vosse E. Infection with *Mycobacterium tuberculosis* Beijing genotype strains is associated with polymorphisms in SLC11A1/NRAMP1 in Indonesian patients with tuberculosis. *J Infect Dis*. 2009; 200:1671–4. [PubMed: 19863441]
- van der Spuy GD, Kremer K, Ndabambi SL, Beyers N, Dunbar R, Marais BJ, van Helden PD, Warren RM. Changing *Mycobacterium tuberculosis* population highlights clade-specific pathogenic characteristics. *Tuberculosis (Edinb)*. 2008; 89:120–5. [PubMed: 19054717]
- WHO. Global tuberculosis control - surveillance, planning, financing. WHO; Geneva, Switzerland: 2010.
- Wirth T, Hildebrand F, Allix-Beguec C, Wolbeling F, Kubica T, Kremer K, van Soolingen D, Rusch-Gerdes S, Loch C, Brisse S, Meyer A, Supply P, Niemann S. Origin, spread and demography of the *Mycobacterium tuberculosis* complex. *PLoS Pathog*. 2008; 4:e1000160. [PubMed: 18802459]
- Woolhouse ME, Webster JP, Domingo E, Charlesworth B, Levin BR. Biological and biomedical implications of the co-evolution of pathogens and their hosts. *Nat Genet*. 2002; 32:569–577. [PubMed: 12457190]
- Zur Wiesch PA, Kouyos R, Engelstadter J, Regoes RR, Bonhoeffer S. Population biological principles of drug-resistance evolution in infectious diseases. *Lancet Infect Dis*. 2011; 11:236–247. [PubMed: 21371657]

Figure 1.

Hypothetical representation of the infection and transmission dynamics of MTBC in HIV-positive (HIV⁺) and HIV-negative (HIV⁻) individuals. Transmission is represented by arrows. When transmission is impaired the arrow is interrupted by a cross. Different colours represent different MTBC genotypes; 1A - “Anybody can make it” hypothesis. 1B - “Superspreader” hypothesis with no transmission to HIV-negative individuals. 1C - “Superspreader” hypothesis with transmission to both HIV-negative and HIV-positive individuals

Table 1

Selection levels acting on MTBC within and between hosts in HIV-positive and -negative individuals.

Levels of selection	Selective pressure		HIV ⁻	HIV ⁺	Host ^a	HIV ⁻	HIV ⁺	MTBC ^b	HIV ⁻	HIV ⁺
Within host	Immune system	MTBC clonal competition	↑	↓	Granuloma	↑	↓	Sputum bacilli	↑	↓
			?	?	Cavitation	↑	↓			
Between host	Spread	Duration of infectiousness	↑	↓	Coughing	↑	↓	Sputum bacilli	↑	↓
			↑	↓						

The direction of the arrows indicate whether each feature is likely to increase, decrease or whether this is unclear (?);

^a human symptoms in response to MTBC infection;

^b traits important for MTBC transmission.

Table 2

Reports on genetic diversity of MTBC in HIV - positive and – negative populations.

MTBC genetic diversity ^a	HIV ⁺ /HIV ⁻	Molecular marker	Region	Nr. of MTBC isolates	Patient recruitment	Reference
~		IS6110-RFLP	South Africa	HIV ⁺ = 65 HIV ⁻ = 56	Community	Middelkoop et al., 2009
~		Spoligo MIRUS	Burkina Faso	HIV ⁺ = 43 HIV ⁻ = 77	Not specified	Godreuil et al., 2007
>		FAFLP	Peru	HIV ⁺ = 80 HIV ⁻ = 25	Hospital	Ahmed et al., 2003
~		IS6110-RFLP	Uganda	HIV ⁺ = 80 HIV ⁻ = 103	Hospital and health care centres	Asiimwe et al., 2009
~		IS6110-RFLP PCR fingerprinting	Sardinia	HIV ⁺ = 39 HIV ⁻ = 22	Hospital	Sechi et al., 1996
~		IS6110-RFLP	Japan	HIV ⁺ = 86 HIV ⁻ = 87	Hospital	Otsuka et al., 2005
~		IS6110-RFLP	Tanzania	HIV ⁺ = 68 HIV ⁻ = 66	Community	Yang et al., 1995

^a symbols: “~”= similar genetic diversity; “>” = higher diversity,