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BCG vaccination following latent TB treatment: Possible implications for different settings

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ABSTRACT

Despite much progress globally, TB is still one of the top 10 causes of death worldwide. Several studies have shown the importance of implementing different preventive strategies alongside treatment of TB disease, including BCG vaccination and treatment of latent tuberculosis infection (LTBI). Large-scale population level LTBI treatment is not currently part of WHO guidelines which recommend LTBI treatment only to high risk populations. Moreover, BCG has been widely used in the past decades to both prevent infection with M. tuberculosis and reduce rates of reactivation. In this viewpoint we discuss the hypothesis of BCG vaccination following latent TB treatment and its potential impact across different settings.

The last century has seen dramatic changes in tuberculosis (TB) worldwide. The development of vaccination and effective antimicrobial treatment, combined with better living standards, led to the decline of TB in Western Europe and North America. More recently, the global TB epidemic has been compounded by emergence of drug-resistant strains and co-infection with other morbidities such as HIV and diabetes, especially in low and middle income settings. Consequently, despite much progress globally, TB is still one of the top 10 causes of death worldwide.

When individuals are exposed to *Mycobacterium tuberculosis* and infected, they are thought to enter a non-infectious latent stage where they can immediately progress to full-blown disease, or spend months, years or, in the majority of cases, their whole life with a lifelong low probability of reactivating. This probability can be magnified if they develop immunosuppression. Until recently, the global effort to end TB has largely focussed on active TB treatment which does not address the large pool of latently infected individuals that is estimated to comprise at least a quarter of the world population (Houben and Dodd, 2016). Several studies have shown the importance of implementing different preventive strategies alongside treatment of TB disease (Abu-Raddad et al., 2009), including treatment of latent tuberculosis infection (LTBI) (Ziv et al., 2001) and especially in high HIV-prevalent settings (Mwinga et al., 1998; Lawn et al., 2010; Houben et al., 2014). However, due to the low prognostic value of existing assays and lack of a well-established LTBI treatment success monitoring tools/biomarkers, large-scale population level LTBI treatment is not currently part of WHO guidelines. Current guidelines offer LTBI treatment only to high risk populations such as HIV positive individuals and young children (<5 years) who are contacts of active cases, while treatment may also be considered for older child and adult contacts (WHO, 2018). The population level impact of targeting only a limited number of individuals is, however, likely limited as the majority of individuals who will develop TB are not easily identified as recent contacts and do not have HIV. Consequently, this strategy fails to identify the large number of TB cases that will arise from a wider pool of remotely exposed individuals with a low risk of progression (Figure 1).

We used a simple SEEIR compartmental model of infectious disease transmission (susceptible S, early latent E_e, late latent E_l, infectious I and recovered R) with two exposed compartments, to compare three scenarios: no LTBI treatment (yellow line), 50% of early-latency treatment only (dark blue line) and 50% of early-latency treatment plus 10% of late latent treatment (green line). Early-latency treatment is not enough to concretely reduce the number of active TB infections. However, because of the high number of late-latency infections in the populations, even treating a small percentage of them would mean treating a very high number of individuals, which is rarely a realistic scenario.

Studies (Stagg et al., 2014) have shown that short duration rifamycin based therapy is more efficacious than other approaches at preventing active TB. However the effects of large-scale

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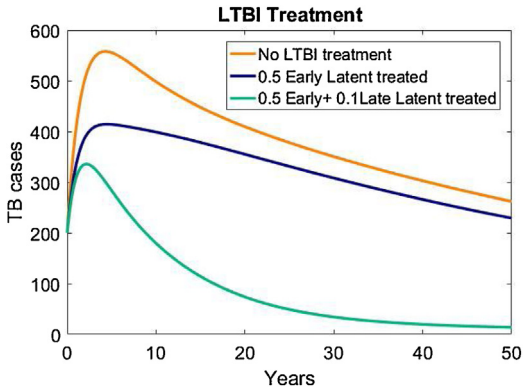

Figure 1. An example of LTBI treatment in a population.

population level LTBI treatment are difficult to predict in the long run, particularly in highly endemic settings. Uncertainty exists in relation to our inability to define LTBI cure, one exploratory study (Biraro et al., 2015) showed that isoniazid preventive therapy led to effects on the immune response to *M. tuberculosis*, however decreased levels of cytokines and antibodies are not enough to predict the complete clearance of TB infection. Both tuberculin skin test (TST) and interferon-ϒ release assay (IGRA) cannot distinguish current infection from prior remote exposure, and test results continue to be positive even after LTBI treatment completion. Furthermore, LTBI treatment does not offer protection against reinfection, limiting the durability of protection in regions characterised by high force of infection (e.g. mines).

Our previous work has shown that BCG is highly efficacious if given to individuals who are not already infected with *M. tuberculosis*, determined by absence of a response to tuberculin (Mangtani et al., 2014; Abubakar et al., 2013). This systematic review specifically demonstrated that the absence of prior *M. tuberculosis* infection or sensitization with environmental mycobacteria is associated with higher efficacy of BCG against pulmonary tuberculosis and possibly against miliary and meningeal tuberculosis. BCG does not work in those known to be infected by *M. tuberculosis*. The inference from this analysis is that prior infection to *M. tuberculosis* blocks or masks the effect of BCG vaccination. It is therefore reasonable to hypothesise that there may be a different immune response to BCG vaccination among individuals who have completed treatment for LTBI, compared to people with untreated LTBI. In this case, it is possible to suggest that the clearance of *M. tuberculosis* infection might influence the 'unblocking' of the protective immune response induced by BCG vaccination. Preclearance of *M. tuberculosis* is heterogeneous (some individuals will effectively have *M. tuberculosis* cleared while it will be residual in others), a recent small underpowered study (Suliman et al., 2016) has suggested that it has little effect on the classical lymphocyte immune response, but highlighted a surprising durability of memory NKT-like and NK cells after BCG revaccination. Moreover, ensuring the individual status related to infection prior to BCG vaccination is also important in preventing skin reactions such as Koch-like reactions.

A recent trial found that BCG revaccination works as well as a novel vaccine (H4:IC31) in preventing sustained IGRA conversion (Nemes et al., 2018) among IGRA-negative individuals, although the authors acknowledged that there is no definitive test for acquisition, persistence, or clearance of *M. tuberculosis* infection. This raises a research question on whether BCG vaccination or revaccination may confer protection to those individuals who successfully obtain clearance of *M. tuberculosis* using a rifamycin-based regimen. There are several reasons why this strategy, if successful, will contribute to ending the global TB epidemic.

First, immunisation with BCG is one of the most common TB interventions, particularly in children in endemic settings where it is usually part of the childhood immunization program. Roy et al. (2014) showed that, while it offers limited protection against infection, it offers 71% protection against disease and a duration of effect of 10–15 years. Exploring the impact of BCG vaccination following LTBI treatment at a population level would provide a further avenue to strengthen TB control.

Second, in high-incidence countries the number of people latently infected is high and, while mass treatment of these individuals with a positive IGRA or TST is not realistic, even if LTBI treatment is limited to direct contacts of active cases, vaccination post treatment may protect them from re-infection in a high transmission setting for another 10–20 years.

The combination of LTBI treatment and BCG vaccination could also be offered to other high risk populations. In the specific case of mine workers, for example, if vaccine coverage is sufficiently high, this could potentially create herd immunity. Other risk groups such as individuals affected by diabetes and silicosis may also benefit from this strategy. A combined LTBI treatment BCG vaccination strategy could also have a positive impact in countries with high prevalence of drug-resistant strains. An effective preventive treatment could avoid longer, more expensive treatments in cases of multi-drug resistant and extensively drug-resistant strains.

In low-incidence countries, high risk groups include migrants, drug users and those with a history of incarceration. While the force of infection in the general population is very low, in some of these high risk groups, levels of transmission can be very high (Sacchi et al., 2015; Carbone et al., 2015). If the majority of individuals originating from high-incidence countries resides in the same area, there can also be ongoing transmission within these households which may be prevented by a BCG post LTBI treatment strategy.

The search for new tools to end the TB epidemic will require us to revisit the use of existing tools and ensure maximal benefit is obtained. While our hypothesis is supported by a range of related observations, only a trial to establish protection by BCG following latent TB treatment can confirm this.

Conflict of interest

No conflict of interest applies.

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Ethical approval

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