Exploring the Ethics of Tuberculosis Human Challenge Models

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Abstract

TB human challenge studies could accelerate TB vaccine development by reducing uncertainty in early-stage vaccine testing, selecting promising vaccine candidates for large-scale field trials, and identifying an immune correlate of protection. However, ethical concerns regarding the exposure of trial participants and bystanders to significant risk have been a limiting factor for TB human challenge models. We analyze the expected social value and risks of different types of TB human challenge models, and conclude that given the massive public health burden of TB, challenge models with even scant probabilities of expediting TB vaccine authorization have enormous expected humanitarian value, saving between 33,000 and 1,375,000 lives over the next ten years. We argue that attenuated *M.tb* challenge trials can be conducted ethically, and discuss the benefits and drawbacks of conducting virulent *M.tb* challenge trials.

Keywords: human challenge trials, research ethics, tuberculosis

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Background

1.1 Human challenge studies to advance vaccine development

Human challenge studies— trials in which volunteers are deliberately exposed to a pathogen— have contributed vital scientific knowledge to advance vaccine development in recent decades (Amrita and Kang 2020). Challenge models have been used for a wide range of diseases, including malaria, influenza, dengue, norovirus, rhinovirus, typhoid, streptococcus, and most recently COVID-19 (Cohen 2016). Studies involving deliberate infection are particularly useful when field studies to gauge vaccine efficacy are lengthy and expensive. In such cases, efficacy data from challenge studies combined with data from safety studies may be sufficient for vaccine approval. This was the path of licensure for Vaxchora, the first FDA-approved cholera vaccine (Mosley 2017). More commonly, challenge data can help reduce uncertainty in the early stages of vaccine development by allowing for the optimal allocation of resources toward the most promising vaccine candidates, reducing the costs of clinical development, and encouraging investment in larger-scale trials (Roestenberg et al. 2018).

Supplementary questions regarding vaccination, such as optimal method of administration and vaccine dosage, can also be investigated through challenge studies. In addition to directly testing vaccines, challenge studies can advance scientific understanding about pathogens more broadly by revealing precise data on disease pathogenesis, correlates of immune protection, viral kinetics and shedding, all of which can indirectly support vaccine development and inform public health policy (Expert Committee On Biological Standardization 2016)[5].

1.2 TB vaccine development and the state of TB human challenge studies

In recent years, there has been growing interest in the role of human challenge studies to advance tuberculosis (TB) vaccine development (Brazier and McShane 2020; Davids et al. 2020; Kaufmann et al. 2016; McShane 2020; Robertson 2007).

The Bacillus Calmette–Guérin (BCG) vaccine, the only available TB vaccine, was developed and licensed nearly one hundred years ago. Despite nearly universal BCG coverage in TB-endemic regions (World Health Organization 2021). TB caused 1.4 million deaths in 2019, more deaths than any other pathogen World Health Organization 2020). This is in part because BCG is just 19% effective at preventing infection in children, and 58% effective at preventing disease (Roy et al. 2014). Effectiveness tends to wane almost entirely in adolescence and adulthood, leading to significant death rates amongst adults ages 50 and older, although there are some areas in which BCG confers durable protection (Usher et al. 2019). The 2001 Global Tuberculosis Report estimates that BCG prevents only 5% of all vaccine-preventable deaths from TB (World Health Organization 2001).

Two new TB vaccine approaches that may have advantages over a single infant BCG vaccination have recently shown promise in clinical trials (Geddes 2021). Firstly, a Phase 2b trial showed that M72/AS01E, a combination of two *Mycobacterium tuberculosis* (*M.tb*) protein fragments, protected adults with latent *M.tb* infection (LTBI) from disease with an efficacy rate of 50% compared to unvaccinated adults with LTBI (Tait et al. 2019). Secondly, a Phase 2 trial showed that a BCG booster dose was 45% efficacious at reducing sustained *M.tb* infection (Nemes et al. 2018). However, it remains to be seen whether BCG revaccination protects against disease, and one study has shown that it did not Rodrigues et al. 2005). Preventing infection alone would take decades to impact disease rates.

While no other TB vaccine candidates have yet shown efficacy in clinical trials, several other vaccine candidates are in the pipeline, including *M.tb*VAC, which is based on a live-attenuated strain of *M.tb* and could therefore possibly be of use as a challenge agent (Marinova et al. 2017).

These vaccine candidates may significantly reduce TB disease burden, however, several structural barriers may prolong their late-stage trialing and authorization. These barriers can be addressed through a human challenge model.

1.3 Limitations of animal models

Animal challenge models do not adequately represent the complexity of *M.tb* infection and TB disease in humans. The availability of *M.tb* challenge models in mice, guinea pigs, cattle, rabbits, and non-human primates have elucidated certain pathways in pathogen-host interaction, but none recapitulate all aspects of human TB (Singh et al. 2018). This has led to increased advocacy for human TB models to be more biologically relevant and can therefore reveal more useful data on TB pathogenesis[7]. TB studies can also significantly increase the usefulness of animal models by allowing researchers to bridge vaccine efficacy between animal models and human models. In such a study, researchers would look to validate desirable correlates of vaccine protection in virulent animal models following attenuated human models.

1.4 Phase 3 trials can be lengthy and expensive

Phase 3 trials to gauge TB vaccine efficacy have several limitations. First, they take several years on average, causing millions of TB deaths in the meantime. Large Phase 3 trials are also expensive: a recent rotavirus Phase 3 trial cost over $100 million to conduct (Light et al. 2009). Due to its scale and length, a Phase 3 trial with a TB vaccine candidate is likely to cost a similar amount.
Since TB primarily affects the global poor, funding Phase 3 trials is an especially unattractive economic prospect for pharmaceutical companies. A lack of funding has been a consistent obstacle for TB vaccine research (Venkatesan 2021).

Human challenge trials can address the pitfalls of Phase 3 trials by allowing for quick reads on vaccine efficacy to prioritize vaccines for larger-scale trials. Reducing uncertainty in the early stages of vaccine development can be of enormous utility in convincing funders and stakeholders that Phase 3 trials are worth the time and investment (Roestenberg et al. 2018). In particular, they are a useful way of down-selecting which vaccine candidates should progress to field efficacy studies. Investors who may not otherwise fund larger efficacy studies may be convinced to do so on grounds that a vaccine candidate performed well in challenge studies, shaving years off of vaccine development. It is possible that eventually, efficacy data from challenge studies, in combination with efficacy data from Phase 2b trials and safety data from larger field studies, may be sufficient for vaccine authorization, obviating the need for a lengthy Phase 3 trial.

1.5 Correlates of immune protection

Unlike other infectious diseases such as influenza, there is no identified immune correlate of protection for TB, making authorization by surrogate endpoint impossible and limiting early estimates on vaccine efficacy. TB researchers face a catch-22 without the use of a human challenge trial: a candidate correlate of protection can only be validated in the clinical trial of an effective vaccine, yet given the limitations of Phase 3 trials, clinical trials of an effective vaccine may not be feasible without a validated correlate of protection (Bhatt et al. 2015).

Social Value of a TB Human Challenge Model

To determine whether or not the social value of a clinical trial is sufficient to ethically justify the risks to trial participants, it is first necessary to elucidate the expected social value of the trial. How many lives might a human TB challenge trial save? How much ill-health might such a model alleviate?

Rid and Roestenberg provide a framework to determine the expected social value of human challenge trials by considering both (a) the magnitude of the disease health burden in relation to (b) the probability that a trial contributes to the mitigation of this disease burden (Rid and Roestenberg 2020). In the rest of this section, we describe the global TB disease burden and offer a range of estimates for how many lives an TB challenge model might save.

2.1 Magnitude of TB disease burden

In 2019, TB caused an estimated 10 million illnesses and 1.4 million deaths, making it the world's deadliest pathogen and the leading cause of death for people with HIV. Of the 40 million people who have been treated for TB since 2018, 1.5 million people had developed multidrug-resistant TB, and were therefore unaffected by rifampicin, the most affected first-line TB treatment (World Health Organization 2020). TB overwhelmingly affects the global poor and contributes to cycles of poverty in which TB illness reduces economic mobility, and crowded conditions and impaired immune function associated with poverty lead to greater disease spread (Zaman 2010). Lengthy treatment regimens contribute to this cycle, with a meta-analysis of TB patients in Africa finding that direct and indirect medical costs associated with TB are substantial and often "catastrophic" for those in the income-poorest 20% of the population (Barter et al. 2021).

There are several effective public health interventions that have contributed to a decline in TB over the past decade, including a 14% decrease in deaths from 2015 to 2019. These include increased diagnosis, drug susceptibility testing, preventative treatment for high-risk populations including HIV-positive populations, and the mitigation of environmental determinants of TB such as poverty (Uplekar et al. 2015). Despite these efforts, few countries have met the 2020 milestones set out by the WHO's End TB Strategy, with the poorest countries falling behind the most. Global TB incidence is falling around 2% a year, but needs to accelerate to approximately 4-5% to reach key WHO milestones of reducing TB deaths by 90% by 2035 (World Health Organization 2020). Public health efforts were further stymied by the COVID-19 pandemic, which led to an estimated increase of 400,000 deaths from the year prior (Chakaya et al. 2021). Given the slow pace of TB control efforts, it is clear that the authorization and large-scale distribution of a more effective TB vaccine are essential for significant reductions in TB incidence and death in the coming decade (Hatherill et al. 2020). The exceptional negative global public health effects of TB mean that even low probabilities of contributing to the development of a more effective TB vaccine could have enormously positive humanitarian effects.

Table 1: Estimated lives saved by a TB challenge model over the next ten years†

	Probability that a new TB challenge model speeds new TB vaccine authorization relative to other trial designs by reducing uncertainty in early stage vaccine development	**Years that a new TB challenge model saves in authorizing new TB vaccine relative to other trial designs**	**Risk difference in mortality between new authorized TB vaccine and current standard of vaccination**	**Estimated lives saved over next 10 years by using new TB challenge model††**
Low-end estimate	0.1	3	0.1	33,000
Middle-end estimate	0.25	4	0.3	330,000
High-end estimate	0.5	5	0.5	1,375,000

† In the absence of rigorous modeling of TB deaths through 2030 following the COVID-19 pandemic, we optimistically (and therefore, in the context of our model, conservatively) assume that TB deaths decrease by 4% per year over the next ten years from the estimated 1.4 million deaths in 2019.

†† Calculated as follows: (Probability that a new TB challenge model speeds new TB vaccine authorization relative to other trial designs) x (Years that a new TB challenge model saves in authorizing new TB vaccine relative to other trial designs) x (Difference in reduction of mortality between new authorized TB vaccine and next best alternative) x (Expected average lives lost per year globally from TB)

2.2 Probability that an TB *challenge trial contributes to TB mitigation*

Having described the significant global disease burden of TB and the importance of continued TB vaccine development, the next step in estimating the expected social value of a TB human challenge trial is discerning the likelihood that such a study would contribute to the speedier authorization of more effective TB vaccines.

As Rid and Roestenberg observe, the "complexity, uncertainty and dynamic nature" of biomedical research in general, and human challenge studies in particular, make precise and robust predictions of the social value of research very difficult. Nonetheless, Rid and Roestenberg outline several crucial considerations for making this judgement, including the novelty and innovation of research questions, feasibility and rigor of research conduct, and influence on future research with the potential to lead to health benefits (Rid and Roestenberg 2020).

Leading TB vaccinologists agree that establishing a TB challenge model would significantly aid in vaccine development (McShane 2020; Robertson 2007). We previously discussed the unique use cases of TB human challenge models in an earlier section, *TB vaccine development and the state of TB human challenge studies*, which include: the speedy testing of promising vaccine candidates for down-selection and optimal resource reallocation, reducing uncertainty in early-stage vaccine development to encourage investment in larger-scale TB efficacy trials, the identification of an immune correlate of TB protection to enable future vaccine testing via surrogate endpoint, the optimization of vaccine route of administration and dosage size, and the study of TB pathogenesis. Several TB challenge models are still in development and thus may not be feasible for several years; however, given the slow pace of traditional TB vaccine development and the consistently high disease burden of TB, challenge models that are established in the near future will likely still have significant utility.

Looking to precedent, human challenge models have been essential to advancing vaccine development for diseases that are endemic in similar regions to TB, including cholera and malaria[1,3]. Hokey et al. write that the same may be possible for TB vaccine development (Hokey 2014):

> "The human challenge model could change the field of TB vaccine development as the malaria human challenge model did for malaria vaccines, not only by providing a less expensive and rapid method for assessing potential vaccine efficacy, but also by permitting more rapid progress toward the identification of an immune correlate of protection."

In Table 1, we offer low, middle, and high-end estimates of the lives saved *ex ante through* a TB challenge model, assuming an average rate of total TB deaths over the next decade of approximately 1.1 million per year†.

For instance, in our middle-end estimate, we say that if a given TB challenge model is 25% more likely to speed the authorization of a 30% more efficacious TB vaccine by 4 years, then the challenge model will save 330,000 lives *ex ante.*

Table 1 has several limitations. Above all, the ever-changing nature of disease burden means that our assumptions in the model may not be accurate at the time when researchers are deciding whether or not to conduct a specific TB challenge trial. Since there is no rigorous mathematical modelling of the public health effects of speeding the authorization of the two most promising next-generation TB vaccines, namely M72/AS01E and BCG revaccination, we employed simple probabilities for estimates for vaccine efficacy and the speed of vaccine rollout. Moreover, our low, middle, and high-end estimates correlate specific probabilities that an TB challenge model speeds vaccine research with specific probabilities that such a vaccine is more or less effective, but there is no *a priori* reason why these figures should be correlated.

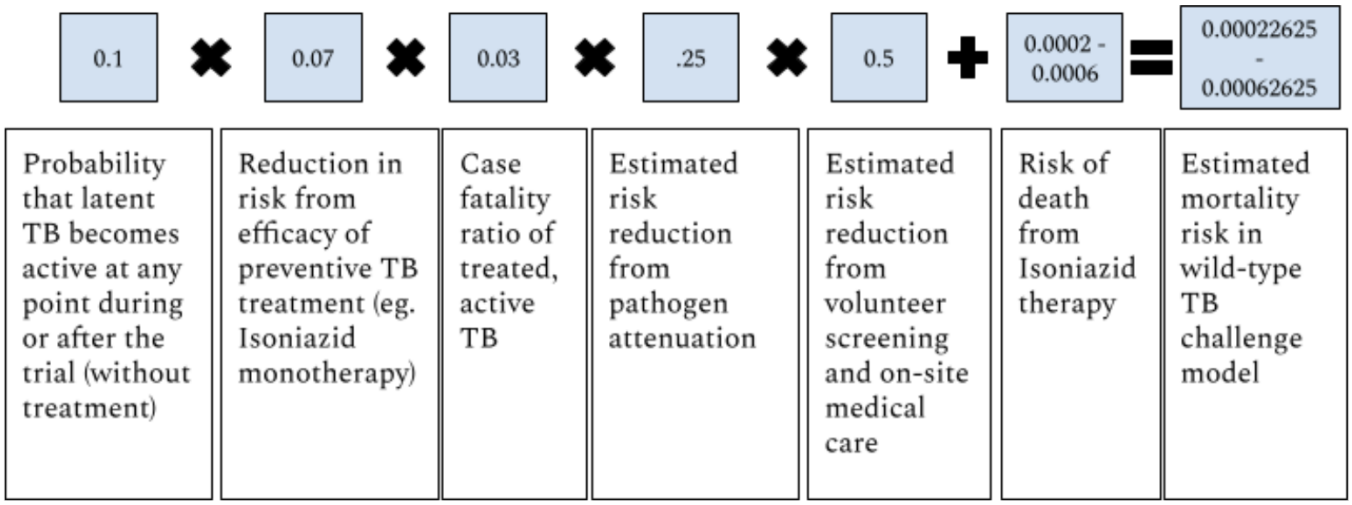
Despite its limitations, we think Table 1 decisively illustrates that even with low probabilities of speeding the authorization of slightly better TB vaccines, TB human challenge models can have significant global public health value. In fact, the table is likely conservative in its estimation of the reduction of disease burden in these trials for three reasons. Firstly, it does not account for the full range of TB disease burden, such as morbidity, cost of treatment, and macroeconomic effects. In total, TB is responsible for 40 million lost disability-adjusted-life-years annually (Kassebaum 2016). Secondly, it focuses solely on the short-term value of challenge models in speeding vaccine development, not accounting for the long-run value of possibly discerning correlates of TB immune protection, which could aid TB vaccine development for decades to come. Thirdly, it does not account for the compounding effect of TB vaccination in reducing TB deaths by curbing disease transmission.

The expected social value of a TB human challenge trial is largely dependent on the specific type of trial. Table 2 offers a breakdown of the use cases, limitations, and risks associated with various TB challenge models. In the next section, we discuss the risks of conducting different types of TB human challenges.

Risks of a TB Human Challenge Model

TB human challenge models may have significant public health value, but is this value high enough to ethically justify giving volunteers TB? In the rest of this article, we analyze the risks of TB, first in general, and then in the context of different types of human challenge trials, with a focus on attenuated pulmonary *M.tb* challenge

Figure 1: Estimated mortality following Mtb infection in an attenuated Mtb challenge trial



models. We conclude that attenuated *M.tb* challenge trials can be conducted ethically. We also explore the benefits and drawbacks of virulent *M.tb* human challenge models.

3.1 Risks of TB

What are the rates of mortality and morbidity for a given case of TB? Upon infection, patients will develop latent TB, a symptom-free condition which, without treatment, will turn active 5-10% of the tim (Centers for Disease Control and Prevention 2021). Preventative treatments for those with latent TB, such as Isoniazid monotherapy, reduce the likelihood that latent TB becomes active by 93% assuming full patient compliance with therapy (Kim and Kim 2018).
While active TB is curable 90% of the time with an antibiotic cocktail consisting of Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol (TB Alert 2015), active TB still leads to death 3% of the time for HIV-negative patients (Straetemans et al. 2011). TB antibiotics carry their own risks: Isoniazid, a primary component of TB treatment, can cause hepatotoxicity which results in death between 0.02% and 0.06% of the time (Kabbara et al. 2016). Considering the probability that latent TB turns active, the mortality rates of active TB, and the mortality rates of Isoniazid, we estimate that the overall mortality rate following *M.tb* infection in the general population, even with the best treatment, is likely between 0.000221 - 0.000705 (see Figure 1).

In addition to short-term mortality risk, well-treated TB disease also involves significant long-term negative health effects. In a study of all-cause mortality for people with treated TB, Romanowski et al. find “significantly increased mortality following treatment compared with the general population or matched controls” (Romanowski et al. 2019). Pulmonary TB is associated with long-term lung complications, such as fibrosis, lung scarring, bronchiectasis, and chronic pulmonary disease (Chakaya 2016). In a study of 2,137 South African miners with a history of TB, Hnizdo et al. find that impairment of lung function was found in 18%, 27%, and 35% of subjects after one, two, or three episodes of the TB (Hnizso et al. 2000). TB treatment itself also carries long-term risks: microbiomic perturbation caused by TB therapy is long-lasting, which can cause and exacerbate other diseases (Schwartz et al. 2020; Wipperman et al. 2017).

While latent TB is not transmissible, active TB has an R naught between 0.23 and 4.3; R naught being lower in high-income countries like Netherlands and higher in low-income countries like China and India (Ma et al. 2018). Each TB case therefore carries a significant risk of community transmission; however, this risk can be minimized through active monitoring of at-risk individuals and subsequent safety procedures, as discussed in the following section.

3.2 Risks in the context of an attenuated TB human challenge model

In the context of a human challenge study, TB risks to volunteers are likely to be significantly lower than risks in the general population for three reasons. First is the attenuation of the pathogen itself. The probability of mortality and morbidity would decrease upon exposure to a strain of *M.tb* that has a limited period of replication and/or regulated expression of kill switches. Such an attenuated model could significantly reduce the chances of latent TB infection becoming active long after the commencement of the study, when a volunteer may be immunocompromised. While it is difficult to estimate a priori exactly how much an attenuated model might reduce the risks of TB, we assume conservatively in Figure 1 that the process of attenuation will likely reduce the risk of death in an TB challenge trial by 75%.

Secondly, researchers can select volunteers in the lowest risk profile, that is, young volunteers with no TB comorbidities. This is likely to reduce risks considerably, as the majority of TB deaths occur for people that are HIV positive and/or people with low body mass indices (Bhargava and Bhargava 2020). The elderly and very young are also at disproportionately high risk of TB disease (Wipperman et al. 2017). Prescreening for healthy volunteers is limited by the possibility that a volunteer ages significantly and becomes immunocompromised after the trial, when they are still susceptible to the activation of latent TB. An attenuated model reduces this likelihood.

Thirdly, unlike many TB-endemic regions which have poor health infrastructure, *M.tb* challenge trial participants will have access to world-class treatments, as well as excellent and timely medical care in the case of any adverse events. We estimate in Figure 1 that in tandem, volunteer prescreening and safety measures are likely to reduce mortality following *M.tb* infection in an *M.tb* challenge model by 50%. The total estimated mortality risk following *M.tb* infection in an attenuated *M.tb* challenge trial is between 0.0022625 and 0.00062625.

The mortality estimation in Figure 1 does not capture the full range of risks in an attenuated human challenge trial. Firstly, virulent *M.tb* challenge models also include some risk of community transmission; however, the likelihood is very small and likely to be easily controllable. The risks of a trial subject developing active TB in a challenge study are approximately 0.07%, and the likelihood that this leads to another active TB case outside of the study is orders of magnitude lower given both a) the attenuation pathogen, b) the low underlying probability of latent TB becoming active, and c) the availability of preventive therapy. Active monitoring of *M.tb* challenge volunteers can help ensure that they quarantine and follow best practices should they develop symptoms of active TB can minimize this risk.

Despite its low probability, community TB transmission presents a unique ethical concern by potentially exposing people to risk who are not enrolled in the study as research subjects. The benefits of conducting an *M.tb* challenge trial in

Table 2: Use cases, limitations, and risks of different types of TB challenge trials

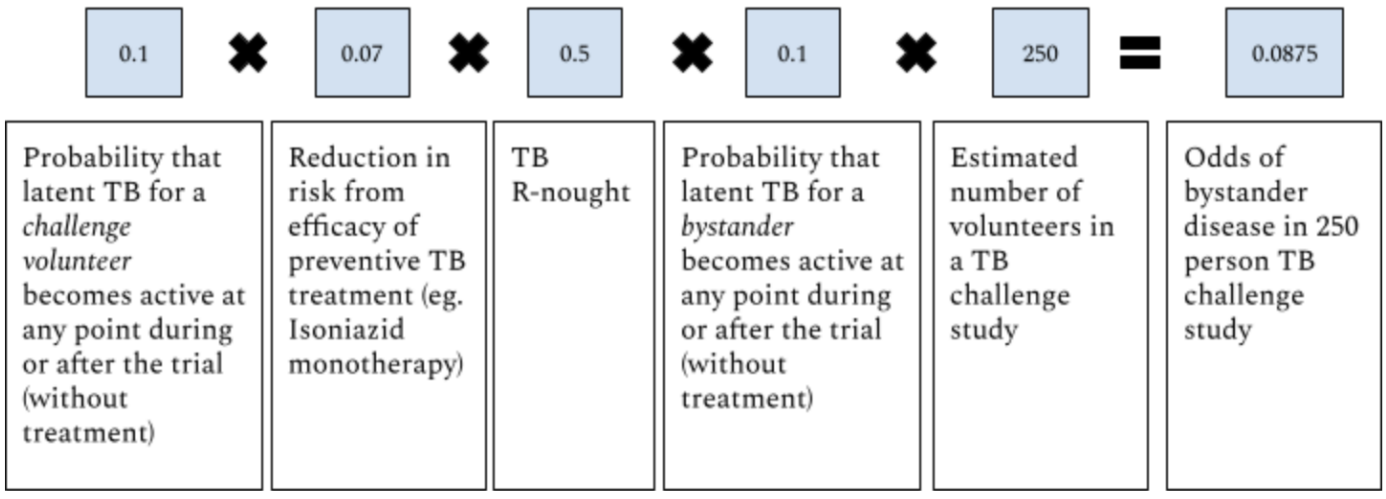
TB Challenge Model	**Advantages of the Model**	**Scientific Limitations**	**Risks to Volunteers**
Aerosol BCG challenge model (Davids et al. 2020; Hokey 2014)	● Proven safety and feasibility by Davids et al. ○ Intradermal BCG challenges have also demonstrated safety and feasibility (Minhinnick et al. 2016) ● Can be used as a similar proxy for *M.tb* since BCG has >99% sequence to Mtb at nucleotide level ● To the extent that BCG mimics *M.tb*, can be used to identify biosignatures of TB risk, explore TB pathogenesis, and test in-the-pipeline TB vaccines	● BCG is not generally a pathogenic strain that causes typical TB and lacks critical virulence genes ● Target antigens unique to *M.tb* would not be suitable for the BCG challenge model ● Confirmation that BCG challenge reflects pulmonary vaccine effect may ultimately require pulmonary challenge trials and comparison of validated immune correlates of protection (O'Shea and McShane 2016)	● Extremely low risks of short-term mortality and disease, long-term sequelae, and community transmission, as demonstrated by Davids et al.
Intradermal *M.tb* challenge model (Kaufmann et al. 2016)	● Greater biological relevance than BCG ● Detection of TB is more feasible than pulmonary *M.tb* challenge models	● Less biologically relevant than pulmonary model, and therefore unclear if sufficient to determine ICPs and downselect vaccine candidates	● Significantly lower safety concerns than attenuated and virulent pulmonary models
Attenuated pulmonary *M.tb* challenge model (Kaufmann et al. 2016)	● Depending on level and type of attenuation, may balance safety concerns and biological relevance	● Feasibility issues, including a lack of an attenuated strain and difficulty detecting the bacterial burden	● Significantly than a virulent Mtb model, depending on level of attenuation
Virulent *M.tb*	● Most biologically	● Feasibility issues, most notably	● Likely of death

challenge model (Kaufmann et al. 2016)	relevant challenge model	difficulty detecting bacterial burden	between .002021% and .006105% (see Figure 1) ● Significant long-term sequelae associated with cured TB and TB treatments ● Slight risk of community transmission from late re-activation due to failure to eradicate TB

high-burden regions, where the marginal increase in community transmission would be lower, must be weighed against the benefits of conducting a trial in high-income countries where medical care for community members is stronger and the *M.tb* reproduction rate is lower. Additionally, given the fraught history of outsourcing risky medical research to low-income countries, *M.tb* challenge trials in endemic regions should warrant exceptional scrutiny and ethical consideration (Hawkins and Emanuel 2008).

Ethical principles for managing risks to populations not involved in the trial itself can be borrowed and adapted from other studies that pose diffuse risks to communities, such as field trials of genetically modified disease-resistant mosquitoes. These principles include only running a trial when the targeted disease is a public health problem in the area in which it is conducted, the benefits to the community are likely to outweigh the risk, community leaders approve of the trial, and measures are put in place to protect the health of at-risk community members (Resnik 2014).

Figure 2: Estimated TB bystander risk from a wild-type Mtb human challenge trial†



†Sources for probabilities are identical to Figure 1. Source for TB R-nought is Ma et al., 2018.

Secondly, even an *M.tb* challenge model with low risks of mortality would involve possible risks of long-term morbidity. can be reduced by using an attenuated strain of TB, as efforts are underway to create an attenuated *M.tb* strain that has a limited period of replication. We argue in the following section that it is not unusual for altruistic individuals to voluntarily incur significant long-term risk for the common good, as is the case with certain types of living organ donation.

The exact risks and benefits of a given TB challenge study will depend on trial design and the pathogen in use. Table 2 explores the use cases, limitations, and risks of different TB challenge trials. In the following section, we explore the ethics of virulent *M.tb* human challenge trials.

Virulent TB Human Challenge Trials

Using attenuated *M.tb* as a challenge agent would reduce risks to volunteers and bystanders considerably in a challenge trial compared to virulent *M.tb*; however, it may do so at the cost of reducing the biological relevance, and in turn, the public health value, of the challenge model. In particular, the less a challenge agent mimics a virulent pathogen, the lower the probability that the challenge agent can be used to speed vaccine authorization or help discern immune correlates of protection for the virulent pathogen.

Thus, there are benefits and costs to using a virulent pathogen in a challenge trial. A virulent challenge agent may provide more decisive evidence of early-stage vaccine efficacy, and therefore may put promising vaccine candidates on a more expedited path to field trials than an attenuated challenge agent. A virulent model could also plausibly be more easily combined with Phase 2b data and safety data to be sufficient for vaccine licensure. Lastly, a virulent model could in principle be used to validate suspected correlates of protection observed in attenuated models.

However, these benefits should not be overstated. On its own, an attenuated *M.tb* challenge model may sufficiently mimic virulent *M.tb* such that any biological dissimilarity is functionally trivial. Additionally, as we explained in a previous section, a well-established attenuated *M.tb* challenge model could also be used to bridge human and animal vaccine studies in virulent animal models, possibly making a virulent human model less necessary. The costs of conducting a virulent model are also significant: trial volunteers would be put at greater risk of post-trial activation of latent TB infection. If trial participants or community members are immunocompromised, this risk, while not wholly dissimilar to other risks taken in public health contexts (see Table 3), would be considerable.

If attenuated models can capture the vast majority of the public health value of virulent *M.tb* challenge trials, then virulent trials would be unnecessary and unethical. However, if attenuated models face significant limitations— for instance, by proving to be technically infeasible or significantly dissimilar from the virulent pathogen such that they are ineffectual for vaccine testing— then trials with the virulent pathogen would warrant serious consideration.

Could it be Ethical to Give People TB?

The ethical status of any given clinical trial is dependent on its specific risk-reward ratio, making it impossible to determine *a priori* whether or not an *M.tb* challenge trial is ethical absent a detailed trial protocol with rigorous estimations of the danger to volunteers and the upsides of research. Further research is needed both to develop various *M.tb* challenge models and to model the optimal balance between biological relevance of the challenge agent with risks to volunteers (Kaufmann et al. 2016).

Nevertheless, using our estimations of possible risks and rewards in various types of TB challenge models, we contend that all attenuated *M.tb* challenge trials analyzed in this paper could be conducted ethically, given the massive humanitarian potential of these trials to save lives across the world by speeding next-generation TB vaccine authorization and distribution. Our main justification for this claim is that the risks of attenuated *M.tb* challenge models, while significant, are unexceptional when compared with other voluntary risks taken in both medical and nonmedical contexts. The expected social value of these trials, however, is exceptional.

Commentators on the ethics of clinical trials have pointed to societal comparator risks as a possible gauge for determining the ethical upper bound of risk for trial participants (Paquette and Shah, 2020). In Table 3, we show that the risks of mortality in *M.tb* challenge trials are on par with other common altruistic risks taken both in medical contexts (e.g. living organ donation) and vocational contexts (e.g. trucking and logging).

Table 3: TB Challenge Trial Compared to Other Common Procedures and Risks

Activity	**Micromorts (one in a million risk of death)**
Driving to New York from Los Angeles and back (Vally 2017)	22
Attenuated *M.tb* human challenge trial (Figure 1)	226 - 626
Living kidney donation (National Kidney Foundation 2017)	310
Brazilian butt lift (Mofid et al. 2017)	435
Motorcycling to New York from Los Angeles and back (Vally 2017)	897
Virulent *M.tb* human challenge trial†	905 - 2,504
Working as a trucker in the US for 5 years (Roberts 2019)	1,400
Working as a logger for 5 years (Centers for Disease Control and Prevention 2021)	3,685
Right liver lobe donation (Walter et al. 2008)	4,000

† Micromorts for a virulent *M.tb* human challenge trial are calculated by omitting the attenuation risk reduction multiplier used in Figure 1

While Table 3 does not include morbidity risks of comparator activities, several of the risks described have significant long-term negative health effects as well. For instance, left liver donors experience morbidity rates of 12.4%.

Of the risks listed in Table 3, participation in a TB human challenge trial unquestionably has the greatest public health value, possibly leading to tens or even hundreds of thousands of lives saved (see Table 1). If it is ethical to allow fully consenting adults to incur risks that have significantly *less* public health value— including cosmetic surgeries which have no public health value at all— then it is certainly ethically acceptable to allow for attenuated human challenge models.

Another related yet independent reason to approve of attenuated *M.tb* human challenge trials is non-paternalism. An essential aspect of inclusive medical research is taking seriously the rights and interests of all stakeholders, including volunteer candidates. Here, the interests of volunteer candidates must be understood broadly to include the altruistic interests of volunteers to contribute to medical research and save lives (Chappell and Singer 2020). Historically, bioethics has often dismissed the possibility that individuals are willing to take significant risks to promote the well-being of strangers. Non-directed living kidney donations, which involve both a nontrivial risk of death during surgery and an increased risk of end-stage renal disease, were prohibited until the 1960s, ostensibly for the sake of donor candidates, whose interests were overridden for fear that they were pathological or deranged (Marsh and Beyda 2020). Now, we understand that volunteers can take legitimate and informed risks for the public good, and thousands of lives have been saved by allowing non-directed kidney donation.

The bioethical stance of risk-taking in clinical trials must evolve in a similar way, especially in light of overwhelming empirical evidence that individuals are willing to take significant risks in clinical trials with high social value (Rohrig and Manheim 2021). In a 2020 academic survey of nearly 2,000 prospective volunteers for a COVID-19 human challenge trial, Rose et al. found that the median volunteer candidate would be willing to participate in a COVID-19 human challenge trial that involved a 1% risk of death (Rose et al. 2021), orders of magnitude higher than the actual risk of both COVID-19 challenge studies and TB challenge studies. These volunteers were no more risk-tolerant than the general population, though they were unusually altruistic.

Similar to the outpour of volunteers interested in participating in COVID-19 human challenge trials, we anticipate no shortage of volunteers willing to risk their health to speed the authorization of a better TB vaccine. However, this optimistic forecast should be verified via surveys and public consultations before investing significant resources into TB challenge studies. If volunteers do come forward, then we override the altruism of these prospective challenge volunteer candidates at the cost of tens of thousands of needless deaths in the world's most vulnerable populations.

The Future of Human Challenge Trials

Human challenge trials are a critical tool in the toolbox in fighting infectious diseases that take millions of lives annually, and they may be particularly valuable in pandemic scenarios that render rapid field trials implausible. Especially as advances in mRNA vaccine technology shorten the timeline for vaccine design and manufacture, clinical trials will pose the primary bottleneck for getting life-saving vaccines to market, making the role of challenge trials even more important.

In the case of TB, challenge trials may be an essential step in ridding the world of a disease that has caused untold suffering since the time of Pharaohs. For other infectious diseases, challenge trials have similar

humanitarian potential, but can only actualize this potential by exposing volunteers to risk. Ethicists should continue to develop action-guiding frameworks on acceptable levels of risk for human challenge trials to reduce uncertainty and friction in the decision-making process. To the extent possible, these estimates should be quantified and made commensurable by being expressed in similar terms, such as expected lives saved/lost or expected disability-adjusted-life-years saved/lost. Especially for pandemic contexts, evidentiary standards needed to demonstrate the risks and benefits of challenge trials should be clarified in advance, since lengthy ethical deliberations during pandemic outbreaks cost lives.

We contend that in further research, due attention must be paid to the growing evidence that fully informed and consenting individuals are willing to take on altruistic risk in medical contexts to advance research and save lives, as shown by the increasing number of non-directed living kidney donors and the thousands of volunteers for COVID-19 human challenge trials.

Conclusion

One person dies from TB every 20 seconds. Better vaccines are needed to end TB and save lives. While more rigorous modeling must be done to discern the risks and benefits of different TB challenge models, we show that using conservative assumptions, the benefits of attenuated *M.tb* challenge trials are likely sufficient to justify the risks to volunteers.

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