Clinical trials of TB vaccines in the era of increased access to preventive antibiotic treatment

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Abstract

An estimated 10.6 million people develop tuberculosis each year, a failure in epidemic control accentuated by the absence of effective vaccines for preventing infection or disease in adolescents and adults. In their absence, prevention of tuberculosis has relied on testing for infection and treatment with antibiotics to prevent illness in people at highest risk of progression to disease, known as tuberculosis preventive treatment (TPT). Novel tuberculosis vaccines are in development and phase 3 efficacy trials are imminent. The development of effective, shorter, safer, simpler antibiotic regimens has broadened the groups of people eligible to receive. TPT beyond people living with human immunodeficiency virus (HIV) infection and child contacts of people diagnosed with tuberculosis. Consequently, future tuberculosis vaccine trials will open in an era of increased TPT access. This existing prevention standard has important implications for tuberculosis vaccine trials of disease prevention in adults and adolescents, for which safety and sufficient accrual of cases are critical. This paper examines the urgent need to evaluate new tuberculosis vaccines considering the ethical duty to provide TPT as part of a standard preventive package to at-risk trial participants. We observe how HIV vaccine trials have incorporated a highly effective preventive intervention (pre-exposure prophylaxis), outline possible tuberculosis vaccine trial designs that integrate TPT and summarize considerations for each in terms of scientific validity, trial efficiency, participant safety, and ethics.

Key messages

- In the absence of highly effective vaccines, tuberculosis preventive treatment (TPT) has remained the current standard of prevention for individuals at risk for developing tuberculosis.
- While recent tuberculosis vaccine trials have been evaluated in persons not eligible for TPT or specified TPT as an exclusion criterion, future trials will open in an era in which global and national normative guidelines recommend TPT for broader groups of people at risk of tuberculosis beyond people living with HIV and child contacts of people with active tuberculosis disease.
- Tuberculosis vaccine trials should offer participants a standard-of-tuberculosis-prevention package that includes TPT for participants eligible to receive it according to global and local guidelines. The standard of prevention package should be defined in close consultation with communities affected by tuberculosis.
- Simply restricting trial participants to individuals who are not eligible for TPT is not desirable, as it misses an opportunity to generate evidence on new TB vaccines in those who need them the most.
- Drawing inspiration from how trials of HIV vaccines have approached provision of pre-exposure prophylaxis and other prevention modalities, we discuss five possible study designs that incorporate TPT, each of which raises specific safety, operational and ethical considerations: inclusion of a general population regardless of TPT eligibility; inclusion of high-risk populations who decline TPT; inclusion of individuals who recently completed TPT; comparison of tuberculosis vaccine+TPT *vs* Placebo+TPT in high-risk population to assess the added effectiveness; direct comparison of TB vaccine *vs* TPT in high risk groups. Simulation studies of the study designs will be important to test the implications of each approach on safety, sample size, likely benefit-risk or impact and therefore cost.
- The future acceptability of and public trust in future TB vaccines may depend on how decisions about TPT are made together by researchers, funders, and community representatives and what trade-offs future trial participants are willing to make. Understanding these factors should be a feature of TB vaccines preparedness.
- Novel trial designs that answer multiple questions and are inclusive of the populations of people at risk of TB in all their diversity will be necessary to maximise the public good of future TB vaccine trials.

Introduction

An estimated 10.6 million people develop active tuberculosis disease each year—pointing to a serious unmet need for prevention.[1] Once infected with *Mycobacterium tuberculosis* (*Mtb*) around 5-15% of people are estimated to develop active disease,[2] which requires 4-6 months of treatment with a multidrug regimen. Treatment of infection, also known as TB preventive treatment (TPT), reduces the risk of progression to disease. For decades, preventing TB disease has largely been limited to TPT with daily isoniazid monotherapy given for 6 months or more (IPT) to people at highest risk of progressing from infection to disease, namely: people living with HIV (PLHIV) and child contacts of people with TB five years of age and under.[3] First introduced in 1921[4] and still the only licensed vaccine against *Mtb*, the Bacille Calmette-Guérin (BCG) vaccine given at birth protects infants and young children against severe forms of TB but vaccination offers inconsistent protection against pulmonary TB to adolescents and adults, who account for most *Mtb* transmission. BCG at birth has thus not resulted in desired long-term protection and reductions in TB incidence at a population level. Moreover, our understanding of the correlates of protection required to advance vaccine development remains incomplete. Eliminating TB in line with the WHO End TB Strategy 2035 target to reduce the incidence rate of TB by 90% compared to 2015 levels will involve developing and introducing safe, effective, and affordable new TB vaccines.[5]

Recently, advances have been made in preclinical and clinical TB vaccine development; candidates, approaches and bottlenecks in TB vaccine development are extensively reviewed elsewhere.[6-8] A phase IIb trial in South Africa showed that revaccination of *Mtb* unexposed and HIV uninfected adolescents with BCG had an estimated efficacy of about 45% (95% CI 6.4–68.1) against sustained *Mtb* infection, indicated by serial positive interferon-gamma release assays (IGRA) suggesting infection with *Mtb*.[9] In addition, the subunit TB vaccine candidate M72/AS01E conferred 49.7% (95% CI: 2.1–74.2) protection against developing bacteriologically-confirmed pulmonary TB disease for three years post-vaccination in a phase IIb trial among HIV uninfected, *Mtb* sensitized adults in Kenya, South Africa, and Zambia.[10] These trials were conducted during the era in which national and WHO guidelines recommended TPT for limited high-risk groups. As such, TB vaccine trials that enrolled HIV uninfected adolescents and adults did not provide TPT to participants who entered trials with reactive IGRA results suggestive of *Mtb* infection, those who recorded IGRA conversion during study, or those with recent exposure to TB. However, since 2018 WHO has expanded TPT recommendations to include HIV uninfected adults and adolescents at highest risk of disease progression from recent exposure to *Mtb* and endorsed a wider array of TPT regimens, including several shorter and simpler alternative regimens to at least six months of isoniazid monotherapy with improved safety, tolerability, and adherence.[3] National programmes are increasingly adopting the new guidance, in addition to considering TPT for individuals in congregate

settings, health care workers and individuals with clinical risk factors that heighten risk of TB disease such as people with diabetes. Developers, sponsors and trialists of new TB vaccines will need to consider this changed but still evolving standard of prevention in the design and conduct of future clinical trials of TB vaccines.

A TB Vaccine R&D Roadmap by Cobelens and colleagues recently outlined broad priorities to encourage research and development of novel vaccines;[6] a roadmap by Miner et al does the same, but with a focus on TB vaccines in PLHIV.[7] Both roadmaps raise the challenge of incorporating TPT into clinical trials. We dissect this particular challenge through specific aims, first by exploring the ethical and regulatory considerations on how TB vaccine trials can adopt standard of prevention and care that includes TPT. Second, we draw lessons from the HIV vaccine field on how to integrate biomedical prevention options into vaccine trials. Finally, we propose possible TB vaccine trial designs that incorporate TPT and summarize considerations for each in terms of scientific validity, trial efficiency, participant safety, and ethics.

Advances in TB Preventive Treatment

Innovations in TB vaccine development have occurred in parallel to major improvements in TPT that have delivered shorter, safer alternatives to 6 or 9 months of isoniazid preventive treatment (IPT). Alongside IPT, WHO now recommends short-course TPT regimens that pair isoniazid (H) with either rifampicin (R) or rifapentine (P) or consist of rifampicin alone.[3] Options are three months of daily isoniazid with rifampicin (3HR), three months of weekly isoniazid with rifapentine (3HP), one month of daily isoniazid with rifapentine (1HP) or four months of rifampicin alone (4R). The current guidelines state that PLHIV of all ages and HIV-negative child contacts aged < 5 years should receive TPT; a positive test for *Mtb* infection while useful is not required to initiate TPT in these populations.[3] In contrast to previous guidelines, WHO additionally recommends that HIV-uninfected household contacts "may be given TB preventive treatment" if found not to have TB after clinical evaluation. In this group, a test to confirm *Mtb* infection before beginning TPT is "desirable," but "treatment may be justifiable without a LTBI test based on an assessment of the individual's risk of exposure and for the development of active TB in a given setting."[3] The decision to provide TPT for contacts, regardless of the requirement for infection testing, largely lies with the national governments. TPT options for people exposed to rifamycin- and/or isoniazid -resistant TB are also expanding, based on evidence from observational studies while waiting for results of ongoing clinical trials.[11,12] Table 1 summarizes groups at-risk of TB and current WHO recommendations for TPT and testing.

Importantly, the WHO recommendations are intended for all countries, regardless of TB incidence or resource constraints. While there may be differences, national guidelines, particularly in high TB burden countries (where future trials are likely to be conducted), increasingly reflect WHO standards. By the end of 2019, 65% (24 out of 37) of countries that were on at least one of the WHO lists of TB, multidrug-resistant TB, and TB/HIV high-burden countries had policies indicating the use of short-course TPT regimens, 95% (35/37) had policies recommending TPT for all PLHIV, and 51% (19/37) had policies on preventive treatment for household contacts aged > five years and older.[13] Around a third of countries also indicated other risk groups for tuberculosis including prisoners (11/37), healthcare workers (11/37), miners or people with silicosis (14/37), and people with diabetes (12/37) as eligible for TPT.[13] More expansive normative guidelines accompany more ambitious commitments to prevent TB. At the 2018 United Nations High-Level Meeting on TB, member states pledged to give TPT to 30 million people by 2022.[14] WHO reports that 12.5 million people received TPT from 2018 to 2021, including 10.3 million PLHIV (exceeding the global coverage target of 6 million by 2022).[1] However, substantial TPT coverage gaps persist for child contacts (1.6 million out of 4 million) and for HIV-uninfected household contacts older than five years (600,000 of 20 million).[1]

These advances in TPT have changed the landscape in which clinical trials of new TB vaccines will take place. TB vaccine trials will likely enrol varying proportions of the overall study population from one or more groups who have an indication for TPT according to global and local guidelines. Moreover, in future, the groups indicated to receive TPT may expand to include a broader proportion of potential vaccine trial participants as research to optimize the safety, tolerability, and effectiveness of short-course TPT regimens progresses (Table 2). TB vaccine developers will need to reconcile the need to conduct TB vaccine trials in the populations where new vaccines might have the most impact with the ethical obligation to provide study participants with access to existing effective preventive interventions, while preserving the scientific validity and feasibility of the trial.

Ethics, Human Rights and Community Considerations

The advent of safe, effective, short-course TB preventive treatment—and the expansion of normative guidance recommending its use in the populations in Table 1has raised two related questions: (a) Should TPT replace placebo as the control in efficacy trials of new TB vaccines? (b) Even if TPT does not replace placebo, should it be offered to some (or all) participants who enrol into TB vaccine trials as part of a “standard of prevention” package provided to both intervention and control groups? Answering these questions requires considering science and trial design alongside ethics guidance, human rights standards, and the perspectives of communities that will bear the consequences of any decision.

(a) Standard of care

A useful starting point for considering the role of TPT in TB vaccine trials is selecting an appropriate control, or comparator; this is known as the standard of care. The control arm of clinical studies can be a known effective intervention, a placebo, or no intervention. To date, all trials of new TB vaccines for adolescents or adults have used placebo controls. The rationale was justified by two reasons: (1) a need to ensure high internal validity and reduce bias in the outcome by maintaining investigator blinding to treatment allocation (thus making "no intervention" an unacceptable control), and (2) the absence of alternative effective preventive interventions to replace, or be given in addition to, placebo.

First, examining ethical guidance: the Council for International Organizations of Medical Sciences (CIOMS) guidelines start from a general rule that participants in the control group of a trial should receive *"an established effective intervention,"* if one exists.[15] Where an established effective intervention exists, placebo can take its place if two conditions are met: (1) *"there are compelling scientific reasons for using placebo,"* and (2) withholding the intervention will only result in a minor increase above minimal risk in a setting where risks are minimized and mitigated. The Declaration of Helsinki of the World Medical Association sets a slightly stricter standard in stating that *"the benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s),"* (emphasis added). The text of Helsinki Declaration implies a universal standard—"*best proven*"— but does not specify whether this refers to what is accessible locally versus globally.[16] As in CIOMS, the Helsinki Declaration outlines exceptions to this general rule: where use of placebo would be necessary to determine the efficacy and safety of a new intervention as supported by "*compelling and scientifically sound methodological reasons*" and where *"the patients who receive any intervention less effective than the best proven one .will not be subject to additional risks of serious or irreversible harm."*

TPT can be considered an "established effective intervention" (CIOMS) and "best proven intervention" (Helsinki) for preventing infection with *Mtb* from progressing to TB disease. This is the same use case for new TB vaccines in adolescents and adults. Do TB vaccine trials satisfy the conditions that would allow for use of placebo despite the availability of TPT? Both the CIOMS guidelines and Helsinki Declaration allow for placebo use by appeal to compelling scientific or methodological reasons. This might apply if the degree of protection afforded by TPT would make it inordinately difficult to demonstrate the superiority of a new vaccine compared directly against TPT without significantly increasing trial size, follow-up time, and thus cost to an impractical or unachievable extent. Investigators might also argue that TPT is not an appropriate comparator since not every trial participant may be eligible to receive TPT

under existing global or local guidance, or TPT may not be appropriate for the individual even if they were deemed eligible. Therefore, from a clinical trial design perspective, it might not always be appropriate to randomize all participants to vaccine *vs* TPT. Both reasons for the continued use of placebo could apply to TB vaccine trials, but the second line of argument is worth exploring in detail.

Imminent late-stage efficacy trials of TB vaccines intend to enrol a general population of adolescents or adults living in places with moderate-to-high TB incidence.[17] A general population refers to one that is not pre-selected due to specific risks other than that the individuals reside in a setting of non-negligible or heightened risk to TB infection and progression to disease. Many of these potential trial participants will have a positive IGRA test suggestive of exposure to *Mtb* ("postexposure vaccination") and thus a probable higher risk of developing active TB disease in some of those with reactive results.[2] These individuals would be eligible to receive TPT if they were living with HIV, were close contacts of persons with TB, or had other clinical risk factors. However, most individuals recruited to join a TB vaccine trial enrolling among the general population will not belong to one of these groups, even if IGRA positive. Similarly, not everyone with negative IGRA at trial enrolment remains disease-free; consequently, some TB vaccine trials will also choose to enrol IGRA-negative individuals ("pre-exposure vaccination") to generate data for vaccine licensure in this broader population. TB vaccine trials in the general population are thus likely to enrol individuals with heterogenous risk: some participants will belong to groups strongly recommended to receive TPT and likely to derive clear benefit from it, others will belong to groups where the recommendation for TPT is less clear or conditional, and the majority will fall outside of TPT guidance. Thus, for most enrolled individuals, the benefits of providing TPT are likely to be limited. However, an individual's risk of TB disease should be established at baseline and during follow up so that risk mitigation and appropriate care can be given to individuals. In the future, TB vaccine trials may look beyond the general population for targeting enrolment as recent roadmaps for TB vaccine research encourage designs that promote greater diversity and inclusivity across risk groups.[7] The discussion on providing the 'best proven intervention' as a comparator, and where this duty lies, becomes pertinent if the field evolves in this direction.

In addition to appealing to scientific and methodological reasons, investigators would need to demonstrate that continued use of placebo would not place participants at additional risk of serious harm. This determination requires careful consideration; the Helsinki Declaration cautions that *"Extreme care must be taken to avoid abuse of this option."*[16] One way of exercising extreme care is ethicist Jeremy Sugarman's idea of a *"rebuttal presumption."* Writing in the context of preexposure prophylaxis (PrEP) and HIV vaccine trials, Sugarman argues that given evidence of the efficacy and safety of PrEP in

preventing HIV, investigators of trials that opt for passive referrals to PrEP services or restrict PrEP usage among participants must make the case for why they cannot or will not provide PrEP through the trial directly.[18] The rebuttal presumption places the burden of proof on restricting access to a known effective intervention rather than the reverse. Taking up the rebuttal presumption might yield different answers for different groups of trial participants. It would be difficult to argue that withholding TPT from trial participants with HIV would pass the Helsinki standard of "no additional risk of serious harm." In contrast, the risk of not providing TPT might be "no more than minimal" (CIOMS) for IGRA negative adults, or even IGRA positive participants without HIV and those who are not in close contact with someone with TB unless there are additional risk factors for progression to disease. If the outcome of the rebuttal presumption is that TPT must be offered to some participants, but not necessarily to others, then the simplest way forward would be to maintain placebo-control and approach TPT as part of a "standard of prevention" package made available to trial participants across all arms. What would such a preventive package include and how would it be operationalized?

(b) Standard of prevention

The standard of prevention for TB is defined as those interventions for preventing TB recommended by the WHO, which includes but is not limited to TPT.[19] "TB prevention" and control extends beyond TPT to encompass a suite of related activities, including screening and diagnosis, adherence counselling, infection control, HIV care, treatment of comorbidities, and structural interventions such as social protection. Not all these elements are the responsibility of the trial sponsor to provide.[20] A clinical trial may offer participants interventions such as TPT, HIV testing and care referral, infection control at the research site, and information on how to reduce risk of TB infection, but it cannot substitute for public or private health systems. At the same time, in places where TPT is not routinely provided by the health system, investigators may still want to provide or offer TPT to trial participants in order to meet global standards of care or to counteract community or individual risk and discomfort arising from trial participation.

Identifying a minimum standard prevention package for trial participants, and then deciding how to provide it, requires deliberation among a diverse group of stakeholders with representation of scientists, funders, trial sponsors, ethicists, regulators, civil society, and—not least—members of TB-affected communities.[21] These voices are likely to express different first-order concerns about the role of TPT in TB vaccine trials. The funder sensitive to trial costs wants to ensure that limited resources are used efficiently and that studies are designed with a reasonable chance of success. Community members want a

say in studies that stand to benefit them, an idea articulated in the 1983 Denver Principles and enshrined in methodologies such as Good Participatory Practice.[22,23]

Could the issue of TPT be avoided altogether by simply excluding the high-risk groups who should receive it? We assert such a blanket exclusion would be contrary to human rights standards. Article 15 of the International Covenant on Economic, Social and Cultural Rights (ICESCR) establishes the right of everyone to enjoy the benefits and applications of scientific progress (i.e., the right to science).[24] Two elements of the right to science are helpful for the present discussion. First is the imperative of non-discrimination. Under the right to science, governments "have a duty to make available and accessible to all persons, without discrimination, especially to the most vulnerable, all the best available applications of scientific progress necessary to enjoy the highest attainable standard of health."[25] This legal standard encompasses an obligation to ensure non-discrimination in access to the best available scientific applications for health. It also directs science to focus on populations living in contexts that render them vulnerable to ill health. In the context of TB research, this would include many of the populations at risk of *Mtb* infection by virtue of setting or circumstance and those at high risk of subsequent progression to TB disease related to clinical risk factors or comorbidities. This focus on vulnerable populations is meant to protect but not to exclude. That is, vulnerable populations should receive all due protections warranted by their higher risk, but this protection should not come at the expense of their participation in research.[26] To receive the direct benefit of TB vaccines research, PLHIV, household contacts, and perhaps other high-risk populations need to be represented in studies. Incorporating TPT into vaccine trial design could facilitate that inclusion for some groups.

Second is the idea that people have a right to participate in medical research as more than trial participants. The Committee on Economic, Social and Cultural Rights has said: *"The right cannot be interpreted as establishing a rigid distinction between the scientist who produces science and the general population, entitled only to enjoy the benefits derived from research conducted by scientists."* Instead, every person has a right *"to take part in scientific progress and in decisions concerning its direction."*[25] This emphasis on participation establishes a duty to engage affected communities on issues such as standard of prevention and creates opportunity to provide input on trial design. Decisions on how to incorporate TPT into a standard of prevention should be made together with representatives from the communities where vaccine trials will take place after a process of meaningful and sustained engagement.

Learning from HIV: Role of PrEP in HIV Vaccine Trials

Researchers and sponsors thinking through how TPT provision may change vaccine study design can borrow lessons from how clinical trials of HIV vaccines have approached offering preexposure prophylaxis (PrEP) to study participants.[27] Like TPT, PrEP is a highly effective preventive intervention. Despite the overwhelming demonstration of PrEP safety and efficacy in diverse populations at risk of HIV, by the end of 2021 fewer than two million people across the globe had ever initiated PrEP outside of a clinical trial.[28] The slow scale-up of PrEP has highlighted enough of a difference between global and local standards of prevention to raise the question: do researchers have an obligation to provide an intervention that would not be otherwise available?

In February 2021 UNAIDS answered this question in an update to its *Ethical Considerations in HIV Prevention Trials* which contains 14 guidance points for trials of HIV vaccines and other prevention tools in the era of PrEP.[29] Guidance point 11 (standard of prevention) states: "Researchers and trial sponsors should, at a minimum, ensure access to the package of prevention methods recommended by the WHO for every participant throughout the trial and follow-up." The package of prevention includes all preventive interventions recommended by WHO, including but not limited to PrEP. Departure from this standard package should only occur if communities affected by HIV accept "a compelling scientific or biological rationale for the departure" after meaningful engagement.

The UNAIDS *Ethical Considerations* document recognizes that the search for HIV vaccines "is becoming increasingly complex as proven effective [prevention] methods come to the market" and calls for devising "suitable and ethically acceptable [trial] designs" that account for PrEP and other highly efficacious prevention tools. UNAIDS sketches the design of a vaccine trial that would enrol and randomize participants who opt out of PrEP when offered it at screening. All participants would receive information on the option to take PrEP at screening. Only those who decline would be randomized to either placebo or investigational vaccine. These individuals would still have access to other elements in the WHO standard prevention package and could elect to start PrEP at any time during the study. Sometimes called the "decliners design," this is the approach taken by the Mosaico trial (HVTN706/HPX3002; NCT03964415).

Table 3 illustrates the opt-out design of the Mosaico trial as well as approaches taken by two other phase III HIV vaccine trials. Imbokodo (HVTN705/HPX2008; NCT03060629) employed an "all-comers design" in which participants were enrolled and randomized to vaccine or placebo whether or not they elected to take PrEP when offered at screening. This was also the design of the Uhambo study (HVTN702; NCT02968849). In contrast, the PrEPVacc trial integrates PrEP into the design of the study

itself by enrolling all participants into a concurrent, open-label, randomized comparison of two PrEP options (TAF/FTC and TDF/FTC) in the first 26 weeks. During this period, participants are also randomized to one of three vaccine arms and receive the first three doses of the three vaccine regimens being studied.

Although one can draw important similarities between PrEP and TPT, there are also notable differences that warrant caution in extrapolating lessons from HIV to TB vaccine trial design. PrEP is taken preexposure and the exposure is largely predictable and recognizable as exposure. TPT is usually taken post-exposure—except when given to some PLHIV—and the exposure is generally not predictable and often not recognizable as exposure. For that reason, with some exceptions, TPT ideally requires testing for exposure (e.g., proxy indication of Mtb infection using an IGRA or tuberculin skin test) whereas PrEP does not. *Per exposure,* PrEP has much shorter duration with less burden on the individual, less risk of adverse drug reactions than TPT, and subsequently deemed less burdensome on the health system tasked with its delivery. A failure to prevent either disease bears serious, though different, consequences to affected individuals. TB is treatable and curable within a discrete period, however, a proportion of TB patients are likely to relapse and some left with post TB lung disease that is associated with significant morbidity and mortality Conversely, HIV is treatable and, until a functional cure is discovered, treatment must be taken for life. Taken together the statements imply different benefit-risk considerations for the two preventive interventions.

TPT and Novel TB Vaccine Trial Designs

Several TB vaccine candidates have entered or are about to enter pre-licensure phase 2b (focused on safety, immunogenicity and exploration of clinical efficacy) and 3 (focused on clinical efficacy and safety) evaluation in adults and adolescents.[17] An appraisal of summary information on trial registries indicates TPT is approached in one of two ways—either not mentioned at all, or a history or presence of TPT declared an exclusion criterion. Inspired by the HIV and PreP study designs, in Table 4 we propose possible backbone study designs considering TPT in trials of a novel TB vaccines and discuss implications of each design for trial efficiency, participant safety, and ethics. We present designs for simple standalone two-arm, individually randomized trials of a vaccine to prevent disease to illustrate these points but acknowledge that hybrid designs in cluster-randomised, multi-arm, or platform trials may be options where appropriate, and depending on the phase of vaccine evaluation. The proposed designs are applicable to people exposed to drug-resistant TB, whose options for preventive treatment continue to increase; vaccines will likely be effective regardless of drug resistance. Even though we focus our examples on a prevention of disease endpoint, the ensuing discussion is not limited to such trials and

applies to any TB vaccine trial, regardless of endpoint, that intend to include individuals at high risk of developing TB infection and disease who are recommended TPT.

In an "**All comers design**" trial participants are enrolled in the study regardless of whether they would be eligible to receive TPT as part of a standard of prevention package. That is, both people eligible and ineligible for TPT could enrol. This design would be suitable for an efficacy trial among a general population in a high incidence setting, or a trial prioritising a certain high-risk population in an intermediate- or low-TB-incidence setting for recruitment. There is an ethical imperative to establish if there are specific risk factors for infection/disease at baseline and ascertain need for TPT. This ensures that people eligible for TPT are identified and appropriate care implemented. The trial would provide TPT to eligible individuals, either directly or via referral, in line with WHO guidance. Compared to a trial in which no TPT is taken, fewer clinical endpoints may be reached so the sample size of an all-comers trial will need to be increased depending on the proportion of participants that receive TPT, expected adherence to TPT, and assumed TPT effectiveness and durability of the protective effect. In a trial that enrols from the general population, only a small proportion of individuals are likely to be eligible for TPT. The impact on event rates and thus concerns on trial efficiency will be less than in a trial design that specifically targets a particular high-risk population for enrolment. The "all comers" design would also be appropriate for post-licensure trials seeking to determine the best use case for a novel prevention of disease vaccine or explore sub-group effects in individually or cluster randomised effectiveness trials. The timing of TPT in relation to vaccination will depend on the type of trial—a prelicensure phase 2a or 3 safety and efficacy trial would likely seek to avoid concurrent administration of vaccine and TPT and retain ability to discern between adverse events linked to one intervention versus the other. Participants referred for TPT would then be eligible for the vaccine trial upon completion of preventive treatment. For groups who are not eligible for TPT, the safety of the vaccine can be evaluated as in usual stand-alone vaccine trials.

The "**Decliners design,**" where participants enrolled are those who are effectively counselled for TPT, offered and decline, might be the better option for a trial among contacts or other high-risk populations in both low- and high-incidence settings. A decliners design has the advantage that, in the absence of TPT, the trial sample size (i.e. those randomized) will not need to be increased, but the limitations are considerable. Many more people will need to be screened for enrolment than in other designs. High TPT uptake in good programmes may limit the utility of this design; there are concern of poor generalisability to other populations and settings. A main ethical concern is possible pre-selection since reasons for declining TPT may be associated with social or economic vulnerability. Thorough education and

counselling on TPT during screening may mitigate, though not eliminate, the risk of exploitation since other direct and ancillary benefits may encourage trial participation among vulnerable individuals. A design that would address these limitations would be to enrol a cohort of people who reside in a high-risk for infection setting and have completed a course of TPT in the recent past. This would be possible in contexts where TPT implementation records exist. Such 'Recent TPT Takers' could be incorporated within other trial designs (e.g. the Decliners design and All Comers) or perhaps serve as a standalone study design in places with sizable, well-functioning TPT programs. Individuals who discontinue TPT could also be included; however, the sample size needs to account for possible reduction of event rates due to partial protection. Unlike the All comers design, the Decliners design would allow evaluation of safety of a novel vaccine in at-risk groups, without interference from TPT.

Similar to the PrePVacc trial (NCT04066881), trials of novel TB vaccines could integrate TPT in a "**TPTVacc design**" rather than circumvent the intervention. An example would be a simple two-arm, individually randomized trial of a novel TB vaccine plus TPT, compared to TPT plus placebo among high-risk populations who are eligible for TPT, regardless of infection testing, to assess the added value of combined prevention. There is a risk of overlapping toxicities if the interventions are administered concurrently, potentially obscuring assignation of adverse events to vaccine or TPT regimen, thus the optimal timing of vaccination with respect to TPT would need to be determined. Similarly, where TPT may directly interfere with the vaccine's immunogenicity (e.g. live-attenuated vaccines) optimal timing of TPT/vaccination would need to be considered. Early phase trials could be used to inform the optimal timing, for example, by comparing the safety and immunogenicity of multiple timing strategies. Like the "All comers design", sample size will need to be increased due to the reduced event rates by TPT. The implication of TPT for vaccine efficacy would depend on the presumed mechanism of protection by TPT, which is currently unknown. If TPT clears latent infection (i.e., a sterilizing effect) and vaccination follows TPT the trial would approximate preexposure vaccination, although imperfectly since the treated population would likely retain immune memory from previous *Mtb* infection. However, if TPT only pushes latent infections back into immunological containment then the trial could be one of post-exposure vaccination but likely with a reduced rate of disease progression. It is also possible that the mechanism would not be dichotomous and could engender a combination of effects. The choice of TPT regimen requires consideration; it would be reasonable to give the same standard of care regimen to all arms so that differences do not bias vaccine effectiveness or obscure interpretation of effects. However, novel methods are emerging that permit randomisation to personalised standard of care that is decided for that individual at that time and would allow standardised comparison of effects for different regimens.[30] In addition to determining the added value of the two prevention modalities, the "TPTVacc design" could

serve as the backbone for a trial seeking to determine if a new TB vaccine should replace TPT in a specific population.

A standalone "Direct Comparison design" can be used to evaluate whether TPT can be replaced by vaccines in high-risk groups currently eligible for TPT. This would likely only be ethical once a minimum vaccine efficacy has been demonstrated. Demonstration of efficacy from phase 2b or 3 trials would therefore increase acceptability and feasibility. The choice of TPT regimen is crucial in this design; multiple factors would need to be considered. Factors such as the type of regimen, duration and frequency would determine durability of protection (e.g., 1HP *vs* 36H for PLHIV) and overall effectiveness. This design would also allow a direct comparison of the safety of TPT *vs* a new vaccine, which would provide additional essential data to inform the replacement. This design could be a non-inferiority design if a new vaccine offers additional value such as safety and ease of use (e.g. a single shot and no concern about the development of drug resistance).

Conclusion

Considering TPT explicitly in trials of novel TB vaccines has implications for study design, trial efficiency, participant safety, ethics, and human rights responsibilities, and, for some designs, generalizability of trial results. Because of the challenges associated with these implications, developers may prefer study designs that restrict enrolment to people for whom TPT is not indicated. However, such trials will miss an opportunity to generate safety and efficacy data on new TB vaccines in some of the populations that need them the most. The recent experience of HIV vaccine trials shows that it is possible to develop trial designs that allow researchers to meet their ethical obligation to provide a standard of prevention while also retaining the scientific ability to assess the safety and efficacy of novel vaccines. Simulation studies of the study designs for novel TB vaccines proposed in this paper will be important to test the implications of each design on safety, sample size, likely benefit-risk or impact and therefore cost, as has been done in the HIV vaccine field.[27]

As vaccine developers prepare to initiate phase 2b and 3 trials for TB candidate vaccines, it will be important to define a standard prevention package owed to all trial participants or subsets of trial participants and articulate the place of TPT within that package. This articulation should always start with an assumption of TPT eligibility in line with normative guidance and place the burden of proof on researchers to justify why TPT can be removed from the standard prevention package in the case of certain groups or circumstances. TPT involves a comprehensive set of

linked activities that begin with identification of people at risk of TB, and screening for and ruling out of active disease before providing antibiotics to treat TB infection and prevent progression to disease. This is the standard of prevention for people currently recommended TPT for priority risk groups, including PLHIV and recent contacts of people with TB. Most importantly, discussions on the standard prevention package should occur in close concert with individuals and communities affected by TB that will be asked to host clinical trials of TB vaccines. The future acceptability of and public trust in future TB vaccines may depend on how decisions about TPT are made together by researchers, funders, and community representatives and what trade-offs future trial participants are willing to make.

Search strategy and selection criteria

This perspective view builds on discussions during meetings among the members of The Epidemiology, Modelling and Trial Designs Research Community of Collaboration for TB Vaccine Discovery (https://www.ctvd.org/communities/epidemiology-modeling-and-trial-designs-community). We included references included in presentations during those meetings that were selected by individual presenters by review of the literature, WHO guidelines, UNAIDS Ethical considerations in HIV prevention trials, Treatment Action Group pipeline reports, and two TB vaccine R&D Road Maps, as well as the working group members' personal collection of articles. We selected references that were considered relevant to the topic of this article based on the authors' assessment.

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Contributors

Conceived the idea: MXR and MF. Contributed to the design of the work and to the interpretation: All authors. MXR and MF wrote the first draft. Re-visioning of the work and revising it for important intellectual content: All authors. Final approval of the published version: All authors. MXR and MF agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of interests

The authors declare no competing interests.

Table 1 Populations at highest risk of progressing to TB and WHO recommendations for TB preventive testing and treatment		
Population at risk	**2018 WHO recommendations**	
	TB preventive treatment	**Test for *Mtb* infection**
*People living with HIV (adults and adolescents, including people on antiretroviral treatment, pregnant women, and those previously treated for TB, irrespective of degree of immunosuppression)	Should receive TPT.	*No
*Children living with HIV (aged ≥12 months, without TB after clinical evaluation	Should receive TPT.	*No
*Infants living with HIV (aged <12 months	Should receive TPT	*No
*Children <5 years old who are household contacts of persons with bacteriologically confirmed pulmonary TB disease	Should receive TPT	*No
Adults, adolescents, and children aged > 5 years who are household contacts of persons with bacteriologically confirmed pulmonary TB disease	May be given TPT	**Test for infection desirable
People with clinical risk factors such as people initiating anti-TNF treatment, undergoing dialysis, preparing for organ transplant, or with silicosis	Should be systematically tested and treated for *Mtb* infection	Yes
Prisoners, health workers, immigrants from countries with a high TB burden, homeless people and people who use drugs	Systematic testing and treatment of *Mtb* infection may be considered	Yes
People with diabetes, people who engage in the harmful use of alcohol, tobacco smokers and underweight people	***Systematic testing and treatment of *Mtb* infection is not recommended	NA

*Recommendations are based on WHO consolidated guidelines on tuberculosis: module 1: prevention: tuberculosis preventive treatment. Geneva, Switzerland: WHO, 2020.[3] *Test for LTBI not an absolute requirement. Poor accuracy of current tests for infection (IGRA and PPD TST) and poor access to diagnostic tests informed this decision. ** "Treatment may be justifiable without a LTBI test based on an assessment of the individual's Risk of exposure and for the development of active TB in a given setting.")***Risk of disease is recognised but paucity of*

data on benefit-risk balance currently precludes WHO recommendation. TPT guidance for this group may differ by country burden or level of income. Mtb; Mycobacterium tuberculosis. NA; not applicable

Table 2: Ongoing and Planned Clinical Trials of TPT in Adolescents and/or Adults

Study type	TPT regimens	Study name (registry number)
Comparisons of 3HP and 1HP for efficacy, safety, effectiveness, and/or treatment success	3HP, 1HP	○ HIV-NAT 3HP *vs* 1HP (NCT03785106), ○ SDR Risk Study (NCT04094012), ○ Ultra Curto (NCT04703075), ○ 1 to 3 (NCT05118490)
Drug-drug interaction of 3HP with antiretrovirals to treat HIV	3HP with DTG, 3HP with TAF, 3HP with DTG + DRV/c, 3HP with BIC/FTC/TAF	○ DOLPHIN Too (NCT03435146), ○ YODA (NCT03510468), ○ 3HP with DRV/c (NCT02771249), ○ Rifapentine with BIC/FTC/TAF (NCT04551573)
Drug-drug interaction studies of 1HP with antiretrovirals to treat HIV	1HP with DTG, 1HP with BIC/FTC/TAF	○ A5372 (NCT04272242), ○ BIC/FTC/TAF (NCT04551573)
Studies of 3HP and/or 1HP in children	3HP	○ TBTC Study 35 (NCT03730181), ○ DOLPHIN Kids (NCT05122767), ○ IMPAACT P2024 (NA)
Studies of 3HP or 1HP in pregnant women	1HP	○ DOLPHIN Moms (NCT05122026)
Trials of 3HP or 1HP in people with diabetes	3HP 1HP	○ PROTID (NCT04600167), ○ BALANCE (NA)
Trials of other rifamycin-based TPT regimens	6 weeks of daily rifapentine 2 months of high-dose rifampicin	○ ASTERoiD/TBTC Study 37 (NCT03474029), ○ 2R2 (NCT03988933)
Trials of TPT for people exposed to drug-resistant TB	6 mo. levofloxacin (*vs* placebo), 6 mo. delamanid (*vs* 6H)	○ TB CHAMP (ISRCTN92634082), ○ V-QUIN (ACTRN12616000215426), ○ PHOENIx (NCT03568383)