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The potential impact of new TB vaccines on the burden of TB in people living with HIV in South Africa

Short title: Impact of TB vaccines in people with HIV

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Abstract

Background: People living with HIV (PLHIV) are at increased risk of tuberculosis (TB). New TB vaccines may help reduce this burden. New TB vaccine candidates are safe and immunogenic in PLHIV.There is currently limited data on vaccine efficacy in this population.

Methods: Using mathematical modelling we explored the potential impact of a novel TB vaccine on TB burden in PLHIV in South Africa between 2030-2050. We compared the impact of a vaccine delivered irrespective of HIV status to vaccination of either PLHIV or people without HIV. We explored the impact of reduced vaccine efficacy and duration of protection in PLHIV relative to people without HIV on our model predictions.

Results: Vaccination irrespective of HIV status, with a vaccine with equal efficacy and duration in PLHIV, could avert up to 1.01 (95% range: 0.96–1.22) million TB cases in PLHIV. Restricting vaccination to PLHIV or people without HIV would achieve 65% (60–70) and 48% (46–53) of the total impact respectively. These results are strongly dependent on the assumed efficacy and duration of protection in PLHIV. Further information on these characteristics is important to identify the most efficient use of new vaccines to reduce TB burden in PLHIV.

Conclusions: Our results suggest that new vaccines could play an important role in reducing the TB burden in PLHIV. Vaccines targeted at people without HIV individuals could provide significant indirect benefit to PLHIV, but vaccines which are safe and effective in PLHIV will be critical to maximizing the impact in this population.

Keywords: Tuberculosis; HIV; vaccines; modelling; South Africa

Introduction

People living with human immunodeficiency virus (HIV) (PLHIV) are at high risk of developing tuberculosis (TB) and dying from the disease due to reductions in immune function caused by HIV. The widespread roll out of antiretroviral therapy (ART) has been critical to reducing the incidence of HIV associated TB however even in individuals established on long term ART the risk of TB remains higher than in people without HIV [1]. Preventive therapy [2] and regular TB screening [3, 4] have also been shown to be effective tools in preventing and treating TB in PLHIV. Despite this,globally, 6% of incident TB cases (700,000 cases) and 13% of deaths due to TB (167,000 deaths) were in PLHIV [5]. In countries with high HIV prevalence such as South Africa, more than half of all TB cases and deaths are in PLHIV [5].

New TB vaccines could be an important tool to prevent TB in PLHIV. The best way to utilize a new vaccine to maximise benefit in this population is unclear [6]. The impact of any new vaccine on the TB burden in PLHIV will be influenced by acceptability and uptake of vaccination in PLHIV, and the wider population, as well as effects of HIV infection on vaccine efficacy and durability of protection, and the safety profile in people with compromised immune systems.

Trials of several new TB vaccine candidates have demonstrated immunogenicity in PLHIV, together with acceptable safety profiles [7-12]. However, it is unclear how immune responses will translate into efficacy against TB disease in people with compromised immune systems. The only prevention of disease (POD) TB vaccine efficacy study conducted in PLHIV demonstrated 39% (4–61) efficacy against a secondary endpoint of definite TB disease [13] however the trial was ended early due to slow accrual of cases.

Mathematical modelling provides one way to explore the potential effects of new POD TB vaccines on the TB burden in PLHIV and how this may depend on currently unknown vaccine characteristics. Modelling can also estimate the indirect benefit in PLHIV of vaccination of people without HIV, which may reduce secondary transmission of Mycobacterium tuberculosis (*M.tb*) to this high-risk population. Previous mathematical modelling has explored the effect of including PLHIV in vaccination campaigns on the TB burden in the general population [14-16] but to our knowledge no studies have considered the impact of vaccination on TB burden in PLHIV as their primary aim.

In this paper we used a mathematical model to look at the potential impact on TB burden in PLHIV in South Africa of a prophylactic TB vaccine for adults and adolescents based on the WHO Preferred Product Characteristics (PPC) for a new TB vaccine [17]. We explored how this might vary based on the efficacy and duration of protection realised in PLHIV and the impact of strategies targeting the whole population, or strategies restricted to people without HIV (if a vaccine was not safe in PLHIV) or PLHIV (if resources are limited).

Methods

Model structure

We used a previously developed mathematical model of TB in South Africa [16]. The model describes transmission, progression and treatment of TB. It is stratified by age, socio-economic status and HIV status. The structure of the core TB component is shown in figure 1 and full details are given in supplementary text 1, http://links.lww.com/QAD/D344 and supplementary figure 1, http://links.lww.com/QAD/D345.

The HIV component of the model is shown in figure 2. The population is stratified into 9 HIV states: HIV uninfected (H_0); undiagnosed HIV infection (H_u); diagnosed HIV infection, not on ART (H_d); on ART but not virally suppressed (A_n); on ART and virally suppressed (A_s). Each of the HIV infected states (H_u, H_d, A_s, A_n) is further divided in two based on a CD4 count threshold of 350. Individuals can move between HIV states based on rates of diagnosis, treatment initiation (and discontinuation) and viral suppression (and rebound). The decision to stratify the model at a CD4 count of 350 was based on the availability of data on TB risks using this threshold. We also assume that the effect of ART on TB risk depend on the CD4 count at treatment initiation [18].

We do not model HIV infection dynamically but instead apply an external age and time dependent risk of HIV infection based on UNAIDS projections [19]. An individual's HIV status affects the rate of transitions between TB states. We assume that HIV increases susceptibility to infection with M.tb,

increases the risk of developing TB disease, reduces the rate of natural recovery from TB and increases the risk of TB associated mortality.

Full details of the HIV model and its interaction with the TB model are given in supplementary text 1, http://links.lww.com/QAD/D344 and supplementary figure 2, http://links.lww.com/QAD/D345. Model parameters are listed in supplementary tables 1-5, http://links.lww.com/QAD/D345.

Model calibration

The model was calibrated to demographic, TB and HIV data from South Africa to make projections of the future burden of TB in the absence of new vaccines. Calibration targets included TB incidence, prevalence and mortality rates, HIV prevalence, ART coverage and levels of viral suppression. The model was calibrated using history matching with emulation [20] using the R package hmer [21]. This process allowed us to efficiently explore the high-dimensional parameter space to identify 1000 parameter sets that were consistent with the calibration targets. Full details of the calibration process are given in supplementary text 1, http://links.lww.com/QAD/D344 and calibration targets are listed in supplementary table 6, http://links.lww.com/QAD/D345.

Vaccine characteristic

We modelled a prophylactic vaccine for adults and adolescents based on the minimal desired characteristics in the WHO Preferred Product Characteristics for New Tuberculosis Vaccines [17]. In our primary analysis, we assumed a POD TB vaccine would provide 50% protection against TB disease and 10 years duration of protection. We assumed that the vaccine would be efficacious irrespective of an individual's prior exposure to *M.tb (ie 'any infection'; 'AI').*

We carried out sensitivity analysis of these assumptions, considering vaccines which protected against both infection with *M.tb* and development of TB disease (*prevention of infection and disease; POID*) and vaccines which were only effective in individuals who were currently infected with *M.tb (CI)*. In this case, we assumed that no testing for *M.tb* infection would be carried out, so vaccines would be given to both people with and without *M.tb* infection but would only be effective in those with current infection.

As there is limited data on how HIV infection may affect the efficacy or duration of protection of new TB vaccines, we allowed the relative efficacy and duration of protection in PLHIV to vary from 10% to 100% (same efficacy and duration of protection as in people without HIV) in increments of 10%. We assumed that the vaccine characteristics were determined by the current HIV status of an individual, not their HIV status at time of vaccination.

Vaccination scenarios

We compared 3 vaccination scenarios which are listed below together with their key assumptions. The HIV states included in each scenario are shown by the dashed line sin figure 2. These are not intended to represent the precise details of how a vaccine may be used, but rather to explore the broad ways in which a vaccine may be deployed in a high HIV prevalence setting.

Scenario 1 - Vaccination irrespective of HIV status

- The vaccine is safe in PLHIV
- There is no constraint on vaccine production or other resources

Scenario 2 - Vaccination of known PLHIV in care

- The vaccine is safe in PLHIV
- Vaccine availability is limited so focus on high-risk population
- No additional HIV testing is carried out

Scenario 3 - Vaccination of people without HIV

- The vaccine is not safe in PLHIV
- HIV testing is carried out prior to vaccination (but not explicitly modelled)

In all scenarios we assumed that the new vaccine would be introduced in 2030. We also assumed that people would only be vaccinated once and that there would be no repeat vaccination. We assumed the delivery of the vaccine would depend on HIV status. In PLHIV who know their status, we simulated 70% annual coverage among unvaccinated individuals aged 15 years or older. This approximates an initial campaign among previously diagnosed individuals followed by routine vaccination of newly diagnosed individuals. In people without HIV and PLHIV who do not know their status we simulated a one-off campaign in 2030 in 16–44-year-olds followed by routine vaccination of 15-year-olds, both with 70% coverage.

Outputs

Our primary outcomes were the cumulative number of TB cases averted in PLHIV between vaccine introduction in 2030 and 2050, and the number needed to vaccinate (NNV) per case averted in PLHIV. The NNV was calculated as the cumulative number of individuals vaccinated (irrespective of HIV status) divided by the cumulative number of cases averted in PLHIV. We also estimated the cumulative number of deaths due to TB averted in PLHIV and the NNV per death averted over the same time period.

All results are based on the 1000 parameter sets generated by model calibration. For each parameter set we compared the simulated vaccine scenario to the corresponding baseline scenario without vaccination and calculated the outcomes described above. Results are presented as the median and 95% range calculated over all 1000 parameter sets. Results of the calibration are shown in supplementary figures 3, 4 and 5, http://links.lww.com/QAD/D345.

Results

All results presented in this section are estimates for the period from vaccine introduction in 2030 to 2050.

Figure 3 shows the model results when vaccination is given to both PLHIV and people without HIV (*scenario 1*) for a vaccine meeting the WHO PPCs. Figure 3A shows the cumulative number of TB cases in PLHIV averted while figure 3B shows the NNV per TB case averted in PLHIV.

For a vaccine which has equal efficacy and duration of protection in PLHIV (top right corner of figure 3A) our model estimates that 1.01 (95% range: 0.96–1.22) million cases and 216,000 (187,000-254,000) deaths could be averted (see supplementary figure 11, http://links.lww.com/QAD/D345). This equates to 26% (24–28) of the estimated TB cases that would occur in PLHIV between 2030 and 2050 in our baseline projection in the absence of vaccination. This result is strongly dependent on the assumed relative efficacy and duration of protection of vaccination in PLHIV compared to people without HIV. If the efficacy and duration of protection in PLHIV were only 10% of those in HIV uninfected individuals the estimated number of cases averted is 0.40 (0.37–0.46) million or 10% (9–12) of the baseline burden (bottom left corner of figure 3A).

Model outputs indicate that this vaccination scenario involves vaccinating approximately 46 million people (10 million PLHIV and 36 million people without HIV). For a vaccine which has equal efficacy and duration of protection in PLHIV (top right corner of figure 3B) the estimated NNV per TB case averted is 45 (38–48). As discussed above, the number of TB cases averted in PLHIV is reduced if vaccine efficacy and duration of protection in PLHIV are reduced. As a result, the NNV is increased. If the efficacy and duration of protection in PLHIV were only 10% of those in HIV uninfected individuals the estimated NNV is 113 (110–125) (bottom left corner of figure 3B).

We observed the same qualitative patterns for vaccines which also protect against infection and/or only work in people currently infected with *M.tb* (see supplementary figure 8, http://links.lww.com/QAD/D345). For a vaccine which protects against infection and disease and is effective in individuals with and without *M.tb* infection he number of cases averted could increase to 1.47 (1.39–1.75) million (38% (34–41) of the baseline burden) while the NNV would be reduced to 31 (27–33).

Figure 4 shows the number of TB cases averted in PLHIV by vaccinating either PLHIV (*scenario 2*, figure 4A) or people without HIV (*scenario 3*, figure 4B).

If vaccination is restricted to PLHIV (*scenario 2*), for a vaccine which has equal efficacy and duration of protection in PLHIV (top right corner figure 4A) our model estimates that 0.66 (95% range: 0.60–0.84) million cases and 132,000 (112,000-163,000) deaths could be averted (see supplementary figure 12, http://links.lww.com/QAD/D345). This equates to 65% (60–70) of the cases and 61% (57-69) of the deaths that could be averted by vaccinating everyone irrespective of HIV status (*scenario 1*). If the efficacy and duration of protection in PLHIV are only 10% of those in people without HIV (bottom left corner of figure 4A) then vaccinating PLHIV would prevent 0.011 (0.010–0.015) million cases (2.9% (2.3–3.3) of the impact of vaccinating everyone).

If the vaccine is not safe in PLHIV and vaccination is restricted to people without HIV (*scenario 3*), vaccination could avert 0.43 (0.37–0.51) million TB cases and 93,000 (74,000-115,000) deaths in PLHIV (figure 4B). The impact of only vaccinating HIV uninfected individuals is largely independent

of the relative efficacy and duration in PLHIV although there is some small variation due to our assumption that people who are infected with HIV after vaccination may experience some reduction in their level of protection.

Comparing this to a vaccine which could be used irrespective of HIV status, we find that this is 48% (46–53) of the impact predicted with a vaccine which has a relative efficacy and duration of protection of 100% in PLHIV and 98% of the impact predicted with a vaccine which has relative efficacy and duration of protection of 10% in PLHIV.

Supplementary figure 6, http://links.lww.com/QAD/D345 directly compares the number of cases averted in PLHIV for each scenario for our most optimistic (100% relative efficacy and duration) and most pessimistic (10% relative efficacy and duration) assumptions.

Results for vaccines which also protect against infection and/or only work in people currently infected with M.tb follow the same qualitative patterns. Full results of these sensitivity analyses are shown in the supplementary figure 9, http://links.lww.com/QAD/D345.

Vaccination of known PLHIV (*scenario 2*) requires approximately 12 million people to be vaccinated while vaccination of people without HIV (*scenario 3*) requires approximately 36 million people to be vaccinated.

Figure 5 shows the ratio of the NNV per case averted when vaccination is limited by HIV status (*scenarios 2 and 3*), to the NNV when vaccination is given irrespective of HIV status (*scenario 1*). If this ratio is less than one (shown by red colours in figure 5) it is more efficient (lower NNV) if vaccination is limited by HIV status; if this ratio is greater than 1 (shown by blue colours in figure 5) it is more efficient to vaccinate everyone irrespective of HIV status.

For a vaccine which has equal efficacy and duration of protection in PLHIV, restricting vaccination to PLHIV gives an NNV of 18 (16–21). This is 0.41 (0.38–0.45) times the NNV of vaccinating everyone (top right corner of figure 5A), so in this case, it is more efficient to only vaccinate PLHIV rather than both groups. Figure 5A illustrates that there is a threshold, as either the relative efficacy or relative duration are reduced, at which it becomes more efficient to vaccinate irrespective of HIV status. With our worst-case assumption (10% relative efficacy and duration) the NNV when vaccinating only PLHIV is 1054 (893–1187), approximately 9 times that of vaccinating irrespective of HIV status.

The pattern is reversed when considering vaccination restricted to people without HIV (figure 5B). Here it is less efficient to use a vaccine that is only safe in HIV uninfected people compared to a vaccine that could be used in everyone when the relative efficacy and duration of protection in PLHIV is high, and switches to be more efficient as the relative values in PLHIV are reduced.

Supplementary figure 7, http://links.lww.com/QAD/D345 directly compares the NNV per case averted for each scenario for our most optimistic (100% relative efficacy and duration) and most pessimistic (10% relative efficacy and duration).

As for the other outputs, these qualitative patterns were replicated when we considered vaccines which also protect against infection and/or only work in people currently infected with M.tb (see supplementary figure 10, http://links.lww.com/QAD/D345).

Figures showing the corresponding results for deaths averted and the NNV per death averted can be found in the supplementary figures 12 and 13, http://links.lww.com/QAD/D345.

Discussion

Our results suggest that new TB vaccines could significantly reduce the burden of TB in PLHIV in a high HIV prevalence setting such as South Africa. A prevention of disease (POD) TB vaccine meeting the minimum criteria in the WHO PPC, and which was equally efficacious in PLHIV, could avert 1.01 (95% range: 0.96–1.22) million TB cases in PLHIV if given to both PLHIV and people without HIV. If vaccine availability (or other resources) is limited, only vaccinating PLHIV could achieve 65% (60–70) of this impact, and require 25% of the number of vaccinations, resulting in a NNV per case averted that is 60% lower. A vaccine which was not safe in PLHIV could achieve 48% (46–53) of the impact but be less efficient, with a NNV that is 50% higher.

Several studies [8-10, 12] have shown that new vaccine candidates are immunogenic in PLHIV however, how this might translate into efficacy in this population is unknown. We therefore explored a wide range of values for the vaccine characteristics in PLHIV ranging from 10% to 100% of the efficacy and duration of protection in HIV uninfected individuals. As expected, our results are highly dependent on this assumption with lower impact observed from vaccinating irrespective of HIV status (*scenario 1*) or vaccinating only PLHIV (*scenario 2*) as the relative efficacy and/or duration of protection in PLHIV was reduced. The impact of a vaccine which is only given to people without HIV is largely independent of this assumption, with some small variation due to our assumption that people who are infected with HIV after vaccination may see some reduction in their level of protection.

While the number of cases averted by vaccinating either PLHIV (*scenario 2*) or HIV uninfected individuals (*scenario 3*) is always lower than the impact of vaccinating irrespective of HIV status (*scenario 1*) we find that under certain conditions it is more efficient (in terms of NNV) to vaccinate one or the other sub-group. The most efficient strategy depended on the relative efficacy and duration of protection in PLHIV. While the relative duration of protection is unlikely to be determined in the short term, estimates of the relative efficacy of any new candidate in PLHIV will be important to identifying the most efficient way to utilize a new vaccine to reduce the TB burden in PLHIV.

Previous modelling studies have shown how including PLHIV in vaccination programs is likely to be important in maximizing the impact of new TB vaccines on the overall burden of TB in high HIV prevalence settings such as South Africa [14-16]. To our knowledge this is the first modelling study to explicitly consider the impact of vaccination on TB burden in PLHIV as its primary aim.

As with any modelling study our work makes a number of simplifying assumptions which may affect our conclusions.

We explored a range of assumptions about the relative efficacy and duration of protection of vaccination in PLHIV compared to HIV uninfected individuals but did not vary the values in HIV uninfected individuals from the minimum characteristics in the WHO PPC (50% efficacy, 10 years duration of protection). Varying these assumptions would have changed the magnitude of the impacts predicted by our model, but not the qualitative differences between scenarios targeting sub-groups by HIV status.

We also did not explore uncertainty in vaccine introduction date, coverage or scale up rates. As above varying these parameters would have changed the estimated number of cases averted in our model. Our assumption of equal coverage in PLHIV and HIV uninfected individuals is likely to be important when comparing strategies targeting different HIV sub-groups. It is possible that higher coverage could be achieved in PLHIV, a population already engaged in health care. On the other hand, it is possible that acceptance of a new vaccine may be lower in PLHIV due to concerns around safety or interactions with ART. Uptake of vaccination may also decline over time as the incidence of TB and therefore the perceived benefit of vaccination reduces. Declines in uptake would reduce the impact of a vaccine however the potential effects by HIV status are unclear. One plausible hypothesis is that uptake would remain higher in PLHIV who are at higher risk of TB and for whom the benefit of vaccination is higher. In this case, the benefit of vaccinating PLHIV over HIV uninfected individuals would increase.

We assumed the efficacy and duration of protection in PLHIV did not depend on their levels of immunosuppression or ART status. The majority of studies demonstrating immune responses to new TB vaccine candidates in PLHIV have been limited to people with high CD4 counts or those established on ART [7-9]. Evidence from other vaccine preventable diseases suggests that efficacy in PLHIV varies by levels of immunosuppression and ART uptake [22]. Lower efficacy in people not on ART may have implications for both the overall impact of a new vaccine but also the timing of vaccination relative to ART initiation. We plan to explore these questions in future work.

Our modelling assumed that all other HIV and TB care will remain at current levels in the future. Declines in future TB burden due to non-vaccine improvements would likely reduce the impact of new vaccines. In particular, increases in ART coverage may alter our conclusions about the relative benefits of targeting different HIV sub-groups for vaccination. Future work will explore this issue by applying the model to a range of settings with different HIV prevalence and ART coverage. We also do not explicitly model Bacillus Calmette-Guérin (BCG) vaccination. BCG is routinely given to infants in South Africa; the effects of this vaccination are implicitly included in our model calibration. There is also renewed interest in the use of BCG re-vaccination of adolescents and adults as a tool to reduce TB burden [23] however given concerns around the use of BCG in PLHIV we did not consider this in this paper.

We do not explicitly model drug-resistant TB, rather our model parameterisation implicitly includes drug-sensitive and drug-resistant forms of TB and that assumes vaccination is equally effective against both forms. If this assumption is not correct our model may overestimate the impact of new vaccines. There is also evidence that HIV may drive the acquisition of resistance to TB drugs during treatment [24]. In this case, reductions in HIV associated TB through vaccination may have bigger impacts on the burden of drug-resistant TB than vaccination of HIV uninfected individuals.

Our model includes age assortative mixing patterns but assumes that mixing by other characteristics, specifically HIV status, is random. Contact studies have found that the HIV status of individual does not affect their overall rates of contact or the age pattern of those contacts [25] however there is no data on the assortativity of contact by HIV status. If PLHIV make more contacts with other PLHIV (for example due to geographical or socioeconomic factors) then this may affect our results, potentially reducing the indirect benefit in PLHIV of vaccination of HIV uninfected people and increasing the impact of targeting vaccination to PLHIV.

Conclusion

Our results suggest that new POD TB vaccines could play an important role in reducing the TB burden in PLHIV. Vaccines targeted at HIV uninfected individuals could provide significant indirect benefit to PLHIV, but vaccines which are safe and effective in PLHIV will be critical to maximizing the impact in this population. If resources are constrained, data on the relative efficacy of vaccine sin PLHIV will be important for assessing the most efficient way to utilize vaccines to reduce TB burden in PLHIV.

Author Roles

TS, RGW, RAC and GC were responsible for the conception and the design of the work. TOPS and RB developed software. TS carried out the analysis. All authors analysed and interpreted the results. TS drafted the manuscript. All authors were responsible for reviewing the manuscript and approving the final version.

References

1. Gupta, A., et al., *Tuberculosis incidence rates during 8 years of follow-up of an antiretroviral treatment cohort in South Africa: comparison with rates in the community.* PLoS One, 2012. **7**(3): p. e34156.

2. Akolo, C., et al., *Treatment of latent tuberculosis infection in HIV infected persons (Review).* Cochrane Database Syst Rev, 2010. **20**(1).

3. Dhana, A., et al., *Tuberculosis screening among HIV-positive inpatients: a systematic review and individual participant data meta-analysis.* Lancet HIV, 2022. **9**(4): p. e233-e241.

4. Dhana, A., et al., *Tuberculosis screening among ambulatory people living with HIV: a systematic review and individual participant data meta-analysis.* Lancet Infect Dis, 2022. **22**(4): p. 507-518.

5. World Health Organisation. *Global Tuberculosis Report*. 2022 [accessed 2021; Available from: https://apps.who.int/iris/handle/10665/363752.

6. Miner, M.D., et al., *Developing tuberculosis vaccines for people with HIV: consensus statements from an international expert panel.* Lancet HIV, 2022. **9**(11): p. e791-e800.

7. von Reyn, C.F., et al., *Safety and immunogenicity of an inactivated whole cell tuberculosis vaccine booster in adults primed with BCG: A randomized, controlled trial of DAR-901.* PLOS ONE, 2017. **12**(5): p. e0175215.

8. Kumarasamy, N., et al., *Long-term safety and immunogenicity of the M72/AS01E candidate tuberculosis vaccine in HIV-positive and -negative Indian adults: Results from a phase II randomized controlled trial.* 2018. **97**(45): p. e13120.

9. Kumarasamy, N., et al., *A Randomized, Controlled Safety, and Immunogenicity Trial of the M72/AS01 Candidate Tuberculosis Vaccine in HIV-Positive Indian Adults.* 2016. **95**(3): p. e2459.

10. Thacher, E.G., et al., *Safety and immunogenicity of the M72/AS01 candidate tuberculosis vaccine in HIV-infected adults on combination antiretroviral therapy: a phase I/II, randomized trial.* 2014. **28**(12): p. 1769-1781.

11. Reither, K., et al., *Safety and Immunogenicity of H1/IC31®, an Adjuvanted TB Subunit Vaccine, in HIV-Infected Adults with CD4+ Lymphocyte Counts Greater than 350 cells/mm3: A Phase II, Multi-Centre, Double-Blind, Randomized, Placebo-Controlled Trial.* PLOS ONE, 2014. **9**(12): p. e114602.

12. Ndiaye, B.P., et al., *Safety, immunogenicity, and efficacy of the candidate tuberculosis vaccine MVA85A in healthy adults infected with HIV-1: a randomised, placebo-controlled, phase 2 trial.* The Lancet Respiratory Medicine, 2015. **3**(3): p. 190-200.

13. von Reyn, C.F., et al., *Prevention of tuberculosis in Bacille Calmette–Guérin-primed, HIV-infected adults boosted with an inactivated whole-cell mycobacterial vaccine.* 2010. **24**(5): p. 675-685.

14. Harris, R.C., et al., *Potential impact of tuberculosis vaccines in China, South Africa, and India.* Sci Transl Med, 2020. **12**(564).

15. Jayawardana, S., et al., *Feasibility of novel adult tuberculosis vaccination in South Africa: a cost-effectiveness and budget impact analysis.* NPJ Vaccines, 2022. **7**(1): p. 138.

16. Sumner, T., et al., *Modelling the health and economic impacts ofM72/AS01(E) vaccination and BCG-revaccination: Estimates for South Africa.* Vaccine, 2024. **42**(6): p. 1311-1318.

17. World Health Organisation. *WHO preferred product characteristics for new tuberculosis vaccines*. 2018; Available from: http://apps.who.int/iris/handle/10665/273089.

18. Bock, P., et al., *Incidence of Tuberculosis Among HIV-Positive Individuals Initiating Antiretroviral Treatment at Higher CD4 Counts in the HPTN 071 (PopART) Trial in South Africa.* J Acquir Immune Defic Syndr, 2018. **77**(1): p. 93-101.

19. UN AIDS, *HIV estimates with uncertianty bounds 1990-2020*. 2021.

20. Scarponi, D., et al., *Demonstrating multi-country calibration of a tuberculosis model using new history matching and emulation package - hmer.* Epidemics, 2023. **43**: p. 100678.

21. Iskauskas, A., *hmer: History Matching and Emulation package*. 2022.

22. Crum-Cianflone, N.F. and M.R. Wallace, *Vaccination in HIV-Infected Adults.* AIDS Patient Care and STDs, 2014. **28**(8): p. 397-410.

23. Nemes, E., et al., *Prevention of M. tuberculosis Infection with H4:IC31 Vaccine or BCG Revaccination.* N Engl J Med, 2018. **379**(2): p. 138-149.

24. Cox, H., et al., *Potential contribution of HIV during first-line tuberculosis treatment to subsequent rifampicin-monoresistant tuberculosis and acquired tuberculosis drug resistance in South Africa: a retrospective molecular epidemiology study.* Lancet Microbe, 2021. **2**(11): p. e584-e593.

25. Thindwa, D., et al., *Social mixing patterns relevant to infectious diseases spread by close contact in urban Blantyre, Malawi.* Epidemics, 2022. **40**: p. 100590.

Figure 1. Tuberculosis natural history model structure. Boxes show the TB states included in the model, lines and arrows show the transitions between them. For clarity mortality and births are not shown. *U_N = Uninfected-Naive; L_F = Latent-Fast; L_S = Latent-Slow; L_0 = Latent-Zero, D_S = Subclinical Disease; D_C = Clinical Disease; T = On-Treatment; R = Recovered. Subscript j represents parameters that vary by age, and subscript k represents parameters that vary over time.*

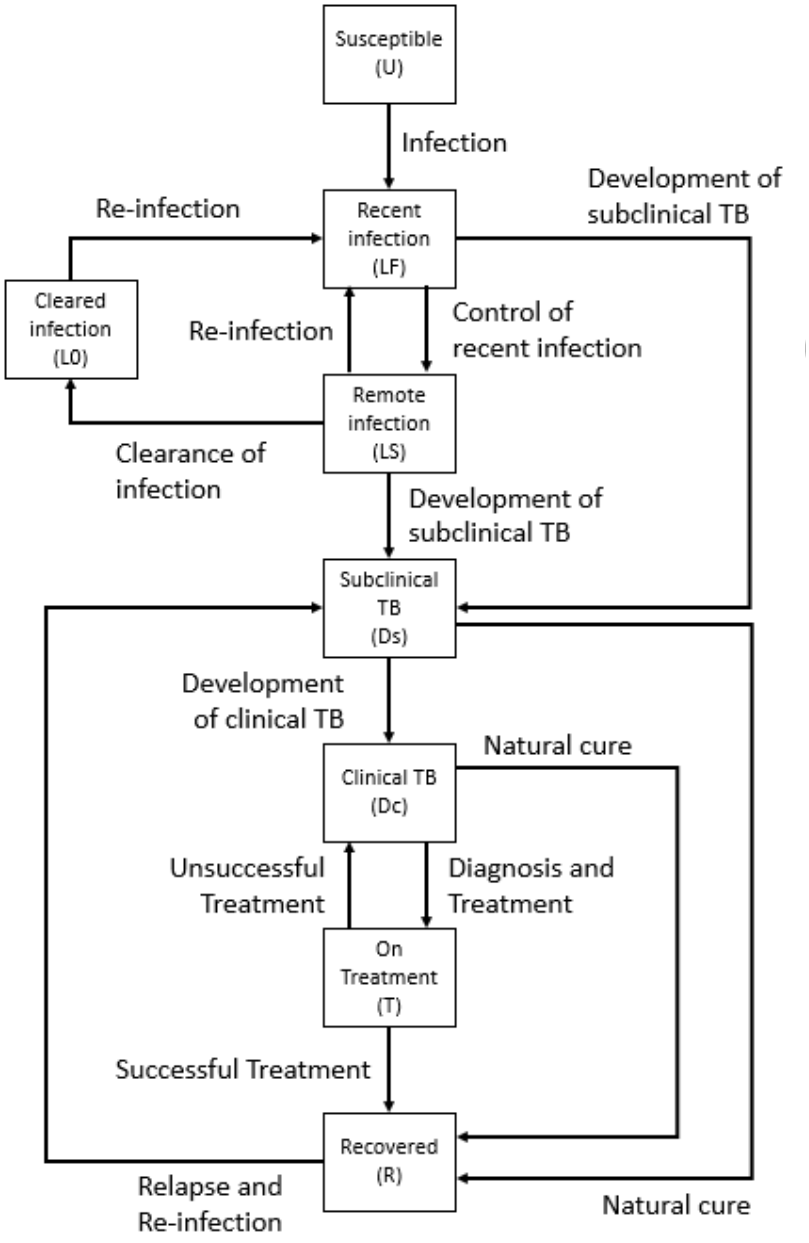

Figure 2. HIV model structure. Boxes show the HIV states included in the model, lines and arrows show the transitions between them. For clarity mortality is not shown. The dashed rectangles highlight the HIV states included in the vaccination scenarios described in section 2.4. *H_0 = HIV uninfected; H_u = undiagnosed HIV infection; H_d = diagnosed HIV infection, not on ART; A_n = on ART but not virally suppressed; As = on ART and virally suppressed. Subscripts 1 and 2 refer to CD4 counts above and below 350 respectively*.

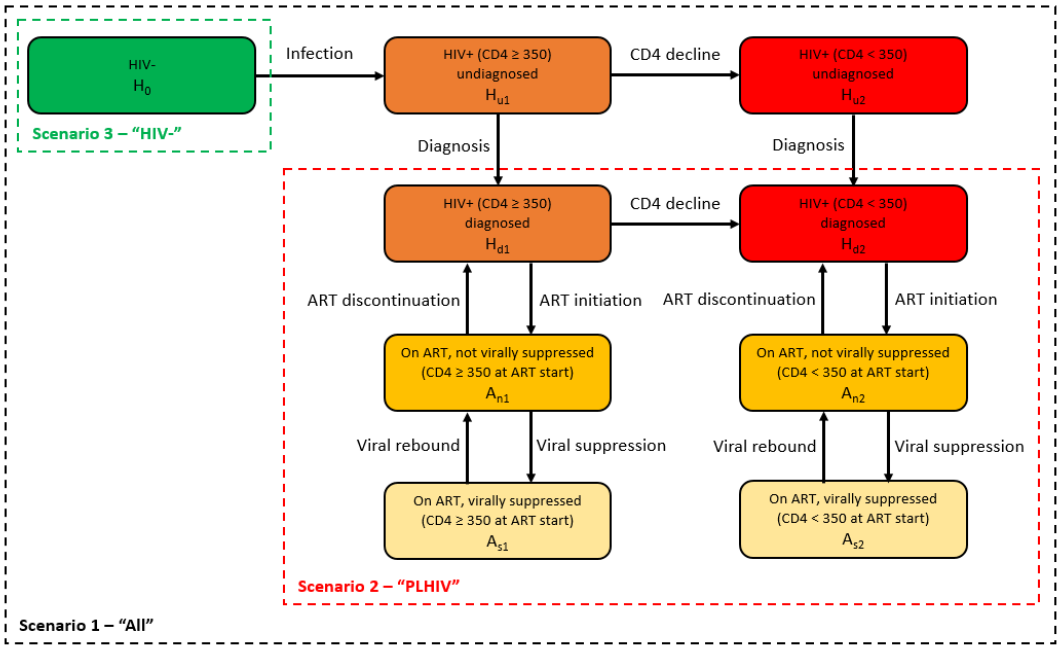

Figure 3 – **TB cases averted and NNV with vaccination of the whole population (scenario 1)**. A): cumulative TB cases averted in PLHIV (2030–2050) (in millions). B): NNV per TB case averted in PLHIV (2030–2050). Y-axis shows the efficacy in PLHIV relative to people without HIV (%) and x-axis shows duration of protection in PLHIV relative to people without HIV (%). (Note different colour scales for left and right panels).

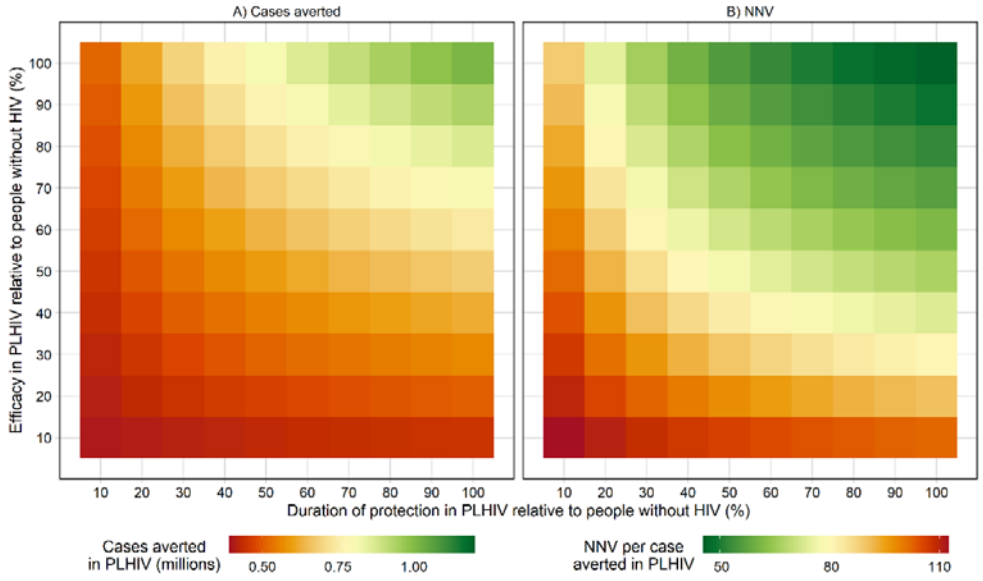

Figure 4 – TB cases averted in PLHIV when vaccination is limited by HIV status. A): vaccination of known PLHIV (*scenario 2*). B): vaccination of HIV uninfected individuals (*scenario 3*). Y-axis shows the efficacy in PLHIV relative to people without HIV (%) and x-axis shows duration of protection in PLHIV relative to people without HIV (%).

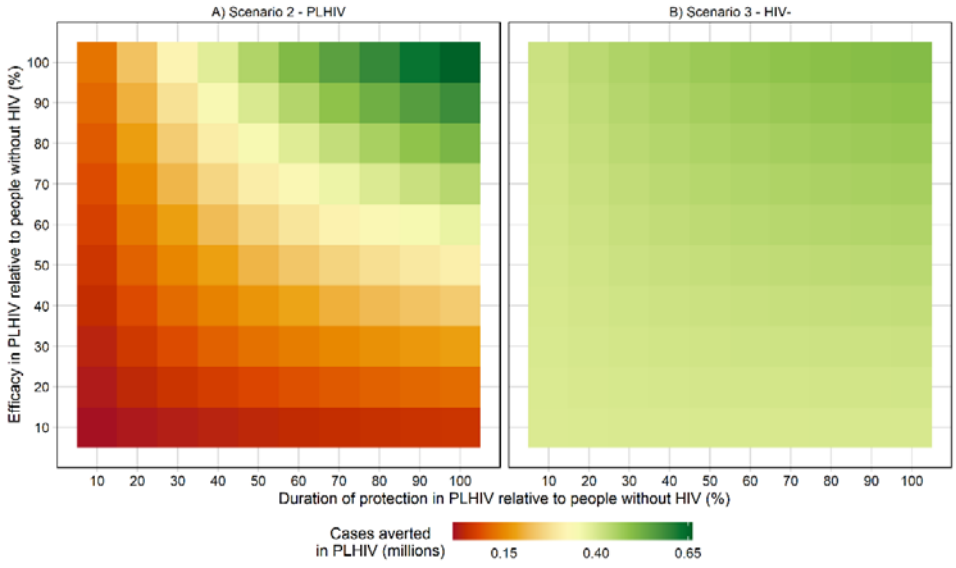

Figure 5 - Ratio of the NNV per TB case averted when vaccination is limited by HIV status compared to vaccinating everyone. A): vaccination of known PLHIV (*scenario 2*). B): vaccination of HIV uninfected individuals (*scenario 3*). Y-axis shows the efficacy in PLHIV relative to people without HIV (%) and x-axis shows duration of protection in PLHIV relative to people without HIV (%). (Note different colour scales for A and B).