OPEN

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

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

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

Results: Vaccination irrespective of HIV status, with a vaccine with equal efficacy and duration in PWH, could avert up to 1.01 (95% range: 0.96–1.22) million TB cases in PWH. Restricting vaccination to PWH 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 PWH. Further information on these characteristics is important to identify the most efficient use of new vaccines to reduce TB burden in PWH.

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

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Introduction

People with HIV (PWH) are at a 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 PWH. Despite this, globally, 6% of incident TB cases (700 000 cases) and 13% of deaths due to TB (167 000 deaths) were in PWH [5].

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In countries with high HIV prevalence such as South Africa, more than half of all TB cases and deaths are in PWH [5].

New TB vaccines could be an important tool to prevent TB in PWH. The best way to utilize a new vaccine to maximize benefit in this population is unclear [6]. The impact of any new vaccine on the TB burden in PWH will be influenced by acceptability and uptake of vaccination in PWH, 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 PWH, 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 PWH 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 modeling provides one way to explore the potential effects of new POD TB vaccines on the TB burden in PWH and how this may depend on currently unknown vaccine characteristics. Modeling can also estimate the indirect benefit in PWH of vaccination of people without HIV, which may reduce secondary transmission of *Mycobacterium tuberculosis* (*M.tb*) to this high-risk population. Previous mathematical modeling has explored the effect of including PWH 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 PWH as their primary aim.

In this study, we used a mathematical model to look at the potential impact on TB burden in PWH 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 realized in PWH and the impact of strategies targeting the whole population, or strategies restricted to people without HIV (if a vaccine was not well tolerated in PWH) or PWH (if resources are limited).

Materials and 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, socioeconomic status, and HIV status. The structure of the core TB component is shown in Fig. 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 Fig. 2. The population is stratified into nine 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 $CD4^+$ cell 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 $CD4^+$ cell 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 $CD4^+$ cell count at treatment initiation [18].

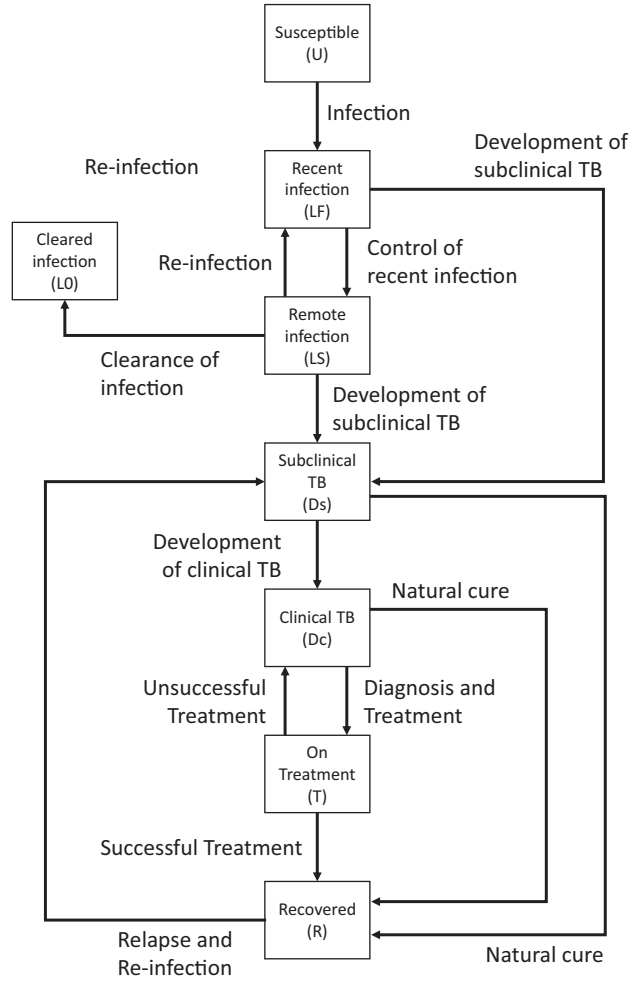

Fig. 1. Tuberculosis natural history model structure. Boxes show the TB states included in the model, lines and arrows show the transitions between them. For clarity mortality and births are not shown.

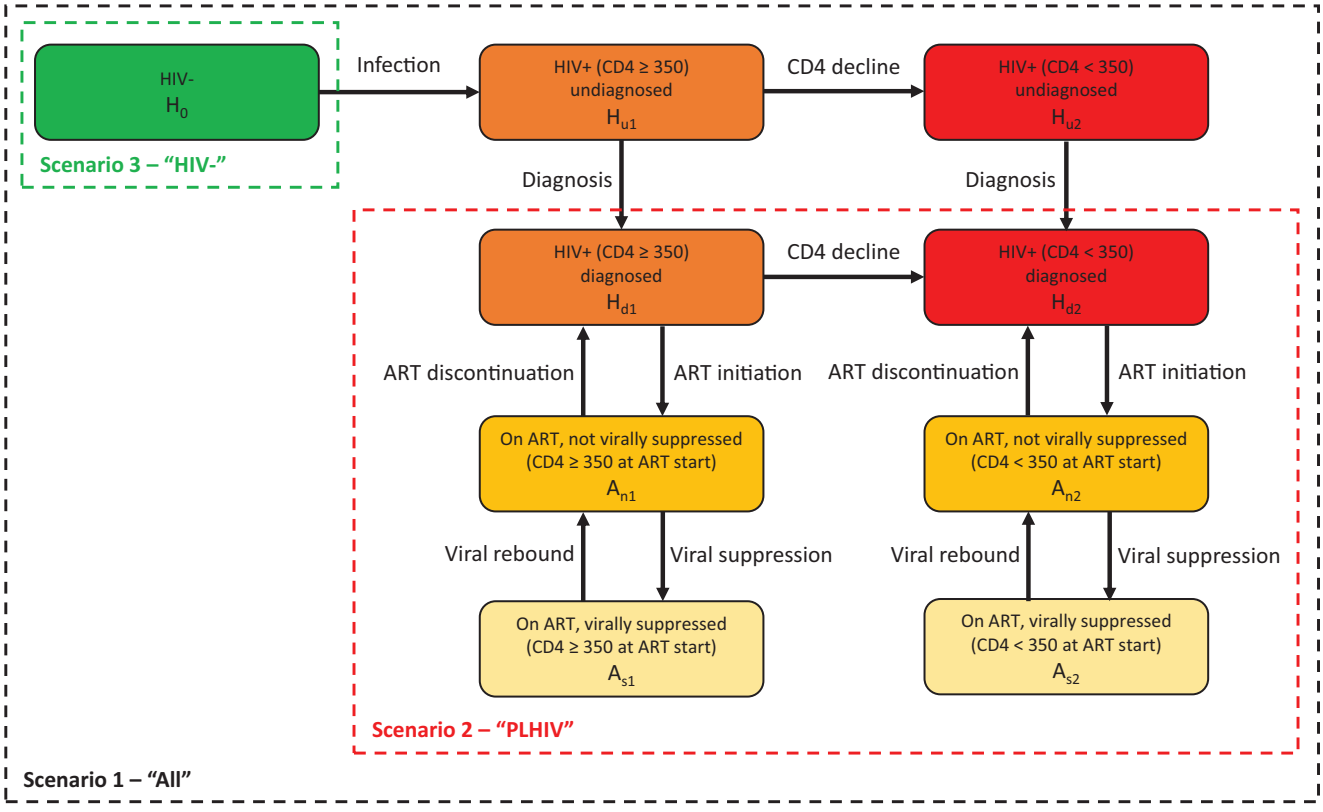

Fig. 2. HIV model structure. Boxes show the HIV states included in the model, lines and arrows show the transitions between them. For clarity, mortality is not shown. The dashed rectangles highlight the HIV states included in the vaccination scenarios described in section 2.4.

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 modeled 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 (i.e., "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 are 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 PWH 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 three vaccination scenarios which are listed below together with their key assumptions. The HIV states included in each scenario are shown by the dashed lines in Fig. 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

(1) The vaccine is well tolerated in PWH.
(2) There is no constraint on vaccine production or other resources.

Scenario 2 - Vaccination of known PWH in care

(1) The vaccine is well tolerated in PWH.
(2) Vaccine availability is limited so focus is on high-risk population.
(3) No additional HIV testing is carried out.

Scenario 3 - Vaccination of people without HIV

(1) The vaccine is not well tolerated in PWH.
(2) HIV testing is carried out prior to vaccination (but not explicitly modeled).

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 PWH 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 PWH who do not know their status, we simulated a one-off campaign in 2030 in 16 to 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 PWH between vaccine introduction in 2030 and 2050, and the number needed to vaccinate (NNV) per case averted in PWH. The NNV was calculated as the cumulative number of individuals vaccinated (irrespective of HIV status) divided by the cumulative number of cases averted in PWH. We also estimated the cumulative number of deaths due to TB averted in PWH 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 PWH and people without HIV (*scenario 1*) for a vaccine meeting the WHO PPCs. Figure 3a shows the cumulative number of TB cases in PWH averted, while Fig. 3b shows the NNV per TB case averted in PWH.

For a vaccine which has equal efficacy and duration of protection in PWH (top right corner of Fig. 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 PWH 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 PWH compared to people without HIV. If the efficacy and duration of protection in PWH 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 Fig. 3a).

Model outputs indicate that this vaccination scenario involves vaccinating approximately 46 million people (10 million PWH and 36 million people without HIV). For a vaccine which has equal efficacy and duration of protection in PWH (top right corner of Fig. 3b), the estimated NNV per TB case averted is 45 (38–48). As discussed above, the number of TB cases averted in PWH is reduced if vaccine efficacy and duration of protection in PWH are reduced. As a result, the NNV is increased.

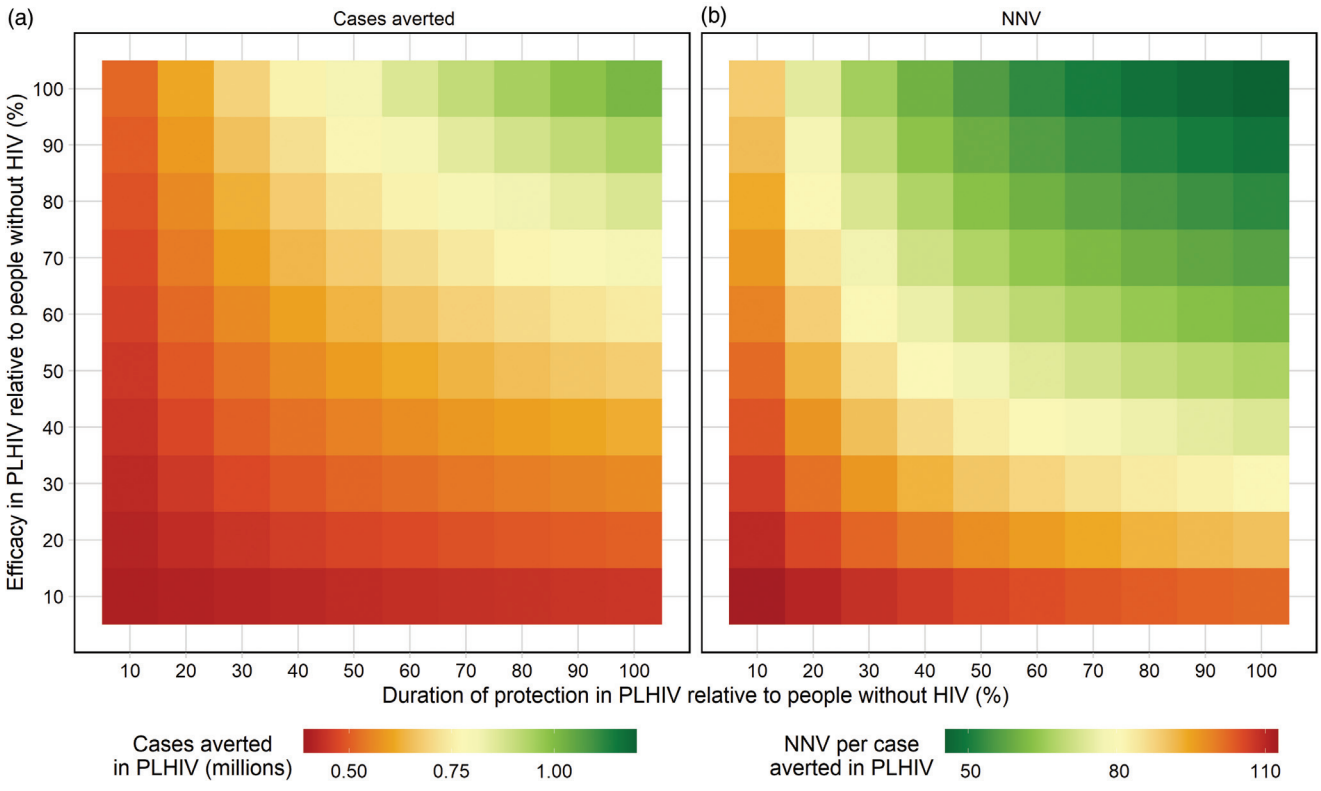

Fig. 3. Tuberculosis cases averted and number needed to vaccinate with vaccination of the whole population (scenario 1). (a) Cumulative TB cases averted in PWH (2030–2050) (in millions). (b) NNV per TB case averted in PWH (2030–2050). Y-axis shows the efficacy in PWH relative to people without HIV (%) and x-axis shows duration of protection in PWH relative to people without HIV (%). (Note: different color scales for left and right panels).

If the efficacy and duration of protection in PWH were only 10% of those in HIV-uninfected individuals, the estimated NNV is 113 (110–125) (bottom left corner of Fig. 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, the 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 PWH by vaccinating either PWH (*scenario 2*, Fig. 4a) or people without HIV (*scenario 3*, Fig. 4b).

If vaccination is restricted to PWH (*scenario 2*), for a vaccine which has equal efficacy and duration of protection in PWH (top right corner Fig. 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 PWH are only 10% of those in people without HIV (bottom left corner of Fig. 4a), then vaccinating PWH 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 well tolerated in PWH 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 PWH (Fig. 4b). The impact of only vaccinating HIV-uninfected individuals is largely independent of the relative efficacy and duration in PWH, 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 PWH and 98% of the impact predicted with a vaccine, which has relative efficacy and duration of protection of 10% in PWH.

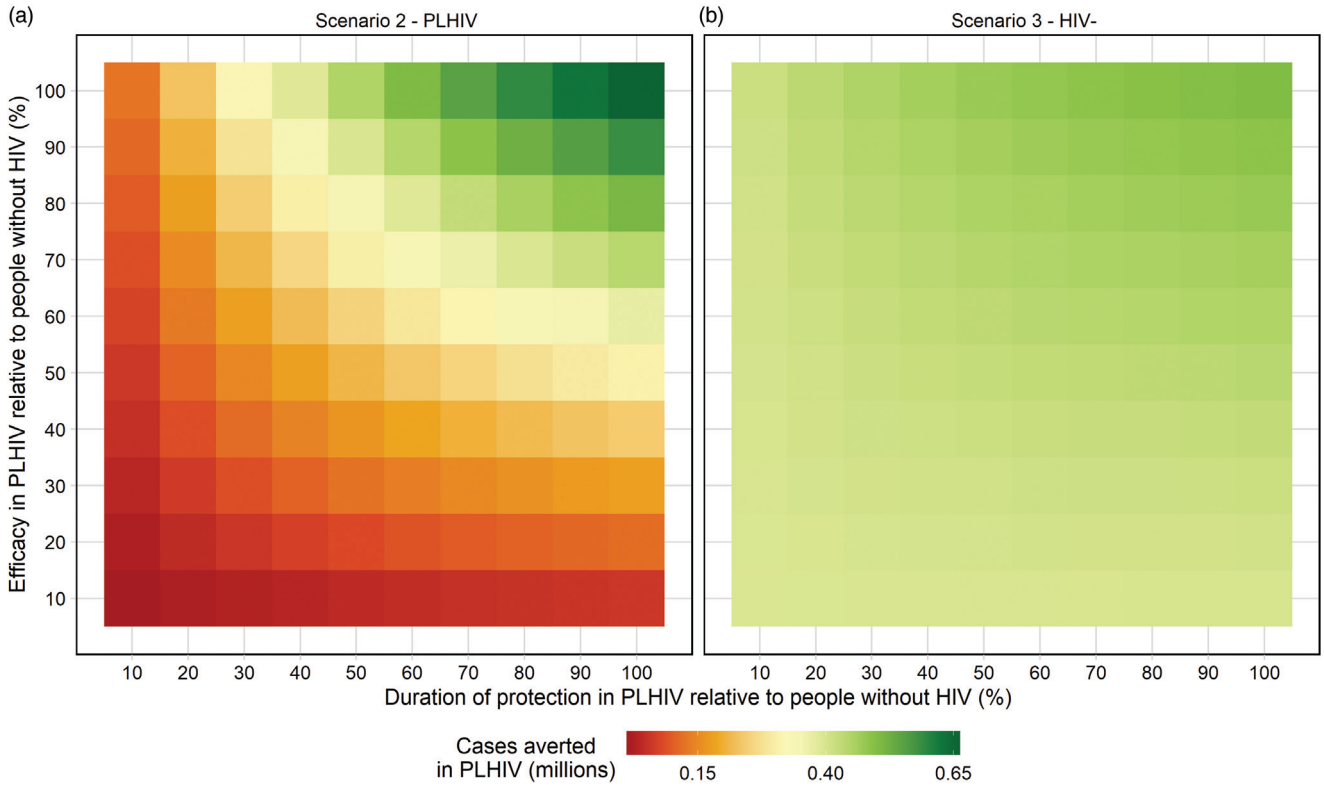

Fig. 4. Tuberculosis cases averted in PWH when vaccination is limited by HIV status. (a) Vaccination of known PWH (*scenario 2*). (b) Vaccination of HIV-uninfected individuals (*scenario 3*). Y-axis shows the efficacy in PWH relative to people without HIV (%) and x-axis shows duration of protection in PWH relative to people without HIV (%).

Supplementary Figure 6 , http://links.lww.com/QAD/D345 directly compares the number of cases averted in PWH 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 PWH (*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 colors in Fig. 5), it is more efficient (lower NNV) if vaccination is limited by HIV status; if this ratio is greater than 1 (shown by blue colors in Fig. 5), it is more efficient to vaccinate everyone irrespective of HIV status.

For a vaccine which has equal efficacy and duration of protection in PWH, restricting vaccination to PWH 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 Fig. 5a), so in this case, it is more efficient to only vaccinate PWH 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 PWH is 1054 (893–1187), approximately nine times that of vaccinating irrespective of HIV status.

The pattern is reversed when considering vaccination restricted to people without HIV (Fig. 5b). Here, it is less efficient to use a vaccine that is only well tolerated in HIV-uninfected people compared to a vaccine that could be used in everyone when the relative efficacy and duration of protection in PWH is high, and switches to be more efficient as the relative values in PWH 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

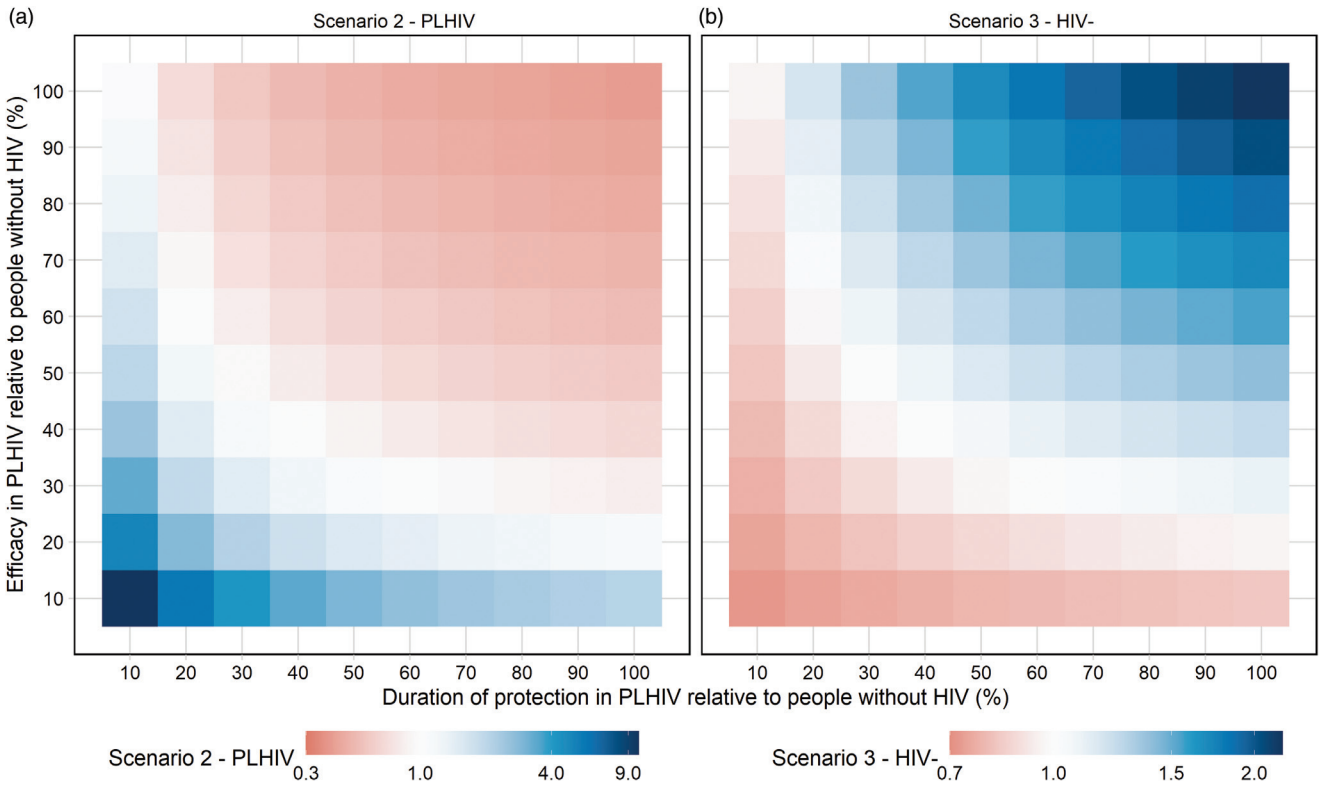

Fig. 5. Ratio of the number needed to vaccinate per tuberculosis case averted when vaccination is limited by HIV status compared to vaccinating everyone. (a) vaccination of known PWH (*scenario 2*). (b) Vaccination of HIV-uninfected individuals (*scenario 3*). Y-axis shows the efficacy in PWH relative to people without HIV (%) and x-axis shows duration of protection in PWH relative to people without HIV (%). (Note different color scales for a and b).

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 PWH in a high HIV prevalence setting such as South Africa. A POD TB vaccine meeting the minimum criteria in the WHO PPC, and which was equally efficacious in PWH, could avert 1.01 (95% range: 0.96–1.22) million TB cases in PWH if given to both PWH and people without HIV. If vaccine availability (or other resources) is limited, only vaccinating PWH 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 PWH 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 PWH; 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 PWH 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 PWH (*scenario 2*), as the relative efficacy and/or duration of protection in PWH 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 PWH (*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 PWH. 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 PWH will be important to identifying the most efficient way to utilize a new vaccine to reduce the TB burden in PWH.

Previous modeling studies have shown how including PWH 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 modeling study to explicitly consider the impact of vaccination on TB burden in PWH as its primary aim.

As with any modeling 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 PWH 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 stated above, varying these parameters would have changed the estimated number of cases averted in our model. Our assumption of equal coverage in PWH 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 PWH, a population already engaged in healthcare. On the contrary, it is possible that acceptance of a new vaccine may be lower in PWH 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 PWH who are at a higher risk of TB and for whom the benefit of vaccination is higher. In this case, the benefit of vaccinating PWH over HIV-uninfected individuals would increase.

We assumed the efficacy and duration of protection in PWH did not depend on their levels of immunosuppression or ART status. The majority of studies demonstrating immune responses to new TB vaccine candidates in PWH have been limited to people with high $CD4^+$ cell counts or those established on ART [7–9]. Evidence from other vaccine preventable diseases suggests that efficacy in PWH 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 and the timing of vaccination relative to ART initiation. We plan to explore these questions in future work.

Our modeling assumed that all other HIV and TB care will remain at current levels in the future. Declines in future TB burden due to nonvaccine 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 PWH we did not consider this in this study.

We do not explicitly model drug-resistant TB, rather our model parameterization 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 are no data on the assortativity of contact by HIV status. If PWH make more contacts with other PWH (e.g., due to geographical or socioeconomic factors), then this may affect our results, potentially reducing the indirect benefit in PWH of vaccination of HIV-uninfected people and increasing the impact of targeting vaccination to PWH.

Conclusion

Our results suggest that new POD TB vaccines could play an important role in reducing the TB burden in PWH. Vaccines targeted at HIV-uninfected individuals could provide significant indirect benefit to PWH, but vaccines which are well tolerated and effective in PWH will be critical to maximizing the impact in this population. If resources are constrained, data on the relative efficacy

of vaccines in PWH will be important for assessing the most efficient way to utilize vaccines to reduce TB burden in PWH.

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T.S., R.G.W., R.A.C., and G.C. were responsible for the conception and the design of the work. T.O.P.S. and R.B. developed software. T.S. carried out the analysis. All authors analyzed and interpreted the results. T.S. drafted the manuscript. All authors were responsible for reviewing the manuscript and approving the final version.

Conflicts of interest

There are no conflicts of interest.

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