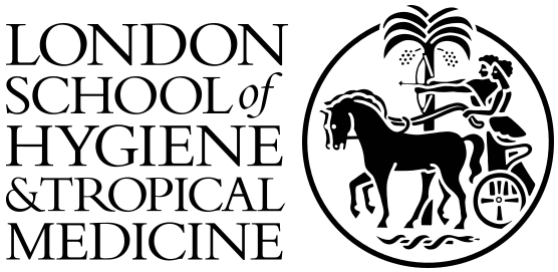

Impact of targeted tuberculosis vaccination among mining population in South Africa: A model-based study

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Running Head: Mine-targeted TB vaccines

Abstract

Optimizing the use of new tools, such as vaccines, may play a crucial role in reaching global targets for tuberculosis (TB) control. Some of the most promising candidate vaccines target adults. However, high-coverage mass vaccinations may be logistically more challenging for adults than for children. Vaccine delivery strategies targeting high-risk groups or settings might yield proportionally greater impact than strategies that target the general population. We developed an individual-based TB transmission model representing a hypothetical population consisting of South African gold miners and the associated labor-sending communities. We simulated implementation of a post-infection adult vaccine with 60% efficacy and mean 10-year duration of effect, and compared the impact of a mine-targeted vaccination strategy, where miners were vaccinated while in the mines, against a community-targeted strategy, where random individuals within the labor-sending communities were vaccinated. Mine-targeted vaccination averted an estimated 0.37 TB cases per vaccine dose, versus 0.25 for community-targeted vaccination, for a relative efficacy of 1.46 (95% range: 1.13-1.91). The added benefit of mine-targeted vaccination primarily reflected the disproportionate demographic burden of TB among adult males as a whole. As novel vaccines for TB are developed, venue-based vaccine delivery targeting high-risk demographic groups may improve both feasibility and transmission impact.

Keywords: Tuberculosis, TB vaccine, Mathematical modeling, South African gold mines, Targeted vaccination

Introduction

Effective tuberculosis (TB) vaccines have the potential to facilitate significant progress in reducing the global burden of TB [1], which is the leading infectious cause of human mortality [2]. There are numerous candidate vaccines in the pipeline, and many of the most promising candidates target adolescents and adults [3]. Adult vaccines are projected to have the greatest impact on TB incidence [4], but unlike with infant vaccines where mass vaccinations with high coverage are common, it may be logistically challenging to achieve similarly high coverage with adult vaccines. Furthermore, vaccine supplies for any TB vaccine are likely to be severely constrained during the initial roll-out phase. Hence, it is important to deliver adult vaccines in ways that maximize impact on TB incidence given a limited number of vaccine doses.

One potential method for optimizing vaccine delivery is to target settings that foster *M. tuberculosis* transmission, such as crowded and poorly ventilated settings. These transmission "hotspots" may play a disproportionately large role in TB transmission because the majority of transmission events may occur within these settings [5,6]. The gold mines of South Africa are a widely recognized transmission hotspot for TB, with reported incidence in the past up to 3,000-5,000 per 100,000 per year [7-9]. Just as targeted vaccine delivery has been successful against other geographically heterogeneous infections (e.g., cholera [10,11], malaria [12,13], foot-and-mouth disease [14]), TB vaccine delivery strategies that target mines might yield proportionally greater impact than strategies that target the broader population, as the same number of doses could avert a larger number of

secondary transmission events. Not only might miners be at higher risk of acquiring TB, but mines as "hotspots" might also fuel epidemics in the overall community, and targeting such hotspots may beneficial to communities as a whole [15]. Furthermore, mining companies routinely offer occupational health services to their employees, which may provide a logistically simplified and less costly approach to large-scale vaccine delivery in a very high-risk population.

In order to understand the impact of different vaccination targeting strategies, an important first step is to quantify the impact of a feasible targeting strategy in an epidemiologically relevant setting, relative to simply targeting high-risk communities as a whole. In this study, we aimed to estimate the relative impact of occupationally targeted vaccine delivery strategies centered on the South African gold mines. We modeled and calibrated a hypothetical population that consisted of the mines and the labor-sending communities from which the mining workforce is recruited. We compared two vaccination strategies: a mine-targeted strategy, where vaccines were delivered to those working in the mines, and a community-targeted strategy, where vaccines were delivered to randomly selected adults in the labor-sending communities. The primary outcome (TB cases averted over a 20 year period) was measured in the entire model population, including both the mines and the labor sending communities, thus providing an estimate of the relative impact of mine-targeted versus community-targeted vaccination.

Methods

Model Development

We developed an individual-based transmission model to characterize the transmission dynamics of TB in a model population consisting of the mines and the associated labor-sending communities. The model (Web Fig. 1) features components that describe (i) the composition of mines and miners' mixing patterns; (ii) natural history of TB; (iii) HIV prevalence and HIV-TB co-infection dynamics; (iv) demographic processes; and (v) mechanistic description of vaccines.

Mines and labor-sending community:

The model population consisted of permanent residents of the labor sending districts and the migratory sub-population of those districts that work in the mines (Web Fig. 1[A]). We assumed that a sizable fraction of the population (range explored: 20-70% of adult males) would consist of miners, who when employed, travel between the mines and the home community. To reflect this, individuals were modeled as taking one of two potential life history trajectories: those who become miners and those who do not. Individuals who become miners are modeled as eligible to work in the mines between the ages of 18 and 60. Once a miner turns 18, he becomes a career miner after an average wait-time for recruitment ($\tau_{recruit}$). After recruitment, employed miners spend a portion of their time working in the mine (mixing only with other miners) and the remainder of their time at

home (mixing with others in the labor-sending community). We assumed that miners actively working at the mine remain at the mine for an average specified time (τ_{mine}) before returning home, and upon returning home, remain at home for an average time (τ_{home}) before returning to the mine (See Web Fig. 1A, right panel for model schematic, and Web Table 1 for parameters estimates used in the model.).

Natural history of TB:

We adapted previously developed models to describe the natural history of TB [6, 16,17]. (Web Fig. 1[B].) In our model, an individual's TB status can be: uninfected (U); latently infected with TB (L); and infectious with active TB disease (A). Upon exposure to TB, uninfected individuals may either develop latent infection or progress immediately to develop active TB. Latently infected individuals can subsequently develop active TB disease, either by endogenous reactivation or by reinfection followed by rapid progression. TB transmission was modeled separately in the mines and in the labor-sending community. Within each setting, we assumed homogeneous mixing among individuals, such that the *per capita* hazard of infection was proportional to the number of infectious individuals in that setting multiplied by the setting-specific transmission rate. We define *the transmission rate* as the average number of secondary transmissions per infectious person-year. Successful treatment of TB was modeled as return to the latent state. To capture age- and sex-specific differences in TB incidence, we allowed for separate rates of rapid progression to active TB after initial infection and reactivation after remote infection. These rates were modeled as piecewise constant functions of age; thus, in any given model simulation, we assume four

different baseline rates (male/female, older/younger). The values of these four rates, as well as the age at which the transition from lower to higher rates occurs, are assumed to be modified by HIV and are fit to match the age-specific TB incidence data.

HIV prevalence, ART coverage, and HIV-TB co-infection:

We modeled the acquisition of HIV infection to be age- and sex-dependent, but independent of TB status. We allowed for separate HIV acquisition rates for males and females reflective of differences in HIV prevalence between the two sexes. We modeled the rates as piecewise functions of age, categorized as 2-15, 15-25, and 25-40 years old. HIV infection was modeled to sequentially progress through four stages, differentiated by CD4+ T-cell counts: (i) > 500; (ii) 350-500; (iii) 200-350; and (iv) < 200. (Web Fig. 1[B]). On the basis of literature estimates [17], we assumed that in the absence of treatment, individuals spend two years on average in each stage. We also included antiretroviral therapy (ART), assuming that the rate at which individuals received ART depended on their CD4+ counts and fitting these rates to age-specific ART coverage among adults in South Africa.

We assumed that HIV increased the risk of TB disease by increasing both the risk of rapid progression and reactivation of latent infection. We assumed that, compared to HIV-negative individuals, the incidence of TB would be 2, 4, 8, and 16 times higher among HIV-positive individuals with CD4+ counts >500, 350-500, 200-350, and <200, respectively [18-21]. Finally, we assumed HIV-specific mortality rates of 0.1/year for individuals with CD4+ counts higher than 200, and 0.35/year in individuals with CD4+ counts less than 200 [22].

Demography:

The population was modeled to have a *per capita* birth rate and an age-specific mortality rate, which was based on a Siler mortality model [23]. Individuals with active TB were additionally subject to TB-specific mortality (μ_{TB}), HIV-positive individuals were additionally subject to HIV-specific mortality, and HIV-positive individuals with active TB were additionally subject to both.

Vaccines:

The characteristics of the modeled vaccine were instantiated in consultation with experts at the Aeras Foundation, as those most useful to represent actual vaccines in development. We modeled a post-infection vaccine that prevents progression to TB disease, but does not prevent TB infection. This hypothetical, emblematic vaccine protects individuals against TB disease by preventing rapid progression following recent exposure or re-exposure, and by preventing reactivation of previously acquired latent TB infection. We assumed the vaccine to have 60% efficacy regardless of HIV status, with a protection lasting 10 years on average. We define *vaccine efficacy* in a biological sense, as the percentage of independent potential disease-causing events that would be averted by a vaccine. This definition of efficacy is not necessarily equivalent to efficacy in an epidemiological sense (as would be measured in a clinical trial), where each trial participant may experience more than one disease-causing event.

Data and Model Calibration

We used multiple sources of data to sequentially calibrate different components of the model. For the demographic model, we assumed a constant *per capita* birth rate, and an age-specific background mortality model fitted to the South African age-specific mortality rates in 2011 [24]. For the HIV model, we fit age- and sex-specific HIV acquisition rates and ART treatment rates to reflect the population level prevalence of HIV and ART coverage in 2011 [25]. Comparisons between the data and model simulations are reported in Web Table 1 and shown in Fig. 1.

We used data collected during the Thibela TB study [7, 26] to inform the model population. The Thibela TB study enrolled 15 mine clusters across three South African provinces: Gauteng, North West, and Free State. The miners were almost exclusively male (females < 1%), with more than 60% of miners falling between the ages of 30 and 50. (Web Fig 2[B]) Reported TB incidence at the start of the study was 3,460 per 100,000/year. (Fig 1[D]) We identified 4 districts across 2 South African provinces: Ugu and Sisonke in Kwa-Zulu Natal, and OR Tambo and Alfred Nzo in Eastern Cape, as communities likely to be representative of the labor-sending communities serving the Thibela TB mines, and from which data could be readily accessed. We collected demographic data from Statistics South Africa [27] and TB notification rates in these districts from the Annual Tuberculosis Report of South Africa [28] (Fig. 1[D]). We observed that, while the average TB incidence in the labor-sending communities was 1,230 per 100,000/year (almost one-third of that in the mines), the TB incidence among middle-aged males in those communities was generally above 3,000 per

100,000/year (Fig. 1, solid blue bars in panel C versus solid bar in panel D). Finally, we assumed effects of HIV on TB incidence in both mines and the labor-sending community as described above [18-21]. (Fig. 1[E])

We fit the model to reflect data elements concerning (1) age- and sex-specific TB incidence, (2) demographic composition of the mines, (3) TB incidence in the mines, and (4) HIV-TB coinfection dynamics. We first generated 216,000 parameter sets, where each parameter was sampled from a reasonable range using Latin hypercube sampling. For each parameter set, we simulated the model, first without HIV until an approximate equilibrium was reached, and then with HIV dynamics in the final 30 years. We then selected the parameter sets that generated simulations that matched all four sets of data elements to within a tolerance of +/-35% of the reported value. We used these selected parameter sets as viable simulations, and used them to estimate the impact of vaccination.

Vaccine dynamics

We simulated two 20-year vaccination campaigns; (i) mine-targeted vaccination strategy, where vaccines were administered to all miners, including new miners at recruitment and current miners at their medical examination as they return to the mines; and (ii) community-targeted vaccination strategy, where vaccines were delivered randomly to adults (10-60 years) in the labor-sending population. The number of vaccine doses delivered per year was modeled to be equal in both strategies. We calculated the total number of TB cases averted in the total population (including both the mines and the labor-sending communities) over

20 years of vaccination, by comparing the simulations without vaccination against the simulations with each vaccination strategy.

Sensitivity analyses

To explore the sensitivity of the results to the model parameters, we calculated partial rank correlation coefficients [29] (PRCC) within the set of selected parameters, comparing the difference between the two vaccine delivery strategies, in terms of the number of TB cases averted over a 20-year period.

Additionally, we conducted a series of sensitivity analyses to explore the sensitivity of the primary outcome to (i) uncertainty in vaccine efficacy (Web Appendix 1); (ii) vaccine uptake (Web Appendix 2); vaccine mechanism (Web Appendix 3); size of the mining population (Web Appendix 4); and impact of vaccination over time (Web Appendix 5). We also explored a scenario (Web Appendix 6) where heterogeneity in mixing was introduced in the population via household structure [30]. Finally, we explored an alternative scenario (Web Appendix 7) where the transmission rates within the mines were allowed to be higher than those within the labor-sending community, to allow for potentially higher effective contact rates in the mines.

Results

Among 216,000 model simulations initialized with parameters sampled from distributions detailed in Web Table 1, 2,374 simulations matched the data within the pre-specified +/- 35% window. These selected simulations fit the epidemiological data reasonably well (Fig. 1C–F). In these data-consistent simulations, a median 22,000 (95% range: 9,660-31,800) vaccines were delivered (Fig. 2[C&D]) per 100,000 over 20 years. When these vaccines were delivered to the labor-sending community, a median 5,510 (95% range: 2,360-10,000) TB cases were averted over 20 years, or 0.254 cases averted per vaccine dose. By comparison, vaccination campaigns that targeted miners averted a median 8,090 (95% range: 3,750-13,300) total TB cases (Fig. 2[A&B]), or 0.374 TB cases per vaccine dose (Fig. 2[E]).

The mine-targeted strategy achieved higher impact than the community-targeted strategy in more than 99% of data-consistent simulations. Specifically, mine-targeted vaccination campaigns averted 1.46 (95% range: 1.13-1.91) times more TB cases than community-targeted vaccination (Fig. 2[F]). The relative impact of targeting was expectedly more prominent in the targeted population (i.e., miners and adults) and persisted over time (relative impact in year 20 remained 1.41, 95% range: 1.08-1.9). (Web Appendix 5)

The characteristic that most strongly influenced the primary outcome was the percentage of TB occurring in adult males (Fig. 3). Thus, where a greater proportion of incident TB occurs in adult men, mine-focused vaccination strategies are expected to have greater relative impact. The proportion of the population who became miners was inversely

associated with the primary outcome; when more members of the population were miners, the population-based vaccination strategy covered a larger proportion of miners, thus attenuating the relative impact of mine-targeted vaccination strategy. However, this effect was small (relative impact 1.48 in populations below the median mining population size versus 1.44 in populations above, Web Appendix 4).

In an alternate model scenario (see Web Appendix 7), in which transmission rates within the mines were allowed to be up to twice as large as in the labor-sending community, substantially fewer proportions of simulations were consistent with the observed data (280 out of 108,000, versus 2,374 out of 216,000). In those simulations, the relative impact of targeting the mines was not substantially affected (1.46 versus 1.54) and fell within the respective uncertainty ranges, suggesting that counterbalancing effects (e.g., reduced interactions between miners and the labor-sending community) are required under those scenarios to make the model fit the observed epidemiological data.

Discussion

In this work, we aimed to estimate the impact of vaccination strategies that targeted South African gold mines, relative to population-based strategies that targeted the labor-sending communities as a whole. We found that TB vaccines could have substantial impact in this setting, averting more than 0.25 cases of active TB per vaccine dose delivered. Vaccination strategies targeting miners were moderately (1.46 times) more effective than strategies

targeting the labor-sending communities, suggesting that occupationally targeted TB vaccination could be a useful strategy in high-burden settings like South Africa.

The relative impact of mine-targeted vaccination was strongly dependent on the proportion of incident TB occurring in adult men, suggesting that such occupationally targeted strategies may be most effective when strong demographic gradients in TB incidence exist. In contrast, the relative impact of mine-targeted vaccination was less dependent on mine-specific factors. Particularly, even when the mines were allowed to have higher TB transmission rates than the labor-sending community as a whole, the relative impact of mine-targeted vaccination remained essentially unchanged (See Web Appendix 7).

Although the average TB incidence in the mining population was almost three times higher than the average TB incidence in the labor-sending community, the reported incidence in the mines was very similar to the TB incidence of adult men in the labor-sending population. Thus, the demographic composition of the mines is such that mine-targeted vaccination is essentially demographically targeted vaccination, i.e. vaccinating adult males in the labor-sending community would target people with the same expected TB incidence as the mine-targeted strategy. As a result, although targeting miners can have modest to moderate relative benefit, the underlying reason for this benefit may more reflect the disproportionate burden of TB among adult males, than the mines serving as true transmission hotspots in these communities.

There are several potential reasons that miners, with their extreme occupational risk, might have similar TB incidence to young adult non-mining men in the labor-sending community.

These might include (1) a healthy worker effect (miners are more likely to acquire TB in the mines, but only healthy miners remain in employment); (2) socioeconomic factors (miners may be wealthier and/or healthier than the general community, which may offset any increased transmission in the mines themselves); and (3) secular trends (mines may have historically contributed to the higher population incidence of TB in the labor-sending communities, but conditions in the mines – including more intensive screening for TB – may have improved over time). Mines have operated for centuries, and the labor sending communities are likely to consist of retired miners, who may have high risk of TB due to factors such as silicosis, which might manifest only after long delays and hence be more prevalent in the community than the mines.

Our study was limited by the data available to inform our model. Data on HIV prevalence were not available specifically for either the mines or the labor-sending districts, and we used national estimates for South Africa as proxies for both populations. Hence, our work did not account for potential differences in HIV-TB co-dynamics between the mines and the labor-sending community. Data on miners' travel and mixing patterns were also limited, and our estimates for the amount of time spent in the mines were based on miners' self-reported responses to a survey questionnaire. The model did not account for mixing with peri-mining communities surrounding the mines, which might differ from the labor-sending communities. Our model did not include silica dust exposure and silicosis, which are strong independent risk factors for TB. The reported silicosis prevalence was relatively low (2.6%) in the miners in the Thibela TB study [7]. However, higher silicosis rates have previously been reported among miners, the prevalence of observable silicosis will increase with age,

and the Thibela TB mines may not represent the risk that miners in general experience. Finally, it should be noted that many vaccine characteristics (e.g., mechanism and duration of effect, heterogeneity in immunological “take", and efficacy, including differences between HIV-positive and HIV-negative individuals) are unknown and difficult to assess prior to implementation, even with a large-scale clinical trial. Our sensitivity analyses suggest that the relative value of mine-targeted vaccination is robust to uncertainty in vaccine efficacy, uptake, the size of targeted mining population, and moderate heterogeneity in mixing. We note that the effectiveness of the vaccine itself may be highly dependent on the mechanism of protection derived from the vaccine. In particular, pre-infection vaccines that protect against infection only (and not TB disease) may have limited effectiveness when delivered to adults in a high-prevalance setting like South Africa, as the vast majority of individuals will be infected prior to vaccination, and the immunological effects of a vaccine in such individuals with some degree of existing natural immunity will likely remain uncertain.

In summary, we found that, relative to a community-targeted strategy that focused on vaccinating adults in high-incidence labor-sending districts, a mine-targeted vaccination strategy provided moderate (1.45-fold) relative improvement. The absolute impact of TB vaccination (0.375 cases averted per dose), as well as the absolute impact of mine-targeted vaccination (over 8,000 TB cases per 100,000 over 20 years) was substantial, reflecting the tremendous incidence of TB in the overall population. The relative benefit achieved by targeting the mines largely reflects the fact that mine-focused strategies target a demographic group with higher TB incidence: adult males. Mines, in this context, may

serve as a mechanism via which demographic groups with higher risk of TB can be identified, and they may also be logistically more accessible than general adult populations.

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References

[1] Abu-Raddad LJ, Sabatelli L, Achterberg JT, et al. Epidemiological benefits of more-effective tuberculosis vaccines, drugs, and diagnostics. *Proceedings of the National Academy of Sciences* 2009;106(33):13980–13985. 10.1073/pnas.0901720106.

[2] World Health Organization. Global tuberculosis Report 2015. http://apps.who.int/iris/bitstream/10665/191102/1/9789241565059_eng.pdf. Accessed January 12, 2017.

[3] Marinova, D., Gonzalo-Asensio, J., Aguilo,et al. 2013 Recent developments in tuberculosis vaccines. *Expert Rev Vaccines* 2013;12:1431–1448. 10.1586/14760584.2013.856765.

[4] Knight GM, Griffiths UK, Summer T, et al. Impact and cost-effectiveness of new tuberculosis vaccines in low- and middle-income countries. *Proceedings of the National Academy of Sciences* 2014;111(43):15520–15525. 10.1073/pnas.1404386111.

[5] Dowdy DW, Golub JE, Chaisson RE, et al. Heterogeneity in tuberculosis transmission and the role of geographic hotspots in propagating epidemics. *Proceedings of the National Academy of Sciences* 2012;109(24):9557–9562. 10.1073/pnas.1203517109.

[6] Shrestha S, Chatterjee S, Rao KD, et al. Potential impact of spatially targeted adult tuberculosis vaccine in Gujarat, India. *Journal of Royal Society, Interface* 2016; 13:20151016. 10.1098/rsif.2015.1016

[7] Churchyard GJ, Fielding KL, Lewis JJ, et al. A trial of mass isoniazid preventive therapy for tuberculosis control. *New England Journal of Medicine* 2014;370(4):301–310. 10.1056/NEJMoa1214289.

[8] Corbett EL, Churchyard GJ, Charalambous S, et al. Morbidity and mortality in south african gold miners: Impact of untreated disease due to human immunodeficiency virus. *Clinical Infectious Diseases* 2002;34(9):1251–1258. 10.1086/339540.

[9] van Halsema CL, Fielding KL, Chihota VN, et al. Trends in drug-resistant tuberculosis in a gold-mining workforce in South Africa, 2002-2008. *The International Journal of Tuberculosis and Lung Disease* 2012;16(7):967–973. 10.5588/ijtld.11.0122.

[10] Chao DL, Halloran ME, Longini IM Jr. Vaccination strategies for epidemic cholera in Haiti with implications for the developing world. *Proc Natl Acad Sci USA* 2011;108(17):7081-7085.

[11] Azman AS, Luquero FJ, Rodrigues A et al. Urban cholera transmission hotspots and their implications for reactive vaccination: evidence from Bissau city, Guinea Bissau. *PLoS Negl Trop Dis* 2012; 6:e1901. doi:10.1371/journal.pntd.0001901

[12] Carter R, Medis KN, Roberts D. Spatial targeting against malaria. *Bull World Health Organ* 2000; 78:1401-1411.

[13] Bousema T, Drakeley C, Gesase S et al. Identification of Hot Spots of Malaria Transmission for Targeted Malaria Control. *J Infect Dis* 2010;201:1764-1774. doi:10.1086/652456

[14] Keeling MJ, Woolhouse MEJ, May RM et al. Modelling vaccination strategies against foot-and-mouth disease. *Nature* 2003;421:136-142

[15] Dowdy DW, Azman AS, Kendall EA, et al. Transforming the fight against tuberculosis: targeting catalysts of transmission. *Clinical Infectious Diseases* 2014; 59:1123-1129. 10.1093/cid/ciu506

[16] Blower SM, Mclean AR, Porco TC, et al. The intrinsic transmission dynamics of tuberculosis epidemics. *Nature medicine* 1995;1(8):815–821.

[17] Williams BG, Granich R, De Cock KM, et al. Antiretroviral therapy for tuberculosis control in nine african countries. *Proceedings of the National Academy of Sciences* 2010;107(45):19485–19489. 10.1073/pnas.1005660107.

[18] Williams BG, Dye C. Antiretroviral drugs for tuberculosis control in the era of HIV/AIDS. *Science* 2003;301(5639):1535–1537. 10.1126/science.1086845.

[19] Holmes CB, Wood R, Badri M, et al. CD4 decline and incidence of opportunistic infections in cape town, south africa: Implications for prophylaxis and treatment. *JAIDS Journal of Acquired Immune Deficiency Syndromes* 2006;42(4):464–469.

[20] Lawn SD, Myer L, Edwards D, et al. Short-term and long-term risk of tuberculosis associated with CD4 cell recovery during antiretroviral therapy in South Africa. *AIDS* 2009;23(13):1717–1725. 10.1097/QAD.0b013e32832d3b6d.

[21] Badri M, Wilson D, Wood R. Effect of highly active antiretroviral therapy on incidence of tuberculosis in south africa: a cohort study. *The Lancet* 2002;359(9323):2059–2064. http://dx.doi.org/10.1016/S0140-6736(02)08904-3.

[22] Williams BG, Korenromp EL, Gouws E, et al. HIV infection, antiretroviral therapy, and CD4+ cell count distributions in african populations. *Journal of Infectious Diseases* 2006;194(10):1450–1458. 10.1086/508206.

[23] Siler W. A competing-risk model for animal mortality. *Ecology* 1979;60(4):pp. 750–757.

[24] Statistics South Africa. Mortality and causes of death in South Africa, 2013: Findings from death notification, 2014. http://www.statssa.gov.za/publications/P03093/P030932013.pdf. Accessed January 12, 2017.

[25] Shisana O, Rehle T, Simbayi L, et al. South African National HIV Prevalence, Incidence and Behavior Survey, 2012. HSRC Press; Cape Town: 2014. http://www.hsrc.ac.za/en/research-data/view/6871. Accessed January 12, 2017.

[26] Fielding KL, Grant AD, Hayes RJ, et al. Thibela TB: Design and methods of a cluster randomised trial of the effect of community-wide isoniazid preventive therapy on tuberculosis amongst gold miners in south africa. *Contemporary Clinical Trials* 2011;32(3):382 – 392. http://dx.doi.org/10.1016/j.cct.2010.12.008.

[27] Statistics South Africa. http://www.statssa.gov.za. Accessed January 12, 2017.

[28] National TB Control And Management Cluster, National Department of Health, South Africa. Annual Tuberculosis Report for South Africa – 2012.

[29] Sanchez MA, Blower SM. Uncertainty and sensitivity analysis of the basic reproductive rate: Tuberculosis as an example. *American Journal of Epidemiology* 1997;145(12):1127–1137.

[30] Verver S, Warren RM, Munch Z, et al. Proportion of tuberculosis transmission that takes place in households in a high-incidence area. *The Lancet* 2004;363:212-214. doi:10.1016/S0140-6736(03)15332-9

[31] World Bank. World development indicators. 2016 http://databank.worldbank.org/data/reports.aspx?source=world-development-indicators. Accessed January 12, 2017.

[32] Dye C, Garnett GP, Sleeman K, et al. Prospects for worldwide tuberculosis control under the WHO DOTS strategy. *The Lancet* 1998;352(9144):1886–1891. 10.1016/S0140-6736(98)03199-7.

[33] Vynnycky E, Fine P, et al. The natural history of tuberculosis: The implications of age-dependent risks of disease and the role of reinfection. *Epidemiology and infection* 1997;119(2):183–201.

[34] Horsburgh Jr CR, O'Donnell M, Chamblee S, et al. Revisiting rates of reactivation tuberculosis: A population-based approach. *American Journal of Respiratory and Critical Care Medicine* 2010;182(3):420–425.

[35] Sutherland I, Švandová E, Radhakrishna S. The development of clinical tuberculosis following infection with tubercle bacilli: 1. A theoretical model for the development of clinical tuberculosis following infection, linking from data on the risk of tuberculous infection and the incidence of clinical tuberculosis in the netherlands. *Tubercle* 1982;63(4):255–268. http://dx.doi.org/10.1016/S0041-3879(82)80013-5.

[36] Vynnycky E, Fine P. The annual risk of infection with *Mycobacterium tuberculosis* in England and Wales since 1901. *The International Journal of Tuberculosis and Lung Disease* 1997;1(5):389–396.

[37] Basu S, Orenstein E, Galvani AP. The theoretical influence of immunity between strain groups on the progression of drug-resistant tuberculosis epidemics. *J Infect Dis* 2008;198:1502–1513.

[38] Andrews JR, Noubary F, Walensky RP, et al. Risk of progression to active tuberculosis following reinfection with mycobacterium tuberculosis. *Clinical Infectious Diseases* 2012;54(6):784–791. 10.1093/cid/cir951.

Figure 1: **Data, fitted model, and model simulations.** [A] Population pyramids: data in shown in solid bars and model fits shown in hatched bars [B] Age and sex-specific HIV prevalence as reported in the South African prevalence survey [21] (shown in solid bars), and fitted prevalences (shown in hatched bars). [C] Age and sex-specific TB incidence (per 100,000 per year) in the entire model population. Data represents notified TB cases aggregated in 4 districts (Ugu, Sisonke, OR Tambo, and Alfred Nzo) averaged between 2011 and 2012, and scaled by the appropriate population (shown as solid red and blue bars for females and males, respectively) [28]. Model simulations are shown in hatched bars (bars represent medians, and vertical lines represent 95% range). [D] TB incidence (per 100,000 per year) among miners: data in the Thibela TB mines are shown as a solid bar, and model simulations as a hatched bar. [E] We modeled the interaction between TB and HIV to manifest as an increased incidence of TB among HIV-positive individuals, by factors of 2, 4, 8 and 16 (shown by solid bars). The corresponding model simulations are shown by hatched bars.

Figure 2: **Comparisons of mine and community targeted vaccines.** [A] Cumulative TB cases averted over time by the two vaccination campaigns: red shows the campaign where the vaccine was targeted to the mines, and grey shows the campaign where the vaccine was targeted to the labor-sending community. [B] The two histograms show the distributions of total TB cases averted over the 20 year period. Community-targeted delivery (grey bars) averted a median of 5,510 cases (95% range:2,360-10,000), whereas, mine-targeted delivery (red bars) averted 8,090 cases (95% range: 3,750-13,300). Solid lines represent the medians of all data-consistent simulations, and dotted lines represent the 2.5^{th} and 97.5^{th} percentiles. [C] Cumulative vaccine doses delivered (the same for both delivery strategies) over time during the 20 year vaccine campaign. [D] Distribution of total vaccines delivered over 20 years (median: 22,000; 95% range: 9,660-31,800) [E] TB cases averted per vaccine delivered; grey for the community-targeted delivery (median: 0.254; 95% range: 0.178-0.387), and red for the mine-targeted delivery (median: 0.374; 95% range: 0.274-0.527). [F] Impact of mine-targeted vaccine delivery on TB incidence over 20 years, relative to community-targeted delivery (median 1.46; 95% range: 1.13-1.91).

Figure 3: **Partial rank correlation coefficients (PRCCs).** Presented are partial rank correlation coefficients (PRCCs) comparing each model parameter (or parameter combination) with the primary outcome, total TB cases averted over 20 years of vaccination that was delivered to the mines relative to the vaccine that was delivered to the labor sending community. Only parameters with $|PRCC|>.05$ are shown, and only two factors (percentage of TB occurring in adult men, and percentage of the population engaged in mining) had absolute values of PRCC >0.15. See Web Fig. 14 in the Web Appendix for PRCCs associated with the complete list of parameters.