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Modeling the implementation of population-level isoniazid preventive therapy for tuberculosis control in a high HIV-prevalence setting

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Background: We model the epidemiological impact of providing isoniazid preventive therapy (IPT) to South African adolescents, among whom HIV prevalence is low, latent tuberculosis (TB) prevalence is high, and school-based programs may enable population-level coverage.

Methods: We simulate a dynamic compartmental model of age-structured HIV and TB coepidemics in South Africa. HIV dynamics are modeled by infection status, $CD4^+$ cell count, and antiretroviral therapy; TB dynamics are modeled by disease stage, diagnosis, treatment, and IPT status. We analyze the effects of continuous IPT coverage among adolescents from 5 (baseline) to 90%.

Results: Our model is calibrated to WHO and the Joint United Nations Programme on HIV/AIDS epidemiological estimates. In simulations, increasing IPT coverage to 50% among adolescents reduced active TB incidence by 5–34%. Increasing coverage to 90% led to a 9–40% reduction in active TB incidence. Expanded IPT access causes TB incidence to decline in the general population of HIV-positive individuals, as well as in adult HIV-positive individuals.

Conclusion: Targeting IPT to a secondary school population with high latent TB prevalence and low-HIV prevalence, in which risk of false-negative diagnosis of active TB is low and IPT benefits are more established, could have substantial benefits to adolescents and spillover benefits to the adult population.

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Keywords: isoniazid preventive therapy, latent tuberculosis, South Africa, tuberculosis, tuberculosis/HIV coinfection

Introduction

Tuberculosis (TB) is the second greatest infectious cause of mortality worldwide [1]. Over two billion people are estimated to have latent infection, which does not cause disease symptoms, but increases the risk of reactivation and disease. For that reason, individuals diagnosed with latent TB in most countries with low prevalence of latent TB are treated with a regimen known as isoniazid preventive therapy (IPT), which presumably cures the latent TB infection, thus reducing the risk of future TB reactivation and disease.

The WHO is promoting the use of IPT in all contexts, and has been monitoring IPT coverage rates since 2003 [1]. However, in high-TB burden contexts, only a small fraction of individuals infected with latent TB is treated with IPT [2,3]. Developing countries typically are not able to screen for latent TB at the community level, as public health systems can be overwhelmed in treating cases of active TB. They are therefore largely unable to screen asymptomatic individuals for latent TB, leaving large numbers of latent TB cases untreated. In addition to competing resource needs, barriers include possible monitoring requirements for liver function for individuals on IPT [4], concerns about the

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development of drug resistance [5], and challenges of distinguishing between latent and active TB in areas of high HIV prevalence (inadvertently providing IPT to a person suffering from active TB could result in delay of appropriate treatment and development of resistance).

Individuals infected with latent TB who are, or who become, HIV-positive, have an elevated risk of TB activation [6,7]. Therefore, the WHO has recommended IPT for all HIV-positive individuals infected with latent TB [8]. This recommendation has led to debate surrounding its potential effectiveness, and the possibility of increasing the prevalence of drug resistance [5].

A recent study raised concerns over long-term benefits of IPT among miners in South Africa [9]. The study found significant rates of reinfection with TB following IPT discontinuation. This study echoes other epidemiological evidence suggesting high rates of reinfection in areas of high TB prevalence [9,10]. On balance, however, the evidence tends to favor IPT as an effective intervention for latent TB; a meta-analysis of trials among HIV-positive populations found IPT led to a 40% risk ratio reduction in cases of active TB in tuberculin skin-test positive individuals [11].

Although some modeling studies suggest that IPT does not create more selection for drug resistance at the individual level than would otherwise occur [12], others have cautioned that IPT will create selection pressure for drug resistant TB strains at the community level [5]. However, drug-resistant TB strains are often subject to significant negative selection pressure associated with maintaining resistance [13]; and, empirical evidence indicates that in the past, drug resistance at the community level has not increased as a result of broadly available IPT [14,15]. The development of some amount of resistance is indeed a potential risk whenever IPT is used in a population with ongoing TB transmission; furthermore, the complexity of monitoring TB treatment in a high-burden area should not be underestimated. However, a secondary school-based intervention such as the one we propose would minimize the possibility of emergence of resistance compared with other similar settings [5].

The intervention we propose also addresses concerns about inadvertently providing IPT to individuals infected with active TB who are misdiagnosed as having latent TB. A misdiagnosis is more likely to occur in HIV-positive individuals. By targeting adolescents, an age group in whom HIV prevalence is low, it is possible to reduce the likelihood of monotherapy for active TB.

Methods

Model structure

We employ a dynamic, deterministic, compartmental model to simulate the introduction of continuous IPT by age group in South Africa. Our ordinary differential equation-based model includes three sets of dynamics relevant to disease transmission: aging, HIV infection, and TB infection (Fig. 1). The model is calibrated as described below according to overall HIV prevalence, antiretroviral therapy (ART) scale-up in the region, HIV prevalence in TB cases, and percent of all TB deaths that are HIV positive, based on the Global TB Report [16] and the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates [17] (Table S2, http://links.lww.com/QAD/B332).

Demographic dynamics

Individuals age through the life stages as children, adolescents, and adults. We calibrate the population size based on United Nations estimates [18] (Table 1). Estimates of latent TB prevalence among adolescents as compared with adults are based on a local study by Middelkoop *et al.* [19].

Tuberculosis dynamics

In our model, both slow and rapid TB disease progression pathways are considered [20]. We do not model active TB in children because, for the purpose of this analysis, we consider their contribution to population level TB transmission and mortality to be less relevant; although they can be infected with latent TB in our model, they are not affected by active TB and their mortality is not influenced by TB. Adolescents and adults move between the following disease states: susceptible to TB, latently infected and not treated with IPT, latently infected and treated with IPT, diagnosed accurately with active TB but not yet treated, having active TB and treated with combination drug therapy, having active TB but incorrectly diagnosed as latently infected without IPT, and having active TB but incorrectly diagnosed as latently infected with IPT. TB activation can occur through either slow or rapid pathways, respectively; that is individuals infected with TB can remain in the latent phase before progressing to active TB, or TB activation can occur immediately upon infection. Infected individuals can return to susceptibility, that is, achieve cure, following IPT in the case of latent TB, or following combination therapy in the case of active TB. We also adjust for reinfection [21].

The benefits of IPT include a return to TB susceptibility (a cure for existing infection) among 47% of the population. They also include a TB activation rate while taking IPT that is five to 90 times slower than among those not taking IPT. The imperfect cure rate of IPT, resulting from both efficacy and treatment interruption is reflected in the partial cure rate of IPT used in the model. Individuals remain on IPT as they age until they achieve cure. The model was dynamically calibrated according to declining TB incidence in 2012 [16], as well as to TB mortality [16]. All parameter values can be found in Table 2.

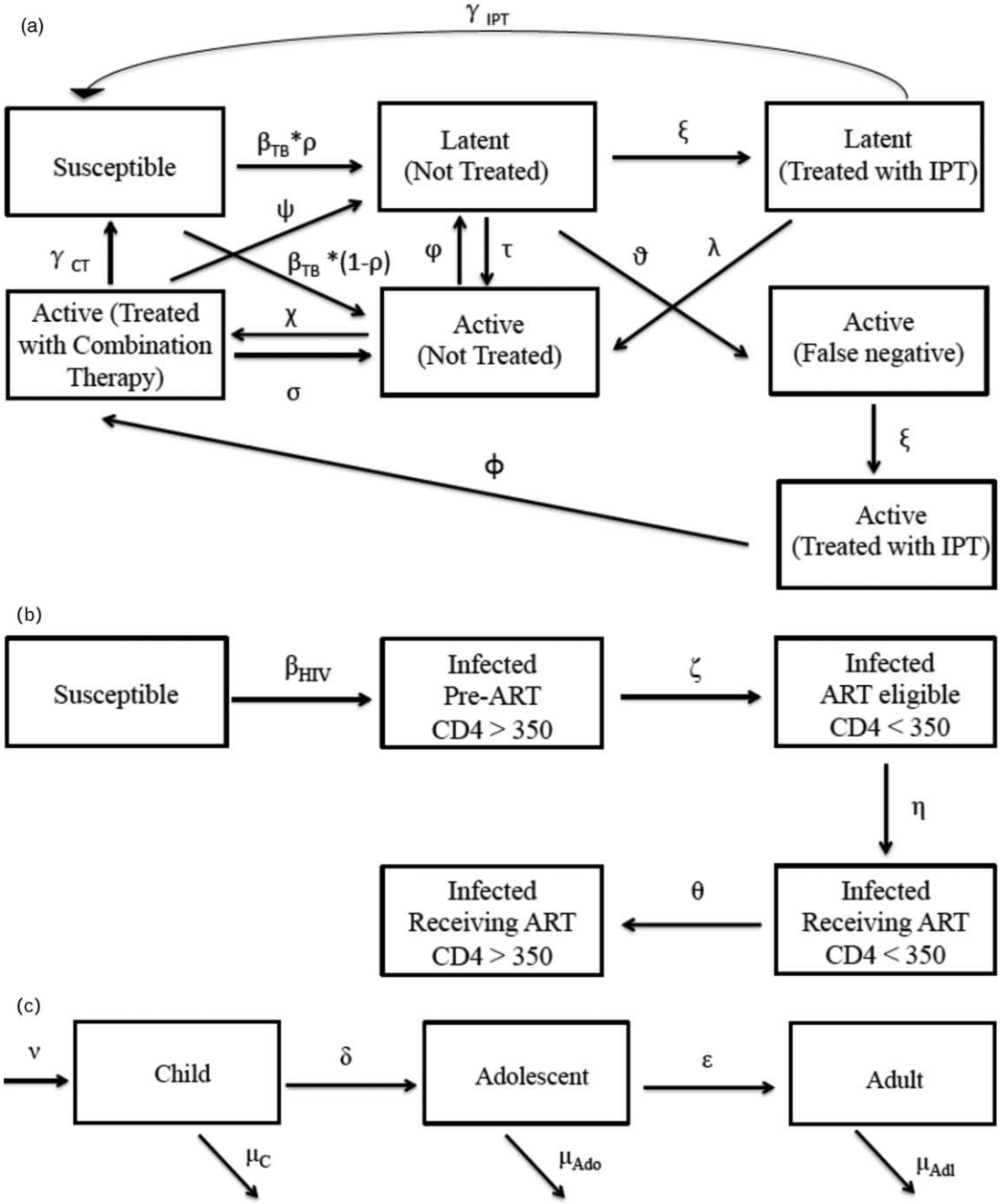

Fig. 1. Tuberculosis, HIV, and demographic dynamics of the model, followed by a parameter key. (a) Tuberculosis dynamics in adolescents and adults, (b) HIV dynamics, (c) aging dynamics.

HIV dynamics

HIV is represented by progression through the stages of being uninfected, infected with HIV prior to ART eligibility, ART-eligible prior to initiating treatment on ART with a low $CD4^+$ cell count, and on ART with high $CD4^+$ cell count. Effective ART is associated with lowered rate of TB activation by a factor of 18, and with lowered TB related mortality compared with HIV-positive without ART. The model is dynamically calibrated to reflect the recent scale up of ART coverage in South Africa, a driver of recent declines in TB incidence.

Modeling strategies

The primary purpose of our model is to investigate unexplored aspects of the potential effectiveness of IPT at the population level. Our model addresses concerns surrounding reinfection with latent TB following IPT in a high TB prevalence, high HIV prevalence population that has limited resources, by exploring the potential

TB parameters	
Transmission rate	β_{TB}
Latency rate upon infection in HIV−	ρ_{HIV-}
Latency rate upon infection in HIV+	ρ_{HIV+}
Latency rate upon infection in HIV+ on ART	ρ_{ART}
TB activation rate in HIV−	τ_{HIV-}
TB activation rate in HIV+	τ_{HIV+}
TB activation rate in ART	τ_{ART}
TB treatment rate	χ
Recovery rate for combination therapy	γ_{CT}
Return to latency after combination therapy	ψ
Recovery rate for IPT	γ_{IPT}
TB activation rate on IPT for HIV−	λ_{HIV-}
TB activation rate on IPT for HIV+	λ_{HIV+}
Non-cure on combination therapy	σ
Natural cure rate	φ
Incorrect diagnosis rate in HIV−	ϑ
Incorrect diagnosis rate in HIV+	ϑ
Incorrect diagnosis rate in HIV+ on ART	ϑ
Correct move from IPT to combination therapy	ϕ
Re-infection adjustment	ϖ
Baseline IPT access rate	ξ
Default rate on IPT	ι
Rate of ceasing IPT	κ
HIV parameters	
HIV infection in adolescents	β_{HIV}
HIV infection in adults	β_{HIV}
Progression of $CD4^+$ cell count	ζ
Access to ART	η
Recovery of $CD4^+$ cell count on ART	θ
Demographic parameters	
Child natural mortality	μ_C
Adolescent natural mortality	μ_{Ado}
Adult natural mortality	μ_{Adl}
HIV+ pre-ART adolescent mortality	$\mu_{Ado,Pre\text{-}ART}$
HIV+ pre-ART adult mortality	$\mu_{Adl,Pre\text{-}ART}$
HIV+ ART-eligible adolescent mortality	$\mu_{Ado,ART\text{-}Eligible}$
HIV+ ART-eligible adult mortality	$\mu_{Adl,ART\text{-}Eligible}$
HIV+ on ART low $CD4^+$ cell count adolescent mortality	$\mu_{Ado,LowCD4}$
HIV+ on ART low $CD4^+$ cell count adult mortality	$\mu_{Adl,LowCD4}$
HIV+ on ART high $CD4^+$ cell count adolescent mortality	$\mu_{Ado,HighCD4}$
HIV+ on ART high $CD4^+$ cell count adult mortality	$\mu_{Adl,HighCD4}$
TB adolescent mortality	$\mu_{Ado,TB}$
TB adult mortality	$\mu_{Adl,TB}$
TB & HIV+ pre-ART adolescent mortality	$\mu_{Ado,Pre\text{-}ART,TB}$
TB & HIV+ pre-ART adult mortality	$\mu_{Adl,Pre\text{-}ART,TB}$
TB & HIV+ ART-eligible adolescent mortality	$\mu_{Ado,ART\text{-}Eligible,TB}$
TB & HIV+ ART-eligible adult mortality	$\mu_{Adl,ART\text{-}Eligible,TB}$
TB & HIV+ low $CD4^+$ cell count adolescent mortality	$\mu_{Ado,LowCD4,TB}$
TB & HIV+ low $CD4^+$ cell count adult mortality	$\mu_{Adl,LowCD4,TB}$
TB & HIV+ high $CD4^+$ cell count adolescent mortality	$\mu_{Ado,HighCD4,TB}$
TB & HIV+ high $CD4^+$ cell count adult mortality	$\mu_{Adl,HighCD4,TB}$
Births	ν
Aging rate from children to adolescents	δ

Fig. 1. (Continued)

effects of a public health intervention in which IPT is provided to adolescents through the secondary school system. It is strategic to examine such an intervention in adolescents in a high HIV prevalence area, as HIV infection is a major predictive factor in the activation of latent TB, and adolescence precedes peak transmission of HIV. Given that HIV-negative individuals are a reservoir for transmitting TB to HIV-positive individuals, treating

Table 1. Key outcomes.

	Incidence		
Year	5% IPT coverage	50% IPT coverage	90% IPT coverage
2012	1113	1113	1113
2013	1076	1076	1076
2014	1041	1041	1041
2015	1008	1008	1008
2016	978	978	978
2017	951	951	951
2018	927	877	847
2019	906	814	772
2020	887	761	716
2021	871	718	671
2022	857	682	634
2023	845	651	603
2024	835	626	576
2025	827	605	554
2026	821	587	535
2027	816	572	520
2028	813	560	508
2029	811	551	498
2030	811	545	492
2031	813	541	487
2032	815	539	486

	Mortality		
Year	5% IPT coverage	50% IPT coverage	90% IPT coverage
2012	268	268	268
2013	257	257	257
2014	245	245	245
2015	234	234	234
2016	224	224	224
2017	214	214	214
2018	206	204	203
2019	198	192	188
2020	192	179	173
2021	186	167	161
2022	181	157	150
2023	176	149	141
2024	172	141	133
2025	169	135	126
2026	166	129	121
2027	163	125	116
2028	161	121	112
2029	160	118	109
2030	159	115	106
2031	158	113	104
2032	158	112	103

Calibration targets used in the model. IPT, isoniazid preventive therapy.

HIV-negative individuals with IPT could have a substantial impact on TB in both HIV-positive and HIV-negative individuals. The school system also provides a logistically feasible pathway to target a population that can be easily followed, screened for latent TB, and if infected, offered IPT and monitored for reinfection via the secondary school system. Following calibration of the model, sensitivity analysis to key parameters is performed.

Our models for HIV and TB dynamics are shown in Fig. 1a and b, respectively. For each population group, mortality is composed of HIV-specific mortality, TB-specific mortality, and background mortality, as shown in Fig. 1c. Increasing IPT coverage among adolescents from the 5% baseline to 50 or 90% is analyzed. We model the introduction of IPT beginning in 2016.

The analytic code is available from the authors upon request; all analyses were performed using R (R language software, initial contributors: Robert Gentleman and Ross Ihaka, 1996, University of Aukland, New Zealand). No human participants or animals were involved in the conduct of this research.

Calibration

Calibration is based on estimates from the Global TB Report 2014 [16], the UNAIDS Report on the Global AIDS Epidemic [17], and the United Nations Population Division [18]. In 2012, the first year of our model, calibration yields an overall adolescent and adult population TB incidence of 1113 per 100 000 person years, adolescent and adult TB mortality of 268 per 100 000, and active TB prevalence of 1849 per 100 000. The total population is approximately 51 million. HIV prevalence is 15%, with ART coverage scaled up from 25% of all HIV-infected individuals in 2007, to 31% in 2012, to 55% in 2022. In addition to the static calibration of TB incidence to its absolute value in 2012, TB incidence is dynamically calibrated to approximate a rate of decline of 3.3% per year in 2012, as driven by scale-up of ART access. Forty-nine percent of new TB cases and 41% of TB mortality occur in HIV+ individuals in 2012. The calibration targets are shown in Table 1.

Sensitivity analyses

We perform sensitivity analysis for key parameters. We explore the sensitivity of TB incidence to variation in some of the most uncertain and influential parameters: TB transmission rate (Fig. S2, http://links.lww.com/QAD/B332), recovery rate on IPT (Fig. S3, http://links.lww.com/QAD/B332), TB activation rate in HIV-positive individuals infected with latent TB (Fig. S4, http://links.lww.com/QAD/B332), and the rate at which individuals discontinue IPT treatment (Fig. S5, http://links.lww.com/QAD/B332). The calibration resulting from the original baseline values is applied consistently across all sensitivity analyses.

Results

Isoniazid preventive therapy program in schools

We used the model to explore the effects of continuing at current baseline levels of IPT (5%), moderate scale up (50%), and significant scale up (90%). Results are represented graphically in Fig. 2, and key numerical results are shown in Table 3. At the baseline rate of 5% IPT coverage, we estimate that TB incidence will decline

Table 2. Parameters.

TB parameters[a]

Parameter	Description	Calibrated value	Source
Transmission rate	Rate of TB transmission	0.0000004	Sensitivity analysis
Latency rate upon infection in HIV−	Rate at which HIV− individuals infected with TB remain latently, rather than actively, infected	0.9	Abu-Raddad *et al.* [22][b]
Latency rate upon infection in HIV+	Rate at which HIV+ individuals infected with TB remain latently, rather than actively, infected	0.5	Lawn *et al.* [7]
Latency rate upon infection in HIV+ on ART	Rate at which HIV+ individuals on ART infected with TB remain latently, rather than actively, infected	0.9	Abu-Raddad *et al.* [22][b]
TB activation rate in HIV−	Rate at which HIV− individuals experience latent TB activation	0.005	Horsburgh [23]
TB activation rate in HIV+	Rate at which HIV+ individuals experience latent TB activation	0.09	Sensitivity analysis
TB activation rate in ART	Rate at which HIV+ individuals on ART experience latent TB activation	0.005	Horsburgh [23]
TB treatment rate	Rate at which TB is treated with combination therapy	0.9	WHO [1]
Recovery rate for combination therapy	Rate at which individuals with TB recover when treated with combination therapy	0.9	WHO [1], Bacaër *et al.* [24][b]
Return to latency after combination therapy	Rate at which individuals receiving combination therapy for active TB return to latent TB	0.08	Suen *et al.* [25][b]
Recovery rate for IPT	Rate at which individuals recover on IPT	0.47	Zelner *et al.* [26]
TB activation rate on IPT for HIV−	Rate at which HIV− individuals latently infected with TB experience TB activation	0.0001	Houben *et al.* [27][b]
TB activation rate on IPT for HIV+	Rate at which HIV+ individuals latently infected with TB experience TB activation	0.0001	Houben *et al.* [27][b], Selwyn *et al.* [28], Lin and Flynn [29]
Non-cure on combination therapy	Rate at which individuals who have received combination therapy are not cured	0.02	Suen *et al.* [25][b]
Natural cure rate	Rate at which individuals with active TB experience spontaneous resolution to latent TB	0.1	Tiemersma *et al.* [30]
Incorrect diagnosis rate in HIV−	Rate at which HIV− individuals who are actively infected with TB are incorrectly diagnosed as latently infected	0.00001	Boehme *et al.* [31]
Incorrect diagnosis rate in HIV+	Rate at which HIV+ individuals not on ART who are actively infected with TB are incorrectly diagnosed as latently infected	0.0001	Boehme *et al.* [31]
Incorrect diagnosis rate in HIV+ on ART	Rate at which HIV+ individuals on ART who are actively infected with TB are incorrectly diagnosed as latently infected	0.00001	Boehme *et al.* [31]
Correct move from IPT to combination therapy	Rate at which individuals who had incorrectly been placed on combination therapy are redirected to IPT	0.9	Boehme *et al.* [31]
Reinfection adjustment	Factor to adjust for the possibility of reinfection with TB following treatment and cure	0.21	Andrews *et al.* [21][b]
IPT access rate	Rate at which individuals latently infected with TB are placed on IPT	0.05/0.5/0.9	Sensitivity analysis
Default rate on IPT	Rate at which individuals on IPT default	0	Sensitivity analysis
Rate of ceasing IPT	Rate at which individuals on IPT stop treatment	0	Sensitivity analysis

HIV parameters[c]

Parameter	Description	Value	Source
HIV infection in adolescents	Rate at which adolescents are infected with HIV	0.0000000039	Auvert *et al.* [32]
HIV infection in adults	Rate at which adults are infected with HIV	0.0000000039	Calibration

Table 2 (*continued*)

HIV parameters[c]

Parameter	Description	Value	Source
Progression of $CD4^+$ cell count	Rate at which individuals infected with HIV progress to ART eligibility (experience $CD4^+$ cell count decline)	0.13	Mellors *et al.* [33]
Access to ART	Rate at which eligible HIV+ individuals are placed on ART	0.02/ 0.1	Calibration
Recovery of $CD4^+$ cell count on ART	Rate at which HIV+ individuals on ART experience $CD4^+$ cell count recovery	0.01	Calibration

Demographic parameters[d]

Parameter	Description	Value
Child natural mortality	Mortality rate among children not infected with TB or HIV	0.001
Adolescent natural mortality	Mortality rate among adolescents not infected with TB or HIV	0.009
Adult natural mortality	Mortality rate among adults not infected with TB or HIV	0.02
HIV+ pre-ART adolescent mortality	Mortality rate among adolescents who are HIV+ and not yet eligible for ART	0.02
HIV+ pre-ART adult mortality	Mortality rate among adults who are HIV+ and not yet eligible for ART	0.03
HIV+ ART-eligible adolescent mortality	Mortality rate among adolescents who are HIV+ and eligible for ART	0.05
HIV+ ART-eligible adult mortality	Mortality rate among adults who are HIV+ and eligible for ART	0.05
HIV+ on ART low $CD4^+$ cell count adolescent mortality	Mortality rate among adolescents who are HIV+ and on ART with low $CD4^+$ cell count	0.09
HIV+ on ART low $CD4^+$ cell count Adult Mortality	Mortality rate among adults who are HIV+ and on ART with low $CD4^+$ cell count	0.02
HIV+ on ART High $CD4^+$ cell count adolescent mortality	Mortality rate among adolescents who are HIV+ and on ART with high $CD4^+$ cell count	0.09
HIV+ on ART high $CD4^+$ cell count adult mortality	Mortality rate among adults who are HIV+ and on ART with high $CD4^+$ cell count	0.02
TB adolescent mortality	Mortality rate among adolescents who are infected with TB, and are HIV−	0.058
TB adult mortality	Mortality rate among adults who are infected with TB, and are HIV−	0.068
TB & HIV+ pre-ART adolescent mortality	Mortality rate among adolescents who are infected with TB, and are HIV+, not yet eligible for ART	0.12
TB & HIV+ pre-ART adult mortality	Mortality rate among adults who are infected with TB, and are HIV+, not yet eligible for ART	0.23
TB & HIV+ ART-eligible adolescent mortality	Mortality rate among adolescents who are infected with TB, and are HIV+, and eligible for ART	0.17
TB & HIV+ ART-eligible adult mortality	Mortality rate among adults who are infected with TB, and are HIV+, and eligible for ART	0.3
TB & HIV+ low $CD4^+$ cell count adolescent mortality	Mortality rate among adolescents who are infected with TB, and are HIV+, on ART with low $CD4^+$ cell count	0.07
TB & HIV+ low $CD4^+$ cell count adult mortality	Mortality rate among adults who are infected with TB, and are HIV+, on ART with low $CD4^+$ cell count	0.1
TB & HIV+ high $CD4^+$ cell count adolescent mortality	Mortality rate among adolescents who are infected with TB, and are HIV+, on ART with high $CD4^+$ cell count	0.062
TB & HIV+ high $CD4^+$ cell count adult mortality	Mortality rate among adults who are infected with TB, and are HIV+, on ART with high $CD4^+$ cell count	0.072
Births	Birth rate	0.03
Aging rate from children to adolescents	Rate at which children age into the adolescent group	0.0769
Aging rate from adolescents to adults	Rate at which adolescents age into the adult group	0.2

Parameters used in the model. All parameters subject to adjustment for calibration. ART, antiretroviral therapy; IPT, isoniazid preventive therapy; TB, tuberculosis.

[a]With regard to the units of the TB and HIV parameters, each of these parameters is reported as the fraction of the population within a given compartment flowing out of that compartment into another specified by the model diagram per unit time.

[b]Parameter taken as either an input or an output from a modeling publication.

[c]With regard to the units of the TB and HIV parameters, each parameter is reported as the fraction of the population within a given compartment flowing out of that compartment into another specified by the model diagram per unit time.

[d]All demographic parameters were generated via calibration to the population structure.

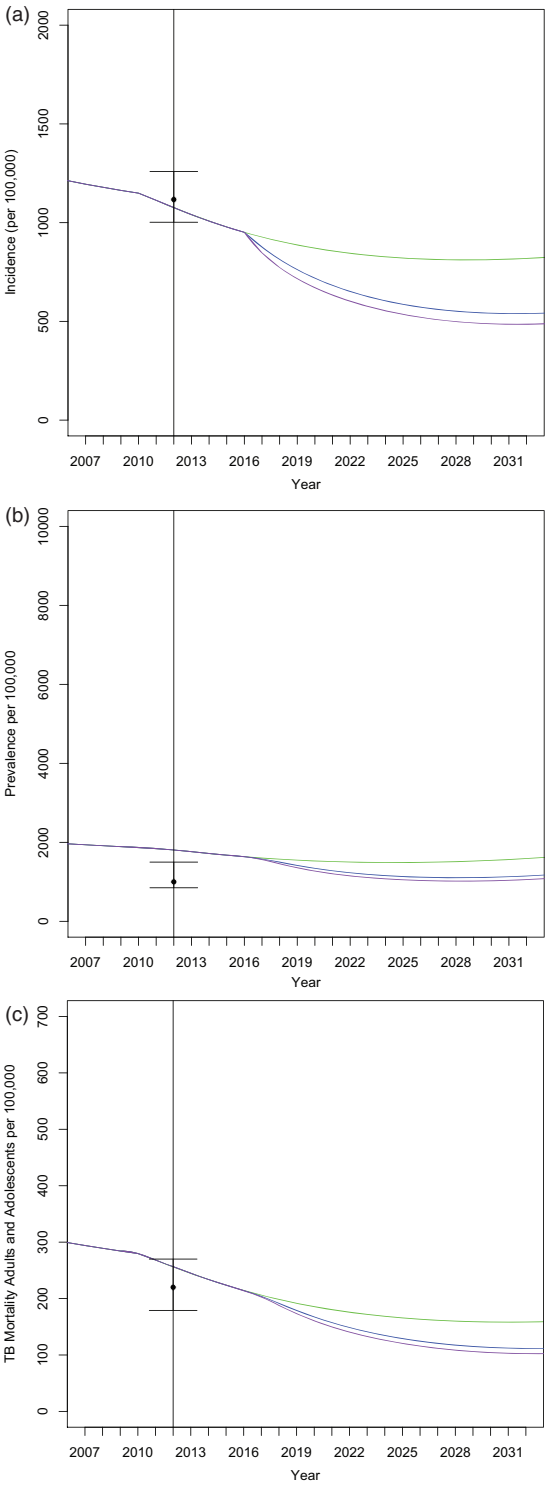

Fig. 2. Effects of isoniazid preventive therapy on key tuberculosis disease indicators. Bars indicate calibration target ranges. The baseline isoniazid preventive therapy case is shown in green, 50% isoniazid preventive therapy coverage in the blue intervention line, and 90% isoniazid preventive therapy coverage in the purple intervention line. (a) Tuberculosis Incidence in general population aged 14 and older, (b) tuberculosis prevalence in the general population aged 14 and older, (c) tuberculosis mortality in the general population aged 14 and older.

in the general population aged 14 and above between 0 and 3.3% per year by the end of the simulation in the year 2032.

Increasing IPT coverage among adolescents is expected to further reduce TB incidence. Beginning in the year following IPT introduction in 2016, the reduction in TB incidence in the 50% IPT access scenario each year, compared with baseline, is between 5 and 34%. Although the fastest decrease in incidence rates occurs in the beginning of the simulation period, gains in incident cases averted relative to baseline tended to increase with time, indicating that averted ongoing transmission may further multiply the benefits of expanded IPT access. In our model, as a result of 50% IPT access in adolescents, TB incidence decreases in both adolescents and adults; in adolescents by as much as 47% and in adults by as much as 30%, in some years, relative to baseline (Fig. S6, http://links.lww.com/QAD/B332).

A scale up of IPT to 90% among adolescents further increases the anticipated benefits of IPT. At the end of the 20-year period, as a result of 90% IPT access in adolescents, TB incidence in adolescents decreases by 55% and in adults by 36% relative to baseline. We show the impact of IPT on additional variables in Fig. 3.

Sensitivity to transmission parameters and role of reinfection

We show sensitivity of TB incidence to two of the most uncertain parameters under baseline IPT coverage: TB transmission rate (Fig. S2, http://links.lww.com/QAD/B332) and the activation among HIV-positive individuals (Fig. S4, http://links.lww.com/QAD/B332). TB incidence is significantly more sensitive to rate of transmission than to the relative activation rate among HIV+ individuals.

Sensitivity of tuberculosis incidence to recovery rate on isoniazid preventive therapy

We explore the sensitivity of TB incidence to the recovery rate (return to susceptibility) of latently infected individuals taking IPT; this parameter is subject to some uncertainty as there is not currently a diagnostic available that can detect cure of latent TB following treatment with IPT (Fig. S3, http://links.lww.com/QAD/B332). In our simulations, the effects of IPT recovery rate appear to be less important than the proportion of the population on IPT in influencing TB incidence.

Effects of HIV and demographic parameters

We observe that HIV infection rate (Fig. S7, http://links.lww.com/QAD/B332) and population birth rate (Fig. S8, http://links.lww.com/QAD/B332) were major drivers of the impact of IPT. TB incidence increases with both birth rate and HIV incidence; the impact of IPT increases with TB incidence. At birth rates of 0.04 and

Table 3. Key calibration targets and calibration values achieved.

Calibration indicator	Target value	Calibration value achieved	Source
Incidence	1117	1113.13	Global TB Report
Mortality	220	268.33	Global TB Report
HIV prevalence in adult population	15	14.99	South African National HIV Incidence, Prevalence and Behavior Survey
ART coverage among HIV+	31	30.91	South African National HIV Incidence, Prevalence and Behavior Survey
HIV-positivity in TB deaths	74	40.82	Global TB Report

Key numerical outcomes for TB incidence and mortality over time, at varying IPT coverage levels. ART, antiretroviral therapy; IPT, isoniazid preventive therapy; TB, tuberculosis.

greater, baseline TB incidence increases, rather than decreases, over time.

Sensitivity to stopping isoniazid preventive therapy treatment

We explore the impact of stopping IPT treatment once individuals return to susceptibility following cessation of IPT treatment (Fig. S5, http://links.lww.com/QAD/B332). As expected, TB incidence increases consistently with the rate of IPT discontinuation. The duration of IPT treatment in areas with ongoing TB transmission is likely to affect of the impact of the IPT program.

Expanding isoniazid preventive therapy beyond schools

We also explore the effects of expanding IPT coverage not only in schools, but in the adult population as well. Although large-scale coverage expansion among adults may not be feasible, we find the effects of IPT to be even more substantial (Fig. S9, http://links.lww.com/QAD/B332). In sum, IPT coverage of 50% in the general population aged 14 and older results in a reduction of TB incidence by 96% compared with baseline after 20 years; 90% coverage leads to a reduction of 98% compared with baseline after 20 years.

Effects of expanded isoniazid preventive therapy on tuberculosis incidence in HIV-positive population

Expanded IPT access causes TB incidence to decline in both the general population of HIV-positive individuals (Fig. S10, http://links.lww.com/QAD/B332), as well as in adult HIV-positive individuals specifically (Fig. S11, http://links.lww.com/QAD/B332). At 50% IPT access, gains of 29% were observed in the general population, and gains of 41% were observed in adult HIV-positive individuals specifically. At 90% IPT access, gains of 36 and 48% were observed for these populations, respectively.

Discussion

Our model departs from previous work on latent TB in South Africa in that it considers the complexity associated with HIV and demographic dynamics in effectively implementing IPT. By designing a program that strategically targets a segment of the population that has yet to experience peak HIV infection, we are able to address latent TB prior to increase in one of the most important determinants of TB activation.

We show that expanding IPT delivery is associated with lowered TB prevalence and mortality (Fig. 2), including among HIV-infected individuals (Figs. S10 and S11, http://links.lww.com/QAD/B332). IPT is also associated with lowered TB incidence at lower transmission rates (Fig. S2, http://links.lww.com/QAD/B332).

We also show that an IPT intervention targeted at adolescents has an impact on key TB epidemiological indicators in the general population, including adults outside the intervention target age group (Fig. S6, http://links.lww.com/QAD/B332). Although the results indicate the superiority of full population IPT in an ideal scenario, the benefits to those outside the target group generated by the intervention we propose indicate that this intervention would be strategic in a resource-constrained area.

Our model has some limitations. First, our calibrated prevalence value is at the higher end of the probable range for the region, as is the fraction of TB deaths occurring in HIV-positive individuals. However, we are confident in our model as TB incidence, total TB mortality, and HIV prevalence are all well within expected ranges, especially considering that prevalence is often vulnerable to under-reporting. Second, though we show simulated results for incidence and mortality over a 20-year period, in the last 3 years of our predicted range, across the base case and all IPT levels, we observe a very slight increase in TB incidence toward the end of the simulation period. We do not consider this minor departure from the otherwise consistent trend to be significant, due to both its extremely low magnitude, and its presence only at the tail end of the simulation period, as simulations approaching 20 years necessarily feature some uncertainty. We also observe some oscillation in the relationship between transmission rate and incidence at low values of the transmission rate. However, the values at which this phenomenon is observed are low enough that they are

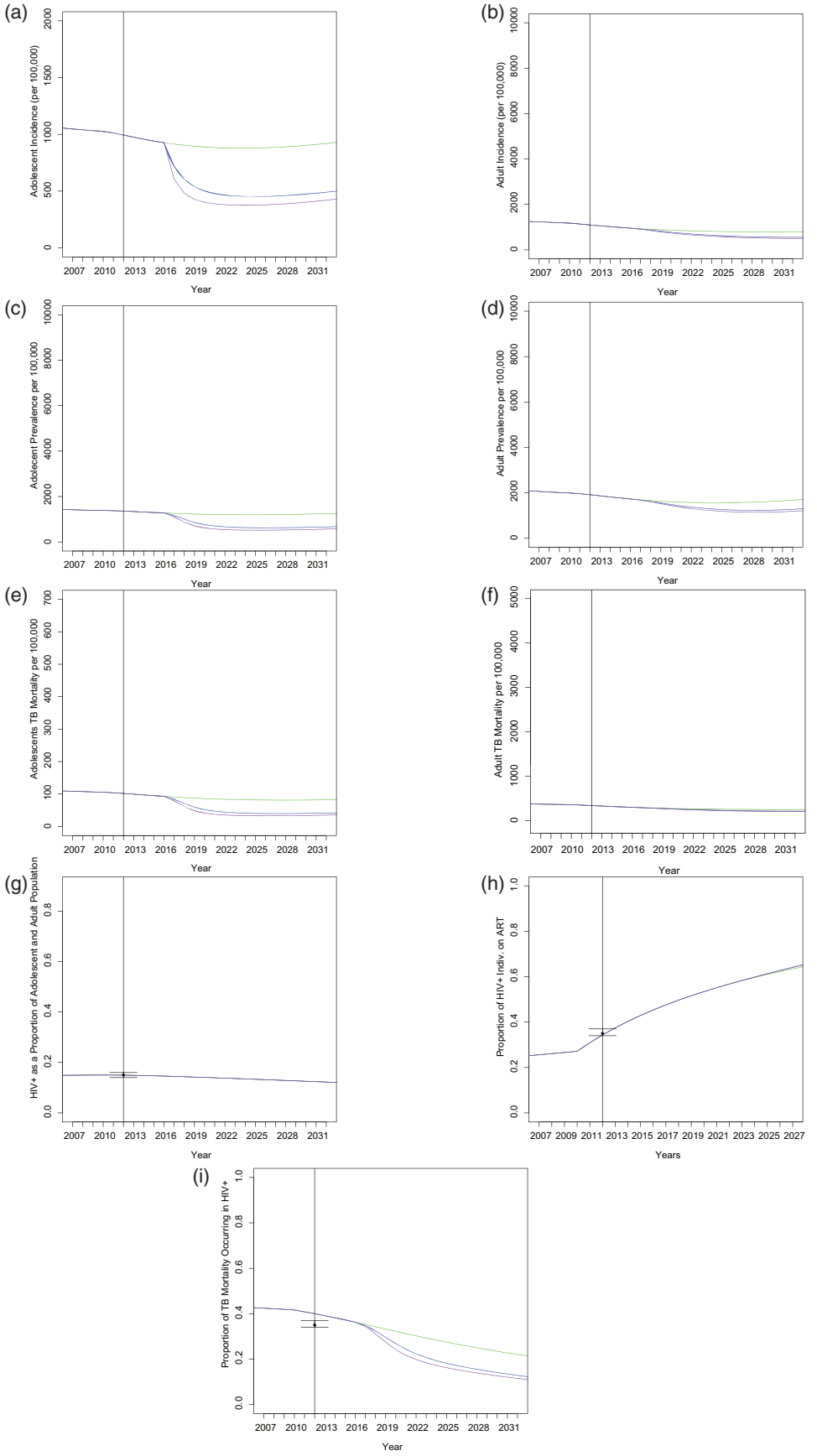

Fig. 3. Effects of varying isoniazid preventive therapy access on additional variables.

likely outside of the realistic epidemiological range of values for this parameter (Table 1). Finally, the HIV model employed is somewhat simplified, particularly with regard to aspects of HIV treatment such as ART treatment interruption. Nonetheless, we believe that the essence of this relationship between HIV infection and TB incidence is captured.

Accurate diagnosis of TB will always be an issue, especially in the case of smear-negative TB, which presents a challenge in implementing the program we propose. For a program such as the one we propose to be effective, individuals must be correctly diagnosed and effectively monitored for adverse events that may occur as a result of IPT; the school-based nature of this program would facilitate such monitoring for adverse events. Although a diagnostic that detects recovery from latent TB is not currently available, we are optimistic about the possibility of improvements in this space. Given the small absolute number of individuals who will develop active TB over the course of their lifetimes, under such a program, there will likely be individuals who undergo treatment with IPT, who never would have developed TB. Implementation of such a program will likely be challenging, and require collaboration at multiple levels among community organizations, local and national governments, and potentially, international donors.

The concern has been raised that IPT could paradoxically cause TB incidence to increase as the result of rapid reinfection following cure. We show the results of simulation using a theoretical parameter under which such reinfection could occur (Fig. S12, http://links.lww.com/QAD/B332). However, the parameter range required for this outcome is far from the biologically probable parameter range, suggesting that such an outcome would be unlikely.

Although there is no empirical evidence to support concerns about selection for TB strains resistant to isoniazid as a result of the potential increase in selective pressure for resistance in the presence of IPT, any preventative use of antibiotics should proceed with appropriate caution, thorough analysis of the potential risks and benefits at the population level, and regular evaluation of resistance levels. If new data were to emerge that challenged the findings of the Thibela study, there would be cause to re-evaluate the implementation of such an intervention. However, in the absence of such data, these concerns do not provide cause to delay mass IPT.

The issue of drug-resistant latent TB could also be a concern. Although it appears that IPT actually has some effectiveness against IPT-resistant bacteria when infection is latent, depending on the mechanism of resistance [34], if an increase in prevalence of IPT resistance among individuals with latent TB were to occur, it could limit the effectiveness of this intervention.

Although whole population IPT would of course be ideal, our model suggests that a targeted program of community level IPT in adolescents could be of great help in reducing TB transmission and activation among both adolescents and adults.

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Author contributions: A.S.R. and E.B. designed the study. A.S.R., M.W.F., and E.B. iterated the model. A.S.R., E.B., and M.W.F. analyzed data. A.S.R. coded the model and wrote the article. A.S.R., M.W.F, and E.B. reviewed and revised the article.

Conflicts of interest

During a portion of the time this work was in progress, A.S.R. was employed as an intern by the Bill and Melinda Gates Foundation. She was subsequently employed as an intern, a consultant, and a postdoctoral fellow by the Global Public Health division of Johnson & Johnson, on work unrelated to this project. She is not currently employed by either organization.

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