Supporting Appendix

Results and parameter values

Table S1 contains natural history parameter values of the natural history model. The series of differential equations representing the age-structured mathematical model of tuberculosis was programmed in Berkeley Madonna (Technical Appendix). Using the Downhill Simplex method(1), both the contact rate and the case detection ratio were permitted to vary while fitting the model to the annual incidence rates of pulmonary smear-positive disease and tuberculosis-related mortality reported by the WHO for 2006 (2) (Table S2). The case detection ratio was permitted to vary because of suspected under-reporting of treatment among cases.

Table S1: Key tuberculosis natural history parameters.

Assumption	Parameter Value	Value Range for the Sensitivity Analysis (Min, Max)	Sources
Proportion of new cases entering fast breakdown upon infection			
Children	5%	(4.3%, 5.8%)	(4-14)
Adults	15%	(12.8%, 17.3%)	(4-14)
Progression rate (per year) from latency to early TB disease for unvaccinated progressors			
Fast progressors	0.9		(12, 15-23)
With adjustment for early TB disease	1.64	(1.39, 1.89)	Assumption
Slow progressors	0.00075	(0.00064, 0.00086)	(12, 15-23)
Fractional reduction in susceptibility to reinfection due to prior exposure to TB	65%	(55.3%, 74.8%)	(12, 24, 25)
Proportions of new unvaccinated TB disease cases flowing from latency			
Smear-positive pulmonary			
Children	10%	(8.5%, 11.5%)	(26, 27)

Assumption	Parameter Value	Value Range for the Sensitivity Analysis (Min, Max)	Sources
Adults	50%	(42.5%, 57.5%)	(15, 23, 24, 27-30)
Smear-negative pulmonary			
Children	65%	Adjusted to total to	(14, 27)
Adults	40%	100%	(14, 27)
Non-pulmonary			
Children	25%	Adjusted to total to	(26, 31-33)
Adults	10%	100%	(15, 23, 24, 27-30)
TB disease mortality rate (per year) for unvaccinated and untreated subjects			
Smear-positive pulmonary	0.25	(0.213, 0.288)	(4, 17, 24, 27, 34-43)
Smear-negative pulmonary	0.10	(0.085, 0.115)	(4, 17, 24, 27, 34-43)
Non-pulmonary	0.10	(0.085, 0.115)	(4, 17, 24, 27, 34-43)
Spontaneous recovery rate (per year) from TB disease	0.1	(0.085, 0.115)	(4, 40-42, 44, 45)
Relative infectivity for smear-negative pulmonary disease with respect to untreated smear-positive pulmonary disease subjects	25%	(21.3%, 28.8%)	(46)

Table S2: Key region-specific tuberculosis epidemiology parameters (2).

Region	Population (1000s)	Incidence of SP (per million)	TB-related mortality rate (per million)	Treatment success proportion	Unsuccessful Treatment Proportions					WHO Case Detection Ratio (CDR) – *prior to multiplication by the CDRFitFactor*			Contact rate (*eta*)	CDR fit factor
					Death	Treatment Failure	Default	Trans-ferred	Not Evaluated	SP	SN	NP		
AFRH	539,801	1,673	842	0.75	0.07	0.01	0.09	0.05	0.03	0.51	0.43	0.43	185.026	1.43166
AFRL	198,283	931	448	0.72	0.05	0.02	0.14	0.04	0.02	0.49	0.25	0.25	151.423	1.77444
AMR	560,276	268	85	0.79	0.05	0.01	0.07	0.05	0.03	0.80	0.42	0.42	169.835	1.22237
EEUR	387,265	430	148	0.71	0.04	0.05	0.05	0.02	0.12	0.47	0.81	0.81	101.063	1.22819
EMR	541,704	468	206	0.83	0.03	0.01	0.08	0.03	0.03	0.45	0.53	0.53	101.767	1.42458
SEAR	1,656,529	808	309	0.84	0.04	0.02	0.06	0.01	0.03	0.64	0.51	0.51	154.851	1.26211
WPR	1,595,689	532	182	0.92	0.02	0.01	0.02	0.01	0.02	0.78	0.50	0.50	159.837	1.13285

AFRH = Africa, annual incidence of HIV $\geq$ 4%; AFRL = Africa, annual incidence of HIV < 4%; AMR = Latin America; EEUR = Eastern Europe; EMR = Eastern Mediterranean; SEAR = South-East Asia; WPR = Western Pacific; SP = sputum smear-positive pulmonary tuberculosis

Rates of change of TB incidence and TB-related mortality

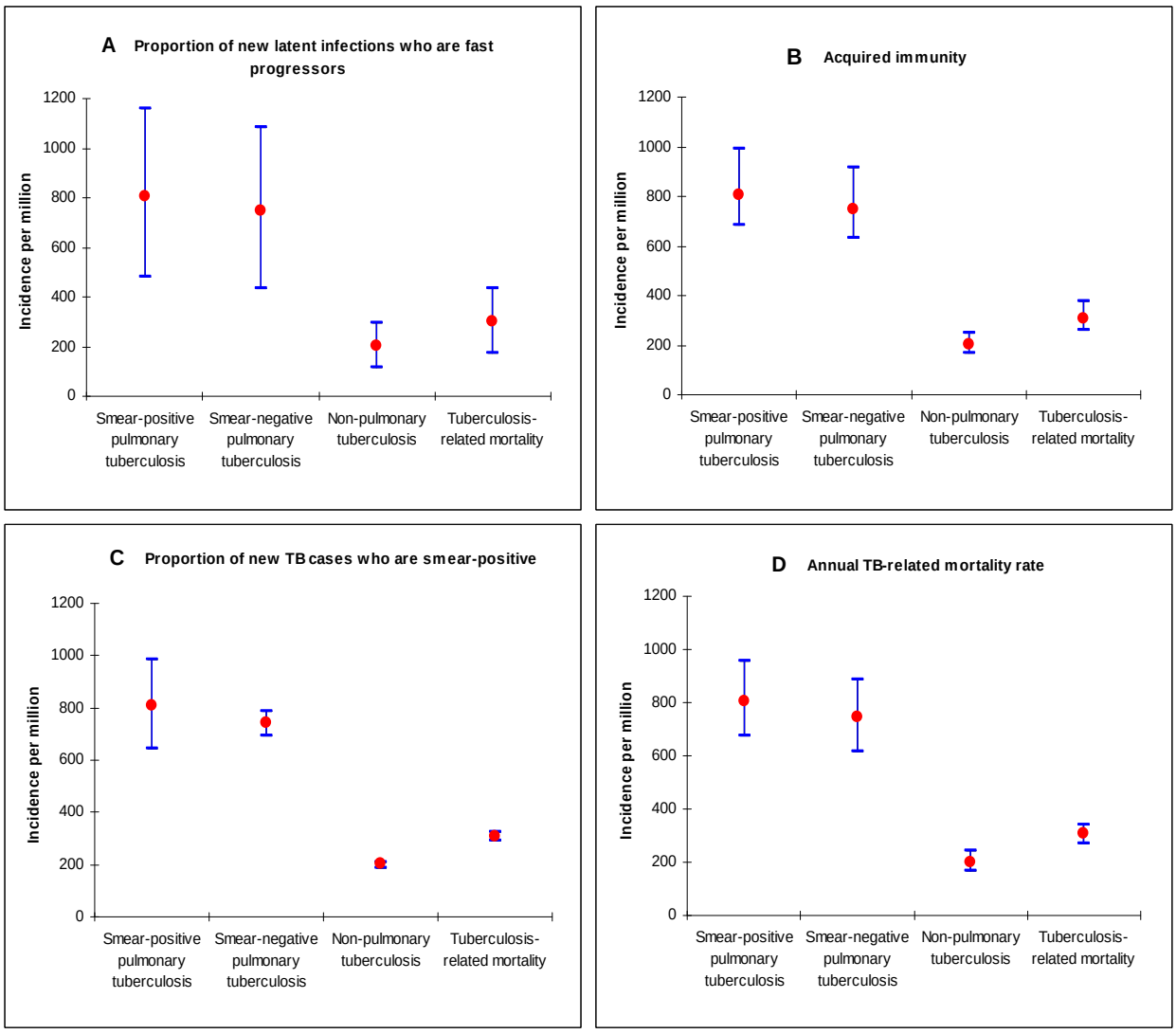
The benefits from all of the novel treatment regimens are immediate (results not shown). For the active-treatment regimens, the magnitude of the effect is greatest within the first 2 years, steadily waning thereafter until approximately 2044. At this point, the incidence rates of TB disease and TB-related death no longer decline. The mass latent therapy treatment regimen and its combination with active treatment regimen 2 results in a large reduction in the incidence of TB disease within the first two years. Then, as the reservoir of individuals with latent slow infection is depleted, the magnitude of the incidence reduction drops precipitously over the next year. Three years after intervention implementation (2018), the magnitude of the annual reduction in the incidence of TB disease for regimens involving latent therapy wanes steadily with annual incidence rates continuing to decline past 2050.

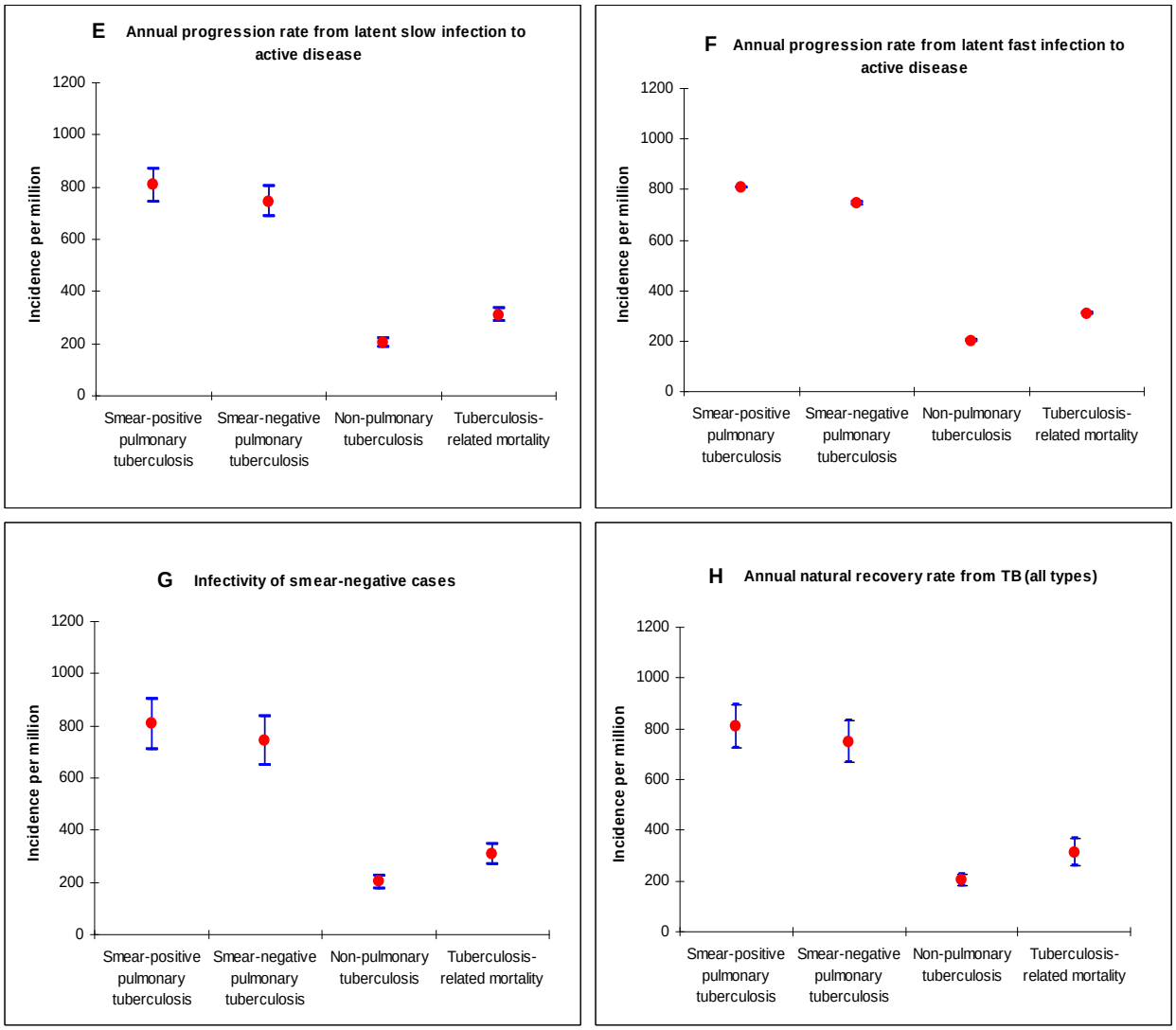
Sensitivity and uncertainty analyses

To explore the sensitivity of our model results to parameter values, we conducted univariate sensitivity and uncertainty analyses over specified ranges for representative parameter values. We varied each parameter over a range of ±15% of the original parameter value, completing 11 runs evenly spaced over the range. For each particular parameter, each age group experiences the same percent change from its original parameter value within a single model run. The selection of these natural history (Figure S1A-H) and novel intervention (Figure S2A-D) parameters for presentation reflects those that are most influential within this formulation of the model, and their results are representative across all model parameters. Given the available evidentiary support, the ranges of variation represent plausible values for these parameters. The purpose of these sensitivity analyses serves both to establish the model sensitivity to the parameter values,

as well as to ascertain whether the uncertainty in the parameter value used in the main results significantly affects the model results.

Figure S1: Sensitivity of TB natural history parameters.

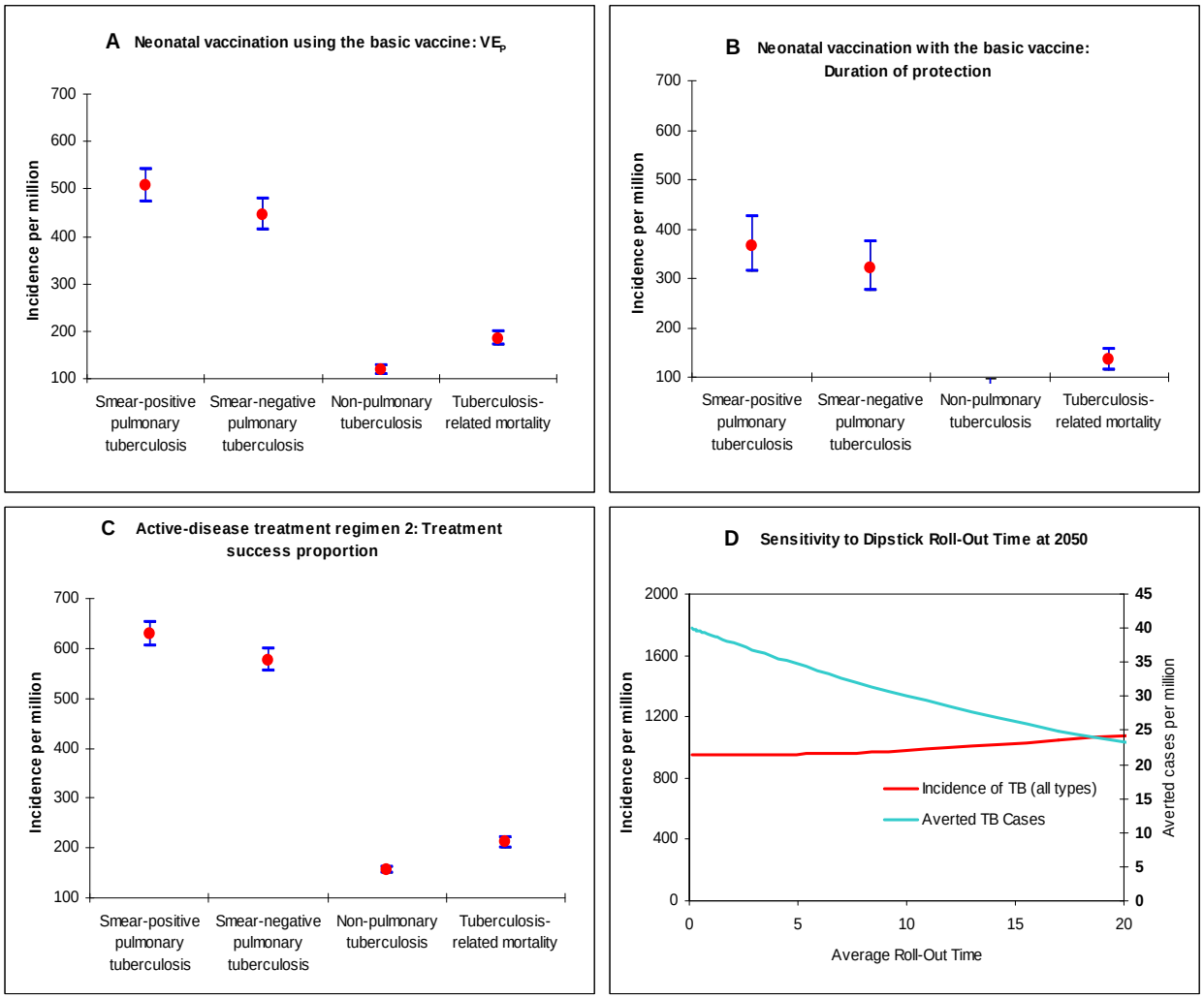




An examination of the natural history parameters (Figure S1) shows that of those parameters tested, the model is most sensitive to a change in the proportion of new latent infections who are fast progressors. For example, a ±15% change in the proportion of new latent infections who are fast progressors results in an ~±41% change in the incidence per million of smear-positive pulmonary TB, a ~±42% change in the incidence per million of smear-negative pulmonary TB, a ~±42% change in the incidence per million of non-pulmonary TB, and a ~±41% change in the incidence per million of TB-related mortality (Figure S1A). By contrast, for a ±15% change in

the annual progression rate from latent fast infection to active disease results in a ~±0.3% change in the incidence per million of smear-positive pulmonary TB, a ~±0.4% change in the incidence per million of smear-negative pulmonary TB, a ~±0.4% change in the incidence per million of non-pulmonary TB, and a ~±0.4% change in the incidence per million of TB-related mortality (Figure S1F).

Figure S2: Sensitivity of novel intervention parameters.



An examination of the novel intervention parameters (Figure S2) shows that variation in either the fraction of persons becoming slow rather than fast progressors, or the duration of protection has relatively little effect on smear-positive and smear-negative incidences, and a reduced effect on non-pulmonary TB or TB-related mortality (Figure S2A-B). A ±15% change in the fraction of persons becoming slow rather than fast progressors results in a ~±7% change in the incidence per million of smear-positive pulmonary TB, a ~±8% change in the incidence per million of smear-negative pulmonary TB, a ~±8% change in the incidence per million of non-pulmonary TB, and a ~±7% change in the incidence per million of TB-related mortality (Figure S2A). Variation in the treatment success proportion has even smaller effects on final incidence of smear-positive, smear-negative and non-pulmonary TB, as well as TB-related mortality (Figure S2C). Although incidence at 2050 is not greatly affected if the average roll out time of NAAT varies from 0 to 20 years, the cumulative number of cases averted substantially decreases (Figure S2D).

Overall, the model is robust to uncertainty in the parameter values, and the changes that do occur in the model results are predictable based on the construction of the model.

At a VE_P of 60%, the Aeras target value, the vaccine's reduction of the probability of becoming a fast progressor produces a stronger reduction in TB incidence by 2050 than either of two additional effects on infectiousness and lifetime probability of developing active TB disease, alone or combined (results not shown).

Other WHO regions

The results for the other WHO regions (2) are qualitatively similar (Table S3). In the Eastern European region, where the current active disease treatment success proportion is just 71%, the percentage of cases prevented by the novel treatment regimens by 2050 was higher, 10%, 22%, and 26%, than in the Southeast Asia region, 6%, 15%, 17%. The numbers for the two African regions are optimistic, as they do not account for HIV in the regions or differing efficacy of the novel interventions in HIV-infected people. The effect of HIV on novel TB therapies was studied by Sanchez et al (3).

Table S3: Regional estimates of the number of tuberculosis cases (all types) and tuberculosis-related deaths prevented from 2015 to 2050 with novel interventions.

Intervention Strategy	Cases of tuberculosis (all types)							Tuberculosis-related deaths						
	AFRH	AFRL	AMR	EEUR	EMR	SEAR	WPR	AFRH	AFRL	AMR	EEUR	EMR	SEAR	WPR
	Cumulative incidence (millions)													
No novel intervention	70.4	14.1	11.2	12.5	19.1	101.7	64.0	15.9	3.1	1.7	2.1	3.9	17.9	10.2
	Cumulative number prevented (millions)													
Vaccination														
Neonatal vaccination with adolescent boost:														
Basic pre-exposure vaccine only	12.7	2.5	2.0	1.8	3.0	18.2	11.5	2.6	0.5	0.3	0.2	0.6	3.0	1.7
Basic pre-exposure vaccine with the additional effects	17.9	3.3	2.5	2.3	3.9	23.8	14.9	3.7	0.6	0.3	0.3	0.7	3.9	2.2
Mass vaccination (includes neonatal vaccination):														
Basic pre-exposure vaccine only	35.9	9.0	8.0	8.8	13.4	68.2	44.7	7.7	1.8	1.1	1.4	2.6	11.5	6.7
Basic pre-exposure vaccine with the additional effects	43.5	9.9	8.5	9.4	14.3	74.0	47.8	9.3	2.0	1.2	1.5	2.8	12.4	7.2
Neonatal vaccination with 3-year mass catch-up, basic pre-exposure vaccine with additional effects	38.2	9.0	7.9	8.7	13.3	67.9	44.4	8.2	1.8	1.1	1.4	2.6	11.4	6.7
Mass vaccination with only a post-exposure effect	16.3	3.7	3.4	3.9	6.1	30.1	19.9	3.5	0.7	0.4	0.6	1.2	5.0	2.9
Neonatal vaccination, basic pre-exposure with additional effects, plus mass vaccination with post-exposure effect	51.3	9.6	7.6	8.7	13.5	73.2	45.3	10.9	1.9	1.0	1.4	2.6	12.3	6.8
Mass vaccination with basic pre-exposure vaccine, plus mass vaccination with post-exposure effect	47.1	10.7	9.1	10.1	15.4	80.2	51.5	10.1	2.2	1.2	1.6	3.0	13.5	7.7
Mass vaccination with basic pre-exposure vaccine with additional effects, plus mass vaccination with post-exposure effect	57.3	11.7	9.5	10.6	16.3	85.9	54.4	12.3	2.4	1.3	1.7	3.2	14.5	8.2
Neonatal vaccination with 3-year mass catch-up, basic pre-exposure with additional effects, plus mass vaccination with post-exposure effect	56.4	11.4	9.3	10.4	15.9	83.8	59.1	12.1	2.3	1.3	1.7	3.1	14.1	8.0
Treatment regimens														
Active-disease regimen 1	8.0	1.6	1.0	1.6	2.0	8.3	2.6	2.5	0.5	0.2	0.3	0.5	2.0	0.5
Active-disease regimen 2	16.3	3.3	2.0	3.5	4.1	19.3	6.2	5.0	0.9	0.4	0.7	1.1	4.5	1.3
Active-disease regimen 3	19.5	3.9	2.5	4.1	5.0	22.9	7.5	5.9	1.1	0.5	0.9	1.3	5.3	1.5
Mass latent therapy	34.0	7.8	6.8	8.1	12.7	64.8	41.4	7.3	1.6	0.9	1.3	2.5	10.8	6.1
Active-disease regimen 2 plus mass latent therapy	48.2	9.9	7.8	9.7	14.5	75.6	44.5	11.0	2.1	1.1	1.6	2.9	13.1	6.7
Diagnostics														
LED	-	-	1.6	-	-	11.7	10.4	-	-	0.3	-	-	4.2	3.0
NAAT	-	-	3.6	-	-	24.4	17.2	-	-	0.6	-	-	4.2	2.6
Dipstick	-	-	5.0	-	-	39.4	25.4	-	-	0.8	-	-	8.0	3.9
Combination														
Mass vaccination with basic pre-exposure effects plus active-disease regimen 2 plus NAAT	-	-	9.0	-	-	77.8	49.3	-	-	1.4	-	-	13.9	7.7

Even without taking the complications due to HIV into account, in the Sub-Saharan region with high HIV incidence, and to a lesser extent, in the Sub-Saharan region with low HIV incidence, mass vaccination with a pre-exposure vaccine prevents relatively fewer case and deaths than in the other regions (Table S3). The reason is due to the higher TB incidence, and consequently prevalence, in these two regions (Table S2), so the prevalence of uninfected people to benefit from a pre-exposure vaccine is much lower. Preventive treatment of latently infected people is 20 to 25% less effective than in the South-East Asia region (2).

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