

Supplementary Material

for

The epidemiological impact, costs, and cost-effectiveness of implementing household contact investigation with tuberculosis preventive treatment in Nepal: a model-based analysis.

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S1. WHO algorithm for targeted diagnosis and treatment of LTBI

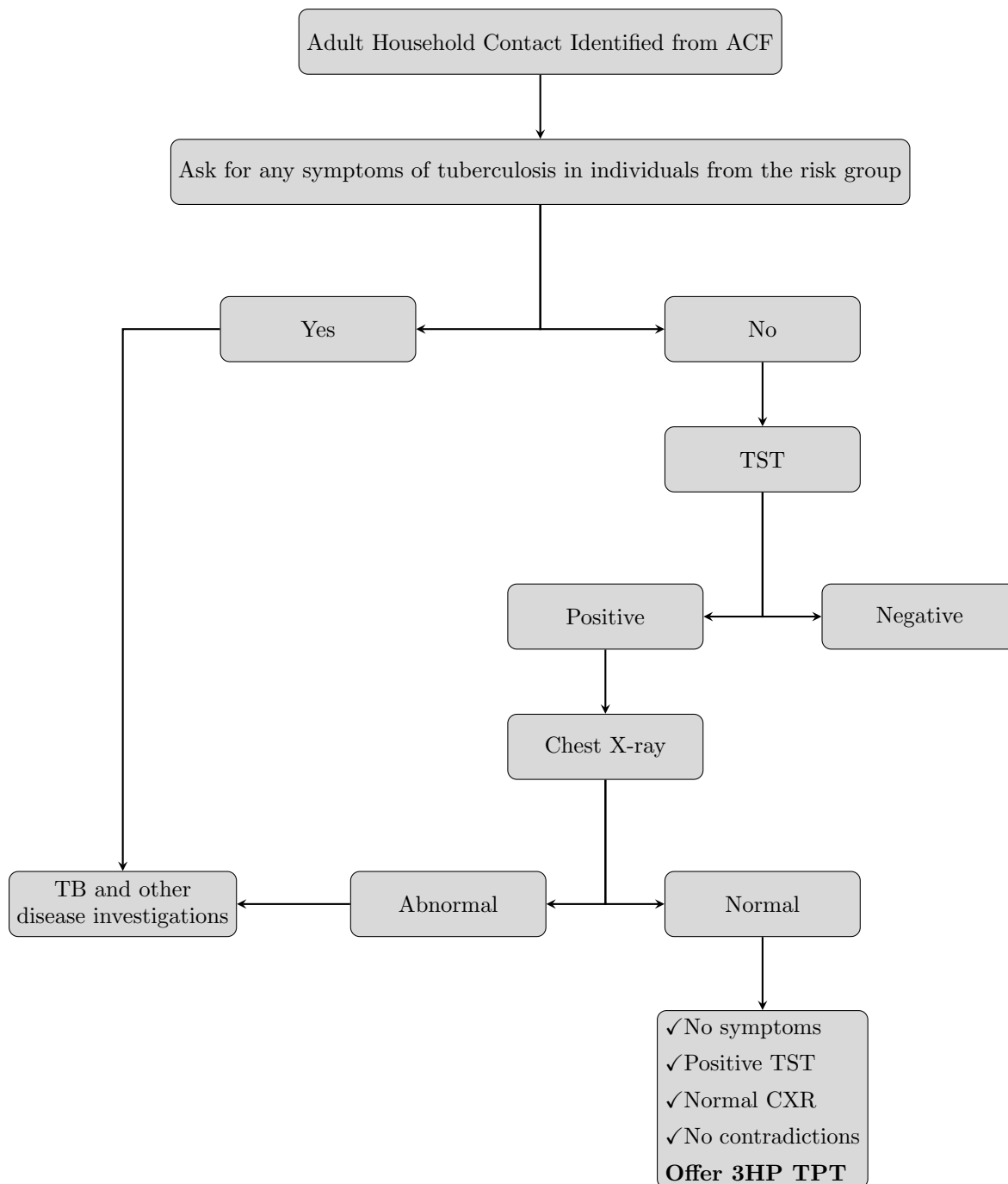


Figure S1: WHO algorithm for targeted diagnosis and treatment of latent tuberculosis infection
 ACF: active case finding, CXR: Chest X-ray, TB: tuberculosis, LTBI: latent TB infection, TPT: TB preventive treatment, TST: tuberculin skin test, 3HP: 3 months of once-weekly isoniazid (H) plus rifapentine (P)

S2. Model Description

Using compartmental models we incorporated the natural history and transmission dynamics of tuberculosis (TB) in Nepal. We have included both latent and active stages of tuberculosis and our model consisted of six compartments: susceptible individuals (S), early latent tuberculosis infection (EL), late latent (LL), asymptomatic active TB (ATB), symptomatic active TB (STB) and recovered individuals (R).

S3. Model Equations

The total population at time t is given by:

$$N = S + EL + LL + ATB + STB + R$$

The force of infection, λ , is defined as:

$$\lambda = \beta e^{-t\beta_{\text{dec}}} \frac{ATB + STB}{N}$$

where β is the transmission rate, β_{dec} is the annual rate of decline in transmission, and the fraction represents the proportion of infectious individuals in the population. Here, we assume equal infectiousness for asymptomatic and symptomatic TB.

The transitions between the compartments are modeled using following differential equations:

Susceptible individuals (S)

$$\frac{dS}{dt} = bN - \lambda S - \mu S$$

where individuals become susceptible as they are born (bN) and exit as people get infected (λS), or due to natural death (μS).

Early latent TB infection (EL)

$$\frac{dEL}{dt} = \lambda S + \phi_0 LL + \phi_0 R - \omega EL - \sigma_1 EL - w_1 EL - \mu EL$$

where susceptible individuals enter this compartment as they are infected (λS) or reinfected ($\phi_0 LL$ & $\phi_0 R$), and individuals exit as they stabilize to late latent infection (ωEL), progress to active TB (early progression, $\sigma_1 EL$) or self-recovery (to recovered, $w_1 EL$) or die due to natural causes (μEL). ϕ_0 is given by ϕ (protection against reinfection) $\times \lambda$ (force of infection).

Late latent TB infection (LL)

$$\frac{dLL}{dt} = \omega EL - \sigma_2 LL - \phi_0 LL - w_2 LL - \mu LL$$

where individuals enter from early latent TB (ωEL) and leave due to activation ($\sigma_2 LL$), reinfection ($\phi_0 LL$), self-recovery ($w_2 LL$), or die due to natural causes (μLL).

Asymptomatic active TB (ATB)

$$\frac{dATB}{dt} = \sigma_2 LL + \sigma_1 EL + r_1 STB - \gamma ATB - \rho_2 ATB - \mu_{\text{atb}} ATB - \mu ATB$$

where individuals progress from latency ($\sigma_2 LL$ & $\sigma_1 EL$) or regress from symptomatic TB ($r_1 STB$) and exit via progression (γATB) or spontaneous resolution ($\rho_2 ATB$) or death (due to tuberculosis ($\mu_{\text{atb}} ATB$) or natural causes (μATB).

Symptomatic active TB (STB)

$$\frac{dSTB}{dt} = \gamma ATB - \rho_1 STB - r_1 STB - \mu_{\text{stb}} STB - \mu STB$$

where individuals progress from asymptomatic TB (γATB) and either recover (as they are treated, $\rho_1 STB$), be reinfected or relapse ($r_1 STB$), or die due to tuberculosis ($\mu_{\text{stb}} STB$) or natural causes (μSTB).

Recovered individuals (R)

$$\frac{dR}{dt} = \rho_1 STB + \rho_2 ATB + w_1 EL + w_2 LL - \phi_0 R - \mu R$$

where individuals enter through recovery ($\rho_1 STB$, $\rho_2 ATB$, $w_1 EL$ & $w_2 LL$) and exit due to reinfection ($\phi_0 R$) or natural death (μR).

S4. Model Parameters

Table S1: List of the parameters and the posterior estimates obtained for Chitwan and Pyuthan.

Epidemiological Parameters	Chitwan	Pyuthan	Source/Notes
Transmission rate (No. of susceptibles infected by an index case in 1 year), β	20.62 (11.31 - 29.54)	21.47 (11.49 - 29.56)	Calibrated with prior uniform distribution of 10—30
Annual decline in transmission rate, β_{dec}	0.018 (0.011 - 0.027)	0.018 (0.011 - 0.026)	Calibrated to fit annual incidence decline of 3% ¹
Rate of stabilization (rate of transition from early to late latent state), per year, ω	0.257 (0.179 - 0.322)	0.255 (0.179 - 0.322)	Calibrated with prior uniform distribution of 3—6 years. ^{2,3}
Rate of progression for early latent to asymptomatic active TB (early progression), per year, σ_1	0.039 (0.026 - 0.054)	0.040 (0.026 - 0.054)	Calibrated with prior uniform distribution of 0.025 - 0.055 ²
Rate of progression from late latent to asymptomatic active TB (late progression), per year, σ_2	0.0025 (0.0019 - 0.0031)	0.0025 (0.0019 - 0.0031)	Calibrated with prior uniform distribution of 1.87e-4 - 3.12e-4
Rate of progression from asymptomatic to symptomatic active TB, γ	1.66 (1.08 - 1.99)	1.70 (1.15 - 1.99)	Calibrated using prior uniform distribution of 6—24 months. ⁴
Rate of recovery (1/(time taken for recovery)), ρ_1	1.25 (0.67 - 1.91)	1.35 (0.80 - 1.95)	Calibrated using prior uniform distribution of 6—24 months
Protection against reinfection, (%), ϕ	0.327 (0.205 - 0.487)	0.332 (0.207 - 0.487)	Calibrated using prior uniform distribution of 0.2—0.5
Rate of regression from symptomatic to asymptomatic TB, r_1	1.07 (0.53 - 1.89)	1.04 (0.53 - 1.88)	Calibrated using prior uniform distribution of 6—24 months
Annual birth rate (b)	0.024 (0.016 - 0.033)	0.024 (0.016 - 0.033)	Prior uniform distribution of 0.015—0.033 assumed ⁶
Annual death rate (μ)	0.014 (0.009 - 0.020)	0.014 (0.009 - 0.020)	Calibrated using life-expectancy of 75 years. ⁷
Annual death rate among asymptomatic individuals (μ_{atb})	0.022 (0.015 - 0.030)	0.022 (0.015 - 0.030)	Calibrated to fit national TB mortality rate
Annual death rate among symptomatic individuals (μ_{stb})	0.205 (0.153 - 0.283)	0.201 (0.153 - 0.283)	Calibrated to fit national TB mortality rate
Rate of self-recovery without treatment in asymptomatic active TB, per year, ρ_2	0.309 (0.207 - 0.396)	0.309 (0.207 - 0.395)	Calibrated using prior uniform distribution of 0.2 to 0.4. ⁸
Self-clearance from early latent infection, per year, w_1	0.157 (0.083 - 0.245)	0.152 (0.084 - 0.244)	Calibrated using prior uniform distributinon of 0.08—0.25 ⁹
Self-clearance from late latent infection, per year, w_2	0.016 (0.008 - 0.025)	0.016 (0.008 - 0.025)	Calibrated using prior uniform distribution of 0.008—0.025 ¹⁰

*The point estimates indicate the median value of the parameter obtained from the calibration and the values in the brackets indicate 95% uncertainty intervals.
TB: Tuberculosis*

S5. Calibrated Parameters Distribution - Chitwan

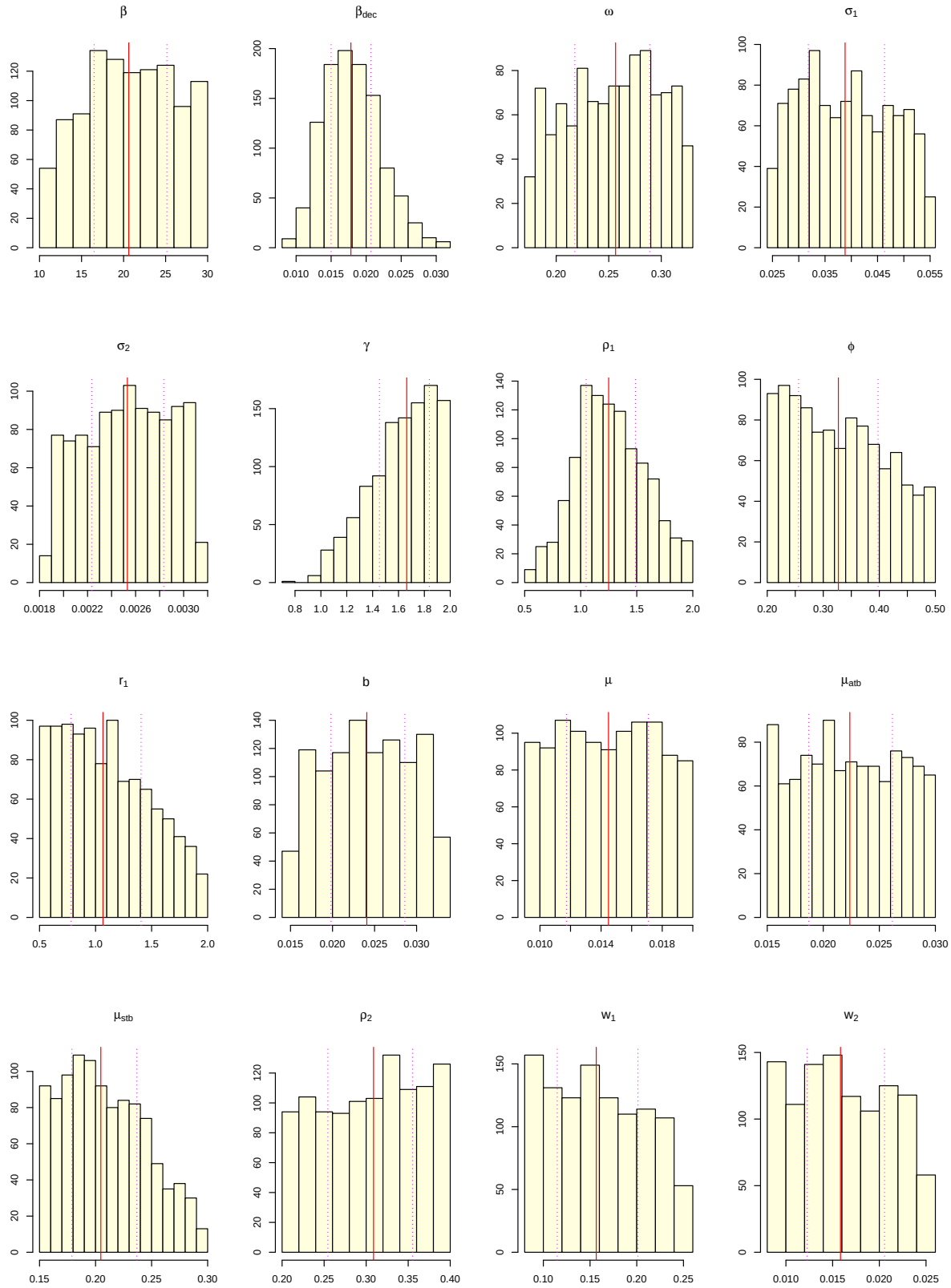


Figure S2: Parameter distribution for Chitwan district obtained from the calibration. The solid red line indicates the median and dashed red lines indicate the first and third quartiles.

S6. Calibrated Parameters Distribution - Pyuthan

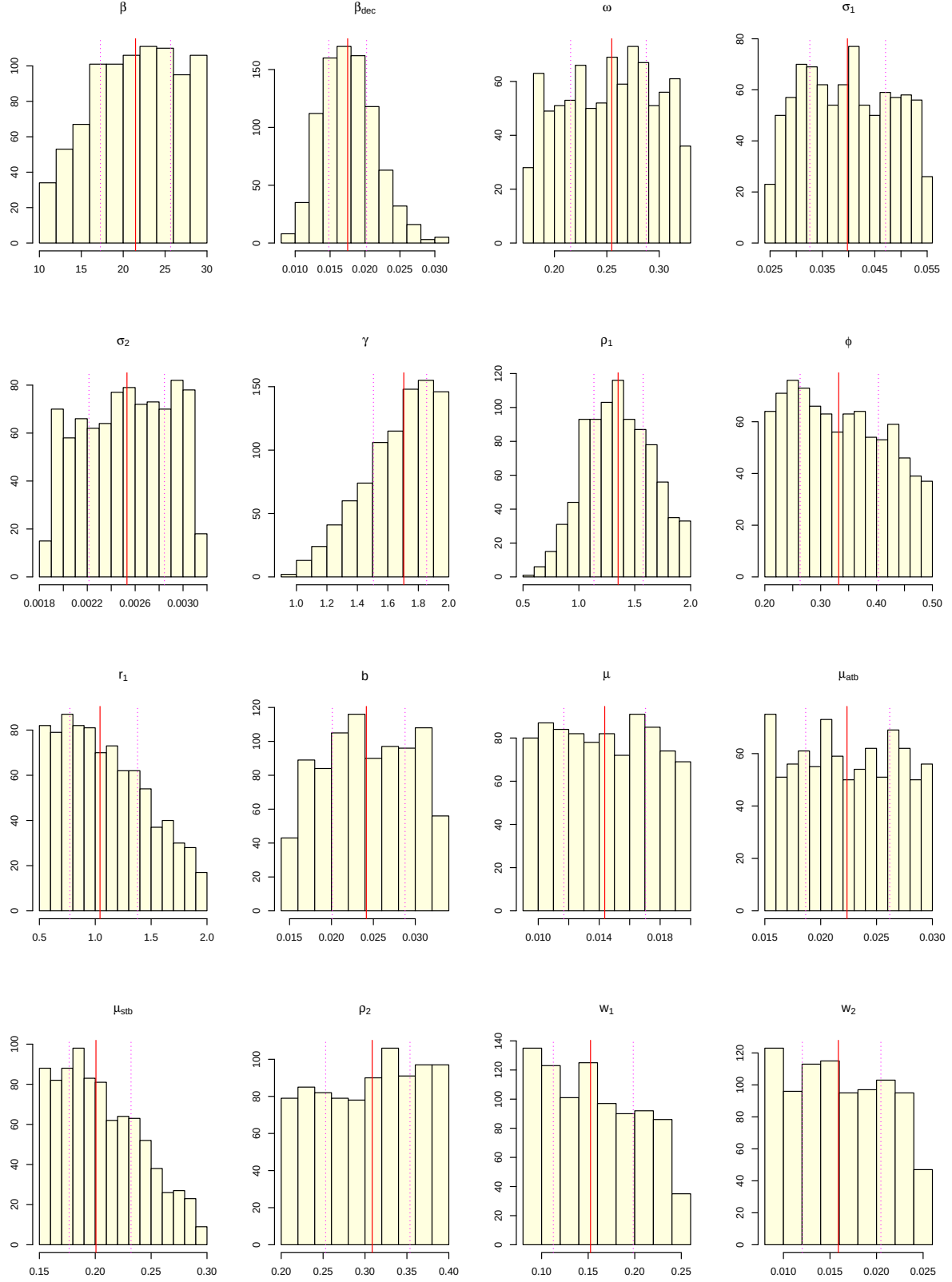


Figure S3: Parameter distribution for Pyuthan district obtained from the calibration. The solid red line indicates the median and dashed red lines indicate the first and third quartiles.

S7. Model Calibration Targets and Assumptions

Table S2: Calibration targets and the acceptable ranges considered for Chitwan and Pyuthan

Indicators	Chitwan	Pyuthan	Source/Notes
TB Prevalence, per 100 000	392 (294 - 490)	400 (300 - 500)	Nepal TB Prevalence Survey 2018-2019
TB Incidence, per 100 000	294 (200 - 368)	330 (247 - 405)	Calculated Based on Notification to Incidence ratio
TB Mortality, per 100 000	34 (26 - 42)		Nepal National TB Report 2019
Annual Incidence Decline (%)	3		WHO estimates/Nepal TB Prevalence Survey 2018-2019
Total Population	719859	232019	Census 2021, Central Bureau of Statistics, Nepal

TB: Tuberculosis, WHO: World Health Organization

The values in *Table S2* indicate the calibration targets. To capture the uncertainty in the model, we considered acceptable range as $\pm 25\%$ of the targets, as shown in the brackets in the table. To allow for model to come to equilibrium, we simulated the model for 100 years without considering any decline in transmission. As the model reached equilibrium, we simulated the model for another 20 years allowing the transmission to decline (including β_{dec}). The estimates at the end of the simulation were assumed to represent year 2022 - the year when the intervention was carried out. The prior distribution of the parameters (100000 parameter sets) was obtained using Latent Hypercube Sampling and the parameter combinations that yielded the district wise epidemiological indicators corresponding to *Table S2* on year 2022 were selected as listed in *Table S1*. This calibration process yielded 1067 accepted parameter sets for Chitwan and 884 for Pyuthan. The calibration outputs from the selected parameters distribution are show in *Figure 2* in the main text.

S8. Intervention Details

Table S3: The parameters assumed for the scale up scenario where household contacts of all the notified people with TB are screened and treated for latent tuberculosis infection.

Parameters	Chitwan	Pyuthan	Source/Notes
Epidemiological Parameters			
Proportion TB infections that are recent	0.5 - 0.8		Assumed
Proportion TB positive that are asymptomatic	0.5 - 0.8		Assumed
Proportion household contacts with active TB	0.02 - 0.06		¹¹ (Wider range assumed)
Treatment efficacy of 3-months isoniazid and rifapentine therapy	91%		¹²
Treatment success of directly observed treatment shortcourse for active TB	92%		¹³
Annual case notification rate (PBC), per 100 000	126	79	¹³
Average household size	4	4.13	¹⁴
Tuberculosis cases notified, yearly	907	126	Estimated, calculated from CNR and total population
Percentage of family members eligible for TST test	82	69	Intervention results
Percentage willing for TST test	94	82	Proportion who provided consent for TST in the intervention
Percentage testing positive for TST	45.9	45.9	Intervention results
Percentage willing to take 3HP	91	97	Intervention results
Percentage completion	95		Intervention results
Cost Parameters			
Cost of Implementation (3HP + ACF)	\$129.8	\$197.6	Primary data from financial records
Cost of TB diagnosis (using GeneXpert)		\$14.07	Cost inflated to 2022 figures and taken from previous research*
Cost of TB Treatment/Future cost saving	\$300.24 (\$292.42 - \$402.37)		Cost inflated to 2022 figures and the range was determined by combining 3 reference studies. ^{15–17}
Average life expectancy of TB patients in Nepal, years	30.9 (21.5 - 44.8)		Estimated ¹⁸
Disability weight	0.333 (0.224 - 0.454)		¹⁹
Duration of disease/duration of disability in survivors, years	1.8 (1.4 - 2.1)		Estimated ¹⁸

TB: Tuberculosis, PBC: Pulmonary Bacteriological Confirmed, CNR: Case Notification Ratio: TST: Tuberculin Skin Test, 3HP: 3-months isoniazide and rifapentine

*Unit cost was estimated using a detailed financial record of previously implemented project. The estimate includes capital cost of GeneXpert modules, calibrators, enablers for quality diagnosis (including AC, refrigerator, batteries, stabilizer), recurring cartridge expenses, laboratory equipment and laboratory personnel allowances.²⁰

We used results from the intervention (mentioned as intervention results in Table S3) and tuberculosis data national reports to estimate the impact of scale up scenario. As there is need to rule out active TB before testing and providing preventive treatment therapy, we simulated the scenario to account for both the impact of preventive therapy and active TB. We assumed that for every 38 household contacts screened there will be one active case identified. The epidemiological parameters in this table apply only to the hypothetical scale-up scenario modelled in the sensitivity analysis. We took into account the willingness of the family members' to participate in TST as well as to take 3HP if positive.

S9. Total Cases and Deaths Averted

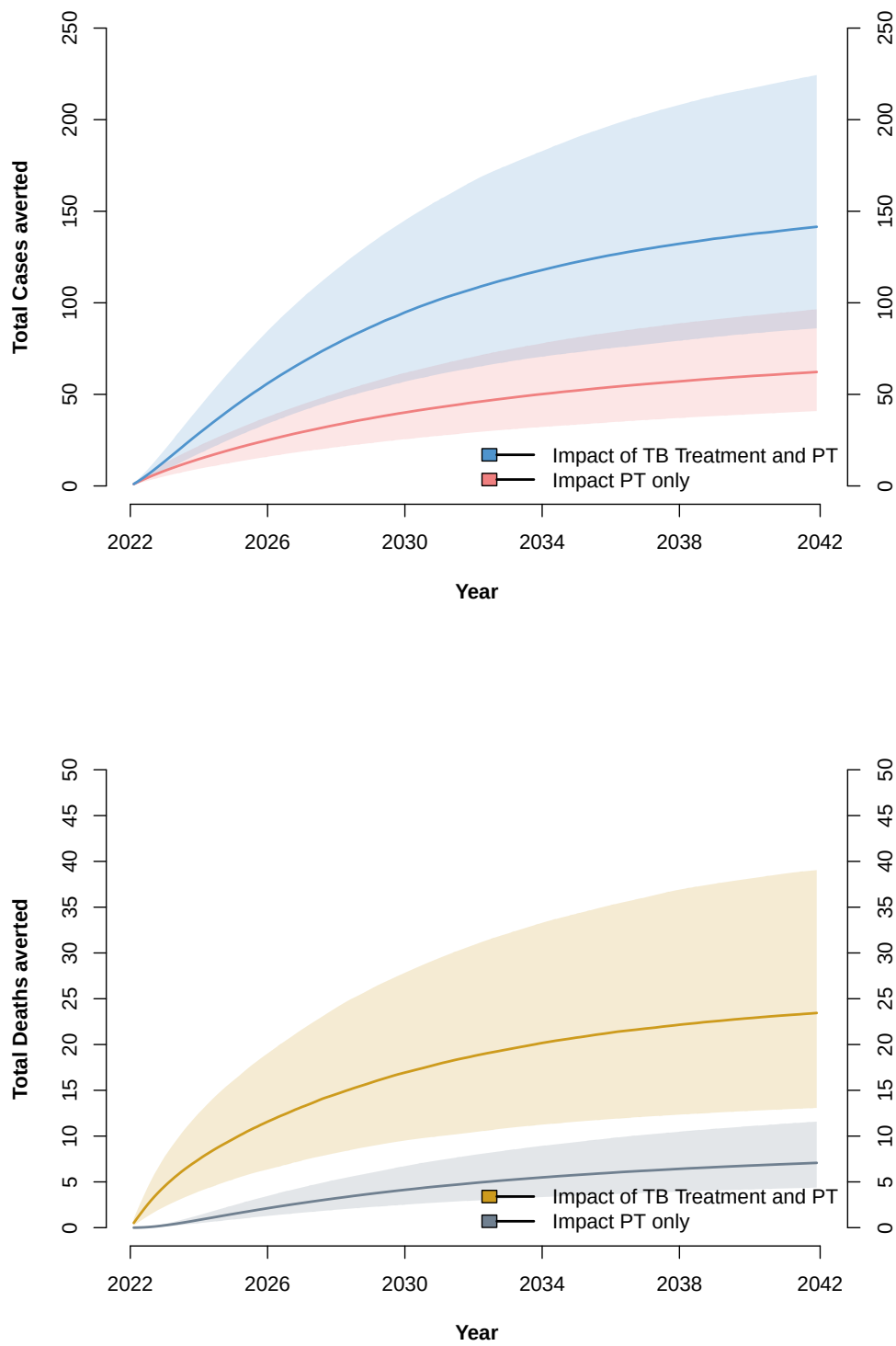


Figure S4: Total cases and deaths averted over 20 years calculated as sum of district-wise total cases and deaths averted. The solid lines indicate the median estimates and the shaded areas indicate 95% uncertainty intervals.

S10. Cost Effectiveness Results

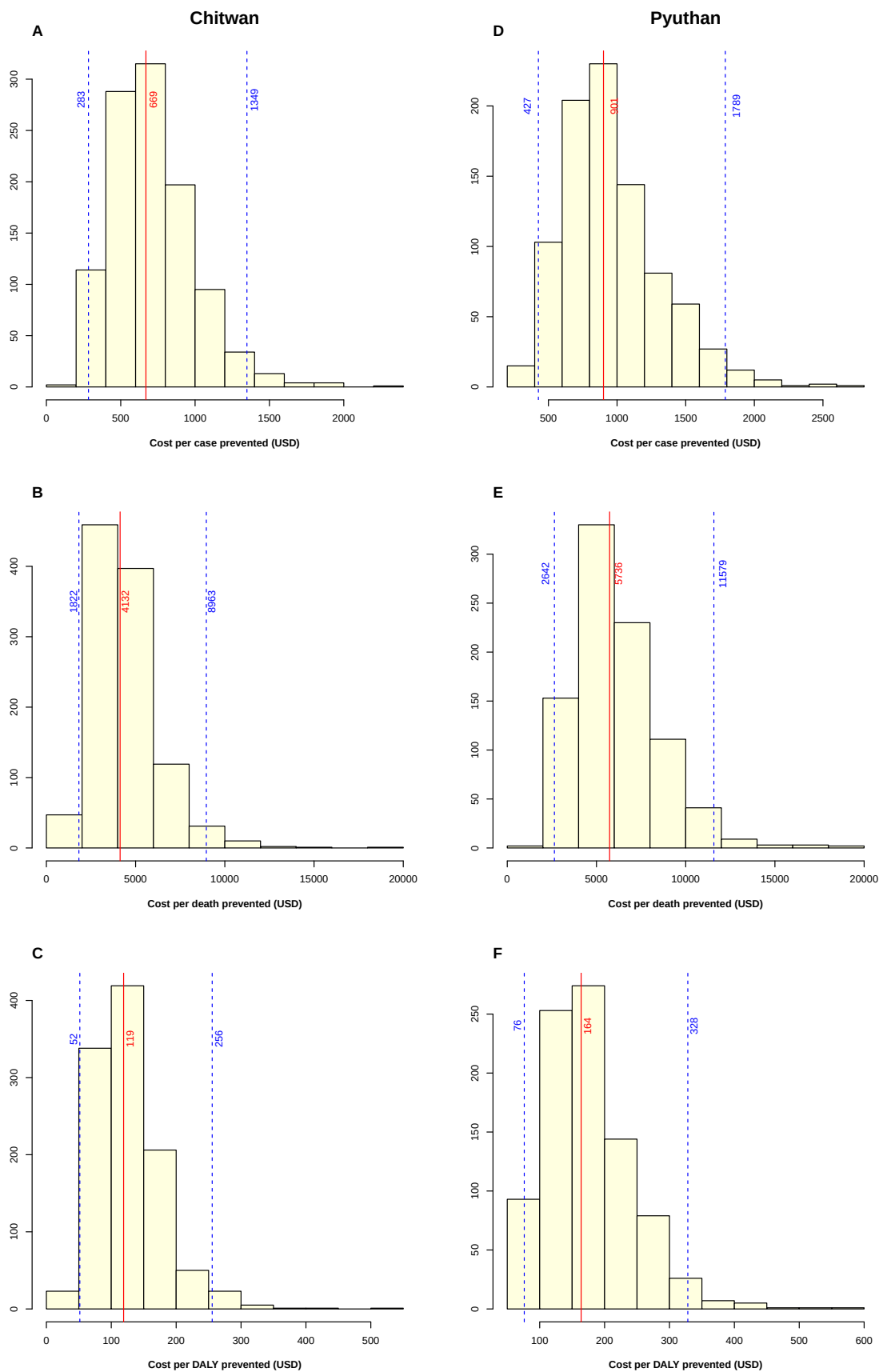


Figure S5: Histograms showing the distribution of the cost effectiveness results for all the simulation results. The red solid lines denote the median estimates from the simulation and blue dashed lines indicate the 95% uncertainty intervals.

S11. CHEERS Checklist

Table S4: Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 checklist

Section/Topic	Item No	Guidance for Reporting	Reported in Section
TITLE			
Title	1	Identify the study as an economic evaluation and specify the intervention being compared.	Title
ABSTRACT			
Abstract	2	Provide a structured summary that highlights context, key methods, results and alternative analyses.	Abstract
INTRODUCTION			
Background and Objectives	3	Give the context for the study, the study question and its practical relevance for decision making in policy or practice.	Introduction, Paragraph 1-4
METHODS			
Health Economic Analysis Plan	4	Indicate whether a health economic analysis plan was developed and where available.	NA
Study Population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	NA
Setting and Location	6	Provide relevant contextual information that may influence findings.	Methods, Paragraph 2
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Methods, Paragraph 7
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Methods, Paragraph 1
Time Horizon	9	State the time horizon for the study and why appropriate.	Methods, Paragraph 1
Discount Rate	10	Report the discount rate(s) and reason chosen.	Methods, Paragraph 7
Selection of Outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harms(s).	Methods, Paragraph 7
Measurement of Outcomes	12	Describe how the outcomes used to capture benefit(s) and harm(s) were measured.	Supplementary Material, Table S1
Valuation of Outcomes	13	Describe the population and methods used to measure and value outcomes.	Supplementary Material, Table S1
Measurement and Valuation of Resources and Costs	14	Describe how costs were valued.	Table 1
Currency, price date and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Table 1
Rationale and Description and Model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	Methods, Paragraph 3
Analytics and Assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Methods, Paragraph 4
Characterizing Heterogeneity	18	Describe any methods used for estimating how the results of the study vary for sub-groups.	NA
Characterizing distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	NA

Section/Topic	Item No	Guidance for Reporting	Reported in Section
Characterizing uncertainty	20	Describe methods to characterize any sources of uncertainty in the analysis.	Methods, Paragraph 8
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (e.g., clinicians or payers) in the design of the study.	NA
RESULTS			
Study Parameters	22	Report all analytic inputs (e.g., values, ranges, references) including uncertainty or distributional assumptions.	Supplementary Material, Table S1
Summary of Main Results	23	Report the main values for the main categories of costs and outcomes of interest and summarize them in the most appropriate overall measure.	Results Paragraph 3-4, Table 2
Effect of Main Uncertainty	24	Describe how uncertainty about analytic judgements, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Results, Paragraph 6-7
Effect of engagement with patients and others affected by the study	25	Report on any difference patients/service recipients, the general public, communities, or stakeholder involvement made to the approach of findings of the study.	NA
DISCUSSION			
Study findings, limitations, generalizability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could impact patients, policy, or practice.	Discussion, Paragraph 1-4
OTHER RELEVANT INFORMATION			
Source of Funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis.	Declarations
Conflict of Interest	28	Report authors conflicts of interest according to the journal or International Committee of Medical Journal Editors requirements.	Declarations

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