Active screening for tuberculosis in high-incidence Inuit communities: a cost-effectiveness analysis

Additional File 1

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Methods

The following sections describe model parameters, methods for calculating secondary infections and secondary active TB cases, methods for simulating repeated outbreaks, costs considered, all strategies that were simulated using data from both villages, and all scenario analyses.

Screening Campaigns. In 2019, the Nunavik Regional Board of Health and Social Services (NRBHSS) led active screening campaigns in Village 1 (population approximately 1,000) and Village 2 (population approximately 1,500). These campaigns were community-wide: anyone not already known and evaluated for active TB or LTBI was eligible, without age restrictions. This meant that in Village 1, approximately 60% of the population was eligible for screening, and in Village 2, approximately 70% were eligible. The NRBHSS worked with local staff as well as staff flown into the villages to organize these screening campaigns. Several types of staff were required to operationalize screening activities, such as nurses, translators, HR staff, physicians, public health practitioners, administrative staff, and communications officers. Community members were engaged by local public health authorities using educational materials and encouraged to participate through incentives such as prize draws. Screening included on-site tuberculin skin testing and chest radiographs. In both villages, over 90% of individuals who were eligible for screening in 2019 participated in the screening campaigns.

Model Parameters. Table S1 lists all model parameters for both villages, separated into key parameter categories. Table S2 illustrates how TB cascade parameters (for both active TB and LTBI) were impacted by the presence of active screening, in both villages.

Table S1. Model parameters

Parameter	Type of Distribution for Probabilistic Sensitivity Analysis	Value in Village 1 (Range for Probabilistic Sensitivity Analysis)	Value in Village 2 (Range for Probabilistic Sensitivity Analysis)	Source
TB PATHOGENESIS				
Probability of progression to active TB†	Beta	0.05-0.265 (range ± 25%)	0.05-0.265 (range ± 25%)	[1]
Probability of reactivation to active TB†	Beta	0.0005-0.075 (range ± 25%)	0.0005-0.075 (range ± 25%)	[2,3]
Annual risk of infection	Beta	0.0095 (0.0071 - 0.0119)	0.0095 (0.0071 - 0.0119)	[4]

Appendix 1, as supplied by the authors. Appendix to: Uppal A, Nsengiyumva NP, Signor C, et al. Active screening for tuberculosis in high-incidence Inuit communities in Canada: a cost-effectiveness analysis. *CMAJ* 2021. doi: 10.1503/cmaj.210447.

Parameter	Type of Distribution for Probabilistic Sensitivity Analysis	Value in Village 1 (Range for Probabilistic Sensitivity Analysis)	Value in Village 2 (Range for Probabilistic Sensitivity Analysis)	Source
Average secondary infections per index TB case	Uniform	0.67 (0.50 – 0.84)	0.67 (0.50 – 0.84)	[1,5]
Average secondary active TB cases per index TB case	Uniform	1.82 (1.37 – 2.28)	1.23 (0.92 - 1.54)	[6]
Immunity conferred by previous infection	Beta	0.55 (0.4125 - 0.6875)	0.55 (0.4125 - 0.6875)	[3]
Probability of recovery following active TB treatment	Beta	0.928 (0.9 - 1)	0.928 (0.9 - 1)	[4]
Probability of recovery following complete LTBI treatment	Beta	0.875 (0.9 – 0.925)	0.875 (0.9 – 0.925)	[7]
Probability of recovery following incomplete LTBI treatment	Beta	0.21 (0 – 0.3)	0.21 (0 – 0.3)	[3]
Probability of relapse following recovery from active TB treatment	Beta	0.015 (0.0075 - 0.025)	0.015 (0.0075 - 0.025)	[8]
Probability of spontaneous recovery from active TB	Beta	0.25 (0.2 - 0.3)	0.25 (0.2 - 0.3)	[9]
Probability of dying from active TB during treatment	Beta	0 (0 - 0)	0 (0 - 0)	[7]
Probability of dying of untreated TB if smear negative	Beta	0.02 (0.015 - 0.025)	0.02 (0.015 - 0.025)	[8]
Probability of dying of untreated TB if smear positive	Beta	0.07 (0.053 - 0.086)	0.07 (0.053 - 0.086)	[8]
CASCADE PROBABILITIES††				
Probability of diagnosing active TB (with active screening)	NA	1	1	[10]
Probability of diagnosing active TB (without active screening)**	NA	0.82	0.56	[10]
Probability of diagnosing new LTBI (with active screening)	NA	1	0.99	[10]
Probability of diagnosing new LTBI (without active screening)**	NA	0.83	0.71	[10]
Probability of diagnosing longstanding LTBI (with active screening)	NA	1	1	[10]
Probability of diagnosing longstanding LTBI (without active screening)**	NA	0.983	0.998	[10]
Probability of coming for a follow up visit to read TST	NA	0.86	0.86	[22]
Probability of starting active TB treatment when diagnosed (with or without active screening)	NA	1	1	Assumption
Probability of starting latent TB treatment (without active screening)	NA	0.7	0.7	[6]
Probability of starting treatment for new infection (with active screening)	NA	0.72	0.71	[10]
Probability of starting treatment for longstanding infection (with active screening)	NA	0.69	0.7	[10]
Probability of completing active TB treatment (with or without active screening)	NA	0.997	0.997	[6]

Parameter	Type of Distribution for Probabilistic Sensitivity Analysis	Value in Village 1 (Range for Probabilistic Sensitivity Analysis)	Value in Village 2 (Range for Probabilistic Sensitivity Analysis)	Source
Probability of completing LTBI treatment (with or without active screening)*	NA	0.75	0.6	[10]
Median proportion of total doses taken among those who don't complete treatment for LTBI	Beta	0.25 (0.18 – 0.5)	0.25 (0.18 – 0.5)	[21]
OTHER PROBABILITIES				
Proportion of population at baseline in LTBI states	NA	48%	33%	[6]
Proportion of population at baseline in susceptible states	NA	49%	66%	[6]
Proportion of Population at baseline in active TB states	NA	3%	1%	[6]
Probability of adverse event during active TB treatment	Beta	0.051 (0.01 - 0.1)	0.051 (0.01 - 0.1)	[11]
Probability of adverse event during LTBI treatment	Beta	0.003 (0.001 - 0.0045)	0.003 (0.001 - 0.0045)	[23]
Probability of non-TB-related death (background mortality)††	NA	0.014-0.021	0.014-0.021	[24]
Probability of being smear positive (with active screening)††	NA	0.12	0.13	[6]
Probability of being smear positive (without active screening)††	NA	0.15	0.11	[6]
Probability that someone being evaluated for LTBI undergoes sputum examination††	NA	0.23	0	[6]
Probability of producing adequate sputum sample	Beta	0.82 (0.747 – 0.896)	0.82 (0.747 – 0.896)	[20]
Number of days hospitalized if smear negative	Uniform	14 (11 - 18)	14 (11 - 18)	[6]
Number of days hospitalized if smear positive	Uniform	60 (45 - 75)	60 (45 - 75)	[6]
Number of days hospitalized for suspicion of active TB	Uniform	1 (0 - 1)	1 (0 - 1)	[6]
Probability of being hospitalized for suspicion of active TB	Beta	0.05 (0.0375 - 0.0625)	0.05 (0.0375 - 0.0625)	Assumption
COSTS RELATED TO ACTIVE SCREENING				
Cost of active screening: amount spent on local amenities	Triangular	$10,821 ($8,116 - $13,526)	$41,118 ($30,839 - $51,398)	[10]
Cost of active screening: average spent on car rental	Triangular	$2,391 ($1,793 - $2,989)	$28,140 ($21,105 - $35,175)	[10]
Cost of active screening: average spent on charter flight	Triangular	$3,563 ($2,672 - $4,454)	$23,703 ($17,777 - $29,629)	[10]
Cost of active screening: average spent per cleaner	Triangular	$338 ($254 - $423)	$0 ($0 - $0)	[10]
Cost of active screening: amount spent on communication and mobilization	Triangular	$2,865 ($2,149 - $3,581)	$30,228 ($22,671 - $37,785)	[10]

Parameter	Type of Distribution for Probabilistic Sensitivity Analysis	Value in Village 1 (Range for Probabilistic Sensitivity Analysis)	Value in Village 2 (Range for Probabilistic Sensitivity Analysis)	Source
Cost of active screening: average spent on construction for lodging	Triangular	$32,153 ($24,115 - $40,191)	$0 ($0 - $0)	[10]
Cost of active screening: average spent per consultant	Triangular	$12,095 ($9,071 - $15,119)	$10,212 ($7,659 - $12,765)	[10]
Cost of active screening: average spent per driver	Triangular	$1,434 ($1,076 - $1,793)	$0 ($0 - $0)	[10]
Cost of active screening: amount spent on equipment and materials related to lodging and transport	Triangular	$4,755 ($3,566 - $5,944)	$1,753 ($1,315 - $2,191)	[10]
Cost of active screening: average spent on additional hotel stay per staff	Triangular	$0 ($0 - $0)	$3,983 ($2,987 - $4,979)	[10]
Cost of active screening: average spent per human resources and logistics staff	Triangular	$225,000 ($168,750 - $281,250)	$0 ($0 - $0)	[10]
Cost of active screening: average spent per lab technician	Triangular	$9,535 ($7,151 - $11,919)	$0 ($0 - $0)	[10]
Cost of active screening: average spent per local staff	Triangular	$0 ($0 - $0)	$15,346 ($11,510 - $19,183)	[10]
Cost of active screening: average spent to lodge each staff member	Triangular	$2,984 ($2,238 - $3,730)	$5,452 ($4,089 - $6,815)	[10]
Cost of active screening: average spent per nurse	Triangular	$19,539 ($14,654 - $24,424)	$21,148 ($15,861 - $26,435)	[10]
Cost of active screening: average spent on other staff	Triangular	$0 ($0 - $0)	$100,649 ($75,487 - $125,811)	[10]
Cost of active screening: average spent per pharmacy technician	Triangular	$11,695 ($8,771 - $14,619)	$19,505 ($14,629 - $24,381)	[10]
Cost of active screening: amount spent on supplies	Triangular	$29,405 ($22,054 - $36,756)	$31,902 ($23,927 - $39,878)	[10]
Cost of active screening: amount spent on training and workshops	Triangular	$1,256 ($942 - $1,570)	$29,692 ($22,269 - $37,115)	[10]
Cost of active screening: average spent per translator	Triangular	$1,336 ($1,002 - $1,670)	$4,200 ($3,150 - $5,250)	[10]
Cost of active screening: average for other lodging costs	Triangular	$0 ($0 - $0)	$3,870 ($2,903 - $4,838)	[10]
COSTS RELATED TO MANAGEMENT OF TB AND LTBI				
Cost of adverse event due to active TB treatment	Triangular	$16,364 ($12,273 - $20,455)	$16,364 ($12,273 - $20,455)	[11]
Cost of adverse event during LTBI treatment	Triangular	$782 ($587 - $978)	$782 ($587 - $978)	[12]
Cost of chest x-ray	Triangular	$31 ($23 - $39)	$31 ($23 - $39)	[13]
Cost of DOT for active TB	Triangular	$197 ($148 - $246)	$197 ($148 - $246)	[4,14]

Parameter	Type of Distribution for Probabilistic Sensitivity Analysis	Value in Village 1 (Range for Probabilistic Sensitivity Analysis)	Value in Village 2 (Range for Probabilistic Sensitivity Analysis)	Source
Cost of medication for active TB	Triangular	$674 ($506 - $843)	$674 ($506 - $843)	[15]
Cost of medication for latent TB	Triangular	$114 ($86 - $143)	$114 ($86 - $143)	[15]
Cost of flight (non-medical evacuation charter)	Triangular	$305 ($229 - $381)	$305 ($229 - $381)	[10]
Cost of medical evacuation charter to regional hospital	Triangular	$6,713 ($5,035 - $8,391)	$6,713 ($5,035 - $8,391)	[16]
Cost of follow up visit	Triangular	$9 ($7 - $11)	$9 ($7 - $11)	[17, 18]
Cost of hospitalization per day	Triangular	$2,050 ($1,538 - $2,563)	$2,050 ($1,538 - $2,563)	[19]
Cost of induced sputum collection	Triangular	$76 ($57 - $95)	$76 ($57 - $95)	[13]
Cost of spontaneous sputum collection	Triangular	$65 ($49 - $81)	$65 ($49 - $81)	[13]
Cost of sending sputum samples to regional hospital	Triangular	$4 ($3 - $5)	$4 ($3 - $5)	[20]
Cost of physical exam	Triangular	$167 ($125 - $209)	$167 ($125 - $209)	[13,17]
Cost of TST	Triangular	$34 ($26 - $43)	$34 ($26 - $43)	[10,13,17]
Cost of visits to manage active TB treatment	Triangular	$436 ($327 - $545)	$436 ($327 - $545)	[6,17]
Cost of visits to manage LTBI treatment	Triangular	$41 ($31 - $51)	$41 ($31 - $51)	[6,17,18]
Cost of GeneXpert analysis	Triangular	$69 ($52 - $86)	$69 ($52 - $86)	[20]

NA = not applicable

Assumptions were vetted by regional experts

† The probabilities of progression and reactivation change over time. At each time point, a ±25% range was evaluated in probabilistic sensitivity analysis

†† Cascade probabilities (with the exception of median proportion of total LTBI treatment doses taken) reflect the realities of the two communities. As such, we did not consider fluctuations in these parameters in probabilistic sensitivity analysis. We did, however, consider changes in certain cascade probabilities in scenario analyses. For similar reasons, parameters such as the background mortality and probability of being smear positive were not considered in probabilistic sensitivity analysis.

*Assumption that probability of completing LTBI treatment does not change with the addition of active screening

**Assumption that persons found through active screening would not have been diagnosed otherwise

Clinical Pathways & TB Cascade. We considered clinical pathways for individuals with active TB or LTBI who were undiagnosed or diagnosed and not treated. Individuals with LTBI who fell into this category eventually moved into the longstanding LTBI branch, where they could recover without becoming reinfected, recover and become reinfected, or reactivate to active TB. In the case that community-wide screening was repeated in subsequent cycles of the model, these individuals could be diagnosed with LTBI and would follow the respective treatment pathway. On the other hand, individuals with active TB who were undiagnosed or diagnosed and not treated had a probability of dying or remaining with active TB otherwise, as well as spontaneous recovery. Notably, the probabilities of diagnosing and treating individuals with active TB were high, so most were diagnosed and treated (Table S2).

Active screening may influence probabilities of diagnosis, treatment initiation and treatment completion for both active TB and LTBI. We assumed that any persons with LTBI detected during active screening in each community would not have otherwise been found, as active screening supplemented established, ongoing contact investigation practices. Similarly, we assumed that persons with active TB found as a result of active screening in each community would have otherwise been found after symptom onset, i.e. when they became more infectious. We used data from years when there was no active screening, as well as data from 2019, when active screening took place, to inform changes in TB cascade parameters, as described in Table S2.

Table S2. Calculating TB cascade parameters using 2019 program data

TB Cascade Variable	**Value in Village 1**	**Value in Village 2**	**Reference**
Active TB			
DIAGNOSIS			
(a) true number of individuals with active TB at the beginning of 2019	33	16	Calculated
(b) number of individuals with known active TB at the beginning of 2019	27	9	[6]
(c) number of additional individuals diagnosed during active screening	6	7	[10]
(d) diagnosis rate in absence of active screening; (b)÷(a)	82%	56%	Calculated
(e) diagnosis rate in presence of active screening; (b + c)÷(a)	100%	100%	Calculated
TREATMENT INITIATION			
(f) treatment initiation rate in absence of active screening	100%	100%	[6]
(g) treatment initiation rate in presence of active screening	100%	100%	[6]
TREATMENT COMPLETION			
(h) treatment completion rate in absence of active screening	99.7%	99.7%	[4]
(i) treatment completion rate in presence of active screening	99.7%	99.7%	[4]
LTBI*			
DIAGNOSIS			
(a) true number of individuals with LTBI at the beginning of 2019	138	104	Calculated
(b) number of individuals with known LTBI at the beginning of 2019	114	74	[6]

(c) number of additional individuals diagnosed during active screening	23	29	[10]
(d) diagnosis rate in absence of active screening; (b)÷(a)	83%	71%	Calculated
(e) diagnosis rate in presence of active screening; (b + c)÷(a)	100%	99%	Calculated
TREATMENT INITIATION			
(f) among those actively screened, number who start treatment	19	21	[10]
(g) treatment initiation rate in absence of active screening	70%	70%	[6]
(h) treatment initiation rate in presence of active screening; (b + c)÷(b*g + f)	72%	71%	Calculated
TREATMENT COMPLETION			
(i) treatment completion rate in absence of active screening	75%	60%	[6]
(j) treatment completion rate in presence of active screening	75%	60%	[6]

* LTBI refers to “new” infection, meaning infection among individuals who either had previously unknown status or had tested negative for LTBI

Secondary Infections & Active Cases. The total predicted number of incident active TB cases was used to estimate secondary infections and secondary active TB cases, using a ratio of secondary infections and active cases per index case that was informed by historical regional data [6]. The number of secondary infections was calculated by multiplying the number of incident active TB cases by the average number of household contacts in Nunavik (2.36) [5] and the average proportion of household contacts with secondary infection (26%; not specific to Nunavik) [1]. Similarly, the number of secondary active TB cases was calculated by multiplying the number of incident active TB cases by the proportion of smear positive individuals and the average number of secondary cases per index case, as listed in Table S3. Data in Table S3 comes from pooled estimates during both outbreak and non-outbreak years in the communities. We were not able to obtain the same type of data for the average number of persons with new LTBI per index active TB case, hence the other method of calculation.

Table S3. Number of secondary active TB cases per index case by smear status in both villages

Average number of secondary cases by index case in 2017-2019	Village 1	Village 2
Smear-positive	4.9	2.8
Smear-negative	1.4	1.0

The proportion of smear positive individuals (out of all individuals diagnosed with active TB) in Village 1 was 12% and 13% in Village 2, in 2019 [6].

In other words,

> ***Number of secondary infections*** = *number of incident active TB cases * average number of household contacts * proportion of household contacts with secondary infection*
>
> ***Number of secondary active TB cases*** = *number of incident active TB cases * proportion of smear positive individuals in the village * average number of secondary active TB cases per index case dependent on smear status and village*

The clinical pathway for secondary infections and secondary active TB cases resembled that of new infections and index active TB cases. We took measures not to double count these individuals; during each cycle of the model, persons with secondary LTBI and secondary active TB were taken from the pool of susceptible individuals.

Longstanding Infections. Longstanding infections were calculated in each cycle of the model's analytic horizon as the sum of those with LTBI who were (1) never diagnosed, (2) diagnosed, but never treated, and (3) diagnosed, treated, but never completed treatment. These individuals were especially important for simulating repeated outbreaks, as described in the following section.

Simulating Outbreaks. Outbreaks were simulated by changing three parameters in the two villages: the annual risk of infection (i.e. the transmission parameter), the probability of progression, and the probability of reactivation. First, the annual risk of infection was set to 5% during outbreak years, in lieu of 0.95%. 5% is the upper bound of the estimate for the annual risk of infection that was derived from literature in Nunavut, a jurisdiction that has had a similar pattern of outbreaks to communities in Nunavik [1]. There is evidence from Village 1 that the annual risk of infection increased during outbreaks [6]. Second, we increased the rate at which individuals would progress or reactivate to active TB. Both progression and reactivation parameters started off high (26.5% and 7.5%, respectively), reflecting data from a Nunavik community in 2010, which was experiencing an outbreak at the time [1]. In the absence of outbreaks, both of these parameters would decline over the course of five years to 5% and 0.05%, respectively. However, in order to simulate outbreaks, these two parameters would increase to their baseline values (26.5% and 7.5%) during the cycle of the model that the outbreak occurred. Following an outbreak cycle, the three parameters would go back to their lower values. Because the outbreak in 2010 was large, we tested lower peaks of progression and reactivation in scenario analyses.

Costs. All costs were considered from the health system perspective, meaning that any out-of-pocket costs borne by patients were not included—although there were no direct charges made to patients. Cost inputs fell into two categories. The first category included costs related to active screening. These costs came from Nunavik program data and reflected the steps needed to conduct active screening activities in both communities in 2019. The second category included costs related to standard TB care. Wherever possible, these costs came from Nunavik, or Nunavut when necessary. Where such information was unavailable, costs came from published literature, but were confirmed with regional experts. We considered several components of active TB treatment and LTBI treatment, such as medication, hospital visits, adverse events, hospitalization, and medical evacuation (in the case of severe illness requiring treatment in larger cities). Aside from medication and hospital visits, which applied to all undergoing treatment, some components of treatment (e.g. cost of adverse events) were pro-rated according to the probability of that event arising.

Incorporation of Additional Strategies. The following strategies were considered, given a single outbreak in 2019 (Strategies A and B were considered in the main text):

A. **No active screening:** This strategy was the counterfactual; i.e. what was predicted to occur had no active screening program been introduced to either community in 2019. We used background rates of diagnosis, treatment initiation and treatment completion for both active TB and LTBI, informed by data from each community during years where there was no active screening.

B. **Community wide active screening in 2019:** Both Village 1 and Village 2 had active, community-based screening programs in 2019. This strategy incorporated program data to reflect increased rates of diagnosis, treatment initiation, and treatment completion compared to Strategy A.

D. **Community wide active screening in 2019 and active screening for new infections only in 2020, given a single outbreak in 2019:** This strategy used active screening data from 2019 to inform a hypothetical repeated screening effort in 2020. The key difference between the screening program in 2019 and 2020 in this strategy was that the screening in 2020 was solely focused on diagnosing new infections. Hence only those who were previously skin test negative, or had unknown infection status were eligible to be screened in 2020; we assumed that everyone eligible for screening in 2020 would be screened.

E. **Community wide active screening in 2019 and 2020, given a single outbreak in 2019:** This strategy also incorporated repeated screening in 2020. The 2020 screening focused on both LTBI and active TB. Hence individuals without infection, with previously negative skin tests, and those with unknown status were eligible for LTBI screening, and all others were eligible for active TB screening. As with Strategy D, we assumed that all those eligible for repeat screening in 2020 would be screened accordingly.

The following strategies were considered, given an outbreak in 2019, and every three years following that (Strategies A, B and C were also considered in the main text):

A. **No active screening:** This strategy was the counterfactual; i.e. what was predicted to occur had no active screening program been introduced to either community in 2019. We used background rates of diagnosis, treatment initiation and treatment completion for both active TB and LTBI, informed by data from each community during years where there was no active screening.

B. **Community wide active screening in 2019:** Both Village 1 and Village 2 had active, community-based screening programs in 2019. This strategy incorporated program data to reflect increased rates of diagnosis, treatment initiation, and treatment completion compared to Strategy A.

C. **Community wide active screening every two years for twenty years total:** Community wide active screening was simulated every two years for the entire analytic horizon of 20 years.

F. **Community wide active screening annually for twenty years total, in the presence of repeated outbreaks every three years:** Similar to scenario C, but with screening conducted annually.

Scenario Analyses. Model assumptions were evaluated using extensive univariate sensitivity analysis as well as scenario analyses. Univariate sensitivity analyses allowed us to identify parameters that were most influential in driving model outcomes, and to incorporate uncertainty around each parameter's point estimate. On the other hand, scenario analyses addressed specific assumptions related to program efficiencies and community characteristics. We considered the following seven scenarios:

1) **Strengthened LTBI cascade:** Rates of LTBI diagnosis are already high in both communities, but rates of treatment initiation and completion may be improved (with active screening, they stand at approximately 70% in both communities). Strengthening the cascade is always a goal of TB care, so we considered a scenario where treatment initiation and completion rates were increased to 80%.

2) **Local staff for active screening:** During active screening in both communities, many staff members were flown in from the South. Village 1 and Village 2, however, have their own community health workers. To mimic building local capacity, we considered a scenario where community health workers were not flown into the communities. All other staff, such as nurses, were still flown into both communities.

3) **Reduced adherence to the second round of screening:** Strategies C, D, E, and F rely on multiple rounds of screening. In our base case analysis, we assumed that everyone who is eligible for repeated rounds of screening undergoes active screening, however, there may be some level of fatigue associated with consecutive courses of screening. In this scenario, we reduced the level of adherence to 50% for any screening event following the one in 2019.

4) **Outbreak Intensity x0.75:** In the base case analyses (main text analyses), the probabilities of progression and reactivation jumped up to 26.5% and 7.5%, respectively, during an outbreak. These values reflect a relatively large outbreak that occurred in a Nunavik community in 2010. This scenario reduced the high values of progression and reactivation during outbreaks by 25%, so that they would jump up to 19.9% and 5.6%, respectively, instead.

5) **Outbreak Intensity x0.5:** This scenario was very similar to the one above, except the high values of progression and reactivation were reduced by 50%, so that they would jump up to 13.3% and 3.8%, respectively.

6) **Outbreak Intensity Progressively Decreasing:** This scenario assumed that outbreak intensity would progressively decrease each time an outbreak would occur. As such, outbreak intensity was high during the first outbreak, then reduced by 10-15 percentage

points each outbreak, so that by the last outbreak, the values of progression and reactivation were 5.3% and 1.5% (80% reduction from 26.5% and 7.5%), respectively, which approaches their values during non-outbreak years.

7) **Lower rates of LTBI diagnosis:** As shown in Table S2, the rates of diagnosis are quite high in both villages, even without active screening. In this scenario, we reduced rates of LTBI diagnosis, both with and without active screening, by 25%.

Results

Tables S4 and S5 illustrate the results for Strategies A, B, D and E, given a single outbreak in 2019. Tables S6 and S7 illustrate the results for Strategy A, B, C, and F, given an outbreak in 2019 and every three years following that. Figures S1 and S2 illustrate the results of all scenario analyses. Figures S3-S6 illustrate the results of univariate sensitivity analyses. Lastly, Figures S7-S10 illustrate the results of probabilistic sensitivity analyses.

Results: Additional Strategies

Table S4. Outcomes over 20 years in Village 1 and Village 2, given a single outbreak in 2019

*Strategy**	*Cost*	*Incident Active TB*	*Incident LTBI*	*Longstanding LTBI*	*TB-Related Deaths*	*Secondary Infections*	*Secondary Active TB*
Village 1							
B	$6,996,027 ($5,647,525 to $8,975,360)	90 (79 to 103)	38 (33 to 45)	61 (56 to 66)	0.6 (0.4 to 0.7)	19 (16 to 21)	50 (44 to 58)
D	$7,001,561 ($5,773,909 to $8,818,454)	77 (67 to 90)	29 (25 to 34)	55 (51 to 60)	0.3 (0.3 to 0.4)	16 (14 to 19)	43 (38 to 51)
E	$7,004,953 ($5,685,476 to $8,979,622)	90 (79 to 103)	38 (33 to 45)	60 (56 to 66)	0.5 (0.4 to 0.7)	19 (16 to 21)	50 (44 to 58)
A	$7,493,340 ($5,927,277 to $9,748,954)	103 (90 to 118)	42 (36 to 48)	70 (66 to 76)	0.9 (0.7 to 1.0)	21 (18 to 24)	60 (52 to 68)
Village 2							
A	$5,034,527 ($3,978,665 to $6,536,382)	83 (73 to 95)	42 (40 to 49)	63 (58 to 68)	2.0 (1.6 to 2.5)	20 (18 to 22)	35 (31 to 40)
B	$5,139,231 ($4,085,546 to $6,660,691)	79 (69 to 90)	41 (39 to 48)	55 (51 to 60)	1.6 (1.3 to 2.0)	19 (16 to 21)	34 (30 to 39)
D	$5,645,676 ($4,671,551 to $7,037,729)	68 (58 to 80)	33 (32 to 39)	50 (46 to 54)	0.8 (0.7 to 1.1)	16 (14 to 19)	29 (25 to 34)
E	$5,659,758 ($4,639,224 to $7,153,740)	78 (69 to 89)	40 (39 to 47)	54 (50 to 59)	1.6 (1.3 to 2.0)	19 (16 to 21)	34 (30 to 38)

Values in parentheses indicate 95% uncertainty ranges.
**Strategy A: No active screening; Strategy B: Community wide active screening in 2019; Strategy D: Community wide active screening in 2019 and active screening for new infections only in 2020; Strategy E: Community wide active screening in 2019 and 2020*

Table S5. Incremental cost per active TB case averted in Village 1 and Village 2, given a single outbreak in 2019

*Strategy**	*Incremental cost per person compared to the preceding strategy*	*Incremental cost per active TB case averted compared to preceding strategy*	*Incremental cost per active TB case averted compared to Strategy A*
Village 1			
B	--	--	Dominant**
D	$4 (-$616 to $601)	$442 (-$343,317 to $330,701)	Dominant**
E	$2 (-$565 to $607)	Dominated**	Dominant**
A	$348 (-$281 to $1,074)	Dominated**	--
Village 2			
A	--	--	--
B	$47 (-$269 to $352)	$22,134 (-$543,096 to $658,464)	$22,134 (-$543,096 to $658,464)
D	$227 (-$91 to $527)	$48,382 (-$791,889 to $646,889)	$40,213 (-$389,481 to $862,579)
E	$6 (-$292 to $315)	Dominated**	$121,165 (-$1,461,462 to $1,445,503)

Values in brackets indicate 95% uncertainty ranges. Incremental cost per active TB case averted is the difference in costs divided by the difference in active TB cases (primary and secondary) between two strategies. The population of Village 1 at the end of the simulation was 1402 and the population of Village 2 was 2235.

**Strategy A: No active screening; Strategy B: Community wide active screening in 2019; Strategy D: Community wide active screening in 2019 and active screening for new infections only in 2020; Strategy E: Community wide active screening in 2019 and 2020*

*** Dominated means that a strategy is more costly and less effective than the one it is being compared to, while dominant means that a strategy is less costly and more effective than the one it is being compared to.*

Table S6. Outcomes over 20 years in Village 1 and Village 2, given an outbreak in 2019 and every three years thereafter

*Strategy**	*Cost*	*Incident Active TB*	*Incident LTBI*	*Longstanding LTBI*	*TB-Related Deaths*	*Secondary Infections*	*Secondary Active TB*
Village 1							
B	$14,745,984 ($11,715,969 to $18,606,081)	249 (227 to 266)	87 (83 to 94)	83 (79 to 91)	1.5 (1.2 to 1.8)	51 (46 to 54)	136 (124 to 146)
C	$15,691,149 ($13,059,608 to $18,908,752)	102 (90 to 117)	30 (29 to 35)	55 (52 to 60)	0.3 (0.2 to 0.3)	21 (19 to 24)	57 (50 to 65)
A	$16,359,259 ($12,846,266 to $20,772,912)	276 (252 to 294)	94 (89 to 101)	94 (90 to 103)	1.9 (1.6 to 2.3)	55 (50 to 59)	156 (141 to 166)
F	$22,511,235 ($18,085,183 to $27,448,274)	89 (77 to 102)	26 (24 to 29)	51 (48 to 56)	0.0 (0.0 to 0.0)	19 (16 to 21)	50 (43 to 57)
Village 2							
A	$12,028,207 ($9,462,816 to $15,376,583)	239 (218 to 255)	91 (85 to 97)	89 (85 to 97)	4.8 (4.0 to 5.6)	55 (51 to 59)	98 (89 to 105)
B	$12,203,936 ($9,613,500 to $15,465,190)	232 (211 to 248)	88 (83 to 95)	81 (77 to 89)	4.5 (3.7 to 5.4)	54 (49 to 58)	97 (88 to 104)
C	$15,008,450 ($13,665,701 to $17,132,157)	99 (87 to 112)	38 (35 to 43)	50 (47 to 55)	0.6 (0.5 to 0.7)	24 (21 to 27)	43 (37 to 48)
F	$22,097,123 ($20,635,826 to $24,558,585)	83 (72 to 95)	32 (29 to 37)	46 (42 to 50)	0.0 (0.0 to 0.0)	20 (17 to 23)	36 (31 to 41)

Values in brackets indicate 95% uncertainty ranges.
** Strategy A: No active screening; Strategy B: Community wide active screening in 2019; Strategy C: Community wide active screening every two years for 20 years total; Strategy F: Community wide active screening annually for twenty years total*

Appendix 1, as supplied by the authors. Appendix to: Uppal A, Nsengiyumva NP, Signor C, et al. Active screening for tuberculosis in high-incidence Inuit communities in Canada: a cost-effectiveness analysis. *CMAJ* 2021. doi: 10.1503/cmaj.210447.

Table S7. Incremental cost per active TB case averted in Village 1 and Village 2, given an outbreak in 2019 and every three years thereafter

*Strategy**	*Incremental cost per person compared to the preceding strategy*	*Incremental cost per active TB case averted compared to preceding strategy*	*Incremental cost per active TB case averted compared to Strategy A*
Village 1			
B	--	--	Dominant
C	$674 (-$1,427 to $2,808)	$6,430 (-$29,131 to $13,658)	Dominant
A	$477 (-$1,827 to $2,865)	Dominated	--
F	$2,753 ($790 to $8,132)	$32,797 ($6,078 to $64,884)	$32,797 ($6,078 to $64,884)
Village 2			
A	--	--	--
B	$79 (-$426 to $558)	$24,282 (-$618,200 to $679,744)	$24,282 (-$618,200 to $679,744)
C	$1,255 ($460 to $2,087)	$21,129 ($7,282 to $39,428)	$21,292 ($7,992 to $38,660)
F	$3,172 ($2,776 to $3,678)	$453,014 ($190,638 to $2,855,190)	$64,702 ($48,630 to $88,877)

Values in brackets indicate 95% uncertainty ranges. Incremental cost per active TB case averted is the difference in costs divided by the difference in active TB cases (primary and secondary) between two strategies. The population of Village 1 at the end of the simulation was 1402 and the population of Village 2 was 2235.

** Strategy A: No active screening; Strategy B: Community wide active screening in 2019; Strategy C: Community wide active screening every two years for 20 years total; Strategy F: Community wide active screening annually for twenty years total*

*** Dominated means that a strategy is more costly and less effective than the one it is being compared to, while dominant means that a strategy is less costly and more effective than the one it is being compared to.*

Results: Scenario Analyses

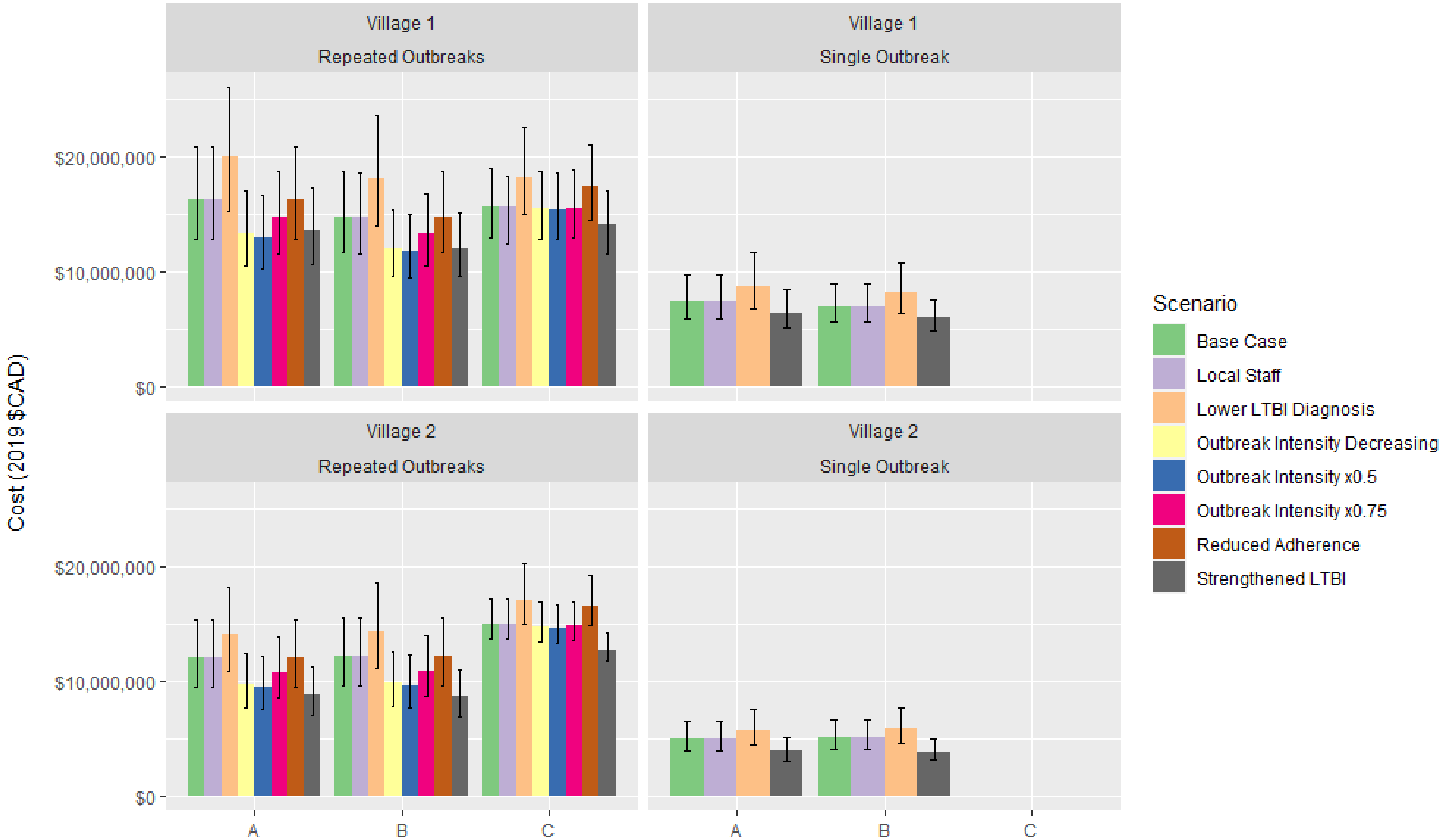

Figure S1. Cost outcomes over 20 years for all scenarios in Village 1 and Village 2. X-axis legend: Strategy A: No active screening; Strategy B: Community wide active screening in 2019; Strategy C: Community wide active screening every two years for 20 years. Error bars represent 95% uncertainty ranges.

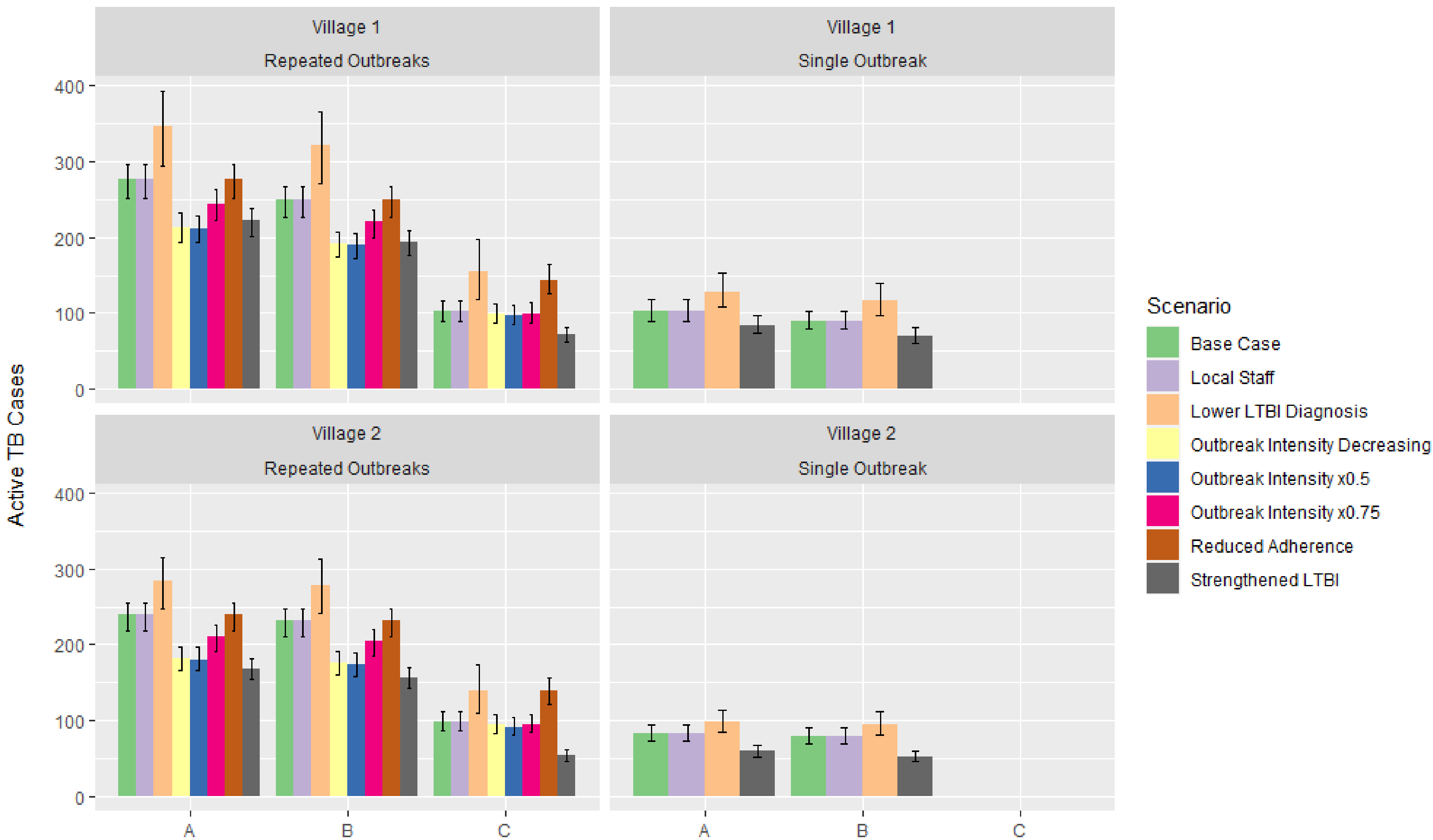

Figure S2. Number of active TB cases over 20 years for all scenarios in Village 1 and Village 2. X-axis legend: Strategy A: No active screening; Strategy B: Community wide active screening in 2019; Strategy C: Community wide active screening every two years for 20 years. Error bars represent 95% uncertainty ranges.

Table S8. All scenario analysis results

Outbreak Status	Village	Scenario	Strategy	Cost	Active TB Cases	Cost: Low	Cost: High	Active TB Cases: Low	Active TB Cases: High
Repeated	1	Base Case	A	$16,359,259	276	$12,832,993	$20,867,686	251	295
Repeated	1	Base Case	B	$14,745,984	249	$11,730,036	$18,714,978	226	266
Repeated	1	Base Case	C	$15,691,149	102	$13,020,951	$18,980,447	90	116
Repeated	1	Strengthened LTBI	A	$13,565,899	222	$10,648,005	$17,259,884	201	238
Repeated	1	Strengthened LTBI	B	$12,053,920	194	$9,595,547	$15,201,632	176	209
Repeated	1	Strengthened LTBI	C	$14,115,953	71	$11,579,326	$17,021,748	62	82
Repeated	1	Outbreak Intensity x0.5	A	$13,024,727	211	$10,298,825	$16,679,404	193	229
Repeated	1	Outbreak Intensity x0.5	B	$11,834,939	189	$9,449,061	$15,042,292	172	205
Repeated	1	Outbreak Intensity x0.5	C	$15,391,897	96	$12,787,179	$18,575,656	85	110
Repeated	1	Outbreak Intensity x0.75	A	$14,732,415	244	$11,523,026	$18,777,829	223	263
Repeated	1	Outbreak Intensity x0.75	B	$13,326,094	220	$10,543,138	$16,861,868	200	236
Repeated	1	Outbreak Intensity x0.75	C	$15,542,021	99	$12,901,575	$18,801,793	87	114
Repeated	1	Outbreak Intensity Decreasing	A	$13,287,737	213	$10,494,208	$17,026,898	194	232
Repeated	1	Outbreak Intensity Decreasing	B	$12,063,973	191	$9,664,294	$15,351,868	174	207
Repeated	1	Outbreak Intensity Decreasing	C	$15,511,652	99	$12,864,214	$18,754,439	87	113
Repeated	1	Local Staff	A	$16,359,259	276	$12,832,993	$20,867,686	251	295
Repeated	1	Local Staff	B	$14,745,508	249	$11,574,572	$18,569,976	226	266
Repeated	1	Local Staff	C	$15,677,288	102	$12,447,748	$18,342,142	90	116
Repeated	1	Reduced Adherence	A	$16,359,259	276	$12,832,993	$20,867,686	251	295
Repeated	1	Reduced Adherence	B	$14,745,984	249	$11,730,036	$18,714,978	226	266
Repeated	1	Reduced Adherence	C	$17,411,846	144	$14,469,461	$21,013,495	125	164
Repeated	1	Lower LTBI Diagnosis	A	$19,998,062	347	$15,261,861	$26,001,714	294	392
Repeated	1	Lower LTBI Diagnosis	B	$18,143,036	321	$13,979,740	$23,601,984	270	366
Repeated	1	Lower LTBI Diagnosis	C	$18,222,725	154	$14,977,013	$22,640,592	119	198

Outbreak Status	Village	Scenario	Strategy	Cost	Active TB Cases	Cost: Low	Cost: High	Active TB Cases: Low	Active TB Cases: High
Repeated	2	Base Case	A	$12,028,207	239	$9,462,816	$15,376,583	218	255
Repeated	2	Base Case	B	$12,203,936	232	$9,613,500	$15,465,190	211	248
Repeated	2	Base Case	C	$15,008,450	99	$13,665,701	$17,132,157	87	112
Repeated	2	Strengthened LTBI	A	$8,809,318	168	$6,967,803	$11,260,810	154	181
Repeated	2	Strengthened LTBI	B	$8,698,480	157	$6,899,541	$11,069,285	143	169
Repeated	2	Strengthened LTBI	C	$12,700,053	53	$11,798,663	$14,256,772	46	61
Repeated	2	Outbreak Intensity x0.5	A	$9,430,327	180	$7,504,871	$12,169,181	165	196
Repeated	2	Outbreak Intensity x0.5	B	$9,579,346	174	$7,643,429	$12,280,009	159	189
Repeated	2	Outbreak Intensity x0.5	C	$14,617,531	91	$13,367,071	$16,683,944	80	104
Repeated	2	Outbreak Intensity x0.75	A	$10,760,435	210	$8,508,643	$13,825,367	192	226
Repeated	2	Outbreak Intensity x0.75	B	$10,923,006	204	$8,677,313	$13,923,560	185	220
Repeated	2	Outbreak Intensity x0.75	C	$14,813,953	95	$13,531,655	$16,948,370	84	108
Repeated	2	Outbreak Intensity Decreasing	A	$9,661,053	182	$7,641,654	$12,468,109	166	197
Repeated	2	Outbreak Intensity Decreasing	B	$9,812,274	175	$7,765,975	$12,578,619	160	191
Repeated	2	Outbreak Intensity Decreasing	C	$14,762,240	94	$13,497,523	$16,901,232	82	107
Repeated	2	Local Staff	A	$12,028,207	239	$9,462,816	$15,376,583	218	255
Repeated	2	Local Staff	B	$12,203,936	232	$9,613,500	$15,465,190	211	248
Repeated	2	Local Staff	C	$15,008,450	99	$13,665,701	$17,132,157	87	112
Repeated	2	Reduced Adherence	A	$12,028,207	239	$9,462,816	$15,376,583	218	255
Repeated	2	Reduced Adherence	B	$12,203,936	232	$9,613,500	$15,465,190	211	248
Repeated	2	Reduced Adherence	C	$16,576,533	139	$14,881,011	$19,256,691	121	157
Repeated	2	Lower LTBI Diagnosis	A	$14,040,450	284	$10,882,334	$18,186,037	248	315
Repeated	2	Lower LTBI Diagnosis	B	$14,377,396	279	$11,075,105	$18,605,230	242	312
Repeated	2	Lower LTBI Diagnosis	C	$16,978,544	139	$14,955,534	$20,247,870	110	174
Single	1	Base Case	A	$7,493,340	103	$5,927,277	$9,748,954	90	118
Single	1	Base Case	B	$6,996,027	90	$5,647,525	$8,975,360	79	103
Single	1	Strengthened LTBI	A	$6,456,462	84	$5,095,052	$8,420,016	73	96

Outbreak Status	Village	Scenario	Strategy	Cost	Active TB Cases	Cost: Low	Cost: High	Active TB Cases: Low	Active TB Cases: High
Single	1	Strengthened LTBI	B	$5,998,226	70	$4,864,534	$7,606,907	61	81
Single	1	Local Staff	A	$7,493,340	103	$5,927,277	$9,748,954	90	118
Single	1	Local Staff	B	$6,995,551	90	$5,624,667	$8,941,536	79	103
Single	1	Lower LTBI Diagnosis	A	$8,788,731	128	$6,819,381	$11,668,638	108	153
Single	1	Lower LTBI Diagnosis	B	$8,177,016	116	$6,452,799	$10,725,792	96	140
Single	2	Base Case	A	$5,034,527	83	$3,978,665	$6,536,382	73	95
Single	2	Base Case	B	$5,139,231	79	$4,085,546	$6,660,691	69	90
Single	2	Strengthened LTBI	A	$3,903,293	59	$3,093,574	$5,050,255	52	68
Single	2	Strengthened LTBI	B	$3,866,123	52	$3,122,848	$4,931,604	46	60
Single	2	Local Staff	A	$5,034,527	83	$3,978,665	$6,536,382	73	95
Single	2	Local Staff	B	$5,139,231	79	$4,085,546	$6,660,691	69	90
Single	2	Lower LTBI Diagnosis	A	$5,701,595	98	$4,496,403	$7,491,771	84	114
Single	2	Lower LTBI Diagnosis	B	$5,864,065	95	$4,605,265	$7,674,281	80	111

Results: Univariate Sensitivity Analyses

The following two figures show how cost-effectiveness of Strategy B compared to Strategy A was affected by changes in model parameters, in both villages.

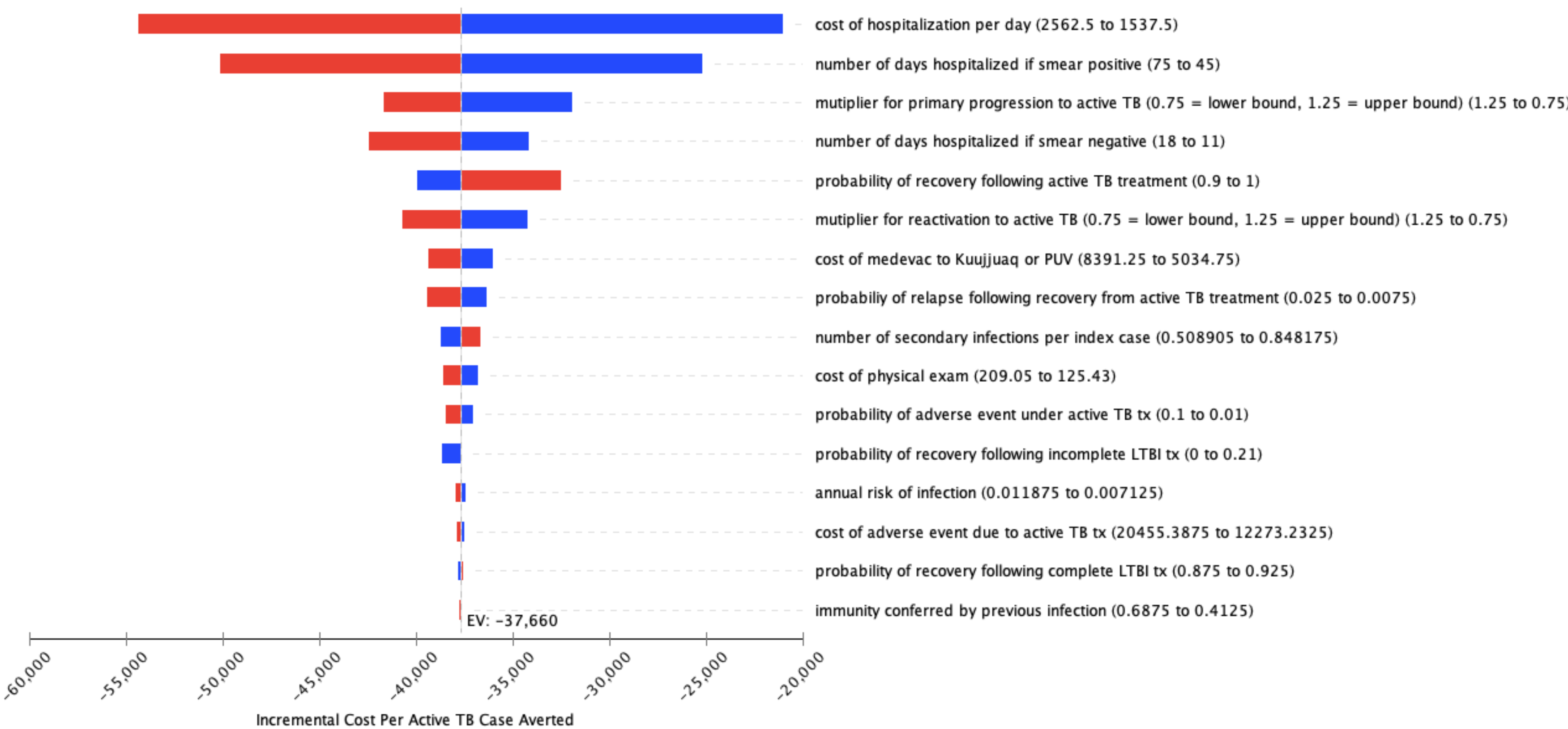

Figure S3. One-way sensitivity analysis for incremental cost per active TB case averted comparing once-off active screening to no active screening given a single outbreak, in Village 1. Red = high value of parameter; Blue = low value of parameter. Because parameters for progression and reactivation were changing over time, a “multiplier” was included in one-way sensitivity analysis (multiplier = 1 in the base case).

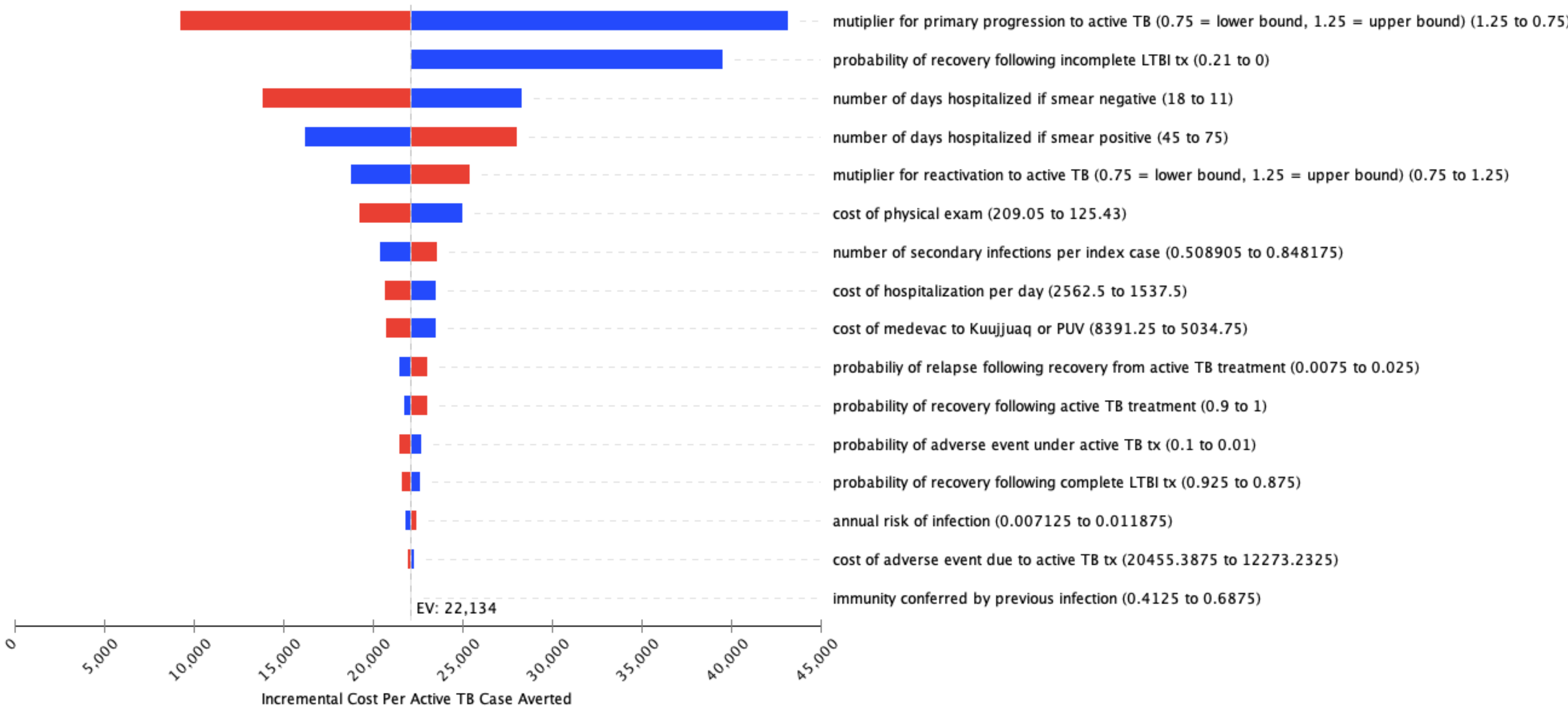

Figure S4. One-way sensitivity analysis for incremental cost per active TB case averted comparing once-off active screening to no active screening given a single outbreak, in Village 2. Red = high value of parameter; Blue = low value of parameter. Because parameters for progression and reactivation were changing over time, a “multiplier” was included in one-way sensitivity analysis (multiplier = 1 in the base case).

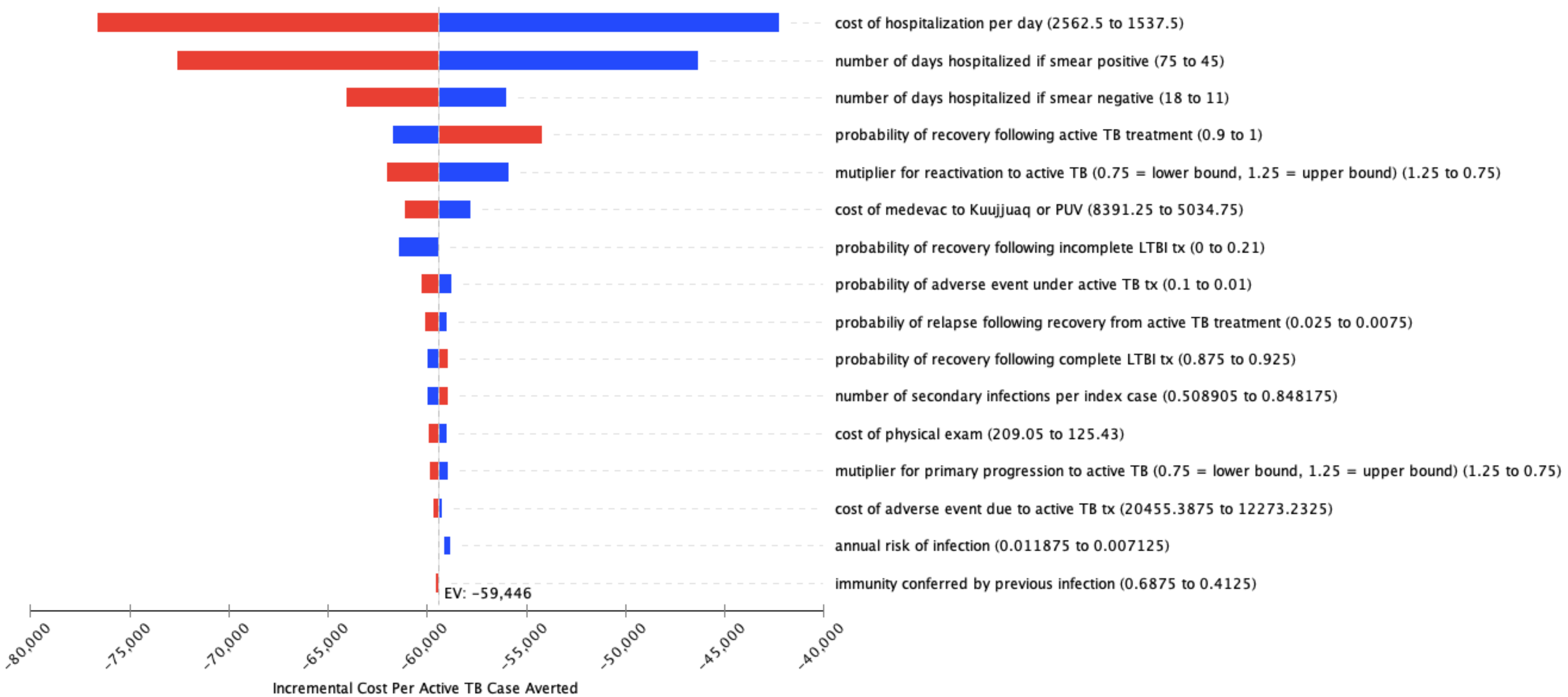

Figure S5. One-way sensitivity analysis for incremental cost per active TB case averted comparing once-off active screening to no active screening given repeated outbreaks, in Village 1. Red = high value of parameter; Blue = low value of parameter. Because parameters for progression and reactivation were changing over time, a “multiplier” was included in one-way sensitivity analysis (multiplier = 1 in the base case).

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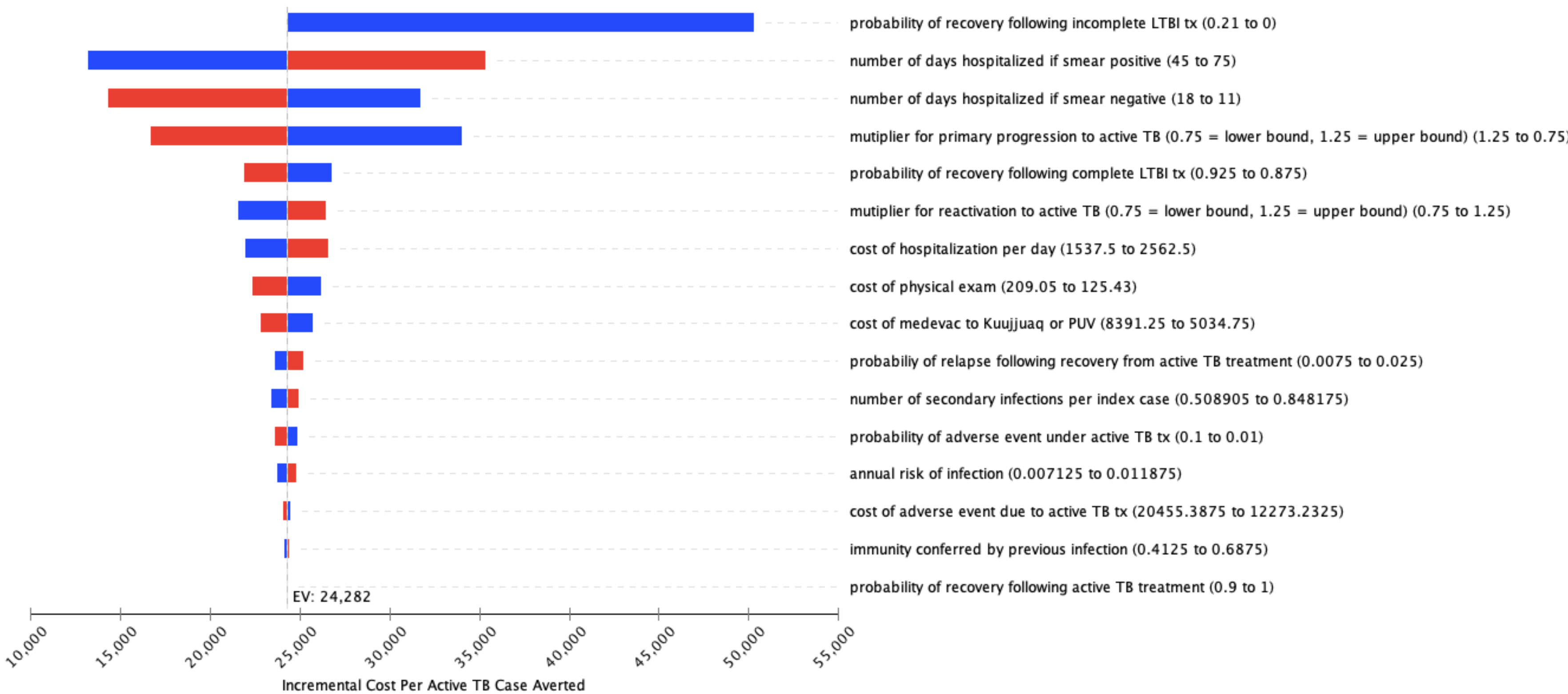

Figure S6. One-way sensitivity analysis for incremental cost per active TB case averted comparing once-off active screening to no active screening given repeated outbreaks, in Village 2. Red = high value of parameter; Blue = low value of parameter. Because parameters for progression and reactivation were changing over time, a “multiplier” was included in one-way sensitivity analysis (multiplier = 1 in the base case).

Results: Probabilistic Sensitivity Analyses

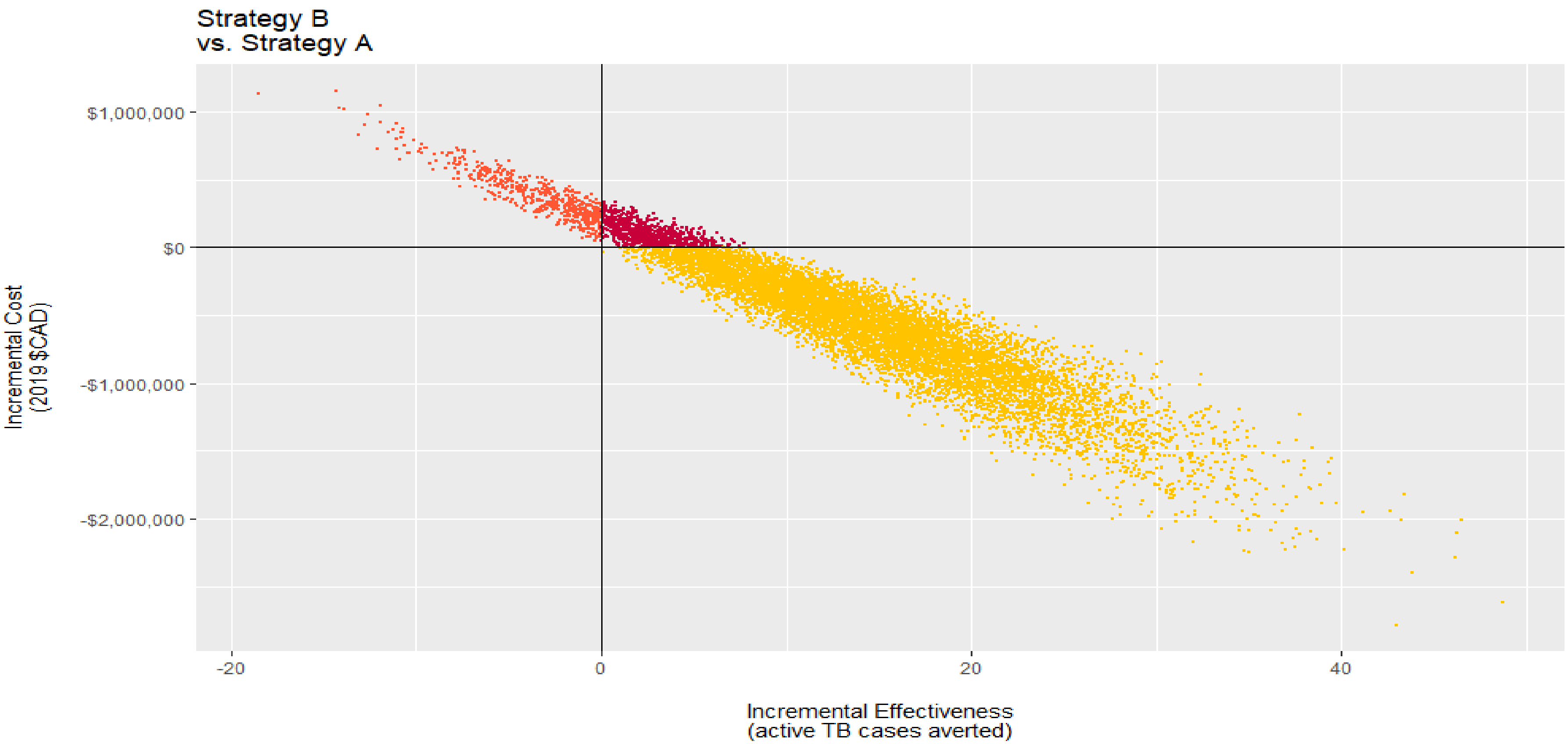

Figure S7. Probabilistic sensitivity analysis for Village 1 given a single outbreak. Each data point represents an incremental cost per active TB case averted comparing Strategy B (one round of active screening) to Strategy A (no active screening) given a single outbreak in 2019. There are 10,000 data points. The solid black lines divide the four quadrants of the cost-effectiveness plane: the upper left (Strategy B is more costly and less effective than Strategy A, i.e. B is dominated by A; points shown in orange); the upper right (Strategy B is more costly and more effective than Strategy A; points shown in red); the lower right (Strategy B is less costly and more effective than Strategy A, i.e. B dominates A; points shown in yellow); the lower left (Strategy

B is less costly and less effective than Strategy A); Moving clockwise from the upper left quadrant, the proportions of simulations in each quadrant are: 5%, 8%, 86%, and 0%.

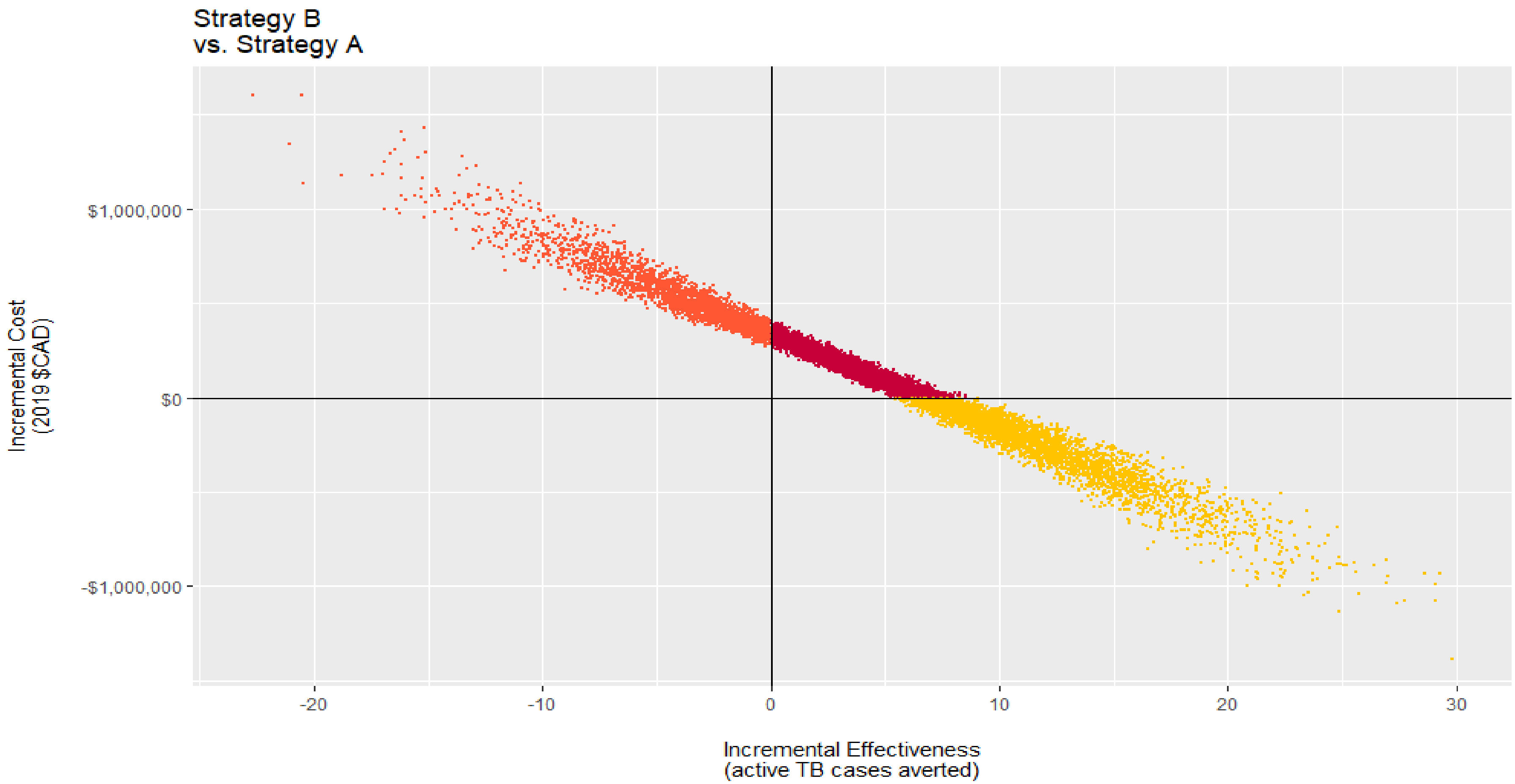

Figure S8. Probabilistic sensitivity analysis for Village 2 given a single outbreak. Each data point represents an incremental cost per active TB case averted comparing Strategy B (one round of active screening) to Strategy A (no active screening) given a single outbreak in 2019. There are 10,000 data points. The solid black lines divide the four quadrants of the cost-effectiveness plane: the upper left (Strategy B is more costly and less effective than Strategy A, i.e. B is dominated by A; points shown in orange); the upper right (Strategy B is more costly and more effective than Strategy A; points shown in red); the lower right

(Strategy B is less costly and more effective than Strategy A, i.e. B dominates A; points shown in yellow); the lower left (Strategy B is less costly and less effective than Strategy A); Moving clockwise from the upper left quadrant, the proportions of simulations in each quadrant are: 26%, 36%, 38%, and 0%.

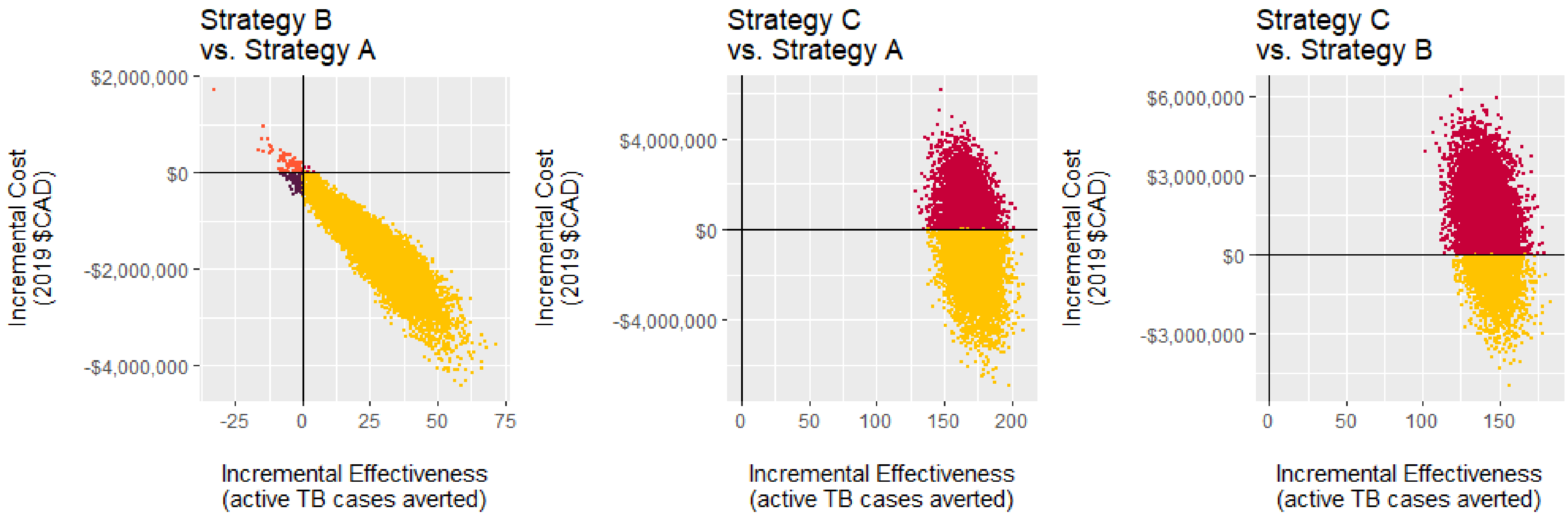

Figure S9. Probabilistic sensitivity analysis for Village 1 given repeated outbreaks. In the graphs from left to right, each data point represents an incremental cost per active TB case averted comparing a) Strategy B (one round of active screening) to Strategy A (no active screening), b) Strategy C (biennial active screening) to Strategy A, and c) Strategy C to Strategy B, all given an outbreak every three years. There are 10,000 data points in each of the three graphs. The solid black lines divide the four quadrants of the cost-effectiveness plane: the upper left (more costly and less effective; points shown in orange); the upper right (more costly and more effective; points shown in red); the lower right (less costly and more effective; points shown in yellow); and the lower left (less costly and less effective; points shown in purple). For Strategy B vs. Strategy A, moving clockwise from the upper left quadrant, the proportions of simulations in each quadrant are: 1%, 0%, 98%, and 1%. For Strategy C vs. Strategy A, moving clockwise from the upper left quadrant, the proportions of simulations in each quadrant are: 0%, 38%, 62%, and 0%. For Strategy C vs. Strategy B, moving clockwise from the upper left quadrant, the proportions of simulations in each quadrant are: 0%, 75%, 25%, and 0%.

Figure S10. Probabilistic sensitivity analysis for Village 2 given repeated outbreaks. In the graphs from left to right, each data point represents an incremental cost per active TB case averted comparing a) Strategy B (one round of active screening) to Strategy A (no active screening), b) Strategy C (biennial active screening) to Strategy A, and c) Strategy C to Strategy B, all given an outbreak every three years. There are 10,000 data points in each of the three graphs. The solid black lines divide the four quadrants of the cost-effectiveness plane: the upper left (more costly and less effective; points shown in orange); the upper right (more costly and more effective; points shown in red); the lower right (less costly and more effective; points shown in yellow); and the lower left (less costly and less effective). For Strategy B vs. Strategy A, moving clockwise from the upper left quadrant, the proportions of simulations in each quadrant are: 25%, 37%, 37%, and 0%. For Strategy C vs. Strategy A, moving clockwise from the upper left quadrant, the proportions of simulations in each quadrant are: 0%, 100%, 0%, and 0%. For Strategy C vs. Strategy B, moving clockwise from the upper left quadrant, the proportions of simulations in each quadrant are likewise: 0%, 100%, 0%, and 0%.

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