

Innovative Timing Strategies for Tuberculosis Household Contact Investigation: Cost-Effectiveness Analysis from a Randomized Trial in Rural and Urban South Africa (Kharituwe Study)

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## Supplementary Appendix

### Time and Motion

Time and motion (TAM) data was collected to assess all field-based activities conducted by study personnel at both rural and urban sites, spanning from their arrival at the study office to the conclusion of their activities and departure from the office.

During each observation day, either the observing intern or self-reporting staff member recorded start and end times for each discrete activity they completed. Times and activities were recorded in a continuous manner with no time gaps between activities. The daily TAM forms also captured information regarding the total number of hours the staff member worked that day in order to calculate the percentage of their workday that was observed.

Each site was asked to complete ten TAM forms during both standard and novel visits for an anticipated 20 forms per site and 40 forms in total. Novel visit days to be observed were specified in collaboration between study coordinators as they required completion during specified times during the year (for holiday visits) or specific days (for evening/weekend visits). Completed forms were recorded using an Android-based tablet or phone and saved directly in REDCap, while optional paper forms were transferred by a data manager into the same REDCap project.<sup>1,2</sup> The data validation process involved assessment of each TAM form, based on the completeness and adherence to the time and activity reporting guidelines provided. Feedback and quality reports were given to local study coordinators and staff over the observation period. Any data discrepancies were resolved by two independent reviewers reviewing the original data. Observed times, both in total and broken down per day, were calculated and assessed for both sites separately. TAM results are presented in Supplementary Table 1.

On average, there were twice as many households visited per day in urban Soshanguve compared to rural Limpopo. Additionally, the mean travel time between homes in rural Limpopo was greater than the mean travel time in urban Soshanguve at 3·8 and 3·24 hours, respectively.

### DALYs Averted

Our calculation of TB-attributable DALYs is presented below. Since the main Kharitwe study did not include long-term patient follow-up data, we assumed each patient diagnosed with TB experienced one year with disability. Additionally, an age-specific probability of mortality was applied to {2} to estimate the fraction of people with incident TB who would die of TB. This probability of TB mortality is derived from the observed TB mortality within the population of South Africa.<sup>3</sup> Additionally, we applied a 3% annual discount rate to our calculations.<sup>4</sup>

$$YLD = (\text{disability weight}) * \left(\frac{1}{0.03}\right) * (1 - e^{(-0.03 * \text{years lived with disability})}) \{1\}$$

$$YLL = \left[ (e^{(-0.03 * \text{years lived with disability})}) * \left(\frac{1}{0.03}\right) * (1 - e^{(-0.03 * \text{years of life lost})}) \right] * (\text{TB Mortality Rate}) \{2\}$$

$$\text{DALYs averted} = YLD + YLL \{3\}$$

### Cost-Effectiveness Threshold

The cost-effectiveness threshold used in this analysis is based on estimates by Edeka and Stacey, who aimed to capture the health opportunity cost of healthcare spending in South Africa. Their approach explicitly considers the trade-offs involved in resource allocation decisions under constrained health budgets.

Edeka and Stacey define the cost-effectiveness threshold as 1% of total health expenditure by the number of DALYs averted:

$$\text{Cost per DALY averted}_t = \frac{1\% \times \text{total health spending}_t}{\text{DALYs averted}_t} \{4\}$$

This calculation illustrates that the cost per DALY averted is influenced by the size of the health budget, increasing or decreasing in proportion to changes in total healthcare spending.<sup>9</sup> By incorporating year-specific data on health expenditure, mortality, and morbidity, the estimate remains relevant to South Africa's economic and healthcare context.

The resulting threshold, \$3,015 per DALY averted, is approximately 53% of South Africa's GDP per capita in 2015. This percentage is less than the World Health Organization (WHO) recommended thresholds of one to three times GDP per capita.<sup>9</sup> It is a pragmatic benchmark given the country's budgetary constraints and health spending levels, offering a cost-effectiveness threshold that is both evidence-based and contextually appropriate.

## Sensitivity Analysis

Supplementary Table 2 provides an overview of the parameter values and assumptions used in all sensitivity analyses. For all sensitivity analyses, TB prevalence was varied by  $\pm 25\%$  of its base value. All cost related parameter values and years living with TB were varied by  $\pm 50\%$  of the base value. The range for age-specific probability of TB mortality was varied by  $\pm 15\%$  of the base value.

## Results

Over the Kharituwe study intervention period from September 2020 to August 2023, 3,145 eligible index individuals were approached for enrollment in rural Limpopo, with a response rate of 64% (n = 2,001). In urban Soshanguve, 3,010 individuals were approached, with 80% (n = 2,416) successfully enrolled. In Limpopo, at least one household contact person was screened for 877 of 1335 (65.7%) index participants in the standard arm versus 379 of 666 (56.9%) in the novel (holiday) arm. In Soshanguve, corresponding screening success was 742 of 1612 (46%) in the standard arm and 282 of 804 (35.1%) in the novel (off-peak) arm. Additionally, in Limpopo, 1.6 secondary TB diagnoses per 100 index participants were made in the standard arm versus 1.2 per 100 in the holiday arm (difference: 0.2 [95% CI: -6.2, 1.5], p=0.4). In Soshanguve, 2.4 secondary TB diagnoses per 100 index participants with TB were made in the standard arm, versus 2.1 per 100 in the off-peak arm (difference: 0.3 [95% CI: -9.4, 1.6], p=0.6).

Supplementary Table 3 presents a summary of outcomes collected during January to December 2022, separated by site and strategy arm. Over the one-year analysis period (2022), there were 1,175 index participants enrolled in rural Limpopo and 941 enrolled in urban Soshanguve. In Limpopo, 69.6% of contact persons (n = 1,375) in the standard arm and 71.2% (n = 505) in the novel arm provided a sputum specimen, versus 96.8% (n = 639) and 97.9% (n = 237) in urban Soshanguve. Moreover, among the 1,880 contact persons able to provide sputum in rural Limpopo, 16 had a confirmed TB diagnosis, whereas in urban Soshanguve, 22 out of 876 contact persons were diagnosed with confirmed TB.

Supplementary Table 4 summarizes the characteristics of successfully enrolled participants in 2022, stratified by site and strategy arm. In rural Limpopo, the median age of enrolled index participants was 42 years (IQR: 32, 52) in the standard arm and 41 years (32, 54) in the holiday arm. Among contact persons, the median age was 18 years (6, 37) in the standard arm and 17 years (6, 37) in the holiday arm – reflecting the higher proportion of children and adolescents in rural households. In urban Soshanguve, the median age of enrolled index participants was 41 years (32, 54) in the standard arm and 44 years (34, 54) in the off-peak arm. Moreover, the median age of contact persons was 33 years (20, 54) in the standard arm and 29 years (17, 47) in the off-peak arm.

The distribution of sex among enrolled index participants was similar across study arms. In rural Limpopo, males comprised 56.5% (n = 441) of the standard arm and 57.1% (n = 225) of the holiday arm. In urban Soshanguve, the standard arm included 63.3% (n = 397) males, while the off-peak arm had a lower proportion at 57.6% (n = 181). Among household contacts, females were the majority in all study arms. In rural Limpopo, males accounted for 37.7% (n = 745) in the standard arm and 39.6% (n = 281) in the holiday arm. Similarly, in the urban setting, males comprised 36.7% (n = 242) in the standard arm and 36% (n = 87) in the off-peak arm.

We also observed differences in the proportion of contact persons with a current cough that produced sputum between settings. In rural Limpopo, 17.2% (n = 340) of contact persons in the standard arm and 15.7% (n = 111) in

the holiday arm reported a current cough. In urban Soshanguve, 6·5% (n = 43) and 5·8% (n = 14) of contact persons reported a current cough in the standard and off-peak arms, respectively.

### *Estimated Cost of Each Strategy*

Supplementary Table 5 presents a summary of our programmatic and non-programmatic cost estimates derived from our budgetary review. Given the higher number of contact persons in the standard strategy arms, a correspondingly greater percentage of the total cost was assigned to the standard strategy arm in both settings. Respective to programmatic costs, the estimated cost of standard contact investigation in rural Limpopo was US\$109,700 compared to US\$61,400 under the holiday strategy. Similarly, the estimated cost of the standard strategy in urban Soshanguve was US\$53,100 compared to US\$30,700 under the off-peak strategy. Personnel and travel costs were the main drivers of the estimated cost of each strategy across both settings.

### *Two-Way Sensitivity Analysis Results: Personnel Costs and TB Prevalence*

A two-way sensitivity analysis was conducted to examine the interaction between personnel costs and TB prevalence, providing insights into how resource investment impacts disease burden and inform resource allocation decisions. Each contour plot illustrates how the ICER estimate (\$/DALY averted) varies across different levels of TB prevalence and personnel costs. As personnel costs increase, total costs also rise, reflecting the higher expenditure on human resources. Meanwhile, as TB prevalence increases, the number of DALYs averted also tends to increase. These plots show that the most cost-effective scenarios appear in the top left corner, corresponding to high TB prevalence and low personnel costs.

The steeper contour lines observed in the urban plots (Figure 1b) indicate that ICER estimates in urban settings are more sensitive to changes in TB prevalence and personnel costs compared to rural settings. In urban areas, small fluctuations in either parameter led to large shifts in ICER estimates, suggesting that personnel costs play a dominant role in driving total costs. In rural settings, both personnel and travel costs are key cost drivers.

### *Probabilistic Sensitivity Analysis (PSA) Results: Novel versus Standard Strategies*

The initial objective of our analysis was to depict the novel and standard strategies in a competitive framework, aligning with the approach adopted in the primary Kharituwe study. However, our primary findings in Table 3 suggest that contact investigation during regular working hours is likely to be more cost-effective than holiday-based and off-peak contact investigation. Supplementary Figure 2 illustrates the outcomes of our PSA comparing the novel and standard household investigation strategies in both settings.

In rural Limpopo, 2·5% of simulations resulted in positive ICER estimates (i.e., suggesting that holiday-based contact investigation was more costly and more effective than standard contact investigation); only 0·4% of these simulations fell below South Africa's cost-effectiveness threshold of US\$3015 per DALY averted. In urban Soshanguve, positive ICER estimates were observed in 33·1% of iterations, with 18·8% falling below the cost-effectiveness threshold. All negative ICER estimates were associated with higher costs and lower effectiveness for the novel strategies.

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## Supplementary Tables

**Supplementary Table 1: Time and motion data**

	Rural Limpopo	Urban Soshanguve	Overall
<b>Hours per day observed, mean (SD)</b>	8.99 (2.06)	8.66 (1.14)	8.83 (1.66)
Hours of travel, mean (SD)	3.8 (1.5)	3.24 (0.64)	3.53 (1.19)
Hours of household visits, mean (SD)	2.23 (1.42)	2.99 (1.25)	2.57 (1.38)
Hours of admin activities, mean (SD)	2.36 (1.38)	1.29 (0.75)	1.84 (1.23)
Hours of other* activities, mean (SD)	0.67 (0.67)	1.48 (1.22)	1.09 (1.06)
<b>Households visited per day, mean (SD)</b>	2.1 (1.3)	4.2 (1.6)	3 (1.8)
Minutes of travel per visit, median (IQR)	129 (71.3-188.5)	49 (36.94-77.92)	76 (49.4-173.5)
Minutes at household per visit, median (IQR)	60.5 (41.5-91.5)	41.9 (34.2-59.1)	55.8 (38.75-71.83)

Abbreviations: SD, standard deviation, IQR, interquartile range.

\* Follow-up, lab/sputum collection, recruitment, other

**Supplementary Table 2: Model Parameters Used in the Base Case Analysis and Distributions Used for the Sensitivity Analyses**

Parameter	Base Value	Range for Sensitivity Analysis	Distribution	Reference
Personnel programmatic costs (rural)	\$88,000	\$44,000 – \$132,000	Gamma	Calculated
Personnel programmatic costs (urban)	\$76,200	\$38,100 – \$114,300	Gamma	Calculated
Travel programmatic costs (rural)	\$77,300	\$38,700 – \$116,000	Gamma	Calculated
TB Prevalence*				
Standard (rural)	0.9%	0.7% – 1.1%	Beta	[5,6,7]
Holiday (rural)	0.8%	0.6% – 1.0%		
Standard (urban)	2.4%	1.8% – 2.9%		
Off-Peak (urban)	3.0%	2.2% – 3.7%		
Years living with TB	1	0.5 – 1.5	Gamma	Assumed
TB disability weight	0.33	0.22 – 0.45	Beta	[8]
TB probability of mortality			Beta	[3]
0-4	8.4%	7.1% – 9.7%		
5-14	4.7%	3.4% – 5.4%		
15-24	5.5%	4.7% – 6.3%		
25-54	13.8%	11.7% – 15.9%		
55-74	15.7%	13.4% – 18.1%		
75+	23.3%	19.8% – 26.8%		

Abbreviations: TB, tuberculosis.

\* TB prevalence is based on the number of contact persons diagnosed with TB in the main Kharituwe study during 2022.

**Supplementary Table 3: Summary of participant outcomes in rural Limpopo and urban Soshanguve, South Africa (2022)**

	Rural Limpopo			Urban Soshanguve		
	Standard	Novel	Total	Standard	Novel	Total
<b>Index Patients</b>						
Index patients enrolled*	781 (66·5%)	394 (33·5%)	1,175	627 (66·6%)	314 (33·4%)	941
Mode of diagnosis						
Xpert	201 (25·7%)	113 (28·7%)	314 (26·7%)	292 (46·6%)	138 (44·0%)	430 (45·7%)
Smear	18 (2·3%)	7 (1·8%)	25 (2·2%)	2 (0·3%)	2 (0·6%)	4 (0·4%)
Culture	4 (0·5%)	1 (0·2%)	5 (0·4%)	2 (0·3%)	2 (0·6%)	4 (0·4%)
Chest x-ray	558 (71·5%)	273 (69·3%)	831 (70·7%)	331 (52·8%)	172 (54·8%)	503 (53·5%)
<b>Contact Persons</b>						
Contact persons enrolled*	1,976 (73·6%)	709 (26·4%)	2,685	660 (73·2%)	242 (26·8%)	902
Able to provide sputum	1,375 (69·6%)	505 (71·2%)	1,880 (70·0%)	639 (96·8%)	237 (97·9%)	876 (97·1%)
Confirmed positive TB diagnosis among contact persons able to provide sputum	12 (0·9%)	4 (0·8%)	16 (0·9%)	15 (2·4%)	7 (3·0%)	22 (2·5%)

Abbreviations: TB, tuberculosis.

\*Randomization of enrolled index patients occurred using an allocation ratio of 2 (standard strategy): 1 (novel strategy).

**Supplementary Table 4: Characteristics of participants successfully enrolled in rural Limpopo and urban Soshanguve, South Africa (2022)**

	Rural Limpopo		Urban Soshanguve	
	Standard	Novel	Standard	Novel
<b>Index Patients</b>	N = 781	N = 394	N = 627	N = 314
Male sex	441 (56.5%)	225 (57.1%)	397 (63.3%)	181 (57.6%)
Median age in years (IQR)	42 (32, 52)	41 (32, 54)	41 (32, 54)	44 (34, 54)
Median household size (IQR)	3 (2, 5)	3 (1, 5)	2 (1, 2)	2 (1, 3)
Occupation				
Employed / student	213 (27.3%)	106 (26.9%)	151 (24.1%)	84 (26.8%)
Retired/school-age minor	144 (18.4%)	78 (19.8%)	128 (20.4%)	76 (24.2%)
Unemployed	402 (51.5%)	196 (49.7%)	347 (55.3%)	154 (49.0%)
Critically ill / deceased / missing	22 (2.8%)	14 (3.6%)	1 (0.2%)	0 (0.0%)
<b>Contact Persons</b>	N = 1,976	N = 709	N = 660	N = 242
Male sex	745 (37.7%)	281 (39.6%)	242 (36.7%)	87 (36.0%)
Median age in years (IQR)	18 (6, 37)	17 (6, 37)	33 (20, 54)	29 (17, 47)
Current cough	340 (17.2%)	111 (15.7%)	43 (6.5%)	14 (5.8%)
Occupation				
Employed / student	772 (39.1%)	318 (44.8%)	252 (38.2%)	99 (40.9%)
Retired/school-age minor	629 (31.8%)	221 (31.2%)	133 (20.1%)	45 (18.6%)
Unemployed	574 (29.0%)	170 (24.0%)	275 (41.7%)	98 (40.5%)
Critically ill / deceased / missing	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Abbreviations: IQR, interquartile range.				

**Supplementary Table 5: Summary of programmatic and non-programmatic cost estimates of household contact investigation for tuberculosis in South Africa, 2022 US dollars**

Category	Rural Limpopo		Urban Soshanguve	
	Programmatic Costs	Non-Programmatic Costs	Programmatic Costs	Non-Programmatic Costs
<b>Total*</b>				
Total	\$171,100	\$103,400	\$83,800	\$73,400
Standard	\$109,700	\$66,300	\$53,100	\$46,500
Novel	\$61,400	\$37,100	\$30,700	\$26,900
<b>Personnel</b>				
Total	\$88,000	\$57,900	\$76,200	\$53,500
Standard	\$56,400	\$37,100	\$48,300	\$33,900
Novel	\$31,600	\$20,800	\$27,900	\$19,600
<b>Training</b>				
Total	\$470	\$470	\$470	\$470
Standard	\$300	\$300	\$300	\$300
Novel	\$170	\$170	\$170	\$170
<b>Travel</b>				
Total	\$77,300	\$1,800	\$4,900	..
Standard	\$49,600	\$1,100	\$3,100	..
Novel	\$27,700	\$700	\$1,800	..
<b>Other/Operational**</b>				
Total	\$5,300	\$43,200	\$2,300	\$19,400
Standard	\$3,400	\$27,700	\$1,500	\$12,300
Novel	\$1,900	\$15,500	\$800	\$7,100

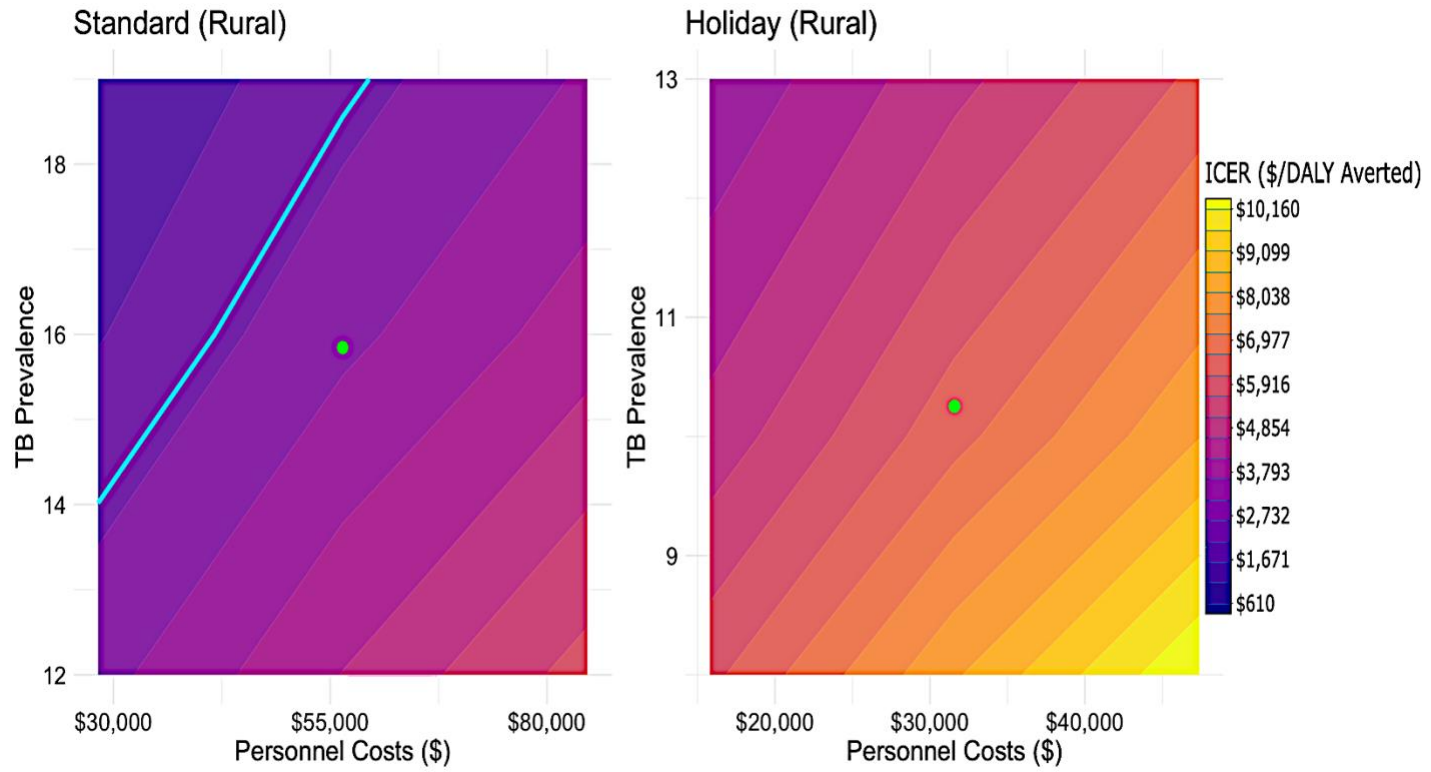
\*The number of index participants allocated to the standard strategy was twice as great as the number allocated to the novel strategy (holiday-based investigation in rural Limpopo and off-peak investigation in urban Soshanguve).

\*\*Other/Operational costs include building and clinic expenses, utilities, consumables, IT support, computer expenses, telecommunications, stationery and printing expenses, and translations.

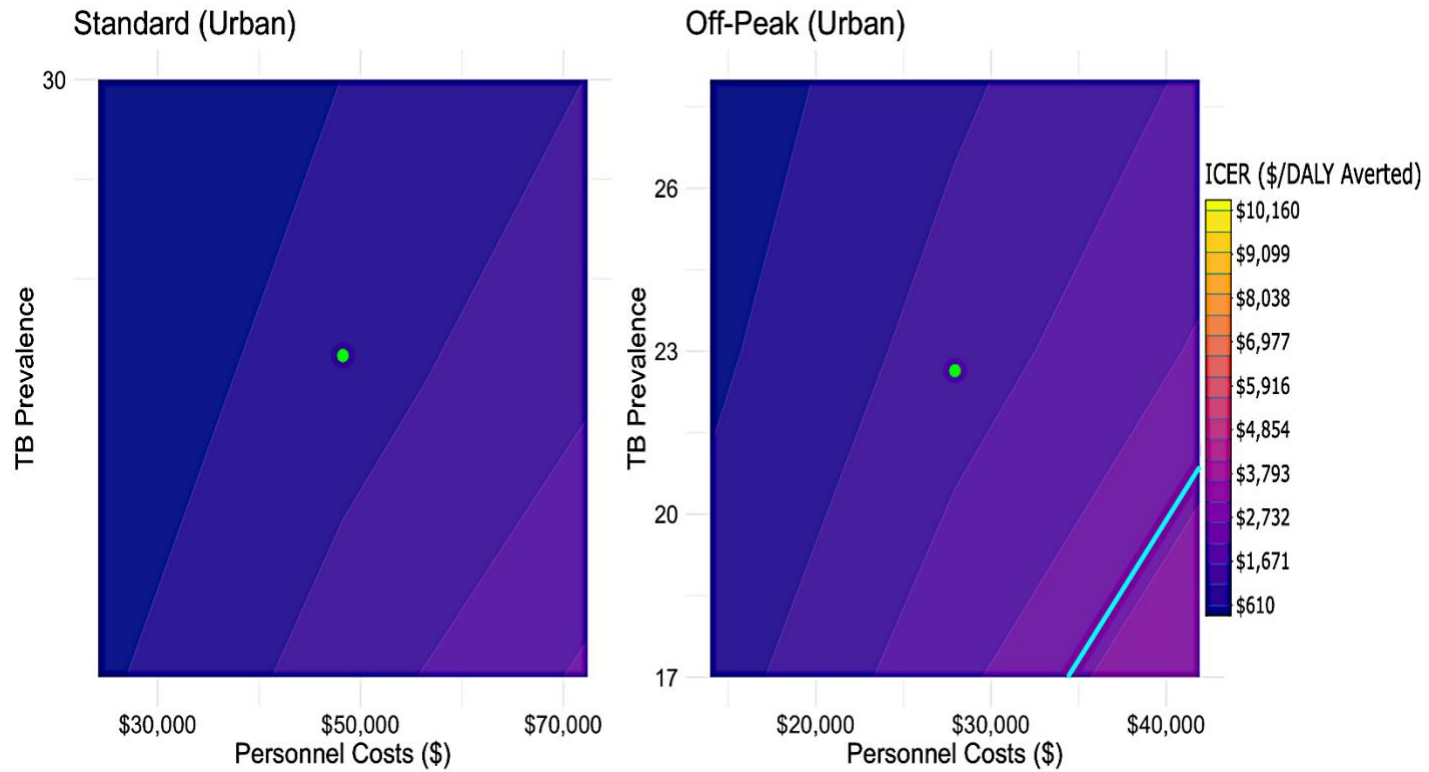
## Supplementary Figures

### Supplementary Figure 1: Impact of Personnel Costs and TB Prevalence on Cost-Effectiveness Outcomes

**Figure 1a: Rural Setting**

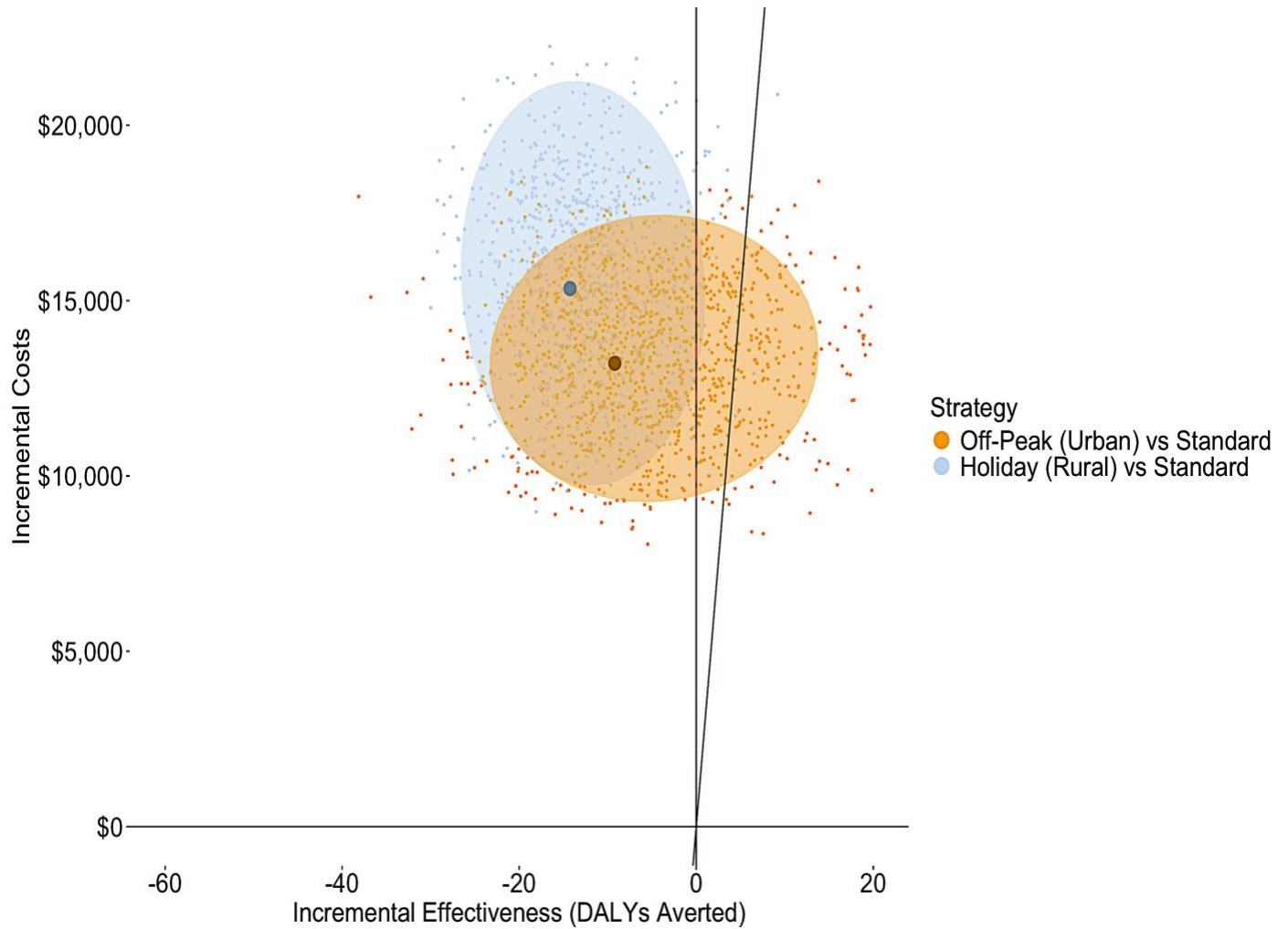


**Figure 1b: Urban Setting**



These contour plots illustrate the results of a two-way sensitivity analysis, examining arm- and site-specific personnel costs in relation to TB prevalence (secondary cases per 1,000 index individuals with TB). The x-axis represents personnel costs, while the y-axis represents TB prevalence. The color gradient corresponds to incremental cost-effectiveness ratio (ICER) estimates- darker shades indicate lower ICERs (i.e., more cost-effective scenarios), whereas lighter shades indicate higher ICERs (i.e., less cost-effective scenarios). A solid cyan line denotes South Africa’s cost-effectiveness threshold of US\$3,015 per disability-adjusted life year (DALY) averted; scenarios with ICERs below this threshold are considered cost-effective (i.e., darker shades).<sup>9</sup> There is no solid cyan line in the Holiday (Rural) plot in Figure 1a because all ICER estimates are not cost-effective and substantially exceed the cost-effectiveness threshold. In contrast, there is no solid cyan line in the Standard (Urban) plot in Figure 1b, given all ICER estimates for standard contact investigation in urban Soshanguve are cost-effective and fall well below the cost-effectiveness threshold. The base-case ICER estimate for each strategy is also included as a green dot. All costs are reported in 2022 US dollars.

**Supplementary Figure 2: Cost-Effectiveness Scatterplots Comparing Standard and Novel TB Contact Investigation Strategies**



These cost-effectiveness scatterplots were generated by running 1,000 simulations in a probabilistic sensitivity analysis. Each point on the scatter plot represents an iteration of the simulation, with the corresponding incremental cost-effectiveness ratio (ICER) estimate comparing the strategy of interest to a hypothetical no contact investigation approach. The base-case ICER estimate for each strategy compared to a hypothetical no contact investigation approach is also included as a dark circle toward the center of each ellipse. The estimated country-specific cost-effectiveness threshold for South Africa (US\$3015 per disability-adjusted life year averted) is shown as a diagonal line.<sup>9</sup> Points falling below the cost-effectiveness threshold are considered cost-effective. Costs are reported in 2022 US dollars.