Innovative timing strategies for tuberculosis household contact investigation: cost-effectiveness analysis from a randomized trial in rural and urban South Africa (Kharituwe Study)

Neenah Young,[a,g,*] Patrick Biché,[a] Mbali Mohlamonyane,[b] Matshidiso Morolo,[c] Babalwa Maholwana,[c] Khatija Ahmed,[c,d,e] Neil Martinson,[b,f] Colleen F. Hanrahan,[a] and David W. Dowdy[a]

[a]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
[b]Perinatal HIV Research Unit (PHRU), University of the Witwatersrand, Johannesburg, South Africa
[c]Setshaba Research Centre, Tshwane, Soshanguve, South Africa
[d]Department of Medical Microbiology, School of Medicine, Faculty of Health Sciences, University of Pretoria, South Africa
[e]Department of Paediatrics & Child Health, School of Clinical Medicine, University of the Witwatersrand, Johannesburg, South Africa
[f]Johns Hopkins University Center for TB Research, Baltimore, MD, USA

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Summary

Background Household contact investigation (HCI) for tuberculosis (TB) is recommended but often limited by resource constraints, particularly for individuals unavailable during business hours.

Methods We conducted an economic evaluation from January 1, 2022, through December 31, 2022, nested within a randomized trial in South Africa ("Kharituwe") comparing standard HCI for TB and two novel strategies: HCI during holiday periods in a rural setting and off-peak HCI during weekends and evenings in an urban setting. Costs were derived from 2022 expenditures, and secondary TB cases were defined by positive sputum cultures. As a secondary outcome of the Kharituwe Study, we assessed the incremental cost-effectiveness ratio (ICER) of each strategy against a hypothetical no-HCI scenario from the health system perspective in 2022 US dollars. Cost-effectiveness was assessed using a country-specific willingness-to-pay threshold of US$3015 per disability-adjusted life year (DALY) averted. The trial is registered with clincaltrials.gov (NCT04520113).

Findings Relative to a hypothetical no-HCI approach, standard HCI was estimated to cost US$1400 [95% uncertainty interval (UI): $1000–$2100] per DALY averted in the urban setting and US$3600 [95% UI: $2500–$5400] in the rural setting. Corresponding cost-effectiveness ratios were US$1900 [95% UI: $1300–$2800] for off-peak (urban) and US$6400 [$3900–$10,000] for holiday-based (rural) HCI. Personnel costs, travel costs (in the rural setting), and TB prevalence among contact persons were primary drivers of cost-effectiveness.

Interpretation HCI for TB is likely cost-effective in urban South Africa and may be cost-effective in rural settings, which face barriers including long travel times and lower TB prevalence. Holiday-based HCI was not found to be cost-effective. Integrating HCI for TB into broader home-based interventions may improve cost-effectiveness.

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Keywords: Tuberculosis; Household contact investigation; South Africa; Economic evaluation

Introduction

Tuberculosis (TB) remains the leading single-agent cause of infectious mortality, causing an estimated 1·3 million deaths in 2022.[1] South Africa has one of the highest TB incidence rates in the world, at 468 per 100,000 population (2022).[2–4]

*Corresponding author. Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, 21205, USA.
E-mail address: nyoung29@jh.edu (N. Young).
[g]First author.

Research in context

Evidence before this study

Past research has indicated that household contact investigation (HCI) for tuberculosis (TB) is broadly recommended and is likely to be cost-effective in low-and middle-income countries (LMICs). However, there is little evidence on the impact and cost-effectiveness of modifying routine HCI to find the additional "missing" cases of TB in high-risk mobile populations of all ages. We searched PubMed for studies of cost-effectiveness of HCI for TB using the search terms ("TB" OR "tuberculosis") AND ("cost-effectiveness" OR "economic evaluation") AND ("contact investigation" OR "contact tracing" OR "contact screening") AND ("household contact" OR "household contacts" OR "contact person" OR "contact persons"). 14 studies were identified that provided estimates of cost-effectiveness of HCI for TB, however, none explicitly evaluated the cost-effectiveness of performing HCI after hours, on weekends, or on holidays.

Added value of this study

To our knowledge, this is the first study to estimate the cost-effectiveness of extending non-routine hours of standard HCI for TB in a high-burden setting, and also the first to provide cost-effectiveness estimates of HCI for TB among contact persons of all ages in South Africa.

Implications of all the available evidence

HCI for TB during regular working hours is likely to be cost-effective in both urban and rural South Africa, as well as many other settings. In urban settings, off-peak (evening/weekend) contact investigation may be cost-effective for individuals not reachable during standard business hours. These results provide additional support for the scale-up of HCI for TB (including to rural locations), consideration of additional flexibility regarding timing in urban settings, and integration of HCI for TB into broader home-based interventions.

Individuals living in the same household as someone diagnosed with TB ("contact persons") have a high prevalence of both TB disease (often 3% or higher) and latent TB infection (LTBI) (often over 40%)—much of which represents recent infection.[5] Evaluating these individuals for TB ("household contact investigation") is highly effective in high-burden settings and has been recommended by the World Health Organization (WHO) for over a decade.[5–8] Effective household contact investigation identifies previously undiagnosed cases of TB among the contacts of an index patient who share the same enclosed living space.[6]

Although household contact investigation (HCI) for TB is widely recommended, uptake and implementation are often poor, especially in low- and middle-income countries (LMICs).[6,9] One barrier to effective HCI is that many contact persons are not regularly at home during standard business hours due to work commitments, educational responsibilities, and other obligations.[10,11] As a result, many individuals who are at highest risk of TB (e.g., young working men) may be missed by HCI that is performed only during standard hours.[12,13] Another major barrier is the resource requirements for TB contact investigation. While models have suggested that TB contact investigation is likely to be cost-effective, it remains uncertain whether the additional cost of enhancements to standard contact investigation—such as extending non-routine hours—would also be cost-effective, especially for individuals who would otherwise not be reached without such enhancements.[14]

To evaluate the effectiveness of TB contact investigation beyond regular business hours, we performed a randomized trial ("Kharituwe") in South Africa that examined two innovative approaches to TB contact investigation compared to a standard strategy: holiday-based in a rural setting and off-peak (evening/weekend) contact investigation in an urban setting.[15] We hypothesized that holiday-based contact investigation might be more effective in the rural context, given typical patterns of travel in Africa where individuals visit their families in rural settings such that larger numbers of contact persons might be available during those times.[16] By contrast, the off-peak strategy was designed to target mobile groups, such as working young-adult men, who often travel to urban centers for employment and also have disproportionately high risk of TB.[13,17] Here, we evaluate the costs and cost-effectiveness of these HCI approaches.

Methods

Setting

The Kharituwe Study was a randomized trial conducted in 45 clinics and hospitals across two regions of South Africa—one in Soshanguve, an urban township outside of Tswhane in Gauteng Province (TB incidence: 330 per 100,000 population), and the second in two districts of rural Limpopo Province (TB incidence: 301 per 100,000 population).[15,18] In rural Limpopo, individuals diagnosed with TB were randomized to standard HCI conducted weekdays between 08:00 and 16:00, versus a holiday-based strategy in which contact investigation was delayed until holiday periods. Households were visited on weekdays during four approximately two-week holiday periods: New Years, Easter, Heritage Day (September 24), and Christmas. In urban Soshanguve, people diagnosed with TB were randomized to standard or off-peak (after 16:00 and weekends) contact investigation.

Index participants were consecutive consenting individuals diagnosed with pulmonary TB through microbiological testing and/or chest X-ray. In rural Limpopo Province, index patients with TB were identified from 12 hospitals located in the Vhembe and Capricorn Districts. In urban Soshanguve, they were identified from 33 primary health care clinics and two district hospitals. Randomization was computer-generated random-permuted blocks of varying sizes, with an allocation ratio of 2 (standard strategy): 1 (novel strategy) using separate randomization sequences for each site.[15]

Data collection

Each consenting contact person was screened for TB, and sputum was collected for testing via liquid mycobacterial growth indicator tube (MGIT, BD Diagnostics, Sparks, MD, USA) culture at the National Institute for Communicable Diseases (NICD) TB Reference Laboratory. Culture results were monitored by study staff. If *M. tuberculosis* was detected on MGIT culture, participants were notified by either phone or an in-person household visit and were subsequently referred to the nearest public-sector clinic for treatment. Reflective of the Kharituwe Study protocol (in which culture was performed instead of Xpert Ultra), we defined a contact person with TB as a positive MGIT culture from a household member of an index participant.[15]

In both rural Limpopo and urban Soshanguve, the intervention period of the Kharituwe Study lasted from September 2020 to August 2023. Enrollment was disrupted by the COVID-19 pandemic. Therefore, for this analysis, we analyzed cost and effectiveness data (described below) from January 1, 2022, through December 31, 2022 (years two to three of enrollment) representing post-pandemic procedures at full capacity.

Budget review

We first performed a complete review of aggregate actual expense data over a full calendar year (2022). Aggregate costing data was separated by month from both sites and collected at the end of study enrollment. All costs from the budgetary review were categorized into five categories: personnel, training, travel, laboratory, and other/operational. All costs were evaluated from the health system perspective and converted to 2022 US dollars (USD) using the mid-year South African Rand (ZAR)-USD exchange rate.[19]

Time and motion

A time and motion (TAM) assessment of all field-based activities was conducted by study personnel at both sites. We developed a standardized time reporting form based on discussion with local study coordinators, staff, and pilot testing in the field. Direct observation of activities was performed from October 2022 to January 2023 (to cover a full holiday period). Key activities were categorized into four categories: travel, household visits, administrative tasks, and other activities.

In urban Soshanguve, all study staff received training to self-report TAM data; in rural Limpopo Province, one staff member was trained to perform TAM observation throughout the observation period. TAM data were used to estimate the following quantities: 1) total duration of a typical workday in carrying out household visits, 2) median unit time for key activities carried out by staff (travel and household visit time), and 3) mean number of households visited in a typical workday. TAM results are given in Supplementary Table S1.

Analysis

Programmatic costs

Our objective in estimating costs was to evaluate the likely cost of various activities if implemented programmatically rather than during a trial. Non-programmatic (i.e., research-related only) expenses refer to costs that were incurred specifically for conducting this study and are unlikely to be relevant if these strategies were implemented in other settings. Since this study was conducted as a clinical trial, additional research-related costs were incurred, such as those for study design, protocol development, ethics approvals, specialized staff training for research protocols, data collection and management systems, and monitoring and evaluation processes specific to the trial. These expenses are unique to the research setting and do not reflect the typical costs of implementing these strategies in routine practice. As a result, they were excluded from the cost-effectiveness analysis to ensure the findings are applicable to real-world programmatic implementation.

Since our aggregated cost data did not distinguish between programmatic and non-programmatic expenses, we collaborated with study staff to estimate the fraction of each unit cost attributed to either programmatic or non-programmatic activities. For costs deemed not fully programmatic or fully non-programmatic, we allocated percentages according to the cost type. Telecommunications, data, computers, and information technology costs were assumed to be 25% programmatic. Rent, building expenses, and printing were assumed to be 10% programmatic while utility costs were assumed to be 50% programmatic. We assumed that study coordinator activities were 25% programmatic, whereas other staff activities were 50% programmatic. All travel costs and laboratory costs (which we took as the cost of a single MGIT culture) were considered programmatic.

Programmatic costs were then allocated between arms using the proportion of participants enrolled in each arm (approximating the 2:1 study allocation ratio). To estimate the cost per contact person screened, programmatic costs in each treatment arm were divided by the respective number of consenting contact persons.

Cost-effectiveness calculations

Our primary cost-effectiveness outcome was the incremental cost per TB-attributable disability-adjusted life year (DALY) averted—a pre-specified secondary outcome of the Kharituwe Study. We estimated this outcome for all four strategies (standard and novel, in rural Limpopo and urban Soshanguve), against a hypothetical "no contact investigation" approach and against the alternative strategy in the same location.

Incremental costs were estimated as described above, and incremental effectiveness (incremental number of contacts diagnosed with TB) was estimated directly from trial data. We selected this approach over a more complex modeling approach to minimize the number of assumptions required regarding future outcomes, and to make those assumptions maximally transparent. To convert the measured number of contacts diagnosed with TB into an estimate of DALYs averted, we assumed that all contacts diagnosed with TB experienced one year of TB-related disability.[20] In addition, we applied an age-specific probability of TB mortality to all contacts diagnosed with TB under the assumption that TB-specific mortality among contact persons would resemble that of the general population of South Africa.[21] We then calculated DALYs averted using the Fox-Rushby and Hanson standard (see Supplementary Appendix).[22] Disability weights were taken from the Global Burden of Disease Study 2019 (GBD 2019).[23] We assumed full health (disability weight = 0) for individuals who had negative TB cultures and discounted future costs and effectiveness at 3% annually.[24]

Incremental effectiveness was calculated as the difference in TB-attributable DALYs averted, comparing standard and novel contact investigation to a hypothetical no contact investigation approach. We evaluated effectiveness and cost-effectiveness in the rural and urban sites separately.

This study adhered to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guideline (see Supplemental File).[25]

Sensitivity analysis

To explore key drivers of our cost and effectiveness estimates, we performed a one-way deterministic sensitivity analysis of all model parameters, with results displayed in tornado diagrams. Additionally, we performed a two-way sensitivity analysis to examine the interaction between personnel costs and TB prevalence.

We also conducted a probabilistic sensitivity analysis using a Monte Carlo simulation with 1000 iterations to evaluate uncertainty in our base-case estimates. Gamma distributions were applied to all cost parameters and to years lived with TB. For other parameters, we constructed a beta distribution around the point estimate, with the mean serving as the mode of the distribution and range based on the calculated or given minimum and maximum values for each parameter. Results from our probabilistic sensitivity analysis are presented using cost-effectiveness scatter plots and cost-effectiveness acceptability curves.

For all sensitivity analyses, TB prevalence was varied by ±25% of its base value. All cost related parameter values and years living with TB were varied by ±50% of the base value. The range for age-specific probability of TB mortality was varied by ±15% of the base value. Parameter values and distributions used for the sensitivity analyses are shown in Supplementary Table S2.

Ethical considerations

All participants provided written informed consent. For index participants who were recently deceased or critically ill, proxy consent was obtained from a next of kin. This study was approved by the Human Research Ethics Committee at the University of the Witwatersrand (Ref 190911B) and the Institutional Review Board at the Johns Hopkins Bloomberg School of Public Health (Ref 11124). The trial is registered with clincaltrials.gov (NCT04520113). A Data Safety Monitoring Board was convened for the study. The board met prior to study initiation and annually thereafter to review accumulated data on safety, study progress, and efficacy, and to provide guidance on any necessary protocol modifications.

Role of the funding source

The study funder, the United States National Institute of Allergy and Infectious Diseases (Grant # 5R01AI147681) had no role in the study's design, collection and analysis of the data, the writing of this report, or the decision to submit the paper for publication.

Results

Over the one-year analysis period (2022), in rural Limpopo we enrolled 1175 index participants (781 standard, 394 holiday) for TB contact investigation, resulting in 2685 contact persons screened (1976 standard, 709 holiday). In urban Soshanguve, we enrolled 941 index participants (627 standard, 314 off-peak) and 902 contact persons (660 standard, 242 off-peak) (Supplementary Table S3). In Limpopo, 69·6% of contact persons (n = 1375) 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 (Supplementary Table S3). Age, sex, and employment status were similar between study arms within each site for both index participants and contact persons (Supplementary Table S4).

The total cost of contact investigation in rural Limpopo was US$274,500, with standard investigation costing US$176,000 and holiday-based investigation costing US$98,500. In urban Soshanguve, the total cost was US$157,200, with standard investigation costing US$99,600 and off-peak investigation costing US$57,600. Component costs and a detailed breakdown by

Category	Rural Limpopo		Urban Soshanguve	
	Standard	Holiday	Standard	Off-Peak
Personnel	$28·56	$44·55	$73·12	$115·45
Training	$0·15	$0·24	$0·45	$0·72
Travel	$25·09	$39·12	$4·66	$7·36
Lab costs[a]	$10·41	$10·41	$10·41	$10·41
Other/Operational[b]	$1·71	$2·67	$2·19	$3·46
Total	$65·93	$96·99	$90·84	$137·50

[a]Lab costs reflect the market price of a single liquid MGIT culture; costs of specimen transport are included in travel. [b]Other/Operational costs include building and clinic expenses, utilities, consumables, IT support, computer expenses, telecommunications, stationery and printing expenses, and translations.

Table 1: **Cost per contact person screened for tuberculosis in South Africa, 2022 US dollars.**

programmatic and non-programmatic allocation are presented in Supplementary Table S5.

Cost per contact person screened

In rural Limpopo, standard TB contact investigation was estimated to cost US$65·93 per contact person screened, versus US$96·99 for holiday-based contact investigation (Table 1). Personnel and travel costs were the largest contributors to both total costs and between-arm differences in costs per contact person screened. In urban Soshanguve, we estimated that standard contact investigation cost US$90·84 per contact person screened, versus US$137·50 for off-peak investigation (Table 1). Personnel costs were again the largest component cost; however, travel costs were substantially lower in urban Soshanguve, compared to rural Limpopo [urban Soshanguve: US$4·66 (standard) and US$7·36 (off-peak) versus rural Limpopo: US$25·09 (standard) and US$39·12 (holiday) per contact person screened].

Cost-effectiveness results

To provide comparable estimates across arms, we calculated cost-effectiveness per 1000 index participants traced (Table 2). In rural Limpopo and relative to a hypothetical no contact investigation approach, we estimated that standard contact investigation would cost US$3600 [95% Uncertainty Interval (UI): $2500–$5400] per DALY averted and holiday-based investigation would cost US$6400 [95% UI: $3900–$10,000] per DALY averted. In urban Soshanguve, corresponding estimates were US$1400 [95% UI: $1000–$2100] per DALY averted with the standard strategy and US$1900 [95% UI: $1300–$2800] per DALY averted with the off-peak strategy.

Sensitivity analyses

In the one-way sensitivity analysis, the most important determinants of cost-effectiveness were personnel costs, travel costs (rural Limpopo only), TB prevalence among contact persons, and the age-specific probability of TB mortality (Fig. 1). The two-way sensitivity analysis illustrates the values of TB prevalence and personnel costs under which each strategy might meet thresholds for cost-effectiveness (Supplementary Figure S1).

Probabilistic sensitivity analysis

In rural Limpopo, standard contact investigation was estimated to fall within South Africa's cost-effectiveness threshold in 15·1% of simulations, versus 0% for holiday-based contact investigation.[23] By contrast, in urban Soshanguve, contact investigation was estimated to be cost-effective in 100% of simulations for the standard strategy and in 99% of simulations for the off-peak strategy (Fig. 2). Comparisons of novel versus standard contact investigation are provided in Supplementary Figure S2. In both settings, standard contact investigation was more likely to reach South Africa's country-specific threshold for cost-effectiveness compared to novel (holiday-based or off-peak) contact investigation (Fig. 3).

Discussion

This cost and cost-effectiveness analysis, integrated into a randomized trial in South Africa, suggests that contact investigation for TB is likely to be cost-effective in the urban context. In the rural setting, travel costs were substantially higher, and the number of positive contact persons detected (per 1000 index participants) was lower, such that the incremental cost-effectiveness of standard HCI was near the country-specific threshold for cost-effectiveness used in this study. In both

Treatment arm	Cost	Positive contact persons	Cost per positive contact person	DALYs averted	Cost per DALY averted
Standard (Rural)	$140,500	15	$9100 [$6100–$12,200]	39	$3600 [$2500–$5400]
Holiday (Rural)	$155,800	10	$15,400 [$10,200–$21,300]	25	$6400 [$3900–$10,000]
Standard (Urban)	$84,700	24	$3500 [$2400–$4700]	61	$1400 [$1000–$2100]
Off-Peak (Urban)	$97,900	22	$4400 [$2900–$6100]	51	$1900 [$1300–$2800]

Abbreviation: DALY, disability-adjusted life year.

Table 2: **Cost and cost-effectiveness of household contact investigation per 1000 index individuals with tuberculosis in South Africa, relative to a hypothetical no contact investigation approach (2022 US dollars).**

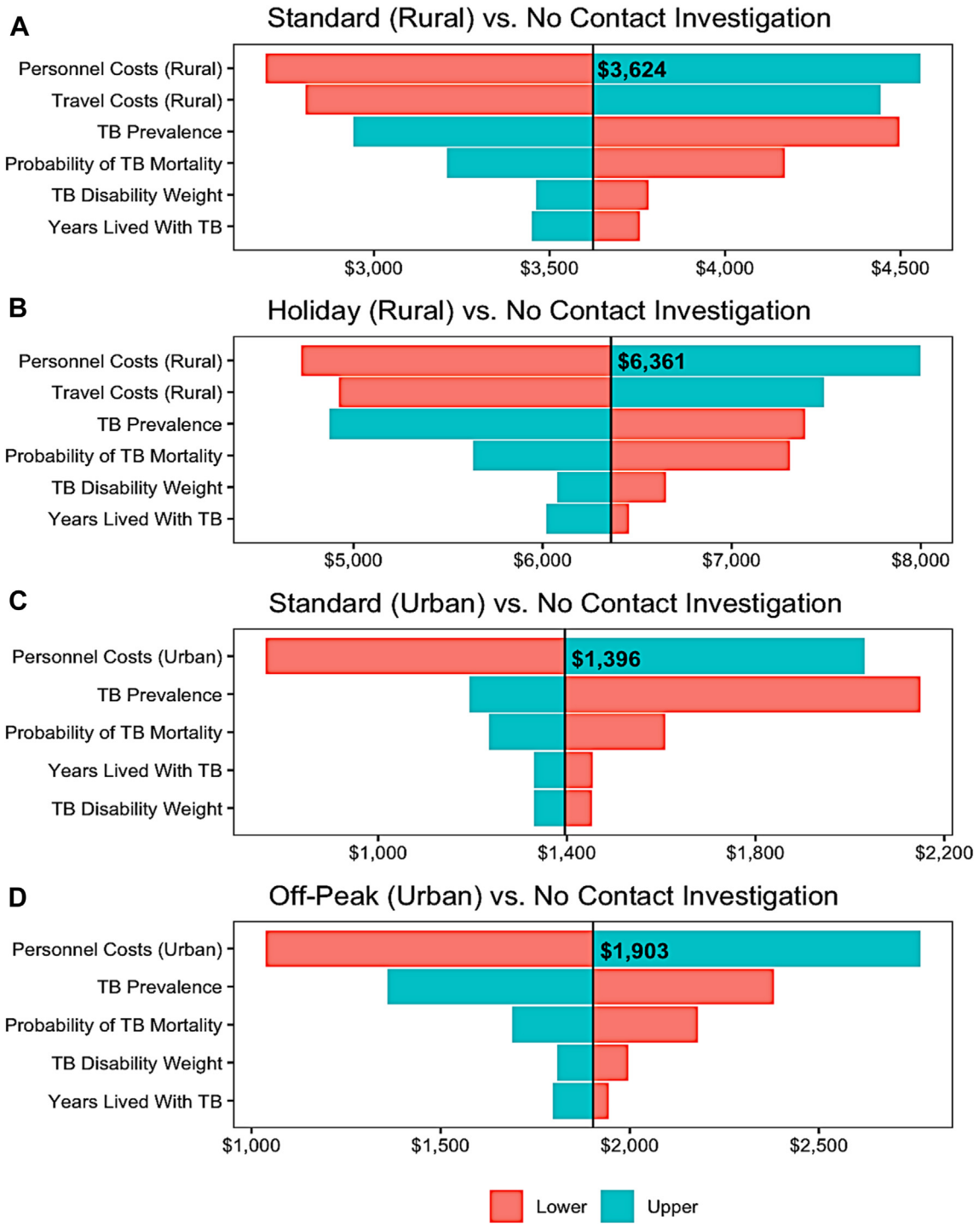

Fig. 1: **One-way sensitivity analysis: cost-effectiveness of contact investigation for tuberculosis in rural and urban South Africa**. Panels A–D present results of our one-way sensitivity analyses evaluating four strategies for TB household contact investigation, each relative to a hypothetical no contact investigation approach. Parameters are ordered according to their influence on the estimated cost-effectiveness estimate along the y-axis, while the x-axis indicates the estimated cost per disability-adjusted life year averted. The length of each bar indicates the difference between the primary estimate of cost-effectiveness (shown as a vertical black line and labeled to the right of the line) and the corresponding estimate when the parameter is at the upper (blue) or lower (red) bound of its range of variation.

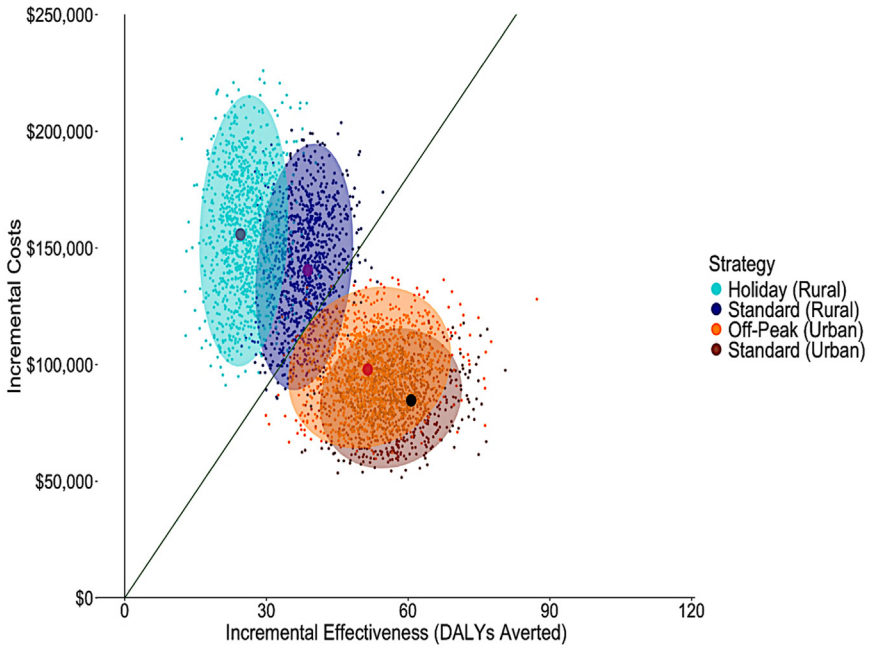

Fig. 2: **Incremental cost-effectiveness scatter plots of household contact investigation strategies for tuberculosis relative to a hypothetical no household contact investigation approach**. These cost-effectiveness scatterplots were generated by running 1000 simulations in a probabilistic sensitivity 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.[26] Points falling below the cost-effectiveness threshold are considered cost-effective. Costs are reported in 2022 US dollars.

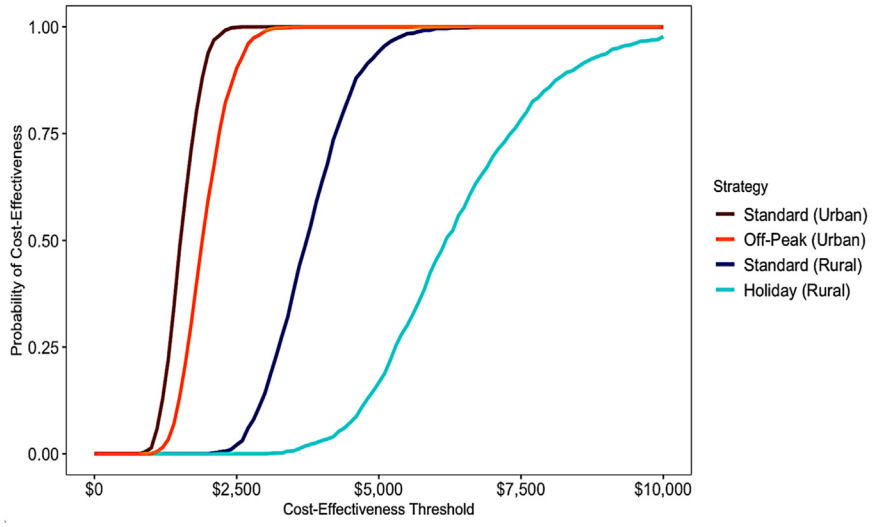

Fig. 3: **Cost-effectiveness acceptability curves**. These cost-effectiveness acceptability curves present the probability of each of four contact investigation strategies being cost-effective (y-axis) across a spectrum of different cost-effectiveness thresholds (shown on the x-axis), compared to a hypothetical no contact investigation approach. Results are based on probabilistic sensitivity analysis as described in the manuscript text. All costs are given in 2022 US dollars.

settings, the novel strategies for the timing of contact investigation (off-peak and holiday-based, respectively) were less cost-effective than standard timing; however, for contact persons who would not be reached if contact investigation was limited to standard business hours, off-peak contact investigation remained likely cost-effective in the urban setting.

The initial aim of this analysis was to evaluate the incremental cost-effectiveness of the two novel strategies relative to standard contact investigation. In both settings, we estimated that standard HCI would cost less and avert more DALYs than off-peak or holiday-based contact investigation—suggesting that standard timing would be preferred ("dominant") relative to novel timing. Having demonstrated this, we then chose to evaluate all four strategies against a hypothetical comparator of no contact investigation, recognizing that some contact persons (e.g., working men) are unlikely to be reached during regular business hours. Our results suggest that, for these individuals, off-peak contact investigation is still likely to be cost-effective relative to no evaluation in urban settings like Soshanguve—but investigations performed during regular business hours is economically preferred. In the rural setting, cost-effectiveness of standard HCI was near the prespecified cost-effectiveness threshold, while holiday-based HCI was not cost-effective.

This analysis supports findings from other cost-effectiveness analyses, indicating that HCI for TB requires substantial resources on a per-contact basis, even though this expenditure provides good value-for-money. For instance, a study in Kampala, Uganda evaluated a strategy very similar to our standard contact investigation approach; these authors similarly found TB contact investigation to be cost-effective, although the cost per case detected ($416) was substantially lower than estimated here.[27] This difference reflects both the higher cost of personnel in South Africa and the relatively low yield of contact investigation in our study (≤24 contact persons diagnosed with TB per 1000 index participants enrolled) (Table 2). In our rural site, travel between households was also a major expense. Personnel and travel costs are consistently the major components of the overall cost—and therefore also key drivers (in addition to TB prevalence) of the cost-effectiveness—of HCI.[27–29]

Previous research suggests that TB interventions in urban settings are generally more cost-effective than those in rural areas. TB burden tends to be higher in urban settings due to factors such as overcrowding and density of urban populations, high HIV prevalence, and increased occupational exposure from work-related travel into cities. These conditions may contribute to a higher yield of TB cases, improving the cost-effectiveness of urban strategies.[30,31] Additionally, the nature of urban employment—such as shift work and informal labor arrangements (i.e., street vendors)—may make off-peak strategies inherently more viable, as these strategies allow greater flexibility in accessing healthcare services outside of traditional hours. Many urban workers, particularly those in informal jobs, lack paid leave or have rigid work schedules, making it difficult to attend healthcare visits during standard hours.[32] In contrast, rural areas face logistical challenges that impact cost-effectiveness. Lower TB prevalence in rural settings reduces the number of detected cases relative to resources invested, while longer travel distances increase operational costs for both patients and healthcare personnel (e.g., fuel, vehicle rentals, and public transportation fares).[30] Poverty also remains more widespread in rural areas, which may further limit access to healthcare services and exacerbate financial burdens for patients.[33] Additionally, the dispersed nature of rural populations may require more extensive outreach efforts, further increasing costs.[30]

To improve future implementation of TB contact investigation, especially in the face of the substantial human and financial resources required for household visits, further studies could evaluate strategies to increase the efficiency and utility of personnel time. Such strategies may include optimizing scheduling such that more households and/or contact persons could be visited per trip and incorporating community engagement (e.g., co-designing visit schedules to align with household availability to enhance participation and uptake of screening services). Additionally, TB HCI could be delivered via alternative community-based models (e.g., with Community Caregiver Outreach Teams) and/or integrated into broader home-based interventions (e.g., for maternal and child health, management of HIV and non-communicable diseases), thereby distributing both personnel time and travel costs across multiple disease prevention initiatives. This approach of integrated care has been demonstrated to be feasible and acceptable in settings such as Cameroon and Uganda.[34–36]

Our results should be interpreted in light of certain limitations. Although our estimates were linked to a randomized trial, this trial did not include formal assessment of disease progression or long-term follow-up. As such, our estimates of DALYs averted required an assumption that TB-attributable mortality among contact persons (who may, for example, be more likely to seek care) would be similar to that for the general population in South Africa who develops TB. We also did not explicitly incorporate HIV into these calculations, as HIV status was not always known—and HIV status may strongly influence the cost-effectiveness of TB contact investigation, especially if new patients with HIV are identified.[29] Third, although cost estimates were derived from aggregate actual expense data over one full calendar year, the method by which we allocated costs as programmatic or research-related may have introduced bias, leading to either underestimation or overestimation of total programmatic costs. For example, we assigned a larger proportion of overhead costs to standard contact

investigation than to the novel strategies, reflecting the larger number of index participants and contact persons in the standard arm. Although these costs were not a major driver of overall costs, we may have overestimated those costs for the standard arm and underestimated such costs in the novel arms.

In generalizing our findings to other settings, we found that cost-effectiveness is optimized in settings with high TB prevalence (among contact persons), and in urban settings relative to rural ones. In South Africa relative to many other high-burden settings, both personnel costs and cost-effectiveness thresholds are likely to be higher, reflecting South Africa's higher gross domestic product; TB prevalence in South Africa is also high—though the prevalence of TB among contact persons was lower in this study than has been seen elsewhere.[37] Specific decisions regarding cost-effectiveness in any given context will depend on key contextual factors, including healthcare infrastructure, economic conditions (e.g., personnel costs and cost-effectiveness thresholds), and the cost of implementing alternative interventions. Future studies could include linked cost estimates from pragmatic evaluations of HCI in non-research-based settings for more generalizable cost-effectiveness results. Additionally, variance in costs and cost-effectiveness thresholds across different settings emphasize the need for additional research on implementation and cost-effectiveness in diverse contexts or conditions.

In summary, this analysis illustrates the likely cost-effectiveness of HCI for TB while providing insights into differences between rural and urban settings, including considerations for holiday-based and off-peak HCI. Our findings suggest that standard HCI is generally preferred, but off-peak contact investigation may still be cost-effective in urban settings for individuals who may not be reachable or decline to be reached during standard hours. The primary drivers of cost-effectiveness are the prevalence of TB among contact persons, costs of personnel, and the cost of transport (in the rural setting). These results provide additional support for the scale-up of TB HCI and its integration into broader home-based interventions.

Contributors

DWD, NM, KA, and CFH conceptualized the study. DWD, NM, KA, CFH, BM, PB, MM, and MM2 supported investigation. NY and PB accessed and verified the underlying data. DWD, NY, and PB finalized the methodology. NY worked on the software and visualization. NY conducted the formal analysis. NY and DWD wrote the original draft. All co-authors reviewed and edited the manuscript.

Data sharing statement

Datasets generated or analyzed during this study are available upon request by contacting the corresponding author.

Declaration of interests

DWD reports a grant to their institution from the United States National Institute of Allergy and Infectious Diseases. CFH reports payments to their institution, unrelated to this work, from the National Heart, Lung, and Blood Institute. NM reports a grant to their institution from the United States National Institutes of Health; a grant to their institution unrelated to this work from Pfizer; unpaid participation on a Data Safety and Monitoring Board (DSMB) for a trial of novel treatments for disseminated TB; and unpaid roles on the boards of the Setshaba Research Centre and the Wits Health Consortium. All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103259.

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