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Effectiveness of active case-finding strategies in tuberculosis control in Kampala, Uganda

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SUMMARY

BACKGROUND: Passive case finding (PCF) is the strategy implemented by most developing countries to detect new cases of tuberculosis (TB), but detection rates remain low. Active case finding (ACF) is an alternative strategy, although cost is a barrier to implementation. We estimated the cost-effectiveness of a city-wide ACF programme in Kampala, Uganda, compared to the PCF strategy.

METHODS: We developed a decision tree and Markov model to compare ACF vs. PCF across several outcome measures. Parameter estimates for costs, probabilities and utility scores were obtained from published reports and peer-reviewed journal articles. The main outcome measures were TB cases detected, deaths averted, life years saved (LYS) and quality-adjusted life years (QALYs).

RESULTS: Our model found that ACF implemented city-wide would result in an additional 1594 TB cases detected in 1 year, 675 deaths averted over a 5-year period, 21 928 LYS, and would cost an additional US$109 per additional QALY. The 25–34 year age group received most health benefits (556 cases detected, 229 deaths averted, 8058 LYS), and the programme was most cost-effective in the 45–54 year age group (US$51/QALY).

CONCLUSIONS: ACF is an effective strategy for TB control and improving quality of life and is also cost-effective.

KEY WORDS: tuberculosis; active case finding; passive case finding; quality-adjusted life years; life years saved

UGANDA is a high tuberculosis (TB) burden country, with an estimated incidence of 209 cases per 100 000 population.[1] TB case finding in the Ugandan National Tuberculosis and Leprosy Program (NTLP) has so far been limited to passive case finding (PCF), i.e., self-referral of symptomatic individuals to health facilities, which is the strategy currently recommended by the World Health Organization (WHO).[2] Despite using PCF and the DOTS strategy, fewer than half of all new cases are detected and treated each year.[1] The low detection rate may be attributed to poor health-seeking behaviour by symptomatic patients and limited accessibility of health services.[3]

Active case finding (ACF) has been proposed as an alternative strategy to improve detection and treatment rates in resource-poor high human immunodeficiency virus (HIV) burden countries.[4,5] Although several models exist, most involve house-to-house surveys conducted by community health workers.[4] Numerous studies have demonstrated the effectiveness of ACF in resource-poor countries, including several randomised trials and observational studies.[6–8] A house-to-house survey in a slum district of Kampala found 33 new TB cases among 930 people screened.[9] Thus, areas with high TB and HIV prevalence may benefit most from ACF.[10] Mathematical models have suggested that ACF or intensified case finding may have substantial benefits in high-prevalence countries.[11] ACF involves additional costs, which is a barrier to implementation in resource-poor countries. However, the cost-effectiveness of ACF has not been thoroughly evaluated at the population level.

We sought to determine if ACF is a cost-effective strategy for TB case detection in Kampala, Uganda, compared to PCF. We hypothesised that ACF strategy would identify and bring people with TB into treatment who would have not sought diagnostic services on their own initiative, thereby increasing case detection.

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METHODS

We developed a decision tree model to evaluate and compare the cost and effectiveness of PCF alone and the ACF of symptomatic individuals combined with PCF in Kampala. Our ACF model involved door-to-door contact with individuals to screen for new cases of TB using the community care model.[12] Community health workers chosen by village leaders would conduct screening using an organisational model already implemented by the Ugandan NTLP in a community-based DOTS programme.[13] Persons with TB who are missed by ACF may still be detected through PCF by presenting to a health facility. A Markov model was used to follow simulated patients over time. Parameters for our model were obtained from published literature and reports.

As this study did not involve human subjects, approval from an institutional review board was not required.

Setting

Kampala, Uganda, was chosen because of its high population density and TB incidence rates compared to rural areas. Kampala is situated in the central region of Uganda, covering a surface area of 195 km^2, and is divided into five administrative divisions.

Study population

The main study population included Ugandan residents of Kampala. As sputum testing is difficult for children aged $<$10 years, only persons aged $\geqslant$10 years were included in our study.

Time horizon

We chose a 5-year analytic horizon for our model to allow adequate time for follow-up, which may include several rounds of TB treatment and recurrence. We chose a Markov cycle time of 4 months as this is the largest common divisor between 8 months—the average length of a treatment regimen,[14] and 12 months—which is what most parameters in literature are based on. We believed a 1-year timeframe would be sufficient for the implementation of ACF for the entire population of Kampala.

Model parameters and costs

Model parameters were based on findings from published peer-reviewed literature. Preference was given to estimates from higher order studies such as randomised trials and prospective observational studies and those conducted in populations similar to Uganda. Probabilities used in the model include sensitivity and specificity of sputum microscopy tests, treatment success rates, disease recurrence rates, mortality rates and likelihood of presenting to a clinic with disease symptoms (Table 1).[3,9,14–23] The range for each variable was based on estimates and confidence intervals found in all studies or a range of clinically plausible values, whichever was larger.

Costs were assessed from the governmental perspective, and adjusted to 2011 US dollars using currency conversion rates and the Uganda consumer price index.[29,30] The governmental perspective was chosen because the NTLP and the Ministry of Health are key decision makers in TB control in Uganda. Treatment costs include cost of drugs, laboratory tests and personnel (Table 1).[9,24–28] We used published estimates of Category I (2HRZE/6EH*) and II (2SHRZE/1HRZE/5HRE) regimen costs for Uganda.[13,24] Costs for management of multidrug-resistant TB (MDR-TB) were based on estimates from a lower-income country.[25] For ACF estimates, we used cost estimates from a pilot ACF survey conducted in a low-income parish in Kampala.[9]

Outcome measures

Quality-adjusted life years (QALYs) were calculated based on health state utility score at each state of the model. We used published utilities to calculate QALYs (Table 2).[31] Life years saved (LYS) counts each additional life year without adjusting for quality of life or disability. Smear-positive cases detected were calculated with a binary variable in our model. If persons were detected and treated at any point, they were flagged as detected cases. If they died before treatment or never sought treatment, they were undetected. We also calculated deaths averted by comparing the number of deaths for each strategy over a 5-year period. The Markov model simulation runs for a period of 5 years, and we added age-specific life expectancy in the final state to all persons who survived to fully capture the benefit from an averted death. To obtain city-wide estimates for all outcomes, we multiplied per-person outcomes by the population of Kampala for each age group.

Cost-effectiveness analysis

We conducted an incremental cost-effectiveness analysis of the ACF strategy in terms of US$ per additional QALYs. Markov methods were used to model health state transitions, as simplified in Figure 1. The model consists of five states: well, receiving treatment, recovery post-treatment, treatment failure or relapse (following receipt of a Category I or II regimen) and died. A baseline annual rate of 3% was used to discount future costs and QALYs. A decision threshold of two times the per capita gross domestic product (GDP) per QALY (US$700/QALY) was used to determine whether a strategy was cost-effective. A more conservative US$350/QALY (1 $\times$ GDP) cut-off was also considered for the purposes of comparison.[32,33]

*H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol; S = streptomycin. Numbers before the letters indicate the duration in months of the phase of treatment.

Table 1 Parameters used in the model

	Probability	Range	Reference
Sensitivity of the smear test	0.600	0.300–0.800	15,16
Specificity of the smear test	0.970	0.900–1.000	15,16
Presents early to clinic if TB-positive	0.697	0.638–0.756	3
Presents to clinic with cough, but TB-negative	0.136	0.050–0.300	17,18
HIV-negative patients on Category I or first-line regimen			
Treatment success	0.89	0.85–0.92	14
Treatment failure/relapse	0.05	0.03–0.07	14
Treatment mortality	0.03	0.02–0.06	14
HIV-positive patients on Category I or first-line regimen			
Treatment success	0.70	0.67–0.72	19
Treatment failure/relapse	0.14	0.12–0.15	19
Treatment mortality	0.17	0.15–0.18	19
HIV-negative on Category II or retreatment regimen			
Treatment success	0.80	0.73–0.86	20
Treatment failure	0.09	0.05–0.14	20
Treatment mortality	0.07	0.04–0.12	20
HIV-positive on Category II or retreatment regimen			
Treatment success	0.74	0.66–0.80	20
Treatment failure	0.04	0.02–0.08	20
Treatment mortality	0.20	0.14–0.27	20
HIV-negative on MDR-TB treatment regimen			
Treatment success	0.80	0.58–0.92	21
Treatment mortality	0.20	0.08–0.42	21
HIV-positive on MDR-TB treatment regimen			
Treatment success	0.68	0.54–0.79	21
Treatment mortality	0.32	0.21–0.45	21
Death after treatment failure (annual)	0.134	0.067–0.201	18
Death if healthy (annual)	0.018	0.001–0.050	18
Responds to antibiotics if TB-positive (temporarily)	0.113	0.000–0.300	17,22
Death if present to clinic with advanced symptoms	0.225	0.193–0.355	23
Missed by ACF if TB-positive	0.800	0.600–1.000	9
Tested by ACF when patient does not have TB	0.037	0.001–0.200	9*
Prevalence of TB by age group, years			18
10–14	0.006	0.003–0.012	
15–24	0.014	0.007–0.028	
25–34	0.038	0.019–0.076	
35–44	0.066	0.033–0.102	
45–54	0.079	0.039–0.158	
55–64	0.083	0.041–0.166	
⩾65	0.083	0.041–0.166	
Description of costs	Cost, US$		
Category I or first-line regimen (2RHZE/6HE)	15.00	5.00–50.00	24
Category II or retreatment regimen (2SRHZE/1HRZE/5HRE)	110.70	50.00–250.00	24
MDR-TB drug treatment	3355.00	2000.00–5000.00	25
Standard antibiotic treatment	1.62	0.81–3.24	26
Sputum culture test for TB	48.00	30.00–55.00	24
Sputum smear test	2.99	1.50–5.98	27
Chest X-ray	8.14	4.07–16.28	28
ACF programme (cost per person)	2.86	1.43–5.72	9

*Parameter derived from authors' calculations based on data in this paper.
TB = tuberculosis; HIV = human immunodeficiency virus; MDR-TB = multidrug-resistant TB; ACF = active case-finding; R = rifampicin; H = isoniazid; Z = pyrazinamide; E = ethambutol; S = streptomycin.

Assumptions

We assumed that the natural history of TB varied by HIV status based on our parameters (Table 1). All patients who are identified with smear-positive TB are treated whether the case is detected using ACF or in a health facility, and non-adherence would be minimal. The sensitivity and specificity of sputum smear microscopy would the same, regardless of HIV status. For simplicity, we categorised each TB case as either early or late detection. We assumed that all cases detected by house-to-house surveys were detected early. Survival and treatment success were assumed to be marginally better among cases detected early compared to those detected at an advanced stage. We assumed that TB patients detected by ACF or PCF received the same treatment.[7] We assumed that those with latent TB and those without TB had similar health utilities, regardless of HIV status.[31]

Sensitivity analysis

All variables in the model were analysed over a broad range of clinically plausible values. Where available,

Table 2 Health state utilities

Health states	Utility score	Range	Reference
Very mild TB symptoms	0.84	0.73–0.95	31
Mild TB symptoms	0.68	0.63–0.73	31
Moderate TB symptoms	0.64	0.54–0.74	31
Severe TB symptoms	0.59	0.44–0.74	31
Very severe TB symptoms	0.54	0.46–0.62	31
TB with very well-controlled symptoms	0.85	0.76–0.94	31
TB with well-controlled symptoms	0.73	0.60–0.86	31
TB with adequately controlled symptoms	0.60	0.49–0.71	31
Post-treatment recovery (1 year)	0.90	0.80–1.00	31
Well	1.00	1.00–1.00	
Deceased	0.00	0.00–0.00	

TB = tuberculosis.

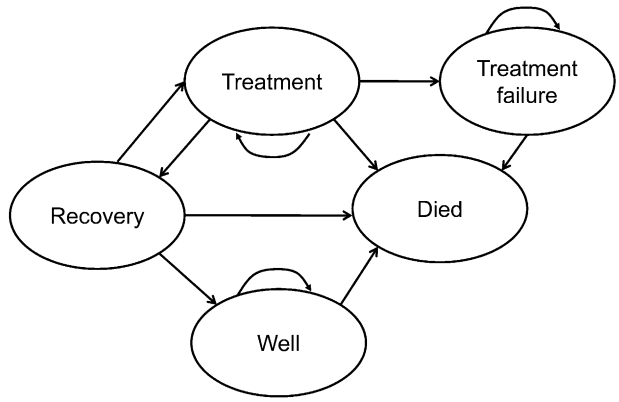

Figure 1 Simplified Markov state diagram. Persons with detected cases of TB enter in the 'treatment' phase, including false-positives. Persons without TB enter in the 'well' state. 'Recovery' refers to a state up to 1 year post-treatment in which a treated patient may relapse and require retreatment. Persons may stay in the 'treatment' phase if they fail to respond to treatment (i.e., they are retreated with second- or third-line drugs). After third-line treatment, additional treatment is no longer attempted and they move to the 'treatment failure' category.

95% confidence intervals (CIs) were used. The range for all costs was ±50% of the baseline estimate. The model was re-analysed for each parameter using end points of the range, while holding all other variables at baseline (univariate sensitivity analysis). A variable was considered sensitive if plausible changes could alter the incremental cost-effectiveness ratio sufficiently that a switch to a different strategy would be preferable.

To further test the robustness of our conclusions, we conducted a probabilistic sensitivity analysis. Probability distributions were created for all of the parameters in the model. For cost estimates based on specific cost proxies, such as cost of treatment published by the Ugandan Ministry of Health, we used a normal distribution equal to the mean ± 25%.[34] For all other parameters we used baseline value for the mean and estimated the standard error based on approximation that the range used for one-way sensitivity analysis represented a 95%CI, with range approximately equal to 4 times the standard error.[34] We used Monte Carlo simulation to create 1000 samples, for which expected values were calculated. We then calculated the proportion of samples for each strategy that was cost-effective.

All decision tree analysis and Monte Carlo simulations used to derive outcomes, cost-effectiveness and sensitivity analysis were performed using TreeAge Pro version 2009 (TreeAge Software Inc, Watertown, MA, USA).

RESULTS

Cases detected

The ACF strategy detected 1594 more cases of TB than the PCF strategy alone. The incremental benefit of more cases detected was highest in the 25–34 year age group, with an additional 556 cases detected (Table 3). The additional benefit was lowest in the youngest and oldest age groups. Higher prevalence rates of TB among older age groups are the reason for increased cases detected; however, the lower population in the older age groups somewhat offsets this increase.

Quality-adjusted life years

ACF was more effective in terms of increasing QALYs than PCF for all age groups (Table 4). The incremental benefit varied by age group and, in general, age

Table 3 Cases detected using ACF and PCF*

Age group, years	Population	Total TB cases	Cases detected		Additional cases detected from ACF	Increase in detection from ACF %
			PCF	ACF		
10–14	97 832	567	466	515	49	10.5
15–24	243 955	3415	2808	3099	291	10.4
25–34	171 449	6515	5356	5912	556	10.4
35–44	71 209	4700	3864	4265	401	10.4
45–54	30 283	2392	1967	2171	204	10.4
55–64	12 214	1014	833	920	87	10.4
⩾65	7734	642	528	583	55	10.4
Total	536 844	18 678	15 822	17 465	1643	10.4

* The estimated number of cases of TB in each age group in a single year, the number that would be detected under both ACF and PCF strategies and the difference between the two.
ACF = active case finding; PCF = passive case finding; TB = tuberculosis.

Table 4 Cost-effectiveness of ACF vs. PCF alone*

Age group, years	Strategy	Cost per person US$	Additional cost US$	QALYs	Additional QALYs	ICER (cost per additional QALY) US$	Total costs US$
10–14	PCF	0.92		26.6510			
	ACF+PCF	3.80	2.88	26.6563	0.0053	537.85	281 000
15–24	PCF	1.23		24.8330			
	ACF+PCF	4.11	2.87	24.8461	0.0131	218.73	700 000
25–34	PCF	2.15		22.3086			
	ACF+PCF	5.01	2.86	22.3420	0.0334	85.49	490 000
35–44	PCF	3.23		20.1223			
	ACF+PCF	6.07	2.84	20.1755	0.0532	53.33	202 000
45–54	PCF	3.73		17.5297			
	ACF+PCF	6.56	2.83	17.5856	0.0560	50.59	86 000
55–64	PCF	3.88		14.3159			
	ACF+PCF	6.71	2.83	14.3642	0.0484	58.47	35 000
⩾ 65	PCF	3.88		9.7130			
	ACF+PCF	6.71	2.83	9.7464	0.0333	84.83	22 000
Total	PCF	1.80		23.2652			
	ACF+PCF	4.67	2.86	23.2915	0.0262	109.07	1 535 000

*Total cost per person is the per capita cost to run each programme.
ACF = active case finding; PCF = passive case finding; QALY = quality-adjusted life years; ICER = incremental cost-effectiveness ratio.

groups with a higher prevalence of disease gained more benefit through ACF compared to lower prevalence age groups. Persons in the 45–54 year age group received most marginal benefit from the ACF programme, with an average of 0.056 additional QALYs per person.

Cost-effectiveness

Using incremental QALYs as the effectiveness measure, we found that the ACF strategy cost US$109/per additional QALY when conducted in our main study population of age ⩾15 years (Table 4). This is lower than our decision threshold. ACF becomes even more cost-effective as age increases in our model up until the 45–54 year age group, after which it becomes slightly less cost-effective for older age groups, but is still under our willingness-to-pay (WTP) threshold. The programme is least cost-effective in the 10–14 year age group, with a cost of US$538/additional QALY. Our model predicts a total programme cost of US$1.53 million to conduct the programme over the entire Kampala population aged ⩾10 years.

Life years saved and deaths averted

The ACF strategy results in an increase in number of LYS across all age groups (Figure 2). The ACF programme would lead to 21 928 additional LYS and an estimated 675 deaths averted over a 5-year period. The 25–34 year age group would benefit the most, with an estimated 229 deaths averted and 8058 LYS.

Sensitivity analysis

One-way sensitivity analysis was performed on each variable in the model over the plausible range of values. The model was not sensitive to any variables, including HIV co-infection rate and the sensitivity of the diagnostic tests. For ACF not to be cost-effective at US$350/QALY, the cost of the programme would have to be $14.30 per capita, which is six times higher than our baseline estimate, or the prevalence would need to be reduced by two thirds.

Results from our probabilistic sensitivity analysis show that strategies were equally cost-effective when WTP was approximately US$140/QALY (Figure 3). Using a WTP threshold of US$700/QALY resulted in ACF being cost-effective in 95% of the samples. Using a US$350/QALY threshold, ACF was cost-effective in 81% of the samples.

DISCUSSION

Our model of a one-off ACF programme for adults in Kampala, Uganda, showed that such a programme would improve the health of the population based on

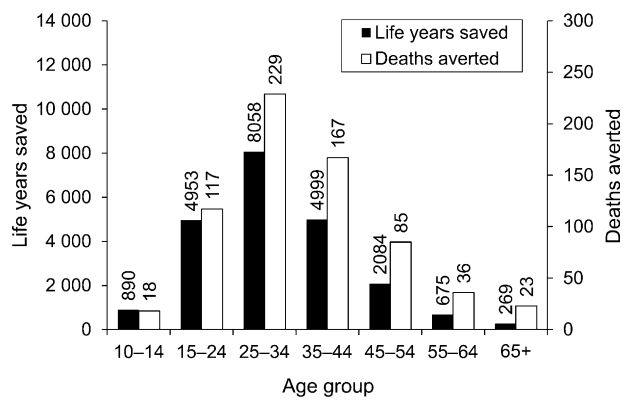

Figure 2 Additional life years saved and deaths averted under the ACF programme. Black columns show the number of life years saved in each age group; white columns show deaths averted in a 5-year period under ACF. ACF = active case finding.

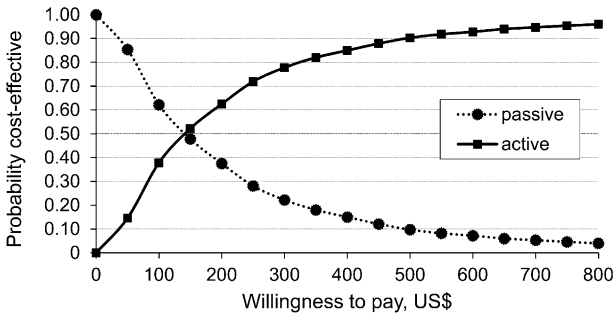

Figure 3 Probabilistic sensitivity analysis. These curves show, for each strategy, the proportion of 1000 simulated samples for which that strategy was cost-effective at varying levels of willingness to pay per additional QALY. QALY = quality-adjusted life years.

several key outcome measures. This programme was also shown to be cost-effective in nearly all age groups in our model using a conservative 1 × GDP threshold. This finding makes the ACF model well suited to Kampala and other urban settings where there is a higher population of younger adults.

Our model also shows that the ACF programme could save an estimated 675 lives over a 5-year period. These deaths may be averted in two ways: first, by detecting and treating cases that would otherwise go undetected under PCF alone, and second, through earlier detection of active TB and subsequent earlier treatment, which would likely lead to higher survival rates, particularly in TB-HIV co-infected individuals.[35] On calculating LYS, we found that the programme could save an additional 21 198 life years in the Kampala population.

Two variables—TB prevalence and cost of the ACF programme—have the potential to make the ACF programme not cost-effective outside of our plausible range of values. Prevalence would have to drop by two thirds, which may occur in the future or in certain sub-populations. The cost of the ACF programme would have to increase six fold for it not to be cost-effective at the US$350/QALY level.

Although the city-wide ACF programme would be cost-effective, the total estimated cost of $1.53 million dollars may be a barrier to its implementation. External funding sources through foundations or foreign aid may be necessary, or the programme may need to cover the city over a longer period of time, spreading out the cost burden. Another option would be to target informal settlements (slum areas) where there is overcrowding and a large number of people can be tested cost-effectively. We did not include the highly effective Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) detection method in our model, as it is currently prohibitively expensive, at a cost of between US$17 and $120 per test.[35] This should change in the future as the technology becomes more widely available.

Limitations

For simplicity, we limited our model to a one-off ACF programme conducted over a year, and assumed that TB prevalence and incidence remained constant. In practice, we could expect incidence to decrease over time as more cases are detected and TB transmission is reduced. This would reduce the cost-effectiveness of the ACF programme over time if it were implemented on an ongoing basis. Our rationale for choosing a one-off ACF model, besides simplicity, was that any implementation of this magnitude would likely have to come from external support, which is more likely to be available for a one-off, pilot intervention rather than for an open-ended programme. The results from that programme could be used to investigate whether a sustained ACF programme is both cost-effective and feasible. A number of factors will impact the effectiveness of ACF in the field, including elements such as the stigma of HIV-associated TB. We built into the model that some 20% of persons would be entirely missed by ACF. Our parameter estimates were based on an actual pilot study in one neighbourhood in Kampala, and we assumed that the sensitivity and specificity of the sputum smear test was the same in ACF as PCF. If health workers in ACF are not well trained, these tests may have lower sensitivity, and this would reduce the impact of ACF.

CONCLUSION

We have created a model for ACF and PCF strategies in Kampala, Uganda. Our model shows that an ACF strategy would lead to better outcomes in terms of more TB cases detected, deaths averted, LYS and increased QALYs. The ACF programme would be cost-effective in this population.

Conflict of interest: none declared.

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RÉSUMÉ

CONTEXTE : Le dépistage passif des cas (PCF) est la stratégie mise en œuvre par la plupart des pays en développement pour détecter les nouveaux cas de tuberculose (TB), mais les taux de détection y restent faibles. Un dépistage actif des cas (ACF) est une stratégie alternative, mais son coût constitue une barrière à sa mise en œuvre. Nous avons estimé le rapport coût-efficacité d'un programme ACF par comparaison avec la stratégie PCF dans l'ensemble de la ville de Kampala, Ouganda.

MÉTHODES : Nous avons élaboré un arbre de décision et un modèle de Markov pour comparer les dépistages ACF versus PCF avec plusieurs mesures de résultats. Les estimations de paramètres de coût, les probabilités et les scores d'utilité ont été obtenus à partir des rapports et d'articles publiés. Les mesures principales de résultats ont été les cas de TB détectés, les décès évités, les années de vie sauvées (LYS) et les années de vie ajustées pour la qualité de vie (QALY).

RÉSULTATS : Notre modèle a démontré que l'ACF mis en œuvre dans l'ensemble de la ville entrainerait une détection supplémentaire de 1594 cas TB en 1 an, 675 décès évités au cours d'une période de 5 ans et 21 928 LYS et coûterait un supplément de 109 US dollars par QALY supplémentaire. C'est dans le groupe d'âge de 25 à 34 ans que la plupart des bénéfices-santé sont survenus (556 cas détectés, 229 décès évités, 8058 LYS), et le programme a eu le rapport coût-effacité le plus élevé dans le groupe d'âge de 45 à 54 ans (51$ par QALY).

CONCLUSION : Le dépistage ACF constitue une stratégie efficiente de lutte contre la TB ; il améliore la qualité de vie et a également un bon rapport coût-efficacité.

RESUMEN

MARCO DE REFERENCIA: La búsqueda pasiva de casos (PCF) de tuberculosis (TB) es una estrategia que se aplica en la mayoría de los países desarrollados con el fin de detectar los casos nuevos; sin embargo, las tasas de detección siguen siendo bajas. Otro enfoque posible es la búsqueda activa de casos (ACF), aunque el costo puede constituir un obstáculo a su ejecución. En el presente estudio se comparó la rentabilidad de un programa ACF con la estrategia PCF a escala de toda la ciudad en Kampala, Uganda.

MÉTODOS: Mediante la construcción de un árbol decisional y la aplicación del modelo Markov se compararon las estrategias ACF y PCF con respecto a diversas medidas de rendimiento. El cálculo de las variables de costos y probabilidades y el índice de utilidad se obtuvieron a partir de los informes divulgados y los artículos publicados en revistas con revisores externos. Las principales medidas de evaluación de los resultados fueron el número de casos de TB detectados, las defunciones que se evitaron, los años de vida ganados (LYS) y los años de vida ajustados a la calidad (QALY).

RESULTADOS: El modelo puso en evidencia que al ejecutar la ACF a escala de la ciudad se detectarían 1594 casos suplementarios en un año, se evitarían 675 defunciones en un período de 5 años y se ganarían 21928 LYS, con un costo suplementario de 109 dólares por cada QALY adicional. El mayor beneficio sanitario de la estrategia la obtuvo el grupo entre los 25 años y los 34 años de edad (556 casos detectados, 229 defunciones evitadas y 8058 LYS); el programa fue más rentable en el grupo de 45 años a 54 años (51 dólares por cada QALY).

CONCLUSIÓN: La búsqueda activa de casos constituye una estrategia eficaz de control de la TB, mejora la calidad de vida y es rentable.