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Yield of undetected tuberculosis and human immunodeficiency virus coinfection from active case finding in urban Uganda

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Abstract

OBJECTIVES—To determine the yield of undetected active tuberculosis (TB), TB and human immunodeficiency virus (HIV) coinfection and the number needed to screen (NNS) to detect a case using active case finding (ACF) in an urban community in Kampala, Uganda.

METHODS—In a door-to-door survey conducted in Rubaga community from January 2008 to June 2009, residents aged ≥ 15 years were screened for chronic cough (≥ 2 weeks) and tested for TB disease using smear microscopy and/or culture. Rapid testing was used to screen for HIV infection. The NNS to detect one case was calculated based on population screened and undetected cases found.

RESULTS—Of 5102 participants, 3868 (75.8%) were females; the median age was 24 years (IQR 20–30). Of 199 (4%) with chronic cough, 160 (80.4%) submitted sputum, of whom 39 (24.4%, 95% CI 17.4–31.5) had undetected active TB and 13 (8.1%, 95% CI 6.7–22.9) were TB-HIV co-infected. The NNS to detect one TB case was 131 in the whole study population, but only five among the subgroup with chronic cough.

CONCLUSION—ACF obtained a high yield of previously undetected active TB and TB-HIV cases. The NNS in the general population was 131, but the number needed to test in persons with chronic cough was five. These findings suggest that boosting the identification of persons with chronic cough may increase the overall efficiency of TB case detection at a community level.

Keywords

case detection; tuberculosis; chronic cough; number needed to screen; TB-HIV co-infected

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CASE DETECTION is the principal means of controlling transmission and reducing tuberculosis (TB) incidence.¹ Globally, case detection has stagnated in recent years, while the rate of decline in estimated TB incidence has been slower than expected.^{2,3} Passive case finding (PCF), the detection of active TB or TB-HIV (human immunodeficiency virus) among symptomatic persons voluntarily presenting to the health system, is the standard approach adopted by most National TB Programmes (NTPs).⁴ Using PCF alone, however, leaves large pools of undetected prevalent TB cases who fail to seek care.⁵⁻⁷ Moreover, even with functional NTPs, health system delays occur in TB diagnosis or initiation of treatment. Patients also delay due to a lack of awareness of symptoms or lack of access to health services, particularly in sub-Saharan Africa.⁸⁻¹² Many TB patients infect others before they are diagnosed and placed on effective treatment. Alternative strategies to overcome the detection gap should be geared towards shortening these delays and reducing the potential risk of transmission at community level.

Active case finding (ACF) is a known alternative strategy for case detection.^{4,13} It refers to provider-initiated efforts to find, evaluate and diagnose active TB among asymptomatic and symptomatic individuals who have not sought care.¹³ Ideally, ACF can interrupt the transmission of TB through early detection and prompt initiation of effective treatment.^{4,10,14} ACF can also reduce the risk of death due to TB, particularly among HIV-co-infected individuals.¹⁵ Mathematical models suggest that ACF is one of the most effective ways of reducing TB incidence and mortality.^{1,16} Recent randomised community trials^{14,17,18} and observational studies^{15,19,20} conducted in developing countries have shown that ACF identifies previously undetected TB cases.

Uganda has an estimated annual TB incidence of 234 per 100 000 population; however, only 57% of smear-positive cases were detected in 2011.² The capital district, Kampala, accounts for nearly 25% of Uganda's notified TB caseload.²¹

The purpose of the present study was to determine the yield and the number needed to screen (NNS) to detect a case of undetected TB and TB-HIV in Kampala. This expands on the existing evidence base that supports ACF as a supplementary strategy for TB case detection in Africa.

METHODS

Ethical considerations

The study received approval from the institutional review committees at the University Hospitals, Cleveland, OH; the University of Georgia, Athens, GA, USA; the Makerere University School of Public Health; and the Uganda National Council for Science and Technology, Kampala, Uganda. Written informed consent was obtained from all participants.

Study design, setting and population

We conducted a door-to-door cross-sectional survey of chronic cough in the Rubaga community located in Kampala City, Uganda, from January 2008 to June 2009. The division is subdivided into 13 parishes and 128 villages, with approximately 75 485 households and

400 000 people. About 50% of the population are adults aged ≥ 15 years.²² Individuals can access TB and HIV diagnostic services from two public health centres free of charge or two tertiary private hospitals for a fee. Free treatment is provided in both private and public facilities.

Eligible residents were those aged ≥ 15 years who lived in Rubaga during the survey period. Participants were excluded if there was a language barrier, declined to consent, were not at home on three separate attempts or did not plan to stay in the study area for 2 weeks after the survey date.

A sample size of 5000 participants was calculated to estimate the prevalence of TB with a 95% confidence interval (CI) of 5%, based on a previous ACF study of undiagnosed TB cases in Kampala.²⁰ Participants were selected using a multistage sampling approach. A simple random sample was used to select five of the 13 parishes using a computer-based random number generator and sampling frame from the Uganda Bureau of Statistics, Kampala, Uganda.²³ Weighted proportions-to-village population sizes were calculated to estimate the number of participants to be recruited from each village. This was done to account for the variability in crowding. We identified the first house from a defined central point such as road or drainage junctions in each village, and enrolled a convenience sample of persons at home.

A two-step approach was used to screen for active TB and TB-HIV: a cough interview administered to identify chronic coughers, and diagnostic testing for TB and HIV infection. Trained interviewers administered a cough questionnaire that assessed the presence, duration and frequency of cough. Chronic cough was defined as self-reported cough for ≥ 2 weeks at the time of the survey. Information was collected on socio-demographics, TB history, TB-related symptoms (weight loss, evening fever, haemoptysis, excessive night sweats), health care seeking (assessed as 'evaluation by a health provider since the start of your cough'), previous HIV testing and current treatment for TB or HIV/AIDS (acquired immune-deficiency syndrome). The main study outcomes were undetected active TB and TB-HIV. The secondary outcome was the NNS to identify a single case in the subgroup of interest.

Spot and early morning sputum samples were collected from the chronic coughers at their homes and transported in a cool box to the certified national reference TB laboratory in Kampala. Samples were processed using standard methods,²⁴ and two technicians independently examined the sputum smear for acid-fast bacilli (AFB) and used Löwenstein-Jensen slants for culture. Smears were quantified and reported as negative, scanty, 1 +, 2 +, 3+ per International Union Against Tuberculosis and Lung Disease standards.²⁵ Smear test results were reported within 48–72 h.

Rapid HIV testing was performed using the serial algorithm as recommended by the Ugandan Ministry of Health, Kampala, Uganda.²⁶ Determine HIV-1/2 assay (Abbott Laboratories, Abbott Park, IL, USA) for screening and the HIV-1/2 STAT-PAK Dipstick assay (Chembio Diagnostic System Inc, New York, NY, USA) were used for confirmation. The Uni-Gold test (Trinity Biotech, Bray, Ireland) was used for confirmation in case of

discordance. HIV Western Blot test was performed on a 10% random sample of blood specimens for quality control purposes.

A TB case was defined as a positive sputum smear or culture from one or more collected samples.^{27,28} An HIV case was defined as a positive rapid HIV test according to the Uganda Ministry of Health algorithm.²⁶ A positive TB-HIV co-infected case was defined as a confirmed TB case with a concurrent positive HIV test. New cases identified during the survey were referred to public health centres for further care as appropriate.

Statistical methods

The yield of active TB and TB-HIV cases was calculated as proportions with 95% CIs of undetected cases in chronic coughers. The NNS to identify one case of chronic cough, active TB, TB-HIV and HIV infection was also calculated accordingly. Appropriate statistical tests were used to test for differences in groups at $\alpha = 0.05$. Data were analysed using Stata version 11.0 (StataCorp, College Station, TX, USA).

RESULTS

Study participants

The study enrolled 5102 participants from 4494 households (Figure) and 28 villages visited. The study excluded 2289 people, including 2257 who were not at home (82.3% male) and 32 who declined to consent. Of those enrolled, 3868 (75.8%) were female (median age 24 years, IQR 20–30; Table 1). The prevalence of self-reported cough of any duration was nearly 10.1% (95% CI 9–11). More than half (50.8%) of the participants were aged 15–24 years. Half the sample had had at least 8–13 years of education; 44.2% were employed, and 54.4% had an average weekly income of not more than US\$2. More than one third (38.2%) of the participants reported that they had never undergone HIV testing.

Yield of chronic cough and other tuberculosis-related symptoms

Of the 5102 participants, 199 (4%, 95% CI 3.5–4.5) had cough of ≥ 2 weeks (Table 2). Of the five most common TB-related symptoms, self-reported unintentional weight loss was the most prevalent (35.2%), followed by excessive night sweats (32.7%). Haemoptysis was the least common symptom (6.5%).

Yield of undetected active TB, TB-HIV coinfection and HIV among chronic coughers

Of 199 chronic coughers, 160 (80.4%) submitted sputum for examination, of whom 39 met the criteria for active TB (24.4%, 95% CI 17.8–31.1; Table 2); 26 were HIV-negative or had unknown HIV status (16.3%, 95% CI 2.1–30.5) and 13 (8.1%, 95% CI 6.7–22.9) were found to be HIV-infected. Chronic coughers with and without active TB were similar in socio-demographic and clinical characteristics and health-seeking behaviour. There were 57 (28.6%, 95% CI 22.6–35.5) HIV-positive cases among the chronic coughers. Of these, 25 (44%) were newly diagnosed (Figure).

Sputum smear grade of TB cases detected by ACF

Of the 39 active TB cases, the majority (66.7%) had negative or low AFB sputum smear grade (scanty or + 1). There was no statistically significant difference in levels of smear grades and other characteristics between TB cases with and those without HIV infection (Table 3).

The number needed to screen using ACF to detect TB, TB-HIV and HIV cases

Using chronic cough to screen the general population for TB suspects, the NNS to identify one chronic cougher was 26. To identify one active TB case using cough screening with smear and/or culture testing, the NNS was 131. However, when considering only smear results, the NNS was 170. The number needed to test (NNT) to find one case of TB among those with chronic cough was five (Table 4). When stratifying the subgroup of suspects by HIV status, the NNT was eight for TB-HIV-negative and 15 for TB-HIV co-infected persons.

DISCUSSION

In this door-to-door cough survey of adults living in an African city, we determined the yield of undetected infectious TB using a two-step approach: screening for chronic cough with a questionnaire, followed by smear microscopy and culture for diagnosis. Chronic cough was uncommon in the community at large, with a yield of 4%. The NNS to find a single case of active TB was 131; however, operationally, it could be as high as 170 if only smear microscopy was used. Once it was known that the person had a chronic cough, however, the NNT was only five. This finding suggests that gaining access to residents with chronic cough is a critical step toward an efficient community TB ACF programme. Previous studies have used educational leaflets, flyers, mobile vans with loudspeakers, community awareness campaigns by trained lay workers and cell phone text messaging to enhance case finding among persons with chronic cough.^{14,17,29,30}

The NNS is a useful metric for comparing efficiency across screening programmes in the context of resource allocation. In this study, the NNS of 131 to find a TB case is similar to the median NNS of 148 (range 29–5000) reported in a systematic review from population-based surveys of TB case finding in Africa.³¹ The NNS can vary depending on the prevalence of TB and HIV in the target population, the screening strategy, the sensitivity of the diagnostic tests used and the functionality of NTPs.³² A recent review demonstrated that the NNS to detect a TB case was lower when high-risk populations such as prisoners or the homeless in high-prevalence settings were screened.³³ The NNT of five in persons with chronic cough in our study is consistent with the need to test on average seven suspects (range 3.3–20) to detect one smear-positive case in NTP clinics.²⁵

The high prevalence of 24.4% undetected infectious TB cases among those with chronic cough in Kampala is consonant with another study from the same setting in 2009.²⁰ Importantly, the low diagnostic accuracy of the tests used may have led to missed TB cases or overdiagnosis, particularly given the finding that 16 of 30 smear-positive cases were culture-negative. As this may have been due to either specimen contamination or other

quality problems with culture, corrective measures should be taken. We do not know the true prevalence of undetected TB in this community subgroup of chronic cough. Nonetheless, the value of ACF in identifying pools of undetected infectious TB cases in high TB prevalence settings is well highlighted.

Although the primary goal of ACF is to detect undiagnosed active TB, our study shows that HIV-associated TB was also detected. A higher proportion of smear-positive cases detected were HIV-negative and not -positive. This difference may be explained by diagnostic inaccuracy, particularly when using smear microscopy in HIV-associated TB.³⁴ In Kampala, where HIV prevalence is high and often remains undiagnosed,^{23,35} it is logical to couple HIV testing with TB screening. As indicated in the '3Is' policy recommended by the World Health Organization, intensified TB case finding in HIV-infected persons should continue to be implemented in specialised HIV clinics as an effective way to find TB cases.^{31,33} Nevertheless, ACF for TB-HIV in the general population should not be neglected, as it is especially helpful in uncovering additional, previously unknown, HIV cases.^{19,31}

Our findings support the idea that ACF detects cases much earlier based on smear grade; most detected cases had low smear grades. A similar study in Zambia found that the majority of detected cases had a scanty smear grade at diagnosis.¹⁹ In contrast, in a PCF setting in Uganda, 82% of the TB patients had high smear grades of 3+, suggesting more severe disease at the time of diagnosis.³⁶ Higher smear positivity has been associated with a greater level of TB transmission among close contacts.^{37,38} Theoretically, earlier detection implies shorter duration of infectiousness and a reduced likelihood of transmission. However, what remains unclear is the optimal timing of ACF to attain a meaningful reduction in duration of infectivity to other persons and thus incidence. A standard epidemiological measure that captures the impact of ACF on TB epidemiology is therefore urgently needed.

Our urban population-based study leads to findings that are consistent with existing evidence in support of implementing ACF strategies for case detection in high TB and HIV burden areas. However, the cross-sectional design limits the interpretation of the prevalence of undetected TB and TB-HIV beyond the study period. Possible underestimation of the prevalence may be due to the lack of sputum for evaluation from 19.6% of those with chronic cough, and further diagnostic evaluations should be conducted. Selection bias could arise from the heavily female-skewed sample and non-participation of persons who were not at home during the day. Previous door-to-door studies have shown similar recruitment patterns, as men mostly work outside the home.^{18,20} A study showed that men tended to seek care for TB-related symptoms earlier than females;³⁹ however, ACF may help identify disease earlier among females.

High-quality TB diagnosis, treatment, management and support for patients should be in place before ACF is initiated. Under NTP conditions, barriers to case finding, such as the low sensitivity of smear microscopy, quality assurance problems that render culture testing less sensitive as well as diagnostic delays, could be overcome by the deployment of rapid, highly sensitive point-of-care diagnostics such as Xpert[®] MTB/RIF.^{40,41} Finally, ACF is more resource-intensive than PCF, irrespective of target population; more cost-effectiveness

studies comparing ACF and PCF strategies^{42,43} are therefore needed to inform policy decisions for TB control programmes in Africa.

CONCLUSIONS

ACF obtained a high yield of previously undetected active TB and TB-HIV cases. The NNS in the general population was 131, while the NNT to detect a TB case among persons with chronic cough was five. These findings suggest that boosting the identification of persons with chronic cough may increase the overall efficiency of TB case detection at the community level.

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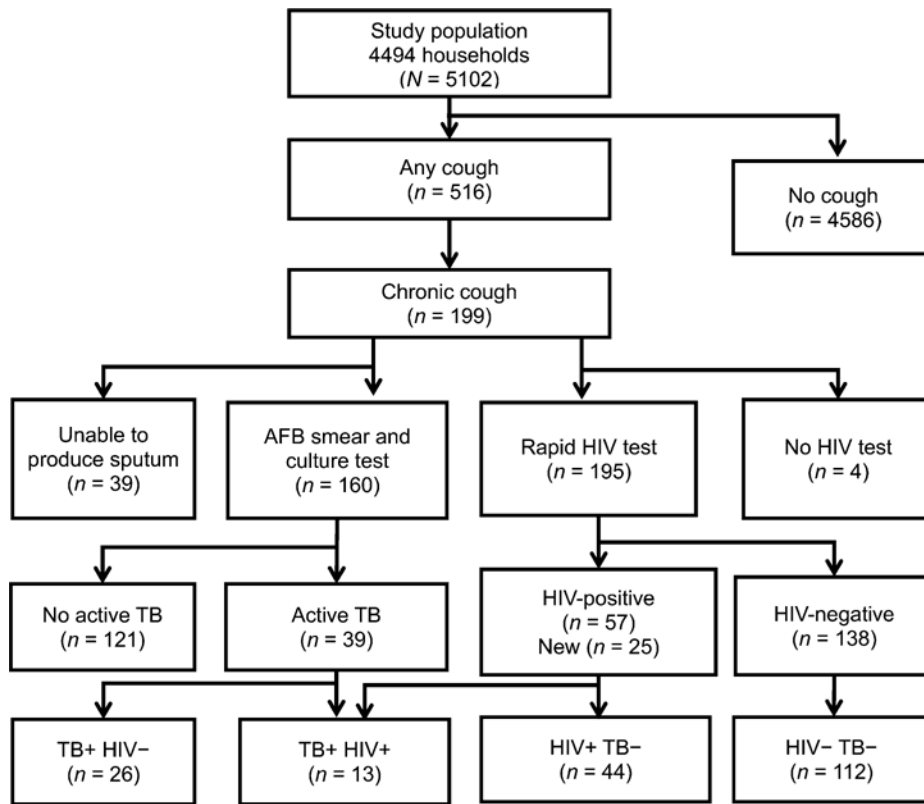


Figure. Flow diagram of study participants in Rubaga Division, Kampala, Uganda. AFB = acid-fast bacilli; HIV = human immunodeficiency virus; TB = tuberculosis; + = positive; - = negative.

Table 1

Baseline characteristics of study participants in Kampala, Uganda, 2008–2009

Characteristic	Total population (N = 5102) n (%)
Age, years, median [IQR]	24 [20–30]
15–24	2592 (50.8)
25–34	1614 (31.7)
35–44	533 (10.8)
45–54	191 (3.7)
≥55	152 (3.0)
Sex	
Female	3868 (75.8)
Male	1234 (24.2)
Marital status	
Never married	1737 (34.1)
Currently married	2583 (50.6)
Previously married	782 (15.6)
Religion	
Catholic	1683 (33.0)
Protestant	1387 (27.2)
Muslim	1255 (24.6)
Others *	777 (15.2)
Education level, years	
None	214 (4.2)
1–7	1872 (36.7)
8–13	2563 (50.2)
>13	453 (8.9)
Employed	
Yes	2325 (45.6)
No	2777 (54.4)
Reported weekly income, UGX, median [IQR] †	4000 [1000–10 000]
None	862 (16.9)
1–<1000	164 (3.2)
1000–5000	2253 (44.2)
5001–10000	797 (15.6)
>10000	1026 (20.1)
Ever tested for HIV	
Yes	3151 (61.8)
No	1951 (38.2)
Presence of cough	
Yes	516 (10.1)
No	4686 (89.9)

* Pentecostal, Seventh Day Adventist or religion not specified.

† 1USD ~ UGX 2500.

IQR = interquartile range; UGX = Ugandan shillings; HIV = human immunodeficiency virus.

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Table 2

Characteristics of undetected TB cases among persons with chronic cough in Kampala, Uganda

Characteristic	Total (n = 199) n (%) [*]	No TB (n = 121) n (%)	Undetected TB (n = 39) n (%)	P value
Produced sputum	160 (80.4)	121 (75.6)	39 (24.4)	
Unable to produce sputum	39 (19.6)			
Sex				
Female	125 (62.8)	80 (66.1)	22 (56.4)	0.273
Male	74 (37.2)	41 (33.1)	17 (43.6)	
Age, years				
15–24	64 (32.2)	43 (35.5)	9 (23.1)	0.263 ⁺
25–34	80 (40.2)	45 (37.2)	17 (43.6)	
35–44	28 (14.1)	17 (14.1)	8 (20.0)	
45–54	13 (6.5)	6 (5.0)	4 (10.3)	
≥55	14 (7)	10 (8.2)	1 (3.0)	
Marital status				
Never married	40 (20.1)	24 (19.8)	8 (20.5)	0.596
Currently married	99 (49.8)	66 (54.5)	18 (46.2)	
Previously married	60 (30.2)	31 (25.6)	13 (33.3)	
Education level (years of school)				
None	22 (11.1)	15 (12.4)	2 (5.1)	0.524 [†]
1–7	106 (53.2)	62 (51.2)	19 (48.7)	
8–13	61 (30.7)	37 (30.6)	16 (41.0)	
>13	10 (5)	7 (5.8)	2 (5.1)	
Cough duration, weeks [‡]				
2–3	71 (35.7)	41 (34.8)	13 (33.3)	0.204 [§]
>3–8	52 (26.1)	36 (30.5)	6 (15.4)	
>8–12	19 (9.6)	11 (9.3)	6 (15.4)	
>12	57 (28.6)	30 (25.4)	14 (35.9)	
TB-related symptoms				
None	90 (45.2)	59 (48.8)	15 (38.5)	0.106 [§]
1–2	58 (29.2)	38 (31.4)	11 (28.2)	
3–5	51 (25.6)	24 (19.8)	13 (33.3)	
Ever undergone HIV testing				
No	83 (41.7)	51 (42.2)	16 (41.0)	0.902
Yes	116 (58.3)	70 (57.9)	23 (59.0)	
HIV status				
Negative	138 (69.4)	86 (72.9)	25 (65.8)	0.154
Positive	57 (28.6)	32 (27.1)	13 (34.2)	
Not done	4 (2)	3	1	
Health care seeking				

Characteristic	Total (n = 199) n (%) [*]	No TB (n = 121) n (%)	Undetected TB (n = 39) n (%)	P value
No	51 (28.7)	31 (28.7)	8 (23.5)	0.556
Yes	127 (71.3)	77 (71.3)	26 (76.5)	

^{*} Other totals may not add up to 199 due to 39 missing AFB smear tests; of 160 only 4 did not produce two samples.

[†] Fisher's exact test.

[‡] Mean and median difference in cough duration not significant.

[§] Test for trend.

TB = tuberculosis; HIV = human immunodeficiency virus; AFB = acid-fast bacilli.

Table 3

Characteristics of 39 previously undetected active tuberculosis cases by HIV status

Characteristic	Total (n = 39) n (%)	HIV-negative (n = 25) n (%)	HIV-positive (n = 13) n (%)	P value
Age, years				
Mean ± SD	33 ± 11	33.5 ± 15.6	31.0 ± 8.9	0.560 [*]
Median [IQR]	29 [25–42]	27 [22–39]	29 [26–33]	0.77 [†]
Sex [‡]				
Not 100%				
Female	22 (56)	15 (60)	7 (53.9)	
Male	17 (44)	10 (40)	6 (46.1)	0.482
AFB smear grade [‡]				
Negative	9 (23.1)	5 (20)	3 (23.1)	0.690
Scanty	13 (33.3)	8 (32)	5 (38.5)	
1+	4 (10.3)	2 (8)	2 (15.4)	
2+	5 (12.8)	3 (12)	2 (15.4)	
3+	8 (20.5)	7 (28)	1 (7.6)	
Smear and culture				
AFB +, culture +	14 (36)	4 (31)	10 (38)	0.713
AFB +, culture–	16 (41)	6 (46)	10 (38)	
AFB–, culture +	9 (23)	3 (23)	6 (24)	
Cough duration, weeks				
Mean ± SD	15.7 ± 26.9	11.0 ± 14.5	14.7 ± 25.3	0.80 [*]
Median [IQR]	8.7 [3–17.4]	4.3 [2.9–8.7]	4.3 [3–13]	0.60 [†]

*
t-test.[†]Mann-Whitney test.[‡]Stratified totals do not add up to 39 as 1 HIV result was missing.

HIV = human immunodeficiency virus; SD = standard deviation; IQR = interquartile range; AFB = acid-fast bacilli; + = positive; – = negative.

Table 4

NNS and NNT to detect a TB suspect, active TB or TB-HIV case using active case finding, Kampala, 2008–2009*

Study population	Total <i>n</i>	NNS (95%CI) [†]	NNT (95%CI) [‡]
All participants enrolled	5102		
Chronic cough (≥2 weeks)	199	26 (23–30)	NA
Previously undetected active TB (smear- and/or culture-positive)	39	131 (96–179)	5 (5.3–4.7)
Previously undetected active TB (smear only)	30	170 (123–256)	7 (7.1–6.3)
TB-HIV-negative	26	196 (145–323)	8 (7.2–8.3)
TB-HIV co-infected	13	393 (222–667)	15 (14–17)
Undetected HIV-positive in those with chronic cough	25	NA	8 (7.4–8.6)

* The risk subgroup constitutes the denominators for NNS or NNT, and numerators are either overall population or those with chronic cough.

[†] Numerator for NNS = 5102; the rest of the numbers in the column with totals constitute the denominators.

[‡] Numerator for NNT = 199; the rest of the numbers in the column with totals below chronic cough constitute the denominators.

NNS = number needed to screen; NNT = number needed to test; TB = tuberculosis; HIV = human immunodeficiency virus; NA = not available.