

Epidemiological impact of mass tuberculosis screening: a 2-year follow-up after a national prevalence survey

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SUMMARY

OBJECTIVE: To assess the epidemiological impact of mass tuberculosis (TB) screening in the community and the prognosis of bacteriologically negative individuals with abnormal findings on chest radiography (CXR).

METHODS: A follow-up study consisting of two parts—a register match of notified TB cases with 22 160 participants in a national TB prevalence survey, and a repeat medical examination for the subjects of a prevalence survey with abnormal findings on CXR—was conducted 2 years after the prevalence survey in Cambodia.

RESULTS: Thirty-four cases with new smear-positive TB were detected by register match, giving a standardised notification ratio of 0.38 (95%CI 0.27–0.52). An additional seven new smear-positive TB cases and 93 new smear-negative, culture-positive TB cases were detected

by medical examination. The incidence rates of bacteriologically positive TB were 8.5% per year (95%CI 6.3–11.2) in cases with a CXR suggestive of active TB and 2.9% per year (95%CI 2.2–3.7) in those with a CXR with other abnormalities.

CONCLUSIONS: Detection and treatment of smear-negative, culture-positive TB cases as well as smear-positive TB cases was associated with a rapid reduction in subsequent incidence of new smear-positive TB. Sputum culture-negative individuals with abnormal CXR findings are at a high risk of disease progression, and require follow-up and potentially preventive treatment.

KEY WORDS: tuberculosis; epidemiology; active case finding; chest radiography; reactivation

WITH 8.8 MILLION estimated incident cases and 1.45 million estimated deaths due to tuberculosis (TB) every year,¹ TB remains a major health threat, particularly in developing countries. Globally, the current decline in the estimated incidence rate of approximately 1.3% per year needs to accelerate to reach the elimination target set for 2050.^{1,2} Continued scale-up of early detection and proper treatment for all forms of TB in line with the Stop TB Strategy is essential.^{2,3}

In the past two decades, much attention has been paid to detecting highly infectious, smear-positive TB with the help of the DOTS strategy, which focuses on persons with TB symptoms who seek medical care. However, the anticipated decline of >5% annually in TB incidence due to improved case detection of smear-positive TB has not been observed in high TB burden countries, even in settings where case-detection rates have been high for an extended period of time.^{2,4,5} Moreover, several population-based surveys have revealed that a substantial proportion of bacteriologically confirmed TB cases identified by the surveys are asymptomatic and undiagnosed in the community.^{2,6,7} With the successful global scale-up of effective anti-tuberculosis treatment, a recent study suggests that

active case finding needs to be re-evaluated in general populations.⁸ This re-evaluation should include improved detection of smear-negative TB cases, as the risk of transmission from such cases is not negligible.^{9–11} Furthermore, smear-negative TB may convert to smear-positive as the disease progresses; early case detection of all types of TB might therefore further reduce transmission.² However, the impact of detecting and treating all bacteriologically confirmed TB cases (both smear-positive and smear-negative, culture-positive TB) in the community is uncertain.

To determine the impact of active screening for TB, we monitored TB notifications for 2 years in the areas where a national prevalence survey had been conducted. An additional objective was to assess the 2-year prognosis of bacteriologically negative individuals with abnormal findings on chest radiography (CXR) through repeat medical examination.

METHODS

In 2002, the Cambodia National Center for Tuberculosis and Leprosy Control conducted the first national TB prevalence survey in 42 clusters selected by the

population proportionate multistage cluster sampling method.⁶ Among 22 160 participants aged ≥ 10 years, 81 cases of smear-positive TB and 190 cases of smear-negative, culture-positive TB were identified by screening based on symptoms (cough ≥ 3 weeks) and/or CXR (any abnormality), and by smear and culture examination for all those screened as positive, per World Health Organization (WHO) recommendations for prevalence surveys.¹² Cases diagnosed with bacteriologically positive TB were referred to a nearby DOTS centre for medical care, including an 8-month treatment regimen. Nearly 90% of these (74 smear-positive and 170 smear-negative, culture-positive TB) had high treatment success rates of more than 90%. Participants with two culture-negative specimens, including those with any CXR abnormality, were not followed up routinely by the National TB Control Programme (NTP).

A follow-up study (Figure) was conducted in the 2002 survey areas to capture subsequent incident cases of TB over the 2 years after the prevalence survey by 1) a register match of both the primary health care centre TB register and the district TB register with all 22 160 participants in the prevalence survey, and 2) a repeat medical examination conducted between August and October 2004 for 1753 subjects who had had abnormal findings on CXR in the prevalence survey.

The medical examination included subject history, CXR and laboratory examinations of two sputum samples (spot and early morning) for all participants. Smear microscopy by Ziehl-Neelsen stain, culture examination on solid media (3% Ogawa and Kudoh) and species identification by the niacin test or MPT64-based (Capilia TB assay; Tauns, Shizuoka, Japan) species confirmation¹³ were used as necessary. A panel of experts composed of two respiratory physicians and/or radiologists made a decision on the final radiological findings. Based on the Japanese CXR classification for TB, which has been widely used to

evaluate patients with pulmonary TB in Japan,^{14,15} a CXR suggestive of active TB was categorised as 'TB-suggestive CXR'; a CXR suggestive of suspect TB, healed TB and other lung diseases was categorised as 'other abnormal CXR'; and no abnormality as 'normal CXR'. Deaths due to TB were identified by the register match or by interviewing family members.

Notification rates in the surveyed areas were calculated as the number of notified cases divided by the total of the individual person-years of observation. Indirect standardisation¹⁶ was used to calculate an age-adjusted expected number of notifications in the 2002 survey areas by using the age-sex specific notification rates of new smear-positive TB from NTP statistics in Cambodia in 2003.¹⁷ For the analysis of the 2-year prognosis among individuals with abnormalities on CXR in the 2002 survey, we used the period from the prevalence survey to the repeat medical examination as the length of time of observation, excluding the 8-month treatment period from the observation period for TB cases identified in the 2002 survey. Data analyses were performed using OpenEpi version 2.3.1 (Centers for Disease Control and Prevention, Atlanta, GA, USA; <http://www.openepi.com/OE2.3/Menu/OpenEpiMenu.htm>); a *P* value of 0.05 was considered significant.

As there was no national ethics committee in place in Cambodia at the time, we obtained verbal informed consent from each participant or guardian during the medical examination.

RESULTS

Observed vs. expected notification rate

The distribution of study subjects with regard to laboratory examinations and CXR status in the prevalence survey and the results of the register match are shown in Table 1. In total, 35 smear-positive TB cases (including 1 recurrent case) and 3 smear-negative cases were captured through the register match. The notification rates for smear-positive TB were similar between the 'TB-suggestive CXR' group (0.64% per year, 95% CI 0.17–1.64), and the 'other abnormal CXR' group (0.67% per year, 95% CI 0.39–1.06). The 'normal CXR' group had a notification rate of 0.03% per year (95% CI 0.02–0.06).

The actual number of new smear-positive TB cases notified in the 2002 survey areas was 34, while the age-adjusted expected number of smear-positive TB cases over 2 years was 90 (Table 2); the standardised notification ratio was thus 0.38 (95% CI 0.27–0.52), which is significantly lower than expected ($P < 0.001$) and shows a 62% reduction in the notification of new smear-positive TB cases in the 2002 survey areas.

Tuberculosis incidence in individuals with abnormal chest X-rays

Of the 1753 subjects with any abnormal CXR in the 2002 survey, 1423 (81%) underwent a repeat

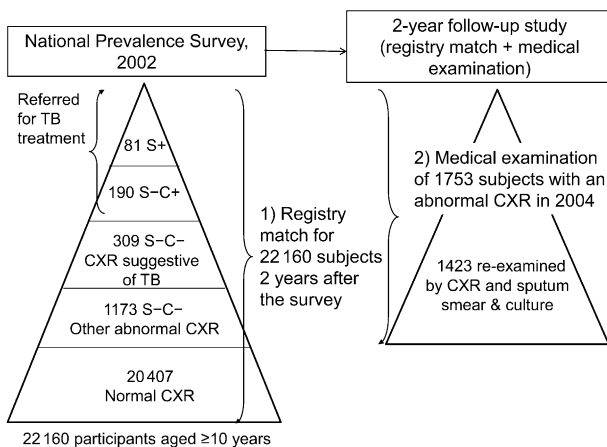


Figure Schematic diagram of the follow-up study. TB = tuberculosis; S+ = smear-positive; S- = smear-negative; C+ = culture-positive; C- = culture-negative; CXR = chest radiograph.

medical examination (Table 3): 10 smear-positive cases were identified, including 7 new cases, and 104 smear-negative, culture-positive cases, including 93 new cases (Table 4). Of the 114 total cases, 46 (40%)

from the 'TB-suggestive CXR' group and 54 (47%) from the 'other abnormal CXR' group developed bacteriologically positive TB.

The incidence rate of new bacteriologically positive

Table 1 Study subjects and results of TB registry match

Study subjects and categories in the prevalence survey, 2002	Partici- pants, <i>n</i>	Male/ female ratio	Years of age in 2004 [†] mean ± SD	Notified cases in 2 years* by TB registry match			
				Cases, <i>n</i>		Smear-positive notification rate	
				Smear- positive TB	Smear- negative TB	%/ year	95%CI
Smear-positive TB	81	2.24	47.1 ± 18.3	1	0	0.88	0.02–4.90
Smear-negative, culture-positive TB	190	1.04	51.8 ± 16.3	0	0	0.00	0.00–1.41 [‡]
TB suggestive CXR	309	1.01	47.8 ± 18.0	4	1	0.64	0.17–1.64
Other abnormal CXR [§]	1 173	0.93	49.5 ± 18.3	16	1	0.67	0.39–1.06
Normal CXR	20 407	0.82	24.8 ± 15.1	14	1 [¶]	0.03	0.02–0.06
Total	22 160	0.85	30.6 ± 17.4	35	3	0.08	0.06–0.11

*2 years between the prevalence survey and the medical examination.

[†]Age in 2004, when the medical examination was carried out.

[‡]The upper limit by OpenEpi was adopted as the numerator is zero.

[§]Suspected TB, healed TB and other lung diseases on CXR.

[¶]Excluding 3 cases with extra-pulmonary TB.

TB = tuberculosis; CXR = chest radiography; SD = standard deviation; CI = confidence interval.

Table 2 Comparison of new smear-positive TB between estimated and notified number in 2 years

	Total	Age group, years						
		0–14	15–24	25–34	35–44	45–54	55–64	≥65
Notification rate of new smear-positive TB by age, 2003, Cambodia NTP, /100 000								
Male	143.0	1.3	54.0	180.1	331.0	439.9	745.6	1105.2
Female	131.4	1.6	46.6	149.6	258.5	417.5	543.5	478.5
Number of subjects by age in the surveyed areas, 2002								
Male	10 157	2274	2998	1619	1377	876	544	469
Female	12 003	2245	3057	2026	1824	1323	768	760
Estimated number of notified cases by age in 2 years								
Male	44.4	0.1	3.2	5.8	9.1	7.7	8.1	10.4
Female	45.1	0.1	2.8	6.1	9.4	11.0	8.3	7.3
Total	89.5	0.1	6.1	11.9	18.5	18.8	16.5	17.60
Actual number of notified cases with new smear-positive TB in 2 years								
Total	34	0	4	4	9	8	5	4
Standardised notification ratio (95%CI)	0.38 (0.27–0.52)	0.00	0.66	0.34	0.49	0.43	0.30	0.23

TB = tuberculosis; NTP = National Tuberculosis Control Programme; CI = confidence interval.

Table 3 Characteristics of subjects in repeat medical examination in 2004

Laboratory results and CXR findings, 2002	Absentees		<i>n</i>	Participants in repeat medical examination, 2004			
	Died (TB-related death) <i>n</i> (<i>n</i>)	Had moved/ were busy <i>n</i>		Male/ female ratio	Years of age mean ± SD	Partici- pation rate %	Months of observation mean ± SD
Smear-positive TB	12 (10)	3	66	2.00	48.7 ± 18.8	81.5	16.8 ± 1.6
Smear-negative, culture-positive TB	13 (7)	10	167	1.14	53.1 ± 15.8	88.4	16.5 ± 1.5
TB suggestive of CXR	10 (2) [†]	31	268	1.05	49.9 ± 18.1	86.7	24.3 ± 1.7
Other abnormal CXR*	37 (2) [‡]	214	922	0.88	52.9 ± 17.4	78.6	24.6 ± 1.8
Total	72 (21)	258	1423	0.97	52.1 ± 17.4	81.2	24.5 ± 1.7

* Suspected TB, healed TB, and other lung diseases on CXR.

[†]2 non-notified cases were reported to have died of an unknown form of TB.

[‡]2 non-notified cases were reported to have died of an unknown form of TB.

TB = tuberculosis; SD = standard deviation; CXR = chest radiography.

Table 4 Results of repeat medical examination

Laboratory results and CXR findings, 2002	Partici- pants <i>n</i>	Laboratory results or CXR findings on repeat medical examination					Incidence rate of bacteriologically positive TB	
		Smear- positive TB	Smear- negative, culture- positive TB	TB suggestive of CXR	Other abnormal CXR	Normal CXR	%/year	95%CI
Smear-positive TB	66	1*	3 [†]	2	57	3	4.3	1.2–11.1
Smear-negative, culture-positive TB	167	2 [‡]	8 [§]	8	141	8	4.4	2.2–7.8
TB-suggestive CXR	268 [¶]	5	41	85	111	26	8.5	6.3–11.2
Other abnormal CXR [#]	922 [¶]	2	52	53	722	93	2.9	2.2–3.7
Total	1423	10	104	148	1031	130	4.1	3.4–5.0

* Cured, but returned with drug-resistant TB.

[†]2 cases completed treatment and 1 case was treated in the private sector.

[‡]2 cases completed treatment.

[§]5 cases completed, 2 cases defaulted and 1 case not registered.

[¶]3 cases in the TB-suggestive CXR group and 3 cases in the other abnormal CXR group were diagnosed with TB (unknown type) in the private sector after the prevalence survey.

[#]Suspected TB, healed TB and other lung diseases on CXR.

CXR = chest radiography; TB = tuberculosis; CI = confidence interval.

TB in the 'TB-suggestive CXR' group was 8.5% per year (95%CI 6.3–11.2), which was significantly higher than the incidence rate of 2.9% per year (95%CI 2.2–3.7) in the 'other abnormal CXR' group ($P < 0.001$, Table 4). The presence of TB symptoms at the time of the 2002 survey was not associated with the occurrence of bacteriologically positive TB in the 'TB-suggestive CXR' group ($P = 0.336$).

Overall incidence rates of new smear-positive tuberculosis from routine notifications and repeat medical examination

Taking the cases identified by both the register match and the repeat medical examination into account, 41 new smear-positive TB cases were detected. Of these, 18 (44%) cases from the 'other abnormal CXR' group, 14 (34%) cases from the 'normal CXR' group and 9 (22%) cases from the 'TB-suggestive CXR' group were identified with new smear-positive TB during the 2-year follow-up (Table 5). The overall incidence of smear-positive TB in the 'TB-suggestive CXR' group was 1.44% per year (95%CI 0.70–2.65), which was higher than in the 'other abnormal CXR' group (0.75% per year, 95%CI 0.46–1.16), although the difference was not statistically significant ($P = 0.124$).

DISCUSSION

Epidemiological impact of detecting and treating all bacteriologically positive tuberculosis

This study revealed a 62% reduction in the number of smear-positive TB cases notified to the NTP over 2 years of follow-up in the survey areas, i.e., 34 cases identified compared with the 90 cases expected. As the survey areas were selected for the national survey using a cluster sampling method, they are representative of the whole country. However, some of the participants in the prevalence survey may have moved away, and the number of notified cases could be underestimated; accordingly, assuming a migration rate of 15% in the register match and in the repeat medical examination, the notified number of new smear-positive TB cases would increase by 18% to 40. With the seven new smear-positive TB cases detected by repeat medical examination, the revised standardised notification ratio is 0.53 (95%CI 0.39–0.69), which is still significantly lower than the expected number of cases ($P < 0.001$).

This observation indicates that initial mass screening using the screening approach recommended by the WHO for prevalence surveys,¹² combined with a

Table 5 Overall incidence rates of new smear-positive TB from routine notification and medical examination

Prevalence survey, 2002		New smear-positive TB detected		Overall incidence rate of new smear-positive TB %/year (95%CI)
CXR findings	<i>n</i>	Registry match	Medical examination	
TB suggestive CXR	300	4	5	1.44 (0.70–2.65)
Other abnormal CXR*	1 173	16	2	0.75 (0.46–1.16)
Normal CXR	20 407	14	Not done	0.03 (0.02–0.06)
Total	21 889	34	7	0.09 (0.07–0.13)

* Suspected TB, healed TB, and other lung diseases on CXR.

TB = tuberculosis; CXR = chest radiography.

routine DOTS-based programme with good treatment outcomes, resulted in a rapid reduction in incidence. Although mass screening by CXR in developing countries has been discouraged due to its high costs and doubtful impact,^{18,19} our study suggests that active case finding can have the potential to substantially reduce TB incidence in high-burden areas when applied to epidemiologically appropriate settings and coupled with strong and effective DOTS.^{8,19-21} The rapid reduction in incidence of smear-positive TB over a short period of time was likely brought about by the detection and treatment of all bacteriological TB cases, which would lead to reduced progression from smear-negative to smear-positive TB as well as reduced transmission.

The role of CXR in TB case finding was recently reexamined due to its higher sensitivity than symptom screening or smear microscopy.²² CXR screening is highly sensitive, particularly when any abnormality is taken as eligibility for bacteriological examination. As 61% of the bacteriologically confirmed TB cases in the prevalence survey⁶ did not meet the definition of cough ≥ 3 weeks as TB suspects and as radiological examination is available only at the hospital and not at the health centre in Cambodia, CXR screening should be recommended for both active and passive case finding. Cost-effectiveness analyses are important before recommending widespread screening, however. A recent study on the cost-effectiveness of active case finding in Cambodia²³ concluded that CXR screening was cost-effective and that it was likely to have additional benefits such as contribution to early case finding and detection of patients from a vulnerable age group, although the study did not assess effectiveness as cases averted or reduction in prevalence.²⁴

Positive conversion in individuals with different previous radiological findings and its contribution to tuberculosis incidence

Several studies conducted before the human immunodeficiency virus (HIV) era showed that the incidence of bacteriologically positive TB among untreated persons with fibrotic, stable CXR lesions suggestive of healed TB varies between 0.26% and 1.36% per year.²⁵⁻²⁸ The incidence rate of 2.9% per year seen in the 'other abnormal CXR' group in the present study is higher, probably because our study subjects had a wider range of CXR abnormalities, including advanced or healed lesions. Another possible factor that could have caused the higher risk is HIV co-infection; a national survey conducted in Cambodia in 2003 showed 11.8% HIV prevalence among TB patients.²⁹ A higher incidence rate of 5.4% per year was observed among tuberculin converters who were HIV-positive.³⁰

The absolute number of smear-positive TB cases from the 'other abnormal CXR' group was double the number from the 'TB-suggestive CXR' group and exceeded the number from the 'normal CXR' group.

As no information about radiological findings except for 'normal' or 'not normal' was provided for either participants or health centre staff, it is improbable that culture-negative subjects with abnormal CXRs would have been more likely to be detected by the NTP than subjects with normal CXR. To accelerate the reduction in TB incidence, more careful follow-up or isoniazid preventive therapy (IPT) should be considered for individuals with abnormal findings on CXR and negative cultures, particularly in settings such as Cambodia, where a significant proportion of disease may occur by reactivation. Without the combination of treatment of latent TB infection, it is difficult in theory to bring incidence down to 1 per million population by 2050 even by treating all active TB cases.³¹

Repeated active case finding

The repeat medical examination 2 years after the initial survey detected 10 additional smear-positive TB cases and 104 additional smear-negative, culture-positive TB cases, including recurrent cases. The routine DOTS-based NTP had detected 35 (78%) of the 45 incident smear-positive cases, and thus seemed to be functioning well in detecting smear-positive TB. However, only 3 (3%) of the 107 incident smear-negative cases had been detected. The second wave of targeted screening thus contributed to the detection of 97% of smear-negative TB cases and 75% (114/152) of the total incident bacteriologically positive cases during the follow-up period. This implies that active case finding in high-risk groups with abnormal findings on CXR should be repeated to avoid weakening the effect of the initial screening. However, the long-term effects of repeated active case finding require further analyses.

The present study has some limitations. First, we did not trace the 258 (15%) absentees from the repeat medical examination, most of whom had moved away from the study site. Although they were not likely to have severe disease, assuming the same incident risk of TB as the participants, one or two of these ($258 \times 10/1423$) would have been likely to have had smear-positive TB. Second, the question might arise as to whether we captured all subsequent smear-positive TB cases in the surveyed areas. As no medical examinations were performed for the 20 407 persons with a normal CXR at baseline, some cases of smear-positive TB may have remained undiagnosed in this group. However, considering that only seven new smear-positive TB cases were detected by repeat medical examination and that 34 (83%) new smear-positive cases were notified under the NTP, the 41 subsequent new smear-positive cases detected in the study comes closer to the true incidence than the notifications reported before the survey. Third, the analysis assumed that smear-positive TB cases were all new cases except for the confirmed recurrent cases identified in the initial survey, as most study subjects

were not aware of their TB history, and smear-positive relapse cases accounted for only 3% of notified cases in the Cambodia NTP.¹⁶

CONCLUSION

Detecting and treating smear-negative, culture-positive TB cases as well as smear-positive TB cases may lead to a rapid reduction in the subsequent incidence of smear-positive TB in high-burden countries. Active case finding using the screening approach recommended for prevalence surveys is an effective measure when applied to settings with large epidemics and when coupled with a well-functioning DOTS-based programme. Careful follow-up or isoniazid preventive therapy for sputum culture-negative individuals with abnormal CXR findings, who are at high risk of disease progression in a short period of time, should be considered in settings where a significant proportion of disease may occur by reactivation, although further studies are required on the feasibility and cost-effectiveness of such interventions.

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R É S U M É

OBJECTIF: Evaluer l'impact épidémiologique du dépistage massif de la tuberculose (TB) dans la collectivité et le pronostic chez les individus à examen bactériologique négatif dont les clichés thoraciques (CXR) révèlent des anomalies.

MÉTHODES: Deux ans après l'enquête de prévalence au Cambodge, on a mené une étude de suivi en deux parties : la collation des cas déclarés de TB du registre avec 22 160 participants dans une enquête nationale de prévalence de la TB et un examen médical répété pour les sujets de l'enquête de prévalence dont le CXR comporte des anomalies.

RÉSULTATS: La comparaison avec le registre a détecté 34 nouveaux cas de TB à bacilloscopie positive, ce qui équivaut à un ratio standardisé de déclaration de 0,38 (IC95% 0,27–0,52). L'examen médical a détecté en plus

sept nouveaux cas de TB à bacilloscopie positive et 93 nouveaux cas à bacilloscopie négative et à culture positive. Les taux d'incidence de TB à examen bactériologique positif ont été de 8,5% par an (IC95% 6,3–11,2) chez ceux dont les CXR étaient suggestifs d'une TB active et de 2,9% par an (IC95% 2,2–3,7) chez ceux dont le CXR comportait d'autres anomalies.

CONCLUSIONS: La détection et le traitement des cas de TB à bacilloscopie négative et à culture positive, ainsi que ceux des cas de TB à bacilloscopie positive, sont en association avec une réduction rapide de l'incidence ultérieure des nouveaux cas de TB à bacilloscopie positive. Les individus dont les cultures de crachats étaient négatives mais dont les CXR comportaient des anomalies sont à risque élevé de progression de la maladie et exigent un suivi et potentiellement un traitement préventif.

R E S U M E N

OBJETIVO: Evaluar la repercusión epidemiológica de la detección colectiva de la tuberculosis (TB) en la comunidad y el pronóstico de las personas con resultados bacteriológicos negativos que presentan imágenes anormales en la radiografía de tórax (CXR).

MÉTODOS: En Camboya, se llevó a cabo un estudio de seguimiento que comportó dos etapas: primero, se cotejaron los registros de los casos de TB notificados con los 22 160 participantes en una encuesta nacional de prevalencia de TB 2 años antes, y se repitió el examen médico a las personas de la encuesta que habían presentado imágenes anormales en la CXR.

RESULTADOS: Al cotejar los datos del registro, se detectaron 34 casos nuevos de TB con baciloscopia positiva, lo cual llevó a un cociente normalizado de notificación de 0,38 (IC95% 0,27–0,52). Con el examen clínico se

detectaron siete casos nuevos suplementarios de TB con baciloscopia positiva y 93 casos nuevos con baciloscopia negativa y cultivo positivo. Las tasas de incidencia de TB confirmada bacteriológicamente fueron 8,5% por año (IC95% 6,3–11,2) en las personas con CXR indicativas de TB activa y 2,9% por año (IC95% 2,2–3,7) en las personas con otro tipo de CXR anormales.

CONCLUSIÓN: La detección y el tratamiento de los casos de TB con baciloscopia negativa y cultivo positivo, además de los casos con baciloscopia positiva, generaron una rápida disminución de las incidencias posteriores de casos nuevos de TB con baciloscopia positiva. Las personas con cultivos negativos de las muestras de esputo e CXR anormales presentan un alto riesgo de progresión hacia la enfermedad activa y precisan un seguimiento y posiblemente un tratamiento preventivo.