Should sputum-negative presumptive TB patients be actively followed to identify missing cases in India?

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Setting: Sputum smear microscopy, the primary diagnostic tool used for diagnosis of tuberculosis (TB) in India's Revised National TB Control Programme (RNTCP), has low sensitivity, resulting in a significant number of TB cases reported as sputum-negative. As the revised guidelines pose challenges in implementation, sputum-negative presumptive TB (SNPT) patients are subjected to 2 weeks of antibiotics, followed by chest X-ray (CXR), resulting in significant loss to care among these cases.

Objective: To determine whether reducing delays in CXR would yield additional TB cases and reduce initial loss to follow-up for diagnosis among SNPT cases.

Methods: In an ongoing intervention in five districts of Maharashtra, SNPT patients were offered upfront CXR.

Results: Of 119 male and 116 female SNPT patients with a mean age of 45 years who were tested by CXR, 32 (14%) were reported with CXR suggestive of TB. Administering upfront CXR in SNPT patients yielded twice as many additional cases, doubling the proportion of cases detected among all those tested as against administering CXR 2 weeks after smear examination.

Conclusion: Our interventional study showed that the yield of TB cases was significantly greater when upfront CXR examination was undertaken without waiting for a 2-week antibiotic trial.

India is one of the 22 high tuberculosis (TB) burden countries and home to approximately 27% of the world's prevalent TB cases.¹ An estimated 2.8 million TB cases are diagnosed annually in India,² and Maharashtra, with an annual TB incidence rate of 197 per 100 000 population, is one of India's high TB burden states.² Maharashtra has been able to achieve high case holding, and has a cure rate of around 85% for new smear-positive cases. Despite these successes, the annual case detection rate has stagnated at less than 75%.²

The diagnosis of pulmonary TB in India remains largely dependent on sputum smear microscopy. The specificity of smear microscopy is high but the sensitivity is variable (20–80%).³ In low- and middle-income countries, most cases of sputum-negative TB (SNTB), accounting for almost 50% of all new TB cases notified annually, are diagnosed on the basis of clinical presentation, radiological findings and other laboratory-based results.⁴ Various algorithms have been proposed to optimise the number of patients correctly diagnosed and treated for SNTB while minimising the over-treatment of patients without the disease, missed TB cases or initial loss to follow-up (LTFU).⁵

India's Revised National TB Control Programme (RNTCP) guidelines recommend that patients with two sputum smear-negative results should be subjected to 2 weeks of broad-spectrum antibiotics, followed by chest X-ray (CXR) if symptoms persist.⁶ The RNTCP recently revised the diagnostic algorithm that suggests upfront CXR for sputum-negative cases followed by a cartridge-based nucleic acid amplification test (CBNAAT) for the confirmation of results where CXR findings are suggestive of TB.⁷ These guidelines have not been rolled out uniformly across the states, however, and earlier guidelines are still being followed in the field due to a lack of resources in the public health system.

Although CBNAAT tests have recently been offered under the RNTCP, the inaccessibility of these tests makes the system dependent on CXR to a large extent as a screening tool among SNTB cases.⁸ In many districts, CXR laboratories are not readily available in the public health facilities, making it difficult to follow the revised RNTCP algorithm of upfront CXR.⁸ While the earlier algorithm reduces the number of CXRs required for the diagnosis of SNTB, it delays treatment for TB cases and increases the risk of initial LTFU before diagnosis due to weak or absent linkages with further diagnostic services. The 2-week antibiotic trial also increases the risk of false-negative diagnoses due to improvement of symptoms in TB patients with secondary, non-tuberculous bacterial infections. This could contribute to continued transmission in the community.

Earlier studies testing a TB diagnostic algorithm based on an antibiotic trial found that clinicians missed nearly 50% of smear-negative, culture-confirmed cases after a positive response to antibiotics.⁹ The World Health Organization has recommended upfront CXR among SNTB cases in low-resource settings to increase the efficiency of diagnostic algorithms for TB.³

Given the above risks, CXR could be offered upfront after a negative smear result in resource-constrained settings with limited access to high sensitivity diagnostic tests such as CBNAAT or sputum culture. A study from Pakistan estimated the cost of CXR examination at US\$1 (the public sector price) per patient, which is similar to the cost of a 5-day course of antibiotics.¹⁰

STUDY POPULATION, DESIGN AND METHODS

We conducted a pilot study within an on-going intervention project of community-based active case find-

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ing as part of the Global Fund-supported Project Axshya in India. The objective of the intervention was to assess whether offering an upfront CXR examination yields additional TB cases.

The pilot intervention planned to provide upfront CXR examinations immediately following a negative sputum smear result without waiting for completion of a 2-week antibiotic course. Project Axshya is implemented in 10 districts of Maharashtra by Population Services International (PSI, New Delhi, India). The intervention was conducted in 16 designated microscopy centres (DMC) in five of the 10 districts where Project Axshya was implemented during April–June 2015. Linkages were established with public radiology facilities (and private facilities where public radiology centres were non-functional) for this purpose.

TB programme officials at state and district levels were actively involved in the intervention. Medical officers posted at intervention DMCs prescribed upfront CXR to smear-negative presumptive TB (SNPT) cases. The interpersonal communication coordinator (IPCC) leading the project activities in the selected districts contacted the SNPT cases to explain the need for a CXR and to obtain consent. Consenting SNPT cases were linked to the identified radiology facilities. Further evaluation of presumptive TB patients by rapid molecular technologies (CBNAAT, etc.) was not undertaken in the absence of programme guidelines at the time of the study and local availability of these technologies.

Study design

This was a descriptive analytical study conducted as part of the regular intervention under the Global Fund-supported Project Axshya.

Study population

All presumptive TB patients whose sputum samples were collected and transported to DMCs through community-based active case finding and found to be sputum-negative during April–June 2015 were included in the study. All patients were line-listed from the DMC laboratory registers and contacted by the project staff. Those who consented to participate in the intervention were offered free upfront CXR examinations.

Selection of public and private facilities for conducting quality CXR

The CXR facilities were primarily selected on the basis of the accessibility of laboratories for the SNPT cases (target population). Public CXR facilities were primarily sought to ensure the acceptability of CXR among the medical officers at the selected DMCs. Wherever the public CXR facilities were non-functional, private sector CXR facilities accessible to the target population with qualified radiologists for reporting the CXR results were selected to administer the CXR examinations.

The SNPT cases identified through the intervention were issued vouchers by the project staff for conducting CXRs at the selected public and private CXR facilities. Through the vouchers, the CXR facilities were able to identify the SNPT patients referred from the project, and the CXR services were provided to these patients against the vouchers issued.

Participant recruitment, data collection and ensuring data quality

The data from the DMC laboratory registers were collected according to a prescribed format by the IPCC. Participants identified from active case finding and found to be sputum-negative were contacted by the project staff and the need for CXR was explained. For those patients who didn't agree, help was received from the medical officers at the DMCs to convince them of the

FIGURE Algorithm followed for the intervention. SNPT = smear-negative presumed TB; CXR = chest X-ray; TB = tuberculosis.

need for CXR. As the CXR was an additional intervention and not routine practice, written consent was obtained from the participants. After consenting, the participants were provided with vouchers for conducting CXRs at the public and private laboratories included in the study. Presumptive TB patients who had taken antibiotics for even 1 day and those who did not provide consent for the CXR were excluded (Figure).

CXR results were read and reported by qualified radiologists at the private and public facilities and were also reviewed by medical officers at the DMCs. SNPT cases were then diagnosed by medical officers based on clinical examination and CXR results, according to RNTCP guidelines. New TB cases identified in the study were initiated on treatment according to guidelines. Standard formats were developed for collecting the data, and project staff were trained on collecting data from the DMCs and the CXR laboratories using these formats. The CXR reports were made by qualified radiologists. Data quality was monitored by programme managers from the project and the data were cross-verified with the DMC registers.

Data analysis

We conducted a descriptive statistical analysis of the data using Microsoft Excel 2016 (Microsoft Corp, Redmond, WA, USA). We calculated the yield of new smear-negative TB (SNTB) cases identified through upfront CXR. We did a comparative analysis of the proportion of the increase in detection of TB among sputum-negative TB cases and the proportion of the decrease in initial LTFU before diagnosis among SNPT cases during the intervention period (April–June 2015). The calculated indicators for the intervention period were compared to the indicators for the same period in the previous year (calculated using programme data).

TABLE 1 Analysis by district of smear and X-ray results among patients tested for TB in five intervention districts of Maharashtra, India, April–June 2015

District	Presumptive TB cases with sputum samples collected and transported to laboratory for diagnosis <i>n</i>	Among (B), cases diagnosed as new SPTB <i>n</i>	Patients diagnosed with SPTB %	Among (B), patients reported as smear-negative on smear examination <i>n</i>	Among (E), cases for whom CXR was paid for by project <i>n</i>	Among (E), cases who underwent CXR on their own in public/private facility <i>n</i>	Total CXR results available <i>n</i>	Among (E), cases who did not undergo CXR for any reason <i>n</i>	Among (H), cases with results suggestive of TB <i>n</i>	Patients diagnosed with TB <i>n</i>
A	B	C	D = (C/B)	E = B–C	F	G	H = F+G	I = (E–H)	J	K = C+J
Kolhapur (rural)	121	8	6.6	113	82	1	83	30	13	21
Kolhapur (urban)	71	9	12.7	62	41	2	43	19	1	10
Sangli (rural)	84	2	2.4	82	35	4	39	43	9	11
Sangli (urban)	54	6	11.1	48	23	0	23	25	1	7
Latur	119	1	0.8	118	47	0	47	71	8	9
Total	449	26	5.8	423	228	7	235	188	32	58

TB = tuberculosis; SPTB = smear-positive pulmonary TB; CXR = chest X-ray.

Ethical considerations

The study protocol was developed with input from the state RNTCP officials. The protocol was approved by the Ethics Advisory Group of the International Union Against Tuberculosis and Lung Disease (Paris, France). Written, informed consent was obtained from each eligible participant before conducting the CXR examination.

RESULTS

Of 423 presumptive TB patients reported as smear-negative on microscopy during the intervention period (April–June 2015, Table 1) across five intervention districts, 235 (56%) consented to undergo upfront CXR without waiting for the results of an antibiotic course. As all those who consented to CXR were escorted by project staff to the CXR facility, there was no time lag in CXR examination after receiving the voucher. Participants were equally distributed between men ($n = 119$, 51%) and women ($n = 116$, 49%). The average age of the patients was 44 years (interquartile range [IQR] 35–47).

Among 235 SNPT patients tested by CXR, 32 (14%) were diagnosed with TB (Table 1). Of the total CXRs performed, most were obtained from private laboratories (80%). Only 20% of patients underwent CXR in government facilities, as nine of the 14 government X-ray laboratories available were not functional and two were not accessible for patients; the 46 (20%) CXRs performed in government facilities were conducted in three laboratories. Among the 32 diagnosed SNPT patients, 28 (88%) were initiated on DOTS by medical officers. The mean time to treatment initiation following diagnosis of SNPT was 3 days. Among the remaining four patients (13%) not initiated on anti-tuberculosis treatment, one died before treatment initiation, one decided to obtain treatment from the private sector, one was prescribed a 14-day antibiotic course by a medical officer and one was unwilling to undergo treatment.

Of 188 (44%) eligible presumptive TB cases who did not undergo immediate upfront CXR, the reasons identified for not doing so were patient-related for 137 (73%) and CXR facility-related

for 51 (27%) (Figure). Of the 188 patients, 99 (53%) refused CXR for personal reasons, 26 (14%) underwent antibiotic treatment in the private sector, 6 (3%) went out of town without leaving contact information, 4 (2%) were bedridden at home, 1 (0.5%) was hospitalised and 1 (0.5%) died before undergoing CXR. Another 46 (24%) patients were unable to reach a CXR facility due to the distance, 3 (2%) had difficulty finding a convenient time to reach the CXR facility during opening hours and 2 (1%) had their CXR rejected due to issues of poor quality.

A comparison of new SNPT cases detected in the same intervention DMCs during the same quarter of the previous year (April–June 2014) (Table 2) showed that administering upfront CXR almost doubled the TB detection rate among presumptive TB patients (12.9% vs. 5.3%, $P < 0.05$) (Table 3).

DISCUSSION

In areas where access to more sensitive diagnostic tests such as CBNAAT or sputum culture is limited, SNPT patients rely on clinicians for a diagnosis based on clinical and radiological findings. While the available literature suggests that the sensitivity and specificity of CXR is relatively low compared with molecular tests such as CBNAAT or drug susceptibility testing, previous studies conducted in settings with low human immunodeficiency virus (HIV) prevalence such as Pakistan showed that the diagnostic skills of primary care clinicians working in low HIV burden settings can be improved significantly using radiological criteria for TB, improving access to X-ray facilities and appropriate training of health professionals.¹⁰ Our study found that using upfront CXR and clinical evaluation without waiting for the results of a 2-week course of antibiotics in SNPT patients helped to identify an equal number of additional SNPT patients to that diagnosed by smear alone, and resulted in the initiation of anti-tuberculosis treatment in 90% of diagnosed patients.

India's RNTCP recently revised a diagnostic algorithm recommending upfront use of CXR without a prior course of antibiotics; this is not, however, uniformly implemented across the country due to the unavailability of functional X-ray facilities.⁸ The accessibility of CXR machines is a huge challenge across the public

TABLE 2 Analysis by district of smear and X-ray results among patients tested for TB in five intervention districts of Maharashtra, India, in the same quarter of the previous year (April–June 2014)

District	Presumptive TB cases with sputum samples collected and transported to laboratory for diagnosis <i>n</i>	Among (B), cases diagnosed as new SPTB <i>n</i>	Patients diagnosed with SPTB %	Among (B), patients reported as smear-negative on smear examination <i>n</i>	Among (E), cases for whom CXR was paid for by project <i>n</i>	Among (E), cases who underwent CXR on their own in public/private facility <i>n</i>	Total CXR results available <i>n</i>	Among (E), cases who did not undergo CXR for any reason <i>n</i>	Among (H), cases with results suggestive of TB <i>n</i>	Patients diagnosed with TB <i>n</i>
A	B	C	D = C/B	E = B–C	F	G	H = F+G	I = E–H	J	K = C+J
Kolhapur (rural)	157	5	3.2	152	0	15	15	137	1	6
Kolhapur (urban)	84	4	4.8	80	0	9	9	71	0	4
Sangli (rural)	104	6	5.8	98	0	9	9	89	2	8
Sangli (urban)	52	1	1.9	51	0	12	12	39	0	1
Latur	134	8	6.0	126	0	11	11	115	1	9
Total	531	24	4.5	507	0	56	56	451	4	28

TB = tuberculosis; SPTB = smear-positive pulmonary TB; CXR = chest X-ray.

health system in terms of following the new guidelines,⁸ and linking with available private CXR laboratories is necessary.

In our study, the use of upfront CXR facilitated early and rapid TB diagnosis among SNPT cases and helped to identify additional new SNTB cases. A large proportion of presumptive cases, however, were unable or unwilling to undergo immediate CXR. We also found that active follow-up of SNPT cases by the project staff resulted in a higher rate of X-ray uptake. This suggests that strong follow-up is required to persuade patients to undertake different diagnostic tests if the tests are not performed at the same time.

Although offering upfront CXR could reduce initial LTFU for diagnosis and facilitate early case detection, the incremental cost-effectiveness of this approach compared to antibiotic drug trials followed by CXR still needs to be evaluated. Furthermore, the expanded coverage of more specific and sensitive diagnostic tests, such as CBNAAT, may expedite diagnosis. In the meantime, a validated, cost-effective TB diagnostic algorithm for resource-constrained settings remains a vital necessity.

Limitations

This study had a number of methodological limitations. As it was a pilot intervention as part of ongoing community-based active case-finding activities, our study participants were identified via convenience sampling. Furthermore, due to resource constraints,

we were unable to validate SNPT diagnoses based on clinical and radiological evidence with a more sensitive TB diagnostic such as sputum culture. We were also unable to evaluate the sensitivity or specificity of this diagnostic algorithm.

We tried to minimise initial LTFU for diagnosis by using project staff to motivate presumptive TB cases and accompany them to undergo CXR. Half of the SNPT patients examined during the study period failed to return, however. We were unable to obtain any clinical information for these patients. Non-attendance at the second visit may have been due to clinical improvement, difficulty in accessing a tertiary facility twice or resorting to other alternatives. Nevertheless, this may have caused attrition bias, restricting our sample to a higher proportion of patients who either failed to respond to antibiotics or who had limited means to seek alternative health care facilities.

CONCLUSION

Our intervention study showed that the yield of TB cases was significantly higher when upfront CXR was performed without waiting for the results of a 2-week antibiotic trial. Administering upfront CXR in SNPT patients doubled the case detection rate among all those tested.

We found a moderate uptake of upfront CXR among presumptive TB patients reported to be sputum-negative in India, and we

TABLE 3 Comparison of TB cases detected by upfront CXR (April–June 2015) and after a 2-week course of antibiotics in smear-negative presumptive TB patients (April–June 2014), Maharashtra, India*

April–June 2014 (CXR undertaken after 2-week course of antibiotics)					April–June 2015 (upfront CXR)				
Total PTB cases tested by sputum AFB <i>n</i>	Total sputum-positive <i>n</i>	Total tested by CXR <i>n</i>	Total cases diagnosed by CXR <i>n</i>	Cases diagnosed by sputum AFB and CXR <i>n</i>	Total PTB cases tested <i>n</i>	Total sputum positive <i>n</i>	Total tested by CXR <i>n</i>	Total cases diagnosed by CXR <i>n</i>	Cases diagnosed by sputum AFB and CXR <i>n</i>
531	24	56	4	28	449	26	235	32	58

*OR 2.66 (95%CI 1.67–4.25).

TB = tuberculosis; CXR = chest X-ray; PTB = pulmonary TB; AFB = acid-fast bacilli.

identified a number of barriers to CXR uptake, including patient refusal, difficulties travelling to the laboratory and a lack of time to pursue additional tests. Even without the 2-week antibiotic trial, initial LTFU for diagnosis was recorded in our study. Although additional research might explore the relative cost-effectiveness of TB algorithms in settings with limited laboratory capacity, our results highlight the need for more sensitive TB diagnostics that provide timely results in locations convenient to patients.

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Contexte : La microscopie de frottis de crachats, le premier outil utilisé dans le diagnostic de la TB dans le programme national TB révisé d'Inde (RNTCP), a une faible sensibilité, ce qui aboutit à un nombre significatif de cas de TB rapportés comme étant à frottis négatif. Comme la mise en œuvre des directives révisées reste un défi, les patients présumés TB à frottis négatif (SNPT) sont soumis à 2 semaines d'antibiotiques suivis par une radiographie pulmonaire (CXR), d'où un nombre significative de cas de SNPT perdus de vue.

Objectif : Déterminer si la réduction du délai de CXR aboutit à détecter des cas de TB supplémentaires et réduit les pertes de vue initiales parmi les cas de SNPT.

Méthodes : Dans le cadre d'une intervention en cours dans cinq

districts de Maharashtra, on a offert aux cas de SNPT une CXR immédiate.

Résultats : Un total de 119 hommes et 116 femmes, patients SNPT, d'âge moyen 45 ans, ont eu une CXR. Parmi ces 235 patients, 32 (14%) ont eu une CXR suggestive de TB. Le recours immédiat à une CXR chez les patients présumés TB à frottis négatif a produit deux fois plus de cas supplémentaires et doublé la proportion de cas détectés parmi les patients ayant bénéficié d'une CXR immédiate par rapport à ceux l'ayant eue 2 semaines après la microscopie de frottis.

Conclusion : Notre étude d'intervention a montré que la détection de cas de TB était significativement plus importante en faisant une CXR immédiate sans attendre les 2 semaines de traitement d'essai par antibiotiques.

Marco de referencia: La baciloscopia del esputo es el principal instrumento utilizado en el diagnóstico de la tuberculosis (TB) en el marco del Programa Revisado de Control de la Tuberculosis de la India (RNTCP) y ofrece una baja sensibilidad, con lo cual un gran número de casos de TB se notifican con baciloscopia negativa. Dadas las dificultades de aplicación de una revisión reciente de las directrices, en los pacientes con presunción clínica de TB y un resultado negativo de la baciloscopia se administran antibióticos de amplio espectro durante 2 semanas seguidos de una radiografía de tórax (CXR), con la consiguiente pérdida de la atención de muchos de los pacientes con baciloscopia negativa.

Objetivo: Determinar si el hecho de acortar la demora en la realización de la CXR mejora el rendimiento diagnóstico de casos de TB y disminuye las pérdidas iniciales durante el seguimiento de los casos con baciloscopia negativa.

Método: En el marco de una intervención en curso en cinco distritos

de Maharashtra, se propuso a los pacientes con presunción clínica de TB y baciloscopia negativa practicar de inmediato la CXR.

Resultados: Se practicó la CXR en pacientes con presunción de TB pulmonar y baciloscopia negativa; participaron 119 pacientes de sexo masculino y 116 de sexo femenino, con una edad promedio de 45 años. De estas 235 personas, en 32 casos el informe de la CXR refería imágenes indicativas de TB (14%). La práctica inmediata de la CXR en los pacientes con presunción clínica de TB que reciben un resultado negativo de la baciloscopia aportó el doble de casos adicionales y duplicó así la proporción de casos detectados en todas las personas examinadas, en comparación con la CXR practicada 2 semanas después de la baciloscopia.

Conclusión: El presente estudio de intervención reveló un aumento considerable del rendimiento diagnóstico de casos de TB cuando se practica la CXR de inmediato, en lugar de esperar el resultado de una antibioterapia de prueba de 2 semanas.