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Early chest X-ray in persons with presumptive tuberculosis increases Xpert® MTB/RIF diagnostic yield and efficiency

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Adult presumptive tuberculosis (TB) patients (n = 1690) were screened for TB using a questionnaire, chest X-ray (CXR) and sputum microscopy for acid-fast bacilli (AFB); *Mycobacterium tuberculosis* culture was performed for 74% of the patients and Xpert® MTB/RIF was done for 17.2%. Among patients recruited, 943 (55.8%) were diagnosed with TB, of whom 870 (92.3%) were bacteriologically confirmed and 73 (7.7%) were clinically diagnosed on the basis of CXR. Using CXR prior to culture or Xpert testing reduces the number needed to screen from 7.6 to 5.0. Using CXR to triage for culture or Xpert testing reduces the number of missed cases and increases the efficiency of culture and Xpert testing.

Indonesia has the third highest tuberculosis (TB) incidence globally.[1] TB patients in Indonesia are mainly identified using passive case finding. *Mycobacterium tuberculosis* culture, the gold standard for diagnosing TB, is included in the national TB diagnosis algorithm (Supplementary Figure S1), but is used only for patients with rifampicin (RIF) resistance as diagnosed using Xpert® MTB/RIF assay (Cepheid, Sunnyvale, CA, USA).[2]

Although Xpert is included in the algorithm from the beginning of the diagnostic process, Bandung City had only three laboratories equipped with Xpert during the study period between 2013 and 2017. Sputum microscopy for acid-fast bacilli (AFB) is widely available in hospitals, private laboratories, and primary health care (PHC) facilities. Chest X-ray (CXR) is also widely available, but is used in the programmatic algorithm only when there is no access to Xpert, and only if sputum microscopy results are negative.

As part of a study on diabetes and TB,[3] we aimed to determine the added value of CXR for TB screening in presumptive TB patients in Bandung during 2014–2017.

METHODS

Presumptive TB patients recruited in Bandung during 2014–2017 were screened using a structured questionnaire in 44 community health centres and outpatient clinics of both a district hospital and a provincial referral hospital. Patients were included if they were ⩾18 years old and had at least two of the following symptoms: cough, productive cough, haemoptysis, fever, night sweats, weight loss, loss of appetite, chest discomfort and breathlessness.

Eligible patients were sent to a TB research clinic at the Faculty of Medicine Universitas Padjadjaran, Bandung City, Indonesia, to undergo physical examination, AFB and CXR. CXR was categorised as 'negative' if there were no abnormalities, or if there were abnormalities deemed not to be related to TB by the radiologist. CRX was 'positive' if the reading was suggestive of TB. MTB culture was done for patients using microscopic observation drug susceptibility assay (MODS).[4] Xpert was performed for patients who were suspected to have multidrug-resistant TB (MDR-TB) or on the pulmonologist's request. Patients with a positive CXR, but a negative bacteriology, were referred to a pulmonologist to determine whether they should be treated. The decision to treat was made based on a lack of clinical and radiological improvement after 2 weeks of non-specific antibiotics, or worsening of symptoms during follow-up. TB cases were categorised as bacteriologically confirmed TB if either sputum AFB, culture or Xpert was positive, or clinically diagnosed TB if bacteriologically negative, but the pulmonologist decided to start treatment.

The study was approved by the Ethics Committee London School of Hygiene & Tropical Medicine (London, UK; ref: 6449) and the Health Research Ethics Committee Faculty of Medicine, Universitas Padjadjaran (Bandung City, Indonesia; no:377/ UN6.C2.1.2/ KEPK/PN/2013).

RESULTS

Of 1758 patients, 1690 (96.1%) had complete AFB and CXR results and were included in the analysis. Of these, 55% were males, the median age was 45.5 years (interquartile range 32.5–57.4) , and 93% had cough for ⩾2 weeks (Table). As many as 1122 (66.4%) patients had a positive CXR, and 800 (47.3%) had positive AFB. Among the 1251 (74.0%) patients whose sputum was cultured, 743 (85.4%) had a positive result; among the 291 (17.2%) patients tested using Xpert, MTB was detected in 142 patients, with 16 RIF-resistant. The prevalence of TB was 55.8% (n = 943, 95% confidence interval [CI] 53.4–58.2), of whom 92.3% (n = 870, 95%CI 90.4–93.9) were bacteriologically confirmed and 7.7% (n = 73, 95%CI 5.8–9.3) were clinically diagnosed. Using AFB and CXR as the initial diagnostic tests, 800 AFB-positive patients were diagnosed as bacteriologically confirmed TB. An additional 138 cases (65 microbiologically confirmed and 73 clinically diagnosed) were diagnosed and confirmed for

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TABLE Clinical characteristics of presumptive TB patients, Bandung City, Indonesia, 2013-2017

Clinical characteristics	All patients (*n* = 1690) *n* (%)	AFB-positive (*n* = 800) *n* (%)	AFB-negative, CXR-positive (*n* = 355) *n* (%)
Male sex	933 (55.2)	449 (56.1)	211 (59.4)
Age, years, median [IQR]	45.5 [32.5–57.4]	40.8 [29.4–51.3]	50.0 [38.0–60.0]
Cough	1678 (99.3)	796 (99.5)	348 (98.0)
Duration of cough			
No cough	12 (0.7)	4 (0.5)	7 (2.0)
<1 week	45 (2.7)	9 (1.1)	16 (4.5)
1 week	52 (3.1)	18 (2.3)	16 (4.5)
2 weeks	358 (21.2)	75 (9.4)	101 (28.5)
3 weeks	162 (9.6)	56 (7.0)	35 (9.9)
>3 weeks	1057 (62.5)	636 (79.5)	179 (50.4)
Don't know	4 (0.2)	2 (0.3)	1 (0.3)
Cough with sputum	1551 (91.8)	739 (92.4)	314 (88.5)
Haemoptysis	272 (16.1)	91 (11.4)	82 (23.1)
Breathlessness	894 (52.9)	449 (56.1)	209 (58.9)
Chest discomfort	1094 (64.7)	524 (65.5)	231 (65.1)
Fever	1216 (72.0)	630 (78.8)	234 (65.9)
Night sweat	1224 (72.4)	610 (76.3)	253 (71.3)
Weight loss	1312 (77.6)	696 (87.0)	262 (73.8)
Loss of appetite	1173 (69.4)	604 (75.5)	252 (71.0)
Sputum microscopy			
Negative	890 (52.7)	0 (0.0)	355 (100.0)
Scanty	72 (4.3)	72 (9.0)	0 (0.0)
1+	208 (12.3)	208 (26.0)	0 (0.0)
2++	207 (12.2)	207 (25.9)	0 (0.0)
3+++	313 (18.5)	313 (39.1)	0 (0.0)
MTB culture result			
Negative	508 (30.1)	60 (7.5)	245 (69.0)
Positive	743 (44.0)	687 (85.9)	51 (14.4)
Not indicated or missing	439 (26.0)	53 (6.6)	59 (16.6)
Xpert MTB/RIF			
Not indicated	1399 (82.8)	675 (84.4)	219 (61.7)
MTB not detected	148 (8.8)	9 (1.1)	110 (31.0)
MTB+, RIF–	126 (7.5)	100 (12.5)	25 (7.0)
MTB+, RIF+	16 (0.9)	16 (2.0)	0 (0.0)
Error/indeterminate	1 (0.1)	0 (0.0)	1 (0.3)
Chest X-ray			
Normal/abnormal not TB	568 (33.6)	33 (4.1)	0 (0.0)
Suggestive of TB	1122 (66.4)	767 (95.9)	355 (100.0)
TB cases treated			
Bacteriologically confirmed	870 (51.5)	800 (100.0)	65 (18.3)
No bacteriological confirmation	73 (4.3)	0 (0.0)	73 (20.6)

TB = tuberculosis; AFB = acid-fast bacilli; CXR = chest X-ray; MTB = *Mycobacterium tuberculosis*; + = positive; – = negative.

treatment among CXR-positive patients using culture or Xpert; five TB cases that were both AFB- and CXR-negative could only be diagnosed using culture or Xpert (Figure). Had we used culture or Xpert testing only for AFB-negative, but CXR-positive patients, we would have tested 355 patients. The estimated yield is 65 more confirmed cases from 322 patients who had culture or Xpert results; the number needed to screen (NNS) to find one TB case was therefore 5.0 (95%CI 4.0–6.3), while five TB-positive patients out of the 210 AFB- and CXR-negative patients who underwent culture or Xpert testing would have been missed (Figure).

Had culture or Xpert been used for all AFB-negative patients without CXR triaging, we would have had to test 890 patients, with an estimated yield of 70 additional cases of 532 patients with available culture or Xpert results (NNS 7.6, 95%CI 6.1–9.6). It is not clear from our study how many of the 73 patients with a clinical diagnosis of TB based on CXR would have been diagnosed and treated had no CXR been done.

DISCUSSION

Using CXR as a triage for culture or Xpert led to more cases being diagnosed and more efficient use of Xpert.

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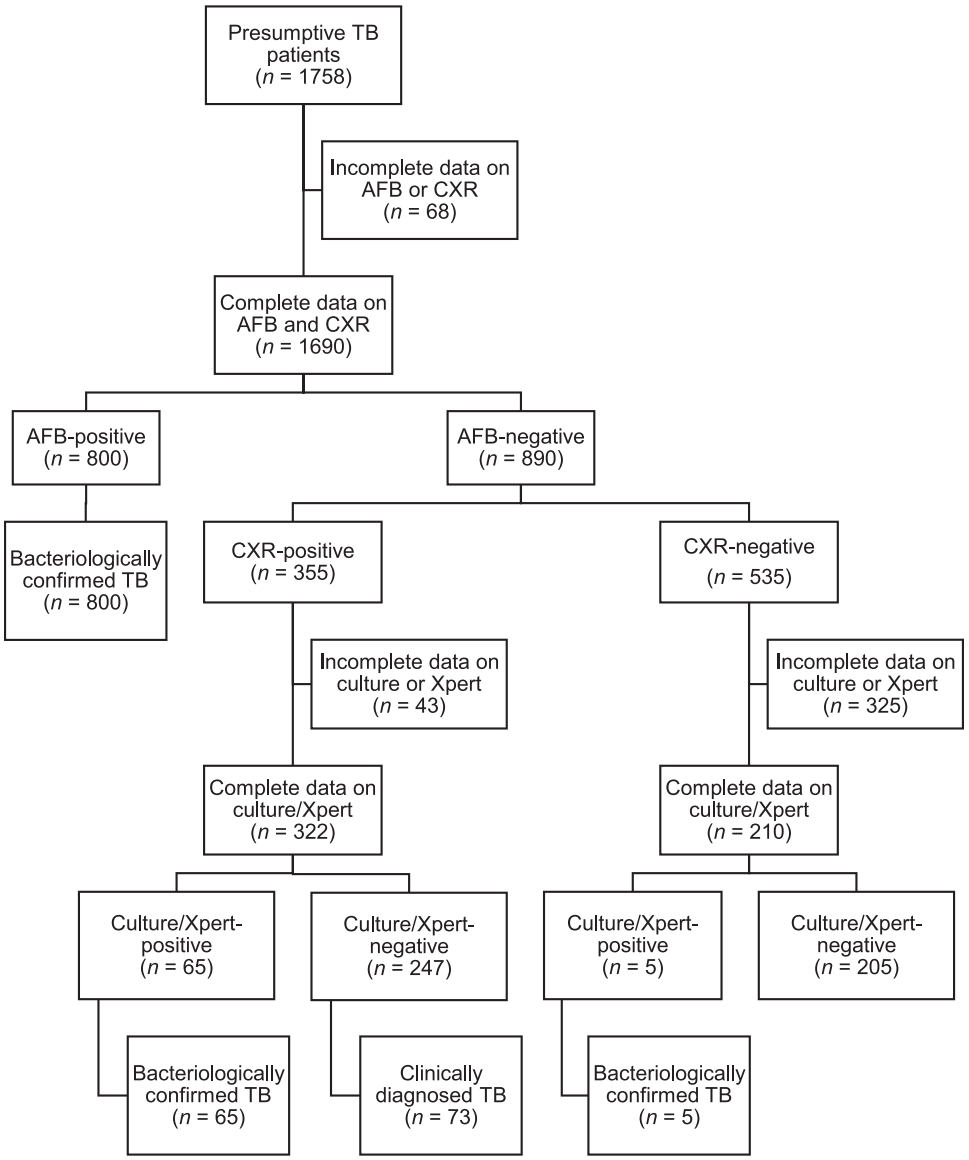

FIGURE Diagnostic flow chart of presumptive TB patients, Bandung City, Indonesia, December 2013-February 2017. TB = tuberculosis; AFB = acid-fast bacilli; CXR = chest X-ray.

Among patients with presumptive TB, more than half (55.8%) were diagnosed with TB disease. Of all TB cases, 870 (51.5%) were bacteriologically confirmed, which is higher than the yield of bacteriologically confirmed TB in the national prevalence survey (*n* = 245/8552, 2.9%) among those who were symptomatic.[5] This could be because our study examined patients who visited health care facilities with at least two TB symptoms, while symptom screening in the national prevalence survey included people in the general population who had cough for at least 2 weeks or had haemoptysis.

Among patients who were CXR-positive and bacteriology-negative, 22.7% (73/322) were treated for TB after an assessment by a pulmonologist, slightly lower than the 28.1% (71/253) of patients treated in Zambia.[6] The discrepancy of those with CXR-positive vs. the number treated shows that the decision to treat clinically diagnosed TB remains a difficult one. Although a proportion of these patients would have been bacteriologically positive if induced sputum and/or bronchoscopy was available,[7] CXR-positive patients with a history of TB could have haemoptysis due to lung damage from their past disease[8] or pulmonary aspergillosis.[9] Infiltrative lesions can also exist due to diseases other than TB.[10]

The main limitation of our study is that culture and Xpert were not performed on all patients. Therefore, some cases may have been missed, and as a result, the prevalence was underestimated and the 95%CIs of the estimated NNS overlapped (4.0–6.3 and 6.1–9.6). The use of upfront AFB and CXR for presumptive TB patients in this study resulted in 675 patients being confirmed based on AFB with no requirement for Xpert testing. If we assume that the proportion of RIF-resistant (RR-TB) cases in this group is the same as the rate of primary RR-TB in the general population of Indonesia (2.4%),[11] then 16 RR-TB patients may had been missed and started on incorrect treatment. A further prospective study with culture and Xpert testing of all patients is needed to confirm our finding.

The World Health Organization recommends that all presumptive TB patients undergo Xpert testing;[12] however, access in

low-resource settings remains limited. Our study showed that using widely available diagnostic tools such as AFB and CXR simultaneously at the start of the TB detection algorithm reduces the number of patients that need to be referred for Xpert testing. This finding is in line with the WHO recommendation that a normal CXR can be used to rule out patients requiring Xpert testing.[10] CXR could result in overdiagnosis if used as the only TB diagnostic tool due to its high sensitivity and low specificity.[13] A national policy and guideline recommending the use of CXR as an initial screening tool among presumptive TB patients is needed.

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Des patients adultes présumés atteints de TB (*n* = 1690) ont été dépistés à l'aide d'un questionnaire, d'une radiographie pulmonaire (CXR) et d'une microscopie de crachats à la recherche des bacilles acido-alcoolo-résistants; une culture de *Mycobacterium tuberculosis* a été réalisée chez 74% des patients et un test Xpert® MTB/RIF, chez 17,2%. Parmi les patients recrutés, 943 (55,8%) ont eu un diagnostic de TB, dont 870 (92,3%) ont été confirmés par bactériologie et 73 (7,7%) ont été diagnostiqués sur la CXR. Recourir à la CXR avant la culture ou le test Xpert réduit le nombre requis pour dépister un cas de 7,6 à 5,0. L'utilisation de la CXR pour le triage avant la culture ou le test Xpert réduit les cas manqués et augmente l'efficacité de l'utilisation de la culture et de l'Xpert.

Se investigó de la tuberculosis (TB) en pacientes adultos con presunción clínica de la enfermedad (*n* = 1690) mediante un cuestionario, la radiografía de tórax (CXR) y la baciloscopia del esputo; se practicó el cultivo para *Mycobacterium tuberculosis* en 74% de los pacientes y la prueba Xpert® MTB/RIF en 17,2%. De los pacientes que participaron se diagnosticó la TB en 943 (55,8%), de los cuales 870 (92,3%) con confirmación bacteriológica y 73 (7,7%) con diagnóstico clínico a partir de la CXR. El hecho de realizar la CXR o la prueba Xpert antes del cultivo disminuye de 7,6 a 5,0 el número de pacientes que deben someterse a detección. El uso de la CXR para seleccionar los casos en que se debe practicar el cultivo o la prueba Xpert disminuye los casos pasados por alto y aumenta la eficiencia del uso del cultivo y la prueba Xpert.

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