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The burden of non-TB lung disease presenting to TB clinics in The Gambia: preliminary data in the Xpert® MTB/Rif era

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In some low and middle-income countries, 10–20% of patients presenting with a persistent cough have tuberculosis (TB). Once TB is excluded, health service provision for alternative diagnoses is limited. We prospectively studied patients with two Xpert-negative sputum results presenting to a TB clinic in The Gambia. Of 239 patients, 108 did not have TB; 65/102 (6 were lost to follow-up) had alternative diagnoses, 24.6% of which were non-respiratory; 37/102 had no diagnosis, 27.0% of whom were HIV-1-positive; 37.8% had a history of TB and 24.3% smoked. We highlight the need for general health service integration with TB platforms and exploration of non-TB patients with chronic respiratory symptoms.

A leading cause of mortality related to non-communicable diseases (NCDs) is chronic respiratory disease, which is estimated to have caused 3.8 million deaths in 2015.[1] While tuberculosis (TB) remains a major problem, in some low- and middle-income countries (LMICs), only 10–20% of patients presenting with a persistent cough have TB.[2] There is thus a large proportion of patients with respiratory symptoms of unknown aetiology.

The advent of the Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA), a nucleic-acid amplification test, has led to earlier diagnoses as same-day results are now possible.[3] Xpert has a sensitivity of 89% compared to sputum culture, the gold standard; importantly, this increased sensitivity means that those who test negative are less likely to have active TB.

TB clinics have been ill equipped, both in terms of staff experience and equipment, to effectively diagnose and treat other respiratory diseases, despite the WHO strategy highlighting the Practical Approach to Lung Health (PAL).[4] We generated preliminary data in The Gambia on the potential of TB platforms to capture, investigate and manage chronic respiratory symptoms in patients classified as not having TB.

MATERIALS AND METHODS

We prospectively recruited all patients from a TB research clinic who did not meet the inclusion criteria (at least one sputum sample positive for TB on Xpert) for the TB Sequel Project, a study exploring the impact of TB on lung function.[5] All patients underwent a chest radiograph and rapid human immunodeficiency virus (HIV) testing (Alere Determine™ HIV-1/2 Ab/Ag; Abbott Laboratories, Chicago, IL, USA), with laboratory serology confirmation if positive (4th generation Liaison XL Murex HIV Ab/Ag assay [DiaSorin, Saluggia, Italy];[6] Hexagon HIV1/2 [HUMAN Diagnostics, Wiesbaden, Germany]; Geenius HIV-1/2 confirmation assay [Bio-Rad, Hercules, CA, USA]) and investigations as clinically indicated (e.g., full blood count, urea and electrolytes, liver function tests, electrocardiogram, echocardiography, pleural aspirate, peak expiratory flow rate, sputum TB culture and/or microbiology). All patients had a minimum of 2- and 4-week follow-ups; the number of follow-up visits was increased according to clinical need. Asthma diagnosis was based on peak expiratory flow rate diary in patients presenting with audible wheeze and a history of more than three symptomatic episodes annually. Diagnoses of bacterial pneumonia were based on suggestive clinical features and chest radiograph infiltrates that resolved following antibiotic treatment. Heart failure was based on consistent clinical features and echocardiography (reduced ejection fraction, <50%). Serial renal function testing results of estimated glomerular filtration rate <15 ml/min/1.73m^2 were classified chronic renal failure.

Ethical Approval

Ethical approval for TB Sequel was obtained from the Medical Research Council (MRC), London, UK, and The Gambia Government/MRC Joint Ethics Committee. Written consent was provided by study participants.

RESULTS

Between September 2017 and July 2018, 239 patients with chronic cough (>2 weeks) and any of the following symptoms—night sweats, fever, weight loss, malaise or chest pain—were screened for TB. Of those who fulfilled the inclusion criteria for TB Sequel, 114 patients had Xpert-positive sputum results. The remaining 125 (52.3%) were Xpert- (n = 63, 50.4%) or Xpert-Ultra- (n = 62, 49.6%) negative on spot and early morning sputum samples (routine use of Xpert-Ultra was implemented in clinic mid-study). Of these 125 patients, 17 were classified as TB on clinical and radiological grounds (Table 1). The remaining 108 (45.1%) were classified as not having TB. Not TB patients were significantly older, heavier, less likely to be male and less likely to smoke than TB patients (defined as those who were sputum Xpert-positive (bacteriologically confirmed) and Xpert-negative (clinically diagnosed) patients (Table 1).

There were four deaths and six LTFU among the 108 (45.1%) 'non-TB' patients included. Of these, 55%

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TABLE 1 Characteristics of all patients (*n* = 239)

	TB Xpert-positive (*n* = 114) *n* (%)	Clinical TB Xpert-negative (*n* = 17) *n* (%)	Not TB (*n* = 108) *n* (%)	TB vs. not TB *P* value*
Age, years, median [IQR]	32 [26–40]	42 [35–52]	40 [28–47]	0.0331
Male:female ratio	2.5:1	2.2:1	1:1	0.0087
HIV-1-positive	10 (8.7)	7 (41.2)	12 (11.1)	NS†
Weight, kg, median [IQR]	51 [46–58]	51 [43–58]	56 [49–64]	0.0015
Former or current smoker	46 (40.4)	5 (29.4)	24 (22.2)	0.0091
Past history of TB	7 (6.1)	5 (29.4)	16 (14.8)	NS†
Deaths	2 (1.8)	0	4 (3.7)	NS†

*Calculated using Mann-Whitney U statistical comparison of unmatched pairs or χ^2 (and Fisher's exact) test as indicated.
†Not significant at threshold of *P* = 0.05.
TB = tuberculosis; IQR = interquartile range; HIV = human immunodeficiency virus.

(60/108) received antibiotics (non-fluoroquinolone) for presumed bacterial infections, providing a future target for community antimicrobial stewardship. Excluding LTFU, none of the 102 developed clinical or radiological signs of TB during a median follow-up period of 2 months (range 1–6 months). Diagnoses were established in 65/102 (63.7%) non-TB patients (Table 2). The majority of these were acute respiratory conditions (75.3%), followed by cardiovascular (20%) and renal disease (3.1%), and one patient (1.5%) with presumed haematological malignancy (Table 2).

The proportions of HIV-1-infected patients in the Xpert-positive group (*n* = 114), Xpert-negative, clinically diagnosed group (*n* = 17) and the non-TB group (*n* = 108) were respectively 8.7%, 41.2% and 11.1%. The HIV positivity rate did not significantly differ between the sputum Xpert-positive TB patients and the non-TB patients.

TABLE 2 Characteristics of non-TB patients with established and unknown diagnoses*

	Diagnosis unknown (*n* = 37) *n* (%)	Established diagnosis (*n* = 65) *n* (%)
HIV-1-positive	10 (27.0)	2 (3.1)
Past history of TB	14 (37.8)	2 (3.1)
Former or current smoker	9 (24.3)	15 (23.0)
Deaths		
Cause unknown	2 (5.4)	—
Presumed lung malignancy	—	1 (1.5)
Haematological malignancy	—	1 (1.5)
Respiratory		
Other bacterial or viral respiratory tract infection	—	32 (49.2)
Pneumonia	—	8 (12.3)
Asthma	—	4 (6.2)
Pleural effusion	—	2 (3.1)
Lung abscess	—	1 (1.5)
Lung malignancy	—	1 (1.5)
Cardiovascular		
Heart failure	—	10 (15.4)
Structural heart disease	—	2 (3.1)
Ischaemic heart disease	—	1 (1.5)
Renal		
Chronic renal failure	—	2 (3.1)

*Patients lost to follow-up have been excluded.
HIV = human immunodeficiency virus; TB = tuberculosis.

The diagnosis in 37/102 (36.3%) not-TB cases remained unknown. A high proportion of these (10/37, 27.0%) were new HIV-1 diagnoses, 14/37 (37.8%) had a past history of TB and 9/37 (24.3%) smoked.

DISCUSSION

Using limited in-country diagnostics, nearly half of all patients presenting to a TB clinic did not have a final diagnosis of TB, and 36% had no alternative diagnosis. Of these, many were HIV-1 positive, and had past histories of TB and smoking, providing insights into potential disease aetiology. While the differential includes infections such as non-tuberculous mycobacteria (NTM) and chronic pulmonary aspergillosis (CPA),[7] it is likely that many represent NCDs, e.g., chronic obstructive pulmonary disease (COPD) or bronchiectasis. Better radiology (e.g., computed tomography scans) and pathogen diagnostic facilities[8] in future studies should aim to characterise this group further. As data from Asia highlight, occupational and environmental air pollutants should also be taken in to account.[9]

The HIV-1 positivity rate in the non-TB group was seven-fold higher than the estimated population rate in The Gambia (1.6%).[10] This is a striking finding in patients who not only do not have TB, but also lack other obvious HIV-associated opportunistic infections (e.g., acute bacterial pneumonia). As our findings are based on secondary care, these may not be representative of community rates, but do support the WHO recommendation to offer HIV testing to all patients with suspected TB, and not just those with confirmed TB. This is important, even in countries with relatively low TB prevalence, such as The Gambia.

As our study was pragmatically performed in the context of routinely available care in The Gambia, it has a number of limitations. More sophisticated diagnostics were unavailable (for example, formal diagnoses of COPD were not possible). Routine culture of smear-negative TB patients is not standard practice in TB programmes in The Gambia, and it was only possible to perform culture on 24 non-TB participants due to resource constraints. Although no one in this group developed active TB, it is possible that some patients may have had NTM lung disease or developed active TB post follow-up.

Even after a decade of PAL strategy, services offered to non-TB patients with chronic respiratory symptoms remain in their infancy in sub-Saharan Africa. As efforts are enhanced to find and treat TB using highly sensitive assays, the opportunity to build NCD pathways integrated into TB platforms still exists. These pre-

liminary findings suggest that further context-specific implementation research focusing on non-TB screen-outs is needed to enable application of the PAL strategy.

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Dans certains pays à revenu faible et moyen, 10–20% des patients se présentant avec une toux persistante ont une tuberculose (TB). Une fois que la TB est exclue, la prise en charge des diagnostics alternatifs est limitée. Nous avons étudié de façon prospective les patients ayant eu deux tests de crachats négatifs à l'Xpert® MTB/RIF se présentant à un dispensaire TB en Gambie. Des 239 patients, 108 n'avaient pas de TB ; 65/102 (6 perdus de vue) ont eu un autre diagnostic (non respiratoire dans 24,6% des cas) ; 37/102 n'ont pas eu de diagnostic, dont 27,0% ont été positifs à l'infection par le virus de l'immunodéficience humaine 1, 37,8% avaient des antécédents de TB et 24,3% fumaient. Nous mettons l'accent sur le besoin d'intégration générale des services de santé avec des plateformes TB et une exploration des patients non TB ayant des symptômes respiratoires chroniques.

En algunos países de recursos bajos y medianos, 10–20% de pacientes que acuden a la consulta con tos persistente presentan tuberculosis (TB). Una vez que se ha excluido el diagnóstico de TB, la provisión de servicios de salud para otras afecciones es escasa. En el presente estudio se analizaron de manera prospectiva los pacientes con dos resultados negativos de la prueba Xpert® MTB/RIF en muestras de esputo, que acudían a un consultorio de TB en Gambia. Ciento ocho de los 239 pacientes no presentaban TB. En 65 de 102 pacientes (seis perdidos durante el seguimiento) se definió un diagnóstico diferente de TB y en 24,6% de los casos se trataba de una afección no respiratoria. En 37 de los 102 pacientes no se formuló un diagnóstico y de estos el 27,0% eran positivos frente al virus de la inmunodeficiencia humana, 37,8% tenían antecedente de TB y 24,3% eran fumadores. Los resultados del estudio destacan la necesidad de integrar los servicios generales de salud con las plataformas de atención de la TB y de explorar a los pacientes con síntomas respiratorios crónicos que no presentan TB.

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