
Article:
Jayasooriya, S. orcid.org/0000-0002-1147-5744, Jobe, A., Badjie, S. et al. (4 more authors) (2019) The burden of non-TB lung disease presenting to TB clinics in The Gambia : preliminary data in the Xpert® MTB/Rif era. Public Health Action, 9 (4). pp. 166-168.

https://doi.org/10.5588/pha.19.0046

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

Shamanthi Jayasooriya[1,2*], Alhajie Jobe[1], Simon Badjie[1], Olumuyiwa Owolabi[1], Andrea Rachow[3], Jayne Sutherland[1], Beate Kampmann[1,4]

1. Vaccines and Immunity Theme, Medical Research Council Unit The Gambia at the London School of Hygiene and Tropical Medicine, The Gambia
2. School of Health Sciences and Related Research (ScHARR), University of Sheffield, UK
3. Division of Infectious Diseases and Tropical Medicine, Medical Centre of the University of Munich, Germany
4. Vaccine Centre, London School of Hygiene and Tropical Medicine, Bloomsbury, London, UK

* Corresponding Author E-mail: s.jayasooriya@sheffield.ac.uk

Summary 100
Text 1017
Key words: Noncommunicable disease, Chronic Respiratory Disease, Tuberculosis, Health Services development, Health Systems

Summary

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

Introduction

A leading cause of NCD-related mortality is chronic respiratory disease, causing an estimated 3.8 million deaths in 2015.[1] While TB is still a major problem, in some low- and middle-income countries (LMIC), only 10-20% of patients presenting with a persistent cough have TB.[2] Thus there is a large proportion of patients with respiratory symptoms of unknown aetiology.

The advent of the Xpert MTB/RIF®, nucleic acid amplification tests, are improving early diagnosis providing same-day results, with a sensitivity of 89% compared to sputum culture as gold standard.[3] 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 experience and equipment to effectively diagnose and treat other respiratory diseases, despite WHO strategy highlighting this (Practical Approach to Lung Health (PAL)).[4] We generated preliminary data in The Gambia exploring 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 by Xpert MTB/RIF assay) for TB sequel, a study exploring the impact of TB on lung function. [5] All patients had a chest radiograph and rapid HIV tests (Alere Determine™ HIV-1/2 Ab/Ag), with laboratory serology confirmation if positive (4th generation DiaSorin Liaison XL Murex HIV Ab/Ag assay,[6] Hexagon HIV1/2, Geenius HIV-1/2 confirmation assay) and investigations as clinically indicated (e.g. Full blood count, Urea and electrolytes, Liver function tests, ECG, Echocardiography, pleural aspirate, Peak Expiratory Flow Rate, Sputum TB Culture and/or microbiology). All patients had two and four week follow-ups minimum, extended 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 (resolving following antibiotic therapy). Heart failure was based on consistent clinical features and echocardiography (reduced ejection fraction, <50%). Serial renal function testing (eGFR <15ml/min/1.73m^2) classified Chronic Renal Failure.

Results

Between September 2017 and July 2018, 239 patients with a chronic cough (> 2weeks) and any of night sweats, fever, weight loss, malaise or chest pain, were screened for TB. Fulfilling the inclusion criteria for TB Sequel, 114 patients had Xpert positive sputum results. The other 125 (52.3%) were Xpert 50.4% (n=63) or Xpert-Ultra 49.6% (n=62) negative on spot and early morning sputa (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. These not TB patients were significantly older, heavier, less likely to be male and less likely to smoke than TB patients (sputum Xpert positive and Xpert negative 'clinical TB' group) (Table 1).

The 108 (45.1%) 'not TB' patients included four deaths and six drop-outs. Of these 55% (60/108) received antibiotics (non-fluoroquinolone) for presumed bacterial infections, providing a future target for community antimicrobial stewardship. Excluding drop-outs none of the 102 developed clinical or radiological signs of TB during a median of 2 months

(range 1-6 months) follow-up. Diagnoses were established in 65/102 (63.7%) not-TB patients (Table 2). The majority of these were acute respiratory conditions (75.3%) followed by cardiovascular (20%) and renal disease (3.1%), with one (1.5%) presumed haematological malignancy (Table 2).

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

The diagnosis remained unknown in 37/102 (36.3%) not-TB cases. 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

Nearly half of all patients presenting to a TB clinic did not have a final diagnosis of TB and thirty-six per cent had no alternative diagnosis made using limited in-country diagnostics. Of these, many were HIV-1 positive, 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. COPD or bronchiectasis. Better radiology (e.g. CT scans) and pathogen diagnostic facilities[8] in future studies should aim to characterise this group further. Occupational and environmental air pollutants should also be taken in to account as data from Asia highlights.[9]

The HIV-1 positivity rate in the not-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). Our findings come from secondary care and may not be representative of community rates, but do support WHO guidance of offering HIV testing to all patients *suspected* of having TB, not just those with confirmed TB. This is important, even in countries with relatively low prevalence, such as The Gambia.

Our study was pragmatically performed in the context of routinely available care in The Gambia, thus has a number of limitations. More sophisticated diagnostics were unavailable (formal diagnoses of COPD weren't possible). Routine culture of smear-negative TB patients is not standard practice in TB programmes in The Gambia and due to resource constraints it was only possible to perform culture on 24 not-TB participants. 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.

A decade post-PAL strategy, services afforded to not-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 preliminary findings suggest further context-specific implementation research focusing on not-TB screen-outs is needed to enable application of the PAL strategy.

Ethical Approval: Ethical approval for TB Sequel was obtained from MRC: The Gambia Government/MRC Joint Ethics Committee. Written consent was obtained from study participants.

Acknowledgements: We would like to thank the TB Case Control Platform staff, clinicians, nurses, field-workers, patients and their families.

Declaration of Authors Contributions: SJ conceived and designed the study; SJ, AJ and SB carried out the clinical assessment, collation and interpretation of data. SJ drafted the manuscript; JS and BK critically revised the manuscript for intellectual content. All authors read and approved the final manuscript.

Patients and the public were not involved in the design, conduct and reporting of the research

Funding: TB Sequel Study (funding BMBF 01KA1613)

Competing interests: None

REFERENCES

1. World Health O. Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach 2013
2. Banda HT, Thomson R, Mortimer K, et al. Community prevalence of chronic respiratory symptoms in rural Malawi: Implications for policy. PLoS ONE [Electronic Resource] 2017;12:e0188437.
3. Yan L, Xiao H, Zhang Q. Systematic review: Comparison of Xpert MTB/RIF, LAMP and SAT methods for the diagnosis of pulmonary tuberculosis. Tuberculosis 2016;96:75-86.
4. Murray JF, Pio A, Ottmani S. PAL: a new and practical approach to lung health. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease 2006;10:1188-91.
5. Rachow A, Ivanova O, Wallis R, et al. TB sequel: incidence, pathogenesis and risk factors of long-term medical and social sequelae of pulmonary TB - a study protocol. BMC Pulm Med 2019;19:4.
6. Lemee V, Leoz M, Etienne M, De Oliveira F, Plantier JC. Performance of the Liaison XL Murex HIV Ab/Ag test on clinical samples representing current epidemic HIV variants. Journal of clinical microbiology 2014;52:3277-9.
7. Oladele RO, Irurhe NK, Foden P, et al. Chronic pulmonary aspergillosis as a cause of smear-negative TB and/or TB treatment failure in Nigerians. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease 2017;21:1056-61.
8. Rosen MJ. Chronic cough due to tuberculosis and other infections: ACCP evidence-based clinical practice guidelines. Chest 2006;129:197S-201S.
9. Song WJ, Chang YS, Faruqi S, et al. Defining Chronic Cough: A Systematic Review of the Epidemiological Literature. Allergy, asthma & immunology research 2016;8:146-55.
10. Levi J, Raymond A, Pozniak A, Vernazza P, Kohler P, Hill A. Can the UNAIDS 90-90-90 target be achieved? A systematic analysis of national HIV treatment cascades. BMJ global health 2016;1:e000010.

	TB GeneXpert positive (n=114)	Clinical TB GeneXpert negative (n=17)	Not TB (n=108)	TB Versus Not TB *p* value*
Age in years	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 in kg	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 (0.0%)	4 (3.7%)	ns

Table 1. Characteristics of all patients (n=239). All values are n (%), except age and weight where median (IQR) is shown. ns = not significant at threshold of p=0.05.

* p values were calculated using Mann-Whitney U statistical comparison of unmatched pairs or chi square (and Fishers exact) Test as indicated.

		Diagnosis Unknown (n=37)	Estal
HIV-1 Positive		10 (27.0%)	
Past history of TB		14 (37.8%)	
Former or current smoker		9 (24.3%)	
Deaths	Cause unknown	2 (5.4%)	
	Presumed Lung Malignancy	-	
	Haematological Malignancy	-	
Respiratory	Other bacterial or viral respiratory tract infection	-	
	Pneumonia	-	
	Asthma	-	
	Pleural effusion	-	
	Lung abscess	-	
	Lung malignancy	-	
Cardiovascular	Heart failure	-	
	Structural heart disease	-	
	Ischaemic heart disease	-	
Renal	Chronic renal failure	-	

Table 2 Characteristics of Not TB patients followed-up with established and unknown diagnoses. Patients lost to follow up have been excluded.