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

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15 Summary 100

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18 Services development, Health Systems

19 Summary

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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.

70 **Introduction**

71
72 A leading cause of NCD-related mortality is chronic respiratory disease, causing an estimated
73 3.8 million deaths in 2015.¹ While TB is still a major problem, in some low- and middle-
74 income countries (LMIC), only 10-20% of patients presenting with a persistent cough have
75 TB.² Thus there is a large proportion of patients with respiratory symptoms of unknown
76 aetiology.

77
78 The advent of the Xpert MTB/RIF[®], nucleic acid amplification tests, are improving early
79 diagnosis providing same-day results, with a sensitivity of 89% compared to sputum culture
80 as gold standard.³ Importantly, this increased sensitivity means that those who test negative
81 are less likely to have active TB.

82
83 TB clinics have been ill equipped both in terms of experience and equipment to effectively
84 diagnose and treat other respiratory diseases, despite WHO strategy highlighting this
85 (Practical Approach to Lung Health (PAL)).⁴ We generated preliminary data in The Gambia
86 exploring the potential of TB platforms to capture, investigate and manage chronic
87 respiratory symptoms in patients classified as not having TB.

88
89 **Materials and Methods**

90 We prospectively recruited all patients from a TB research clinic who did not meet the
91 inclusion criteria (at least one sputum sample positive for TB by Xpert MTB/RIF assay) for TB
92 sequel, a study exploring the impact of TB on lung function.⁵ All patients had a chest
93 radiograph and rapid HIV tests (Alere Determine™ HIV-1/2 Ab/Ag), with laboratory serology
94 confirmation if positive (4th generation DiaSorin Liaison XL Murex HIV Ab/Ag assay,⁶ Hexagon
95 HIV1/2, Geenius HIV-1/2 confirmation assay) and investigations as clinically indicated (e.g.
96 Full blood count, Urea and electrolytes, Liver function tests, ECG, Echocardiography, pleural
97 aspirate, Peak Expiratory Flow Rate, Sputum TB Culture and/or microbiology). All patients
98 had two and four week follow-ups minimum, extended according to clinical need. Asthma
99 diagnosis was based on peak expiratory flow rate diary in patients presenting with audible
100 wheeze and a history of more than three symptomatic episodes annually. Diagnoses of
101 bacterial pneumonia were based on suggestive clinical features and chest radiograph
102 infiltrates (resolving following antibiotic therapy). Heart failure was based on consistent
103 clinical features and echocardiography (reduced ejection fraction, <50%). Serial renal
104 function testing (eGFR <15ml/min/1.73m²) classified Chronic Renal Failure.

105
106 **Results**

107 Between September 2017 and July 2018, 239 patients with a chronic cough (> 2weeks) and
108 any of night sweats, fever, weight loss, malaise or chest pain, were screened for TB. Fulfilling
109 the inclusion criteria for TB Sequel, 114 patients had Xpert positive sputum results. The
110 other 125 (52.3%) were Xpert 50.4% (n=63) or Xpert-Ultra 49.6% (n=62) negative on spot
111 and early morning sputa (routine use of Xpert-Ultra was implemented in clinic mid-study).
112 Of these 125 patients, 17 were classified as TB on clinical and radiological grounds (Table 1).
113 The remaining 108 (45.1%) were classified as not having TB. These not TB patients were
114 significantly older, heavier, less likely to be male and less likely to smoke than TB patients
115 (sputum Xpert positive and Xpert negative 'clinical TB' group) (Table 1).

116
117 The 108 (45.1%) 'not TB' patients included four deaths and six drop-outs. Of these 55%
118 (60/108) received antibiotics (non-fluoroquinolone) for presumed bacterial infections,
119 providing a future target for community antimicrobial stewardship. Excluding drop-outs
120 none of the 102 developed clinical or radiological signs of TB during a median of 2 months

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

125
126 The percentages of HIV-1-infected patients in the Xpert positive group (n=114), Xpert
127 negative 'clinical TB' group (n=17) and not-TB group (n=108) were 8.7%, 41.2% and 11.1%
128 respectively. The HIV positivity rate did not significantly differ between the sputum Xpert
129 positive TB patients and the not TB patients.

130
131 The diagnosis remained unknown in 37/102 (36.3%) not-TB cases. A high proportion of these
132 (10/37; 27.0%) were new HIV-1 diagnoses, 14/37 (37.8%) had a past history of TB and 9/37
133 (24.3%) smoked.

134 135 **Discussion**

136 Nearly half of all patients presenting to a TB clinic did not have a final diagnosis of TB and
137 thirty-six per cent had no alternative diagnosis made using limited in-country diagnostics. Of
138 these, many were HIV-1 positive, had past histories of TB and smoking, providing insights
139 into potential disease aetiology. While the differential includes infections such as non-
140 tuberculous mycobacteria (NTM) and chronic pulmonary aspergillosis (CPA),⁷ it is likely that
141 many represent NCDs, e.g. COPD or bronchiectasis. Better radiology (e.g. CT scans) and
142 pathogen diagnostic facilities⁸ in future studies should aim to characterise this group further.
143 Occupational and environmental air pollutants should also be taken in to account as data
144 from Asia highlights.⁹

145
146 The HIV-1 positivity rate in the not-TB group was seven-fold higher than the estimated
147 population rate in The Gambia (1.6%).¹⁰ This is a striking finding in patients who not only do
148 not have TB, but also lack other obvious HIV-associated opportunistic infections (e.g. acute
149 bacterial pneumonia). Our findings come from secondary care and may not be
150 representative of community rates, but do support WHO guidance of offering HIV testing to
151 all patients *suspected* of having TB, not just those with confirmed TB. This is important, even
152 in countries with relatively low prevalence, such as The Gambia.

153
154 Our study was pragmatically performed in the context of routinely available care in The
155 Gambia, thus has a number of limitations. More sophisticated diagnostics were unavailable
156 (formal diagnoses of COPD weren't possible). Routine culture of smear-negative TB patients
157 is not standard practice in TB programmes in The Gambia and due to resource constraints it
158 was only possible to perform culture on 24 not-TB participants. Although no one in this
159 group developed active TB, it is possible that some patients may have had NTM lung disease
160 or developed active TB post follow-up.

161
162 A decade post-PAL strategy, services afforded to not-TB patients with chronic respiratory
163 symptoms remain in their infancy in Sub Saharan Africa. As efforts are enhanced to find and
164 treat TB using highly sensitive assays, the opportunity to build NCD pathways integrated into
165 TB platforms still exists. These preliminary findings suggest further context-specific
166 implementation research focusing on not-TB screen-outs is needed to enable application of
167 the PAL strategy.

168
169 **Ethical Approval:** Ethical approval for TB Sequel was obtained from MRC: The Gambia
170 Government/MRC Joint Ethics Committee. Written consent was obtained from study
171 participants.

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173 nurses, field-workers, patients and their families.

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

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

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181 **Competing interests:** None

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	TB GeneXpert positive (n=114)	Clinical TB GeneXpert negative (n=17)	Not TB (n=108)	TB Versus Not TB <i>p</i> 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

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

220

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

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		Diagnosis Unknown (n=37)	Estab
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	-	
Respiratory	Haematological Malignancy	-	
	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	-	

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