The relationship between a known diagnosis of tuberculosis and symptom reporting: implications for case detection strategies

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To the Editor:

A high proportion of people screened for tuberculosis (TB) in the community lack typical symptoms [1]. However, many TB screening programmes rely upon symptoms as an initial precursor to subsequent diagnostic testing [2]. This approach can delay diagnosis for people with early TB, resulting in adverse outcomes due to disease progression. Furthermore, data from prevalence surveys and mathematical models have suggested that individuals with bacteriologically confirmed asymptomatic TB may contribute to *Mycobacterium tuberculosis* transmission [3, 4]. Symptoms are subjective and susceptible to recall bias; individuals may describe symptoms differently after learning their diagnosis. The timing of symptom questionnaire response relative to diagnosis may affect the propensity of respondents to report symptoms [5, 6]. This study evaluated the difference in self-reported symptoms pre- and post-TB diagnosis and how self-reported symptoms related to disease severity measures.

We evaluated individuals diagnosed with TB within the Active Case Finding 3 (ACT 3) study, a cluster-randomised controlled trial in Ca Mau, Vietnam [7]. Between 2014 and 2018, adult members of the general population aged ⩾15 years were screened annually for 4 years using GeneXpert MTB/RIF (Xpert) for expectorated sputum at the selected sites. Participants who tested positive for *M. tuberculosis* on Xpert were further evaluated using chest radiography, microscopic examination and sputum culture. A standardised symptom questionnaire was completed at the initial screening (pre-diagnosis questionnaire), and another questionnaire, which also asked about symptoms, was administered to those diagnosed with TB (post-diagnosis questionnaire) annually. TB was diagnosed by clinicians at public TB clinics following the local guidelines, based on the results of the diagnostic tests described above and clinical history. These clinicians were responsible for informing participants of the diagnosis and instituting appropriate treatment.

Participants were individuals with bacteriologically confirmed TB, testing positive on Xpert, and who had at least one mycobacterial culture that grew *M. tuberculosis*. Smear grade and Xpert semi-quantitative grading based on cycle threshold were each used as a proxy for bacillary load. We defined TB as "asymptomatic" if the participant reported no respiratory symptoms (no cough of any duration, sputum production or haemoptysis).

Descriptive statistics were used to summarise socio-demographic characteristics, medical history, microbiology and radiological characteristics, and treatment outcomes reported by the National TB Programme. Comparisons between groups (asymptomatic *versus* symptomatic) were made using the Pearson Chi-square, Fisher's exact or Wilcoxon rank-sum tests, as appropriate. The difference in proportion, 95% confidence intervals, and the p-values were estimated using McNemar's test of paired proportions, not adjusted for clustering. The study received approval from the ethics committees of the University of Sydney (2013/073), National Lung Hospital (407/QĐ- BVPTƯ), and Ministry of Health Vietnam (4443/QĐ-BYT). Written informed consent was obtained from all participants.

In total, 236 participants were diagnosed with bacteriologically confirmed TB during community-wide screening. At pre-diagnosis, 64.8% (153 out of 236) lacked symptoms. Following their diagnosis, 17.8% (42/236) reported no symptoms after being told of their diagnosis, with a difference of 47.0% (95% CI 39.2–54.8; p<0.001) (table 1). The median time between the pre- and post-diagnosis questionnaires was

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Among 236 adults with culture-positive TB, 64.8% were asymptomatic at screening pre-diagnosis, decreasing to 17.8% post-diagnosis. Many asymptomatic individuals were highly infectious, as indicated by high smear grades and bacillary load on Xpert. https://bit.ly/3HIW8C2

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TABLE 1 Symptoms reported, socio-demographic, microbiology and radiological characteristics, and treatment outcome of individuals with culture-positive tuberculosis (TB) pre- and post-TB diagnosis

Symptoms reported[#]	Pre-diagnosis		Post-diagnosis		Difference between the proportion of symptoms reported post-diagnosis *versus* pre diagnosis
	n	% (95% CI)	n	% (95% CI)	% (95% CI)
Total	236	100	236	100	
Cough of any duration	74	31.4 (25.5–37.7)	184	78.0 (72.1–83.1)	46.6 (39.5–53.7)[f]
Sputum	61	25.8 (20.4–31.9)	161	68.2 (61.9–74.1)	42.4 (34.8–49.9)[f]
Haemoptysis	4	1.7 (0.5–4.3)	13	5.5 (3.0–9.2)	3.8 (0.2–7.4)[##]
Asymptomatic[¶]	153	64.8 (58.4–70.9)	42	17.8 (13.1–23.3)	−47.0 (−39.7–−54.3)[f]

Characteristics, and treatment outcomes of individuals with culture-positive TB (n=236)	Pre-diagnosis			Post-diagnosis		
	Asymptomatic[¶], n (row %)	Symptomatic[+], n (row %)	p-value[§]	Asymptomatic[¶], n (row %)	Symptomatic[+], n (row %)	p-value[§]
Total	153 (64.8%)	83 (35.2%)		42 (17.8%)	194 (82.2%)	
Sex			0.529			0.030
Male	128 (64)	72 (36)		31 (15.5)	169 (84.5)	
Female	25 (69.4)	11 (30.6)		11 (30.6)	25 (69.4)	
Age, years, median (IQR)	63 (52–73)	62 (49–71)	0.548	66 (55–72)	62 (49–72)	0.303
Alcohol use in the past month			0.972			0.467
Never	51 (65.4)	27 (34.6)		16 (20.5)	62 (79.5)	
Monthly or less	33 (62.3)	20 (37.7)		11 (20.8)	42 (79.2)	
2–4 times per month	28 (68.3)	13 (31.7)		8 (19.5)	33 (80.5)	
2–3 times per week	16 (61.5)	10 (38.5)		4 (15.4)	22 (84.6)	
⩾4 times per week	25 (65.8)	13 (34.2)		3 (7.9)	35 (92.1)	
Smoking status in the past month			0.005			0.166
Daily or occasionally	70 (56.5)	54 (43.5)		18 (14.5)	106 (85.5)	
Not at all	83 (74.1)	29 (25.9)		24 (21.4)	88 (78.6)	
Diabetes			0.462			0.101
Yes	14 (73.7)	5 (26.3)		6 (31.6)	13 (68.4)	
No/unknown	139 (64.1)	78 (35.9)		36 (16.7)	181 (83.4)	
Poverty card			0.084			0.773
Yes	10 (47.6)	11 (52.4)		4 (19.1)	17 (80.9)	
No/unknown	143 (66.5)	72 (33.5)		38 (17.7)	177 (82.3)	
Health insurance			0.138			0.250
Yes	94 (61.4)	59 (38.6)		24 (15.7)	129 (84.3)	
No	59 (71.1)	24 (28.9)		18 (21.7)	65 (78.3)	
Previous TB history			0.739			0.795
Yes	18 (62.1)	11 (37.9)		4 (13.8)	25 (86.2)	
No/unknown	135 (65.2)	72 (34.8)		38 (18.4)	169 (81.6)	
Smear microscopic examination			0.026			0.007
Negative	67 (61.5)	42 (38.5)		20 (18.4)	89 (81.6)	
Scanty	36 (78.3)	10 (21.7)		14 (30.4)	32 (69.6)	
1+	33 (73.3)	12 (26.7)		8 (17.8)	37 (82.2)	
2+	6 (40.0)	9 (60.0)		0 (0.0)	15 (100.0)	
3+	11 (52.4)	10 (47.6)		0 (0.0)	21 (100.0)	
Xpert MTB/RIF			0.169			0.018
Detected (very low)	31 (62.0)	19 (38.0)		8 (16.0)	42 (84.0)	
Detected (low)	71 (71.7)	28 (28.3)		25 (25.3)	74 (74.7)	
Detected (medium)	37 (55.2)	30 (44.8)		8 (11.9)	59 (88.1)	
Detected (high)	13 (68.4)	6 (31.6)		0 (0.0)	19 (100.0)	
Chest radiograph			0.036			0.085
Consistent with TB	110 (60.1)	73 (39.9)		28 (15.3)	155 (84.7)	
Not TB	29 (78.4)	8 (21.6)		10 (27.0)	27 (73.0)	
Treatment outcomes			1.000			0.159
Success[¶¶]	120 (61.9)	74 (38.1)		30 (15.5)	164 (84.5)	
Loss to follow-up	1 (100.0)	0 (0.0		1 (100.0)	0 (0.0)	

IQR: interquartile range. [#]: symptoms questions asked (in Vietnamese) pre-and-post diagnosis. Pre-diagnosis: 1) Have you had a cough every day for the last 2 weeks or more? 2) Have you coughed up any blood in your sputum in the last month? 3) Have you been coughing up sputum every day for the last 2 weeks or more? Post-diagnosis: During the past 2 weeks (or in the 2 weeks prior to starting TB treatment (for those already on TB treatment), have you experienced any of the following symptoms? 1) Cough; 2) Coughing up blood; 3) Cough with sputum. [¶]: asymptomatic was defined as the absence of cough, sputum, and haemoptysis. [+]: symptomatic was defined as the presence of at least one symptom (cough, sputum or haemoptysis). [§]: p-values estimated using Chi-square and Wilcoxon rank-sum tests for categorical and continuous variables, respectively. Fisher's exact test was used when one or more cells have frequencies <5. p-values not corrected for multiple testing. [f]: p<0.001. [##]: p=0.035. [¶¶]: the sum of cured and treatment completed.

7 days (interquartile range 3–22 days). There were 115 (48.7%) cases of concordant reporting (78 symptomatic both pre- and post-diagnosis; 37 asymptomatic both pre- and post-diagnosis), and 121 (51.3%) cases of discordant reporting (five symptomatic pre-diagnosis but asymptomatic post-diagnosis; 116 asymptomatic pre-diagnosis but asymptomatic post-diagnosis). The test agreement was 48.7% with a kappa 0.14 (95% CI 0.07–0.21). People who reported being current smokers were most likely to report at least one symptom pre-diagnosis, while men were more likely to report at least one symptom post-diagnosis (84.5%). Participants who reported symptoms at either time had significantly higher smear grades and bacillary load measured on Xpert than asymptomatic participants. Similarly, at pre-diagnosis screening, symptomatic participants were more likely to have chest radiograph abnormalities consistent with TB (table 1).

Nearly two-thirds of people with bacteriologically confirmed TB were asymptomatic before their diagnosis. After diagnosis, the prevalence of asymptomatic individuals in the same cohort decreased to 17.8%. This substantial increase in symptom reporting once a diagnosis is given has several important implications. Firstly, it demonstrates that symptoms are unreliable as they depend on the circumstances during which they are asked. Although simple to ascertain, information on symptoms is highly subjective and prone to recall and confirmation biases. Secondly, our study confirms that symptoms have a low sensitivity in detecting prevalent bacteriologically confirmed TB in the community setting. As a result, reliance upon symptoms is likely to lead to inconsistent, irreproducible and unreliable results [5]. Importantly, only smoking (pre-diagnosis) and male gender (post-diagnosis) were identifiable risk factors. These factors were not associated with symptom reporting discrepancy pre- and post-diagnosis (results not shown).

In community-based active case finding for TB, relying solely on symptom screening will significantly underestimate TB prevalence. We found that >60% of bacteriologically confirmed TB cases would have been missed if symptom-based screening were used to triage individuals for additional testing with Xpert or chest radiograph. Many asymptomatic individuals were, in fact, highly infectious, with some having high smear grades and bacterial loads measured on Xpert. This indicates the significant risk of continuing disease transmission in the community if people with asymptomatic TB are not promptly identified and treated [8]. These findings highlight the importance of using more objective measures as the first step in TB screening.

There are some potential limitations in this study design. We did not evaluate the reporting patterns of other non-respiratory TB symptoms (*e.g.* fever and weight loss) pre- and post-diagnosis. We were also unable to account for the effect of the amount of tobacco smoked and the duration (years smoked) on symptom reporting. Different interviewers may have administered the pre- and post-diagnosis survey. Like the participant, the interviewer was unaware of the diagnosis in the pre-diagnosis setting and was aware of the diagnosis in the post-diagnosis setting. This knowledge may have influenced the responses to the questionnaire. Despite this, our study is consistent with the high prevalence of asymptomatic TB disease (previously known as subclinical TB), reported in the literature that assessed TB symptoms during pre-diagnosis screenings in the community [1, 9, 10]. In contrast, studies conducting symptom assessments only after diagnosing TB reported a lower prevalence of asymptomatic TB disease [11, 12]. In addition to the timing of the symptom survey, participants' awareness of being in a prospective follow-up study, contact with people with TB, sociocultural factors and stigma can influence symptom reporting [13, 14]. Therefore, our findings may be most relevant to contexts involving similar sociocultural backgrounds. Generalisability beyond similar settings and populations needs further assessment. Although our study does not directly evaluate the impact of these factors on symptom reporting, it emphasises that studies reporting TB symptoms should clearly state the timing (pre- or post-diagnosis) for accurate interpretation. Hence, studies of asymptomatic TB should report the timing of symptom screening relative to when participants receive their diagnosis, as it can influence how they report prevalent symptoms [15].

This study has important policy implications. As symptom assessment is unreliable for triaging individuals for subsequent testing, screening programmes should not rely upon symptoms alone as an entry point for diagnostic testing. More sensitive tools, such as chest radiography and sputum molecular tests, should be considered as initial tests to improve TB detection during community-wide screening. This is particularly important for people with early-stage disease, the majority of people with prevalent TB in the community. A more sensitive algorithm will likely significantly affect the transmission of *M. tuberculosis* within the community. This approach confers population and individual benefits [16] and aligns with the End TB goals of reducing TB incidence and death by 2035 [17]. Future studies should report the timing and whether participants were aware of their TB diagnosis at the time of symptom screening.

Alvin Kuo Jing Teo[1,2,3], Khanh Boi Luu[4], Frances Garden[5], Cuong Duc Pham[6], Jennifer Ho[5,7,8], Thu-Anh Nguyen[1,2,6], Guy B. Marks[2,5,7,9] and Greg J. Fox[1,2]

[1]Faculty of Medicine and Health, University of Sydney, Sydney, Australia. [2]The University of Sydney Infectious Diseases Institute (Sydney ID), Sydney, Australia. [3]Saw Swee Hock School of Public Health, National University of Singapore and National University Health System, Singapore, Singapore. [4]Woolcock Institute of Medical Research, Hanoi, Vietnam. [5]South West Sydney Clinical Campus, School of Clinical Medicine, University of New South Wales, Sydney, Australia. [6]The University of Sydney Vietnam Institute, Ho Chi Minh City, Vietnam. [7]Woolcock Institute of Medical Research, Sydney, Australia. [8]Cairns Base Hospital, Cairns, Australia. [9]Burnet Institute, Melbourne, Australia.

Corresponding author: Greg J. Fox (gregory.fox@sydney.edu.au)

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