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A data-driven approach to identify suspected TB cases among ALHIV in the Eastern Cape Province of South Africa

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A data-driven approach to identify suspected TB cases among ALHIV in the Eastern Cape Province of South Africa

Abstract

Low rates of tuberculosis (TB) testing have been reported in Southern Africa. Evidence has also shown discrepancies between case notifications and incident TB cases in South Africa. There is also limited evidence on TB rates, especially on adolescents and most particularly on adolescents living with HIV (ALHIV). Therefore, there is a need to evaluate the potential of using the self-reported clinical diagnosis of TB and self-reported TB symptoms to describe the burden of TB among ALHIV.

The objective was to describe the burden of confirmed and 'suspected' TB amongst ALHIV in the Eastern Cape Province of South Africa.

This study is based on data from three waves of a longitudinal study cohort of 1 060 antiretroviral treatment (ART)-initiated adolescents, and 467 HIV-negative adolescents (90% uptake, 94% follow-up, and 97% second follow-up retention with a 3.4% mortality) in Eastern Cape province of South Africa. First, we describe the differences in TB testing and self-reported TB clinic diagnosis in the study over the three waves, as well as socio-demographic characteristics and HIV status. Second, we describe differences in TB symptom reporting over the three waves of data among adolescents. In the statistical analysis, we first use group-based trajectory modelling (GBTM) to model TB symptom trajectories based on past-year self-reported TB symptoms. We then adjust the TB symptom trajectories for self-reported TB clinic diagnosis, to estimate the 'suspected' TB prevalence rates in the sample. Finally, we describe the association between socio-demographic factors and each of the adjusted TB groups.

Only 49.6% of adolescents reported having tested for TB at baseline, and this remains consistent over the three waves. Among those tested for TB, from three to six percent at Wave 3 reported currently having TB. A tenth of the adolescents

who had been tested reported not having or knowing their TB results. In terms of TB symptomology, at baseline about 1 in 5 adolescents reported experiencing any of the five TB symptoms. We identified three long-term TB symptomology groups, namely high TB symptomatic (14.1%), decreasing symptomatic (19.1%), and asymptomatic (66.8%). At baseline HIV-positive status ($p<0.001$), female ($p<0.017$), and rural residence ($p<0.001$) were significantly associated with the model-identified TB symptomatic groups. Over 40% of adolescents in the high TB symptomatic group reported having never tested for TB at baseline. After adjustment of the TB symptom trajectory groups, by means of the self-reported TB, three TB groups were identified, namely confirmed TB, suspected TB, and asymptomatic at each wave. From these groups, we observed a decline in confirmed TB cases over the three waves, from 20% in Wave 1 to 11.6% in Wave 3, and the majority of these cases (over 94%) were among adolescents living with HIV. The rates of suspected TB are estimated to be stable over time with a fifth (19.4% on average) of the sample classified into this group, and the majority of the cases were ALHIV.

Self-reported TB symptoms may be useful for ruling out TB in adolescents, and identifying suspected cases in need of further diagnostic assessment. This may be useful for describing the burden of TB in ALHIV in the face of limited access to TB diagnostics and paucity of population-impact data.

1. Introduction

Tuberculosis remains one of the most common causes of death globally (World Health Organization [WHO], 2018). South Africa has one of the highest global burdens of tuberculosis (TB), largely driven by HIV/AIDS (Churchyard *et al.*, 2014; WHO, 2017). Recent studies in South Africa demonstrate high levels of under-testing and under-reporting of TB in primary health clinics in these endemic settings (Kweza *et al.*, 2018). Further evidence shows that less than 10% of patients living with HIV who attend clinics for TB-related symptoms are screened for TB (Date & Modi, 2015; WHO, 2018). Research among adolescents indicates a significant TB burden among this population group (Snow *et al.*, 2017; Snow *et al.*, 2018). A South African longitudinal study reported a 14% annual rate of TB infection among school-based adolescents (Andrews *et al.*, 2015) against a TB notification of approximately 361 per 100,000 adolescents in the same period, as reported by Bunyasi *et al.* (2020). Moreover, evidence from TB programs indicates that TB incidence in adolescents increases with age (Wood *et al.*, 2011). Adolescents living with HIV, especially those living in resource-constrained settings, remain at high risk of TB infection, and their TB burden has not been characterized in detail. The latest prevalence survey in South Africa also

highlights that this group has one of the highest levels of underreporting (National Department of Health [NDOH], 2021). Moreover, the actual prevalence of TB among adolescents, including those living with HIV, remains unclear (Lönnroth *et al.,* 2010).

Recently, provider-initiated pulmonary tuberculosis (PTB) case-finding within clinics has become an integral part of TB care, especially in resource-constrained settings (Lönnroth *et al.,* 2013; Ohene *et al.,* 2017). Studies have shown that symptom screening may often be a practical approach to improve case-finding when patients self-present for general ill health (Corbett *et al.,* 2005; Mtei *et al.,* 2005). This is useful in the face of the discrepancy between case notifications and estimated TB incidence among adolescents, owing to challenges in confirming TB and a number of barriers that adolescent patients face in accessing care. An estimated 80% of adolescents living with HIV live in sub-Saharan Africa (UNAIDS, 2019), yet only a small proportion of these adolescents in TB-endemic areas have access to medical-PTB diagnostic tests. Moreover, most healthcare providers in sub-Saharan Africa do not have easy access to TB diagnostic tools, leading to poor case detection and diagnosis (Corbett *et al.,* 2010; Snow *et al.,* 2017). In South Africa, TB under-diagnosis has been reported in the South African National TB Prevalence Survey (NDOH, 2021). More so, most of the people found to have TB in the survey did not report having the classic symptoms of TB. This potentially results in discrepancies between confirmed and actual number of TB cases, including among ALHIV. Studies combining both self-reported medical TB diagnosis and the classic TB symptomology could help compute outcomes which would allow for more complex analyses on the risk and protective factors of TB.

In another study in South African, Snow *et al.* (2020) reported a substantial increase in TB incidence during adolescence. This calls for more efforts to utilise existing data on HIV and TB to estimate the prevalence of TB in adolescents. This is critical to ensure a robust measure of TB disease burden among adolescents in resource-limited settings. Therefore, this study seeks to model available self-reported TB diagnosis and TB symptoms data, and describe the point prevalence of suspected and confirmed TB amongst adolescents living with HIV in the Eastern Cape Province of South Africa, a resource-limited setting. This study also compared the estimated number of TB cases based on the self-reported TB and the symptomology model-based results.

2. Methods

2.1 Participants and setting

Mzantsi Wakho study is a prospective longitudinal cohort of adolescents living in the Eastern Cape province of South Africa, focusing on ALHIV. Adolescent participants aged 10-19 years at baseline were recruited from a municipality in Eastern Cape Province of South Africa, with an estimated overall HIV prevalence of 13.6% (Shisana *et al.,* 2014), and an estimated TB prevalence of 5% (Kweza *et al.,* 2018). TB remains one of the top causes of death in this municipality, which continues to face healthcare provision challenges related to limited health infrastructure (Eastern Cape Department of Health, 2015).

To recruit a representative sample of ALHIV, participants enrolled at baseline included both those engaged in care, as well as those lost to follow-up. Eligible participants included ART-eligible 10- to 19-year-old adolescents living with HIV, identified through medical records in 52 public health facilities in the study catchment area, who were traced in their communities, homes, or schools. Adolescents from neighbouring homes and some co-resident adolescents were also interviewed to minimize stigma. Baseline interviews were conducted in 2014-2015, with follow-up interviews in 2016-2017 and second follow-up interviews in 2017-2018. Adolescents provided information on self-reported TB symptoms using questionnaires co-developed and piloted among adolescents affected by HIV in the study area. Concurrently, data from patient files including information on TB diagnosis and treatment were extracted from 52 healthcare facilities in the Eastern Cape Province where ALHIV had received care (Toska *et al.,* 2015).

2.2 Ethical approval

Ethical approval for the Mzantsi Wakho study was granted by Research Ethics Committees at the Universities of Oxford (SSD/CUREC2/12–21) and Cape Town (UCT/CSSR/2019/01), Eastern Cape Departments of Health and Basic Education, and ethical review boards of participating facilities. Voluntary informed consent was obtained from adolescents and caregivers when adolescents were less than 18 years old. Interviews were conducted by trained researchers experienced in interviewing HIV-affected children and adolescents. A social worker advised the adaptation of a referral protocol used in prior studies among adolescents affected by HIV and on specific difficult cases that required referrals to services following adolescent-reported harm or risk of significant harm. As part of this referral protocol, all participants reporting untreated TB (N=27) were supported to access care at appropriate facilities.

2.3 Measures

2.3.1 TB testing and diagnosis data

This study data had two sources of TB-related variables. First, self-reports of TB clinical diagnosis by sputum and skin tests (see Table 1). At baseline, participants were asked if they had ever been tested for TB, and the result of the test. At follow-up and the third wave of the survey, participants were asked if they ever received any tests (chest x-ray, skin, or sputum) for TB in the last year, and to indicate the results of the test. Self-reported TB clinical diagnosis was coded as 1 for those who confirmed having TB or having had TB and recovered, and 0 otherwise (see Table 1).

Table 1: Self-reported TB results over time in Mzantsi Wakho cohort

	Wave 1[1] (N=1 519)	**Wave 2 (N=1 454)**	**Wave 3 (N=1 429)**
Self-reported TB results	**N (%)**	**N (%)**	**N (%)**
No TB (negative result)	365 (24.0)	475 (32.7)	446 (31.2)
Current TB (positive result)	44 (2.9)	25 (1.7)	26 (1.8)
Lifetime TB (in the past or past-year TB)	277 (18.3)	188 (12.9)	139 (9.7)
No results	67 (4.4)	72 (4.9)	52 (3.7)
Never or not tested for TB	766 (50.4)	694 (47.8)	766 (53.6)

Second, patient files were reviewed to identify clinically diagnosed and recorded instances of TB infection and treatment. This was clinic-based data extracted from patient-file records at 67 health care facilities where the adolescents accessed care. Extracted data[2] included an indication of TB test and TB test type: Mantoux, sputum-smear microscopy, or sputum-smear culture. Participants who had a positive result recorded on any one of these three tests were considered to have been diagnosed with TB. Round 1 and 2 of patient file data extraction aligned with Wave 1 and 2 of the main survey respectively. For Wave 1, patient file records were only checked for lifetime/ever having a TB diagnosis (not specified

[1] The response options at baseline where slightly differently worded compared to preceding waves of survey. Refer to Baseline Questionnaire here: http://www.youngcarers.org.za/youthpulse

[2] This data was not used in this study as it was only available at Wave 2.

to the past 12 months) and the TB clinic records could not be verified for current TB. Therefore, we could not derive a past-year TB measure for the baseline based on clinical records. For Wave 2, patient file records were checked specifically for TB tests and results from the past year, which would align with the time window for follow-up interviews. Each record where a TB test was recorded with a positive result we coded as 1, and 0 otherwise. This analysis utilized the different sources of data to derive an estimate of PTB in this cohort.

2.3.2 TB symptomology

In addition to TB testing and diagnosis, adolescents were asked how often they experienced one or more of the following common PTB-related symptoms in the last 12 months[3], as outlined by WHO (2004); cough lasting ≥ 3 weeks, haemoptysis (coughing up blood), productive cough (cough with sputum), chest pains, weight loss, fever and night sweats. These measured items were coded as 1 if they reported sometimes or often, and 0 if they reported never. Based on the high levels of low-grade fever reported by all participants, fever was coded as 1 (often) and 0 (sometimes/never).

2.3.3 Socio-demographic factors

All our analyses controlled for the HIV status of participants as well as other socio-demographic characteristics, namely: age of the adolescent, sex, poverty, informal housing, and rural residence. Poverty was defined as lacking access to at least one basic necessity namely: clothes, three meals per day, more than a pair of shoes, school equipment, school fees, uniform, toiletries, ability to afford a doctor's visit, and access to all required medicine (Wright, 2008).

2.4 Analyses

First, the chi-square χ^2 test was used to assess for differences in TB testing and self-reported TB clinic diagnosis over the three waves, including other socio-demographic characteristics and HIV status. Similarly, differences in TB symptom reporting over the three waves of data among adolescents are described. Second, the group-based trajectory model (GBTM) is used to identify long-term symptom groups (three-wave data) using five symptoms of the initial seven

[3] At baseline, adolescents were asked how often they experienced one or more of the following common PTB-related symptoms in the last 6 months: cough lasting ≥ 3 weeks, haemoptysis (coughing up blood), productive cough (cough with sputum), chest pains, weight loss, fever and night sweats.

symptoms (WHO, 2018). GBTM is a specialized form of growth mixture modelling (Muthén & Kaplan, 2004; Muthén 2002) designed to identify groups of individuals following similar progressions of some behaviour or outcome over some measure of time (Nagin & Odgers, 2010). This is premised on the hypothesis that there exist unobserved sub-groups of individuals who exhibit different patterns of change. The optimal model selection also relies on the information criterion (Akaike's Information Criteria-AIC and Bayesian Information Criteria-BIC) as well as interpretability. Based on the optimal model and selected symptom groupings, the wave-specific symptom profiles were mapped to reflect the changes between waves. Third, according to the established symptom profiles, descriptive summary statistics by baseline socio-demographic factors and self-reported TB diagnosis are presented. Furthermore, the distribution of TB testing and results across the three long-term symptom profiles at each wave is described.

Next, we adjusted the TB symptom trajectory groups for self-reported TB diagnosis to create a hybrid past-year TB trichotomy variable at each wave. The adjustment followed the allocation algorithm with defined TB categories described below:

1. *Asymptomatic* - Allocate all participants in the asymptomatic profile who did not confirm past or current TB. Further, assign participants who confirmed TB negative or were classified into the decreasing symptoms profile.

2. *Confirmed TB* - Assign all participants who confirmed past-year or current self-reported TB.

3. *Suspected TB* - First, assign all individuals who never tested for TB but were classified into the group showing symptoms over time. Second, assign individuals tested for TB who did not get results but were classified into the group showing symptoms over time.

Finally, we assessed the association between the adjusted hybrid TB variable above and adolescent key characteristics including HIV status, using a multinomial logistic regression model. All analysis was conducted in Stata 15.

3. Results

3.1 Socio-demographic characteristics

At baseline, n=1 527 adolescents were enrolled in the Mzantsi Wakho study, of whom n=1 060 were living with HIV. Of these, 1 454 participants were successfully interviewed at follow-up (94.0% retention rate) and 1 429 at second

follow-up (97% retention rate), and were included in this analysis. Table 2 summarizes the socio-demographic characteristics of the sample at follow-up; the majority was female (57.6 %). Over 60% of the sample lived in poor households and about half of the sample confirmed taking a TB test at some point in their lives. About half of the adolescents reported no TB testing in the past year at Wave two and three, while about half reported having never tested for TB at Wave one. Among those tested for TB, between 3 to 6 percent reported currently having TB, and over a fifth reported having TB in the past year. Almost a tenth of the adolescents who tested reported not having or knowing their TB results.

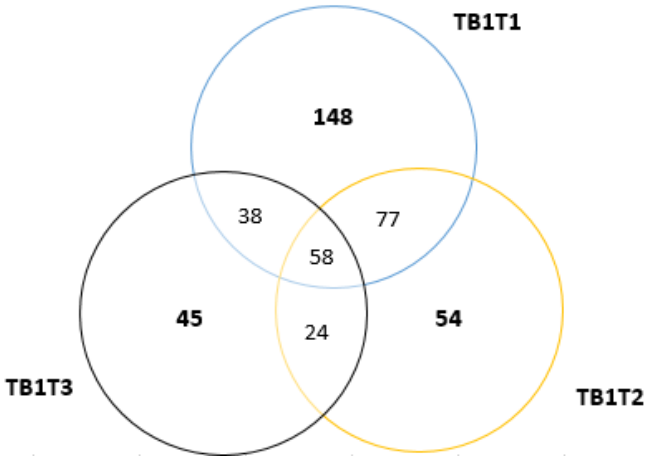
Table 2: Sample characteristics for participants at follow-up

	Wave 1 (N=1 519)	**Wave 2 (N=1 454)**	**Wave 3 (N=1 429)**	
Factors	**N (%)**	**N (%)**	**N (%)**	**p-value**
Age (Mean/SD)	13.9 (2.9)	15.5 (3.1)	16.6 (3.1)	**<0.001**
Female	864 (57)	841 (57.8)	825 (57.7)	0.844
HIV positive	1 046 (68.9)	1 030 (70.8)	1 010 (70.7)	0.423
TB experiences				
TB testing				
1. Never or not tested for TB[4]	766 (50.4)	694 (47.7)	766 (53.6)	0.141
2. Tested for TB	753 (49.6)	760 (52.3)	663 (46.4)	
Self-reported TB clinic diagnosis *(Among those tested)*				
3. Lifetime/past year TB	277 (36.8)	188 (24.7)	139 (21.0)	
4. Current TB	44 (5.8)	25 (3.3)	26 (3.9)	
5. TB negative	365 (48.5)	475 (62.5)	446 (67.3)	
6. No results	67 (8.9)	72 (9.5)	52 (7.8)	
Socio-economic status				
Rural location	403 (26.6)	371 (25.6)	355 (24.9)	0.575
Informal housing	271 (17.9)	189 (13.2)	179 (12.6)	**<0.001**
Poverty	1 007 (66.3)	1 150 (79.1)	962 (67.3)	**<0.001**

Figure 1 below shows the different configurations of self-reported TB over the three-time points, as intersections in a Venn diagram. Besides the decreasing trend over time, observed in Table 2, 58 participants, which is about 3.7% of the total sample, reported currently being TB-positive (sick) or had been diagnosed TB-positive across all the time points.

[4] This question was asked as lifetime TB testing at Wave 1, while past-year testing was assessed for Wave 2 and Wave 3.

Figure 1: Self-reported TB over time



[¥]TB1T1, TB1T2, and TB1T3 stands for dichotomized self-reported TB at each wave respectively.

3.2 Prevalence of TB symptomology over time

Table 3 shows the results for differences in PTB symptom reporting over time for the six TB symptoms included in the questionnaires. At baseline, about 1 in 5 adolescents reported experiencing any of the five TB symptoms. Although there is a decline in symptom reporting over time across all the TB symptoms, the observed prevalence could be indicative of 'suspected' TB cases in this sample. Moreover, the observed decline in TB symptom prevalence could be a general reflection of some methodological issues which include the use of ACASI[5] at both follow-up interviews, recall bias due to changing recall periods in the question's prompts, as well as adolescents growing up which could influence symptom reporting.

Table 3: Descriptive statistics of self-reported TB symptoms

TB symptoms	**Wave 1 (N=1 519)**	**Wave 2 (N=1 454)**	**Wave 3 (N=1 429)**
	N (%)	**N (%)**	**N (%)**
Cough*	355 (23.4)	177 (12.2)	95 (6.7)
Productive Cough*	420 (27.7)	267 (18.4)	93 (6.5)
Weight loss*	386 (26.1)	255 (17.5)	174 (12.2)
Night Sweats*	485 (32)	287 (19.7)	136 (9.5)
Chest pain*	501 (33)	313 (21.5)	167 (11.7)
Fever[§]	195 (12.8)	52 (3.6)	46 (3.2)

* Sometimes or often; [§]often

[5] Audio computer-assisted self-interviewing.

3.3 Group-based trajectory model results

3.3.1 Longitudinal profiles

Based on the observations in the previous sections, we applied an alternative methodology for estimating TB symptom trajectories by aiming to identify individuals who are consistently symptomatic over time. Different variations of the GBTM models, in terms of the number of classes and the number of symptoms, were fit. Based on both our observations and the South African National TB Guidelines[6], a total of five out of the previous seven symptoms were used in this analysis. Three trajectory models were generated ranging from two to four TB symptomology trajectory groups. Increasing the number of groups yielded improvements in statistical fit (BIC, AIC and entropy). However, based on the requirement to have a minimum group size of at least 5% (Østbye, Malhotra & Landerman, 2011), the three-group model was considered the best fit (Table 4).

Table 4: Model fit statistics

Model	BIC (N=22 010)	BIC (N=1 563)	AIC	>5% per group
2 groups	-9 343.7	-9 337.1	-9 323.7	Yes
3 groups	-9 346.1	-9 335.5	-9 314.1	Yes
4 groups	-9 354.8	-9 340.2	-9 310.7	No

Figure 2 below shows the three-group model. Three distinct patterns of TB symptomologies were apparent during the three waves that may be considered as very high TB symptomatic, decreasing symptomatic (which highly decreased during follow-up), and asymptomatic. In the graph, the solid lines represent the estimated symptom trajectories and the symbols represent the group means at each wave. Percentages of estimated group membership probabilities are presented alongside the description of the estimated symptom trajectory. The resulting symptomology group membership is a categorical variable for the full sample of adolescents over three waves, following the assignment of participants to their most likely group. Based on each participant's highest group membership

[6] http://www.tbonline.info/media/uploads/documents/ntcp_adult_tb-guidelines-27.5.2014.pdf

probability, 14.1%, 19.1%, and 66.8% were assigned to each group, respectively. In general, probabilities for all groups decline over time.

Figure 2: TB symptomology group trajectories

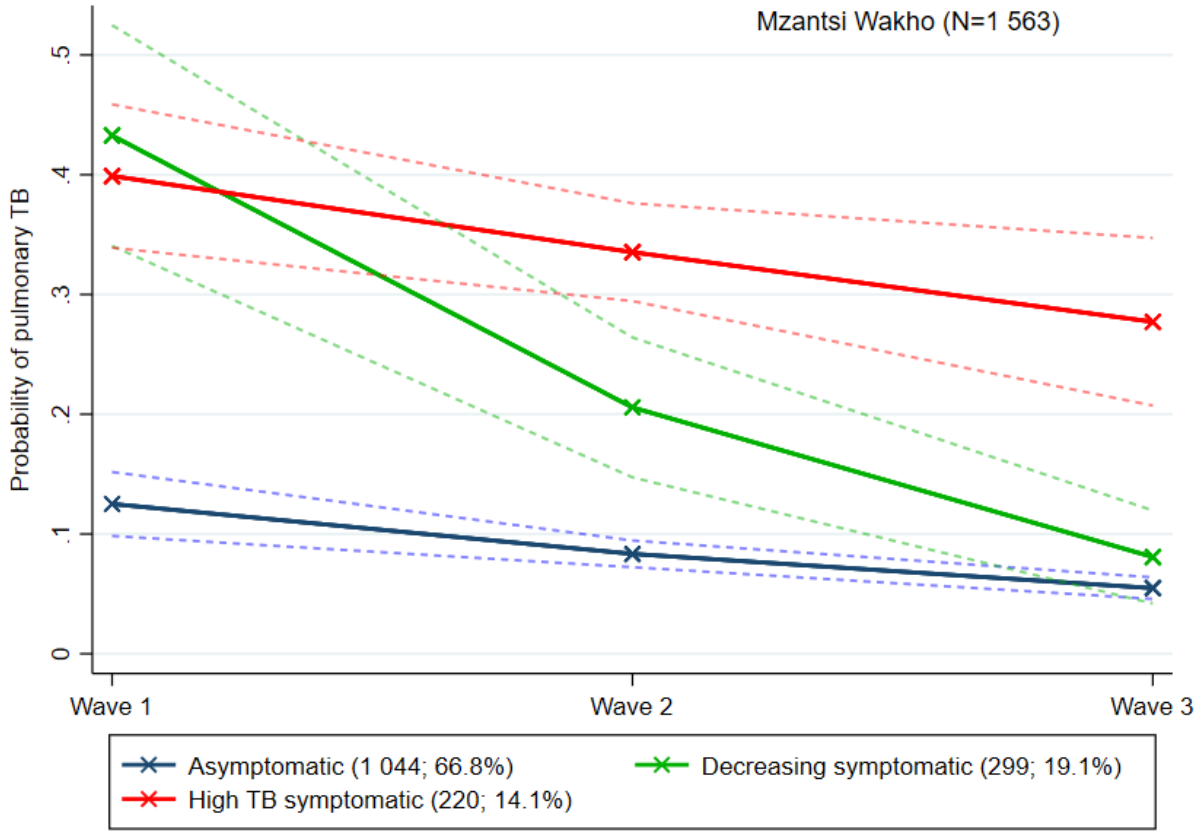


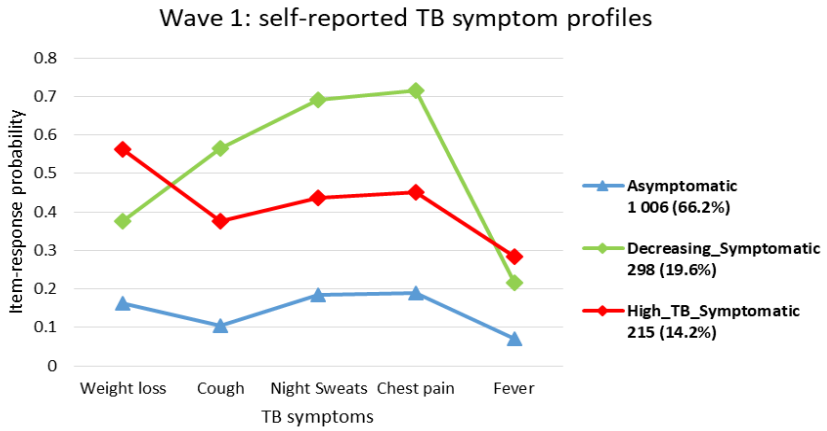
Table 5 shows the baseline characteristics of the symptomology trajectories/ groups. Relative to the asymptomatic group, participants in the decreasing symptomatic and high TB symptomatic groups were more likely to be female (53.0%, 57.0% and 64.1%, p=0.017), living with HIV (60.9%, 87.3% and 77.3%, p<0.001), and less likely to reside in rural areas (28.5%, 20.7%, 19.6%, p=0.001). The majority of adolescents who reported lifetime TB at baseline are in the symptomatic groups, at 28.4% and 22.2%, versus the 14.9% in the asymptomatic group. Over 40% of adolescents in the high TB symptomatic group reported having never tested for TB at baseline.

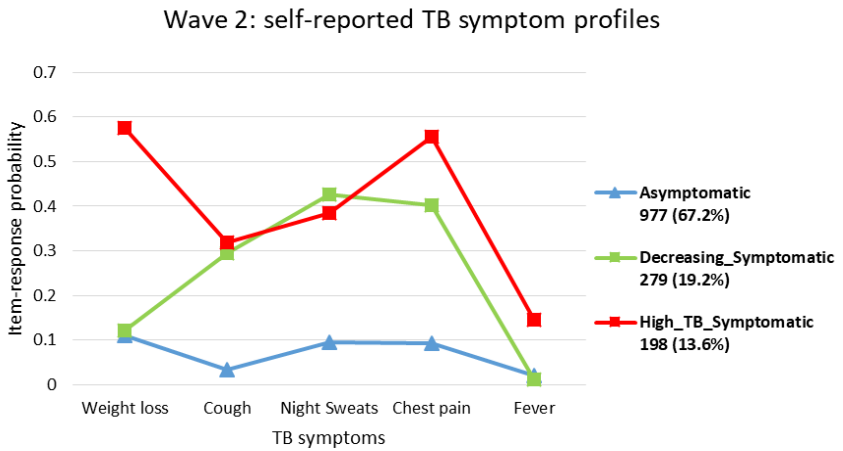
Table 5: Baseline characteristics by TB symptomology trajectory groups

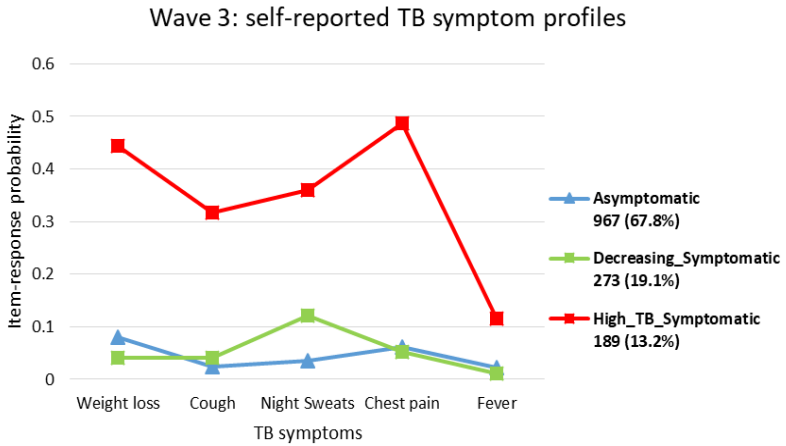
	Total cohort (N=1 563)	**Asymptomatic n=1 044(66.8)**	**Decreasing symptomatic n=299 (19.1)**	**High TB symptomatic n=220 (14.1)**	
Baseline Factors	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**p-value**
Age (15+ years)	644 (41.2)	438 (42.0)	112 (37.5)	94 (42.7)	0.168
Female	864 (55.3)	553 (53.0)	170 (57.0)	141 (64.1)	0.017
Rural	403 (25.8)	298 (28.5)	62 (20.7)	43 (19.6)	0.001
Informal housing	271 (17.3)	183 (17.5)	54 (18.1)	34 (15.5)	0.701
Poverty	512 (32.8)	357 (34.2)	87 (29.1)	68 (31)	0.102
HIV positive	1046 (67.0)	636 (60.9)	240 (80.3)	170 (77.3)	<0.001
Self-reported TB clinic diagnosis					
1. Never tested	766 (50.4)	557 (55.4)	121 (40.6)	88 (40.9)	
2. Life-time TB	277 (18.2)	150 (14.9)	66 (22.2)	61 (28.4)	
3. Current TB	44 (2.9)	20 (2.0)	17 (5.7)	7 (3.3)	
4. TB negative	365 (24.0)	240 (23.9)	72 (24.2)	53 (24.7)	
5. No results	67 (4.4)	39 (3.9)	22 (7.4)	6 (2.8)	

Figure 3 shows the respective symptom profiles which characterize each group at each wave of data collection. The high-TB symptomatic group is high on four out of five symptoms (except fever) and this is consistent over the three time points. In addition, it is interesting to see the whole green curve (decreasing symptomatic) roughly retaining its shape and dropping over time. The most noticeable difference is that the high symptomatic group shows consistently high weight loss and chest pain across time while the decreasing symptomatic group shows high chest pain, although declining with time. While chest pain is indicative of TB disease and lack of treatment, weight loss could be a sign of being chronically ill.

Figure 3: Symptom profiles for respective long-term symptomology groups







3.3.2 Estimating TB at each time point

Based on the above findings, we aimed to estimate the proportion of suspected PTB in this adolescent population following the steps described in Section 2.4. This involves combining two data sources: long-term symptomology grouping (a categorical variable with three nominal levels at each time point) and self-reported TB clinic diagnosis at each time point. As shown in Table 6, about half of the sample (50.4%, 47.7%, and 53.6%) reported to have never tested for TB and this is consistent across time. Around a third of participants (40.9%, 32.8%, and 37.6%) who belonged in the high TB symptomatic profile had never tested for TB.

Table 6: Distribution of TB testing and results across the three long-term symptom profiles

		TB testing and results					
	Long-term TB symptom profiles	Never tested	Lifetime/ Past-year TB	Current TB	No TB	No results	**Total**
Wave 1	Asymptomatic	557 (55.4)	150 (14.9)	20 (2.0)	240 (23.9)	39 (3.9)	**1 006 (100)**
	Decreasing Symptoms	121 (40.6)	66 (22.2)	17 (5.7)	72 (24.2)	22 (7.4)	**298 (100)**
	High TB symptomatic	88 (40.9)	61 (28.4)	7 (3.3)	53 (24.7)	6 (2.8)	**215 (100)**
	Total N (%)	**766 (50.4)**	**277 (18.2)**	**44 (2.9)**	**365 (24.0)**	**67 (4.4)**	**1 519 (100)**
Wave 2	Asymptomatic	524 (53.6)	103 (10.5)	5 (0.5)	308 (31.5)	37 (3.8)	**977 (100)**
	Decreasing Symptoms	105 (37.6)	47 (16.9)	7 (2.5)	97 (35.4)	23 (8.2)	**279 (100)**
	High TB symptomatic	65 (32.8)	38 (19.2)	13 (6.6)	70 (35.4)	12 (6.1)	**198 (100)**
	Total N (%)	**694 (47.7)**	**188 (12.9)**	**25 (1.7)**	**475 (32.7)**	**72 (5)**	**1 454 (100)**
Wave 3	Asymptomatic	567 (58.6)	70 (7.3)	12 (1.2)	284 (29.4)	34 (3.5)	**967 (100)**
	Decreasing Symptoms	128 (46.9)	40 (14.7)	4 (1.5)	89 (32.6)	12 (4.4)	**273 (100)**
	High TB symptomatic	71 (37.6)	29 (15.3)	10 (5.3)	73 (38.6)	6 (3.2)	**189 (100)**
	Total N (%)	**766 (53.6)**	**139 (9.7)**	**26 (1.8)**	**446 (31.2)**	**52 (3.6)**	**1 429 (100)**

3.3.2.1 'Adjusted' TB variable

To derive a hybrid 'adjusted' TB variable, we adjusted the long-term symptom profiles established through GBTM for self-reported TB clinic diagnosis (see Table 6) by following the steps outlined in Section 2.4. These steps involved:

1. Allocating all participants in the asymptomatic profile who did not confirm past or current TB and those who confirmed TB negative as well as in the decreasing symptoms profile to the *asymptomatic category*.
2. Assigning all participants who confirmed past-year and current self-reported TB as *confirmed TB cases.*
3. Assigning all individuals who self-reported never having been tested for TB but showing TB symptoms over time, and individuals who tested for TB, did not get results but showed TB symptoms over time as '*suspected' TB cases*.

Table 7 shows the resulting derived hybrid TB variable (adjusted) at each wave. From the results we observed a general decline in TB over time: confirmed current TB disease declined from 21.1% at Wave 1 to 11.6% at Wave 3 in the whole sample. Nearly two-thirds (59.8%, 66.4% and 68.2%) of the population was TB asymptomatic as identified by the long-term TB symptom profiles adjusted for self-reported TB diagnosis. Suspected TB cases were stable at about a fifth (19.1%, 18.9% and 20.3%) of the total sample over time. The majority of confirmed cases were adolescents living with HIV across all the time points.

Table 7: Distribution of the 'adjusted' TB variable by HIV-status at each wave of data collection

Wave of data collection	HIV status	Asymptomatic	Confirmed TB	Suspected TB	Total
Wave 1	HIV negative	373 (78.9)	17 (3.6)	83 (17.6)	473 (100)
	HIV positive	535 (51.2)	304 (29.1)	207 (19.8)	1046 (100)
	Total	**908 (59.8)**	**321 (21.1)**	**290 (19.1)**	**1519 (100)**
Wave 2	HIV negative	344 (81.1)	11 (2.6)	69 (16.3)	424 (100)
	HIV positive	622 (60.4)	202 (19.6)	206 (20.0)	1030 (100)
	Total	**966 (66.4)**	**213 (14.7)**	**275 (18.9)**	**1454 (100)**
Wave 3	HIV negative	341 (81.4)	13 (3.1)	65 (15.5)	419 (100)
	HIV positive	633 (62.7)	152 (15.1)	225 (22.3)	1010 (100)
	Total	**974 (68.2)**	**165 (11.6)**	**290 (20.3)**	**1429 (100)**

Finally, the multinomial logistic regression results in Table 8 show the association between the hybrid TB variable and socio-demographic characteristics, including HIV, status at each wave. The results show that HIV-positive older adolescents are most likely to be in the confirmed TB group and this pattern is consistently decreasing over time (aOR: 13.3, 10.9 and 6.3). Moreover, younger female urban resident adolescents living with HIV are noticeably likely to be in the suspected TB group. This is a group that continues to show symptoms of TB over time; the majority of this group had not tested for TB.

Table 8: Multinomial logistic regression results for socio-demographic predictors of confirmed and suspected TB among adolescents

	Wave 1 Model	**Wave 2 Model**	**Wave 3 Model**
TB category	**aOR (95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**
0. Asymptomatic	**(Reference category)**		
1. Confirmed TB			
Age	1.07 (1.02-1.12)***	1.08 (1.03-1.14)***	1.01 (0.95-1.06)
Female	0.95 (0.72-1.25)	1.20 (0.87-1.65)	1.44 (1.01-2.06) *
Rural	0.73 (0.53-0.10)*	0.98 (0.70-1.40)	0.97 (0.66-1.43)
HIV-positive	13.30 (8.0-22.15)***	10.90 (5.82-20.3)***	6.29 (3.51-11.30)***
Informal housing	0.94 (0.66-1.34)	1.11 (0.72-1.70)	1.43 (0.91-2.24)
Poverty	1.08 (0.81,1.44)	0.63 (0.41-0.95)**	0.98 (0.69-1.43)
2. Suspected TB			
Age	0.94[§] (0.89-0.98)***	0.93 (0.89-0.98)***	0.93 (0.89-0.97)***
Female	1.59 (1.20-2.11)***	1.38 (1.04-1.84)**	1.45 (1.09-1.92)**
Rural	0.56 (0.40-0.78)***	0.60 (0.43-0.85)***	0.68 (0.49-0.95)*
HIV-positive	1.71 (1.28-2.29)***	1.55 (1.14-2.11)***	1.81 (1.32-2.46)***
Informal housing	0.81 (0.55-1.17)	1.02 (0.68-1.53)	0.89 (0.58-1.35)
Poverty	0.97 (0.73-1.29)	1.29 (0.94-1.77)	0.74 (0.55-0.99)*

*95% CI- 95% confidence interval in parentheses
* p<0.05, ** p<0.01, *** p<0.001; aOR- adjusted odds ratios
[§] Note: Adjusted odds ratios look so close to 1 because they are cubed for a three-year age difference

4. Discussion

This study applied the Group-Based Trajectory Model (GBTM) to describe group-level TB symptomology patterns in a cohort of adolescents living with HIV. The derived TB symptomology groups were further adjusted using self-

reported TB testing diagnosis to compute rates of confirmed and 'suspected' TB in ALHIV in a resource-constrained setting in South Africa. At baseline, about 1 in 5 adolescents in this sample reported at least one TB-related symptom, which is much higher than that reported in previous studies, of which none where among ALHIV (Mahomed *et al.*, 2013; Nduba *et al.*, 2015). High rates of past TB instances were also observed in this study. Based on the GBTM model, three TB symptomology groups over the three waves were identified namely: high TB symptomatic (16.6%); decreasing symptomatic (23.3%); and asymptomatic (60.1%) over the three time points. The majority of adolescents in the high TB symptomatic group reported having never tested for TB at baseline.

After adjusting the model-based groupings for self-reported TB diagnosis, we estimated that the majority of the sample (over 60 %) is *asymptomatic* and this was consistent over three time points. We further observed a decline in the number of confirmed TB cases, from 21.1% in Wave 1 to 11.6% in Wave 3, which is possible given that the majority of these cases get initiated on TB treatment (Sant'Anna, March & Aurílio, 2018). Lastly, in total, we estimated that the rates of suspected TB cases remained stable over time, with a fifth (19.4% on average) of the sample classified into this group. The majority of both the confirmed and suspected TB cases were living with HIV. These high rates of suspected TB (20.7% on average) among ALHIV is not surprising given that this is a vulnerable and high-risk population group living in resource-constrained settings. This calls for more efforts towards active case finding in this vulnerable population group. The estimate of confirmed TB disease is similar to the self-reported lifetime TB of over 14%, reported in the above-mentioned studies (Mahomed *et al.*, 2013; Snow *et al.*, 2017). These findings highlight a gap between confirmed TB cases and potential or 'suspected' TB cases, which is possibly due to TB-underdiagnoses owing to challenges in confirming TB in resource-limited settings.

The multinomial logistic regression results using the adjusted TB classification as outcome showed that age, sex, and HIV status were associated with suspected TB cases relative to the asymptomatic group. HIV-positive older adolescents were likely to be in the confirmed TB group and this pattern was consistent over time. This possibly can be explained by the fact that as adolescents grow older it becomes easier to test for TB. In general bacteriological confirmation is difficult in younger adolescents, hence older adolescents are more likely to be referred for TB testing (Sant'Anna, March & Aurílio, 2018). Moreover, the higher burden of HIV infection among young females likely results in higher levels of TB disease among this group than among young men. This is consistent with what has been

reported in other studies (García-Basteiro *et al.*, 2018; Snow *et al.*, 2018).

Furthermore, we observed low rates of TB testing over time in this sample of adolescents, i.e., a vulnerable population living in resource-constrained settings. About half of the sample reported to have never tested for TB in their lifetime, and the majority (over 60%) are HIV positive which could mean masking of a significant pool of active TB cases classified as 'suspected TB' based on our algorithm. This lack of early diagnosis and treatment of active TB in resource-poor settings with high TB prevalence means that suspected TB contributes significantly to the pool of adolescent TB cases. This could also be related to the fact that very often younger adolescents are less likely to produce sputum and hence Gene-Xpert testing is impossible, thus explains the low TB testing rates observed.

This study is not without limitations, which should be considered while interpreting the results. First, because the questionnaire only asked for symptoms related to PTB, we are not able to determine the rate of extra-pulmonary TB which, if included, might have indicated an even higher rate of TB in this adolescent population. Second, the generalizability of findings on symptom profiles may be limited, since the study was conducted in one health sub-district in South Africa. Third, this study primarily uses self-reported data, which may lead to under-reporting of symptoms of poor health, due to social desirability and recall bias. Given the paucity of age-specific data on TB prevalence among adolescents in South Africa, it's difficult to do a proper comparison of estimates.

In conclusion, these findings show that a combination of both TB medical testing and available data on self-reported TB symptoms may be useful to identify both TB patients, and suspected TB cases for further testing in this vulnerable group. This study has also shown that the GBTM method can be a useful tool to estimate long-term suspected TB burden using self-reported TB symptoms. Further studies could look into establishing an adolescent's history of contact with a TB case, which could provide valuable data on suspected TB diagnosis in the absence of a radiological or immunological diagnosis.

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