

Social Activity Patterns Drive High Rates of Latent Tuberculosis Infection among Adolescents in Urban Tanzania

—Latent TB Infection in Adolescents, Tanzania

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Abstract

SETTING: Dar es Salaam, Tanzania. **OBJECTIVE:** To determine the prevalence of latent tuberculosis (TB) infection (LTBI) among adolescents in a country with a high TB burden, and examine risks of LTBI according to their social activity patterns. **METHODS:** A cross-sectional study nested within a phase 2b randomised, placebo controlled, double blind study and consisted of 824 adolescents, 13 - 15 years old who had received Bacillus Calmette-Guérin (BCG) vaccine, were attending public secondary schools and had no evidence of active tuberculosis (TB). Anthropometric measurements were obtained, a questionnaire administered, and phlebotomy performed for a T spot interferon- γ release assay (IGRA) to detect LTBI. **RESULTS:** Among 824 subjects, 149 (18%) had a positive IGRA. After adjusting for the influence of household socioeconomic status, history of TB contact, living environment and nutritional status, LTBI risk was higher in subjects with than without regular informal encounters with traditional alcoholic beverage drinkers (AOR, 6.37 [1.84 - 22.00]). Other significant factors for LTBI risk included contact with TB patient at school (AOR, 3.34 [1.14 - 9.80]), and living close to a health facility, as was observed among those from houses within a 10 - 30-minute walking distance to the nearest health facility, who were less likely to be IGRA-positive than those who were living within a 10-minute walking dis-

tance (AOR, 0.30 [95%CI, 0.13 - 0.69]). **CONCLUSION:** This IGRA study revealed a high prevalence of LTBI among adolescents in Dar es Salaam, Tanzania with prior BCG immunization. Informal social encounters were identified as independent risk factors for LTBI, along with a history of contact with TB patients, living environment characteristics and household socioeconomic status. Efforts focusing on risk of MTB transmission in adolescents at informal social gatherings will improve interventions to reduce LTBI in this population and consequently the subsequent risk of developing active TB disease.

Keywords

Dar es Salaam, Social Factors, IGRA, T Spot, Adolescents, BCG, DAR 901

1. Introduction

Despite a decline in its global prevalence, tuberculosis (TB) still causes more deaths than other infectious diseases [1]. In 2015, 10.4 million new cases of TB and 1.4 million deaths from TB were reported globally [1]. Twenty countries, including Tanzania, contribute 84% of total global TB cases [1].

About one third of the world's population is infected with the causative agent of TB, *Mycobacterium tuberculosis* (MTB) [2], but most show no signs or symptoms of active disease, *i.e.*, latent TB infection (LTBI) [2]. Approximately 10% of those with LTBI will progress to active TB at some point in their lives [2] [3]. Infant BCG immunization is >70% effective in preventing TB disease for 10 - 15 years [4] [5], after which the level of protection begins to wane [5] [6]. In Tanzania, where TB is endemic, and 91% of all children <12 months of age have received the Bacillus Calmette-Guerin (BCG) vaccine against TB, the annual incidence of TB disease in 2015 was 306/100,000, including 18,000 children <14 years of age [1] [7].

Data on the prevalence of LTBI and risk factors for LTBI in Tanzania are more limited, and are not available for adolescents. This is true despite the high incidence of TB disease among children <14 years old in Tanzania [1], the waning efficacy of BCG vaccine in adolescence [5] [6], the adolescents' increased outdoor activities [8], 43.9% of country population in 2012 being children ≤15 years [9], and the rapid increase in urban populations in Tanzania [9].

The T spot interferon- γ release assay (IGRA) is an advanced TB diagnostic tool, and is more specific than the tuberculin skin testing (TST) in identifying LTBI among BCG-vaccinated individual [10] [11]. Risk factors for LTBI reported from other settings include household contact with infectious TB [12] [13], overcrowding and poor ventilation within households [14] [15], HIV infection [16], underweight [16] and high TB incidence [17]. Most of these studies have been conducted in settings where BCG immunization is routine and have used the TST to identify LTBI.

In this study, we used IGRA as the most specific approach to detect LTBI in

adolescents at school, who had received BCG at birth. Our objectives were to obtain an accurate estimate of the prevalence of LTBI in adolescents, and to identify risk factors for LTBI with a focus on both the home environment and social encounters outside the home.

2. Methods

2.1. Study Procedure

This study was conducted between April 6 and September 23, 2016, in Dar es Salaam, Tanzania, with a population of 5,465,420 as of 2016 [9]. This was part of a larger phase 2b, randomised, placebo-controlled, double-blind study on the safety and efficacy of a three-dose series of DAR-901 an inactivated whole cell vaccine for preventing MTB infection among BCG-vaccinated adolescents [1] [18] [19]. Written informed consent and assent from parents/guardians and study subjects were obtained. Anthropometric measurements and phlebotomy were performed for IGRA, and subjects completed a questionnaire.

2.2. Study Subjects

Subjects were recruited from 16 secondary schools chosen from a list of 139 public non-boarding secondary schools within the Dar es Salaam region [20]. These 16 schools were selected by simple random selection, evaluation of accessibility to a study clinic and willingness of the school administration to participate in the study. Based on the LTBI prevalence rate of 41.7% among adolescents 11 - 15 years old reported in South Africa [21], and the difference in reported incidences of TB in Tanzania and South Africa, with 5% type I error and 5% absolute error, we calculated that our study required a sample size of 571.

Initial screening for the study was performed after obtaining written informed consent and assent from a total of 936 subjects. The inclusion criteria were: age between 13 and 15 years, attendance at a public non-boarding secondary school, evidence of BCG vaccination (either the presence of a scar or documentation) and the absence of signs of active TB or symptoms suggesting active TB disease based on the Tanzanian TB screening questionnaire [22]. Data from 824 subjects that fulfilled the inclusion criteria were analysed. Those with signs and/or symptoms of active TB were referred to specialised TB clinics under the National Tuberculosis and Leprosy Program (NTLP).

2.3. Anthropometric Measurements

Body mass index (BMI) (kg/m^2) was calculated based on height and weight measurements. BMI-for-age percentiles for both genders, obtained using the Centres for Disease Control (CDC) growth charts [23], were categorised as follows: <5%, underweight; 5% - 85%, healthy; 85% - 95%, overweight; >95%, obese.

2.4. Interferon- γ Release Assay (IGRA)

The IGRA was performed using the T-SPOT.TB (Oxford Immunotec, Oxford,

UK) assay according to the manufacturer's instructions. Venous blood samples were analysed at the Tuberculosis Research Institute at Muhimbili University of Health and Allied Sciences (TRIM-TB) in Dar es Salaam, Tanzania [18]. The results were interpreted as positive, negative, borderline or indeterminate according to the published guidelines [18]. Adolescents with positive results were administered the Tanzanian TB screening questionnaire [22] and referred to specialised NTLP TB treatment clinics if signs or symptoms consistent with active TB were present [18].

2.5. A TB Risk Factor Questionnaire

A questionnaire was developed at the Department of Global Health Entrepreneurship of Tokyo Medical and Dental University, and included questions about prior active TB, contact with TB patients, social activity patterns, living environment and household socioeconomic characteristics. The original English version questionnaire was translated into Swahili, which was then back translated to English for confirmation.

After receiving instructions on how to complete the questionnaire, the adolescents were allowed to take the questionnaire home to answer all questions with the help of their parents/guardians. At the time of submission, nurses inspected the completed questionnaires to confirm that they had been filled out correctly. To ensure consistency in instruction and interviews, all nurses involved in the study received a full day of training before initiation of the study.

We obtained the subject's past history of diagnosis and treatment for active TB disease, household contact with a TB patient, knowledge of a neighbour that had TB, and knowledge of a fellow student diagnosed with TB.

To understand the social activity patterns of the adolescents, the questionnaire inquired about the means of transport used to attend school, encounters with traditional alcoholic beverage drinkers, visits to market places and walking distance between the house and the nearest health facility. All these activities increase risks for contact with active TB patients.

In relation to the living environment characteristics, the number of living rooms and bedrooms, brightness from sunlight in living rooms and bedrooms and number of older family members living in the same house were determined.

The education levels of the father and mother, employment of father and household wealth status evaluated according to the Demographic and Health Survey (DHS) guidelines [24] [25] were used.

2.6. Statistical Analysis

Statistical analyses were performed using SPSS Statistics v22.0 (IBM Corp., Armonk, NY, USA). Percentage distributions according to IGRA results were calculated for 824 subjects. After excluding 20 subjects with indeterminate and borderline results, the percentages of IGRA-positive cases according to their characteristics were evaluated using cross-tabulation with the χ^2 test. After ex-

cluding 75 subjects with prior history of TB diagnosis (23 who responded “Yes” and 52 who responded “I do not remember”), logistic regression analysis to examine the association between IGRA positivity and characteristics of the subjects were performed with three models: 1) crude; 2) adjusted by wealth, history of contact with TB patients in their households and in the community; and 3) by wealth, history of contact with TB patients in their households, in the community, living conditions and nutritional status. All missing data were excluded from multiple logistic regression analyses models. In all analyses, $P < 0.05$ indicated statistical significance.

2.7. Ethical Consideration

This study was approved by the Institution Review Boards of the Medical Schools of Tokyo Medical and Dental University, Japan; Muhimbili University of Health and Allied Sciences, Tanzania; and Geisel School of Medicine at Dartmouth, NH, USA. Permission to recruit secondary school students was obtained from the Ministry of Health, Community Development, Gender, Elderly and Children, the Ministry of Education and Vocational Training, and the President’s Office for Regional Administration and Local Government of Tanzania.

3. Results

Table 1 shows the results of IGRA; 18.1% of the 824 subjects were positive and 79.5% were negative.

Table 2 shows the number and percentage of the IGRA-positive cases according to the characteristics for selected variables showing statistically significant associations with the IGRA results.

Table 3 shows the associations between IGRA status and characteristics of 729 adolescents with no history of prior TB, before and after adjusting for other variables. The rate of IGRA positivity was higher in subjects with than without frequent encounters with traditional alcohol beverage drinkers (AOR, 6.37 [1.84 - 22.00]), and those residing in houses within a 10 - 30-minute walking distance to the nearest health facility were less likely to be IGRA-positive than those living

Table 1. IGRA results among adolescents ($n = 824$).

CATEGORY	<i>n</i>	%
IGRA Result		
Positive	149	18.1
Negative	655	79.5
Indeterminate	19	2.3
Borderline	1	0.1
Total	824	100.0

n, number of subjects; %, percentage.

Table 2. IGRA-positive cases according to adolescents' characteristics ($n = 804$, after excluding subjects with indeterminate or borderline test results).

	<i>N</i> = 804	IGRA-positive adolescents			<i>P</i>
		%	<i>n</i>	%	
Gender and nutritional status					
Gender					0.22
Boys	358	44.5	73	20.4	
Girls	446	55.4	76	17.0	
Body Mass Index (BMI) percentile					0.12
<5% [underweight]	23	2.9	6	26.1	
5% - 85% [healthy]	591	73.5	110	18.6	
85% - 95% [overweight]	124	15.4	16	12.9	
>95% [obese]	66	8.21	17	25.8	
History of TB and contact with TB patients					
History of being treated for TB					0.01
No	729	90.7	132	18.1	
Yes	23	2.9	9	39.1	
Unknown	52	6.5			
Contact with TB patient(s) in household					0.03
No	616	76.6	100	16.2	
Yes	90	11.2	23	25.6	
Unknown	98	12.2			
Contact with TB patient(s) in community					<0.01
No	493	61.3	83	16.8	
Yes	59	7.3	25	42.4	
Unknown	252	31.3			
Contact with TB patient(s) at school					<0.01
No	663	82.5	111	16.7	
Yes	34	4.2	14	41.2	
Unknown	107	13.3			
Social activity patterns among adolescents					
Means of transport to and from school					0.04
Public transport	308	38.3	46	14.9	
Walking	476	59.2	99	20.8	
Bicycle	20	2.5	5	25.0	

Continued

Encounter with traditional alcoholic beverage drinkers					0.01
No, never	563	70.0	101	17.9	
Yes, only few times in the past	142	17.7	32	22.5	
Yes, once to a few times monthly	41	5.1	2	4.9	
Yes, once a week or more frequently	32	4.0	11	34.4	
Unknown	26	3.2			
Visits to market places					0.01
Once or less per month	411	51.1	63	15.3	
More than once per month	360	44.8	82	22.8	
Unknown	33	4.1			
Closeness to health facility					0.04
<10 minutes	286	35.6	68	23.8	
10 - 30 minutes	197	24.5	27	13.7	
>30 minutes	96	11.9	17	17.7	
Unknown	225	28.0			
Living environments					
Number of living room(s)					<0.01
0	10	1.2	1	10.0	
1	268	33.3	70	26.1	
2	283	35.2	39	13.8	
Unknown	243	30.2			
Brightness from sunlight in living room(s)					<0.01
Lack of sunlight	13	1.6	2	15.4	
Somewhat bright	438	54.5	100	22.8	
Very bright	222	27.6	22	9.9	
Unknown	131	16.3			
Number of bedrooms(s)					<0.01
1	122	15.2	16	13.1	
2	134	16.7	38	28.4	
3	354	44.0	44	12.4	
≥4	94	11.7	32	34.0	
Unknown	100	12.4			

Continued

Brightness from sunlight in bedroom(s)					0.01
Lack of sunlight at all	21	2.6	3	14.3	
Somewhat bright	540	67.2	113	20.9	
Very bright	154	19.2	16	10.4	
Unknown	89	11.0			
Family members older than adolescent					0.04
1	61	7.6	4	6.6	
2	138	17.2	31	22.5	
≥3	535	66.5	99	18.5	
Unknown	70	8.7			
Household socioeconomic characteristics					
Father's educational attainment					<0.01
No	21	2.6	12	57.1	
Primary education	288	35.8	69	24.0	
Higher education	305	37.9	43	14.1	
Unknown	190	23.6			
Mother's educational attainment					0.03
No	17	2.1	3	17.6	
Primary education	370	46.0	89	24.1	
Higher education	238	29.6	35	14.7	
Unknown	179	22.3			
Father's employment					0.01
Unemployed	29	3.6	1	3.4	
Businessman	448	55.7	94	21.0	
Works in the office	95	11.8	8	8.4	
Industrial worker	39	4.9	10	25.6	
Unknown	193	24.0			
Wealth status of household					0.01
Richest	162	20.1	17	10.5	
Rich	161	20.0	35	21.7	
Middle	158	19.7	27	17.1	
Poor	165	20.5	43	26.1	
Poorest	158	19.7	27	17.1	

TB, Tuberculosis; N, number of subjects after excluding those with borderline and indeterminate IGRA results; %, percentage; n, number of subjects with positive IGRA results; *P*, *P*-value; ≥, more or equal to; ≤, less or equal to; <, less than; >, more than.

Table 3. Association between IGRA positivity and characteristics of adolescents before and after adjustment for socioeconomic status, household and community TB contact, living conditions and nutritional status.

Characteristics	n	MODEL 1 ^a		MODEL 2 ^b		MODEL 3 ^c	
		COR [95%CI]	<i>P</i>	AOR [95%CI]	<i>P</i>	AOR [95%CI]	<i>P</i>
History of contact with TB patients							
Contact with TB patient(s) in household							
No	569	Ref		Ref		Ref	
Yes	74	1.24 [0.66 - 2.32]	0.49	1.16 [0.60 - 2.27]	0.66	1.26 [0.54 - 2.92]	0.60
Contact with TB patient(s) in the community							
No	463	Ref		Ref		Ref	
Yes	51	2.41 [1.26 - 4.62]	0.01	1.92 [0.93 - 3.97]	0.08	2.02 [0.84 - 4.88]	0.12
Contact with TB patient(s) at school							
No	603	Ref		Ref		Ref	
Yes	35	3.57 [1.71 - 7.48]	<0.01	3.55 [1.54 - 8.17]	<0.01	3.34 [1.14 - 9.80]	0.03
Social activity patterns of adolescents							
Encounter with traditional alcoholic beverage drinkers							
Never	522	Ref		Ref		Ref	
Yes, a few times in the past	119	0.85 [0.50 - 1.47]	0.57	0.72 [0.37 - 1.40]	0.33	0.26 [0.09 - 0.81]	0.02
Yes, once to a few times a month	38	0.24 [0.06 - 1.02]	0.05	0.32 [0.07 - 1.38]	0.13	0.40 [0.09 - 1.79]	0.23
Yes, once a week to more frequently	29	3.00 [1.35 - 6.66]	0.01	2.90 [1.15 - 7.34]	0.03	6.37 [1.84 - 22.00]	<0.01
Closeness to health facility							
≤10 mins	259	Ref		Ref		Ref	
10 - 30 mins	177	0.57 [0.34 - 0.96]	0.03	0.44 [0.25 - 0.78]	0.01	0.30 [0.13 - 0.69]	0.01
≥30 minutes	95	0.81 [0.44 - 1.49]	0.50	0.50 [0.23 - 1.06]	0.07	0.58 [0.23 - 1.46]	0.25
Living environment							
Number of living rooms							
1	238	Ref		Ref		Ref	
2	263	0.42 [0.26 - 0.67]	<0.01	0.46 [0.26 - 0.80]	0.01	0.55 [0.30 - 1.00]	0.05
Brightness from sunlight in living room(s)							
Very bright	206	Ref		Ref		Ref	
Somewhat bright	398	2.72 [1.60 - 4.63]	<0.01	2.17 [1.22 - 3.86]	0.01	1.30 [0.61 - 2.80]	0.50
Number of bedrooms							
1	107	Ref		Ref		Ref	
2	127	2.29 [1.15 - 4.56]	0.02	1.91 [0.90 - 4.05]	0.09	1.51 [0.49 - 4.64]	0.48
3	319	0.84 [0.43 - 1.62]	0.60	0.68 [0.33 - 1.41]	0.30	0.35 [0.11 - 1.06]	0.06
≥4	95	3.40 [1.67 - 6.91]	<0.01	3.88 [1.74 - 8.67]	<0.01	3.85 [1.12 - 13.20]	0.03

Continued

Brightness from sunlight in bedrooms								
Very bright	135	Ref		Ref		Ref		
Somewhat bright	492	3.33 [1.69 - 6.58]	<0.01	2.89 [1.39 - 6.00]	<0.01	2.02 [0.74 - 5.50]		0.17
Household socioeconomic characteristics								
Father's educational attainment								
No education	18	Ref		Ref		Ref		
Primary Education	264	0.43 [0.16 - 1.21]	0.11	3.10 [0.34 - 28.07]	0.32	2.43 [0.24 - 24.13]		0.45
Higher education	276	0.18 [0.06 - 0.52]	<0.01	1.66 [0.18 - 15.10]	0.65	1.20 [0.12 - 11.89]		0.87
Mother's educational attainment								
Ref: No education	15	Ref		Ref		Ref		
Primary education	342	1.25 [0.34 - 4.54]	0.74	1.54 [0.38 - 6.26]	0.55	2.20 [0.23 - 20.71]		0.49
Higher education	215	0.70 [0.19 - 2.63]	0.60	1.13 [0.27 - 4.72]	0.87	1.63 [0.17 - 15.77]		0.67
Wealth status of household								
Richest quintile	146	Ref		Ref		Ref		
Rich quintile	140	1.92 [0.92 - 3.97]	0.08	1.66 [0.76 - 3.63]	0.20	1.69 [0.63 - 4.53]		0.29
Middle quintile	142	2.25 [1.10 - 4.61]	0.03	1.70 [0.77 - 3.72]	0.19	2.55 [1.00 - 6.48]		0.05
Poor quintile	157	3.91 [2.00 - 7.64]	<0.01	3.35 [1.67 - 6.72]	<0.01	2.51 [1.02 - 6.19]		0.05
Poorest quintile	144	2.35 [1.16 - 4.76]	0.02	1.71 [0.79 - 3.71]	0.18	1.05 [0.35 - 3.18]		0.93

COR, crude odds ratio; AOR, adjusted odds ratio; *P*, P-value; Ref, reference; 95%CI, 95% Confidence Interval; ≥, more or equal to; ≤, less or equal to; <, less than; >, more than. ^aUnadjusted model; ^bModel adjusted for wealth index, household and community tuberculosis contact; ^cModel adjusted for wealth index, household and community tuberculosis contact, number of living rooms, brightness in the living room and bedroom as well as BMI percentiles.

within a 10-minute walking distance (AOR, 0.30 [95%CI, 0.13 - 0.69]). Significant associations were also observed between IGRA positivity and living in a house with one living room, living in a house with four or more bedrooms, contact with a TB patient at school and wealth status.

4. Discussion

This is the first study to use the IGRA to examine the prevalence of LTBI among in-school adolescents in Tanzania. Encounters with traditional alcoholic beverage drinkers and living environments were identified as risk factors for LTBI, in addition to household socioeconomic status and history of contact with TB patients in the household and community.

The LTBI prevalence rate of 18.1% identified by IGRA among Tanzanian adolescents 13 - 15 years old is lower than the prevalence rate of 41.7% reported for those 11 - 15 years old in Cape Town, South Africa [21], and higher than the rate of 3.4% - 6.2% reported for those 10 - 18 years old in Shanghai, China [12]. These results reflect the order of reported incidence of smear-positive TB, including HIV-positive subjects, per 100,000 population (Tanzania, 306; South

Africa; 834; and China, 67) [1].

Because most Tanzanian adolescents have received BCG [7], the IGRA assay used in the present study provides a more accurate rate of LTBI in this population than the less-specific TST [26] [27].

LTBI was associated with a history of household contact with a TB patient, but this relationship disappeared after excluding subjects with history of prior TB. These findings suggested most subjects who had lived in the same household as a TB patient, might have later been diagnosed with active TB themselves, as postulated by the WHO [2]. There was also a significant association between LTBI and exposure to MTB in schools, a similar finding to a study conducted in South Africa township which concluded most MTB transmission among adolescents occurs outside of the household, particularly in school [8].

Regarding exposure in the community, the risk of acquiring LTBI was higher among adolescents with than without a history of encounters with traditional alcoholic beverage drinkers. This observation indicated a role of informal gatherings within communities in the spread of MTB. Traditional alcoholic beverage drinking is usually done at gatherings that are associated with ideal environments for MTB transmission like small, overcrowded and poor ventilated traditional bars and contact with drinkers who are active TB patients. These drinkers in turn spread MTB to adolescents with whom they interact informally within the community [28]. This supports the findings from the Malawi study, which used whole-genome sequencing to prove >50% of people with MTB had acquired the bacterium from sources other than a TB patient within their households [29].

Living in a house with four or more bedrooms was shown to increase the risk of LTBI, in contrast to previous studies [14] [15]. This may have been partly due to the Tanzania's extended family tradition, whereby those residing in urban areas and in houses with many bedrooms tend to host relatives migrating from rural areas in search of TB treatment services in urban Dar es Salaam [30] [31]. This could result in exposure and transmission of MTB to adolescents living in the host house.

This study also revealed an association between residing in a house located closest to a health facility and IGRA positivity. Residing close to a health facility might increase adolescents' risks for contact with active TB patients who attend those facilities for TB treatment. Consistent with findings from previous studies [14] [15], these results showed the duration of contact with MTB within a shared environment increases the risk of acquiring the bacterium, thus indicating a significant contribution of environmental exposure to MTB to its transmission [8] [29].

Living in a house with two living rooms, compared to one living room, was associated with a lower risk of LTBI. This observation point to an increase in LTBI risk associated with poor ventilation inside the living rooms, supporting reports that overcrowding and poor ventilation increase the risk of acquiring MTB [14] [15]. Our study also showed poor socioeconomic status increased the

risk of acquiring LTBI, consistent with other studies [15] [28].

Our study had notable strengths including being the first study to use IGRA, rather than TST, to identify LTBI among BCG-vaccinated adolescents in Tanzania. Using IGRA also provided logistic advantages as it does not require a subsequent visit 72 hours from inoculation to interpret the test results, hence convenient and contributes to a lower loss-to-follow-up rate than TST. The TB risk factor questionnaire used ensured ability to identify local LTBI risk factors based on locally available evidence. Also, overall recruitment challenges and participation bias were minimized by avoiding mandatory HIV testing among participants as the test, if were mandatory, would have limited voluntary participation to avoid stigma and discrimination since HIV/AIDS is prevalent in Tanzania [32]. Although HIV/AIDS infection is known to increase the risk of TB [33], this study population was expected to have a low prevalence of HIV of <6%, as was observed among adolescents 10 - 19 years old in 2014 [34]. Further, free antiretroviral therapy (ART) for HIV-infected children has been available in Tanzania since 2003 [35], hence subjects with HIV on ART would have been identified since all subjects were asked about concomitant medications.

However, our study also had some limitations including omission of a small number of subjects with missing data while conducting the logistic regression analysis, but since their numbers were small, omitting them did not affect our results. In addition, being cross-sectional in nature, it failed to establish causality assumption. Moreover, our study excluded out-of-school adolescents, which limited generalizability of the findings to all adolescents in Tanzania.

5. Conclusion

This is the first study to use the IGRA to examine LTBI prevalence among in-school adolescents in Tanzania. Informal social encounters were identified as independent risk factors for LTBI, along with a history of contact with TB patients, living environment characteristics and household socioeconomic status. Efforts focusing on risk of MTB transmission in adolescents at informal social gatherings will improve interventions to reduce LTBI in this population and consequently the subsequent risk of developing active TB disease.

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References

- [1] World Health Organization (2016) Global Tuberculosis Report 2016. WHO, Geneva.
- [2] World Health Organization (2015) Guidelines on the Management of Latent Tuberculosis Infection. WHO, Geneva.
- [3] Getahun, H., Matteelli, A., Chaisson, R.E. and Raviglione, M. (2015) Latent *Mycobacterium tuberculosis* Infection. *New England Journal of Medicine*, **372**, 127-135. <https://doi.org/10.1056/NEJMra1405427>
- [4] Roy, A., Eisenhut, M., Harris, R.J., Rodrigues, L.C., Sridhar, S., Habermann, S., *et al.* (2014) Effect of BCG Vaccination against *Mycobacterium tuberculosis* Infection in Children: Systematic Review and Meta-Analysis. *BMJ*, **349**, g4643. <https://doi.org/10.1136/bmj.g4643>
- [5] von Reyn, C.F. (2017) BCG Vaccination. <https://www.uptodate.com/contents/bcg-vaccination>
- [6] von Reyn, C.F. (2017) Correcting the Record on BCG before We License New Vaccines against Tuberculosis. *The Royal Society of Medicine Journals*, **110**, 428-433. <https://doi.org/10.1177/0141076817732965>
- [7] Ministry of Health and Social Welfare (MoHSW) of Government of Tanzania (2016) WHO and UNICEF Estimates of Immunization: Coverage 2016 Revision. Dar es Salaam, The United Republic of Tanzania: MoHSW, 1-3. http://www.who.int/immunization/monitoring_surveillance/data/tza.pdf
- [8] Andrews, J.R., Morrow, C., Walensky, R.P. and Wood, R. (2014) Integrating Social Contact and Environmental Data in Evaluating Tuberculosis Transmission in a South African Township. *Journal of Infectious Diseases*, **210**, 597-603. <https://doi.org/10.1093/infdis/jiu138>
- [9] Tanzania National Bureau of Statistics (NBS) (2016) Tanzania Total Population by District-Regions 2016-2017. Dar es Salaam, The United Republic of Tanzania. <http://www.nbs.go.tz/nbstz/index.php/english/statistics-by-subject/population-and-housing-census/844-tanzania-total-population-by-district-regions-2016>
- [10] Mahomed, H., Hawkrige, T., Verver, S., Abrahams, D., Geiter, L., Hatherill, M., *et al.* (2011) The Tuberculin Skin Test versus QuantiFERON TB Gold® in Predicting Tuberculosis Disease in an Adolescent Cohort Study in South Africa. *PLoS ONE*, **6**, e17984. <https://doi.org/10.1371/journal.pone.0017984>
- [11] Bianchi, L., Galli, L., Moriondo, M., Veneruso, G., Becciolini, L., Azzari, C., *et al.* (2009) Interferon-Gamma Release Assay Improves the Diagnosis of Tuberculosis in Children. *The Pediatric Infectious Disease Journal*, **28**, 510-514. <https://doi.org/10.1097/INF.0b013e31819abf6b>
- [12] Hu, Y., Zhao, Q., Wu, L., Wang, W., Yuan, Z. and Xu, B. (2013) Prevalence of Latent Tuberculosis Infection and Its Risk Factors in Schoolchildren and Adolescents in Shanghai, China. *European Journal of Public Health*, **23**, 1064-1069. <https://doi.org/10.1093/eurpub/ckt105>
- [13] Mumpe-Mwanja, D., Verver, S., Yeka, A., Etwom, A., Waako, J., Ssengooba, W., *et*

- al.* (2015) Prevalence and Risk Factors of Latent Tuberculosis among Adolescents in Rural Eastern Uganda. *African Health Sciences*, **15**, 851-860. <https://doi.org/10.4314/ahs.v15i3.20>
- [14] Kashyap, R.S., Nayak, A.R., Gaherwar, H.M., Husain, A.A., Shekhawat, S.D., Jain, R.K., *et al.* (2014) Latent TB Infection Diagnosis in Population Exposed to TB Subjects in Close and Poor Ventilated High TB Endemic Zone in India. *PLoS ONE*, **9**, e89524. <https://doi.org/10.1371/journal.pone.0089524>
- [15] Lönnroth, K., Jaramillo, E., Williams, B.G., Dye, C. and Raviglione, M. (2009) Drivers of Tuberculosis Epidemics: The Role of Risk Factors and Social Determinants. *Social Science and Medicine*, **68**, 2240-2246. <https://doi.org/10.1016/j.socscimed.2009.03.041>
- [16] Ai, J.-W., Ruan, Q.-L., Liu, Q.-H. and Zhang, W.-H. (2016) Updates on the Risk Factors for Latent Tuberculosis Reactivation and Their Managements. *Emerging Microbes & Infections*, **5**, e10. <https://doi.org/10.1038/emi.2016.10>
- [17] Nguyen, T.H., Odermatt, P., Slesak, G. and Barennes, H. (2009) Risk of Latent Tuberculosis Infection in Children Living in Households with Tuberculosis Patients: A Cross Sectional Survey in Remote Northern Lao People's Democratic Republic. *BMC Infectious Diseases*, **9**, 96. <https://doi.org/10.1186/1471-2334-9-96>
- [18] National Institute for Health (NIH) (2017) DAR-901 TB Booster Vaccine to Prevent TB in Adolescents (DAR-PIA) Dartmouth-Hitchcock Medical Center. <https://clinicaltrials.gov/ct2/show/record/NCT02712424>
- [19] Von Reyn, C.F., Lahey, T., Arbeit, R.D., Landry, B., Kailani, L., Adams, L.V., *et al.* (2017) Safety and Immunogenicity of an Inactivated Whole Cell Tuberculosis Vaccine Booster in Adults Primed with BCG: A Randomized, Controlled Trial of DAR-901. *PLoS ONE*, **12**, e0175215. <https://doi.org/10.1371/journal.pone.0175215>
- [20] President's Office Regional Administration and Local Government (PO-RALG) (2016) List of Registered Secondary Schools Datasets 2016 of the United Republic of Tanzania Government Open Data Portal 2016. The United Republic of Tanzania, Dar es Salaam. <http://opendata.go.tz/dataset/orodha-ya-shule-za-sekondari-2016>
- [21] Wood, R., Liang, H., Wu, H., Middelkoop, K., Oni, T., Rangaka, M.X., *et al.* (2010) Changing Prevalence of Tuberculosis Infection with Increasing Age in High-Burden Townships in South Africa. *International Journal of Tuberculosis and Lung Disease*, **14**, 406-412.
- [22] National AIDS Control Program (NACP) (2012) TB Screening Questionnaire for Children above Age 6 and Adult HIV/AIDS Patients. In: *National Guidelines for Management of HIV and AIDS*, 4th Edition, The United Republic of Tanzania, Dar Es Salaam, 302-304. https://aidsfree.usaid.gov/sites/default/files/hts_policy_tanzania.pdf
- [23] Centers for Disease Control and Prevention (CDC) (2017) National Center for Health Statistics: CDC Growth Charts. https://www.cdc.gov/growthcharts/clinical_charts.htm
- [24] Rutstein, S.O. (2015) Steps to Construct New DHS Wealth Index. https://www.dhsprogram.com/programming/wealth%20index/Steps_to_constructin_g_the_new_DHS_Wealth_Index.pdf
- [25] Vyas, S. and Kumaranayake, L. (2006) Constructing Socio-Economic Status Indices: How to Use Principal Components Analysis. *Health Policy and Planning*, **21**, 459-468. <https://doi.org/10.1093/heapol/czl029>
- [26] Trajman, A., Steffen, R.E., Menzies, D., Trajman, A., Steffen, R.E. and Menzies, D. (2013) Interferon-Gamma Release Assays versus Tuberculin Skin Testing for the

Diagnosis of Latent Tuberculosis Infection: An Overview of the Evidence. *Pulmonary Medicine*, **2013**, Article ID: 601737.

- [27] Kleinert, S., Tony, H.P., Krueger, K., Detert, J., Mielke, F., Rockwitz, K., *et al.* (2012) Screening for Latent Tuberculosis Infection: Performance of Tuberculin Skin Test and Interferon-Gamma Release Assays under Real-Life Conditions. *Annals of the Rheumatic Diseases*, **71**, 1791-1795.
<https://doi.org/10.1136/annrheumdis-2011-200941>
- [28] Schmidt, C.W. (2008) Linking TB and the Environment: An Overlooked Mitigation Strategy. *Environmental Health Perspectives*, **116**, A478-A485.
<https://doi.org/10.1289/ehp.116-a478>
- [29] Glynn, J.R., Guerra-Assunção, J.A., Houben, R.M.G.J., Sichali, L., Mzembe, T., Mwaungulu, L.K., *et al.* (2015) Whole Genome Sequencing Shows a Low Proportion of Tuberculosis Disease Is Attributable to Known Close Contacts in Rural Malawi. *PLoS ONE*, **10**, e0132840. <https://doi.org/10.1371/journal.pone.0132840>
- [30] Wilson, M.E. (1995) Travel and the Emergence of Infectious Diseases. *Emerging Infectious Diseases*, **1**, 39-46. <https://doi.org/10.3201/eid0102.950201>
- [31] Peer, N. (2015) The Converging Burdens of Infectious and Non-Communicable Diseases in Rural-to-Urban Migrant Sub-Saharan African Populations: A Focus on HIV/AIDS, Tuberculosis and Cardio-Metabolic Diseases. *Tropical Diseases, Travel Medicine and Vaccines*, **1**, 6. <https://doi.org/10.1186/s40794-015-0007-4>
- [32] Tanzania Commission for AIDS (TACAIDS), Zanzibar AIDS Commission (ZAC), National Bureau of Statistics (NBS), Office of Chief Government Statistician (OCGS) and ICF International (2013) Tanzania HIV/AIDS and Malaria Indicator Survey 2011-12. Dar es Salaam.
<https://dhsprogram.com/pubs/pdf/AIS11/AIS11.pdf>
- [33] Lahey, T., Mackenzie, T., Arbeit, R.D., Bakari, M., Mtei, L., Matee, M., *et al.* (2013) Recurrent Tuberculosis Risk among HIV-Infected Adults in Tanzania with Prior Active Tuberculosis. *Clinical Infectious Diseases*, **56**, 151-158.
<https://doi.org/10.1093/cid/cis798>
- [34] Avert (2016) HIV and AIDS in Tanzania.
<https://www.avert.org/professionals/hiv-around-world/sub-saharan-africa/tanzania>
- [35] Bratholm, C., Johannessen, A., Naman, E., *et al.* (2010) Drug Resistance Is Widespread among Children Who Receive Long-Term Antiretroviral Treatment at a Rural Tanzanian Hospital. *Journal of Antimicrobial Chemotherapy*, **65**, 1996-2000.
<https://doi.org/10.1093/jac/dkq234>