International Journal of Infectious Diseases 35 (2015) 11–17

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Prevalence of tuberculosis in adolescents, western Kenya: implications for control programs☆

Videlis Nduba [a,b,c,*], Anna H. Van't Hoog [a,b,d], Ellen Mitchell [b,e], Peter Onyango [a], Kayla Laserson [a,f], Martien Borgdorff [a,b,f]

[a] Kenya Medical Research Institute (KEMRI)/CGHR Research and Public Health Collaboration, TB Research Branch, PO Box 1578, Kisumu, Kenya
[b] Academic Medical Centre of the University of Amsterdam, Netherlands
[c] Kenya Medical Research Institute, Centre for Respiratory Diseases Research (CRDR), Nairobi, Kenya
[d] Amsterdam Institute for Global Health and Development, University of Amsterdam, Netherlands
[e] KNCV Tuberculosis Foundation, Netherlands
[f] Center for Global Health, CDC Atlanta, Atlanta, Georgia, USA

ARTICLE INFO

Article history:
Received 1 January 2015
Received in revised form 3 March 2015
Accepted 5 March 2015

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Tuberculosis
Pulmonary
Diagnosis
Epidemiology
Mantoux

SUMMARY

Objective: The aim of this study was to determine the prevalence of tuberculosis (TB) in adolescents in western Kenya.
Methods: A cohort study of 5004 adolescents aged 12–18 years was conducted. Adolescents were screened for prevalent TB using clinical criteria, history of TB contact, and a Mantoux test. Cases of suspected TB were investigated through two sputum examinations (microscopy and liquid culture) and chest radiography.
Results: Out of 5004 adolescents enrolled, 1960 (39.2%) were identified with suspected TB, including 1544 with a positive Mantoux (prevalence 1544/4808, 32.1%), 515 with symptoms suggestive of TB (10.3%), and 144 (2.9%) with household TB contact. Sixteen culture-confirmed (definite) and 18 probable pulmonary TB (PTB) cases were identified, reflecting a prevalence estimate of 3.2/1000 (definite) and 6.8/1000 all PTB, respectively. Only one smear-positive case was detected. The case notification rate among 12–18-year-old adolescents for all TB was 101/100 000, yielding a patient diagnostic rate of 0.13 (95% confidence interval 0.03–3.7) cases detected per person-year for all TB.
Conclusion: The prevalence of PTB among adolescents is high, with the majority of cases not detected routinely. Innovative active case finding including the wider use of Xpert MTB/RIF is needed to detect smear-negative TB among adolescents.

1. Introduction

Tuberculosis (TB) has been declared a global health emergency by the World Health Organization (WHO).[1] No current vaccine has been shown to reliably prevent pulmonary TB in adolescents.[2] The risk of TB disease increases steeply in adolescence, suggesting adolescents may be a suitable target group for vaccination.[3,4] New vaccines are currently being developed,[5–7] and adolescents are considered a convenient target for novel TB vaccine trials because they are easy to reach in schools, are not highly mobile, and do not have many of the comorbidities that exclude adults from trial participation. These trials will be conducted in areas with a high burden of TB disease.

In order to assess the potential for TB vaccine trials among adolescents and build staff capacity, an incidence cohort study was conducted in western Kenya. In this paper, we report TB prevalence at intake of the study cohort.

The WHO reported 8.7 million new cases of TB globally in 2012, of which 0.5 million were in children aged less than 15 years, and 26% of those cases occurred in the Africa region.[8] Kenya reported 103 981 new cases in 2011, with only 6% of those occurring in children under 15 years of age. In the lesser Siaya District, where the study took place, 795 TB cases were registered in 2011, of which 43 (5.4%) were in adolescents aged 12–18 years, equivalent

☆ The work presented in this paper was performed under the KEMRI and CDC Collaboration in western Kenya.

* Corresponding author. Tel.: +254 57 202 2959; fax: +254 57 202 2981.
E-mail addresses: vnduba@kemricdc.org, vnduba@gmail.com (V. Nduba).

http://dx.doi.org/10.1016/j.ijid.2015.03.008

to 101 per 100 000 population; 215 (27%) of these TB cases were smear-positive. Overall reported rates of TB in the study area were approximately 521 per 100 000 population, similar to overall notification rates in Nyanza Province in 2010.[9] HIV prevalence in 15–19-year-olds in Kenya is estimated to be 1.7% according to the Kenya Demographic and Health Survey 2009.[10]

A recent prevalence survey among adults conducted in the same study area reported a TB prevalence among 15–24-year-olds of 3.7 per 1000 (95% confidence interval (CI) 2.2–6.2) among females and 1.8 per 1000 (95% CI 0.8–4.2) among males.[11,12] This prevalence survey used a screening algorithm for adults using symptoms and chest X-rays as primary screening tools.[12] The present study enrolled a younger cohort (aged 12–18 years), primarily composed of youth enrolled in school. Moreover, in order to limit the use of chest radiography, testing for latent TB infection was added as a screening tool to identify those with suspected TB.

The aim of this analysis was to determine the burden of TB among adolescents. Some of the interim results of this study have been reported previously in an abstract.[13]

2. Methods

2.1. Study setting

The Kenya Medical Research Institute (KEMRI)/Centers for Disease Control and Prevention (CDC) Research and Public Health Collaboration, operates a health and demographic surveillance system (HDSS) in the study area. The HDSS provides general demographic and health information (such as population age, structure, density, fertility rates, birth rates, in- and out-migrations, geographic information system (GIS) coordinates, patterns of health care access and utilization, and the local economics of health care), as well as disease- and intervention-specific information.[14]

2.2. Study design and population

A cross-sectional survey was conducted at enrolment into an observational cohort study of adolescents aged 12–18 years living in Karemo Division, Siaya District, Nyanza Province, in western Kenya. Karemo is predominantly rural, and the majority of residents are small-scale farmers and of Luo ethnicity. The study area covered approximately 11 000 adolescents aged 12–18 years and was divided into 17 clusters of approximately equal population size, each containing a school. Nine of these clusters were selected randomly.

Before enrolment commenced in any cluster, personal digital assistants (PDAs) were preloaded with a cluster-specific HDSS database containing information on villages, compounds, and households in which eligible adolescents resided. All adolescents residing in a cluster were approached to participate in the study if they met the study's residency definition. Trained field workers identified households with adolescents with the help of community volunteers called village reporters. While the HDSS defines residents as persons who have lived in the HDSS area for at least 4 months, in this study, we included adolescents who had lived in the area for at least 1 month. All enrolled adolescents who did not meet the HDSS resident criteria were categorized as new residents.

2.3. Consenting

Parents of eligible adolescents were informed and invited to consent; minor assent was also sought from adolescents aged 12–17 years. Mature minors (married, pregnant, or having delivered a baby, or the head of a household)[15,16] and adolescents aged 18 years were requested to give their own independent consent. Thereafter, the parents/guardians and the eligible adolescents were invited to a mobile field site (MFS) consisting of several tents, a field-based computer server, laptops for data entry, a generator, and a mobile chest X-ray truck located in a nearby school, for enrolment into the study.

2.4. TB screening

Adolescents were evaluated at enrolment for symptoms of possible TB, defined as one or more of the following: cough for $\geq$2 weeks, weight loss for $\geq$2 weeks, fever for $\geq$2 weeks, night sweats for $\geq$2 weeks, or hemoptysis and exposure to TB, defined as living in a household where a person had been diagnosed with TB. Participants were queried about clinical and TB treatment history within the last 6 months and/or diagnosis of acute or chronic diseases. Demographic characteristics (e.g., parent/guardian occupations, education, and income, and participant's gender and date of birth (DOB)) were also collected during the interview and reviewed with the study participant.

All participants (except those currently on TB treatment) had a tuberculin skin test (TST) administered by the Mantoux technique using PPD RT23 (Statens Serum Institut, Denmark). The test was read 48–72 h after administration (92%), but late readings were included up to a maximum of 7 days. A Mantoux test result of $\geq$10 mm in HIV-negatives/those with unknown HIV status, or $\geq$5 mm in HIV-positives, was considered positive. Participants with a positive TST, household contact with a TB case in the previous 2 years, or the presence of at least one TB symptom, were asked to provide a spot and early morning sputum and to undergo chest X-ray examination. They were also offered HIV testing.

2.5. Chest X-ray interpretation

Chest X-rays were read by clinical officers trained in using the chest radiograph reading and recording system (CRRS) method, immediately after the radiograph was obtained.[17] Subsequently a CRRS certified medical officer reviewed the chest X-rays before a final decision on subject management was made. All chest X-rays classified as abnormal and a subset of 10% of those read as normal were reviewed by a CRRS certified expert and their opinion was taken to be final in regard to the final interpretation of the chest X-ray.

2.6. Laboratory analyses

Expectorated sputa were digested using Nalc NaOH and concentrated by centrifugation. Digested sputa were inoculated into solid (Lowenstein–Jensen) and liquid (MGIT 960) culture media and examined for acid-fast bacilli (AFB) by fluorescence microscopy (FM). Positive cultures were confirmed as AFB by Ziehl–Neelsen (ZN) staining and speciated with either the Capilia (FIND and Tauns Co. Ltd) or GenoType assay (Hain Diagnostika, Nehren, Germany). Laboratory cross-contamination rates were monitored through processing anonymized artificial sputum as part of study specimens and analyzing the growth of *Mycobacterium tuberculosis* in the TB culture laboratory. At the beginning of the project, sputum samples were stained for FM in a distant laboratory. Due to delays in reading a portion of the FM slides, the florescence was lost and the slides were re-stained with ZN stain to reconfirm smear negativity.

2.7. TB treatment

Adolescents identified with active TB were referred to a Ministry of Health TB clinic for TB treatment. Adolescents with HIV were referred for evaluation for HIV care and treatment services at the Patient Support Centre (PSC) nearest to their homes.

2.8. Sample size

The sample size was determined on the basis of an estimate of active TB incidence, which was estimated at 4 per 1000. Thus, a sample of 5000 adolescents would yield a 95% CI on this estimate of 2.4–6.2 per 1000, based on a Poisson distribution.

2.9. Case definition

A definite case of TB disease was defined as two or more smears positive for AFB or one positive culture confirmed by speciation. A probable case was defined as any pulmonary case diagnosed by a clinician through clinical symptoms and radiographic abnormalities to be consistent with active TB, who did not meet the criteria for a definite case. Participants with only one positive smear were classified as probable TB cases only if they met the clinical definition of TB. Participants with previous TB were only classified as a TB case if they had definite TB, since their symptoms, positive TST, and chest X-ray abnormalities might be attributable to their previous TB episode.

2.10. Data analysis

The prevalence of TB was calculated and adjusted for clustering using survey procedures for SAS version 9.1 (SAS Institute Inc., Cary, NC, USA). Risk factors for prevalent TB were explored with bivariate analysis. The case detection rate is the number of reported cases per 100 000 persons per year divided by the estimated incidence rate per 100 000 per year. TB incidence is uncertain and not measured but estimated; therefore, the case detection rate is uncertain. The patient diagnostic rate (PDR), which is the rate at which prevalent cases are detected by TB control programs, was calculated by dividing the number of all new TB cases per 100 000 among those aged 12–18 years notified by the TB program, by the prevalence of TB per 100 000 in the same age group.[18]

The protocol and informed consent forms were reviewed and approved by the KEMRI local and national scientific steering committees and the KEMRI National Ethical Review Committee and the institutional review boards (IRBs) of the CDC and the AERAS Global TB Vaccine Foundation.

3. Results

Through the HDSS database, 5541 adolescents were identified for screening; parental consent and minor assent was given for 5241 (94.6%). Of the 300 individuals not giving consent, 222 (74%) had not been found at home during home visits by trained field workers. Of the participants consenting to participate in the study, 236 (4.5%) did not turn up for study procedures. Thus, 5004 (90.3%)

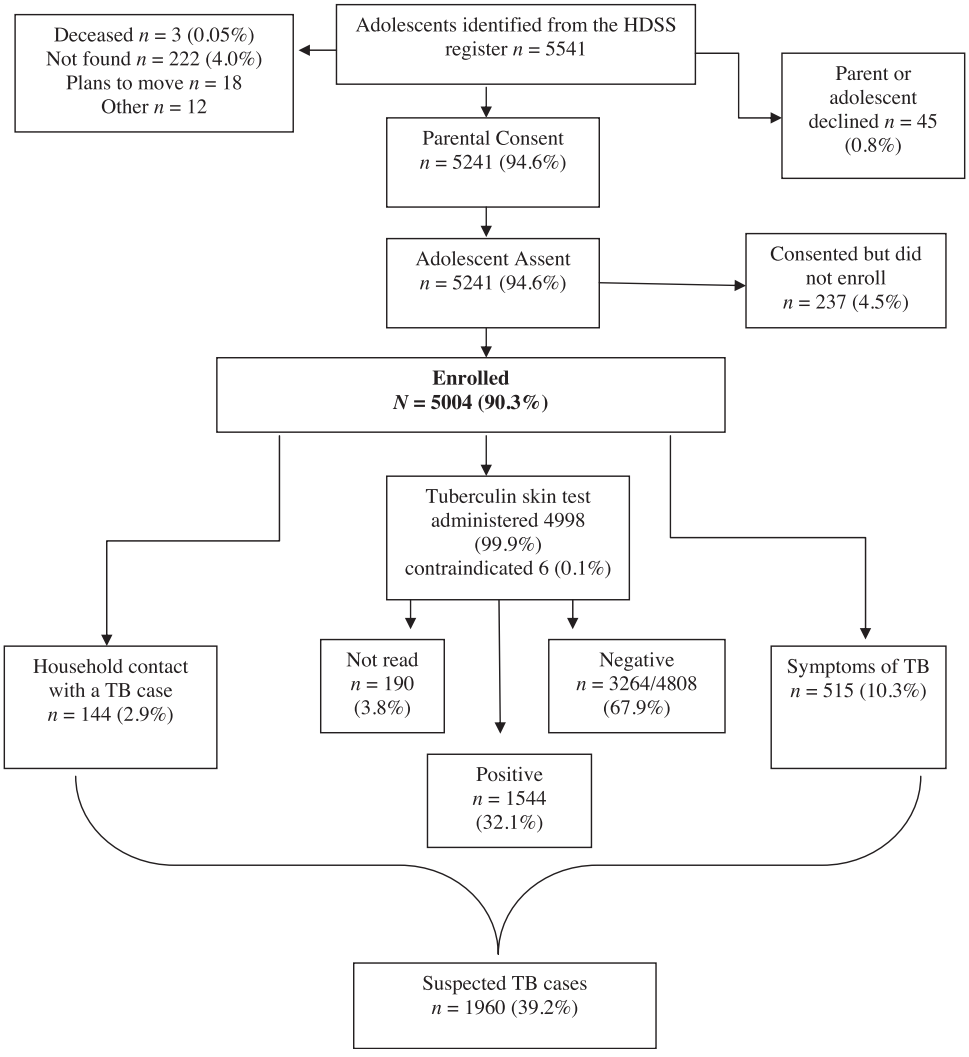

Figure 1. Participant enrolment and TB screening.

Table 1
A comparison of the demographic characteristics of adolescents enrolled into the study with those of the general population of adolescents in the study area

		Study participants	Non-study participants from all clusters	OR	CI
Age, years	Mean	14.4 (SD 1.9)	15.2 (SD 2.0)	$p < 0.01$	
Sex	Female	2425 (48.5%)	2886 (51.9%)	0.87	0.81–0.94
	Male	2579 (51.5%)	2678 (48.1%)		
Residence	Rural	4729 (94.5%)	4671 (87.0%)	0.30	0.26–0.35
	Urban	275 (5.5%)	893 (16.0%)		

OR, odds ratio; CI, confidence interval; SD, standard deviation.

were enrolled into the study and underwent TB screening (Figure 1).

Among the enrolled adolescents, 2579 (52%) were male; the mean age was 14.0 years (standard deviation 1.9 years), and most (4692, 93.8%) were enrolled in school and lived in the rural areas (4729, 94.5%). Compared with the general population of adolescents in the HDSS area, study participants were more likely to be male and live in a rural area (Table 1). At enrolment, 1960 (39.2%) adolescents were found to have suspected TB based on a history of symptoms (515, 10.3%), contact with a TB case (144, 7.4%), and/or a positive TST (1544/4808 read, 32.1% positive) (Figure 2). There was a trend towards increasing Mantoux positivity by age. Comparing adolescents aged 12 years to those aged 18 years, 26.2% and 39.7% were Mantoux-positive, respectively (Table 2).

A minority of participants (12.7%) had more than one criterion for TB investigation. All suspected TB cases underwent a chest X-ray examination and 93 (4.7%) had an abnormal chest X-ray, of which 20 (1.0%) were classified as consistent with TB. Of suspected TB cases, 1862 (95.0%) and 1686 (86.0%) provided a spot and an early morning sputum, respectively. The majority of suspected TB cases agreed to HIV testing and 23 were HIV-infected (1.2%).

A total of 16 definite and 18 probable cases were identified, yielding a cluster-adjusted TB prevalence estimate of 6.8/1000 (95% CI 4.1–9.5) for definite and probable TB combined (design effect 1.04) and 3.2/1000 (95% CI 1.9–4.5) for definite TB. Of the 16 definite TB cases, 15 (93.8%) were smear-negative. Most TB cases were TST-positive (30/34, 88.2%). Very few of the TB cases identified gave a history of symptoms suggestive of TB 6/34 (17.7%) and none reported a history of a household contact with TB. There was no trend of an increasing prevalence of TB with age, neither for definite nor for all types of TB (Table 3).

In the laboratory at that time, there was a TB laboratory cross-contamination rate of 0.03% as measured by artificial sputum cultures, well within the 1.1% standard.[19] Four participants had a positive smear; two were culture-negative, one grew non-tuberculous mycobacteria (NTM), and one was both smear- and culture-positive. A total of 242/5004 (4.8%) adolescents had positive cultures identified as NTMs and were sputum smear-negative. Twenty-five new TB cases were notified in adolescents aged 12–18 years by the TB control program in the study area during 2010. The population of adolescents aged 12–18 years was 24 840, giving a case notification rate of 101/100 000. The rate at which new TB cases were detected as expressed by the PDR was 0.13 (95% CI 0.03–3.7) cases detected per person-year for all types of TB. No risk factors for prevalent TB were identified (Table 4). All definite TB cases were TST-positive and the majority had no chest X-ray abnormalities (Table 5). All of the 18 probable TB cases had chest X-ray abnormalities consistent with TB, 14 were TST-positive, and four had symptoms of TB (Table 5).

4. Discussion

We found a high prevalence of TB among adolescents, with a definite TB prevalence rate of 3.2/1000 and a total prevalence of 6.8/1000 population. Similar studies conducted in South Africa[20] and Uganda[21] to estimate the prevalence of TB among 12–18-year-old adolescents in preparation for future TB vaccine trials, found a prevalence of 3/1000 in South Africa for smear/culture-positive TB and 1.6/1000 for all TB in Uganda. Our prevalence is comparable to that found in the Western Cape, South African study, but more than double that found in rural Uganda, which neighbors Kenya. This high prevalence far exceeds that of the case notification rate in the region and suggests that efforts are needed to improve TB case detection in the population. Future studies should consider the inclusion of even younger children to better characterize the burden of TB disease among adolescents. These findings suggest

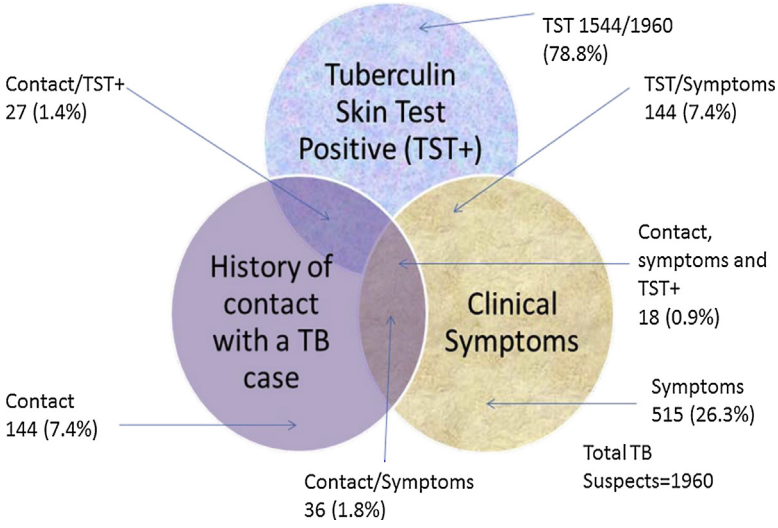

Figure 2. Distribution of suspected TB cases identified at enrolment (N = 1960).

Table 2
Comparing tuberculin skin test positivity by age

Age, years	Number TST-positive (≥10 mm)	Total	% TST-positive
12	265	1012	26.2%
13	256	874	29.3%
14	244	824	29.6%
15	221	689	32.1%
16	260	658	39.5%
17	178	449	39.6%
18	120	302	39.7%

TST, tuberculin skin test.

Table 3
Prevalence rates of all and definite TB cases by age

Age	All TB cases			TB prevalence, per 1000	Culture-confirmed TB cases			TB prevalence, per 1000
	Yes	No	Total		Yes	No	Total	
12	6	1042	1050	5.7	2	1048	1050	1.9
13	7	884	892	7.8	3	889	892	3.4
14	5	842	847	5.9	3	844	847	3.5
15	6	709	715	8.4	4	711	715	5.6
16	5	688	694	7.2	2	692	694	2.9
17	4	478	482	8.3	2	480	482	4.1
18	1	323	324	3.1	0	324	324	0
Total	34	4966	5004	6.8	16	4988	5004	3.2

TB, tuberculosis.

that the pre-adolescent 'golden age' may stop well before the age of 12 years.[22–24] The high PTB prevalence was not explained by HIV, the prevalence of which was quite low among these young adolescents. The high HIV prevalence in the study area, coupled with a high burden of TB disease among HIV-infected individuals, might still be a major driver of TB transmission to adolescents through adult community contacts.

The very low patient diagnostic rate of 0.13 cases detected per person-year for all types of TB indicates that the TB control program is performing suboptimally, presumably because prevalent cases are not always symptomatic or smear-positive, and detecting smear-negative TB is a major challenge for the program with currently used tools. With the prevalence of TB this high, the incidence may be high as well. Obtaining direct incidence estimates through a cohort of adolescents followed up for at least a year, as we are currently performing, would provide incidence estimates useful for the sample size calculations required for adolescent TB vaccine trials.

Table 5
Clinical characteristics of prevalent tuberculosis cases, Siaya District, western Kenya[a]

TB case	Symptoms (*n* = 6)	TST (*n* = 30)	CXR (*n* = 20)	Smear (*n* = 1)	Culture (*n* = 16)
1	–	+	+	–	+
2	–	+	–	–	+
3	+	+	–	–	+
4	–	+	–	–	+
5	–	+	–	–	+
6	–	+	–	–	+
7	–	+	–	–	+
8	–	+	–	+	+
9	–	+	–	–	+
10	–	+	–	–	+
11	+	+	–	–	+
12	–	+	–	–	+
13	–	+	–	–	+
14	–	+	+	–	+
15	–	+	+	–	+
16	–	+	–	–	+
17	–	+	+	–	–
18	+	–	+	–	–
19	–	+	+	–	–
20	–	+	+	–	–
21	–	+	+	–	–
22	–	+	+	–	–
23	–	+	+	–	–
24	–	+	+	–	–
25	–	–	+	–	–
26	–	+	+	–	–
27	–	+	+	–	–
28	+	+	+	–	–
29	+	–	+	–	–
30	–	+	+	–	–
31	–	+	+	–	–
32	–	+	+	–	–
33	–	+	+	–	–
34	+	–	+	–	–

TB, tuberculosis; TST, tuberculin skin test; CXR, chest X-ray.
[a] All cases were HIV-negative and gave no history of household contact with a TB case; +, characteristic present; –, characteristic absent. All the culture-positive cases were defined as definite cases, and all the culture-negative cases were defined as probable cases.

The younger age group enrolled in this study (12–18 years) had comparable TB rates to those from the partly overlapping, but older age group of 15–24 years in the previously reported prevalence survey in this area.[12] That survey found a prevalence rate of 3.7/1000 among females and 1.8/1000 among males. Within the current study, there was no association between age or gender and prevalence. This lack of association could be due to a small sample

Table 4
Characteristics of prevalent tuberculosis cases, Siaya District, western Kenya

		TB cases (cases per 1000)		
		Definite TB cases (*n* = 16)	Probable TB cases (*n* = 18)	Total (*n* = 5004)
Male	Yes	8 (3.1)	13 (5.0)	2576
	No	8 (3.3)	5 (2.1)	2424
Urban residence	Yes	1 (3.7)	1 (3.7)	273
	No	15 (3.2)	17 (3.6)	4727
Enrolled in school	Yes	15 (3.2)	17 (3.6)	4678
	No	1 (3.2)	1 (3.2)	317
Orphaned	Yes	5 (6.6)	0 (0)	760
	No	11 (2.6)	18 (4.3)	4235
New resident	Yes	5 (4.2)	7 (5.8)	1204
	No	11 (2.9)	11 (2.9)	3796
BCG scar present	Yes	12 (2.9)	13 (3.2)	4096
	No	4 (4.5)	5 (5.7)	885
Socio economic status (SES) score		7.2 (3.2)	6 (2.8)	7 (2.7)

TB, tuberculosis; BCG, bacille Calmette–Guérin.

size, which was calculated for estimating incidence and not the prevalence of TB.

The majority of the TB cases found were smear-negative, including most of the culture-confirmed cases. The results of TB culture can be trusted, as indicated by the very low cross-contamination rate of 0.03%. The majority of the definite and probable TB cases had a positive TST, confirming the utility of this test for screening and active case finding. All of the probable cases had a chest X-ray consistent with TB, but were likely found quite early in the disease progression as evidenced by the low number of cases with symptoms. A large number of cultures grew NTM. This indicates the value of culture confirmation and speciation in a community with a very high burden of NTM to ensure proper diagnosis and appropriate treatment for TB. The clinical significance of this high NTM burden and their implications for immune responses to new TB vaccines need to be explored further.[25,26]

The study had some limitations, in particular with respect to the enrolment of out-of-school youth. At the time of conducting the study, data from the Siaya District Education Office indicated that only approximately 40% of adolescents aged 12–18 years in the target area of Siaya District were enrolled in schools. If TB rates were higher in out-of-school youth, TB prevalence may have been underestimated among adolescents. This is similar to the Western Cape, South African study, which enrolled mainly in-school youth and might also have underestimated the prevalence of TB among adolescents in that population.[20] Moreover, since school enrolment was found to decrease with age, we may have obscured an increasing prevalence with age. The decrease in older age groups is ascribed to outmigration by older adolescents completing school and leaving the study area and post-primary adolescents going to secondary schools outside the study area.

In conclusion, our study suggests that adolescents should be treated as a priority for TB control efforts. The national TB program should develop strategies to improve case detection among adolescents, in particular those with smear-negative TB, for instance through wider use of Xpert MTB/RIF. Xpert MTB/RIF is an automated PCR-based assay, with high sensitivity and a turn-around time of under 2 h.[27] Future studies should explore the utility of adding Xpert MTB/RIF as an additional tool for the identification of cases.

Acknowledgements

We would like to acknowledge the Director KEMRI for approval of this manuscript and KEMRI/CDC. KEMRI/CDC is a member of the INDEPTH Network. We also acknowledge the dedicated staff, especially recruitment staff and village reporters who made it possible to contact all potential study participants.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Ethical approval: The protocol and informed consent forms were reviewed and approved by the KEMRI local and national scientific steering committees and the KEMRI National Ethical Review Committee and the institutional review boards of CDC and the AERAS Global TB Vaccine Foundation.

Funding source: This study was supported by grants from The European and Developing Countries Clinical Trials Partnership (grant number: IP_07_32080_003), Aeras Global TB Vaccine Foundation, KNCV TB Foundation, NACCAP, Vienna School of Clinical Research, and San Rafaele Laboratory, Milan, Italy.

Financial disclosure: The authors have no financial relationships relevant to this article to disclose.

Conflict of interest: The KNCV TB foundation provided some funding for the project and participated in manuscript preparation. The other funding agencies did not participate in data analysis or the preparation of this manuscript, or in the decision to submit the manuscript for publication. The authors have no conflicts of interest relevant to this article to disclose.

Contributor statements: Videlis Nduba: Dr Nduba conceptualized and designed the study, oversaw study implementation and data collection, drafted the initial manuscript, carried out the initial and subsequent analyses, and approved the final manuscript as submitted.

Anna H. Van't Hoog and Kayla Laserson: Drs Van't Hoog and Laserson conceptualized and designed the study, provided oversight on study implementation, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Ellen Mitchell: Dr Mitchell provided oversight on study implementation, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Peter Onyango: Mr Onyango supervised data collection and study implementation, and reviewed and approved the final manuscript as submitted.

Martien Borgdorff: Prof. Borgdorff reviewed and revised the manuscript, and approved the final manuscript as submitted.

References

1. World Health Organization. A global emergency report on the TB epidemic. WHO/TB/94.177. WHO; 1994. Available at: http://www.who.int/tb/publications/1994/en/index.html (accessed 15th of June 2014).
2. Colditz GA, Brewer TF, Berkey CS, Wilson ME, Burdick E, Fineberg HV, et al. Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature. *JAMA* 1994;**271**:698–702.
3. Geldenhuys H, Sorsdahl K, Kafaar F, Hatherill M, Hanekom WA, Stein DJ, et al. Risky behaviour and psychosocial correlates in adolescents—is there a link with tuberculosis? *Afr J Psychiatry (Johannesbg)* 2011;**14**:383–7.
4. Marais BJ, Gie RP, Schaaf HS, Hesseling AC, Obihara CC, Nelson LJ, et al. The clinical epidemiology of childhood pulmonary tuberculosis: a critical review of literature from the pre-chemotherapy era. *Int J Tuberc Lung Dis* 2004;**8**:278–85.
5. Hanekom WA, Hawkridge A, Mahomed H, Scriba TJ, Tameris M, Hughes J, et al. SATVI—after 10 years closing in on a new and better vaccine to prevent tuberculosis. *S Afr Med J* 2012;**102**:438–41.
6. Lienhardt C, Fruth U, Greco M. The blueprint for vaccine research and development: walking the path for better TB vaccines. *Tuberculosis (Edinb)* 2012;**92**(Suppl 1):S33–5.
7. Ottenhoff TH, Kaufmann SH. Vaccines against tuberculosis: where are we and where do we need to go? *PLoS Pathog* 2012;**8**:e1002607.
8. World Health Organization. WHO Report 2012: global tuberculosis control. WHO; 2012. Available at: http://www.who.int/tb/publications/global_report/gtbr12_main.pdf (accessed 20th of June 2014).
9. Kenya National Leprosy and Tuberculosis Program report. Kenya: NTP; 2011.
10. Central Bureau of Statistics, Ministry of Health of Kenya and ORC Macro. Kenya demographic health survey 2009. Calverton, MD: CBS, MOH and ORC Macro; 2009.
11. Julious SA. Two-sided confidence intervals for the single proportion: comparison of seven methods by Robert G. Newcombe. *Statistics in Medicine* 1998;**17**:857–72. Stat Med 2005;**24**:3383–4.
12. van't Hoog AH, Laserson KF, Githui WA, Meme HK, Agaya JA, Odeny LO, et al. High prevalence of pulmonary tuberculosis and inadequate case finding in rural western Kenya. *Am J Respir Crit Care Med* 2011;**183**:1245–53.
13. Nduba V, Van't Hoog A, Verver S, Mitchell E, Onyango P, Laserson KF, et al. Is the prevalence of tuberculosis in adolescents in western Kenya high enough for tuberculosis vaccine trials? 42nd World Conference on Lung Health, Lille, France, 2011.
14. Odhiambo FO, Laserson KF, Sewe M, Hamel MJ, Feikin DR, Adazu K, et al. Profile: The KEMRI/CDC Health and Demographic Surveillance System—western Kenya. *Int J Epidemiol* 2012;**41**:977–87. http://dx.doi.org/10.1093/ije/dys108.
15. Amornkul PN, Vandenhoudt H, Nasokho P, Odhiambo F, Mwaengo D, Hightower A, et al. HIV prevalence and associated risk factors among individuals aged 13-34 years in rural western Kenya. *PLoS One* 2009;**4**:e6470.
16. Ministry of Health of Kenya. National guidelines for voluntary counseling and testing. Kenya: National AIDS and STD Control Programme (NASCOP); 2001.
17. Den Boon S, Bateman ED, Enarson DA, Borgdorff MW, Verver S, Lombard CJ, et al. Development and evaluation of a new chest radiograph reading and recording system for epidemiological surveys of tuberculosis and lung disease. *Int J Tuberc Lung Dis* 2005;**9**:1088–96.
18. Borgdorff MW. New measurable indicator for tuberculosis case detection. *Emerg Infect Dis* 2004;**10**:1523–8.
19. van Kampen SC, Anthony RM, Klatser PR. The realistic performance achievable with mycobacterial automated culture systems in high and low prevalence settings. *BMC Infect Dis* 2010;**10**:93.

20. Mahomed H, Ehrlich R, Hawkridge T, Hatherill M, Geiter L, Kafaar F, et al. Screening for TB in high school adolescents in a high burden setting in South Africa. *Tuberculosis (Edinb)* 2013;**93**:357–62.
21. Waako J, Verver S, Wajja A, Ssengooba W, Joloba ML, Colebunders R, et al. Burden of tuberculosis disease among adolescents in a rural cohort in Eastern Uganda. *BMC Infect Dis* 2013;**13**:349.
22. Loeffler AM. Pediatric tuberculosis. *Semin Respir Infect* 2003;**18**:272–91.
23. Marais BJ, Donald PR, Gie RP, Schaaf HS, Beyers N. Diversity of disease in childhood pulmonary tuberculosis. *Ann Trop Paediatr* 2005;**25**:79–86.
24. Zumla A, Malon P, Henderson J, Grange JM. Impact of HIV infection on tuberculosis. *Postgrad Med J* 2000;**76**:259–68.
25. Corbett EL, Hay M, Churchyard GJ, Herselman P, Clayton T, Williams BG, et al. *Mycobacterium kansasii* and *M. scrofulaceum* isolates from HIV-negative South African gold miners: incidence, clinical significance and radiology. *Int J Tuberc Lung Dis* 1999;**3**:501–7.
26. Setiawati L, Endaryanto A, Kusumadewi A, Lestari P. Effect of BCG vaccination and non-tuberculous Mycobacterium infection on interferon gamma specific assay and a tuberculin skin test among children with a tuberculosis contact in Surabaya, Indonesia. *Southeast Asian J Trop Med Public Health* 2011;**42**:1460–8.
27. Evans CA. GeneXpert—a game-changer for tuberculosis control? *PLoS Med* 2011;**8**:e1001064.