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Smoking and HIV associated with subclinical tuberculosis: analysis of a population-based prevalence survey

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SUMMARY

BACKGROUND: Despite multiple tuberculosis (TB) prevalence surveys reporting a relatively high frequency of bacteriologically confirmed, active TB among individuals reporting no typical symptoms of disease, our understanding of this phenomenon is limited.

OBJECTIVE: To quantify the epidemiological burden and estimate associations between individual-level variables and this "subclinical" presentation.

METHODS: We performed a secondary analysis of TB prevalence survey data from the South African communities of the Zambia, South Africa Tuberculosis and AIDS Reduction trial. Generalized estimating equations were used to estimate the association between individual-level demographic, behavioral, socio-economic, and medical variables and the risk of bacteriologically positive TB among participants not reporting any symptoms consistent with active TB.

RESULTS: The crude prevalence of TB was 2222.1 cases per 100 000 population (95% CI 2053.4–2388.5); 44.7% (295/660) of all documented prevalent cases of TB were subclinical. Current tobacco smoking (OR 2.37, 95% CI 1.41–3.99) and HIV-positive status (OR 3.26, 95% CI 2.31–4.61) were significantly associated with subclinical TB.

CONCLUSION: Individuals who smoke or have HIV may be at increased risk of active TB and not report typical symptoms consistent with disease. This suggests possible shortcomings of symptom-based case finding which may need to be addressed in similar settings.

KEY WORDS: incipient TB; determinants; South Africa

IN 2017, only 6.4 of the estimated 10.0 million individuals with incident tuberculosis (TB) worldwide were reported to the World Health Organization (WHO).[1] Several possible mechanisms may contribute to the gap between true TB incidence and TB notifications: 1) individuals with TB may not self-present to health care providers for diagnosis due to poor self-recognition of symptoms and/or barriers to accessing healthcare; 2) individuals with TB may self-present to health care providers, but fail to be accurately diagnosed due to imperfect diagnostic practices or diagnostic tools; and 3) individuals with TB may be accurately diagnosed, but not recorded by standardized reporting systems due to imperfect administrative systems.[2]

Identifying the specific mechanisms responsible for the overall gap between estimated TB incidence and notifications has been highlighted by the WHO and the Global Fund as a major research priority,[1,3] and efforts to study leaks in the "TB care cascade" have helped to quantify deficiencies in diagnosis (mechanism 2 above)[4] and notification (mechanism 3 above).[5] TB diagnosis in most settings requires individuals to recognize their own symptoms and seek care (i.e., passive case-finding); therefore, the frequency of poor self-awareness of symptoms (mechanism 1) is challenging to quantify. TB prevalence surveys, in which all eligible individuals are screened for TB disease regardless of symptoms, have revealed that in some settings a large fraction of individuals with prevalent, undiagnosed TB may be "subclinical" and fail to report any classical symptom of TB, such as cough, fever, weight loss and night sweats. For example, analysis of national TB prevalence surveys in Asia revealed that between 40% and 79% of all individuals with prevalent TB did not report symptoms that met screening criteria.[6] It is not clear how many of individuals detected with subclinical prevalent TB would have eventually become aware of symptoms and seek care.

Esmail et al. recently suggested that the limited evidence of the benefit of active case-finding interventions using symptom-based screening for reducing TB prevalence might be attributable to individuals

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with subclinical TB in transmission.[7] They hypothesized that individuals with chronic cough (for example, due to pre-existing respiratory conditions, smoking, or unrelated respiratory infections) will be less likely to notice the onset of TB symptoms and more likely to transmit *Mycobacterium tuberculosis* due to persistent coughing behavior. Furthermore, these individuals may maintain normal activities and social behaviors, further increasing the likelihood of transmission. While the presence of chronic cough for reasons other than TB has been associated with delays in presentation and diagnosis of TB,[8–12] the epidemiological importance of subclinical TB has not yet been well-characterized.

Here we present a secondary analysis of data from TB prevalence surveys in South Africa to 1) quantify the burden of subclinical TB, and 2) estimate the association between patient-level variables and subclinical TB.

METHODS

Setting and study population

In 2010, TB prevalence surveys were conducted in eight communities in the Western Cape Province of South Africa that were part of the Zambia, South Africa Tuberculosis and AIDS Reduction (ZAMSTAR) trial. Trial communities were selected based on TB notification rates greater than 400/100 000 per annum, high human immunodeficiency virus (HIV) prevalence, and proximity to a TB diagnostic center. Community-level HIV prevalence rates did not exist at the time of site selection; however, expert opinion and available data defined all communities as having an HIV prevalence higher than provincial estimates. The detailed ZAMSTAR study design has been described previously. Below, we provide brief details relevant for this analysis.[13,14]

Data collection

TB prevalence surveys were conducted over a period of 12 months. The communities were divided into >150 clusters demarcated by census enumeration areas, and trained study personnel visited all households. Informed consent was provided by eligible adults (individuals aged ≥18 years who had stayed in the household the previous night). All participants were asked to produce spot respiratory secretion samples, either spontaneously or with the help of breathing techniques. Research assistants administered a structured questionnaire to elicit demographic, behavioral, clinical, and socio-economic information (Supplementary Data S1; https://doi.org/10.6084/m9.figshare.8255912.v1). Participants were asked whether they had cough, fever, drenching night sweats, or weight loss at the time of survey. HIV status was determined by testing participants who provided a finger-prick sample using Determine™ HIV-1&2 test kits (Alere, Waltham, USA). Self-reported status was documented in case of participants who refused consent for HIV testing.

Case definitions

A case of bacteriologically confirmed TB (confirmed TB) was defined as a participant who produced a respiratory sample resulting in a positive culture for *M. tuberculosis*.[13] A subclinical case of TB (subclinical TB) was defined as a participant with bacteriologically confirmed TB who did not report any of the symptoms specified by the WHO for diagnosis of TB: cough, 1 month of fever, weight loss, and night sweats.[15] A symptomatic case of TB (active TB) was defined as a participant with bacteriologically confirmed TB by culture who reported at least one symptom. No TB was defined as having no microbiologic evidence of *M. tuberculosis* on culture.

Data analysis

Crude prevalence of TB was calculated among the entire study population, the population reporting no symptoms associated with TB, and the population reporting at least one of the symptoms associated with TB.

Multivariate generalized estimating equations (GEE) were used to provide population-average estimates of odds ratios (OR) between individual-level variables and the risk of bacteriologically positive TB among participants who did not report any symptoms consistent with TB at the time of the prevalence survey. We included basic demographic (age, sex, race), socio-economic (education, occupation), behavioral (tobacco smoking, alcohol use), and health (previous TB, HIV infection, diabetes) data that have well-documented associations with risk of TB.[16]

Because data collected by cluster violates the independence assumptions made by regression, we selected GEEs and specified an exchangeable correlation structure. GEEs provide reasonable estimates of the log(OR) and standard errors when the number of clusters is large.[17] Variables with $P < 0.05$ after a Bonferroni Correction for multiple comparisons testing were considered to be significantly associated with culture-positive TB. A complete case analysis was performed in order to fit the model. Analyses were performed using R v3.3.2 programming software (R Computing, Vienna, Austria) using the 'geepack' package geeglm() function for the GEEs.[18]

Ethics

Approval for this analysis was given by Stellenbosch University, Tygerberg, South Africa (N17/09/084). Yale University Institutional Review Board, New Haven, CT, USA, exempted this study from a full board review, as the Yale-based investigators did not have identifying data. Approval for the ZAMSTAR

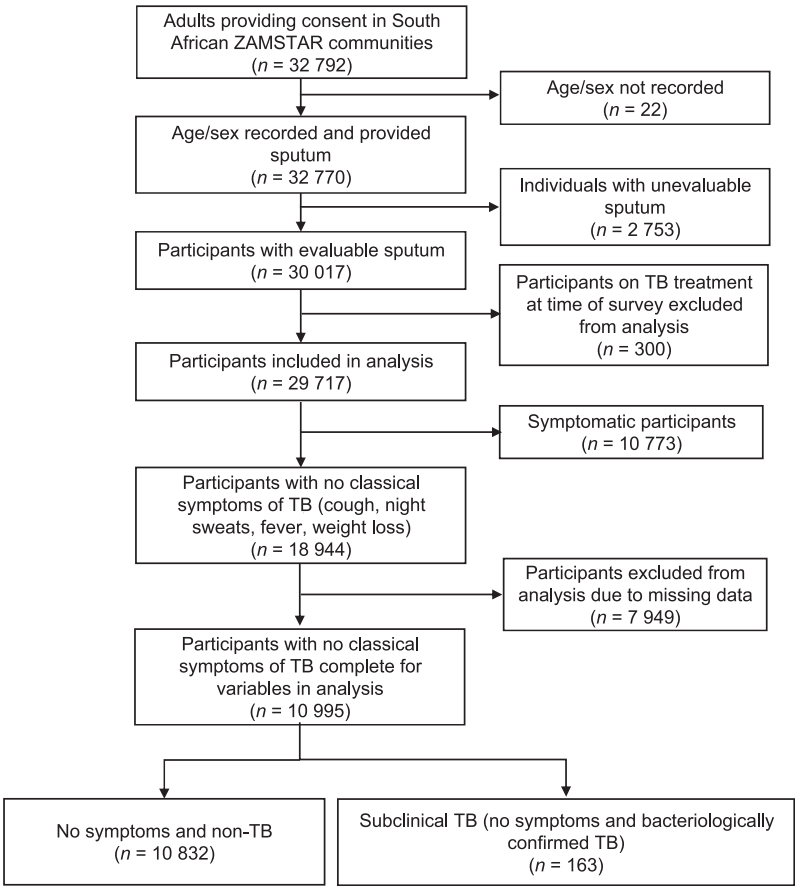

Figure Flow diagram of participants included in this analysis. ZAMSTAR = Zambia, South Africa Tuberculosis and AIDS Reduction; TB = tuberculosis.

trial was given by the Health Research Ethics Committees of Stellenbosch University, the University of Zambia (Lusaka, Zambia), and the London School of Hygiene & Tropical Medicine (London, UK). Written informed consent was provided by participants during the prevalence surveys. Participants did not give consent for data to be shared.

RESULTS

Of the 32 792 eligible adults providing consent to participate in the ZAMSTAR trial prevalence survey in South Africa (78% of those approached), 99.9% (32 770/32 792) had recorded data on age and sex. Evaluable respiratory secretions were obtained from 91.6% (30 017/32 770) of those providing consent. There were 300 participants receiving TB treatment at the time of the survey who were excluded from this analysis.

Of the surveyed participants, 64% (18 944/29 717) reported no symptoms associated with TB (as defined above), and the remaining 36% (10 773/29 717) reported at least one symptom consistent with TB (Figure).

The crude prevalence of TB among those not on treatment within the South African ZAMSTAR trial communities was 2222.1 cases per 100 000 ($n = 660$ cases, 95% CI 2053.4–2388.5 per 100 000). Of the total number of bacteriologically confirmed cases of prevalent TB, 44.7% (295/660) were subclinical. The crude prevalence of TB among participants reporting no symptoms was 1557.2 per 100 000 ($n = 295$, 95% CI 1381.0–1733.5 per 100 000). The crude prevalence of TB among participants reporting symptoms was 3388.1 per 100 000 ($n = 365$, 95% CI 3046.4–3729.8 per 100 000). Demographic breakdown of the data for both the symptomatic and asymptomatic populations and the prevalence of bacteriologically confirmed TB within the levels of each variable are given in Table 1. Among the participants not reporting any symptoms, data on all modeled variables were available for 58% (10 995/18 944). The primary source of missing data was HIV-status—7809 participants did not undergo HIV testing or report HIV status. The proportion of younger males among participants excluded from the analysis was higher than the proportion among participants included in the complete case analysis. Full description of the differences can be found in Supplementary Table S1 (https://doi.org/10.6084/m9.figshare.8255912.v1).

Table 1 Demographic breakdown of all participants in the eight South African ZAMSTAR trial communities (including participants with missing data) grouped by presence of symptoms and showing prevalence of bacteriologically confirmed TB

Variable	No TB with no classical symptoms of TB at time of survey	TB case with no classical symptoms of TB at time of survey	Crude subclinical TB point prevalence (/100 000)	No TB with symptoms at the time of survey	TB case with symptoms at the time of survey	Crude symptomatic TB point prevalence (/100 000)
Total population, *n*	18 649	295	1 557.2	10 408	365	3 388.1
Male sex, *n*	6 923	129	1 829.3	3 949	181	4 382.6
Age group, years						
18–24	2 268	30	1 305.5	1 041	25	2 345.2
25–29	1 250	18	1 419.6	626	20	3 096.0
30–34	944	19	1 973.0	504	25	4 725.9
35–39	729	19	2 540.1	453	23	4 831.9
40–49	907	24	2 577.9	645	48	6 926.4
50–59	470	11	2 286.9	405	23	5 373.8
≥60	351	8	2 228.4	272	17	5 882.4
Missing	4	0	0	3	0	0
Female sex, *n*	11 726	166	1 395.9	6 459	184	2 769.8
Age group, years						
18–24	3 698	55	1 465.5	1 609	45	2 720.7
25–29	2 162	32	1 458.5	1 026	37	3 480.7
30–34	1 567	12	760.0	797	22	2 686.2
35–39	1 211	15	1 223.5	653	14	2 099.0
40–49	1 568	19	1 197.2	1 068	29	2 643.6
50–59	896	16	1 754.4	750	24	3 100.8
≥60	619	17	2 673.0	550	13	2 309.1
Missing	5	0	0	6	0	0
Ethnicity						
Non-Black	1 714	26	1 494.3	854	48	5 321.5
Black	16 935	269	1 563.6	9 554	317	3 211.4
Tobacco smoking						
Never smoker	14 794	204	1 360.2	7 222	212	2 851.8
Ex-smoker	2 330	52	2 183.0	1 965	103	4 980.7
Current smoker	1 525	39	2 493.6	1 221	50	3 933.9
Alcohol use						
Never	10 944	144	1 298.7	4 992	112	2 194.4
Daily	340	11	3 133.9	305	16	4 984.4
Occasional	6 594	121	1 801.9	4 420	197	4 266.8
Ex-drinker	771	19	2 405.1	691	40	5 472.0
Previously infected with TB						
No	16 849	252	1 473.6	8 648	274	3 071.1
Yes	1 794	43	2 340.8	1 756	91	4 926.9
Missing	6	0	0	4	0	0
Diabetes						
No	17 552	279	1 564.7	9 307	338	3 504.4
Yes	1 097	16	1 437.6	1 101	27	2 393.6
HIV status						
Negative	9 356	110	1 162.1	5 710	173	2 940.7
Positive	1 484	53	3 448.3	1 230	76	5 819.3
Missing	7 809	132	1 662.3	3 468	116	3 236.6
Final year of education						
None/Grade 1/Grade 2	841	23	2 662.0	715	34	4 539.4
Grade 3–Grade 6	1 938	54	2 710.8	1 410	55	3 754.3
Grade 7–Grade 10	6 671	113	1 665.7	4 142	167	3 875.6
Grade 11–Grade 12	8 332	97	1 150.8	3 755	101	2 619.3
College/university	867	8	914.3	386	8	2 030.5
Occupation at year of survey						
None or own land	7 485	137	1 797.4	4 340	172	3 812.1
Occasional	1 071	22	2 012.8	1 164	41	3 402.5
Employed	6 462	93	1 418.8	3 070	101	3 185.1
Unable to work	325	8	2 402.4	264	17	6 049.8
Student	2 536	27	1 053.5	1 174	26	2 166.7
Homemaker	770	8	1 028.3	396	8	1 980.2

ZAMSTAR = Zambia, South Africa TB and AIDS Reduction; TB = tuberculosis; HIV = human immunodeficiency virus.

Table 2 Multivariate analysis of predictors of bacteriologically confirmed TB among those participants not reporting any current symptoms of TB*

	OR	95% CI	*P* value
Baseline	0.02	0.01–0.04	<0.001
Sex			
Male			
Female	0.91	0.63–1.31	0.615
Age group, years			
18–24			
25–29	0.87	0.54–1.41	0.572
30–34	0.45	0.24–0.84	0.012†
35–39	1.12	0.67–1.86	0.665
40–49	0.82	0.46–1.44	0.488
50–59	1.14	0.58–2.24	0.706
≥60	0.71	0.29–1.74	0.453
Race			
Other			
Black	1.11	0.66–1.85	0.696
Tobacco smoking			
Never smoker			
Ex-smoker	1.68	1.04–2.71	0.032
Current smoker	2.37	1.41–3.99	0.001†
Alcohol use			
Never			
Daily	0.50	0.13–1.96	0.321
Occasional	1.09	0.75–1.59	0.657
Ex-drinker	1.34	0.69–2.58	0.385
Previously infected with TB			
No			
Yes	1.13	0.73–1.74	0.585
Diabetes			
No			
Yes	1.22	0.69–2.15	0.500
HIV status			
Negative			
Positive	3.26	2.31–4.61	<0.001†
Final year of education			
None/Grade 1/Grade 2			
Grade 3–Grade 6	0.70	0.32–1.52	0.363
Grade 7–Grade 10	0.78	0.38–1.60	0.501
Grade 11–Grade 12	0.61	0.29–1.30	0.204
College/university	0.76	0.27–2.20	0.618
Occupation at year of survey			
None or own land			
Occasional	0.96	0.51–1.81	0.889
Employed	0.84	0.57–1.23	0.359
Unable	1.27	0.43–3.78	0.666
Student	0.81	0.44–1.48	0.487
Home-maker	0.41	0.13–1.31	0.131

* Only variables with sufficiently complete data were included in this analysis (https://doi.org/10.6084/m9.figshare.8255912.v1)
† Indicates significance with $P < 0.05$ and Bonferroni Correction allowing for 10% false-discovery rate.
TB = tuberculosis; OR = odds ratio; CI = confidence interval; HIV = human immunodeficiency virus.

Multivariate analysis on sufficiently complete cases (Table 2) found current tobacco smoking (OR 2.37, 95% CI 1.41–3.99) and HIV-positive status (OR 3.26, 95% CI 2.31–4.61) to be independently associated with an increased risk of subclinical TB. Participants in the 30–34 years age group were less likely to have subclinical TB (OR 0.45, 95% CI 0.24–0.84). History of tobacco smoking was not significant after correcting for multiple hypothesis testing (OR 1.68, 95% CI 1.04–2.71).

DISCUSSION

In our study population ($n = 29\,717$), 44.7% of participants with bacteriologically confirmed prevalent TB did not report any classical TB symptom during the standard screening interview; this is consistent with several other large-scale prevalence studies reporting high burdens of subclinical disease.[6]

A growing body of evidence supports the notion that subclinical disease may be a useful category within the continuum of TB infection and suggests that disease course after infection may include a subclinical state.[19,20] History of smoking and HIV infection are well-known to be associated with active TB disease; these findings are reflected in the subclinically infected individuals in this analysis. This perhaps suggests that subclinical disease may be a subset of active TB disease. Analysis of the symptomatic group (data not shown) did indicate that smoking and HIV infection in the ZAMSTAR survey were also associated with TB disease; however, in the case of smoking, the association was not as strong as with TB disease in the subclinical asymptomatic group. Our analysis of ZAMSTAR prevalence data was not powered to compare the associations.

Molecular and mathematical evidence suggests that it may be useful to think of subclinical TB as distinct from active TB.[20–25] A recent meta-analysis of active case-finding interventions revealed that these interventions have generally failed to show either reductions in community incidence or improvement in individual patient outcomes, although such case-finding lead to earlier disease detection among individuals screened.[26] Dowdy et al. used a model that included subclinical disease to demonstrate the potential limitations of symptom-based screening and to suggest how active case-finding strategies may improve control, especially if those not reporting classical symptoms could be identified.[22] However, the impact of such strategies will depend on quantities for which we currently have little data, such as the relative infectiousness of individuals with bacteriologically confirmed TB who do not have symptoms compared with those who have symptoms, and the natural history of subclinical TB.

Given the nature of the cross-sectional ZAMSTAR prevalence data, information on whether individuals with subclinical TB progressed to symptomatic TB was unavailable. A cohort study may be able to provide insight into determinants of subclinical TB and disease progression; however, the natural history of subclinical TB is challenging to investigate due to ethical concerns of withholding treatment from individuals with bacteriological confirmation. Historical cohorts from the pre-anti-TB chemotherapeutic era may inform the natural history if symptomatic and asymptomatic individuals were investigated for bacteriological confirmation of TB with follow-up.

Narrowing uncertainty around key parameters related to infectiousness of subclinical TB may inform more effective interventions; for example, if individuals with subclinical disease remain in this health state for long periods of time and are likely to transmit *M. tuberculosis*, active-case finding interventions to identify individuals with subclinical disease would be especially attractive.

Our analysis supports Esmail et al.'s hypothesis that behaviors and health conditions that mask recognition of classical TB symptoms, such as smoking, may inform the design of active case-finding interventions with greater impact. Since upper respiratory infections and chronic cough associated with cigarette smoking may impede self-recognition of TB symptoms and delay healthcare seeking, the strong association between subclinical TB and current cigarette smoking shown in our analysis is potentially significant.[27,28] For example, our findings support the possibility of further probing for details about symptoms possibly relating to TB among individuals who smoke and do not report symptoms upon initial screening. Our analysis of the ZAMSTAR trial TB prevalence survey allows us to assess the relationship between smoking behaviors and current TB, therefore avoiding potential recall bias that limit retrospective studies that assess smoking behaviors after a TB diagnosis has been made or among symptomatic individuals seeking a diagnosis.

The ZAMSTAR trial prevalence data provides compelling evidence that HIV infection is also independently associated with subclinical TB. Crude HIV prevalence in the South African ZAMSTAR trial communities, based on individuals who consented to undergo HIV testing or self-report HIV status in the TB prevalence survey, was about 16 100 per 100 000; however, HIV status was missing for more than one third of the population. Previous studies of TB among HIV-positive individuals have identified subclinical disease in these populations, and have posited that subclinical presentation may be related to atypical disease associated with immune suppression.[23,29–31] Our study further supports the importance of screening for TB among individuals infected by HIV in high TB-HIV co-burden settings, and that such screening may need to be more comprehensive than an assessment of symptoms through questionnaires.

Limitations

Our ability to assess the presence of symptoms was based on several questions related to the presence of any cough, fever, weight loss and drenching night sweats (Supplementary Data S1; see https://doi.org/10.6084/m9.figshare.8255912.v1). While responses by surveyed participants to these questions may accurately reflect their ability to recognize their current symptoms, it is not clear whether additional questioning could have revealed the presence of worsening baseline cough or other potential signs of TB.

Our analysis is also limited by substantial missing data, especially related to HIV infection, which may introduce bias. Given that younger adult males are known to have a higher prevalence of active TB, it will be important to investigate potential reasons for the lack of data on HIV status to enhance the strength of future study of subclinical infection.[1]

Radiological data were not available for analysis. Previous studies have shown that radiological findings are variable in the context of subclinical infection,[23,29,32] which is significant, given that many prevalence surveys and diagnostic algorithms rely on the presence/absence of such findings.

CONCLUSION

Nearly 45% of participants with bacteriologically confirmed TB in the South African ZAMSTAR trial TB prevalence surveys denied experiencing any of classical symptoms of TB. Among those participants for which we had sufficiently complete data, current smoking was independently associated with a greater than two-fold odds, and HIV infection was independently associated with a greater than three-fold odds of subclinical TB. These findings confirm the importance of new approaches for detecting disease among individuals with atypical presentation or among individuals who may have other explanations for their symptoms, which can impede self-recognition of TB. While this study provides additional support for claims of the potential importance of subclinical disease, the epidemiological significance of subclinical disease remains unclear, and studies which can address the natural history of subclinical disease and the transmission potential of individuals with subclinical TB will be valuable.

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Conflicts of interest: none declared.

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RÉSUMÉ

CONTEXTE : En dépit de multiples enquêtes de prévalence de la tuberculose (TB) rapportant une fréquence relativement élevée de TB active confirmée par bactériologie parmi des individus ne faisant état d'aucun symptôme typique de la maladie, notre compréhension de ce phénomène reste limitée. Cette étude a pour but d'en quantifier le poids épidémiologique et d'estimer les associations entre variables au niveau individuel et cette forme infra clinique.

MÉTHODE : Nous avons réalisé une analyse secondaire des données d'enquête de prévalence de la TB des communautés d'Afrique du Sud émanant de l'essai « Zambia and South Africa Tuberculosis and AIDS Reduction trial ». Des équations d'estimation généralisées ont été utilisées pour estimer l'association entre les variables individuelles démographiques, comportementales, socioéconomiques et médicales et le risque de TB confirmée par bactériologie parmi les participants ne rapportant pas de symptômes compatibles avec une tuberculose active.

RÉSULTATS : La prévalence brute de la TB a été de 2 222,1 cas par 100 000 (IC 95% 2053,4–2388,5 par 100 000) et 44,7% (295/660) de tous les cas documentés de TB ont été infra cliniques. Le fait de fumer (OR 2,37 ; IC 95% 1,41–3,99) et d'être VIH positif (OR 3,26 ; IC 95% 2,31–4,61) ont été significativement associés à une TB infra clinique.

CONCLUSION : Les personnes qui fument ou sont VIH positives semblent avoir un risque accru de TB active et de ne pas rapporter de symptômes typiques compatibles avec la maladie. Ceci suggère de possibles lacunes du dépistage basé sur les symptômes qui doivent être prises en compte dans des contextes similaires.

RESUMEN

MARCO DE REFERENCIA: Pese a que múltiples estudios sobre la prevalencia de tuberculosis (TB) comunican una frecuencia relativamente alta de enfermedad activa con confirmación bacteriológica en personas que no refieren síntomas característicos de la enfermedad, la comprensión de este fenómeno es limitada. La finalidad del presente estudio fue cuantificar la carga epidemiológica y evaluar las asociaciones entre las variables a escala individual y esta presentación clínica "asintomática".

MÉTODOS: Se realizó un análisis secundario de los datos de prevalencia de TB en las comunidades surafricanas del estudio para la reducción de la TB y el sida en comunidades de Zambia y Suráfrica. Mediante ecuaciones de estimación generalizadas se evaluó la asociación entre las variables demográficas, comportamentales, socioeconómicas y médicas a escala individual y el riesgo de detección de TB con confirmación bacteriológica en los participantes que no referían ningún síntoma indicativo de enfermedad activa.

RESULTADOS: La prevalencia bruta de TB fue 2222,1 casos por 100 000 habitantes (IC95% 2053,4–2388,5 por 100 000) y 44,7% (295/660) de todos los casos de TB documentados fueron asintomáticos. Los factores asociados de manera significativa con una TB asintomática fueron el tabaquismo actual (OR 2,37; IC95% 1,41–3,99) y la situación positiva frente a la infección por el VIH (OR 3,26; IC95% 2,31–4,61).

CONCLUSIÓN: Las personas que fuman o son positivas frente al VIH pueden presentar un riesgo mayor de contraer la TB activa y no referir síntomas indicativos de la enfermedad. Estos resultados ponen de manifiesto posibles puntos débiles en la búsqueda de casos a partir de los síntomas, que se deben tener en cuenta en otros entornos con características similares.