International Journal of Infectious Diseases xxx (xxxx) xxx

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

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

Tobacco smoking impact on tuberculosis treatment outcome: an observational study from West Africa

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ARTICLE INFO

Article history:
Received 3 February 2022
Revised 26 July 2022
Accepted 26 July 2022
Available online xxx

Keywords:
Tobacco
Smoking
Tobacco smoking
Pulmonary tuberculosis
Sub-Saharan Africa
West Africa

ABSTRACT

Objective: Both tuberculosis (TB) and tobacco smoking are preventable health hazards. Few studies have examined the relationship between TB and tobacco smoking in an African setting, where the two health burdens collide heavily. This study aimed to describe the severity of TB disease and treatment outcomes among smokers with TB compared with nonsmokers with TB in Guinea-Bissau.

Methods: We conducted a prospective follow-up study between 2003-2017 in Guinea-Bissau, enrolling adult patients with TB classified as nonsmokers or smokers. Disease severity was assessed using the Bandim TBscore. Multivariate logistic and Cox proportional hazard regressions were used to analyse treatment outcomes.

Results: Of 1780 included patients, 385 were smokers who had smoked for a median 10 years (interquartile range [IQR] 5-20). No difference in disease severity at the time of diagnosis was observed. Smokers were not significantly more prone to a nonsuccessful treatment outcome, although a trend was seen (adjusted odds ratio [OR] 1.24, 95% confidence interval [CI] 0.91-1.70), and smokers tended to be more often lost to follow-up, but this also was not a significant finding (adjusted hazard ratio [HR] 2.09, 95% CI 0.89-4.94).

Conclusion: In a TB high-endemic setting with few tobacco smokers, smoking was not associated with disease severity or worse outcome, possibly because of socioeconomic confounders.

Introduction

The world is striving to end the global tuberculosis (TB) epidemic (World Health Organization, 2021a). Despite great attention and effort, TB incidence rates are only slowly decreasing. In 2021, an estimated 10 million people fell ill with TB, and 1.5 million people died from TB (World Health Organization, 2021a). Of all cases, 24% occurred in the World Health Organisation (WHO) African Region (World Health Organization, 2021a). Simultaneously, great effort is made to reduce global smoking rates (World Health Organization, 2017). In low-income countries, the smoking prevalence is estimated to be 13.2%, although this is based on limited available data (World Health Organization, 2017). With these colliding epidemics, clarifying the consequences of their coexistence is essential (Pai et al., 2007).

Epidemiological and biological studies have associated smoking with the development of active TB, TB incidence, the severity of cavitary lesions, and prolonged sputum conversion rate (Altet et al., 2017; Altet-Gômez et al., 2005; Amere et al., 2018; Lemvik et al., 2014; Maurya et al., 2002; Pai et al., 2007; Rathee et al., 2016; Wejse et al., 2008; Yen et al., 2014). A 2018 review concluded that one in every six cases (population attributable risk of 17.6%) of incident TB could be attributed to smoking (Amere et al., 2018). A number of studies have investigated the association between smoking and clinical TB disease severity (Altet et al., 2017; Altet-Gômez et al., 2005; Bonacci et al., 2013; Chuang et al., 2015; Leung et al., 2003; Mahishale et al., 2015; Rathee et al., 2016; Wang et al., 2007), but studies on treatment outcome, especially mortality, are few and inconclusive (Amere et al., 2018; Bonacci et al., 2013; Chuang et al., 2015; Gegia et al., 2015; Jee et al., 2009; Mahishale et al., 2015; Masjedi et al., 2017;

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https://doi.org/10.1016/j.ijid.2022.07.067

Nijenbandring de Boer et al., 2014; Pai et al., 2007; Rathee et al., 2016). In addition, published literature on smoking and TB in an African setting is scarce (Amere et al., 2018; den Boon et al., 2005; Hill et al., 2006; Lienhardt et al., 2005; Ramin et al., 2008; Tachfouti et al., 2011; Tachfouti et al., 2013).

We hypothesised that being a smoker impacted the clinical severity of TB disease and treatment outcomes negatively. This study aimed to describe the severity of TB disease at treatment initiation and the prevalence of treatment outcomes among smokers with TB compared with nonsmokers with TB in Guinea-Bissau, West Africa.

Study population and methods

Study design and setting

This prospective observational cohort study was conducted at the health- and demographic surveillance site, the Bandim Health Project (BHP), in Guinea-Bissau, West Africa (Lemvik et al., 2014; Rudolf et al., 2014; Virenfeldt et al., 2014). The suburban study area is inhabited by approximately 102,000 people and is situated in the capital Bissau. Guinea-Bissau has one of the highest TB incidence rates in the world. In 2020, the WHO estimated an incidence of 361 per 100,000 in the country (World Health Organization, 2021a), and Lemvik et al. estimated an incidence of 279 per 100,000 in the BHP study area in 2011 (Lemvik et al., 2014).

Participants

We have established an ongoing cohort of newly diagnosed patients with TB living in the study area, who are identified, enrolled, and followed for clinical status during the six months of treatment and for mortality up to two years after enrolment, as described previously (Lemvik et al., 2014; Rudolf et al., 2014; Virenfeldt et al., 2014). All newly diagnosed patients with TB living in the study area, treated at one of three health centres in the study area or the national TB reference hospital, were offered inclusion in the BHP TB cohort. TB diagnosis was according to WHO criteria (World Health Organization, 2021b). This study included patients diagnosed with TB between October 2003 and July 2017. Inclusion criteria were age $\geq$15 years and initiation of TB treatment $<$1 month before inclusion. Baseline clinical data were only collected if patients were included less than 14 days from treatment start. Exclusion criteria were extrapulmonary TB, rifampicin-resistant TB, and missing data on smoking habits.

Data sources and variables

At inclusion, patients answered a sociodemographic questionnaire and underwent a physical examination and HIV quick-testing (Determine HIV-1/2 assay, Abbott Laboratories, Tokyo, Japan). Subsequently, patients were categorised as either HIV-uninfected, HIV-infected, or HIV-unknown because of the potential bias of patients refusing HIV testing because of already known HIV infection.

Patients were asked upon enrolment whether they were current, former, or never smokers. Current smokers were asked how many cigarettes they smoked daily and for how many years they had smoked. Former smokers were asked if they had quit more or less than six months ago. Patients were divided into exposure groups of smokers and nonsmokers. Smokers included current and former smokers who quit less than six months before inclusion (Lam et al., 2013). Nonsmokers included former smokers who quit more than six months before inclusion and never smokers. Alcohol consumption was categorised as “sometimes drinkers” or “everyday drinkers.”

TB disease severity was evaluated using the Bandim TBscore (Rudolf et al., 2014; Wejse et al., 2008). The Bandim TBscore is a clinical scoring tool in which patients receive points if having low body mass index (BMI), small mid-upper arm circumference, haemoptysis, chest pain, dyspnoea, night sweats, anaemic conjunctivae, tachycardia, positive findings at lung auscultation, and/or axillary temperature above 38°C. BMI was calculated as weight (kg) divided by height (m) squared.

Treatment outcome was registered at the health centres at the end of treatment or house visits if treatment was not adhered to. TB treatment outcome was evaluated using the World Health Organization-defined outcome categories: cured, treatment completion, treatment failure, death, lost to follow-up (LTFU), and ‘not evaluated.’ Cured and treatment completion were grouped together as ‘treatment success,’ and treatment failure, death, and LTFU were grouped together as ‘treatment nonsuccess’ for the purpose of statistical analyses.

Bias

Most smokers in Guinea-Bissau are men, whereas nonsmokers represent women and men. Increasing age negatively impacts treatment outcomes, and so does increasing cumulative number of years of smoking, which may or may not come with age. To see the effect of smoking on treatment outcomes when eliminating the bias of sex and advancing age, analyses were adjusted for those confounders in model 1. In model 2, analyses were adjusted for the same confounders as in model 1, and furthermore, sociodemographic variables (educational level, employment status, religion, alcohol consumption, BMI, and HIV infection) were explored as potential confounders.

Statistical methods

All statistical analyses were performed using Stata 11.2 (Stata Corporation, College Station, Texas, USA). Successful versus nonsuccessful treatment outcome was evaluated using multiple logistic regression, and LTFU and mortality were assessed using Cox proportional hazards model. For Cox analyses, the exit date was defined as the date of death, emigration, transfer to another treatment centre, last seen alive (LTFU), or date of treatment completion, whichever came first. Sociodemographic variables were considered confounders if they individually altered the results by $>$10%. Interaction between smoking and age and smoking and alcohol was tested. A Kaplan-Meier plot was used to illustrate survival estimates during treatment.

Two sensitivity analyses were performed. Data were divided into subgroups of HIV-infected and HIV-uninfected patients with TB. The grouping of smokers versus nonsmokers included former smokers, which may or may not have influenced the results. To challenge this grouping, analyses were repeated for smokers versus nonsmokers, with all former smokers excluded.

Results

Participants

Overall, 1946 of 2597 registered patients with TB were included in the TB cohort within the time frame of the present study. Of those, 1779 met the eligibility criteria of the study. See the flowchart in Figure 1 for reasons for noninclusion and exclusions.

Descriptive data

The study population comprised 385 (21.6%) smokers, of which 378 (98.2%) were men and 76 (19.7%) were HIV-infected. Among

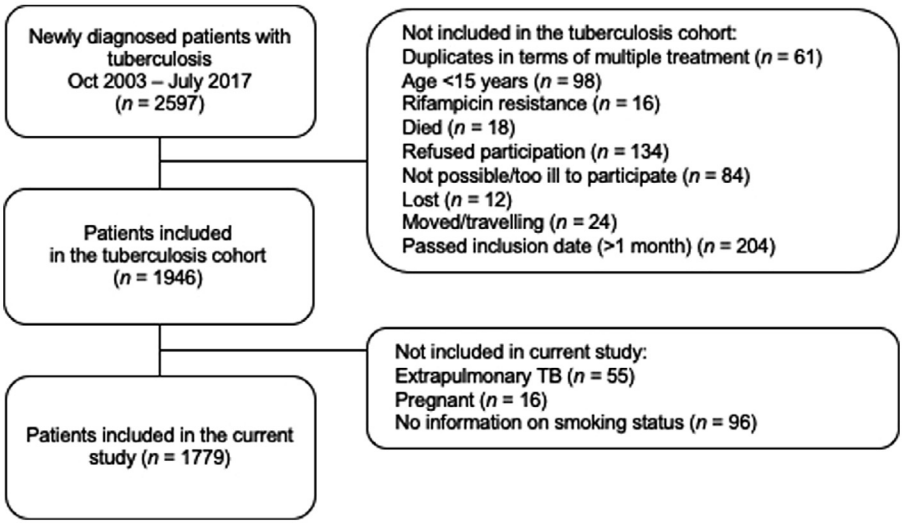

Figure 1. Flowchart

the smokers, 322 (83.6%) had data on years of smoking; the median was 10 years (interquartile range [IQR] 5-20), varying between less than one year to a maximum of 63 years. Only 154 (40.0%) of the smokers had data on daily cigarette consumption, of which 36 (23.4%) smoked <1 cigarette daily, 88 (57.1%) smoked 1-5 cigarettes daily, 18 (11.7%) smoked 6-10 cigarettes daily, and only 12 (7.8%) smoked >10 cigarettes daily.

The median age was 36 years (IQR 28-45) for smokers and 30 years (IQR 24-42) for nonsmokers, see Table 1. Smokers were, to a greater extent, employed, Muslim, and everyday drinkers. More smokers were exposed to household passive smoking and were sputum positive at the time of diagnosis, but fewer smokers were severely undernourished at the time of diagnosis compared with nonsmokers. There was no difference between smokers and nonsmokers concerning clinical disease severity measured by TBscore. Upon examining the individual elements of the TBscore, it was found that smokers more often reported coughing (97.5% versus 94.4%, *P*-value 0.040) and that nonsmokers more often were tachycardic (25.6% versus 18.6%, *P*-value 0.017). There was no difference in the prevalence of dyspnoea, haemoptysis, chest pain, night sweats, anaemic conjunctivae, lung auscultation findings, or axillary temperature >38°C between smokers and nonsmokers (data not shown).

Of the 299 smokers who were sputum positive at treatment initiation, 25 (8.4%) remained sputum positive at two months, 224 (74.9%) converted to sputum negative, and 50 (16.7%) had missing follow-up sputum smear results. A similar sputum conversion trend was observed for nonsmokers (*P*-value 0.120).

Outcome data

The prevalence of treatment outcomes for smokers and nonsmokers are listed in Table 2. Table 3 presents odds ratios of nonsuccessful treatment outcomes for smokers compared with nonsmokers stratified by HIV status, including and excluding former smokers. In model 1, analyses were adjusted for age and sex. In model 2, analyses were adjusted for age, sex, alcohol consumption, BMI, and HIV (the latter only for nonstratified analyses), because those variables individually altered the estimate by >10%. There was no interaction between smoking and age or smoking and alcohol consumption. Smokers had a 24% increased risk of a nonsuccessful treatment outcome compared with nonsmokers, with the true effect ranging from 9% decreased risk to 70% increased risk. HIV-infected smokers had a 59% increased risk, although the increased risk was markedly decreased to 26% when adjusting for alcohol consumption and BMI. The opposite was seen for HIV-negative smokers, who had an increased risk of 19%, which increased to 54% when adjusting for alcohol consumption and BMI. The estimated risks were all augmented when former smokers were excluded from analyses. A Kaplan-Meier plot illustrates survival estimates during treatment in Figure 2.

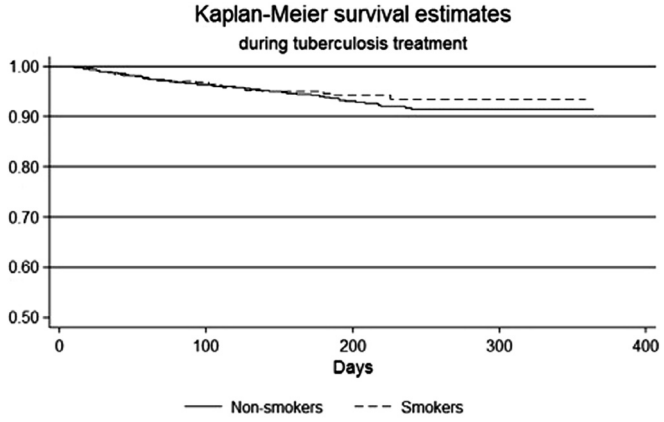

Figure 2. Kaplan-Meier survival estimates for smokers versus nonsmokers during tuberculosis treatment

Discussion

Key results

Smokers in Bissau were light smokers; most smoked only between 0-5 cigarettes per day for a median of 10 years. There was no difference in clinical TB disease severity at treatment initiation between smokers and nonsmokers. Smokers had an increased risk of a nonsuccessful treatment outcome, especially of being LTFU.

Only a few studies have investigated the association between smoking and TB disease severity at diagnosis. Bonacci et al. found that both light and heavy smokers reported haemoptysis and fever more frequently than nonsmokers (Bonacci et al., 2013). Leung

Table 1
[a] Baseline characteristics of adults with active pulmonary tuberculosis, Guinea-Bissau.

	Nonsmokers (n = 1394)	Smokers (n = 385)	*P-value*
Male sex, *n* (%)	785 (56.3)	378 (98.2)	<0.001
Age (years), median [IQR]	30 [24-42]	36 [28-45]	<0.001
HIV-status, *n* (%)			0.015
HIV-infected	371 (26.6)	76 (19.7)	
HIV-uninfected	916 (65.7)	282 (73.3)	
Unknown HIV-status	107 (7.7)	27 (7.0)	
Educational level, *n* (%)	338 (24.4)	65 (17.2)	<0.001
No education	638 (46.0)410 (29.6)	236 (62.6)76 (20.2)	
Basic education (£9 years)			
Higher education (>9 years)			
Employed, *n* (%)	681 (49.1)	297 (77.1)	<0.001
Alcohol consumption, *n* (%)			<0.001
Everyday drinkers	202 (20.8)	129 (41.3)	
Sometimes drinkers	769 (79.2)	183 (58.7)	
Religion, *n* (%)			<0.001
Animist	344 (24.7)	106 (27.6)	
Catholic	522 (37.5)	116 (30.2)	
Protestant	147 (10.6)	12 (3.1)	
Muslim	337 (24.2)	135 (35.2)	
Other	41 (3.0)	15 (3.9)	
BMI (kg/m^2), *n* (%)			0.022
Severely underweight, <16 kg/m^2	191 (17.5)395 (36.3)	41 (13.3)126 (40.9)	
Moderately underweight, 16-18.5 kg/m^2	464 (42.6)	138 (44.8)	
Normal weight, 18.5-25 kg/m^2	39 (3.6)	3 (1.0)	
Overweight, >25 kg/m^2			
Exposed to household passive smoking, *n* (%)	328 (25.0)	136 (36.1)	<0.001
Previous TB treatment, *n* (%)	99 (7.1)	21 (5.5)	0.254
BCG scar present, *n* (%)	558 (41.8)	143 (38.6)	0.276
Positive first sputum exam, *n* (%)	1027 (75.5)	299 (80.0)	0.070
Treatment delay (days), median [IQR]	79 [48-136]	80.5 [48-145]	0.615
TBscore, mean ± SD	5.79 ± 2.29	5.84 ± 2.26	0.770

BCG = Bacillus Calmette-Guérin vaccine against tuberculosis; BMI = body mass index; IQR = interquartile range; SD = standard deviation; TB = tuberculosis; TBscore = clinical scoring tool for disease severity, see Method section for explanation.
[a] Missing information (if n >20): 423 nonsmokers and 73 smokers had missing data on alcohol consumption. A total of 82 nonsmokers and eight smokers had missing info on exposure to passive smoking. A total of 59 nonsmokers and 15 smokers had missing info on BCG scar. A total of 25 nonsmokers and nine smokers had missing data on treatment delay.

Table 2
Smoking status and tuberculosis (TB) treatment outcomes at the end of treatment.

	Nonsmokers *n* (%)	Smokers *n* (%)
Success		
Cured	714 (53.5)	187 (51.5)
Treatment completed	392 (29.3)	96 (26.4)
Nonsuccess		
Treatment failed	7 (0.5)	1 (0.3)
Died	95 (7.1)	21 (5.8)
Lost to follow-up	128 (9.6)	58 (16.0)
Not evaluated	*58*	*22*

et al. found that smokers were more likely to complain about cough and dyspnoea (Leung et al., 2003). We found that smokers reported coughing more frequently than nonsmokers but otherwise were comparable to nonsmokers regarding clinical symptoms. This could be because smokers were only light smokers in our setting. We found that nonsmokers were more undernourished than smokers. This could be explained by the fact that, in our setting, more smokers were employed and thus could afford food and cigarettes. We believe these circumstances are the reason we did not find any difference in clinical disease severity in our study. A study from Spain found that smoking is responsible for greater disease severity based on cavitary lesions and sputum smear (Altet-Gômez et al., 2005). We also found that smokers were more often sputum positive at treatment initiation, but smokers had similar 2-month conversion rates to nonsmokers.

Table 3
Odds ratio (OR) for nonsuccess at the end of tuberculosis (TB) treatment for smokers compared with nonsmokers stratified by HIV-status.

	OR crude (95% CI)	OR model 1[a] (95% CI)	OR model 2[b] (95% CI)
All patients	n = 1699 1.36 (1.02-1.81)	n = 1699 1.24 (0.91-1.70)	n = 991 1.44 (0.96-2.17)
HIV-infected	n = 423 1.88 (1.11-3.20)	n = 423 1.59 (0.89-2.82)	n = 219 1.26 (0.56-2.83)
HIV-uninfected	n = 1148 1.34 (0.92-1.96)	n = 1148 1.19 (0.79-1.81)	n = 660 1.54 (0.91-2.60)
Sensitivity analyses			
Former smokers excluded	n = 1407 1.51 (1.05-2.17)	n = 1407 1.40 (0.94-2.09)	n = 827 1.54 (0.93-2.55)
HIV-infected	n = 352 2.07 (0.97-4.41)	n = 352 1.69 (0.75-3.79)	n = 182 1.31 (0.43-3.96)
HIV-uninfected	n = 938 1.69 (1.05-2.72)	n = 938 1.64 (0.97-2.79)	n = 541 1.74 (0.91-3.36)

CI = confidence interval; OR = odds ratio; TB = tuberculosis
[a] Model 1: adjusted for age and sex.
[b] Model 2: adjusted for age, sex, alcohol consumption, body mass index, and HIV status (the latter only for nonstratified analyses). A total of 423 (30.3%) nonsmokers and 73 (19.0%) smokers have missing information on alcohol consumption. A total of 107 (7.7%) nonsmokers and 27 (7.0%) smokers have unknown or missing information on HIV status.

Regarding TB treatment outcomes, including the risk of being LTFU, the present study results are in accordance with some of the existing literature. A 2017 clinical trial found that nonsmokers and quitters had significantly higher cure rates than smokers (83.4%, 80.8%, and 67.6%, respectively) (Masjedi et al., 2017). An observational study from 2016 concluded that smokers had a poorer treatment success rate than nonsmokers and former smokers (69%, 93.8%, and 90.9%, respectively) owing to a high LTFU rate (Rathee et al., 2016). These findings are consistent in many studies (Altet-Gômez et al., 2005; Chuang et al., 2015; Gegia et al., 2015; Mahishale et al., 2015). Several studies show that the association is true even for the lightest smokers (typically <10 cigarettes/day) (Altet et al., 2017; Bonacci et al., 2013; Jee et al., 2009; Lin et al., 2009; Maurya et al., 2002; Nijenbandring de Boer et al., 2014; Ramin et al., 2008).

When it comes to mortality risk, however, the literature is contradictory. Numerous studies show that smoking is not associated with increased mortality among patients with pulmonary TB (Altet-Gômez et al., 2005; Bates et al., 2007; Pai et al., 2007; Wang et al., 2007). However, others show that smoking increases mortality by as much as 9-fold (Amere et al., 2018; Bonacci et al., 2013; Jee et al., 2009; van Zyl Smit et al., 2010; Wen et al., 2010). In the present study, we found that smokers did not have an increased risk of death, except if HIV-infected. A large number of patients who were LTFU could potentially have died within a short period after being LTFU, as is often demonstrated in other types of studies (Nordentoft et al., 2017). Thus, mortality is likely underestimated in settings with a high LTFU rate like ours.

This study had some limitations. The data on smoking habits are liable to be affected by information bias, as the patients may not have provided full information on current or previous smoking and the amount of daily smoking. Inclusion in the cohort required extra effort, which could have caused very ill patients to refuse inclusion. Patients too ill to give informed consent were not included if they either passed the inclusion date or died before. Hypothetically, these patients could be the heaviest smokers causing a true effect to be underestimated.

Because of the high prevalence of illiteracy in Guinea-Bissau, interviewer-administered questionnaires were necessary. Smokers may have been reported as nonsmokers because of shame or stigmatisation, thus diminishing a possible effect of smoking (Connor Gorber et al., 2009). Another consideration is the possibility of participants changing smoking status during TB treatment.

Smokers who quit less than six months before treatment initiation were grouped together with current smokers on the assumption that they quit smoking because of disease symptoms but otherwise still resembled current smokers regarding pathophysiology. Former smokers who quit more than six months ago were considered equal to nonsmokers because of the very low cigarette use reported by smokers. Previous studies have shown that smoking cessation at treatment initiation made quitters respond similar to nonsmokers rather prompt (Nijenbandring de Boer et al., 2014; Rathee et al., 2016). There was no indication that the classification of former smokers biased the results greatly, as results were only enhanced when former smokers were excluded.

In Guinea-Bissau, TB diagnosis is primarily based on sputum smear microscopy and clinical judgement (Wejse, 2014). The scarcity of resources means that drug-resistant strains are diagnosed with delay or not at all. Thus, some patients could have hosted drug-resistant TB strains. No other studies have evaluated the association between smoking and TB treatment outcomes in a Sub-Saharan African setting. Therefore, it is not possible to say whether the generated results represent a general deviating trend in Africa. In the present study, light smokers represented a patient group with difficulty adhering to treatment. Health programmes should therefore pay attention to smokers with TB, who may represent a vulnerable patient group.

Conclusions

Smokers in Bissau were, on average, light smokers, who were more often Muslim, employed, and everyday drinkers. Smoking did not impact the clinical severity of TB disease at the time of diagnosis. Smokers had an increased risk of a nonsuccessful treatment outcome, especially because of an increased risk of being LTFU during treatment.

Transparency declaration

This article is part of a supplement entitled Commemorating World Tuberculosis Day March 24th, 2022: “Invest to End TB. Save Lives” published with support from an unrestricted educational grant from QIAGEN Sciences Inc.

Conflicts of interest

The authors have no competing interests to declare.

Funding

This study was funded by the European and Developing Countries Clinical Trials Partnership (EDCTP) and a grant from the Novo Nordisk Foundation (NNF15OC0018034). The funders had no role in the design, analysis, or writing of this article.

Ethics statement

The study abided by the Declaration of Helsinki. Written informed consent by signature or fingerprint, if illiterate, was provided by all subjects before inclusion. The tuberculosis cohort studies were permitted by the National Ethics Committee (MINSAP 220405).

Author contributions

VFG, FR and CW conceived the idea for the study and initiated data collection. JGB has written the first draft of the manuscript together with CBP who provided helpt with dataanalysis and manuscript set up and input from VFG, FR and CW. NMS added manuscript revisions and handled references, all authors revised and edited as well as accepted the final version of the manuscript.

Disclaimer

Author’s statements and views expressed in the article are their own and not the official position of the affiliated institutions or funders.

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