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INFECTIOUS DISEASES

Investigation of the risk factors for tuberculosis: a case–control study in three countries in West Africa

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Background Host-related and environment-related factors have been shown to play a role in the development of tuberculosis (TB), but few studies were carried out to identify their respective roles in resource-poor countries.

Methods A multicentre case–control study was conducted in Guinée, Guinea Bissau, and The Gambia, from January 1999 to March 2001. Cases were newly detected smear positive TB patients. Two controls were recruited for each case, one within the household of the case, and one in the community.

Results Regarding host-related factors, univariate analysis by conditional logistic regression of 687 matched pairs of cases and household controls showed that TB was associated with male sex, family history of TB, absence of a BCG scar, smoking, alcohol, anaemia, HIV infection, and history and treatment of worm infection. In a multivariable model based on 601 matched pairs, male sex, family history of TB, smoking, and HIV infection were independent risk factors of TB. The investigation of environmental factors based on the comparison of 816 cases/community control pairs showed that the risk of TB was associated with single marital status, family history of TB, adult crowding, and renting the house. In a final model assessing the combined effect of host and environmental factors, TB was associated with male sex, HIV infection, smoking (with a dose–effect relationship), history of asthma, family history of TB, marital status, adult crowding, and renting the house.

Conclusion TB is a multifactorial disorder, in which environment interacts with host-related factors. This study provided useful information for the assessment of host and environmental factors of TB for the improvement of TB control activities in developing countries.

Keywords Tuberculosis, risk factors, epidemiology, developing countries

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† This paper is dedicated to the memory of Professor Steve Bennett, a major contributor to the study, who died unexpectedly in March 2003.
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The development of tuberculosis (TB) in man is a two-stage process in which a susceptible person exposed to an infectious TB case becomes infected and may later develop the disease, depending upon various factors. In individuals infected with *Mycobacterium tuberculosis*, any condition modifying the balance established in the body between the host's immune defences and the tubercle bacilli can have an impact on the risk of developing the disease. Factors that have been shown to influence this balance have been investigated for a long time, and were reported to be both 'intrinsic' and 'extrinsic' to the host.[1] However, in most studies investigating risk factors for TB, host-related and environmental factors were usually investigated separately, using different designs, making it

impossible to assess their respective effects.[2,3] In addition, most of these studies were conducted in industrialized countries, and apart from the studies showing the effect of HIV infection,[4] very few were carried out in resource-poor countries.[2] With the re-emergence of TB, affecting mainly developing countries, there is a need to re-examine the contribution of environmental and host-related factors for TB and identify factors that can influence the development of TB in man, in order to adjust and adapt TB control policies.

To explore these, we conducted a multicentre case–control study in three countries in West Africa, The Gambia, Guinée Conakry, and Guinea Bissau, from January 1999 to March 2001. These countries were chosen as they had almost similar ethnic mix, socioeconomic indicators and geographical environment, as well as a comparable epidemiological burden of TB to enable suitable recruitment. In each country, the study has been reviewed and approved by the local/national Ethics Committee, and informed consent was obtained from cases and controls prior to enrolment.

Methods

The detailed methodology of the study has been described elsewhere.[5] Briefly, in each study site, newly detected sputum smear positive pulmonary TB patients >15 years who had presented at major urban health centres were eligible for inclusion. Pulmonary TB was confirmed by two consecutive smears positive for acid-fast bacilli and/or a positive culture. The household (in this study, household was defined as the extended family living together in the same area and eating from the same pot) of each case was visited and information collected on various demographic and socioeconomic variables.

For each case, two types of controls were recruited. First, a healthy control was selected at random within the household of the TB case. This control was age-matched to within 10 years of the case. Then, a healthy community control was selected at random in the neighbourhood of the case's household, by choosing a random direction from the case's home and visiting the fifth dwelling on the right. If, as commonly observed, several households lived in the same dwelling, one household was selected by drawing lots. After explaining the study to the members of the household, a control was identified, age-matched to within 10 years of the case. If there were several possible candidates within the household, the control was chosen by drawing lots. If the household head declined to take part in the study, the same procedure was repeated to select another household in the neighbourhood.

Information was collected from cases and controls on a wide range of potential host-related and environment-related risk factors for TB. These included factors already identified in previous studies[2,3] and factors expected to predispose to TB in the particular situation of developing countries. Standardized questionnaires were addressed to the study subjects by field assistants using the appropriate colloquial language, after checking the accuracy of translation with the interviewers. The presence of a BCG scar on the left or right deltoid region of the arm was checked. Blood samples were obtained from each case and control for a full blood count and HIV testing, after the patient was pre-test counselled and gave informed consent. Individuals positive for HIV infection were referred for post-test counselling and appropriate care, according to the national guidelines in use in each site.

Data were double entered using Epi-Info (version 6, CDC, Atlanta, GA) and transferred to STATA (version 7, Stata Corporation, College Station, TX) for analysis. Analysis was conducted on data from the three sites combined, using index case and household control pairs to assess the effect of host-related factors and index cases and community control pairs to assess the effect of environmental risk factors. Finally, cases and community controls were compared to assess the combined effect of host-related and environmental factors. Odds ratios (OR) and their 95% confidence intervals (CIs) were estimated using conditional logistic regression, with TB as an outcome. The likelihood ratio test was used to test the association between the explanatory variables and the risk of TB and for linear trend and interaction. Univariate analysis was performed to examine the effect of each variable of interest on the risk of TB. Multivariate models were then constructed, including variables that showed a significant statistical effect in the prediction of TB in univariate analysis ($P < 0.05$). In this paper, we present the results for the three sites combined. (Individual country site analysis was carried out in order to explore any specific aspect when data differed substantially among the three sites (large variations of effect or different direction of effect) but the results are not reported here.)

Results

During the study period, 846 cases, 702 household controls, and 828 community controls were recruited in the three countries. From the analysis, 24 TB cases were excluded, as smear positive pulmonary TB was not confirmed or because major data were missing. As a result, 822 index cases who satisfied the case definition were included in the analysis. Of these, 687 had a household control and 816 had a community control, allowing matched-pair analysis. The distribution by country is shown in Table 1.

Investigation of host-related factors

Results from univariate analysis carried out on the 687 cases/household control pairs are displayed in Table 2. As can be

Table 1 Main demographic variables for index cases, household and community controls recruited in the study

	Cases	Household controls	Community controls	Total
Country				
Gambia	317	305	316	938
Conakry	269	239	269	777
Bissau	236	143	231	610
Total	822	687	816	2325
Sex: M/F				
Gambia	233/84	143/162	184/132	560/378
Conakry	171/98	116/123	132/137	419/358
Bissau	148/88	66/77	109/122	323/287
Age (mean, SD)				
Gambia	31.9 (12.7)	30.0 (10.7)	31.9 (10.8)	31.3 (11.5)
Conakry	28.8 (10.3)	28.4 (9.8)	30.1 (10.3)	29.1 (10.2)
Bissau	35.7 (12.1)	31.5 (11.4)	35.3 (12.0)	34.6 (12.0)

Table 2 Host-related factors for TB: comparison of TB cases and household controls (univariate analysis)

Variable	Total no. of pairs	Controls *n* (%)	Cases *n* (%)	OR (95% CI)	*P*-value
Sex					
Female	687	362 (53)	215 (31)	1	<0.0001
Male		325 (47)	472 (69)	2.32 (1.85, 2.94)	
Marital status					
Married	671	359 (54)	310 (46)	1	
Single		289 (43)	323 (48)	1.86 (1.30, 2.64)	
Widowed/divorced		23 (3)	38 (6)	2.34 (1.30, 4.22)	0.0003
Former TB					
No/unsure	675	660 (98)	638 (95)	1	0.001
Yes		15 (2)	37 (5)	2.69 (1.42, 5.09)	
Family history of TB					
No/unsure	673	558 (83)	504 (75)	1	<0.0001
Yes		115 (17)	169 (25)	2.38 (1.64, 3.47)	
Smoking					
Never	669	526 (79)	377 (56)	1	<0.001
Past		32 (5)	59 (9)	2.38 (1.50, 3.77)	
Current		111 (17)	233 (35)	3.14 (2.35, 4.21)	
Alcohol					
Never	672	546 (81)	509 (76)	1	<0.001
Current/past		126 (19)	163 (24)	1.84 (1.28, 2.66)	
Drug					
No	663	657 (99)	646 (97)	1	0.02
Yes		6 (1)	17 (3)	2.83 (1.12, 7.19)	
Attaya					
Never	665	258 (39)	241 (36)	1	0.26
Ever		407 (61)	424 (64)	1.16 (0.89, 1.50)	
BCG scar					
No/unsure	687	325 (47)	364 (53)	1	0.02
Yes		362 (53)	323 (47)	0.77 (0.61, 0.97)	
HIV status					
Negative	609	562 (92)	537 (88)	1	0.002
Positive		47 (8)	72 (12)	2.34 (1.29, 3.54)	
History of worms					
No	673	503 (75)	468 (70)	1	0.01
Yes		170 (25)	205 (30)	1.43 (1.08, 1.90)	
Treatment for worms					
No	673	532 (79)	507 (75)	1	0.05
Yes		141 (21)	166 (25)	1.37 (1.00, 1.88)	
History of asthma					
No	674	665 (99)	669 (99)	1	0.28
Yes		9 (1)	5 (1)	0.56 (0.19,1.66)	
Treatment of asthma					
No	674	669 (99)	670 (99)	1	0.74
Yes		5 (1)	4 (1)	0.80 (0.21,2.98)	
Diabetes					
No/unsure	674	672 (100)	665 (99)	1	0.03
Yes		2 (0.3)	9 (1)	4.5 (0.97, 20.8)	
Haemoglobin					
⩾12.5	574	295 (51)	113 (20)	1	<0.0001
10–12.49		226 (39)	291 (51)	3.51 (2.57, 4.79)	
<10		53 (9)	170 (30)	10.84 (6.8, 17.2)	

seen, male gender was found to increase the risk of TB in the three countries. Widowed/divorced and single individuals were at a higher risk of developing TB than married individuals. A former episode of TB in the case, or among his/her family, strongly increased that risk. The risk of TB was also found to increase with smoking, with a significant dose–response trend according to duration of smoking ($P < 0.001$), as well as with alcohol intake and drug use. Drinking tea in small groups of adults ('attaya') was not associated with the risk of TB. The presence of a BCG scar appeared protective against TB. HIV infection, history of worm infection, and recent treatment of worms were found to increase the risk of TB, but there was no effect of history or treatment of asthma. Finally, TB was associated with diabetes and anaemia, with a significant linear trend for decreasing levels of haemoglobin ($P < 0.001$).

A multivariable model was then constructed, based on the results of the univariate analysis. The inclusion of age-group as a categorical variable in the model did not change the effect of the other variables, indicating that there was no residual confounding of age. The haemoglobin variable was not kept in the model, as its inclusion dramatically reduced the number of pairs on which to perform the analysis. Former history of TB was also not included in the model, being on the causal pathway to TB. A total of 601 matched pairs of cases and household controls were available for analysis (Table 3). TB was found to be associated with male sex, family history of TB, HIV infection, and smoking, with a persistent dose–response effect according to duration of smoking.

Investigation of environmental factors

A total of 816 matched case–community control pairs were available for the analysis (Table 1). Environmental factors were investigated using a wide range of variables collected at the household level (Table 4). The risk of TB increased with the number of households in the compound, and with the number of persons in the household. More particularly, the risk increased with the number of adults in the household (*P*-value for linear trend <0.01) although TB was not associated with the number of persons per room in the household. The risk of TB increased if houses were built with mud-brick compared with cement walls, and if the floor was made of earth/soil rather than cement, but these effects were not statistically significant. The absence of a ceiling in the house was protective against TB. The risk of TB was not associated with the number of windows in the house. Variables assessing utilities and hygiene in the household (water source, electricity, presence of latrines, and waste disposal) were not associated with TB.

Table 3 Host related factors for TB: comparison of TB cases and household controls (multivariate analysis) ($n = 601$ pairs)

Variable	Controls	Cases	OR	95% CI	P^a
Sex					
Female	317 (53)	180 (30)	1		<0.001
Male	284 (47)	421 (70)	1.64	1.23–2.17	
Family history of TB					
No	499 (83)	458 (76)	1		
Yes	102 (17)	143 (24)	2.03	1.33–3.10	0.007
HIV infection					
Negative	556 (93)	533 (89)	1		
Positive	45 (7)	68 (11)	2.14	1.23–3.73	0.006
Smoking					
Never	477 (79)	333 (55)	1		
Past	27 (4)	55 (9)	1.82	1.05–3.15	
Current	97 (16)	213 (35)	2.54	1.77–3.66	<0.001

[a] *P*-value for likelihood ratio test.

As observed with household controls (see above), the risk of TB increased with a reported family history of TB. More specifically, the risk increased with the number of persons in the household having had TB in the past (*P*-value for linear trend <0.001). Based on further data collected in The Gambia and Guinee Conakry (data were not available for Bissau), it was found that the risk of TB was even higher if the former TB case was among closely linked family members (father, mother, son, daughter, brother, or sister) than among more remote family members (OR: 1.60, 95% CI 0.62–4.18), although this effect was not statistically significant (data not shown).

At an individual level (Table 4), the risk of TB was higher in singles than in married individuals. Skilled manual workers and farmers were the most at risk of TB compared with unskilled manual workers. There was no association with religion, years of schooling, and the type of school (secular vs koranic). The risk of TB was not affected by ownership of the house by the case/control or his/her family. There was no association either with ownership of specific items or with the presence of animals in the household.

A multivariate model was then constructed, including variables of interest that showed a statistically significant association with TB both at the household and individual level, adjusting for sex and HIV infection (Table 5). The risk of TB was found to be associated with marital status, family history of TB, number of adults in the household, and ownership of the house by the case's family.

Combined host and environmental factors

Finally, in order to assess together the effect of host and environmental factors, a model was built including in the above model host-related variables that were found to have an effect in earlier analyses (see Investigation of host-related factors), using the case-community control pairs ($n = 688$ pairs) (Table 6). The risk of TB was found to be higher in males than in females. Among host-related factors, not surprisingly, TB was associated with HIV infection. History of asthma appeared strongly protective against TB in this population. Smoking was consistently found to increase the risk of TB, with a significant dose–response effect according to duration of smoking. Among social and environmental factors, family history of TB, marital status, number of adults in the household, and ownership of the house remained independent risk factors for TB.

In order to evaluate a possible country effect, we tested in the multivariate model for a possible interaction of each variable with country. No interaction was found for sex, smoking, HIV infection, marital status, family history of TB, or ownership of house, which showed a consistent effect on TB throughout study sites. However, there was an interaction between number of adults and country, the effect on the risk of TB being higher in Bissau (OR: 6.19, 95% CI 2.25–16.96) than in Conakry

Table 4 Environment risk factors for TB: comparison of TB cases and community controls (univariate analysis)

Variable	Total no. of pairs	Controls *n* (%)	Cases *n* (%)	OR (95% CI)	*P*-value
Demographic and household related factors					
Number of HHs[a] in the compound					
1	816	231 (28)	209 (28)	1	
2–4		431 (53)	347 (42)	0.95 (0.72, 1.25)	
>4		154 (19)	260 (32)	2.25 (1.61, 3.15)	<0.001
Number of people in HH					
1–5	813	265 (33)	264 (32)	1	
6–10		344 (42)	274 (34)	0.81 (0.64, 1.03)	
>10		204 (25)	275 (34)	1.39 (1.07, 1.82)	<0.01
Number of adults in HH					
1–5	813	203 (25)	176 (21)	1	
6–10		356 (44)	298 (37)	1.40 (1.11, 1.76)	
>10		254 (31)	339 (42)	2.85 (1.88, 4.29)	<0.001
Persons per room (ppr)					
<1	746	35 (5)	31 (4)	1	
1–2		367 (49)	345 (46)	1.07 (0.64, 1.82)	
>2		344 (46)	370 (50)	1.26 (0.73, 2.16)	0.4
Family history of TB					
0	813	772 (95)	676 (83)	1	
1 member		38 (4.6)	100 (12)	2.90 (1.96, 4.29)	
>1 member		3 (0.4)	37 (5)	13.37 (4.10, 43.61)	<0.001
Walls					
Cement	567	292 (52)	279 (49)	1	
Mudbrick/other		275 (48)	288 (51)	1.54 (0.92, 2.57)	0.09
Floor					
Cement	1132	517 (91)	505 (89)	1	
Mud, earth		49 (9)	61 (11)	1.32 (0.86, 2.01)	0.2
Ceiling					
Yes	741	327 (44)	352 (47)	1	
No		414 (56)	389 (53)	0.79 (0.63, 1.00)	0.05
Number of windows					
0	816	85 (10)	104 (13)	1	
1		619 (76)	608 (74)	0.73 (0.52, 1.01)	
>2		112 (14)	104 (13)	0.71 (0.47, 1.09)	0.11
Water					
Tap	751	121 (16)	146 (20)	1	
Well		497 (66)	491 (65)	0.86 (0.65, 1.14)	
Other		133 (17)	114 (15)	0.74 (0.41, 1.27)	0.2
Electricity					
Yes	741	352 (47)	378 (51)	1	
No		389 (53)	363 (49)	0.78 (0.58, 1.03)	0.07
Latrines					
Yes	751	690 (92)	684 (91)	1	
No		61 (8)	67 (9)	1.14 (0.7, 1.70)	0.6
Waste					
Inside compound	581	343 (59)	339 (58)	1	
Outside		238 (41)	242 (42)	1.07 (0.74, 1.53)	0.3

Table 4 continued

Variable	Total no. of pairs	Controls *n* (%)	Cases *n* (%)	OR (95% CI)	*P*-value
Socioeconomic factors					
Marital status					
Married	805	466 (58)	388 (48)	1	
Single		276 (34)	358 (44)	1.92 (1.48, 2.46)	
Widowed/divorced		63 (8)	59 (7)	1.13 (0.75, 1.71)	<0.001
Occupation					
Unemployed	807	206 (26)	192 (24)	1.20 (0.86, 1.67)	
Unskilled manual		243 (30)	184 (23)	1	
Farmer		6 (1)	19 (2)	5.78 (1.89, 17.67)	
Skilled manual		185 (23)	255 (32)	1.91 (1.44, 2.54)	
Non-manual		136 (17)	130 (16)	1.21 (0.85, 1.71)	
Professional		31 (4)	27 (3)	1.20 (0.69, 2.10)	<0.001
Religion					
Muslim	794	593 (75)	604 (76)	1	
Christian		140 (18)	124 (16)	0.80 (0.55, 1.16)	
Other		61 (8)	66 (8)	0.98 (0.56, 1.72)	0.41
Schooling					
No	800	309 (39)	310 (39)	1	
1–5 years		123 (15)	133 (16)	1.08 (0.79, 1.46)	
>5 years		368 (46)	357 (45)	0.96 (0.76, 1.21)	0.8
Ownership of house					
Yes	792	517 (65)	511 (65)	1	
No		275 (35)	281 (35)	1.04 (0.83, 1.30)	0.7
Ownership of selected items[b]					
0	736	75 (10)	86 (12)	1	
1–3		507 (69)	460 (62)	0.80 (0.57, 1.12)	
>4		154 (21)	190 (26)	1.16 (0.79, 1.72)	0.40
Presence of animals					
Yes	751	352 (47)	327 (44)	1.16 (0.93, 1.45)	0.1
No		399 (53)	424 (56)	1	

[a] HH = household.

[b] Selected items = fan, radio, bicycle, fridge, TV, motorbike, aircondition.

(OR: 3.15, 95% CI 1.25–7.94) and in The Gambia (OR: 1.99, 95% CI 1.05–3.77) (*P*-value for interaction <0.01). The effect of history of asthma was consistent throughout sites, but strongest in The Gambia. Finally, socioeconomic variables showed variable directions of effect according to countries, reflecting the complexity of the situation, but the effect of ownership of house was consistent in the three sites.

Discussion

The present study is one of the first to examine risk factors of TB consistently in a large sample and in a multicountry design, allowing the investigation of the respective effects of these factors and their consistency between countries.

Two types of controls were recruited in the study. The recruitment of household controls was based on the assumption that the effect of potential host-related risk factors would be best estimated in situations where the effect of environmental factors could be controlled for. Thus, it was expected that variations in the risk of TB observed with given variables would truly reflect the effect of these variables for a given environment.

As recruitment of community controls was difficult in the absence of a sampling frame (street address, postcode, telephone number, and recent census enumeration), we decided to select control households by choosing a random direction from the case's home and visiting the fifth dwelling on the right.[5] The nature of this sampling process for controls means that households, rather than persons, were selected with equal probability. This was considered appropriate, as community controls were selected mainly for the evaluation of environmental risk factors. However, a person in a small household would have had a higher probability of selection as a

Table 5 Environment (household and socioeconomic) factors for TB—comparison of TB cases and community controls; multivariate analysis (n = 690 pairs)

Variable	Controls n (%)	Cases n (%)	OR[a]	95% CI	P[b]
Marital status					
Married	402 (58)	331 (48)	1		
Single	240 (35)	313 (45)	1.63	1.19–2.22	
Widowed/divorced	48 (7)	46 (7)	1.41	0.85–2.32	0.006
Family history of TB					
No	622 (90)	526 (76)	1		
Yes	68 (10)	164 (24)	3.25	2.31–4.57	<0.001
Number of adults in HH[c]					
1–5	465 (67)	390 (57)	1		
6–10	191 (28)	217 (31)	1.40	1.05–1.85	<0.001
>10	34 (5)	83 (12)	2.67	1.64–4.34	
Ownership of house					
Yes	453 (66)	444 (64)	1		
No	237 (34)	246 (36)	1.40	1.05–1.86	0.019

[a] Adjusted for sex and HIV infection.

[b] P-value for likelihood ratio test (LRT).

[c] HH = household.

Table 6 Combined environmental and host-related factors for TB—comparison of TB cases and community controls; multivariate analysis (n = 688 pairs)

Variable	Controls n (%)	Cases n (%)	OR	95% CI	P[a]
Sex					
Male	363 (53)	461 (67)	1.43	1.05–1.95	0.022
Female	325 (47)	227 (33)	1		
HIV infection					
No	640 (93)	607 (88)	1		
Yes	48 (7)	81 (12)	2.07	1.33–3.25	0.001
Smoking					
Never	163 (24)	239 (35)	1		
Past	35 (5)	61 (9)	1.53	1.11–2.10	0.003
Current	490 (71)	388 (56)	2.03	1.22–3.39	
History of asthma					
No	672 (97)	683 (99)	1		
Yes	16 (3)	5 (1)	0.28	0.09–0.84	0.015
Marital status					
Married	400 (58)	330 (48)	1		
Single	240 (35)	312 (45)	1.67	1.21–2.30	
Widowed/ divorced	48 (7)	46 (7)	1.48	0.89–2.47	0.004
Family history of TB					
No	620 (90)	524 (76)	1		
Yes	68 (10)	164 (24)	3.24	2.29–4.59	<0.001
Number of adults in HH[b]					
1–5	463 (67)	389 (57)	1		
6–10	191 (28)	216 (31)	1.37	1.03–1.82	<0.001
>10	34 (5)	83 (12)	2.80	1.71–4.57	
Ownership of house					
Yes	451 (66)	442 (64)	1		
No	237 (34)	246 (36)	1.42	1.07–1.90	0.016

[a] P-value for likelihood ratio test (LRT).

[b] HH = household.

community control than a person in a large household. In order to account for this potential bias, we did control for household size in the multivariate analysis.

Recall bias occurs in case–control studies if patients remember past exposures differently from controls. In this study, recall bias might have led to the underestimation of the effect of intercurrent disease (asthma and worm infection), as sick persons are usually more likely to remember a pathological event than healthy persons. For that reason, we limited our question on concomitant disease to a short recall period (1 year), and differentiated between history and treatment of given diseases.

Another concern in case–control studies is that the disease may affect exposure, so the results could in fact be a sign of reverse causality. This could be the situation with smoking, as, in the sites of the study, health workers strongly advise newly diagnosed TB cases to give up this habit. For that reason, we collected information on the duration of smoking, in order to differentiate past from current smoking, so reverse causality is unlikely to explain the findings.

The observed association of TB with male sex is in agreement with what has been reported in most countries in Africa, where notification rates are higher for men than for women.[6,7] Whether the male excess among the study population reflects a selective under-reporting or under-diagnosis of female patients or a true background sex difference is difficult to assess.[8] There are considerable sex differences with regard to stigma and its social consequences, which may result in differential health-seeking behaviour and access to care between males and females.[9,10] However, the consistent effect of male gender observed, both with household and community controls and throughout the sites, suggests that selective under-diagnosis relating to gender is unlikely. Of note, a genome-wide linkage study searching for regions of the human genome containing TB susceptibility genes suggested a linkage between regions of the chromosome X and TB, with a lod score of 1.77, which could contribute to the excess of TB in males in many populations.[11]

Smoking results in histological changes in the lower respiratory tract, including peribronchial inflammation, fibrosis, vascular intimal thickening, and destruction of alveoli.[12] This leads to alterations in the epithelial function, such as reduced ciliary activity, decreased clearance of inhaled substances, and abnormal vascular and epithelial permeability. In this study, cigarette smoking was an independent risk factor for TB, with a

clear dose–response effect with duration of smoking. These results are consistent with those reported in two case–control studies carried out in Spain and in India, where a similar dose-dependent association between tobacco smoking and pulmonary TB was reported.[13,14] Our findings thus support the hypothesis of an increased vulnerability of smokers to the infection and development of TB, most probably owing to patho-physiological changes in the lungs induced by chronic smoking.[12,13] As smoking is becoming an increasing public health problem in resource-poor countries, especially in the younger age groups, these results reinforce the need to take appropriate public health measures, following the recommendations contained in the WHO Framework Convention on Tobacco Control, issued in 2003 by the WHO.[15] This matter should also be addressed in TB control programme policies, and TB control staff should be trained in providing advice to TB patients and their relatives on the cessation of smoking.

Since the start of the pandemic, HIV infection has emerged as the most important risk factor for the development of TB in individuals infected with *M. tuberculosis*.[4] According to WHO, ~30% of TB cases arising among the 15–49-year-old adults in sub-Saharan Africa are attributable to HIV,[6] and a continuous 10% per year increase in TB is projected in countries most severely affected by HIV infection.[16] The major factors contributing to the HIV associated TB epidemic in Africa are the high risk of reactivation of latent TB infection in HIV infected persons and the high risk of progressive TB disease owing to HIV infection, associated with the high TB transmission rate in the community. Therefore, it is essential to include HIV infection as a risk factor when trying to identify the role of other factors on the risk of developing TB.[17]

The presence of a BCG scar was not independently associated with protection against TB. The sensitivity of scar reading is extremely variable, and BCG scar size has been shown to depend on vaccine strains and doses, prior tuberculin sensitivity, and age.[18] A study in Malawi showed that BCG scar was a highly sensitive indicator of vaccination status when vaccine was properly handled and given at over 3 months of age, but in infants <1 month of age vaccinated in health centres, sensitivity of BCG scar had declined to <80% by 4 years post-vaccination.[19] According to the authors, this low sensitivity may be attributable to vaccinations being carried out under non-optimal health centre conditions—which is likely to be the situation in the three sites of this study, where BCG vaccinations are given at birth or first contact with health services. However, it must be noted that our study was not set up to assess the efficacy of BCG in the study sites, but our data are consistent with others reporting an absence of a relationship between BCG scar and protection against TB in adults in Africa.[20]

We observed a consistent effect of former experience of TB within the household, and this effect increased with the number of persons who had TB in the past. Furthermore, there was some evidence that this effect was higher when the former TB case was in close family link with the index TB case, as compared with unrelated household members. We showed earlier that, within the households of TB cases, the risk of TB infection increased with social proximity to the case, and that this effect was persistently higher in first-degree than in more distant relatives.[21] This clustering of TB within families, already noticed by epidemiologists decades ago,[22,23] could reflect not only the facility of transmission within the household, but also a genetic contribution to the susceptibility to TB.[24] This aspect has been investigated in the present study[25] and results from combined case–control and linkage analysis have so far showed that vitamin D receptor variants might have an impact on susceptibility to TB.[26]

We found that the risk of TB was associated with the number of adults in the household. Data were consistent across the three countries, with a stronger effect in Bissau, probably related to the particular housing structure in that country, with all adults sharing a single airspace. Classically, studies have measured crowding as the density of persons per room in a given household.[27–29] The fact that we did not find an association between TB and the number of persons per room, but found an independent association between TB and the number of adults in the household is probably related to the wide mobility of persons within the household, polygamy, as well as to the variability of housing within the sites.

Adult crowding reflects the increased likelihood of coming into contact with persons excreting the bacilli in crowded environments, but is also a marker of socioeconomic status (SES). TB has indeed always been associated with poverty. In industrialized countries, TB was classically associated with poor living conditions.[29–33] However, few studies were conducted in resource-poor countries, to investigate the effect of socio-economic factors on TB and their results were inconclusive: while some studies found that the risk of TB was higher in poor living areas,[34,35] others failed to show an association between low SES and active TB in adults,[36] or even showed a reverse association.[17]

SES is difficult to measure, and there are no uniform criteria to assess it. Former studies conducted in industrialized countries to evaluate the effect of poverty on the risk of TB have been heavily dependent on the definition of specific indices and on the methodological design used.[2] Most of these were ecological studies based on the measurement of SES indices at the population level,[28,37–39] but few were based on an assessment of SES at the individual level.[32,40] In addition, indicators developed in the north might not be appropriate for the south, owing to socioeconomic and cultural differences.[2] In the present study, we collected information on a range of variables expected to reflect SES. Several of them showed some degree of association with TB in univariate analysis, but they did not have an independent effect on the risk of TB in multivariate analysis, when adjusting on main demographic variables, showing probable correlation. Information on income was difficult to obtain, owing to the fact that income-generating activities were frequently carried out within the 'informal' economic sector or were highly seasonal and variable in time. In addition, it was difficult to assess whether the income of the case/control would indeed reflect the overall income of the household. However, ownership of the house by the case's family appeared to be a consistent marker of SES throughout study sites.

Marital status similarly reflects both demographic and SES of individuals. In West Africa, widowed and divorced persons, especially women, rely heavily on family solidarity, and in the absence of this solidarity, may experience severe socioeconomic difficulties. Single persons are usually younger than married

persons and have a different lifestyle, especially males, who often migrate to towns in search of a job where they frequently live alone or with friends. Thus, in Bissau, being single and living alone was an independent risk factor for TB.[41]

Subjects with TB were less likely to report a history of asthma than community controls. A putative link between exposure to mycobacteria and a decreased risk of atopic disease was suggested in a study of Japanese children in whom strongly positive tuberculin responses in early life were associated with a reduced risk of asthma in later childhood.[42] In an ecological study carried out in 23 industrialized countries, TB notification rates were inversely associated with lifetime prevalence of wheeze and asthma.[43] These findings are consistent with the hypothesis that natural exposure to *M. tuberculosis* in childhood may have a role in inhibiting atopy. It has been shown that mycobacteria elicit a Th1 immune response in humans leading to the production of IL-12, IFNγ, and TNFα,[44] which has been shown to cross-inhibit Th2 responses.[45] Thus, it is possible that mycobacterial exposure decreases the development of atopy through the inhibition of Th2 immune mechanisms, which is consistent with both the above epidemiological findings and our earlier findings of a high Th1 activity in exposed household controls.[46]

In conclusion, this combined analysis carried out in three countries in West Africa confirmed the multifactorial aspect of TB disease, with host-related factors interacting with the environment to contribute to the overall phenotype. Findings of the study were presented and discussed with NTCP staff in the three countries. This led to recommendations for the improvement of TB control with the identification of specific targets, such as enhanced health education on TB and its risk factors and improved case-finding activities within the families of TB cases.

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