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## Assessment and evaluation of contact as a risk factor for tuberculosis in rural Africa

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### Summary

**Setting**—Rural district in Malawi.

**Objective**—To determine the effect of inaccurate recall on estimates of the proportion of tuberculosis cases attributable to contact with identifiable prior cases.

**Design**—Case-control study of laboratory-confirmed tuberculosis cases and community controls, comparing family, household and area contacts identified from a database of tuberculosis cases with those named at interview. Estimation of prior contact as a risk factor for tuberculosis and identified factors associated with being a named contact.

**Results**—95% of named contacts were known tuberculosis cases. The proportion of total identified contacts who were named at interview was 75%, similar for cases and controls. Cases were twice as likely as controls to identify prior contacts. Adding database information did not affect odds ratios, but increased the proportion of tuberculosis cases attributable to prior contact. Smear-positive, male, and HIV-negative tuberculosis patients were more likely to be named by subsequent cases. Identifiable recent contact with known smear-positive cases accounted for 12.5% of the tuberculosis burden.

**Conclusions**—Reporting of putative source contacts showed little evidence of recall bias and gave estimates of the relative risk of tuberculosis associated with identifiable contact. The lower likelihood of HIV-positive cases being named as contacts may reflect reduced infectiousness.

### Keywords

Tuberculosis; Contact; Malawi; Epidemiology; HIV

## INTRODUCTION

Although close contact is a well recognised risk factor for tuberculosis, the proportion of tuberculosis cases found attributable to identifiable contact with other cases is generally low<sup>1,2</sup>. This proportion can be estimated through traditional case-control studies, asking about contacts, or by molecular epidemiological studies in which cases with shared DNA-fingerprint patterns (“clusters”) are investigated. Estimates in sub-Saharan Africa of the proportion of “clustered” cases with identifiable links range from 11-27%<sup>3,4</sup>. It is higher in low incidence settings, but still under 50%<sup>5-7</sup>.

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Both methods rely on potentially inaccurate patient recall. Exposures to cases may be unknown or forgotten, or individuals with other illnesses may be reported. Recall bias encourages more complete reporting by cases than controls, overestimating relative risks.

The Karonga Prevention Study (KPS) in northern Malawi provides a unique opportunity to compare contacts recalled by cases and community controls with those identifiable from a population database (created from two total population surveys and subsequent large studies of leprosy, tuberculosis and HIV), and to compare the results from independent data sources. We also investigated the factors associated with tuberculosis cases subsequently being identified as contacts, and high risk contacts.

## METHODS

Karonga district has a rural population of 240,000 with adult HIV prevalence of 13%<sup>8</sup>. Total population surveys were conducted in the 1980s and, since 1986, screening for tuberculosis has occurred during all studies and amongst patients presenting at health facilities. Sputum and other specimens are examined microscopically and cultured on site, with species identification done in the UK<sup>1</sup>. Tuberculosis cases are recorded in the project database.

From 1996-2001, Karonga residents aged 15+ years with a first episode of laboratory-confirmed tuberculosis were included in a case control study<sup>1</sup>. Cases (or relatives of those who had died, left the district, were minors or very ill) and an appropriate informant from their household were asked to provide consent and, if they did so, were interviewed.

Controls were frequency-matched by age, sex and area to the distribution of tuberculosis cases using a field based random sampling scheme<sup>9</sup>. Those with current or previous tuberculosis were excluded.

Cases and controls were asked if they knew of family, past or current household members, or other people who had had tuberculosis within the last five years, irrespective of their perception of risk. Whether or not the individual had contact with the patient during their illness was ascertained and those with no contact were excluded. From 1998 onwards, the household head and other senior members were asked about the individual's relationship and contact with tuberculosis cases to maximise recall, also improving comparability between cases and controls despite different initial interview settings. The term "contact" refers to an individual as a putative source of infection.

Cases and controls were offered HIV testing with pre- and post-test counselling by trained staff<sup>8,10</sup>.

All study participants were assigned identity numbers and their parents identified. At the time of this study most district residents aged 10+ had been previously surveyed. At home visits, household numbers and accurate map grid references were assigned. For the purposes of analysis, the district is divided into "areas" based on latitude and urbanisation. Genetic, household, and geographical links between any two people could be established. Couples with children in the district are identified as "co-parents".

Contacts identified at interview were categorised as family, household, neighbour, or other. Information on bedroom-sharing or nursing a TB case was recorded from 1998.

Database classification included first degree relatives and spouses as family contacts, and assigned as household contacts those resident in the same household as a tuberculosis patient. An individual living within 50 metres of a tuberculosis patient was a "neighbour".

Contacts were grouped into “household”, “close family but not household”, “neighbour” and “other”.

Reported and database-identified contacts were compared. Cases (or controls) could name multiple contacts, and contacts could be named by multiple individuals.

For subsequent analyses each case and control was included only once. Case-control data were analysed to assess the importance of at least one family, household or neighbourhood contact, adjusted for potential confounders (age, sex, area, HIV-status). Separate analyses were performed with interview and database data, and for “all” contacts and for those with smear-positive disease.

The database of tuberculosis patients was analysed to determine which characteristics affect subsequent identification as a contact by an incident case or control.

The proportion of tuberculosis attributable to contact (the population attributable fraction) was calculated;

$$PAF = P_{\text{cases}} ([RR - 1] / RR)$$

where  $P_{\text{cases}}$  is the prevalence of exposure to prior contacts amongst cases and RR is represented by the adjusted odds ratio for the association of tuberculosis with exposure to prior contacts<sup>11</sup>.

Approval for the study was granted by the Malawi National Health Sciences Research Committee and the Ethics Committee of the London School of Hygiene and Tropical Medicine.

## RESULTS

Data on 598 tuberculosis cases (73 with extra-pulmonary TB) and 992 controls are included. No tuberculosis patients, and fewer than 10 controls refused to be interviewed. HIV results were available on 478/598(80%) cases and 859/992(87%) controls.

Amongst cases, 361(60%) did not name any contacts, 171(29%) named one and 66(11%) named 2-6. The corresponding figures for controls were 743(75%), 192(19%) and 57(6%).

In 273/325(84%) of case-contact pairings, the contact was said to have been treated in Karonga, and 257(94%) were confirmed from the database. Of the remainder, 16/52 (31%) were confirmed as tuberculosis. Of the 273 on the database, 184(67%) were recorded as having had smear-positive pulmonary tuberculosis.

Results for the contacts named by controls were similar. Of 318 control-contact pairs, 280(88%) were said to have been treated in Karonga, and 269(96%) were confirmed. Of the remainder, 12/38(32%) were confirmed. Of the 281 on the database, 156(56%) had smear-positive pulmonary tuberculosis.

From the database we identified 151 prior contacts for cases for the same time period (60 household, 67 close family/not same household, 24 neighbours), and 154 prior contacts for controls (29 household, 54 close family/not same household, and 71 neighbours).

Of the 151 prior contacts of cases identified by the database, 64(42%) went unreported by the patient (20 household, 25 close family but not same household, 19 neighbours). For controls, the 154 data-base identified contacts included 90(54%) unreported (6 household,

23 close family but not same household, and 61 neighbours). Table 1 shows the numbers of case-contact and control-contact pairs, according to how the contact was ascertained, for prior exposures with confirmed, smear-positive pulmonary tuberculosis. Including exposures with smear-negative culture positive cases gave similar results (numbers too small for statistical comparison). Overall 227/302(75%) of all (reported and/or database-identified) family, household and neighbour contacts were reported, similar for cases (79%) and controls (71%,  $p=0.12$ ). There was no evidence that the relationship between the database-derived and reported contacts varied by age, sex or HIV-status of the case or control.

A case-control analysis based on contacts identified through reporting was compared with an analysis based on database-identified contacts, to further assess reporting bias (Table 2). Analyses were restricted to contacts with smear-positive disease. There were variations between the odds ratios, however these were not statistically significant and were not consistently higher for reported compared to database-derived contacts.

Overall, 7%(229/3264) of individuals diagnosed and/or registered with tuberculosis in Karonga district during 1992-2001 were named as prior contacts by at least one index case (Table 3). Restricting to the 592 cases diagnosed during 1996/1997 with a complete 5 year "follow up", to allow equal opportunity to be named by a subsequent case, 75(13%) were named.

The percentage named by a case varied by tuberculosis type: 11% of confirmed smear-positive pulmonary tuberculosis, 6% of confirmed smear-negative pulmonary tuberculosis, 3% of unconfirmed pulmonary tuberculosis (including "smear-positive" cases with single scanty smears) and 5% of extra-pulmonary tuberculosis. Overall the percentage named varied little by sex, but among confirmed, smear-positive tuberculosis patients, male patients were more likely to be named as prior contacts by an index case than were female patients (12.5%(86/687) vs. 9.5%(64/674),  $p=0.06$  controlling for diagnosis year). This association was not seen in controls; (10.4% of females compared to 9.5% of males,  $p=0.57$ , for smear-positive cases).

HIV-positive tuberculosis patients diagnosed in 1992-2001 were less likely than HIV-negative patients to be named as a contact of a case, both overall (7.0%(70/994) vs 12.2%(62/508)  $p<0.001$ ), and after restriction to confirmed, smear-positive pulmonary cases (10.0%(45/448) vs 15.8%(47/298)  $p=0.02$ ). These differences remained significant (and became more pronounced) when likelihood of being named as a household contact only was examined, and did not change when adjusted for degree of smear positivity. Weaker trends were seen for the contacts of controls [10.5%(104/994) of HIV-positive vs 11.4%(58/508) of HIV-negative tuberculosis patients ] overall, and [10.5%(47/448) vs 14.1%(42/298)  $p=0.13$ ] after restriction to confirmed, smear-positive pulmonary patients.

Spouses were named as prior contacts by 30/598(5.0%) cases and 10/992(1.0%) controls; 15 and 3 were smear-positive respectively, giving an OR of 5.3 (CI 1.3-22.3, adjusted for the age, sex, area and HIV status of the case), for the association of smear-positive spousal contact and tuberculosis. Twelve of the 15 index cases who had spouses with smear-positive tuberculosis were women, of whom 9 were HIV-positive. Bedroom-sharing, or nursing a prior contact was reported by 55/423(13%) cases and 46/990(4.6%) controls. For 28 cases and 11 controls the contact was smear-positive, giving an OR, adjusted for the age, sex, area and HIV status of the case of 4.8 (2.0-11.2). Among those who reported spousal contact, and were asked about nursing, 17/21(81.0%) of cases and 9/10(90.0%) controls had also nursed spouses.

PAFs were lower when restricted to smear-positive contacts, and higher when database and interview data were combined (Table 4). Overall 12.5% of tuberculosis was attributable to prior contact with a smear-positive case. The PAF for prior contact with a spouse with smear-positive tuberculosis was 2.0%(0.6-2.4), and for nursing or bedroom-sharing was 5.2%(3.3-6.0).

## DISCUSSION

Successful active case finding or the success of a policy of isoniazid preventive therapy in contacts of cases is related to the proportion of the tuberculosis in the population that is attributable to identifiable contact. Interpreting contact histories may give inaccurate estimates because of recall bias, missed contacts, and lack of knowledge of who has tuberculosis. This paper uses long term epidemiological information on the population and on tuberculosis cases to determine the proportion of named contacts who had confirmed and smear-positive tuberculosis; and to quantify recall bias.

A very high proportion (95%) of named prior contacts had tuberculosis confirmed from our database. This was similar for cases and controls, suggesting that validity of recall was high and that there was little over-reporting of other sick individuals by cases in a country with a medium burden of tuberculosis. Two thirds of the named prior contacts of the cases had had smear-positive disease.

The proportion of all identified prior contacts named in the interviews was similar for cases and controls (Table 1). The similarity of odds ratios derived from interview data and from the database also suggests recall bias was small in this study.

Restricting the analysis to smear-positive contacts increased odds ratios slightly for the contact associations, as expected, since smear-positive cases are more infectious. Smear status was unknown for those contacts not found in the database, so the proportion of cases with smear-positive contacts (and hence the PAF) is underestimated. The estimate of the PAF using all contacts is higher, as the extra contacts outweigh the lower estimates of the odds ratio. The best estimate of the proportion of tuberculosis cases attributable to an identifiable exposure to smear-positive case in the previous 5 years is 12.5%.

Contact histories are inevitably incomplete so these data provide a minimum estimate, although they may be relatively more complete in a community where a long history of tuberculosis studies may mean patients are more identifiable. The database was used to validate reports, but is imperfect. Households are dynamic structures and misclassification occurs. The database is efficient at identifying close relatives, leading to a lower proportion of family contacts being reported than for the other groups (Table 1). In addition some of the database-identified relatives, neighbours and household members may not have actually met during the infectious period. Nevertheless, it is clear, as in other studies<sup>1,2</sup> that a minority of cases are attributable to identifiable recent family or household exposure.

The probability of a tuberculosis patient subsequently being named as a putative source contact by another patient depends partly on infectiousness, given that a more infectious case will lead to a larger number of future cases than will a less infectious case. It will also be affected by social mixing patterns and whether the diagnosis is known and openly discussed, as seems to happen in Karonga. Differences between men and women are probably explained by different social mixing patterns. HIV-positivity could have led to decreased mixing (if patients were sicker) and this is supported by the control data where HIV-positive past cases were less likely to be named by controls. However HIV-positivity is unlikely to affect mixing with close family or household members and the differences by HIV-status in the likelihood of being named (by a case) as a contact, were more marked

when household contact alone was considered. This is consistent with other evidence of reduced transmission from HIV-positive compared to HIV-negative cases 12-14 irrespective of smear positivity, perhaps due to reduced duration of infectiousness, if HIV-positive patients seek treatment or die sooner<sup>13-15</sup>.

Spouses, especially wives, of smear-positive patients were at particularly high risk. In this community, sick men are usually nursed by wives, and sick women return to their families. Compared to men of the same age, young women are more likely to be tuberculin negative and hence at risk of primary disease<sup>16,17,18</sup> and are more likely to be HIV-positive. There was also an increased risk of disease among close relatives of cases compared to other non-household contacts. Though this may be mediated in part by genetic determinants<sup>19</sup>; the effect is probably due largely to closeness of the contact<sup>20,21</sup>.

In conclusion, in this setting, recall of contacts was good, with little evidence of differential recall between cases and controls for recent contacts. The small proportion of smear-positive cases subsequently named as contacts, and the calculated attributable fractions suggest that provision of preventive therapy to all contacts of smear-positive cases could only reduce tuberculosis incidence by 12.5% in this population, possibly more in the long term if tuberculosis with an incubation period longer than 5 years is considered. The proportion in populations where tuberculosis is rare, or social mixing differs, will vary. However household contacts, particularly spouses and carers, have high relative risks, and are easy to target, despite minimal overall impact<sup>4,22,23</sup>. In many countries, tuberculosis inpatients are nursed by relatives (who are thereby additionally exposed to other patients), who could be screened and offered health education and preventive therapy when indicated. This study also confirms findings, using other approaches, that HIV-positive tuberculosis cases transmit *M. tuberculosis* less effectively than HIV negatives, irrespective of smear-positivity.

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TABLE 1

Identification of prior contacts with confirmed smear-positive pulmonary tuberculosis, by nature of contact. All case/control-contact pairs are included.

Nature of contact	Ascertainment	Case		Control		P <sup>1</sup>
		n	%	n	%	
<b>Household</b>	Database only	9	18	3	20	
	Both	27	53	10	67	
	Reported only	15	29	2	13	
	Proportion reported of total	42/51	82	12/15	80	<i>p</i> =0.84
<b>Close family but not household</b>	Database only	12	24	9	26	
	Both	21	43	8	24	
	Reported only	16	33	17	50	
	Proportion reported of total	37/49	76	25/34	74	<i>p</i> =0.84
<b>Neighbour</b>	Database only	10	21	32	30	
	Both	4	8	8	8	
	Reported only	34	71	65	62	
	Proportion reported of total	38/48	79	73/105	70	<i>p</i> =0.22

<sup>1</sup>In addition 74 "other" contacts were identified by 57 cases and 44 by 44 controls. A single contact can be named by more than one case or control

The analysis is little affected by allowing for multiple reporting of contacts as most individuals have only one contact of each type.

<sup>1</sup> comparison of the proportion of total contacts that were reported at interview between cases and controls

TABLE 2

Comparison of case-control analyses of contact as a risk factor for tuberculosis using reported or database-identified contacts. (Analyses restricted to contacts with confirmed smear-positive pulmonary tuberculosis). Each case or control is included only once.

Nature of contact	Cases n=598		Control n=992		Adj OR <sup>1</sup>	95% CI
	N <sup>4</sup>	% <sup>2</sup>	N	%		
ANY incl. not classifiable in db <sup>3</sup>	Reported	25	137	14	2.0	(1.4-2.7)
	Database	68	66	7	1.7	(1.1-2.7)
ANY excl. not classifiable in db	Reported	16	98	10	1.6	(1.1-2.4)
	Database	68	66	7	1.7	(1.1-2.7)
<b>Household</b>	Reported	6	11	1	4.4	(1.9-10.3)
	Database	18	3	14	2.0	(0.8-4.7)
<b>Close family but not household</b>	Reported	33	6	24	2.3	(1.2-4.5)
	Database	42	7	16	5.0	(2.5-10.3)
<b>Neighbour</b>	Reported	32	5	65	0.8	(0.5-1.5)
	Database	13	2	36	0.5	(0.2-1.2)

<sup>1</sup> OR adjusted for age, sex, area of residence, and HIV status of case/control

<sup>2</sup> Percentage with contact

<sup>3</sup> ie including contacts reported who were non-household/close family/neighbour eg acquaintances, colleagues etc.

<sup>4</sup> number reporting a contact

**Table 3**

Likelihood of a TB patient diagnosed in 1992 – 2001 being recognised as a contact by one or more subsequent (index) cases or controls. Each TB patient is included only once for each analysis (recognition by cases or controls).

	Totals	Named by one or more subsequent (index) cases N, %	OR, Adj OR (adj for year of diagnosis)	Named by one or more controls N, %	OR, Adj OR (adj for year of diagnosis)
All	3264	229 7.0%		250 7.7%	
All with complete followup	592	75 12.7%		86 14.5%	
Male (sm +)	687	86 12.5%	ref	65 9.5%	ref
Female (sm +)	674	64 9.5%	0.73 0.72 (0.51-1.02), p=0.06	70 10.4%	1.11 1.04 (0.72-1.51), p=0.82
Smear pos pulmonary	1361	150 11.0%	ref	135 9.9%	ref
Smear neg pulmonary	261	15 5.8%	0.49 0.47 (0.27-0.83), p=0.007	22 8.4%	0.84 0.68 (0.41-1.11), p=0.12
Unconfirmed pulmonary	1012	29 2.9%	0.24 0.25 (0.17-0.39), p<0.001	56 5.5%	0.53 0.49 (0.35-0.68), p<0.001
Extra pulmonary	585	31 5.3%	0.45 0.43 (0.29-0.66), p<0.001	36 6.2%	0.60 0.50 (0.33-0.74), p<0.001
HIV pos (all)	994	70 7.0%	0.54 0.50 (0.34-0.73), p<0.001	104 10.5%	0.91 0.80 (0.56-1.15), p=0.23
HIV neg (all)	508	62 12.2%	ref	58 11.4%	Ref
HIV pos (sm +)	448	45 10.0%	0.60 0.59 (0.38-0.94), p=0.02	47 10.5%	0.71 0.70 (0.44-1.12), p=0.13
HIV neg (sm +)	298	47 15.8%	ref	42 14.1%	Ref

sm + = sputum smear positive

TABLE 4

Proportion of tuberculosis cases attributable to identifiable contact, comparing information from interviews with combined data including information from the database. Results are presented both overall and restricted to contacts with confirmed smear-positive pulmonary tuberculosis. Each case or control is included only once.

Nature of contact	Information from interviews only					Combined data							
	% with 1 contact	Cases n=598	Controls n=992	Adj OR <sup>1</sup>	95% CI	PAF (%)	95% CI	% with 1 contact	Cases n=598	Controls n=992	Adj OR <sup>1</sup>	95% CI	PAF (%)
Any	Smear+	25	14	2.0	1.4-2.7	12.5	7.2-15.8	28	17	1.8	(1.3-2.5)	12.4	6.5-16.8
	All	40	25	2.0	1.5-2.6	19.2	12.7-24.3	44	30	1.8	(1.3-2.3)	19.4	10.1-2.5
Household, close family and neighbour	Smear+	16	10	1.6	1.1-2.4	6.0	1.5-9.3	20	13	1.5	(1.1-2.2)	6.7	1.8-10.9
	All	28	18	1.6	1.2-2.2	10.5	4.7-15.3	34	24	1.5	(1.1-2.0)	11.3	3.1-17.0
Household	Smear+	6	1	4.4	1.9-10.3	4.7	2.9-5.4	7	2	3.9	(1.9-8.0)	5.2	3.3-6.1
	All	11	3	2.7	1.5-4.7	6.6	3.7-8.3	13	4	2.6	(1.6-4.3)	7.7	4.7-9.6
Close family not household	Smear+	6	2	2.3	1.2-4.5	3.1	0.9-4.3	8	3	2.7	(1.5-4.8)	4.8	2.6-6.1
	All	12	7	1.8	1.2-2.8	5.3	1.6-11.7	15	9	1.9	(1.3-2.9)	7.2	3.5-10.0
Neighbour	Smear+	5	7	0.8	0.5-1.5	0.0	0-0.0	7	9	0.6	(0.4-1.1)	0.0	0-0.6
	All	9	10	0.9	0.6-1.4	0.0	0.0-2.6	10	14	0.7	(0.4-1.0)	0.0	0-0.0

<sup>1</sup>OR adjusted for age, sex, area of residence, and HIV status of case/control