INT J TUBERC LUNG DIS 15(6):782–788

doi:10.5588/ijtld.09.0327

Risk of tuberculosis among contacts of isoniazid-resistant and isoniazid-susceptible cases

Tuberculosis Research Centre, Indian Council of Medical Research (ICMR), Chennai, India*

SUMMARY

OBJECTIVE: To compare the risk to household contacts of isoniazid (INH) susceptible and INH-resistant cases of tuberculosis (TB) in a rural community in South India.

METHODS: In all, 5562 contacts of INH-susceptible and 779 contacts of INH-resistant patients and 246 845 persons with no TB case in the home were followed for 15 years, with surveys every 2.5 years comprising radiographic and sputum examination, selective follow-up of high-risk individuals and passive surveillance. If a new case developed, the household members were assigned to the 'INH-susceptible' (n = 7088) or 'INH-resistant' series (n = 526), whichever appropriate. Logistic regression and Cox's proportional hazards model were employed.

RESULTS: The baseline prevalence of tuberculous infection was respectively 70% and 56% in contacts of INH-resistant and INH-susceptible patients ($P < 0.001$), compared to 46% in non-contacts. The incidence of culture-positive TB was respectively 295 and 311 per 100 000, compared to 162/100 000 in non-contacts. The adjusted hazard ratios were 2.4 and 2.0 for contacts of INH-resistant and INH-susceptible patients.

CONCLUSION: The baseline prevalence of tuberculous infection was substantially higher in contacts of INH-resistant than INH-susceptible patients, but the incidence of tuberculous disease over a 15-year follow-up was similar in the two series, and twice as high as in non-contacts.

KEY WORDS: infectivity; INH-resistant TB; risk; contacts; hazard ratios

CONTACTS of tuberculous patients constitute a vulnerable group, and various studies have shown that they have a higher prevalence of tuberculous infection and disease[1–6] than non-contacts. In the 1950s, there were some reports that isoniazid (INH) resistant strains of tubercle bacilli had lowered virulence in guinea pigs[7–10] and monkeys.[11] Subsequent publications suggested that virulence in man also might be lowered; fewer contacts of INH-resistant patients underwent tuberculin conversion over an 18-month period (5.6% of 89) than contacts of INH-susceptible patients (12.1% of 488),[12] and the proportion who developed tuberculosis (TB) was lower in contacts with at least 3 months of exposure to INH-resistant strains (9.7% of 72) than in those without such exposure (15.5% of 161).[13] Both studies were, however, based on relatively small numbers and the contrasts were non-significant ($P > 0.1$). We therefore decided to reinvestigate, in a unique data set, the hypothesis of lower disease incidence due to contact with INH-resistant than INH-susceptible cases of TB.

MATERIALS AND METHODS

A double-blind randomised controlled trial was initiated in 1968 in over 272 179 subjects in rural south India to assess the protective efficacy of bacille Calmette-Guérin (BCG) vaccination.[14] Over the next 30 months, all persons were allocated at random to a placebo, a low BCG dose (0.01 mg) or a high BCG dose (0.1 mg). The main finding of the trial, that BCG had no protective effect in this community, has already been reported earlier,[14–16] as was the finding that household contacts of TB patients had a significantly higher incidence of TB than subjects in the same community with no household exposure to TB.[6] Further analyses were then undertaken to compare the risk of TB to contacts of INH-resistant cases with that for contacts of INH-susceptible cases.

Subjects who, at intake, had a positive smear/culture (n = 2076), an abnormal radiograph (n = 16 633) or no radiograph (n = 209), and contacts of cases with no initial drug susceptibility test results (n = 75), were excluded from incidence analyses. The remaining 253 186 subjects were analysed by type of exposure: those exposed to an INH-susceptible patient at intake (n = 5562), those exposed to an INH-resistant patient at intake (n = 779, including

*This report was prepared by S. Radhakrishnan, Institute for Research in Medical Statistics, Madras Chapter (ICMR), and R. Subramani, Epidemiology Unit, Tuberculosis Research Centre, Chennai, who was responsible for data management and analysis.

Correspondence to: R Subramani, Epidemiology Unit, Tuberculosis Research Centre, Mayor V R Ramanathan Road, Chetput, Chennai 600 031, India. Tel: (+91) 44 2836 9654. Fax: (+91) 44 2836 2528. e-mail: subramanir@trcchennai.in

Article submitted 24 August 2010. Final version accepted 1 December 2010.

326 exposed to highly resistant strains, i.e., minimum inhibitory concentration > 5 μg/ml), and those with no exposure to a TB case at home (n = 246 845 controls). A household was defined as a group of persons living together and sharing food from the same kitchen.

No new household members (by marriage or birth) were included during the trial. If a new case developed during follow-up in contacts of INH-resistant patients or in non-contacts, members of the household were reassigned to the 'INH-susceptible' series (n = 7088) or the 'INH-resistant' series (n = 526), depending on the INH susceptibility status of the new case.

Investigations at intake

All individuals underwent tuberculin sensitivity testing (3 tuberculin unit [TU] purified protein derivative [PPD]-S, 10 TU PPD-B) at intake, and were classified as non-infected or infected.[17] Those aged ⩾5 years were initially screened by mass miniature radiography and subsequently once every 2.5 years. Every village was visited; persons with an abnormal radiograph at the previous round or who had been absent, and those with symptoms, were offered radiography (selective follow-up) once every 10 months. Those with an abnormal radiograph or symptoms had sputum examined for acid-fast bacilli (AFB) and culture for *Mycobacterium tuberculosis*; if the culture was positive, INH susceptibility and identification tests (niacin test, growth at 25°C and para-nitrobenzoic acid/catalase test) were undertaken.

To identify cases occurring between routine surveys, passive surveillance was employed. A TB clinic was established at the local government hospital with a static radiographic unit and sputum collection facilities. Any person reporting there with symptoms suggestive of TB could be examined on any morning. In addition, 10 rural general peripheral health institutions in the area were visited along with a radiographic unit every 2–4 weeks for examination of individuals with symptoms referred by medical officers or private practitioners in the area.

Planned follow-up was 15 years. However, in subjects with an initial induration of >15 mm to PPD-S, who were unlikely to benefit from BCG, follow-up was reduced from 7.5 years onwards to a random sample of one third of those eligible, to lessen the workload. Details have been reported earlier.[15]

Fingerprints were taken were taken from all participants at intake, and from all new cases at diagnosis; the latter were matched with the initial fingerprints to confirm the identity of the case. All cases were prescribed anti-tuberculosis treatment as per National TB Programme guidelines at the time.[14]

The Institutional Ethics Committee of the Tuberculosis Research Centre, Indian Council of Medical Research, approved the trial.

Estimation of incidence

For each 2.5-year period in each of the three series, the population was stratified by sex, age at the start of the risk period (adult, child) and initial infection status (infected, non-infected); the incidence of culture-positive TB was determined for the eight subgroups. To allow for differences in age and sex between periods,[18] and the restrictive follow-up policy adopted after 7.5 years, the incidence in each period was standardised (using the direct method[19]), using the first repeat survey distribution as the standard. The annual incidence was computed from the average of the six incidences.

Due to the non-availability of eligible subjects (with a similar proportion in the three series), sputum could not be collected from 11% in the first and 9% in the second repeat survey, and 3–4% in subsequent repeat surveys. We estimated the number of positive culture results from the relationship between radiographic status at the time and the culture result from those who underwent both examinations. The details have been reported elsewhere.[18]

Statistical methods

From the baseline data on infection, relative risks adjusted for sex and age were estimated using logistic regression.[20] Analysis of variance (ANOVA) was undertaken on standardised incidences, and hazard ratios were estimated using Cox's proportional hazards model,[21,22] with exposure group, sex and PPD-S at intake as variables, age and 'reassignment' from one series to another as time-dependent covariates, and allowing for clustering within households.

Table 1 Comparison of household members in the three exposure groups, according to age, sex and infection status at intake

	INH-susceptible series *n* (%)	INH-resistant series *n* (%)	Control series *n* (%)
Age at intake, years			
0–4	876 (15.7)	129 (16.6)	35 593 (14.4)
5–9	943 (17.0)	140 (18.0)	37 063 (15.0)
10–14	932 (16.8)	136 (17.5)	34 061 (13.8)
15–24	1056 (19.0)	134 (17.2)	39 696 (16.1)
25–34	688 (12.4)	113 (14.5)	36 583 (14.8)
35–44	462 (8.3)	49 (6.3)	27 888 (11.3)
45–54	348 (6.3)	43 (5.5)	19 808 (8.0)
⩾55	257 (4.6)	35 (4.5)	16 153 (6.5)
Total	5562 (100.0)	779 (100.0)	246 845 (100.0)
Mean	19.8	19.0	22.7
Sex			
Male	2533 (45.5)	383 (49.2)	122 581 (49.7)
Female	3029 (54.5)	396 (50.8)	124 264 (50.3)
Infection status at intake			
Not infected*	2444 (43.9)	235 (30.2)	132 400 (53.6)
Infected†	3118 (56.1)	544 (69.8)	114 445 (46.4)

*PPD-S = 0–7 mm; or PPD-S = 8–11 mm with PPD-S–PPD-B < 2 mm.
†PPD-S ⩾ 12 mm or PPD-S = 8–11 mm with PPD-S–PPD-B ⩾ 2 mm.
INH = isoniazid; PPD = purified protein derivative.

Table 2 Prevalence of tuberculous infection in household members, related to the presence of an INH-susceptible or INH-resistant patient at intake

Age, years	Type of household	*n*	TB infection* *n* (%)	RR	Adjusted RR†	95%CI
0–4	No TB case at intake	35 593	1 328 (3.7)	1.0	1.0	
	INH-susceptible patient at intake	876	153 (17.5)	4.7	5.5	4.5–6.6
	INH-resistant patient at intake	129	49 (38.0)	10.2	15.8	11.0–22.7
5–9	No TB case at intake	37 063	5 400 (14.6)	1.0	1.0	
	INH-susceptible patient at intake	943	327 (34.7)	2.4	3.1	2.7–3.6
	INH-resistant patient at intake	140	82 (58.6)	4.0	8.3	5.9–11.6
10–14	No TB case at intake	34 061	10 232 (30.0)	1.0	1.0	
	INH-susceptible patient at intake	932	458 (49.1)	1.6	2.3	2.0–2.6
	INH-resistant patient at intake	136	104 (76.5)	2.5	7.5	5.1–11.2
Total children	No TB case at intake	106 717	16 960 (15.9)	1.0	1.0	
	INH-susceptible patient at intake	2 751	938 (34.1)	2.1	3.0	2.8–3.3
	INH-resistant patient at intake	405	235 (58.0)	3.7	9.9	7.9–12.3
15–29	No TB case at intake	59 475	35 611 (59.9)	1.0	1.0	
	INH-susceptible patient at intake	1 453	1 054 (72.5)	1.2	1.8	1.6–2.0
	INH-resistant patient at intake	198	158 (79.8)	1.3	2.7	1.9–3.8
⩾30	No TB case at intake	80 653	61 874 (76.7)	1.0	1.0	
	INH-susceptible patient at intake	1 358	1 126 (82.9)	1.1	1.7	1.5–2.0
	INH-resistant patient at intake	176	151 (85.8)	1.1	2.0	1.3–3.0
Total adults	No TB case at intake	140 128	97 485 (69.6)	1.0	1.0	
	INH-susceptible patient at intake	2 811	2 180 (77.6)	1.1	1.7	1.6–1.9
	INH-resistant patient at intake	374	309 (82.6)	1.2	2.4	1.8–3.1
Total population	No TB case at intake	246 845	114 445 (46.4)	1.0	1.0	
	INH-susceptible patient at intake	5 562	3 118 (56.1)	1.2	2.3	2.2–2.5
	INH-resistant patient at intake	779	544 (69.8)	1.5	6.3	5.2–7.6

*Defined as PPD-S = 8 –11 mm and PPD-S–PPD-B ⩾ 2 mm; or PPD-S ⩾ 12 mm.
†RR adjusted for sex by logistic regression in individual age groups, and by age group also for total children, total adults and total population.
INH = isoniazid; TB = tuberculosis; RR = relative risk; CI = confidence interval; PPD = purified protein derivative.

RESULTS

Condition at intake

Of the total population of 253 186, 5562 in 1653 households were exposed to an INH-susceptible patient at intake and 779 in 209 households to an INH-resistant patient. The two groups were broadly similar with respect to age and sex (Table 1). However, they were significantly younger than the 246 845 persons in 69 220 households without a TB case; furthermore, the INH-susceptible series had the lowest proportion of males, while the INH-resistant series had the largest proportion infected.

Baseline prevalence of tuberculous infection and disease

Contacts of INH-resistant patients had a consistently higher prevalence of tuberculous infection (70%) than contacts of INH-susceptible patients (56%) and non-contacts (46%); the differences were significant ($P < 0.001$). The adjusted (for sex and age) relative risks were 6.3 in contacts of INH-resistant patients and 2.3 in contacts of INH-susceptible patients (Table 2). The contrasts were more marked in children; the corresponding adjusted relative risks were respectively 9.9 and 3.0. Baseline disease prevalence (adjusted for sex and age), however, was similar, at respectively 21.3% and 21.7%.

Follow-up

Losses occurred over the 15 years of follow-up due to death (1.8%), migration (5.6%) and the restrictive follow-up policy (4.4%). In terms of person-years, the follow-up was similar in the three series in the first 5 years (Table 3). Thereafter, it was slightly poorer in contacts than in the controls. Over the

Table 3 Follow-up achieved in the three exposure groups in each period

Period of follow-up, years	No TB case at home			Contacts of INH-susceptible cases			Contacts of INH-resistant cases		
		Follow-up			Follow-up			Follow-up	
	Subjects *n*	Scheduled py	Achieved %	Subjects *n*	Scheduled py	Achieved %	Subjects *n*	Scheduled py	Achieved %
0–2.5	246 845	617 113	96.3	5562	13 905	96.4	779	1948	95.8
2.5–5	228 609	571 523	95.3	5165	12 913	93.4	713	1783	94.2
5–7.5	211 073	527 683	81.5	4645	11 613	77.4	650	1625	73.3
7.5–10	166 905	417 263	92.9	3473	8683	91.2	464	1160	89.7
10–12.5	148 761	371 903	92.7	3023	7558	91.0	397	993	90.6
12.5–15	130 469	326 173	91.6	2583	6458	90.1	340	850	89.4
Total	246 845	2 831 655	91.8	5562	61 128	90.1	779	8358	88.9

TB = tuberculosis; INH = isoniazid; py = person-years.

Table 4 Additional risk to household contacts from exposure to an INH-susceptible/INH-resistant TB case

Classification of exposure group, type of household	Household members *n**	Person-years of follow up	Emergence of new culture-positive TB cases during follow-up		Relative risk
			n	Incidence /100 000	
At intake					
No TB case at home	246 845	2 600 431	3777	145	1.0
INH-susceptible case at home	5 562	55 064	143	260	1.8
INH-resistant case at home	779	7 434	22	296	2.0
Total	253 186	2 662 929	3942	148	
Taking into consideration new cases that emerged during follow-up					
No TB case at home	246 845	2 555 325	3604	141	1.0
INH-susceptible case at home	12 650	97 105	302	311	2.2
INH-resistant case at home	1 305	10 164	34	335	2.4
Total	260 800	2 662 594	3940†	148	

*As some household members appear in more than one exposure group, the total is larger after shifts in risk categories following the emergence of new cases.
†Excluding two cases whose INH susceptibility status was not determined.
INH = isoniazid; TB = tuberculosis.

entire 15-year period, follow-up was achieved in 89% of contacts of INH-resistant patients and 90% of contacts of INH-susceptible patients, compared to 92% in controls.

Averaged over the six rounds, 73–76% underwent radiograph in the three series, while 93–94% underwent sputum examination.

Risk of developing TB in contacts of TB patients

The observed incidence of culture-positive TB was 145 per 100 000 person-years in household members with no TB case at intake (Table 4), 260 in contacts of INH-susceptible patients (relative risk [RR] = 1.8) and 296 in contacts of INH-resistant patients (RR = 2.0). The corresponding standardised incidence was 165/100 000 in non-contacts, 248 in contacts of INH-susceptible patients, and 258 in contacts of INH-resistant patients; the RRs for the latter two risk groups were similar (respectively 1.5 and 1.6, Table 5). ANOVA showed that the incidence in the two contact series was similar ($P = 0.8$), but was appreciably higher than that in non-contacts ($P = 0.07$).

Cases developing during follow-up and changes in risk group

In all, 3942 new cases of culture-positive TB developed over the 15 years: 3777 in households that had no TB case at intake, 143 in INH-susceptible and 22 in INH-resistant households (Table 4). Of these, respectively 3456, 136 and 18 were INH-susceptible, 279, 6 and 4 were INH-resistant, and 42, 1 and 0 were untested. After the development of a case, the household members were reassigned and the incidence determined. This dropped slightly in the control series, from 145 to 141/100 000 (Table 4), but increased appreciably in the INH-susceptible series (from 260 to 311/100 000) and in the INH-resistant series (from 296 to 335/100 000). The corresponding standardised incidence was similar in the two contact series, 311 and 295/100 000 (Table 5, $P = 0.7$), and was significantly higher than that in non-contacts (162/100 000, $P = 0.002$). Even in initially non-infected contacts, a more informative subset, the incidences in the two contact series were similar, 133 and 120/100 000 ($P = 0.6$).

Table 5 Standardised incidence of culture-positive TB in the three exposure groups in each period

Classification of exposure group, type of household	At risk *n*	Standardised incidence/100 000 of culture-positive TB, by period of follow-up*							Relative risk
		0–2.5 years	2.5–5 years	5–7.5 years	7.5–10 years	10–12.5 years	12.5–15 years	Mean	
At intake									
No TB case at home	246 845	91	126	164	169	210	231	165	1.0
INH-susceptible case at home	5 562	151	204	259	141	304	430	248	1.5
INH-resistant case at home	779	111	367	251	174	466	179	258	1.6
Taking into consideration new cases that emerged during follow-up									
No TB case at home	246 845	91	125	161	164	206	223	162	1.0
INH-susceptible case at home	12 650	272	293	292	237	338	434	311	1.9
INH-resistant case at home	1 305	263	299	273	311	438	183	295	1.8

*Incidence standardised by sex, infection status at intake (not infected, infected) and age (child, adult) at the start of each risk period.
TB = tuberculosis; INH = isoniazid.

In a subset of 505 contacts of highly INH-resistant patients, standardised incidence was 249/100 000, which was not dissimilar to the incidence of 310 in 800 contacts of moderately resistant patients ($P = 0.8$) and 311 in contacts of susceptible patients ($P = 0.8$).

Findings within subsets by sex, age and infection status at intake

In each of six subsets (male, female; adult, child; initially infected, initially non-infected), the hazard ratios (HR) were broadly similar in the INH-susceptible and INH-resistant series ($P \geqslant 0.1$), and consistently higher than in non-contacts (Table 6).

Multivariate analysis with sex, age and tuberculin sensitivity at intake

A multivariate analysis showed that sex, infection status at intake and age had a significant impact on the adjusted HR (aHR; Table 7). The male to female aHR was 2.8 (95% confidence interval [CI] 2.6–3.0). It increased with age, being respectively 2.0, 4.3, 9.1, 13.4, 18.1, 21.4 and 27.0 for subjects aged 5–9, 10–14, 15–24, 25–34, 35–44, 45–54 and ⩾55 years. As regards initial tuberculin sensitivity, the adjusted HR was significantly higher than 1 for all sensitivity groups except 8–11 mm, and increased gradually from 1.9 to 4.0 with the size of the induration. When all prognostic characteristics were allowed for, the HRs were 2.0 for the INH-susceptible series (95%CI 1.7–2.4) and 2.4 for the INH-resistant series (95%CI 1.7–3.4).

Among those non-infected at intake, the standardised incidence was 21/100 000 person-years for female children, 43 for male children, 66 for female adults, and 191 for male adults; the corresponding incidences in the initially infected were respectively 125, 180, 193 and 579. The adjusted HRs were respectively 1.0, 2.0, 3.2 and 8.6 for those non-infected initially, and 6.0, 8.2, 9.8 and 29.1 for those initially infected. Allowing for increase in age during follow-up, these became 1.0, 2.1, 3.7 and 10.9 and 8.3, 12.2, 15.8 and 50.6, respectively (Table 7).

Findings of isoniazid susceptibility testing in new cases emerging during follow-up

In initially non-infected subjects, seven new cases developed in the INH-resistant series, three of whom (43%) were INH-resistant, compared to 5/98 (5%) in the INH-susceptible series (RR = 8.4, $P < 0.01$), and 81/674 (12%) non-contacts. Considering all subjects, the corresponding figures were 10/34 (29%) compared to 15/300 (5%; RR = 5.9, $P \leqslant 0.0001$) and 264/3563 (7%), respectively.

DISCUSSION

The epidemiological impact of INH resistance has always interested public health administrators, but the reported evidence regarding the relative infectiousness of resistant and susceptible strains of tubercle bacilli in humans is not consistent.[23] Snider et al. reported that the risk of infection among contacts of previously untreated patients was not significantly affected by whether the bacilli were susceptible or resistant.[24] Similarly, a study by Teixeira et al. suggested

Table 6 Findings in subsets by sex, age at risk and initial infection status*

Subset	Risk group	Population *n*	Standardised incidence /100 000†	Hazard ratio‡	95%CI
Male	No TB case at home	122 581	241	1.0	
	INH-susceptible case at home	5 946	420	2.1	1.7–2.6
	INH-resistant case at home	632	371	2.3	1.5–3.6
Female	No TB case at home	124 264	83	1.0	
	INH-susceptible case at home	6 704	212	2.0	1.5–2.7
	INH-resistant case at home	673	221	2.6	1.4–4.8
Adult	No TB case at home	140 128	268	1.0	
	INH-susceptible case at home	7 942	489	1.9	1.6–2.3
	INH-resistant case at home	753	516	2.7	1.8–3.8
Child	No TB case at home	106 717	22	1.0	
	INH-susceptible case at home	4 708	25	2.3	1.6–3.4
	INH-resistant case at home	552	3	1.3	0.5–3.5
Infected	No TB case at home	114 445	314	1.0	
	INH-susceptible case at home	5 835	530	1.8	1.4–2.2
	INH-resistant case at home	728	436	2.2	1.5–3.3
Not infected	No TB case at home	132 400	31	1.0	
	INH-susceptible case at home	6 815	133	3.1	2.2–4.4
	INH-resistant case at home	577	120	3.1	1.3–7.1

*The analyses were undertaken after reassigning subjects from one exposure group to another, based on the INH susceptibility status of emerging new cases during follow-up; 4713 subjects who were reassigned and not subsequently tuberculin-tested were assumed to be not infected throughout.
†Estimated within each subset after stratification by two appropriate categories from among sex, age at start of risk period (child, adult) and initial infection status (not infected, infected).
‡Based on Cox's proportionate hazards model with exposure group, sex and PPD-S at intake as variables, and age and 'reassignment' as time-dependent covariates, and allowing for clustering within households.
CI = confidence interval; TB = tuberculosis; INH = isoniazid; PPD = purified protein derivative.

Table 7 Outcome of multivariate analysis

Characteristic	Subjects *n*	Hazard ratio*	95% confidence intervals Lower	Upper
Exposure group				
No exposure to TB case at home	246845	1.0		
Exposed to INH-susceptible case at home	12650	2.0 [2.0]	1.7 [1.7]	2.4 [2.4]
Exposed to INH-resistant case at home	1305	2.4 [1.8]	1.7 [1.2]	3.4 [2.6]
Sex				
Female	129159	1.0		
Male	131641	2.8	2.6	3.0
Age, years				
0–4	36691	1.0		
5–9	38853	2.0	1.5	2.8
10–14	36433	4.3	3.1	6.0
15–24	43213	9.1	6.4	12.9
25–34	38604	13.4	9.0	20.0
35–44	29211	18.1	11.7	28.3
45–54	20799	21.4	13.1	34.8
⩾55	16996	27.0	16.0	45.8
PPD-S at intake, mm				
0–7	121058	1.0		
8–11	19061	1.1	0.9	1.3
12–15	21968	1.9	1.7	2.2
16–19	40740	3.3	2.9	3.7
20–24	39862	4.0	3.6	4.5
⩾25	18111	3.8	3.3	4.3
Clinical risk group†				
Not infected female child	46303	1.0		
Not infected male child	47312	2.1	1.6	2.7
Not infected female adult	28685	3.7	2.8	4.8
Not infected male adult	17492	10.9	8.3	14.4
Infected female child	8521	8.3	5.6	12.3
Infected male child	9841	12.2	8.4	17.6
Infected female adult	48132	15.8	11.0	22.7
Infected male adult	54514	50.6	34.2	74.8

*Based on Cox's proportionate hazards model with exposure group, sex, and PPD-S at intake as variables, age and 'reassignment' as time-dependent covariates, and taking into account clustering within the households.
†Based on tuberculin sensitivity status at intake, sex and age at the start of each risk period. The hazard ratios for the eight clinical subgroups and the three exposure groups (in brackets) are based on Cox's proportionate hazards model, employing clinical risk group and 'reassignment' as time-dependent covariates and taking into account clustering within households.
TB = tuberculosis; INH = isoniazid; PPD = purified protein derivative.

that the prevalence of infection and progression to active TB among household contacts of drug-susceptible and multidrug-resistant TB patients were comparable.[25] On the other hand, Burgos et al. concluded that INH-resistant strains were less likely to produce new drug-resistant cases,[26] a finding in line with their reduced propensity to cluster, as reported in molecular epidemiological studies.[27–29]

Our study has shown that a substantially larger proportion of household contacts of INH-resistant patients had tuberculous infection at intake compared to contacts of INH-susceptible patients. This could be due to more prior transmission, resulting from longer or more frequent exposure to INH-resistant cases, whose treatment response is invariably less satisfactory. Alternative hypotheses may attribute this to differences in environmental or social factors such as ventilation characteristics, crowding, time spent at home or a higher rate of prior infection. However, the observed difference in infection rates did not impact on the subsequent incidence of tuberculous disease, which was 295/100 000 in the INH-resistant and 311/100 000 in the INH-susceptible series. One explanation is that infection in the INH-resistant series was more remote, and disease usually emerges soon after infection. Another is that infected contacts of INH-resistant patients have lowered disease incidence. In the present study, the incidence was indeed lower (436 vs. 530), but the difference (94) was not significant ($P = 0.4$, 95%CI −94–282). The adjusted hazard ratios, too, were similar in the two series ($P = 0.2$). Our investigation, planned primarily to evaluate BCG prophylaxis, cannot distinguish between the various hypotheses propounded above, and appropriately designed new studies are required.

Only 29% of the 34 new cases that developed in contacts exposed solely to an INH-resistant patient at home were resistant to INH, suggesting that the infecting source was from outside the household in 70% of instances. Detailed matching of index cases

with new incident cases was not possible, as no molecular epidemiological testing had been planned. Another weakness is that information regarding treatment details and the bacteriological progress of individual patients, which could have thrown light on the transmission processes, was not collected, nor was periodic assessment of the infection status of the study subjects undertaken, as our main aim was to evaluate BCG prophylaxis. Yet another limitation is that there was no surveillance system for detecting extra-pulmonary cases of TB in children and infants.

The strengths of our community study, however, are many. It is based on large numbers of subjects followed over 15 years with multiple case-finding methods to identify cases, and the use of sophisticated statistical techniques to allow for the effect of other relevant factors. Furthermore, post facto power computations indicate that the study had 92% power to detect a lowering of the risk by half in contacts of INH-resistant patients. Another notable feature, especially as the study was spread over 15 years in children in a country where individuals have no unique social identification number, is the deployment of fingerprint matching to confirm the identity of cases.

To conclude, the baseline prevalence of infection was substantially higher in household contacts of INH-resistant than INH-susceptible TB patients, but the subsequent incidence of disease was similar in the two series.

Acknowledgements

The authors acknowledge the role of all the Project Directors of the Tuberculosis Prevention Trial and the Directors of the Tuberculosis Research Centre in the conduct of the Tuberculosis Prevention Trial. They also thank the entire staff of the Tuberculosis Prevention Trial for their sustained cooperation. Finally, they are greatly indebted to one of the referees for suggesting refinements in the statistical techniques employed.

References

1 Shaw J B, Wynn-Williams N. Infectivity of pulmonary tuberculosis in relation to sputum status. Am Rev Tuberc 1954; 69: 724–732.
2 Grzybowski S, Barnett G D, Styblo K. Contacts of cases of active pulmonary tuberculosis. Bull Int Union Tuberc 1975; 50 (1): 90–106.
3 Van Geuns H A, Meijer J, Styblo K. Results of contact examination in Rotterdam, 1967–1969. Bull Int Union Tuberc 1975; 50 (1): 107–121.
4 Lienhardt C K, Fielding K. Risk factors for tuberculosis infection in sub-Saharan Africa: a contact study in the Gambia. Am J Respir Crit Care Med 2003; 168: 448–455.
5 Becerra M C, Pachao-Torreblana I F. Expanding tuberculosis case detection by screening household contacts. Public Health Rep 2005; 120: 271–277.
6 Tuberculosis Research Centre (ICMR), Chennai. Additional risk of developing TB for household members with a TB case at home at intake: a 15-year study. Int J Tuberc Lung Dis 2007; 11: 282–288.
7 Barnett M, Bushby S R M, Mitchison D A. Virulence and response to treatment with isoniazid in guinea-pigs and mice. Brit J Exp Path 1953; 34: 568–581.
8 Barry V C, Conalty M L, Gaffney E. INH-resistant strains of *Mycobacterium tuberculosis*. Lancet 1953; 1: 978–979.
9 Middlebrook G, Cohn M L. Some observations on the pathogenecity of INH-resistant variants of tubercle bacilli. Science 1953; 118: 297–299.
10 Steenken W Jr, Wolinsky E. Virulence of INH-resistant tubercle bacilli in man. Am Rev Tuberc 1953; 68: 548–556.
11 Schmidt L H. Some observations on the utility of simian pulmonary tuberculosis in defining the therapeutic potentialities of isoniazid. Am Rev Tuberc 1956; 74 (Part 2): 138–153.
12 Narain R, Chandrasekhar P, Pyarelal, Satyanarayanachar R A. Prevalence, fate and infectivity of INH-resistant strains of *Mycobacterium tuberculosis*. In: Proceedings of the 22nd Tuberculosis and Chest Diseases Workers' Conference, Hyderabad, India, February 1967. Delhi, India: Navchetan Press, 1968: pp 37–51.
13 Devadatta S, Dawson J J Y, Fox W, et al. Attack rate of tuberculosis in a 5-year period among close family contacts of tuberculous patients under domiciliary treatment with isoniazid plus PAS or isoniazid alone. Bull World Health Organ 1970; 42: 337–351.
14 Tuberculosis Prevention Trial, Madras. Trial of BCG vaccines in South India for tuberculosis prevention. Indian J Med Res 1980; 72 (Suppl): 1–74.
15 Tuberculosis Research Centre (ICMR), Chennai. Fifteen-year follow up of trial of BCG vaccines in South India for tuberculosis prevention. Indian J Med Res 1999; 110: 56–69.
16 Tuberculosis Research Centre (ICMR), Chennai. Influence of sex, age and non-tuberculous infection at intake on the efficacy of BCG: reanalysis of 15-year data from a double-blind randomized control trial in South India. Indian J Med Res 2006; 123: 119–124.
17 Radhakrishna S, Frieden T R, Subramani R, Narayanan P R. Value of dual testing for identifying tuberculous infection. Tuberculosis 2006; 86: 47–53.
18 Tuberculosis Research Centre, Chetput, Chennai, India. Trends in the prevalence and incidence of tuberculosis in South India. Int J Tuberc Lung Dis 2001; 5: 142–147.
19 Hill A B. Principles of medical statistics. London, UK: Charles Griffin, 1961: p 204.
20 Hosmer D W, Lemeshow S. Applied logistic regression. 2nd ed. Series in Probability & Statistics. Wiley, 2004: pp 31–142.
21 Cox D R. Regression models and life tables (with discussion). J R Stat Soc B 1972; 34: 187–220.
22 Fisher L D, Lin D Y. Time-dependent covariates in the Cox proportional hazards regression model. Ann Rev Public Health 1999; 20: 145–159.
23 Coker R J. Multidrug-resistant tuberculosis: public health challenges. Trop Med Int Health 2004; 9: 25–40.
24 Snider D E Jr, Kelly G D, Cauthen G M, Thompson N J, Kilburn J O. Infection and disease among contacts of tuberculosis cases with drug-resistant and drug-susceptible bacilli. Am Rev Respir Dis 1985; 132: 125–132.
25 Teixeira L, Perkins M D, Johnson J L, et al. Infection and disease among household contacts of patients with multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2001; 5: 321–328.
26 Burgos M, DeRiemer K, Small P M, Hopewell P C, Daley C L. Effect of drug resistance on the generation of secondary cases of tuberculosis. J Infect Dis 2003; 188: 1878–1884.
27 Garcia Garcia M L, Ponce de Leon A, Jimenez-Corona M E, et al. Clinical consequences and transmissibility of drug-resistant tuberculosis in southern Mexico. Arch Intern Med 2000; 160: 630–636.
28 Nitta A T, Knowles L S, Kim J Y, et al. Limited transmission of multidrug-resistant tuberculosis despite a high proportion of infectious cases in Los Angeles County, California. Am J Respir Crit Care Med 2002; 165: 812–817.
29 Van Soolingen D, Borgdoff M W, de Haas P E, et al. Molecular epidemiology of tuberculosis in the Netherlands: a nation-wide study from 1993 through 1997. J Infect Dis 1999; 180: 726–736.

RÉSUMÉ

OBJECTIF : Comparer dans une communauté rurale d'Inde du Sud le risque encouru par des contacts dans le ménage avec des cas de tuberculose (TB) sensibles ou résistants à l'isoniazide (INH).

MÉTHODES : On a suivi pendant 15 ans au total 5.562 sujets-contact de patients sensibles à l'INH et 779 sujets-contact de patients résistants à l'INH ainsi que 246 845 personnes sans contact avec la TB dans le ménage. Les enquêtes réalisées tous les 2 ans et demi comportaient un examen radiologique, un examen des crachats, un suivi sélectif pour les individus à haut risque et une surveillance passive. En cas d'apparition d'un nouveau cas, les membres du ménage étaient ultérieurement considérés comme appartenant aux séries « sensibles à l'INH » (n = 7088) ou « résistantes à l'INH » (n = 526) de manière appropriée. On a utilisé la régression logistique et le modèle de risques proportionnels de Cox.

RÉSULTATS : Au début, la prévalence de l'infection tuberculeuse a été respectivement de 70% et de 56% chez les contacts de patients à germes résistants ou sensibles à l'INH ($P < 0{,}001$) par comparaison avec 46% chez les sujets sans contact. L'incidence correspondante de TB à culture positive a été de 295 et de 311 pour 100 000 par comparaison avec 162/100 000 en l'absence de contact. Les taux de risque ajustés ont été respectivement de 2,4 et de 2,0 pour les sujets-contact de patients résistants ou sensibles à l'INH.

CONCLUSION : Au début, la prévalence de l'infection tuberculeuse est substantiellement plus élevée chez les sujets au contact avec des patients résistants à l'INH qu'avec des patients sensibles à l'INH, mais l'incidence de la maladie tuberculeuse au cours d'un suivi de 15 ans a été similaire dans les deux séries, et deux fois plus élevée que celle des sujets sans contact avec la TB.

RESUMEN

OBJETIVO: Comparar el riesgo de los contactos domiciliarios de casos de tuberculosis (TB) sensible y resistente a isoniazida (INH) en una comunidad rural del sur de la India.

MÉTODOS: Se llevó a cabo un seguimiento de 15 años a 5562 contactos domiciliarios de casos de TB sensible a INH, 779 contactos de casos resistentes y 246 845 personas sin casos de TB en su domicilio, con una evaluación cada 2 años y medio que comportó exámenes radiográficos y del esputo, seguimiento selectivo de las personas con alto riesgo de padecer la enfermedad y vigilancia pasiva. Cuando se presentaba un caso nuevo de TB en las personas del estudio, sus contactos domiciliarios se reasignaban, según correspondiera, al grupo de casos sensibles a INH (n = 7088) o resistentes (n = 526) en función del caso nuevo. En el análisis de los datos se aplicó el modelo de regresión logística y el método de riesgos proporcionales de Cox.

RESULTADOS: La prevalencia inicial de infección tuberculosa en los contactos de pacientes con TB resistente a INH fue 70% y en los contactos de casos sensibles fue 56% ($P < 0{,}001$), comparada con 46% en las personas sin contacto tuberculoso. La incidencia de TB con cultivo positivo fue 295 por 100 000 en los contactos de casos iniciales resistentes, 311/100 000 en los contactos de casos iniciales sensibles y 162/100 000 en el grupo sin contacto domiciliario. La tasa ajustada de riesgos instantáneos fue 2,4 en los contactos de pacientes con TB resistente a INH y 2,0 en los contactos de casos sensibles.

CONCLUSIÓN: La prevalencia inicial de infección tuberculosa fue notoriamente más alta en los contactos de pacientes con TB resistente a INH, pero la incidencia de enfermedad tuberculosa durante el período de 15 años de seguimiento fue equivalente en ambos grupos y dos veces superior a la del grupo de personas sin contacto domiciliario con casos de TB.