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Contact tracing for tuberculosis and treatment for latent infection in a low incidence country

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Abstract

Objective: To determine the yield of contact tracing after exposure to active tuberculosis (TB) cases in a low incidence area for TB as well as completion rate and tolerance to treatment for latent TB infection (LTBI).

Methods: Retrospective study based on a database including all patients evaluated in Geneva during contact tracing procedures; review of medical records of contacts for whom treatment of LTBI was indicated.

Results: 3582 subjects were screened over 10 years (on average 4.3 contacts per index case); 8 (0.2%) had active TB. LTBI was detected in 28% of subjects screened. Foreign origin, exposure and contagiousness of index case were predictive of LTBI. Of the 996 subjects with LTBI, files of 705 subjects followed at our centre were reviewed: treatment was indicated in 571 (81%). Side-effects led to interruption of treatment for LTBI in 32 cases (6.9% of subjects treated); 227 subjects eligible for treatment (40%) either refused or stopped treatment, or were lost to follow-up. Completion rate was 67%.

Conclusions: In a low-incidence environment for TB, contact tracing procedures had a very low yield for detection of active TB cases; acceptance and completion rates for LTBI therapy were in agreement with recent studies.

Key words: tuberculosis; latent tuberculous infection; adherence; contact tracing

Introduction

Since the early 1990s, as in most western industrialized countries, the incidence of tuberculosis (TB) in Switzerland has been steadily decreasing (12.7 cases per 10^5 inhabitants in 1990, 8.0 per 10^5 inhabitants in 2004) [1]. For the Geneva area (440,000 inhabitants, 245 km^2), the incidence of TB is 20 per 10^5 inhabitants i.e. roughly 2.5 times the national incidence, mainly because of a higher proportion of foreign-born subjects. In fact, 80% of all TB cases detected in Geneva are foreign-born.

Prevention of TB relies mainly on the detection of active or latent TB in high risk populations and on contact tracing procedures for each case of active pulmonary TB. Yield of contact tracing procedures, in terms of detection of either active disease or latent TB infection (LTBI), varies with the baseline incidence of TB [2]. Indeed, very high detection rates of active smear-positive cases have been reported in low-income and high incidence countries (up to 15%) [2–4]. In USA and Canada, 20–40% of contacts are found to have LTBI and 1–2% have active TB [5–12]. For patients in whom LTBI is detected, treatment is recommended [13]. However, in subjects with documented LTBI, rate of treatment prescription (45–88%) and completion (16–79%) are often disappointingly low [5–8, 11, 12, 14].

The Geneva area offers a privileged opportunity to study the efficacy of contact tracing procedures in a population with a low TB incidence. Indeed, all contact tracing procedures are supervised by one specialized centre. The present study details 10 years of contact-tracing for TB in the Geneva area, with an emphasis on rate of active and latent infection as well as completion rate and side effects of therapy for LTBI.

This study was performed before the gamma-interferon release assays (IGRA) became available [15]; IGRA are more specific than the tuberculin skin test and recommended in the most recent Swiss [16], ATS/CDC and UK guidelines.

No financial support declared.

Materials and methods

The outpatient clinic of the Division of Pulmonary Diseases of Geneva University Hospital supervises all contact tracing procedures for TB in the Geneva area. All patients either treated for TB, or evaluated in contact tracing procedures, are entered in a database which stores information on gender, age, origin, exposure to index case, microbiological details of index case, BCG, Tuberculin skin test (TST; 2U of RT23 Tuberculin, Statens Serum Institute, Copenhagen, DK), co-morbidities, diagnosis of active, latent or history of TB and treatment prescribed.

This retrospective study includes all subjects evaluated over 10 years for contact with an index TB case with either smear positive and culture positive pulmonary tuberculosis (S+/C+TB), smear negative and culture positive pulmonary TB (S-/C+TB) or smear negative and culture negative pulmonary TB (S-/C-TB). Medical records of all contacts followed by our centre for whom a treatment for LTBI had been recommended were reviewed and acceptance to treatment, adherence (assessed by visit attendance and monthly urinary tests for isoniazid), tolerance (results of monthly ASAT: Aspartate amino-transferase; and ALAT: Alanine amino-transferase, reported side-effects), interruption of treatment and their causes were analyzed.

Two subgroups of subjects were not followed by our centre after initial screening and are not included in our analysis of treatment for LTBI: subjects known to be HIV-infected (referred to our HIV clinic), and children (referred to the Children's hospital or to their paediatrician).

Algorithms used for contact tracing

For subjects exposed to a S+/C+ TB, population screened included household contacts, close friends or relatives, home-care professionals and work or school contacts. For subjects exposed to a S-/C+ or S-/C- TB, household contacts only were screened (fig. 1). TST was considered positive if induration was >10 mm, in agreement with national guidelines [17]. For subjects screened, HIV testing was not mandatory and thus not recorded. For workplace contacts aged >35, unless identified as having a high exposure to the index case, screening consisted of a chest X-ray (CXR) 8–12 weeks after end of exposure. The default treatment prescribed for LTBI was isoniazid (INH) for six months, in accordance with the recommendations prevailing at that time in Switzerland and in the UK [18, 19].

In this study, probable LTBI was defined as having either a TST induration >10 mm or a chest X-ray with images suggestive of prior TB. LTBI is reported as "probable" because of the lack of specificity of the TST and the chest X-ray.

Statistical analysis

Variables are reported as mean x (SD y). Exact Poisson confidence intervals were calculated for incidence of rare events. Comparison between groups was performed using unpaired t tests or chi-square tests when appropriate. Multiple logistic regression was performed to analyse the relationship between significant variables and occurrence of LTBI, probability of pursuing treatment for LTBI, or suffering from side effects. A p level of <0.05 was used for determining statistical significance. Statistical analyses were performed with Stata Statistical Software for PC computers (Version 9.2, 2005; Stata Corporation, College Station, Texas, USA).

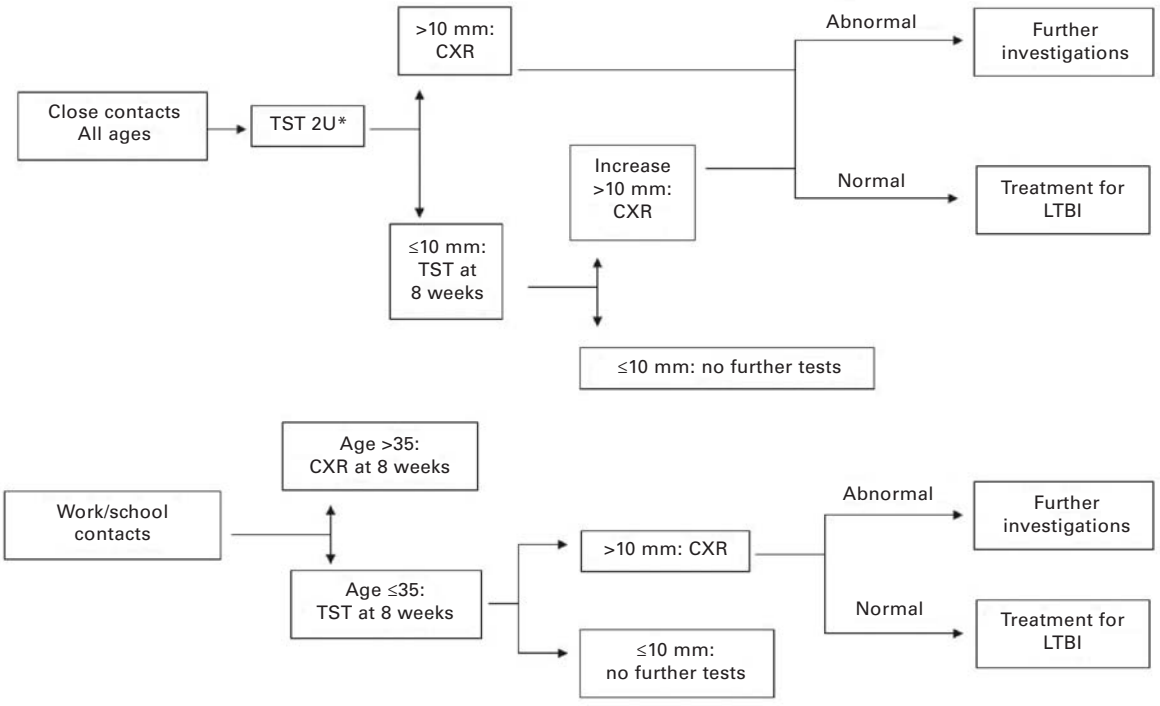


Figure 1

Algorithm used for contact tracing during study period (Jan 1993–Dec 2002). TST: Tuberculin skin test; CXR: Chest X-ray; LTBI: Latent tuberculosis infection.

Results

Between January 1993 and December 2002, 3582 subjects were screened for contact with a patient with TB, 1718 (48%) of whom were evaluated at our centre (table 1). The remaining 1864 were evaluated either by private practitioners or by the Paediatric Department if aged under 16 (n = 356). Only one subject was known to be HIV-infected.

Microbiological status of index case was S+/C+ TB for 84% of subjects screened, S-/C+ TB for 10%, S-/C- pulmonary TB for 2.3% and unknown for 3.8%. Average number of contacts screened per case was 4.3.

Subjects (48% male, 52% female) were (mean (SD)) 36 (18) years of age; 42% were Swiss nationals, 57% were foreign-born subjects, of whom 24% were refugees or seeking asylum (0.5%: status unknown). Swiss subjects (41 (19) years; range: 0-95) were on average 9 years older than foreign-born subjects (32 (15) years; range: 0–92). History of BCG was undetermined in 2506 (70%); 699 (20%) had a history of BCG vaccina-

Table 1

Results of tuberculin skin tests (TST) according to exposure to index case and bacteriological status of index case. S+/C+ : smear positive and culture positive; S-/C+: smear negative and culture positive; S-/C-: smear negative and culture negative

	Swiss				Foreign-born				Swiss and Foreign-born				No TST or result unknown	All	%
Size of TST induration (mm)	**<5 %**	**5–10 %**	**>10 %**	**Total N**	**<5 %**	**5–10 %**	**>10 %**	**Total N**	**<5 %**	**5–10 %**	**>10 %**	**Total N**		**Total N**	
Exposure to index case															
Household contacts	63%	7.7%	29%	453	45%	8.0%	47%	638	53%	7.9%	40%	1091	112	1203	34%
Friends/close relatives	61%	5.2%	34%	271	55%	7.2%	38%	419	57%	6.4%	36%	690	81	771	22%
Home support professionals	64%	5.6%	31%	36	52%	8.9%	39%	56	57%	7.6%	36%	92	41	133	3.7%
Professional or school contacts	61%	10%	28%	383	57%	10%	32%	431	59%	10%	31%	814	583	1397	39%
Exposed during hospital stay	70%	10%	20%	30	50%	30%	20%	10	65%	15%	20%	40	33	73	2.0%
Undetermined				1	33%	0.0%	67%	3	50%	0%	50%	4	1	5	0.1%
Total	62%	7.9%	30%	1174	51%	9%	40%	1557	56%	8%	36%	2731	851	3582	
Characteristics of index case															
S+/C+	62%	8.2%	30%	950	49%	8.7%	42%	1303	55%	8.5%	37%	2253	748	3001	84%
S–/C+	69%	7.7%	23%	143	63%	10%	27%	149	66%	8.9%	25%	292	69	361	10%
S–/C–	55%	0.0%	45%	29	86%	0.0%	14%	36	72%	0.0%	28%	65	19	84	2.3%
Unknown	54%	7.7%	38%	52	43%	7.2%	49%	69	48%	7.4%	45%	121	15	136	3.8%
Total	62%	7.9%	30%	1174	51%	9%	40%	1557	56%	8%	36%	2731	851	3582	

Table 2

Results of multiple logistic regression models for estimating probability of latent tuberculosis infection (LTBI) in contacts, probability of completing treatment for LTBI, and probability of treatment interruption due to side-effects of treatment for LTBI. OR: odds ratio; 95%CI: 95% confidence interval. S+: smear positive; S-: smear negative; C+: culture positive; C-: culture negative. Age is expressed per 10 years. Adjusting for clustering was not possible due to lack of information regarding relationship between index cases and contacts in the original database. This may slightly underestimate confidence intervals.

	Probability of LTBI		Probability of completing treatment		Probability of treatment interruption due to side effects	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Age (per 10 years)	1.01	1.01–1.02	0.99	0.98–1.01	1.03	1.00–1.05
Male gender	1.35	1.15–1.59	0.78	0.52–1.17	1.33	0.71–2.49
Swiss *vs* Foreigner	0.64	0.54–0.76	1.02	0.63–1.63	1.76	0.90–3.44
Relation to index case (reference value: household contacts)						
Friends – close relatives	0.76	0.62–0.93	0.74	0.47–1.18	–	–
Home care professionals	0.80	0.51–1.25	2.14	0.45–10.1	–	–
Workplace or school contact	0.60	0.49–0.73	0.85	0.49–1.45	–	–
Exposed during hospital stay	0.27	0.12–0.60	0.43	0.03–6.98	–	–
Characteristics of index case (reference value: S+/C+)						
S–/C+	0.52	0.39–0.69	–	–	–	–
S–/C–	0.55	0.31–0.96	–	–	–	–

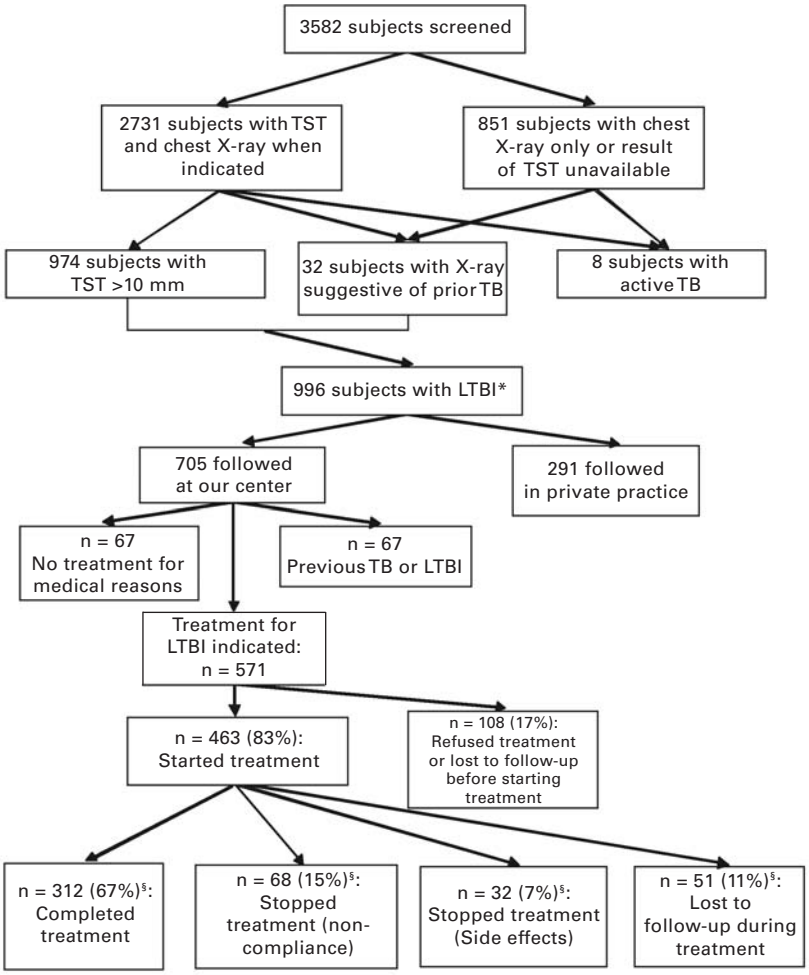
tion, 377 (10%) had none. TST with chest X-ray when indicated were available in 2731 subjects; 851 subjects either had no TST (chest X-ray only) or TST result was unavailable (no information from private practitioner or patient did not show up for reading of TST).

TST induration was <5 mm in 56% of subjects (n = 1530); 5–10 mm in 8.3% (n = 227), and >10 mm in 36% (n = 974). The proportion of skin tests >10 mm was higher in foreign-born subjects than in Swiss nationals (40% versus 30%: table 1).

Thus TST identified 974 subjects with probable LTBI (36% of subjects in whom a skin test was performed). Among them, 105 (3.8%) had a documented TST conversion (increase 10 mm in induration). Among the 3582 subjects screened, X-ray images suggestive of prior TB were found in 32 subjects (0.9%; 95% CI: 0.6–1.3%) and active TB in 8 subjects (0.2%; 95% CI: 0.1–0.4%).

Figure 2

Flow chart of subjects screened for latent tuberculosis infection (LTBI) or TB and outcome of follow-up of patients treated for LTBI. *: Subjects with LTBI had TST >10 mm and/or chest X-ray suggestive of prior TB. §: percentages refer to patients who started treatment.



Combining chest X-ray and TST, a diagnosis of probable LTBI was made in 996 subjects (28% of subjects screened).

Predictors of LTBI

In a multiple logistic regression, male gender and age were significantly associated with a higher rate of LTBI (table 2). Conversely, Swiss nationality was associated with a lower rate of LTBI. Risk of LTBI was significantly related to exposure to the index case and to microbiological status of the index case (table 2).

Treatment for LTBI

Among the 996 subjects with LTBI, 705 were followed at our centre (fig. 2). Of these, 1.4% (n = 10) had a history of treated TB, 0.6% (n = 4) had received previous treatment for LTBI, 0.1% (n = 1) had a history of probably untreated TB and 7.4% (n = 52) had a previously documented positive TST. For 67 (9.5%) subjects, treatment for LTBI was withheld for medical reasons (eg excessive alcohol consumption). Thus, treatment for LTBI was recommended in 571 subjects. Of these, 108 (19%) refused treatment or were lost to follow-up before treatment was initiated. Among the 463 (81%) who started treatment (aged 34.2 (11.5) years; range: 14–82, 21% Swiss), INH was prescribed to 97% (n = 449); 1.7% (n = 8) received rifampicin either alone or in combination with INH; 1.3% (n = 6) received other medications because of resistance of the index case to INH and rifampicin (MDR-TB); 7.6% (n = 38) were switched to rifampicin either because of intolerance (n = 17) or resistance to INH in the index case (n = 21). At 6 months, overall completion rate was 67% (n = 312); treatment was interrupted in 22% (n = 100) after a mean of 84 (49) days (range 3–206), either as a result of non-adherence (n = 68, 15%) or side effects (n = 32, 7%); 11% were lost to follow-up (n = 51). Neither age, gender, foreign origin nor intensity of exposure to index case was predictive of treatment completion by multiple logistic regression (table 2).

INH-related adverse effects and cases in which treatment was changed or interrupted because of adverse effects are shown in table 3. In multiple logistic regression, treatment interruption because of side effects was more likely in older patients. For example, the proportion of patients with ASAT or ALAT >5X upper normal limit was 2.5% for subjects aged 14–34 years, *vs* 4.9% for the 35–49 years age group and 13% for subjects aged >50. Among all subjects, 101 patients (22%) experienced one or more side effects, resulting in change or interruption of treatment in 45 subjects (10%). Hepatotoxicity accounted for change or interruption of treatment in 26 cases (5.6%).

Discussion

This study reports the yield of contact tracing over a 10-year period in a low incidence area for tuberculosis. Prevalence of LTBI in contacts was significantly related to exposure to the index case and to the contagiousness of the index case (table 2). The yield of contact screening for active TB cases was very low (n = 8 cases, 0.2% of subjects screened; 95 % CI: 0.1–0.4%), when compared to previous reports in low-incidence countries [5, 6, 9–12, 20, 21] and far below that reported in developing countries [2, 3]. Among contacts with LTBI for whom treatment was recommended and who were followed at our centre, 81% started treatment (usually isoniazid), of which 67% completed treatment. Treatment was interrupted because of side effects in 7% of subjects and such interruptions were more prevalent in older patients.

Rate of TB detected through contact screening in Europe, USA or Canada ranges from 0.8% to 4.9%, and that of LTBI from 7.6% to 47% [5–12, 14, 20, 22]. In the present study, the rate of TST-based diagnosis of LTBI (36%) was similar to previous reports. Changing the threshold value for TST positivity to 5 mm, in agreement with recent ATS, CDC and IDSA (Infectious Disease Society of America) guidelines, would increase the infection rate by 8.3% (44%), ie in the upper range of previously reported data [23]. Conversely, the number of active cases detected in this study was surprisingly low: the 8 active TB cases represented less than 1% of the 837 cases of active TB reported in Geneva during the study period. The reason for such a low rate of TB is unclear. A plausible hypothesis would be underdetection of infected contacts [24]. This seems unlikely however, because, over the study period, newly detected cases of TB were not related to previous cases, albeit for the above mentioned 8 active cases. Indeed, DNA fingerprinting of mycobacteria in Switzerland shows a very low number of clusters of TB cases [25, 26]. The easy access to care in Geneva even for homeless subjects, illegal immigrants or other high risk groups may contribute to earlier detection of active cases, and thus decrease exposure of community members.

The major goal of contact-tracing is the detection and treatment of newly infected subjects with LTBI. Screening 3582 contacts led to complete treatment for LTBI in at least 312 subjects (number of patients completing treatment and followed by private practitioners is unknown), thus theoretically preventing 11 cases of TB (based on the assumption of a 5% life-time risk of reactivation and a 70% protection by a 6 month regimen of INH) [27]. Among subjects followed by our centre (fig. 2), 32 subjects would be at lifetime risk of developing active TB (5% of the 638 patients for whom treatment for LTBI was indicated, including those for whom it was withheld for medical reasons). Therefore, one can assume that 34% (11/32) of future TB cases were prevented by contact tracing. Similar estimations were derived from a large multicentre evaluation of contact investigations in California [12].

Prevalence of positive TST increased significantly with age, exposure to index case and contagiousness of index case (S+/C+ *vs* S-/C+ or S-/C-). This contrasts with recent reports showing very low associations between exposure to index case and TST status when compared to γ-IFN blood assays [28, 29] (table 2).

Treatment for LTBI was completed in 55% of eligible subjects and 67% of those who started. A total of 40% of eligible subjects refused, stopped their treatment or were lost to follow-up (fig. 2). Reported adherence to treatment for LTBI is highly variable. In a large INH preventive therapy programme in Atlanta, GA, 76% of subjects for whom preventive therapy was indicated started INH, but only 20% completed therapy. Foreign birth and age over 65 years were associated with higher rates of completion in multivariate analysis [7]. In recent US studies of contact investigations, 66–97% of subjects eligible for INH preventive therapy started their treatment, with completion rates of 44–64% [5, 6, 11, 12, 14, 30]. Two smaller Swiss studies reported 68–76% completion rates for patients treated for LTBI, most of whom were immigrants or asylum seekers [31, 32]. In our study, adherence was assessed by recording attendance to monthly visits and results of a qualitative urinary assay for INH. Age, gender, origin and importance of exposure to index case were not predictive of treatment completion (table 2).

Table 3

Isoniazide-related side effects during treatment for latent tuberculosis infection (LTBI). ASAT: Aspartate amino-transferase; and ALAT: Alanine amino-transferase; ULN: upper limit of normal values.

			Treatment changes or interruptions	
Side effects	**N**	**%**	**N**	**%**
Gastro-intestinal symptoms	37	8.2%	8	1.8%
Asthenia	24	5.3%	2	0.4%
Hepatotoxicity				
Increase in ASAT or ALAT (3–5 × ULN)	16	3.6%	7	1.6%
Biological hepatitis (increase in ASAT or ALAT >5 × ULN)	13	2.9%	13	2.9%
Clinical hepatitis	6	1.3%	6	1.3%
Cutaneous drug reaction	5	1.1%	3	0.7%
Neurological symptoms				
Headache	6	1.3%	3	0.7%
Dizziness	4	0.9%	0	0.0%
Paresthesias	3	0.7%	1	0.2%
Tinnitus	1	0.2	1	0.2%
Psychiatric symptoms	1	0.2%	1	0.2%

Increase in ASAT or ALAT above 5 times upper limit of normal (ULN), or above 3 times ULN with symptoms suggesting hepatotoxicity led to interruption of treatment, according to ATS/CDC guidelines [33]. A moderate elevation of ASAT or ALAT is expected in 10–20% of patients treated with INH [34]. As in previous studies, hepatotoxicity increased with age. Interruption of treatment because of liver toxicity occurred in 4.7% of subjects with INH alone, which is slightly higher than previously reported (0.3–4%) [34]. Rate of INH-related clinical hepatitis was similar to previous reports (0.6%) [33]. Monthly liver function testing may lead to a higher detection of INH-induced hepatotoxicity, since it is frequently asymptomatic. Although not recommended by ATS/CDC guidelines nor by recently revised Swiss guidelines [16] (www.lung.ch), as stated by Fountain et al, the rationale for routine testing of ASAT and ALAT is that it probably leads to an earlier detection of liver toxicity. Some of these patients would have probably become symptomatic, had INH been pursued [34].

In summary, this study performed in a low TB incidence area shows that contact tracing for TB in our area has a very low yield in terms of detection of secondary TB cases. Secondly it is associated with a moderate rate of acceptance for LTBI therapy and an average rate of treatment completion. Improving effectiveness of contact tracing thus relies on detecting LTBI with better specificity (ie through algorithms including the γ-IFN assays as stated in the revised Swiss guidelines) and improving both initial acceptance to preventive therapy and completion rates.

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