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Tuberculosis contacts study: Organization and prevalence of latent tuberculosis infection☆

Estudio de contactos de pacientes con tuberculosis: organización y prevalencia de la infección tuberculosa latente

To the Editor:

Contacts tracing of patients with tuberculosis (TB) is a priority for the control of the disease in countries with low prevalence and high economic resources,[1,2] as stated in the Plan for the Prevention and Control of Tuberculosis in Spain, which underlines the need to intensify contact tracing and coordination among all the health centers and teams involved.[3] However, few studies in Spain have analyzed the organization of contacts tracing programs: most have been performed in specific geographical areas and focus on evaluating such programs to identify their weaknesses and work towards improving them.[4,5]

This prospective, observational cohort study of the contacts of tuberculosis patients was therefore aimed at describing the organization of these programs in Spain and the prevalence of latent tuberculous infection among the contacts studied.

Contacts of patients diagnosed with TB between January 2018 and December 2019 were identified and included in the national registry of SEPAR's Integrated Tuberculosis Research Program (PII-TB), which is accessed by user names and passwords provided to the members of the PII-TB Task Force The study was approved by the Research Ethics Committee of all participating centers. Twelve centers from 6 Spanish autonomous communities participated in the study.

The following definitions were established:

a) *Initial index case*: a person of any age diagnosed with TB in a specific household or other comparable environment in which others may have been exposed.
b) *Contact*: any person who has been exposed to an index case and classified according to the time of exposure as: 1) habitual: contact was repeated and occurred more than once a week; and 2) sporadic: only one contact occurred or, if repeated, occurred less than once a week. In any case, to be sporadic, the period of contact had to be less than 6 h.
c) *Secondary case*: a person diagnosed with TB who was identified from among the individuals studied as contacts.
d) *Latent tuberculosis infection (LTBI):* tuberculin skin test (TST) with induration diameter of 5 mm or more and/or positive interferon-γ release assay (IGRA), with no evidence of active disease. The QuantiFERON-TB GOLD in-Tube IGRA was used with a cut-off point of 0.35 IU/ml. The responsible investigator determined which TST and IGRA were to be used and the order in which they were performed.
e) *Dual strategy*: use of both diagnostic techniques, TST and IGRA, regardless of the sequence.

Proportions were compared between groups using the Chi-square test and the 2-tailed Fisher test when the expected values were less than 5. Quantitative variables were compared using the Student's t-test or its non-parametric equivalent, the Mann–Whitney U test. The prevalence of LTBI among contacts was calculated taking into account the total number of contacts. A p-value of less than 0.05 was considered significant.

We analyzed 1035 contacts from 265 index cases, 525 women and 510 men, with a mean age of 37.96 ± 20.13 years; 777 (75.1%) were Spanish natives and 413 (39.9%) were household contacts. Contacts tracing was conducted in specialist tuberculosis clinics in 769 cases (74,2%). Table 1 shows the differences between different healthcare sites where the tracing study was performed.

TST was performed in 844 contacts (81.5%) and IGRA in 469 (45.3%), while both tests were performed in 348 (33.6%). Of the 444 in whom the TST was negative, a second determination was made in 90.7% with a conversion rate of 2.7%; these percentages were 58.8% and 5.2% (9/289), respectively, for the IGRAs. LTBI was diagnosed in 346 (33.4%) and depending on the diagnostic strategy, the prevalence was 48.2% if both TST and IGRA were performed, 27.4% if TST was used alone, and 40.4% if IGRA was used alone (p = 0.01). In 126 contacts, the index case had negative sputum smear and culture or extrapulmonary disease. Of these, 97 (76.9%) were seen in specialist tuberculosis clinics, and LTBI was detected in 24.6% (31/126).

TB was diagnosed in 17 contacts (1.6%): in all of these, the index case had a positive culture.

In our series, LTBI is slightly less prevalent than the 40% to 57% reported in previous studies published in Spain.[4,6] We believe that this may be partly due to the uneven use of diagnostic techniques, since LTBI rates were significantly higher in cases in which a dual strategy was used. Although there is no clear advantage of TST over IGRA, or vice versa, performing both tests together to establish the diagnosis of LTBI improves diagnostic sensitivity.[7] In addition the conversion rate of the IGRA is also higher than that of TST.[8,9] We found that TST and IGRA were performed simultaneously in only 33% of patients, and if the initial test was negative, a second determination was made in a higher percentage of patients undergoing TST than IGRA. We therefore believe that the dual strategy is the most appropriate, and if the initial tests are negative, they should be repeated 8–12 weeks later to determine whether there are conversions; this is one of the aspects to be improved in the performance of contact tracing studies.

Another interesting finding of our study is that tracing of more than 2/3 of the contacts was conducted by a specialist tuberculosis clinic. These facilities differ clearly from other healthcare sites: they perform a higher percentage of dual diagnostic techniques, track contacts outside the family setting, and follow up index

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Table 1
Differences by healthcare site.

	TB clinic	Hospital	Primary care	p
Exposure				0.001
– Family	460 (59.8%)	145 (82.7%)	71 (87.3%)	
– Work	75 (9.8%)	24 (12.7%)		
– Leisure	110 (14.3%)	7 (2.8%)	8 (7.5%)	
– School	124 (16.1%)	5 (1.8%)	6 (5%)	
Index case				0.001
– Culture +	672 (87.3%)	157 (87.5%)	80 (94.1%)	
– Culture –	28 (3.6%)	16 (8.5%)	3 (3.5%)	
– EP	69 (9.1%)	8 (3.9%)	2 (2.4%)	
Dx strategy				0.001
– TST+IGRA	282 (36.6%)	62 (34.4%)	4 (4.7%)	
– TST alone	412 (53.5%)	80 (44.1%)	75 (88.2%)	
– IGRA alone	75 (9.7%)	39 (21.5%)	6 (7.1%)	
LTBI	271 (35.2%)	58 (32%)	17 (20%)	0.03
Follow-up				
– LTBI-T	213 (91.5%)	48 (87.2%)	3 (66.7%)	0.02
– Lost-to-follow-up	48 (6.2%)	14 (7.8%)	23 (27%)	0.01

+: positive; –: negative; Dx strategy: diagnostic strategy; EP: extrapulmonary; IGRA: interferon-g release assays; LTBI: latent tuberculous infection; LTBI-T: latent tuberculous infection treatment completed; TB clinic: specialist tuberculosis clinic; TST: tuberculin skin test.

cases with negative or extrapulmonary culture (86.1% and 76.9%, respectively), with the resulting impact on the detection of infected individuals, the main objective of the contact study. Although contacts tracing in cases of extrapulmonary TB is controversial unless there is another added risk factor,[10] we believe that there are arguments in favor of this approach, including the sizeable proportion of LTBI detected (25% in our study and as high as 35% in others[6]) and the active TB load detected in previous series.[11] Finally, it is also worth noting that, in line with previous reports,[12] care in specialist tuberculosis clinics improved the follow-up of contacts, as shown in Table 1.

Our study has limitations. First, this was an observational study in which several researchers participated, so errors might have been made in some of the variables collected, thus implying a selection bias. However, we should point out that all the researchers were tuberculosis experts actively involved in the PII-TB program, which we believe improved the quality of data collection and reduced this risk, thus endorsing the validity of the results obtained.

We conclude that the dual use of TST and IGRA testing in contacts tracing is recommended to improve sensitivity in the diagnosis of infected individuals. There are also differences between study sites, with specialist tuberculosis units showing better results, suggesting that the process should be centralized in these clinics to offer more homogeneous care.

Authorship

José Antonio Gullón Blanco participated in the conception and design of the study, data collection, analysis and interpretation, and writing of the article.

Teresa Rodrigo Sanz, José María García García and the PII-TB participated in the critical review of the intellectual content and final approval of the submitted manuscript.

Fernando Álvarez Navascués, Eva Tabernero Huguet and Josefina Sabría Mestres collaborated in the final approval of the submitted manuscript. The Task Force of the Integrated Research Program in Tuberculosis (PII-TB) has been involved in data collection.

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