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Scientific Letter

[Translated article] Tuberculosis contacts tracing in Spain: Cost analysis

Estudio de contactos de pacientes con tuberculosis en España: analisis de costes

To the Director,

Contacts tracing of tuberculosis (TB) patients involves significant health expenditure, but while several studies have analyzed the cost of diagnosis or treatment of latent tuberculosis infection (LTBI)[1], few have evaluated cost of the overall process[2]. Furthermore, the most appropriate diagnostic method for LTI is still under debate[3].

We therefore designed this prospective observational study to determine the cost of TB contacts tracing and to conduct a cost-effectiveness analysis of the diagnostic methods and treatment of LTBI.

Contacts of patients diagnosed with TB between January 2018 and December 2019 were included in the National SEPAR Registry of the Integrated Tuberculosis Research Program (PII-TB) database. Research group members were given a username and password to access the registry. Twelve centers from 6 Spanish autonomous communities participated, and the study was approved by all corresponding Ethics and Research Committees.

The following definitions were established:

Index case: case recognized as the source of the infection of other patients and/or infected cases[4].

Secondary case: a contact diagnosed with TB.

Contact: person with exposure to the index case[4].

Latent tuberculosis infection (LTBI): tuberculin skin test (TST) with induration diameter of at least 5 mm and/or positive QuantiFERON TB Gold (QFT) with a cut-off of 0.35 IU/mL[5], and no evidence of active disease.

Diagnostic strategy: techniques used to diagnose LTBI, according to the sequence established at the discretion of the attending physician. Three options were considered: dual (TST plus QFT combined); TST alone; or QFT alone.

Direct costs were extracted from the data provided by the Health Service of the Principality of Asturias[6] and the Catalan Public Health Agency[7], as shown in Table 1. Indirect costs for the treatment and follow-up of active TB cases detected in the contact study were €10,262 per patient[8]. Using these data, we performed a cost-effectiveness analysis of the diagnostic strategy and LTBI treatment. Baseline strategies selected for diagnosis and treatment were TST and a 6-month course of isoniazid (6H), respectively, and the target population consisted of all contacts of the 4832 TB cases diagnosed in Spain in 2018[9], estimating that each of them would have an average of 4 contacts. The number of TB cases avoided was used as a measure of efficacy, assuming that 10% of infected contacts will develop TB during their lifetime[10], and that LTBI treatment reduces the overall risk by between 56% and 75%, depending on the regimen used[11]. The incremental cost-effectiveness ratio (ICER) was calculated to compare the different strategies. When a strategy was less expensive and more effective than the baseline strategy, the ICER was not calculated and that strategy was considered dominant.

Table 1
Indirect costs.

Variable	Cost (€)
Medical consultations	
Initial	120.30
Subsequent	72.20
Blood tests (blood count, biochemistry with liver function tests)	23.48
Sputum smear and sputum culture	19.66
Plain chest X-ray	9.51
Tuberculin skin test	15
QuantiFERON TB Gold	125
LTBI treatment	Cost (€) per patient
Isoniazid for 6 months	18.72
Isoniazid plus rifampicin for 3 months	71.52
Rifampicin for 4 months	83.71
Isoniazid for 9 months	28.08

LTBI: latent tuberculosis infection.

Proportions were compared using the Student's *t*-test or its non-parametric equivalent, the Mann-Whitney *U* test A *p*-value of less than .05 was considered significant.

A total of 1035 contacts of 265 index cases with a mean age of 37.96 ± 20.13 years were identified. The diagnostic strategy was dual in 374 (36.4%), TST in 537 (51.9%), and QFT in 124 (11.7%); the percentage of LTBI in each group was 48.2%, 27.4%, and 40.4%, respectively (P = .01). LTBI was diagnosed in 346 (33.4%) contacts and 295 started treatment: 156 (52.9%) received isoniazid plus rifampicin for 3 months (3HR), 124 (42%) received 6H, 5 (1.9%) received rifampicin for 4 months (4R), and 10 (3.2%) received isoniazid for 9 months; 91.1%, 89.1%, 80%, and 70% completed treatment, respectively (P = .1). Seventeen cases of TB were diagnosed (1.6%).

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Table 2
Cost-effectiveness of the diagnostic strategy and latent tuberculous infection treatment.

	Mean cost (per contact) €	Total cost €	Effectiveness (number of TB cases avoided)	ICER €
Dx				
TST	333.33	5,861,852.25	530	--------
TST plus QFT	486.76*	9,408,097.28	930	8865.61
QFT	412.82	7,977,746.52	780	8463.57
LTBI treatment				
6H	473.24	2,703,146.88	304	---------
3HR	447.08	2,553,720.96	376	Dominant
4R	827.45+	4,726,394.40	344	50,581.18
9H	516.71	2,951,447.52	262	

Dx: diagnostic strategy; LTIT: latent tuberculous infection treatment.
Total cost: calculated for 19,328 contacts with an LTBI prevalence of 33.4%. Effectiveness: number of TB cases avoided, assuming that 10% of infected contacts will develop the disease over their lifetime. ICER (incremental cost-effectiveness ratio) = [total cost of strategy A1-total cost of strategy A2]/[effectiveness of strategy A1-effectiveness of strategy A2]; 6H: isoniazid for 6 months; 3HR: isoniazid and rifampicin for 3 months; 4R: rifampicin for 4 months; 9H: isoniazid for 9 months.
* $P < .05$ with respect to the basic strategy (TST).
\+ $P < .05$ with respect to the basic strategy (6H).

The total cost was €545,491.80: €371,037.80 for direct costs, of which 40.8% was for medical consultations, 26.1% for LTBI treament, and 25.1% for diagnostic studies. The average cost per contact studied was €548.23 (SD 142.97). Dual and QFT strategies were significantly more expensive than TST but more effective, and the 3HR treatment was dominant over 6H. The costs of diagnosis and LTBI treatment and corresponding ICERs are shown in Table 2.

The cost per contact studied was higher than the €368.23 reported in a German study[2], but unlike our series, that study did not include the costs of preventive treatment. In another study conducted in Norway[12], the average cost was €1934, significantly higher than ours, due to differences in the costs charged, especially for medical consultations. If we extrapolate our results to the approximate number of contacts to be evaluated in Spain[9], the estimated total cost of contacts study would be €10.6 million.

With regard to LTBI treatment, the 3HR regimen was less expensive and more effective, confirming that it would be a better choice than 6H. This was also demonstrated in a cost-effectiveness study[13] in which all short regimens, including 3HR, were more cost-effective than 6H, although the authors, unlike us, found that 4R was slightly better; however, our results should be interpreted with caution due to the low representation of 4R in our series.

With regard to diagnosis, the dual strategy and QFT were more expensive but more effective than TST, with an ICER of €8865.61 and €8463.57 per TB case avoided, respectively. If we bear in mind that health interventions with an ICER of up to €30,000 are efficient[14], both strategies would be cost-effective. To determine the best option, we must analyze the ICER together with the potential health benefit of the intervention, – in this case, identifying contacts with LTBI and offering them treatment to reduce the risk of developing TB as well the environment in which the strategy is implemented. Given that the percentage of LTBI is higher when the dual strategy is used, we believe that this would be the most appropriate in a country with a low incidence of disease, such as Spain.

Several studies conducted in low-incidence countries have shown that the use of both interferon-γ release assays (IGRA) and TST techniques is cost-effective in certain groups such as household contacts[3,15] and health workers[16]. Spanish clinical guidelines also recommend this approach in children under the age of 5 and in individuals who are immunocompromised, HIV-positive, or receiving biological drugs, while for the contacts study they recommend that TST be complemented by IGRA in BCG-vaccinated individuals with a positive TST[5,17]. Our study included regular contacts, with exposure time to the index case greater or less than 6 hours a day, and sporadic, who accounted for 36% of the total. The rate of LTBI in both groups was higher when TST and QFT were used, but the difference among sporadic contacts was particularly striking (54.6% versus 19.1% for TST or 30.2% for QFT alone), suggesting that the dual strategy may be the best way of initiating the contacts study, regardless of exposure intensity.

Similarly, Erkens et al.[18] in a series of 10,000 contacts, of which 39% were sporadic, found that adding IGRA to TST modified the diagnosis of LTBI in 40% of contacts. They argue that the higher cost would be balanced by a more accurate indication for preventive treatment, and consider this practice to be the most appropriate in low-prevalence countries.

Our study has some limitations. Firstly, its design has an inherent risk of selection bias. However, it should be noted that one of the main strengths of our study is that all researchers were TB experts who participate regularly in the PII-TB, which we believe ensure the quality of data collection and reduces this possibility of selection bias. Secondly, to determine effectiveness, we estimated that 10% of infected contacts might develop TB over their lifetime, while other studies suggest a rate of 15%[19]; however, we do not believe that this difference reduces the validity of our results. Finally, we did not analyze other indirect costs, such as transport or work absenteeism, so the total cost may be underestimated, but we should remember that this study was conducted in a country with high economic resources, so the likely impact of these factors on the final results would, in our opinion, be marginal.

We conclude that the study of TB contacts generates a significant health expense, derived mainly from diagnostic techniques and the treatment of latent tuberculosis infection. In this respect, we believe that the most appropriate strategy is the sequential use of TST plus QFT in all contacts, and treatment with 3HR.

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Conflict of interests

The authors state that they have no conflicts of interest.

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Appendix.

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