

Tuberculin Reaction Size in Tuberculosis Patient Contacts

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OBJECTIVE: The purpose of this study was to explore the association between tuberculin reaction size in contacts with positive tuberculin skin test results and a variety of contact and index patient variables.

PATIENTS AND METHODS: We reviewed the contact investigation records for tuberculosis patients identified by the Tuberculosis Prevention and Control Center of Lleida, Spain, over a period of 7 years. Patients with pulmonary and/or extrapulmonary disease were included. Tuberculosis infection had been diagnosed using the Mantoux skin test with 2 tuberculin units of purified protein derivative RT-23, and tuberculosis disease had been detected on the basis of clinical data, chest radiographs, and cultures. We examined the association between tuberculin reaction size and contact age, close contact with index patients with positive sputum smears, and diagnosis of tuberculosis disease in contacts. Associations were analyzed using the χ^2 test for linear trend.

RESULTS: Tuberculin reaction size was 10 mm or greater in 85.9% of the 768 contacts analyzed and 15 mm or greater in 63.8%. The percentage of contacts under 15 years of age ($P=.006$) who had close contact with an index patient with a positive sputum smear ($P=.013$) and who were diagnosed with tuberculosis disease ($P=.029$) increased with tuberculin reaction size.

CONCLUSIONS: We found that larger tuberculin reaction size in contacts with positive tuberculin skin test results was most frequently associated with recent infections in the contact, close contact with an index patient with a positive sputum smear, and diagnosis of tuberculosis disease in contact.

Key words: Tuberculosis. Contacts. Tuberculin reaction.

El tamaño de la reacción tuberculínica en contactos de pacientes tuberculosos

OBJETIVO: En este trabajo se ha analizado la asociación del tamaño de las reacciones tuberculínicas con diversas variables del contacto y del caso índice en contactos de pacientes tuberculosos con prueba de la tuberculina positiva.

PACIENTES Y MÉTODOS: Se revisaron los estudios de contactos realizados a pacientes tuberculosos en el Centro de Prevención y Control de la Tuberculosis de Lleida durante un período de 7 años. Se incluyeron en el trabajo las revisiones realizadas a pacientes tuberculosos con localización pulmonar y/o extrapulmonar. Para el diagnóstico de infección tuberculosa se realizó el test de Mantoux con 2 UT de tuberculina PPD-RT23. Para detectar la enfermedad tuberculosa se examinaron la situación clínica, la radiografía de tórax y la bacteriología. Se analizó la asociación entre el tamaño de la reacción tuberculínica con la edad del contacto, con ser conviviente de un caso índice con baciloscopia positiva y con el diagnóstico de enfermedad tuberculosa en el contacto. Para el análisis de las asociaciones anteriores se utilizó la prueba de la χ^2 de tendencia lineal.

RESULTADOS: El 85,9% de los 768 contactos con prueba de la tuberculina positiva presentaron un diámetro de induración de la reacción tuberculínica igual o superior a 10 mm, y el 63,8% una induración igual o superior a 15 mm. Al aumentar el tamaño de la induración tuberculínica se detectó un incremento del porcentaje de contactos menores de 15 años ($p = 0,006$), convivientes de caso índice con baciloscopia positiva ($p = 0,013$) y con diagnóstico de enfermedad tuberculosa ($p = 0,029$).

CONCLUSIONES: Los contactos con prueba de la tuberculina positiva que presentan reacciones de mayor tamaño se han asociado con mayor frecuencia a contactos con infecciones recientes, a contactos convivientes de caso índice con baciloscopia positiva y a contactos con enfermedad tuberculosa.

Palabras clave: Tuberculosis. Contactos. Reacción tuberculínica.

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Introduction

Individuals infected with *Mycobacterium tuberculosis* develop a delayed immune response to tuberculin testing. This reaction causes a small swollen area, or induration, to appear at the site of the skin test.¹⁻⁵ To determine whether a test result is negative or positive, the size of the induration

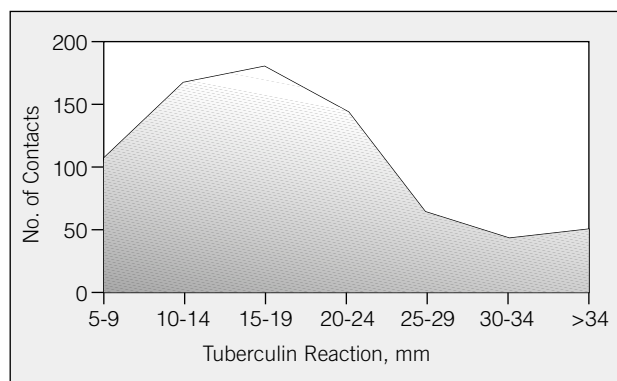


Figure 1. Distribution of induration diameters in contacts with positive tuberculin skin test reactions.

is measured in millimeters. According to the consensus guidelines for the control of tuberculosis in Spain, a positive reaction is considered to be an induration of 5 mm or greater in individuals who have not been vaccinated against tuberculosis and 15 mm or greater in those who have.⁶

A person infected with *M tuberculosis* is more likely to develop active disease if he/she has had close contact with a patient with a positive sputum smear,⁷ if there are radiographic signs of tuberculosis,⁸ and if there is concurrent human immunodeficiency virus infection,⁹⁻¹³ diabetes mellitus,¹⁴ gastrectomy,^{15,16} silicosis,¹⁷ or chronic renal failure.^{18,19} A large number of health professionals believe that tuberculin reactions are larger in patients with tuberculosis disease and in persons with tuberculosis infection who are at greater risk of developing active disease.²⁰

The aim of this study was to analyze tuberculin reaction size in contacts with positive tuberculin skin test results and to study the association between reaction size and contact age, infection risks (degree of contact with the index patient and bacteriologic confirmation of disease in the index patient), and presence of tuberculosis disease in the contact.

Patients and Methods

We reviewed contact investigation records covering a period of 7 years from the Tuberculosis Prevention and Control Center of Lleida, Spain. Contacts were defined as having tuberculosis if they met at least 1 of the following criteria: a) bacteriologic confirmation of *M tuberculosis* (positive sputum smear and/or culture), b) histologic findings (granulomas with caseous necrosis) in biopsy specimens in a compatible clinical picture, and c) clinical radiographic signs of tuberculosis disease and improvement attributable to anti-tuberculosis treatment. Patients with pulmonary and/or extrapulmonary disease were included in the contact investigation.

Persons who had been named by index patients as being in repeated and prolonged contact with them were included in the contact investigation. For the purpose of this study, we defined close contacts as persons who lived in the same household as the index patient or who had a close relationship with them; casual contacts were those who did not meet either of those criteria.

All the contacts analyzed had been given a Mantoux tuberculin skin test consisting of an intradermal injection of 0.1 mL of purified protein derivative (PPD) containing 2 units of PPD-

RT23 with Tween 80. Between 48 and 72 hours after the injection, the skin induration was measured across the forearm as the diameter in millimeters, using the palpation method. An induration size of 5 mm or greater was considered to be a positive test result. The presence of active disease was later determined by chest radiographs, and in some cases, by a microbiological study of respiratory secretions.

Contacts with a positive tuberculin skin reaction were included in the study although anyone who had been vaccinated against tuberculosis was excluded to avoid an interference effect. Contacts were considered to have been vaccinated if they could provide documented proof of the vaccination or had a visible scar.

We analyzed the association between reaction size in contacts with a positive skin test result and the following variables: contact age, tuberculosis transmission risk variables (degree of contact with the index patient and index patient's sputum smear result), and presence of active disease in the contact. Reactions were classified into 3 size categories: 5 to 9 mm, 10 to 14 mm, and 15 mm or greater. Associations were analyzed using the χ^2 test for linear trend and statistical significance was set at a value of *P* less than .05.

Results

We reviewed the contact investigation records for 437 cases and studied a total of 2365 contacts. Of these, we excluded 277 (11.7%) because they had been vaccinated against tuberculosis and a further 5 because a skin test result could not be obtained. Of the remaining 2083 patients, 768 (36.9%) had had a positive tuberculin skin test result and 34 (1.6%) were newly detected cases. Diagnosis of 6 of the 34 new cases was confirmed microbiologically.

The mean (SD) age of the 768 contacts included in the study was 39.2 (20.3) years; 361 (47%) were men. Of the 766 contacts for whom degree of contact was known, 438 (57.2%) were close contacts, and of the 689 contacts of index patients for whom sputum smear test results were available, 517 (75%) had positive respiratory specimens.

The distribution curve for induration diameters showed that the largest percentage of patients (23.8%) had reactions measuring 15 to 19 mm; 22.1% had reactions 10 to 14 mm in diameter, and 19.1% had indurations 20 to 24 mm in size. The remaining size categories had percentages under 10%, except for the 5 to 9 mm range, in which 14.1% of the contacts were placed (Figure 1).

Reactions of 15 mm or greater were most common in contacts under 15 years of age: 6.5% of the contacts in the 5 to 9 mm range were in this age group, compared to 16.4% in the 15 mm or greater range (*P*=.006) (Table 1).

The percentage of close contacts of patients with positive sputum smears increased with tuberculin reaction size, with 35.6% in the 5 to 9 mm range and 47.4% in the 15 mm or greater range (*P*=.013) (Table 2).

No new tuberculosis cases were diagnosed in contacts with reactions of 5 to 9 mm. The percentage of new cases detected among patients with indurations 10 to 14 mm in diameter was 4.7% (8/170) and 5.3% in those with reactions measuring more than 15 mm (*P*=.029) (Table 3).

Discussion

Reaction size was 10 mm or greater in the majority (85.9%) of the 768 contacts with positive tuberculin skin

test results and 15 mm or greater in 63.8%. The percentage of contacts under 15 years of age diagnosed with tuberculosis disease and who were close contacts of index patients with positive sputum smears increased with tuberculin reaction size.

A number of tuberculosis contact studies have found that the rate of tuberculosis infection increases with age, until age 64 years and older.^{21,22} In the present study, we found that induration size was greater in contacts under 15 years of age, a finding that is consistent with another contact study that found larger reactions in this age group.²³ These observations could be due to a greater prevalence of recent infection, as infection through direct contact with the index patient is the most likely explanation for the larger indurations in this age group.

Grzybowski and colleagues,²⁴ however, reported contrasting results on analyzing the size of tuberculin reactions in different age groups of the general population as part of an epidemiological surveillance program. In their study, the percentage of reactions measuring 15 mm or greater increased with age only up to 59 years. This was largely attributed to the high incidence of infection by atypical mycobacteria in the study area and a decrease in infection by *M tuberculosis*.

Because the index patient's sputum smear result and the degree of contact between the patient and the contact are very closely correlated to tuberculosis transmission,²⁵⁻³¹ we decided to analyze those 2 variables as one. We found that that the percentage of close contacts of sputum-smear-positive patients increased with tuberculin reaction size.

All the new tuberculosis cases detected in our study population occurred in contacts with a reaction of 10 mm or greater. A similar study to ours which analyzed 3071 tuberculosis contacts also found that the number of new cases tended to increase with tuberculin reaction size.³² They reported a new case incidence of 7.8% in the 5 to 9 mm range, 11.9% in the 10 to 14 mm range, and 14.7% in the 15 mm or greater range.

A greater incidence of tuberculosis disease in individuals with larger reactions was also reported by 2 international controlled trials in community settings.^{33,34} Those studies found that the difference in the incidence of new cases was greater between individuals with reactions of 5 to 9 mm and 10 to 14 mm than between those with reactions of 10 to 14 mm and 15 mm or greater. To explain these findings, it has been suggested that larger indurations are probably caused by *M tuberculosis* infection and smaller ones by nontuberculous mycobacteria or by vaccination. It is also worth noting that larger reactions are more likely to be due to recent infection and, as such, are associated with a greater risk of developing the disease.

Contradictory findings, however, were reported by a study conducted in 2 populations: close/household contacts of patients with active tuberculosis and patients that had participated in a study of pulmonary tuberculosis diagnosis.³⁵ The authors concluded that larger reaction size in individuals with indurations greater than 5 mm in diameter was not correlated with a greater risk of active disease.

TABLE 1
Association Between Age and Tuberculin Reaction Size in Contacts With Positive Tuberculin Skin Test Results

Variables	Age, y			
	<15		≥15	
	N	%	N	%
Tuberculin reaction size, mm				
5-9	7	6.5	101	93.5
10-14	21	12.4	148	87.6
≥15	80	16.4	409	83.6

χ² test for lineal trend, P=.006.

TABLE 2
Association Between Positive Tuberculin Skin Test Result in Contacts Living With Index Patients With Positive Sputum Smears and Tuberculin Reaction Size

Variables	Close Contact With Index Patients With Positive Sputum Smears			
	<15		≥15	
	No.	%	No.	%
Tuberculin reaction size, mm				
5-9	36	35.6	65	64.4
10-14	58	38.9	91	61.1
≥15	207	47.4	230	52.6

χ² test for lineal trend, P=.013.

TABLE 3
Association Between Diagnosis of Tuberculosis Disease With Size of Tuberculin Reaction in Contacts With Positive Skin Test Results

Variables	Tuberculosis Disease			
	Sí		No	
	No.	%	No.	%
Tuberculin reaction size, mm				
5-9	0	0	108	100
10-14	8	4.7	162	95.3
≥15	26	5.3	464	94.7

χ² test for lineal trend, P=.029.

The above findings indicate that tuberculosis contact investigations should be prioritized according to cost-effectiveness. The key to success can be found in the application of the concentric circle strategy in an appropriate, timely and systematic manner.³⁶ With regard to the second aim of our study, we found that larger reactions in contacts with positive tuberculin skin test results were associated with recent infection (which carries a greater risk of developing into active disease), a greater exposure to infection (close contact with an index patient with a positive sputum smear), and a diagnosis of tuberculosis disease in the contact during the investigation.

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