

Effect of delay in diagnosis on the rate of tuberculosis among close contacts of tuberculosis patients

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تأثير التأخر في التشخيص على معدل السل بين المخالطين الوثيقي الصلة بمرضى السل

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الخلاصة: حاولت دراسات قليلة استكشاف التأخر في تشخيص مرضى السل وأثر ذلك على معدل الإصابة بين المخالطين الوثيقي الصلة بالمرضى. وقد أجريت هنا دراسة مستعرضة للمخالطين الوثيقي الصلة بـ 505 من مرضى السل تم تشخيصهم حديثاً في مركز السل المرجعي في صنعاء، اليمن 2008-2010. وقد وافق مخالطون لـ 89 مريضاً جديداً للسل فقط على المشاركة وإجراء الاختبار الجلدي للتوبركلين. ومن بين 239 مخالطاً تم استقصاؤهم، كانت نتيجة 133 منهم (55.6%) إيجابية لاختبار الجلد. وتم تصنيف الحالات المرضية الدالة على التأخر لأجل طويل في التشخيص أو التأخر لأجل قصير في التشخيص (لن هم أعلى أو أقل من الناصف الإحصائي). ولم يكتشف فرق كبير في عدد المخالطين الذين أصيبوا سواء بين الحالات المرضية الدالة على التأخر لأجل طويل أو التأخر لأجل قصير (اختبار- U مان ويتني). ويمكن باستخدام حجم عينة أكبر، وتقديم المزيد من الحوافز للحث على المشاركة، وباستخدام أدوات استقصائية أخرى تقديم صورة أفضل لنمط انتقال السل بين كافة المخالطين.

ABSTRACT Few studies have explored diagnosis delay by tuberculosis (TB) patients and its effects on the rate of infection among their close contacts. A cross-sectional study of the close contacts of 505 newly diagnosed TB patients was conducted in a TB referral centre in Sana'a, Yemen from 2008 to 2010. Only the close contacts of 89 new TB patients agreed to participate and completed the tuberculin skin test (TST). Of the 239 close contacts investigated, 133 (55.6%) had a positive TST result. Index patients were classified as long or short diagnosis delay (above or below the median). There was no significant difference in the number of infected close contacts between long and short delay index patients (Mann-Whitney U-test). A larger sample size, with more incentives for patients to participate and the use of other investigative tools could provide a better picture of the pattern of TB transmission among all contacts.

Impact du délai diagnostique sur le taux de tuberculose chez les contacts rapprochés des patients tuberculeux

RÉSUMÉ Peu d'études ont examiné le délai diagnostique chez les patients tuberculeux et son impact sur le taux d'infection auprès de leurs contacts rapprochés. Une étude transversale des contacts rapprochés de 505 patients ayant récemment reçu le diagnostic de tuberculose a été menée dans un centre d'orientation-recours pour la tuberculose à Sanaa, (Yémen) entre 2008 et 2010. Seuls les contacts rapprochés de 89 patients ayant récemment reçu le diagnostic ont accepté de participer et de se soumettre au test tuberculinique cutané. Sur un total de 239 contacts rapprochés, 133 (55,6 %) ont présenté des résultats positifs au test. Les cas index ont été classifiés en fonction du délai long ou court (supérieur ou inférieur à la médiane) qui a été nécessaire pour aboutir au diagnostic. Aucune différence significative n'a été observée pour le nombre de contacts rapprochés infectés entre les cas index ayant reçu un diagnostic après un délai long ou après un délai rapide (test U de Mann-Whitney). Une taille d'échantillon plus importante, ainsi que davantage d'incitations à la participation des patients, mais aussi le recours à d'autres outils d'enquête permettraient de brosser un tableau plus précis du mode de transmission de la tuberculose pour l'ensemble des contacts.

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Introduction

Tuberculosis (TB) is a major public health problem in Yemen and is considered the 4th highest cause of death in the country [1]. Because almost 85% of TB cases occur in the productive age groups, the burden of TB is therefore also a socioeconomic concern [2]. The annual prevalence of infection in the total population according to a report in 2005 was 136 per 100 000, with an annual incidence of new cases of 82 per 100 000 [3]. Contact investigation—the identification and follow-up of individuals who could be at risk for TB infection due to their exposure to active TB cases—is considered an important factor in fighting and controlling the spread of TB [4].

TB patients have been characterized as short or long diagnostic delay, according to the time delay between becoming infected and receiving diagnosis and treatment [5]. Long delays potentially exacerbate the risk of TB transmission to others. Reducing the delay in TB diagnosis is therefore a major challenge that confronts many national TB control programmes (NTP) around the world. Similar to other countries with TB cases, the diagnostic delay of the disease in Yemen increases its overall morbidity and mortality because patients serve as reservoirs of the disease and this raises the risk of contacts of TB patients becoming infected [6]. This phenomenon is a serious problem that could hamper the control of TB as well as the success of the NTP in Yemen [7].

Although studies have been made of factors affecting delays in TB diagnosis and treatment [8–10] there has been little research to explore how diagnostic delay affects TB transmission to close contacts. To our knowledge, only 2 previous studies to date have been conducted to determine the effect of diagnostic delay on TB transmission among patients' contacts. Golub et al.'s study in the United States of America

(USA), found a significant association between a long diagnostic delay and higher rates of TB transmission among contacts of black USA-born patients [11]. MacIntyre et al.'s study in Australia found a significant association between the workers in close proximity to a delayed source of infection (during the exposure period) and an increased risk of infection [12]. This important strand of TB prevention efforts should be a major concern of the NTPs in all countries. Understanding TB transmission among contacts could help in reducing new cases of TB infection. This study in Sana'a, Yemen was therefore performed to assess the effect of delay in TB diagnosis on the rate of disease among the close contacts of long and short diagnosis delay TB patients.

Methods

Study design and setting

This cross-sectional study compared the rate of infection among close contacts of new TB index cases with long and short diagnosis delay times. Data were collected using an interview questionnaire for index patients and tuberculin skin tests (TST) for patients' close contacts.

The study was conducted at a TB referral centre at Sana'a, the capital of Yemen. Sana'a has an estimated population of 1.7 million [3]. Patients from other Yemeni cities also use the services of the centre, so patients in this study included TB patients from the entire country.

Study population and sample

The close contacts of newly diagnosed TB patients from the Yemen NTP were the main population of this study. The required sample size was calculated to be 234 TB patients in each of the long and short diagnosis delay patient groups based on a sample size equation [13]. However, sampling was continued for up to 505 new

smear-positive TB patients to cover the required sample size with consideration of probable drop-outs. Thus, 505 new TB patients were recruited for the study over the period June 2008 to March 2010.

Data collection

Interviews

The questionnaire was designed according to a review of the literature [14,15]. Information collected included demographic data of the index patient and the time in days between the onset of TB symptoms and time of starting TB treatment. All new pulmonary TB patients who agreed to participate in this study were interviewed by the researcher or by well-trained health-care providers. Each of the 505 participating patients was asked to bring his/her close contacts for TST to determine which of the close contacts were infected with TB [15].

Tuberculin screening tests

Each close contact brought to the centre underwent a TST. The TST was performed intradermally through injection of 0.1 mL of the tuberculin solution on the left forearm of each of the attending contact of the TB patient. The test was performed according to standard procedures [16]. First, the skin was stretched lightly, and a needlepoint was inserted lengthwise into the superficial layer of the skin of the forearm. Next, 0.1 mL of the tuberculin was slowly injected, and the finger was removed from the end of the plunger before the needle was withdrawn [17]. The tuberculin solution used in the TB referral centre was the same product recommended by the World Health Organization. The results of the TST were read 48 to 72 hours after the test was administered by the same investigator according to standard operating procedure [17]. This procedure relies on observation of the induration (swelling with redness in skin tested area) around the area of the test injection. The indurated

area was detected by palpating the skin. For positive results, the diameter of the induration area must be greater than 15 mm [18,19].

Participants who were subjected to the TST for the first time should be subjected to the same test 2 months after their initial testing in order to confirm the TST results and to determine those whose results changed from negative to positive within those 2 months [11,12,20].

Definitions

All verified new pulmonary TB cases who were diagnosed in the TB referral centre and who participated in the interview for this study were included and considered as index cases [11,12,16].

The close contacts of the index patients were persons who lived with them in the same house/room on a daily basis and spent most of the day with the patient, or people who worked with or had close contact with the patient for a certain period [21].

The diagnosis time for every TB index patient was recorded as the total number of days between the onset of TB symptoms and the time of diagnosis and starting TB treatment. The median diagnosis delay was calculated for the total group of index patients and used as the cut-off for defining groups. Each patient was classified as long delay (above the median) or short delay (below the median) [22,23].

Ethical considerations

The study protocol was approved by the scientific and ethics board of the Ministry of Health and the referral TB centre. In addition, informed consent

was obtained from every available participating close contact (verbal consent) or his/her close relative.

Data management and analysis

The data were coded and transferred to SPSS, version 16 for analysis. Descriptive measures [percentages, mean and standard deviation (SD) and median and interquartile range (IQR)] were used to show the mean differences for the infected close contacts of the long and short delay TB patients. The Mann-Whitney test was performed to determine whether there were statistical differences between the rates (using number of positive contacts) of positive TST results for short- and long-delay TB patients. The test was also performed by using the proportion of TST-positive close contacts instead of the number of positive close contacts. This confirmatory test was performed due to the unequal number of the close contacts for every TB patient.

Results

The median total delay of TB diagnosis was 60 days (IQR 30–90). Of the 505 new smear-positive TB patients recruited for the study 241 had short delays (< 60 days) and 264 had long delays (≥ 60 days).

Only 89 of the 505 new TB patients had close contacts who agreed to participate in this investigation and took the TST. The total number of close contacts recruited by these index patients was 266 [129 (48%) females and 137 (62%) males]. For the analysis 27 close

contacts (10%) were recorded as missing data due to their refusal to return for the interpretation of the test results 72 hours after the TST was administered.

Of the 239 close contacts analysed, 133 (55.6%) had a positive TST result and 106 (44.4%) had a negative result (Table 1). Only 53 of these close contacts were children aged < 10 years old, and 15 of them had positive TST results. Although several of the close contacts agreed to return for a follow-up TST, only 18 returned and were given the TST for the 2nd time. The positive results obtained in the 1st test were all confirmed in the 2nd test.

The median number of TST-positive close contacts of the long delay group was 2 (IQR 1–2) whereas for the close contacts of the short delay group it was 1 (range IQR 0.5–2) (Table 2). The mean number of TST-positive close contacts was 2.1 (2.0) for the long delay group and 1.4 (1.1) for the short delay group. However, the difference in the number of TST-positive close contacts was not statistically significant between the groups ($P > 0.05$, Mann-Whitney U-test).

The data were also analysed by comparing the proportion of close contacts of long delay patients who had positive TST results with those of contacts of short delay patients. This analysis also showed no significant difference between groups ($P > 0.05$, Mann-Whitney U-test) (Table 3).

Discussion

Generally speaking, TB can easily be transmitted from the source patient to those people who come into contact

Table 1 Tuberculin skin test (TST) results among close contacts of tuberculosis index patients with long or short diagnosis delay times

Delayed diagnosis in index case	Total no. of close contacts tested	Positive TST		Negative TST	
		No.	%	No.	%
Long delay	99	56	56.6	43	43.4
Short delay	140	77	55.0	63	45.0
Total	239	133	55.6	106	44.4

Table 2 Number of close contacts of tuberculosis patients who were positive for tuberculin skin test (TST): comparison of long (above median) or short (below median) delay patients

Delayed diagnosis in index case	No. of TST-positive close contacts	No. of TST-positive close contacts per index patient ^a	
		Mean (SD)	Median (IQR)
Long delay	56	2.1 (2.0)	2 (1-2)
Short delay	77	1.4 (1.1)	1 (0.5-2)

^aMann-Whitney U-test not significant.

SD = standard deviation; IQR = interquartile range.

with the source for a certain period [24]. Coughing, sneezing, talking, and even singing can transmit many TB bacilli to people with whom a TB patient comes into contact [25]. In the present study, TB infection was determined through conducting a TST on the close contacts of TB patients and the effect of delay in diagnosis of the index patient and the rate of TB infection among close contacts was analysed.

Most of the close contacts who agreed to participate in the investigation did not live very far from the TB referral centre. Those who did not participate were unwilling to participate due to other commitments (e.g. studying, domestic duties, employment) and unwillingness to undergo the test, among other reasons. Many non-participants also lived far from the centre and did not participate in the study due to financial constraints on travelling. Unfortunately, financial assistance for people to attend the centre was unavailable from the TB control organization. The study recommends that future investigations should involve local and international organizations in order to obtain more support, financial or otherwise, which in turn could enhance TB notifications and control efforts.

According to previous studies, an increase in transmission of TB among contacts due to a long delay in TB diagnosis is considered an expected consequence of the delay [15,26,27]. The present study investigated whether a delay in TB diagnosis increased the number of infected close contacts. Although the median number of positive TST among close contacts of long delay diagnosis TB patients was twice as high as among short delay TB patients (2 versus 1), the difference was not statistically significant based on the Mann-Whitney test. Similarly, comparing the proportions of positive TST close contacts of long and short delay patients also showed no significant difference. Thus long delay diagnosis of the patients did not lead to a significant increase in the number of positive TST among their close contacts. Only close contacts of 89 out of 505 index patients participated in the testing, mostly those who lived near the clinic, and this could be the cause of the non-significant association.

The findings of the present study were inconsistent with those of Golub et al., who found a significantly higher number of positive TST contacts of the long delay TB patients [12]. The difference might be due to differences in

the sample size and in the nature of the participating close contacts. In addition, Golub et al. compared different groups of people, that is, the close contacts of long delay and short delay patients who were born inside and outside the USA. Their study also found a significant association between long delay diagnosis in black patients born in the USA and a higher rate of TB transmission to their close contacts, but did not find the same association with the close contacts of long delay black TB patients born outside the USA [12] (Table 4). Their in-depth investigation on certain groups of people as well as the difference in objectives could have contributed to the difference in their findings and those of the present study. In Australia, MacIntyre et al. found an association between delay and higher rates of TB infection of close contacts of office workers (OR = 4.24; 95% CI: 1.06–19.6) (Table 4) [11]. This finding was also inconsistent with that of the present study. The difference between the previous studies [11,12] and the present study could be due to the fact that in our study few of the identified close contacts of index patients participated and took the TST. In addition, the number of close contacts who returned for the second

Table 3 Proportion of close contacts of tuberculosis patients who were positive for tuberculin skin test (TST): comparison of long (above median) or short (below median) delay patients

Delayed diagnosis in index case	No. of TST-positive close contacts	% of TST-positive close contacts ^a	
		Mean (SD) proportion	Median (IQR) proportion
Long delay	56	64 (37)	67 (46-100)
Short delay	77	51 (39) ^a	50 (10-100)

^aMann-Whitney U-test not significant.

SD = standard deviation; IQR = interquartile range.

Table 4 Comparison between the present study and the previous studies of close contacts of tuberculosis patients

Variable	Sample of close contacts	Length of delay (days)	TST-positive close contacts	Long and short delay close contacts infected		P-value
				Long delay	Short delay	
	No.		No.	No. (%)	No. (%)	
Present study (Yemen)	239	≥ 60	133	77 (58)	56 (42)	> 0.05
Golob et al. (USA)[12]	310 ^a	≥ 60	109	18 (25)	91 (38)	< 0.05
MacIntyer et al. (Australia) [11]	210 ^b	≥ 90	46	0 (0)	46 (100) ^c	< 0.05

^aUSA-born; ^bWork-place close contacts; ^cAll cases were delayed TB patients.
TST = tuberculin skin test.

TST (which could have provided a different outcome in this investigation) was very low. Furthermore, some close contacts did not even return for the interpretation of the first round of TST, which could have also contributed to the inconsistency of the current findings with those of the 2 previous studies mentioned earlier. Limited resources and financial incentives for participants to return hindered some of the close contacts of the TB patients in this study from participating in the investigation. Unfortunately, only a few studies have conducted similar investigations, so further reasons for the differences cannot be determined.

An in-depth investigation with the use of other tools in addition to that used in the present study should be conducted with sufficient financial support in order to provide potential assistance to local TB control and prevention campaigns. This study did not receive any financial support nor was it involved

with any organizations with financial interests. Limited resources meant that the study was conducted in only one area of the country and may have contributed to the low rate of participation, and this limits the generalizability of the findings to other areas (states) in Yemen.

Conclusion and recommendations

No significant difference was found in the rate of TB infection among the close contacts of the long delay and short delay TB patients. A larger sample size and the use of other supporting investigative tools could provide a comprehensive picture of the pattern of TB transmission among all contacts. Further extensive studies with sufficient financial support are recommended in order to obtain a general perspective on the problem of TB transmission throughout Yemen.

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