Mycobacterial Diseases
ISSN: 2161-1068

Matsumoto, Mycobac Dis 2012, 2:3
DOI: 10.4172/2161-1068.1000109

Research Article Open Access

Tuberculosis Infection by Quantiferon and Related Factors in Contact Investigations - Space of Contact and Duration of Contact

Kenji Matsumoto*

Osaka City Public Health Office, Japan

Abstract

Purpose: We evaluated the risk of secondary infection due to close contact using QuantiFERON-TB Gold (QFT-2G) or QuantiFERON-TB Gold In-Tube (QFT-3G) (QFT hereafter) as a parameter of infection.

Methods: The subjects consisted of 686 contacts who were considered to require tuberculosis contact group investigation in public health centers in Osaka City and examined for infection using QFT. Negative QFT results were regarded as "absence of infection" and positive QFT results as "presence of infection", and the risk of infection in the contacts was evaluated. To compare factors between the presence and absence of infection, the χ^2 test or multiple logistic regression analysis was performed. For analysis, SPSS 13.0J for Windows was used, and $p < 0.05$ was considered to be significant.

Results: i) QFT results in the contacts: The QFT result was positive in 88 (12.8%) of the 686 contacts, negative in 525 (76.5%), equivocal in 68 (9.9%), and indeterminate in 5 (0.7%). ii) Infectivity in the index patients and QFT in the contacts: The QFT-positive rate in the contacts was significantly higher in the presence of cavity formation than in its absence in the index patients. iii) QFT in the contacts and the status of contact with index patients: There was a significant linear trend between a decrease in the floor area and an increase in the "presence of infection." with a decrease in the floor area, the rate of "presence of infection" significantly increased. The infection rate in the contacts was 14.2% for a contact time ≤ 7.9 hours, 9.9% for 8-49 hours, and 10.2% for 50-99 hours, but 20.0% for a contact time ≥ 100 hours.When the time of contact with the index patients was ≥ 100 hours, the QFT -positive rate in the contacts was significantly higher.

Discussion: Concerning the contact status, the contact time and floor area of the contact space were significantly correlated with the QFT-positive rate. Comprehensive evaluation of these factors is necessary.

Keywords: Contact investigation; Infection risk; QuantiFERON; Index case; Contact status; Environmental factors; Duration of contact; Space of contact

Introduction

The conventional diagnosis of tubercle infection in contact investigation was mainly based on the tuberculin reaction. However, in Japan, due to the influences of BCG vaccination, overdiagnosis could not be avoided in diagnosis using the tuberculin reaction. Shimouchi et al. [1] evaluated the results of tuberculosis contact group investigation in Osaka City, and reported that the accuracy of diagnosis was a problem since the diagnosis of tubercle infection was based only on the tuberculin reaction. However, due to the introduction of QuantiFERON-TB Gold (QFT-2G) or QuantiFERON-TB Gold In-Tube (QFT-3G), the accuracy of the diagnosis of tubercle infection has markedly increased. Mori et al. [2] reported that the sensitivity and specificity of QFT-2G were 89 and 98%, respectively, although the subjects consisted of patients with active tuberculosis because of the absence of a gold standard for the diagnosis of infection. Similarly, although the subjects consisted of patients with active tuberculosis, Harada et al. [3] reported a sensitivity and specificity of QFT-3G of 92.6 and 98.8%, respectively.

However, the evaluated risk factors for infection vary among contact investigations. There have been no studies on contact investigation in which the infection risk and risk factors including the contact time and space (floor area) were evaluated in detail using QFT-2G or QFT-3G (QFT hereafter) as a parameter of infection. Therefore, using QFT as a parameter of infection, we analyzed the results of tuberculosis contact group investigation performed in public health centers in Osaka City, and evaluated the infection risk.

Methods

The subjects consisted of 686 contacts, who were considered to require contact investigation by the Osaka City Public Health Office Evaluation Committee for Group Investigation (evaluation committee) and examined for tubercle infection using QFT between March 2008 and September 2011.

As factors in index patients possibly associated with infection in contacts, the sex, age, disease type on chest XP images, the grade of sputum smear positivity, and coughing period were investigated. In addition, as the status of contact with index patients, the contact time and floor area of the contact space as an environmental factor were investigated.

QFT results were evaluated in compliance with the Guidelines for the Use of QuantiFERON®TB-2G [4] for QFT-2G and the Guidelines for the Use of QuantiFERON®TB Gold [5] for QFT-3G. Negative QFT results were considered to indicate "absence of infection", positive QFT results were considered to indicate "presence of infection", and the

***Corresponding author:** Kenji Matsumoto, Osaka City Public Health Office, 1-2-7-1000, Asahimachi, Abeno-ku, Osakashi, Osaka 545-0051, Japan, E-mail: ke-matsumoto@city.osaka.lg.jp

Received March 06, 2012; **Accepted** April 18, 2012; **Published** April 20, 2012

Citation: Matsumoto K (2012) Tuberculosis Infection by Quantiferon and Related Factors in Contact Investigations - Space of Contact and Duration of Contact. Mycobac Dis 2:109. doi:10.4172/2161-1068.1000109

infection risk was evaluated. To compare factors between the presence and absence of infection, the t-test was used for continuous quantities and the χ^2 test for discrete quantities. To clarify factors associated with the presence or absence of infection, multiple logistic regression analysis was performed. For analysis, SPSS13.0J for Windows was used, and $p < 0.05$ was regarded as significant.

Results

Background of index patients

There were 129 index patients, consisting of 68 males (52.7%) and 61 females (47.3%). Their ages ranged from 17 to 90 years (mean, 45.9 ± 17.5 years). Chest XP revealed cavity formation in 77 patients (59.7%). All patients were positive for sputum smears, and the grade of positivity was 1+ in 14 patients (10.9%), 2+ in 52 (40.3%), and 3+ in 63 (48.8%). The coughing period was ≥ 2 months in 72 patients (56.7%) (Table 1).

Background of contacts and QFT

The contacts consisted of 366 males (53.4%) and 320 females (46.6%). Their ages ranged from 16 to 56 years (mean, 33.6 ± 9.3 years). The QFT result was negative in 525 contacts (76.5%), positive in 88 (12.8%), equivocal in 68 (9.9%), and indeterminate in 5 (0.7%) (Table 2).

Association between the infectivity of index patients and presence/absence of infection in contacts

Negative OFT results were regarded as "absence of infection" and positive results as "presence of infection", and the infection risk was analyzed using the χ^2 test. No significant difference was observed in the infection rate in the contacts between the sexes of the index patients. The age of the index patients was classified into ≤ 39, 40-59, and ≥ 60 years, but age was not significantly associated with the infection rate in the contacts. The infection rate in the contacts increased with an elevation in the extension of the lesion on chest XP in the index patients. This finding was more marked in the presence of bi- than unilateral lesions in the index patients, but there was no significant association between the infection rate and extent of the lesion for either bi- or unilateral lesions. However, the infection rate in the contacts was significantly higher in the presence of cavity formation than in its absence in the index patients. The infection rate in the contacts increased with a higher grade of sputum smear positivity in the index patients. The infection rate was slightly higher for a coughing period ≥ 2 months than for < 2 months in the index patients (Table 3).

Status of contact with index patients and the presence/absence of infection in contacts

The infection rate in the contacts was 14.2% for a contact time ≤ 7.9 hours, 9.9% for 8-49 hours, and 10.2% for 50-99 hours, but 20.0% for a contact time ≥ 100 hours (Table 4).

The infection rates in the contacts were 9.4 and 3.3% for floor areas of the space of contact of 100-399 and ≥ 400 m^2, respectively. However, the infection rates were 18.5, 23.5, and 16.7% for floor areas of 50-99, 25-49, and ≤ 24 m^2, respectively, being significantly higher than the infection rate for a floor area ≥ 100 m^2. There was a significant linear trend between a decrease in the floor area and an increase in the "presence of infection" with a decrease in the floor area, the rate of "presence of infection" significantly increased (Table 5).

		Incidence
Sex	Male	68(52.7)
	Female	61(47.3)
	Total	129(100)
Age, mean years (Standard Deviation)		45.9(17.5)
Chest X-ray* Lung area	Unilateral	56(43.4)
	Bilateral	71(55.0)
Cavity	Absent	50(38.8)
	Present	77(59.7)
Extent	1	14(10.9)
	2	78(60.5)
	3	35(27.1)
Grade of smear positivity	1+	14(10.9)
	2+	52(40.3)
	3+	63(48.8)
Duration of cough**	Less than 2 months	55(43.3)
	2 months or over	72(56.7)

*Laryngeal tuberculosis; 2 cases, **Unknown duration of cough; 2 cases

Table 1: Background of index cases.

	QFT(QuantiFERON-TB Gold or QuantiFERON-TB Gold In-Tube)				
Age (years)	Negative	Positive	Doubtful	Indeterminate	Total
16—19	33(89.2)	2(5.4)	2(5.4)	0	37(100)
20—29	185(83.0)	21(9.4)	16(7.2)	1(0.4)	223(100)
30—39	161(73.9)	29(13.3)	26(11.9)	2(0.9)	218(100)
40—49	128'70.3)	34(18.7)	18(9.9)	2(1.1)	182(100)
50—56	18(69.2)	2(7.7)	6(23.1)	0	26(100)
Total	525(76.5)	88(12.8)	68(9.9)	5(0.7)	686(100)

Table 2: QFT results of contacts in different age groups.

Factor/Category (index cases)		Incidence of infection (contacts)		Test
		No. tested	***Infected (%)	
Sex	Male	348	48(13.8)	NS
	Female	265	40(15.1)	
Age	-39	304	34(11.2)	
	40-59	190	35(18.4)	NS
	60-	119	19(16.0)	
*Chest X-ray Lung area	Unilateral	269	34(12.6)	NS
	Bilateral	341	54(15.8)	
Cavity	Absent	254	26(10.2)	P<0.05
	Present	356	62(17.4)	
Extent	1	60	5(8.3)	
	2	407	58(14.3)	NS
	3	143	25(17.5)	
Grade of smear positivity	1+	45	4(8.9)	
	2+	297	35(11.8)	P<0.05
	3+	271	49(18.1)	
**Duration of cough	Less than 2 months	261	33(12.6)	NS
	2 months or over	348	55(15.8)	
Total		613	88(14.4)	

*Laryngeal tuberculosis; 2 cases, **Unknown duration of cough; 2 cases ***Infected; Positive-QFT case, non-infected; Negative-QFT case

Table 3: Incidence of infection according to the related factors.

Analysis of presence/absence of infection and associated factors

Multiple logistic regression analysis was performed using negative and positive QFT results in the contacts as dependent variables and the presence/absence of cavity formation, grade of smear positivity, and the coughing period (≥ 2 months, < 2 months) in the index patients, and the contact time (< 100 hours, ≥ 100 hours) and floor area of the contact space (< 50 m^2, ≥ 50 m^2) as independent variables.

Significant differences were observed in cavity formation in the index patients, a contact time ≥ 100 hours, and a floor area < 50 m^2 with odds ratios of 2.1, 2.5, and 2.0, respectively (Table 6).

Discussion

In the Osaka City Public Health Office, whether or not tuberculosis contact group investigation is necessary has been decided by an evaluation committee consisting of multiple physicians, public health nurses, and office workers [6]. The major evaluation items include the grade of sputum smear positivity, coughing period, and disease type on chest XP images in index patients, the time of contact with index patients, frequency of ventilation in the main contact place, and the contact space volume. Therefore, when index patients had a low grade of smear positivity or no coughing, or when the contact place was well ventilated or outdoors, their contacts were often not included as the subjects of contact investigation. Shimouchi et al. [1] summarized the results for the decision regarding the necessity for contact investigation and results of contact investigation, and reported a significantly lower number of patients with secondary infection in the group who required contact investigation than in the group who did not require it, supporting the results of the decision by the evaluation committee. However, since the tuberculin reaction was mainly used for the diagnosis of infection, overdiagnosis may have often occurred in Japan where BCG vaccination is commonly performed, and unnecessary treatment for latent tuberculosis infection may have been administered.

In this study, positive QFT results were regarded as "presence of infection" and negative results as "absence of infection". The infection risk was evaluated after excluding equivocal and indeterminate QFT results. In contacts showing equivocal QFT results, the presence or absence of infection is generally determined based on the infection risk [4,5]. However, since the definition of the infection risk is unclear, such contacts were excluded from the subjects for analysis in this study. The age of the contacts ranged from 16 to 56 years (mean, 33.6 ± 9.3 years). Although the contacts were relatively young, certain percentages of previously infected contacts according to age were considered to be included, as Ohmori reported [7]. Multiple logistic regression analysis with consideration given to age showed significant differences in cavity formation in index patients, the contact time, and floor area of the contact space.

There have been many studies on factors in index patients associated with secondary infection or disease onset in contacts. Shimouchi et al. [1] reported a significantly higher number of secondary cases in the presence of cavity formation, Gaffky scale 5 or higher, a coughing period ≥ 2 months, and a high infection risk index [maximum Gaffky scale × coughing period (month as a unit)] in index patients. Aoki et al. [8] reported that all index patients who caused outbreaks of tuberculosis showed Gaffky scale 3 or more, and most patients (83.3%) had a coughing period 3 months. Inoue et al. [9] reported that positive smears, the cavity formation type, age of 10-39 years, and males were significantly more frequently observed in 109 index cases in outbreaks of tuberculosis. Grzybowski et al. [10] reported a higher incidence of tuberculosis in contacts when index patients were positive for smears than positive for cultures alone. Similarly, Sepkowitz et al. [11] reported that the infection risk in contacts is high for positive smears and low for positive cultures and even lower for negative cultures in index patients. Driver et al. [12] made a diagnosis of infection based on the tuberculin reaction and development of secondary cases, and reported that contacts were significantly more frequently diagnosed with infection in the presence of cavity formation in index patients. These results were consistent with ours, but we could not observe differences in the infection risk among the grades of sputum smear positivity or between the presence and absence of coughing. Since whether contact

	Incidence of infection	
Duration of contact (hours)	No. tested	Infected (%)
-7.9	106	15(14.2)
8-49	161	16(9.9)
50-99	98	10(10.2)
100-	215	43(20.0)
Total	580	84(14.5)

P of trend of linear trend of proportion <0.05, Unknown duration of contact; 33 cases

Table 4: Incidence of infection according to duration of contact.

	Incidence of infection	
Space of contact (sq. meters)	No. tested	Infected (%)
-24	108	18(16.7)
25-49	81	19(23.5)
50-99	151	28(18.5)
100-399	191	18(9.4)
400-	60	2(3.3)
Total	591	85(14.4)

P of trend of linear trend of proportion <0.01, Unknown space of contact; 22 cases

Table 5: Incidence of infection according to area of space where contacts occurred.

Factor/Category		Odds ratio	95%CI	Test
Grade of smear positivity	3+	1.4	0.7-2.0	NS
	1+ or 2+	1		
Chest X-ray Cavity	Present	2.1	1.2-3.5	P<0.01
	Absent	1		
Duration of cough	2 months or over	1.2	0.7-2.0	NS
	Less than 2 months	1		
Duration of contact (hours)	100-	2.5	1.5-4.1	P<0.01
	-99	1		
Space of contact (sq. meters)	-49	2.0	1.2-3.4	P<0.01
	50-	1		

Table 6: Odds ratios of incidence of infection according to various factors (Multiple logistic regression analysis).

investigation is necessary is determined by the evaluation committee, all index patients in this study were smear-positive. In addition, when index patients showed negative smears, a low grade of smear positivity, no coughing, or when the contact place was well ventilated, or the contact time was short; their contacts were excluded from this investigation due to a low infection risk. In general, when index patients show a low grade of smear positivity or no coughing, only very close contacts undergo contact investigation. Therefore, differences in the infection risk may be underestimated.

On the other hand, Fujioka et al. [13] evaluated the results of outbreaks of tuberculosis in non-periodic examinations, and observed infection even in contacts showing a low infection risk index. Therefore, the infection risk cannot be evaluated only based on factors in index patients. To our knowledge, there have been no detailed studies on the status of contact with index patients and infection risk, but there are some case reports. Concerning the status of contact with index patients, the above described Grzybowski et al. [10] observed a significantly higher incidence of tuberculosis in close contacts such as family members. Driver et al. [12] reported a significantly higher infection rate in contacts showing a long contact period. Rogers et al. [14] also reported a higher positive tuberculin conversion rate with a longer contact time. Toyota [15] reported a large-scale outbreak of tuberculosis in a junior high school, and suggested dense classrooms with inadequate ventilation as its factor. We also previously reported a patient in whom tuberculin infection was closely associated with the ventilation frequency and airflow [16]. On the other hand, Takamatsu et al. [17] and Toyota et al. [18] reported outbreaks of tuberculosis in which infection unexpectedly spread to even persons only slightly exposed to index patients. These cases suggest the presence of factors contributing to the spread of infection other than those evaluated in this study.

In this study, in which infection risk factors in index patients were also evaluated, the time of contact with index patients and floor area of the main contact space were significant risk factors for infection. Although we wished to add ventilation frequency to the evaluation items, this factor could not be evaluated because it was unclear in many institutions.

References

1. Shimouchi A, Koda S, Hirota S, Matsumoto K (2009) Evaluation of tuberculosis contact investigation & examination in congregate settings in Osaka city. Kekkaku 84: 491-497.
2. Mori T, Sakatani M, Yamagishi F, Takashima T, Kawabe Y, et al.(2004) Specific Detection of Tuberculosis Infection with an Interferon-gamma Based Assay Using New Antigens. Am J Respir Crit Care Med. 170: 59-64.
3. Harada N, Higuchi K, Yoshiyama T, Kawabe Y, Fujita A, et al. (2008) Comparison of the sensitivity and specificity of two whole blood interferongamma assays for tuberculosis infection. J Infection 56: 348-353.
4. The Preventive Committee of the Japanese Society for Tuberculosis (2006) Guidelines for using the QuantiFERON- TB Gold test. Kekkaku 81: 393-397.
5. The Preventive Committee of the Japanese Society for Tuberculosis (2011) Guidelines for using the QuantiFERON- TB Gold In-Tube. Kekkaku 86: 839-844.
6. Matsumoto K, Tatsumi T, Kamiya N, Arima K, Koda S, et al. (2010) Tuberculosis infection by tuberculin skin test or Quantiferon and related factors in contact investigations. Kekkaku 85: 547-552.
7. Ohmori M (1991) Estimating the year of eradication of tuberculosis in Japan. Kekkaku 66: 819-828.
8. Aoki M (2004) Transmission of tuberculosis (2). Kekkaku 79: 693-703.
9. Takeo Inoue (2008) Characteristics of 109 index cases in TB outbreak. Kekkaku 83: 465-469.
10. Grzybowski S, Barnett GD, Styblo K (1975) Contacts of cases of active pulmonary tuberculosis. Bull Int Union Tuberc 50: 90-106.
11. Sepkowitz KA (1996) How contagious is tuberculosis? Clin Infect Dis 23: 954-962.
12. Driver CR, Balcewicz-Sablinska MK, Kim Z, Scholton J, Munsiff SS (2003) Contact investigation in congregate settings, New York City. Int J Tuberc Lung Dis 7: 432-438.
13. Fujioka M, Funahashi K, Inuduka K, Hattori S, Maruyama S (2000) A study on the risk factors for tuberculosis epidemics observed from the results of extraordinary health examinations. Kekkaku 75: 71-77.
14. Rogers EFH (1962) Epidemiology of an outbreak of tuberculosis among school children. Public Health Report 77: 401-406.
15. Toyota M (2003) Environmental factors relating to a mass outbreak of tuberculosis in a junior high school. Kekkaku 78: 733-738.
16. Matsumoto K, Tatsumi T, Arima K, Koda S, Yoshida H, et al. (2011) An outbreak of tuberculosis in which environmental factors influenced tuberculosis infection. Kekkaku 86: 487-491.
17. Takamatsu I, Kameda M, Inoue T, Toyoshima K (1999) Tuberculosis outbreak among inpatients. Kekkaku 74: 397-404.
18. Toyota M, Morioka S (2001) Tuberculosis outbreak in a junior high school in Kochi city -Studies on Factors Relating to Extent of Tuberculosis Infection and the Efficacy of Isoniazid Chemoprophylaxis. Kekkaku 76: 625-634.