

Original Article

REPRODUCIBILITY OF THE QFT-G-IT ASSAY
IN THE CONTACT EXAMINATION IN WHICH A HIGH POSITIVE RATE
WAS SHOWN INDEPENDENT OF CONTACT TIME¹Hideo YOSHIKAWA and ²Kouichiro BABA

Abstract [Objective] A contact examination conducted using the QuantiFERON[®]-TB GOLD In-Tube (QFT-G-IT) assay shows a high positive rate independent of the closeness of contact. Among individuals with a short contact time of only 1.1 ± 1.3 h with the index tuberculosis (TB) case, the QFT-G-IT assay positive rate was 13.9%, which was considered extraordinarily high (for reference, the proportion of previously infected individuals in the Japanese general population with the same age has been estimated to be approximately 7.3%). We retested the QFT-G-IT-positive contacts to examine the reproducibility of the QFT-G-IT assay and to confirm the reliability of the test results.

[Method] Of the 216 participants who underwent the first examination, 33 who tested positive (23 close contacts and 10 casual contacts) were retested by an experienced technician at the same laboratory; care was taken to minimize possible causes of variations (method of shaking tubes, temperature, vibration during transportation of the specimens, etc.). In addition, the participants were tested using other interferon (IFN)- γ release assays (IGRAs), namely, QuantiFERON[®]-TB GOLD (QFT-G) and T-SPOT, in order to confirm the reliability of the QFT-G-IT assay.

[Result] Among the 33 retested participants, only 7 (4 close contacts and 3 casual contacts) tested positive, and the remaining 26 participants (19 close contacts and 7 casual contacts) had discordant results. Out of the 11 participants (33.3%) in whom IFN- γ levels varied between 0.35 and 0.50 IU/ml (just above the diagnostic cut-off) in the initial test, 10 (90.9%) tested negative, with IFN- γ levels being less than 0.35 IU/ml in the retest. The results of the different IGRAs showed moderate to high agreement, with κ values of 0.406 between QFT-G-IT

and QFT-G and 0.604 between QFT-G-IT and T-SPOT.

[Conclusion] The findings of this study showed that the QFT-G-IT assay was not reproducible and robust. Judging from the agreement between the different IGRAs, it seems that the results of the retest conducted using the QFT-G-IT assay had a higher reliability than those of the initial test. In the QFT-G-IT retest, reversion from positive to negative occurred mostly in the case of participants with initial measurements just above the diagnostic cut-off. Therefore, attention must be given not only to the dichotomous results (positive or negative) but also to the exact level of IFN- γ production. The results of the QFT-G-IT assay may also be affected by various environmental factors. If the QFT-G-IT assay yields a high positive rate disproportionate to the closeness of contact, the result should be carefully interpreted, taking into account the unreliability of the QFT-G-IT assay as a possible cause of discordance. Further studies under various settings are needed to establish the reliability of IGRAs.

Key words : Tuberculosis, Contact examination, QuantiFERON[®]-TB GOLD In-Tube assay, Reproducibility, Contact time, Interferon-gamma release assay (IGRA)

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Short Report

THE POSITIVE RESPONSE RATE WITH QuantiFERON®-TB GOLD In-Tube
IN PATIENTS WITH *MYCOBACTERIUM AVIUM* COMPLEX

Niro OKIMOTO, Fumiyo NANBA, Takeyuki KURIHARA, and Naoyuki MIYASHITA

Abstract [Objective] We studied the positive response rate with QuantiFERON®-TB GOLD In-Tube in patients with *Mycobacterium avium* complex disease.

[Materials and Methods] We evaluated 62 subjects with *M. avium* complex disease. QuantiFERON®-TB GOLD In-Tube was performed for all the subjects. The positive response rate with QuantiFERON®-TB GOLD In-Tube and the history of pulmonary tuberculosis in patients who showed a positive response were evaluated.

[Results] Seven patients (11.3%) showed a positive response with QuantiFERON®-TB GOLD In-Tube. These patients were elderly (age, 72–87 years) and had a history of pulmonary tuberculosis. Eleven other patients with a history of pulmonary tuberculosis showed a negative response with QuantiFERON®-TB GOLD In-Tube.

[Conclusion] Half or less than half of the elderly patients

with *M. avium* complex disease and a history of pulmonary tuberculosis showed a positive response with QuantiFERON®-TB GOLD In-Tube.

Key words : Pulmonary nontuberculous mycobacteriosis, *Mycobacterium avium* complex, QuantiFERON®-TB GOLD In-Tube

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Short Report

**MYCOBACTERIUM IMMUNOGENUM ISOLATED FROM
A METAL WORKER IN JAPAN**

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²Satoshi MITARAI, and ¹Yoshinari KITAHARA

Abstract In the United States and European countries, *Mycobacterium immunogenum* has been identified in metalworking fluids and is reported to be a causative agent of metalworking fluid-associated hypersensitivity pneumonitis. However, in Japan, there has been no reports of *M.immunogenum* isolated from metalworking fluids. This is the first report of isolation of the microorganism from the sputum of a metal-grinding machine worker in Japan. We should consider the possibility of *M.immunogenum* infection in case of non-tuberculosis mycobacteriosis and hypersensitivity pneumonitis in metalworkers.

Key words : *M.immunogenum*, *M.lentiflavum*, Colonization

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————— Case Report —————

A CASE OF PULMONARY TUBERCULOSIS COMPLICATED WITH SEVERE THROMBOCYTOPENIA DURING TREATMENT

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Abstract A 58-year-old man was hospitalized with dyspnea. His sputum tested positive for acid-fast bacilli, and PCR analysis revealed *Mycobacterium tuberculosis*. After the initiation of treatment with isoniazid, rifampicin, ethambutol, and pyrazinamide, the patient developed severe thrombocytopenia. The thrombocytopenia persisted even after the discontinuation of all antituberculosis drugs, and hence, the patient was given blood transfusion. Later, it was found that the patient's platelet-associated IgG level was high, and bone marrow aspiration revealed the presence of megakaryocytes with lesser degree of platelet adhesion. Considering that the patient's thrombocytopenia was induced by an immunological mechanism, he was administered prednisolone; this resulted in the resolution of thrombocytopenia. The patient successfully completed the tuberculosis treatment. Clinicians should

remember that antituberculosis drugs may induce autoimmune thrombocytopenia, and if they experience such a case, they should report it to share information, including the names of possible offending drugs.

Key words : Pulmonary tuberculosis, Drug-induced autoimmune thrombocytopenia, Steroid therapy

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TUBERCULOSIS ANNUAL REPORT 2009

—Series 9. Treatment of TB (2)—

Tuberculosis Surveillance Center, RIT, JATA

Abstract The standard treatment for tuberculosis (TB) is the key to its control. Here, we report on the statistics of treatment status and the duration of hospitalization/treatment.

The place of initial treatment was observed among newly notified TB patients (n=24,170) in 2009. The proportion receiving treatment in hospital was highest (91.8%) in sputum smear-positive pulmonary TB patients (n=9,675) including 2.3% hospitalized mainly due to other diseases. The proportion receiving treatment in hospital was the least (25.1%) among bacteriologically negative pulmonary TB cases, including 10.4% hospitalized mainly due to other diseases. Among sputum smear-positive pulmonary TB cases the proportion of patients receiving treatment in hospital did not differ with age, but among bacteriologically negative pulmonary TB cases, this proportion differed markedly according to age group (e.g., 7.7% of those in their 20s, 24.4% of those in their 50s and 48.8% of those in their 80s).

The duration of hospitalization for TB treatment among newly notified cases in 2008 was observed. The median hospitalization periods were 73 days, 78 days, 45 days, 36 days and 46 days, among new sputum smear-positive pulmonary

TB cases, retreatment sputum smear-positive pulmonary TB cases, other bacillus-positive pulmonary TB cases, bacilli-negative pulmonary TB cases and extra-pulmonary TB cases, respectively.

The duration of TB treatment among newly notified cases in 2008 was observed at the end of 2009. The median treatment duration among all forms of TB was 272 days. The longest median treatment duration was 286 days for retreatment of sputum smear-positive pulmonary TB cases and the shortest was 198 days for bacteriologically negative pulmonary TB cases.

Key words: Tuberculosis, Age, Treatment status, Duration of hospitalization, Duration of treatment, INH, RFP

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THE BACKGROUND OF DRUG-RESISTANT TUBERCULOSIS PATIENTS ON THE BASIS OF THE ANNUAL REPORT DATABASE FOR 2007–2009 IN JAPAN

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Takashi YOSHIYAMA, and Satoshi MITARAI

Abstract In this study, the background of drug-resistant tuberculosis (TB) patients in Japan was analyzed using the annual report database for 2007–2009. The results of the drug susceptibility test of 15,425 patients who were diagnosed with pulmonary TB between 2007 and 2009 were obtained and analyzed.

The chi-square test for independence between susceptibility test results and parameters (i.e., sex, age, nationality, etc.) was conducted. Logistic regression analysis was performed using the variables (20s, 30s, 40s, ..., new treatment, retreatment, etc.) of parameters that were statistically significant by chi-square test.

The risk of multi-drug resistance (MDR) among TB patients who underwent retreatment was significantly high (odds ratio = 11.3, 95%CI: 7.7–16.6, $p < 0.001$, reference = new treatment), and the risk of MDR among foreigners who had entered Japan within the last 5 years was also high (odds ratio = 9.5, 95%CI: 4.6–19.4, $p < 0.001$, reference = Japanese).

Moreover, logistic regression analysis was performed for TB patients who had previously undergone treatment. The risk of MDR was higher among the patients treated after 1970 than those treated before 1970. Especially, the risk of MDR among the patients previously treated in 1990–1999 was extremely high (odds ratio = 20.8, 95%CI: 5.7–75.0, $p < 0.001$, reference = before 1970). The risk of MDR among previously treated foreigners who had entered Japan within the last 5 years was also high (odds ratio = 3.8, 95%CI: 1.1–13.2, $p = 0.036$).

Similar to the results for MDR, the risk of resistance to one or more drugs was significantly high among TB patients who underwent retreatment for TB (odds ratio = 2.2, 95%CI: 1.9–2.6, $p < 0.001$) and foreigners who had entered Japan within the last 5 years (odds ratio = 1.8, 95%CI: 1.3–2.5,

$p < 0.001$); however, their risk of resistance to one or more drugs was lower than that for MDR. In addition, the odds ratios of age groups younger than 80 years to those over 80 years were obtained. They were 2.1 (95%CI: 1.5–2.9) in 0–29 years, 2.2 (95%CI: 1.6–3.0) in 30–39 years, 2.2 (95%CI: 1.7–3.0) in 40–49 years, 2.1 (95%CI: 1.6–2.8) in 50–59 years, 1.9 (95%CI: 1.4–2.5) in 60–69 years, and 1.5 (95%CI: 1.2–1.8) in 70–79 years.

With respect to the background of high MDR among TB patients who underwent retreatment and foreigners who have recently entered Japan, the usage of RFP and poor adherence to drugs and entry from high-prevalence countries with high MDR risk were suspected. Regarding the background of generational differences in resistance to one or more drugs, it was suspected that most people over 80 years of age had been infected with TB bacilli in the distant past, before anti-TB drugs were available, when drug-resistant bacilli had not yet emerged. However, the younger generations have become more susceptible to drug-resistant TB bacilli because anti-TB drugs were being widely used when they were born, and drug-resistant bacilli were prevalent in the world.

Key words: Tuberculosis, Drug resistance, MDR, Resistant to any INH, Retreatment, Foreigner, Age

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TUBERCULOSIS CARE AND NEW HORIZON OF JAPANESE SOCIETY

Chairpersons: ¹Nobukatsu ISHIKAWA and ²Naohiro NAGAYAMA

Abstract Current tuberculosis (TB) problems are reflections of Japanese society. Living or dying alone among the elderly, difficulty in finding jobs or withdrawal into themselves among the youths are features of modern society. The future needs for TB care were discussed on specific topics of TB among the elderly, foreigners and the homeless. Presenters showed the importance of the patient-centered care in collaboration with public health and welfare services. Both patients and staffs will see others shining, as they touch each other in the deep part of human existence. A diabetic ex-TB patient talked his experience in his treatment. His window of mind was gradually opened from inside with the continuous support in DOTS by the staff of the public health center. To accumulate these experiences of a heartwarming atmosphere will have the effective power on establishment of social supporting systems. This symposium can be a step towards humanized society or a new horizon of public health which can answer to another need of inner cry of a sick people particularly among the socially disadvantaged who are the victims of the weakness of society.

1. Current situation and issues of elderly tuberculosis patients: Eriko SHIGETO (NHO Higashihiroshima Medical Center)

By the analysis of 102 tuberculosis patients of 70 years old and above who were registered at Hiroshima Prefectural Health Center in 2009, 41 patients had severe complications such as diabetes mellitus, renal insufficiency, malignancy or cerebrovascular disorder. Their prognosis was rather poor and the ADL tended to be worsened during hospitalization. Though 16 of the 34 deaths were caused with non-tuberculosis diseases, the ratio of the tuberculosis deaths was higher (4/17) among the patients living alone. Sufficient care of the elderly for early diagnosis, care system to treat various complications and patient support are required.

2. Provision of medical interpreters to help foreigners with tuberculosis in Tokyo: Takashi SAWADA (Services for Health in Asian & African Regions (SHARE))

In 2006, Tokyo Metropolitan Government started to dispatch interpreters for foreigners to strengthen DOTS program. Collaboration with NGOs made it possible to train 37 volunteer interpreters, and to provide services in 13 languages, as of 2010. In Japan, the treatment defaulter rate among non-Japanese tuberculosis patients had been remarkably high. But with having the assistance of interpreters, the treatment completion rate has become higher than 80%. It is recommended to expand a similar system to other part of Japan, as the proportion of foreigners among total tuberculosis cases keeps on increasing nationwide.

3. Tuberculosis problems in Japan from the view point of homelessness—through the activities of a NPO supporting the homeless in collaboration with a public health center: Sadako KANAZAWA (Volunteer, NPO Medical Care Team of Shinjuku Renraku-Kai)

It has been 20 years since the issue of homelessness emerged in Japanese society. The people with a history of both tuberculosis and experience of homelessness tend to show a poor prognosis. Our team has played an active role, working with Shinjuku Public Health Center for conducting a screening for tuberculosis every year. It seems that the screening service itself does not make a fundamental solution for homeless people with tuberculosis. Developing a more basic system of 'from street to apartment' is more essential. We believe that understanding the importance of the system is most essential to the people who are involved in health and medical care.

4. What we have learned from DOTS—Toward care by cuddling the patient's mind: Kazuyo ARIMA (PHN, Osaka City Public Health Center)

Osaka City has achieved the goals of DOTS set up by the City's TB Control Guidelines since 2001 such as 80% DOTS implementation rate, halving the defaulter rate and incidence rate. It was shown by analysis that the treatment success depends on 'patient's awareness of the disease', 'appropriate DOTS method for each patient', 'existence of side effects', or

'the relationship between treatment supporters'. Through working for the patients whose treatment management was difficult, we have learned that our attitude towards the patients is a most important first step to build a good relationship and mutual trust with the patients, and DOT is an important tool. For treatment supporters, 'the patient-centered care', 'care by staying close to the patients' or 'cuddling the patient's mind' is most necessary to lead the patients to cure.

5. Patient's view: Through DOTS, my life has been renewed: Kuniyoshi MAEDA (Himawari no kai; Ex-homeless TB patients self-help group)

It is an unforgettable memory that I was hospitalized due to TB back in 2009. I was seriously ill with also diabetes mellitus. Because I had lost everything due to my friend's cheating, I could not trust anyone before the TB treatment. But I learned how to think of others through the daily communication with doctors, nurses, other staff at the hospital, and Public Health Center. They encouraged me every day and I came to desire to answer to their expectations. Public health nurses taught me that building the reliable relationship is so essential for humans, and I may not have realized this importance if I had not been treated for TB, or treated outside Shinjuku. I would rather say that I was lucky to have got TB, as I have become able to trust other people through DOTS TB care. DOTS is not only for medication, but also general health care and counseling. I hope that as many as poor people, especially homeless can have a similar experience by knowing more about TB and using a health service. I would like to cooperate with TB services if I can be useful.

Commentator's Summary: Tuberculosis control and public

health: Toshio TAKATORIGE (Graduate School of Safety Science, Kansai University)

Tuberculosis was ever the biggest health problem in Japan. Ministry of Health and Welfare and Public Health Centers were founded to push forward tuberculosis control. Local governments, companies and people had to follow the national tuberculosis control program uniformly without exception. Currently a new stream of tuberculosis control has been started by DOTS strategy. The aim of DOTS has made all patients take medicine regardless of their social conditions until cure. Every patient is snuggled up and supported whether he is homeless, criminal or a foreigner. The patients also participate in the program actively. The DOTS may be a new public health movement. The strong public health infrastructure is necessary to maintain tuberculosis control towards the low incidence situation. The role of the local government should be more important.

This symposium has also shown that the tuberculosis services must be patients-centered and supported by the people, addressing a new horizon of public health in Japan through tuberculosis control.

Key words: Tuberculosis, Japanese society, Socially disadvantaged, Patient-centered care

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