

Original Article

POSSIBLE PRESENCE OF A BOOSTER EFFECT IN PEOPLE REPEATEDLY EXPOSED TO *MYCOBACTERIUM TUBERCULOSIS* DEMONSTRATED IN A *MYCOBACTERIUM TUBERCULOSIS*-SPECIFIC INTERFERON-GAMMA RELEASE ASSAY

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Abstract [Introduction] Recently, several reports have described a waning response of *Mycobacterium tuberculosis* (TB)-specific interferon-gamma (IFN- γ) release assays (IGRAs) performed years after the initial TB infection. Since a considerable part of elderly people in Japan was infected with TB in their youth, it was hypothesized that if the general population was screened with IGRAs, the mean IFN- γ value of positive subjects (POSITIVES) would be reduced as the age of the subjects increased. Conversely, in subjects who were recently exposed to TB (CONTACTS), it was assumed that the POSITIVES would include subjects with new TB infections who show a high IFN- γ value and those with old TB infections who show a low IFN- γ value. Since the presence of subjects with old infections among the POSITIVES cannot be avoided during examinations, it is hypothesized that the mean IFN- γ value of the POSITIVES decreases as the age of the CONTACTS increases.

[Materials and Methods] To test this hypothesis for CONTACTS, data acquired during the contact examinations at Adachi Public Health Center in Tokyo, Japan were analyzed. Since it is thought that the grade of exposure of the TB index case (INDEX CASE) influences the IFN- γ value, its relationship with the INDEX CASE and the infectivity of the INDEX CASE were also investigated. In the CONTACTS, as only a few healthcare workers are <20 years old or >70 years old, the subjects were chosen from individuals aged in the range of 20–69 years who had been in contact with a TB patient within the past 3 months. The IFN- γ value of the 188 POSITIVES in the 1145 CONTACTS who underwent a contact examination using the IGRA QuantiFERON®-TB Gold In-Tube (QFT-G-IT) assay was investigated. The POSITIVES were divided according to their age class, and their IFN- γ values were compared. In addition, after dividing all POSITIVES into groups to assess their relationship with the INDEX CASE (i.e., household, relative, healthcare worker, and others), the IFN- γ values of the 20–49- and 50–69-year-old classes were compared in each group.

[Results] There was no significant difference in the IFN- γ values between the age classes, (Kruskal-Wallis test, $P=0.598$). When the IFN- γ values of the POSITIVES in the

20–49- and 50–69-year-old classes were compared for each relationship group, the mean IFN- γ value of the POSITIVES increased in proportion to the rise in age only in the healthcare worker group. This occurred even though the mean IFN- γ value of the POSITIVES decreased in many groups as their age increased. A significant difference was confirmed in the IFN- γ values between the age classes in the healthcare worker group (Wilcoxon rank-sum test, $P<0.001$). No significant difference was observed in the infectivity of the INDEX CASE between the age classes in the healthcare worker group.

[Conclusion] Initially, it seemed that the high infectivity of the INDEX CASE affected the IFN- γ values of the POSITIVES in the oldest age class; in other words, the factor expected to decrease actually increased. However, comparison of the IFN- γ value by age class in each relationship group revealed that, in the healthcare worker group only, the IFN- γ value of POSITIVES increased in proportion to the rise in age regardless of infectivity of the INDEX CASE. Since it has been hypothesized that healthcare workers have an increased chance of contact with TB patients than other relationships, this outcome suggests the existence of a booster effect on people who are repeatedly exposed to TB, as assessed using IGRAs, as one of the several possibilities. If this booster effect seen with IGRAs is proven, predicting the development of symptoms and presuming the infection time by using IFN- γ values will be difficult. To validate the present results, animal experiments that can be adjusted for various biases and confounding factors are necessary.

Key words: Tuberculosis, Contact examination, Healthcare worker, QuantiFERON-TB Gold In-Tube (QFT-G-IT), Interferon-gamma release assays (IGRAs), Booster effect

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Original Article

CURRENT STATUS OF MULTIDRUG-RESISTANT TUBERCULOSIS IN JAPAN:
A LITERATURE REVIEW AND META-ANALYSIS

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Abstract A literature review and meta-analysis of the incidence, clinical characteristics, and treatment outcomes associated with multidrug-resistant (MDR) tuberculosis (TB) in Japan was performed. An estimated 110–120 new cases of MDR-TB occur every year, constituting 0.7–0.8% of all cases starting TB chemotherapy in Japan. The frequency of MDR is higher in previously treated TB patients than in primary treatment patients; it is also higher among younger patients. Treatment outcomes are poor; the cure rate as conventionally defined is 50–60%. These primary characteristics of MDR-TB in Japan are similar to those reported abroad, although it appears that the Japanese MDR strains are more resistant, such as having a high frequency of extremely drug-resistant (XDR) strains, and a higher frequency of resistance to fluoroquinolones. However, we should remember that variations among

institutions and the different methodologies used in reported studies are too numerous to allow any rigorous conclusions to be drawn. This will be a major challenge to the promotion of clinical studies and the control of MDR-TB in Japan.

Key words: Tuberculosis, Chemotherapy, Multi-drug resistance, Drug resistance

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Report and Information

MEDICAL SERVICE SYSTEMS FOR TUBERCULOSIS IN LOW-INCIDENCE COUNTRIES

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Abstract [Objectives] Currently, Japan has a near low incidence of tuberculosis (TB); the incidence is below 20/100,000. Considering this incidence, the medical service provision system needs to be restructured and related policies need to be revised. The Revised National Guidelines for TB Control, issued in May 2011 by the Ministry of Health, Labour, and Welfare, provided the policy towards achieving a low incidence of TB. This study aims to provide suggestions for restructuring the medical service system in Japan by analyzing the systems in selected countries with low incidence.

[Method] Between 2004 and 2010, we conducted tours to study TB control and medical services in the UK, the USA, Germany, the Netherlands, and Norway. In these tours, we visited the medical facilities, agencies implementing preventive activities, health departments of central and local governments, reference laboratories, technical agencies, non-governmental organizations, and other organizations involved in TB control in these countries. In addition, we collected information from published papers and related documents through the internet. This paper reports the policies and strategies adopted in these low-incidence countries, especially pertaining to medical service systems, directly observed treatment, short-course (DOTS) services, hospital beds and facilities, objectives and duration of hospitalization, and mechanisms for maintaining quality medical services.

[Results] In all the visited countries, except Germany, TB patients were diagnosed and treated, as well as provided support such as DOTS, by a single organization or agency. In the US and Norway, DOTs was provided to all TB patients at chest centers and/or health centers. On the other hand, in the UK, guidelines from the National Institute for Health and Clinical Excellence (NICE) stated that DOT is not necessary for managing most active TB cases. In these countries there were 3 modes of treating infectious patients: home isolation, hospitalization for the first 2 weeks after initiating treatment, and hospitalization until smear examination results are negative. None of the countries had official standards for hospitalization. Measures to maintain service quality were

integrating service providers, strengthening technical support, training and/or educating experts, and networking of personnel in charge.

[Discussion] The study tours were conducted over 6 years, but no follow-up surveys were conducted. In each visit, we visited only a limited number of medical facilities, which may not be representative of that country. Obviously, this report does not aim to be a comparative study but to provide useful information for discussing the future direction of the medical service system in Japan. In Japan, TB is diagnosed and treated in hospitals and clinics, but contact surveys and other preventive activities are conducted in health centers. In this regard, Japan seems to be unique in that the ways to achieve collaboration among hospitals, health centers, and related organizations are emphasized in the revised National Guidelines for TB Control. Regardless of the DOT target group of a patient, healthcare providers in Japan are expected to ensure patient's adherence through patient-centered support in order to achieve successful treatment. In Japan, the central Government is expected to take responsibility to prevent infection. We suggest that the standards for lengths of hospital stay of TB patients should be revised such that the lengths are based on each patient's bacteriological condition and social setting. The revised National Guidelines for TB Control provide frameworks for ensuring the quality of medical services, but further discussions are warranted in order to plan and implement an effective strategy.

Key words: Tuberculosis, Medical service, Hospitalization, Low incidence, National Guidelines for TB control

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Report and Information

TUBERCULOSIS ANNUAL REPORT 2010**—(4) Tuberculosis in the Elderly—**

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Abstract Since 1999, the notification rates among tuberculosis (TB) patients aged 85 years or above in Japan have been consistently higher than those of patients belonging to other age groups. The annual rates of reduction in age-specific TB notifications were similar among elderly patients (defined as those aged 65 years and above) until the mid-1990s; however, since 2000, the reduction rate in patients aged 65–79 years has accelerated.

The proportion of elderly TB patients has increased 1.6 times, from 36.8% in 1987 to 59.1% in 2010, and the proportion of TB patients aged 80 years or older has increased 3.8 times, from 7.9% to 29.7% during the same period.

The rate of bacteriologically positive TB among pulmonary TB (PTB) patients was higher in the elderly than in patients aged 15–64 years (referred to as “young adults”). The proportion of PTB patients with only non-respiratory symptoms increased with age: 16.2% in patients aged 65–74 years, 20.1% in those aged 75–84 years, and 23.6% in those 85 years and older.

The proportion of TB cases in the elderly where patient delay was ≥ 2 months was approximately twice less than that in young adults (13.8% vs. 25.9%), whereas the proportion of

TB cases in elderly patients where doctor delay was ≥ 1 month was slightly higher than that for young adults (24.2% vs. 20.0%). The elderly PTB patients tended to be diagnosed with TB when they were treated as outpatients or inpatients for diseases other than TB.

Of the newly notified TB patients in 2009, 27.6% died within a year of initiation of TB treatment; of these, 15.9% died within 3 months. The proportion of deaths within 3 months after the initiation of therapy showed substantial increase with age.

Key words: Tuberculosis, Notification rate, Elderly, Annual trend, Epidemiological indicators, Death, Prefecture

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