

— The 88th Annual Meeting Invited Lecture —

NATIONAL SURVEYS OF THE PREVALENCE OF TUBERCULOSIS DISEASE

— Overview, Progress and Lessons Learnt —

Ikushi ONOZAKI

Abstract This is a summary of an invited lecture at the 88th annual assembly of the Japanese Society for Tuberculosis on 28 March 2013. The lecture was carried out in Japanese.

The WHO's Global Task Force on TB Impact Measurement was established in June 2006 to produce a robust, rigorous and widely-endorsed assessment of whether the 2015 targets for reductions in TB incidence, prevalence and mortality are achieved at global and regional levels and in individual countries; to regularly report on progress towards these targets in the years leading up to 2015; and strengthen national capacity in monitoring and evaluation of TB control. Three major and inter-related areas of work were defined and working groups were established to cover each of these areas, Surveillance, Prevalence surveys, and Estimates of TB burden, in 2007.

Before 2000 few countries had implemented nationwide TB disease prevalence surveys except in East Asia. In Africa, no national survey was carried out since early 1960s except Eritrea in 2004 that did not include chest x-ray screening and culture confirmation. In 2007, the Task Force identified more than 50 countries that met epidemiological and other criteria for implementing a survey. Among them, 22 countries were selected as global focus countries to receive intensive support to carry out a survey by 2015.

Following five years of enormous effort in each level, unprecedented progress has been achieved: thirteen including eleven global focus countries carried out a survey with chest

x-ray screening and culture diagnosis between 2007 and today (March 2013). At least six countries are expected to launch a survey in 2013, and seven are already in a pipeline to launch one in 2014. These surveys provide an unbiased estimation of disease burden that is often higher than it was thought when the survey was planned especially in Asian countries. Surveys are also providing a rich source of data to inform programme policy and strategy: In this lecture, lessons learnt from surveys in China, Cambodia and Myanmar were discussed to show impact of DOTS as well as its limitations and challenges caused by rapidly ageing populations in Asia. An overall synthesis of the main implications of the results from recent prevalence surveys implemented in Asia and Africa for post-2015 global TB policy and strategy is also in the pipeline. The summary results and implications will be widely disseminated from 2014 when the results of the surveys in African countries are finalized.

Key words: Tuberculosis, National TB Prevalence Survey, TB Impact Measurement, Millennium Development Goal

Global TB Programme, World Health Organization, Geneva, Switzerland

Correspondence to: Ikushi Onozaki, Global TB Programme, World Health Organization, 20, avenue Appia, 1211 Geneva 27, Switzerland. (E-mail: onozakii@who.int)

—————The 88th Annual Meeting Symposium—————

PROSPECTS FOR THE RENOVATION OF THE MEDICAL SYSTEM
FOR TUBERCULOSIS AND HUMAN RESOURCE
DEVELOPMENT IN THE NEAR FUTURE

Chairpersons: ¹Akira WATANABE and ²Munehiko MORISHITA

Abstract The status of tuberculosis (TB) in Japan was changed to decline and decreased dramatically after The World War II with the great nationwide efforts. Along with the decrease of TB people's attentions to tuberculosis has been reducing significantly, including the medical personnel. In the 1990s, TB returned to increase again, then Emergency Declaration against TB by Minister of Health and Welfare in 1999 drew the public attentions to TB again. Unfortunately, however, there have been many hospitals that cannot deal with TB properly.

On the other hand, non-tuberculous mycobacteriosis (NTM) is increasing recently, which bothers many physicians or pulmonologists.

"Japanese Respiratory Society" (JRS) was founded as "Japan Society of Chest Diseases" derived from "Japanese Society for Tuberculosis" (JSTB) in 1961, when almost all the members were the members of both the Societies. Now, after 50 years of JRS foundation, only one in four members of JRS may join to JSTB. However, the needs for training opportunities about TB and NTM do exist indeed, which is suggested by the fact that "Tuberculosis course", the joint program with JSTB, held in every annual JRS meeting has been filled with a lot of standing audience.

In order to support these needs for training about TB, JSTB began the Certification System for TB and NTM in 2011. More than 1,000 certified physicians were born so far. In addition, the decreased number of JSTB members has returned to increase significantly.

The most important challenge is to make a future countermeasure against TB and NTM, and also to promote the development of human resources based on the current situation and forecast of TB.

This symposium was planned along the theme of this congress, "TB control for the next generation" in response to the wishes of the Congress President Dr. Yamagishi.

On behalf of the Ministry of Health, Labour and Welfare, Dr. Yoshizawa talked about the future measures and challenges, and the human resource development for the future, based on the current situation of the medical system for tuberculosis.

Dr. Fujita, the chairman of the committee of the certification system, talked about the JSTB Certification System, and the prospect of the human resource development.

Dr. Nagai talked about the training opportunities for TB and NTM such as the "Educational seminar" in the annual meeting of JSTB or the "Tuberculosis course" in the annual meeting of JRS.

Nurse and the Public health nurse are also the important members of the medical team for TB. Ms. Nagata talked about the human resources development of nurse responsible for tuberculosis care.

Finally, Dr. Kudo, who originally proposed the JSTB Certification System as the chairman of the future planning committee, addressed the history and the foresights of the near future medical care system for TB as a special remark.

We wish all the members may share the prospects of future medical care for TB and NTM, which may help for improving the future medical system.

1. An administrative viewpoint about future Japanese tuberculosis medical care: Dai YOSHIZAWA (Health Service Bureau, Ministry of Health, Labour and Welfare)

2. The significance and current status of the Japanese Society for Tuberculosis Certification System for a Doctor: Akira FUJITA (Tama-Hokubu Medical Center)

In recent years, the Japan Society for Tuberculosis (JSTB) established a system for certifying the country's tuberculosis (TB) specialists.

The certification is for physicians with expertise in TB and other mycobacterium diseases, and who are experienced in the use of medications appropriate for treating these conditions. The certification also applies to supervising physicians, which is important considering the current environment of TB treatment. Today, there is a decline in the number of TB specialty hospitals, a trend toward shorter hospital stays and regional medical service providers, and a greater need for the medical management of complications.

JSTB started the certification program in 2011. As of March 1, 2013, JSTB had authorized 526 board-certified members and 453 senior fellows. These certified medical professionals, who are in a variety of general hospitals and clinics, are recognized as well-trained providers of standard TB treatment protocols. In achieving this JSTB certification, physicians in the public health center should contribute to the implementation of the Directly Observed Treatment, Short-course (DOTS) policy in collaboration with a health care facility.

3. The way of the training opportunity for the acquisition of points for the Japanese Society for Tuberculosis Certification System: Hideaki NAGAI (Center for Respiratory Diseases, National Hospital Organization Tokyo National Hospital)

The patients with tuberculosis in Japan decrease every year,

but the tuberculosis incidence rate is 17.7 per 100,000 population (2011) which is still high compared with the other developed countries. Japan is a country with middle burden of tuberculosis. Patient's delay and doctor's delay in the clinical course of tuberculosis are major problems, especially the latter means that most of doctors consider tuberculosis to be a past disease and it does not come to their minds.

On the other hand, the patients with nontuberculous mycobacteriosis increase year by year, and it is pointed out that the number of patients infected with *Mycobacterium avium* complex (MAC) is almost the same with the number of smear-positive tuberculosis patients.

The physicians who are familiar with acid-fast bacillus infection are required under these situations. However, the tuberculosis ward decreased and there were a few opportunities for studying tuberculosis. A membership of the Japanese Respiratory Society is 10,954 (as of March 31, 2012), but a membership of the Japanese Society for Tuberculosis (JSTB) is only 3,414 (as of October 22, 2012). There are many pulmonologist who are unconcerned about tuberculosis.

In view of such situation, JSTB made a certification system to bring up the doctor who was familiar with acid-fast bacterial disease, preparing a lot of training courses and lectures.

However, as many tuberculosis wards in the districts were integrated into a few facilities, it is difficult for all pulmonologist to acquire the experience of treating the smear-positive tuberculosis patient. It is one way to incorporate the training in the institution with the tuberculosis ward in the late training course of the respiratory medicine.

If making the unit of tuberculosis ward can maintain beds for tuberculosis patients at many hospitals or if a general hospital can accept the tuberculosis patients with complications in the model beds, it will be convenient not only for the patients

to go to hospitals, but also for the doctors to get an opportunity of the clinical training on tuberculosis.

4. The future of nursing profession in tuberculosis medical service: Yoko NAGATA (Research Institute of Tuberculosis, JATA)

The role of nursing and public health nursing professionals in TB medical service is not only to continue improving their own skills and knowledge but also to educate the public and provide the necessary information regarding TB. Furthermore, they are also expected to play an important role as specialists in the collaboration between public health centers, hospitals and other relevant organizations. In the U.K., TB specialist nurses, as qualified professional, involve themselves in almost every aspect of TB policy, from diagnosis to treatment. In Japan, a new certification system to qualify an expert for mycobacteriosis is to start next year, and it is hoped that the course will contribute to further nurturing specialists in TB medical service and care.

Key words: Tuberculosis, Medical system for tuberculosis, Human resource, The Japanese Society for Tuberculosis, Certification system

¹Research Division for Development of Anti-Infective Agents, Institute of Development, Aging and Cancer, Tohoku University, ²Aichi Medical University Medical Clinic

Correspondence to: Akira Watanabe, Research Division for Development of Anti-Infective Agents, Institute of Development, Aging and Cancer, Tohoku University, 4-1, Seiryomachi, Aoba-ku, Sendai-shi, Miyagi 980-8575 Japan.
(E-mail: akiwa@idac.tohoku.ac.jp)

IMMUNOLOGICAL BACKGROUND ON NON-TUBERCULOUS MYCOBACTERIOSIS

Chairpersons: ¹Masaki FUJITA and ²Toshiaki KIKUCHI

Abstract Nontuberculous mycobacteria (NTM) pulmonary disease is increasing and *Mycobacterium avium* complex (MAC) is the most common cause. NTM pulmonary disease has been linked in a distinct patient phenotype such as thin, post-menopausal women. Their predisposition to infection with NTM suggests that immunologic responses to NTM potentially contribute to pathogenesis of NTM lung disease. In this symposium, we asked four speakers to talk mainly about the immunologic pathogenesis. The topics included immunosuppressive macrophages in patients infected with MAC, pathological findings of MAC pulmonary disease, poor nutrition conditions associated with the progressive NTM pulmonary disease, and hypersensitivity reaction referred to as “hot tub lung”. We hope that the discussion through this symposium will lead to clinical usefulness of this disease.

Opening Remarks: Masaki FUJITA (Department of Respiratory Medicine, Fukuoka University Hospital)

Recently, incidence of pulmonary nontuberculous mycobacteriosis (NTM) is increasing in Japan. Since pulmonary NTM shows resistant to medical treatment, death number of NTM will increase more than that of tuberculosis in near-future. There is no doubt that medical progress is needed for the treatment of NTM. However, immunological response has been still unknown. NTM exist in environment. We do not know why such environmental pathogenic NTM infects to the host, how cause pulmonary diseases and, which is important host or bacteria? The aim of this symposium is to promote a better understanding the immunological response to NTM. We hope this symposium provide a spark for the progress in NTM treatment.

1. The background of basic immunologic research on nontuberculous mycobacteria: Yutaka TATANO, Haruaki TOMIOKA (Department of Microbiology and Immunology, Shimane University School of Medicine)

Pathogenic mycobacteria including *Mycobacterium tuberculosis* (Mtb) and *Mycobacterium avium* complex (MAC) are intracellular bacterial parasites. Macrophages (MΦs) play a central role as antimicrobial effector cells in the expression of host resistance to mycobacterial infections.

Recently, the possibility was suggested that the apoptotic cell death of MΦs during mycobacterial infection potentiates the bactericidal function of MΦs against intramacrophage mycobacteria, especially Mtb and *M. bovis* BCG (BCG). However, the antimicrobial mechanisms of MΦ apoptosis have yet to be defined.

Meanwhile, it is known that Th1 and Th1-like cytokines, such as IFN- γ , IL-2, TNF- α , and GM-CSF, play crucial roles in the expression of host resistance against mycobacterial infections. These cytokines activate innate immunity cells, especially MΦs.

Recently, many reports have suggested that IL-17A, a proinflammatory cytokine, plays a pivotal role in protection against various bacterial infection including mycobacteria such as Mtb and BCG. Moreover, we found that MAC infection-induced splenic MΦs (MAC-MΦ) induce Th17 polarization.

Here, we present the bactericidal mechanisms involved in the apoptosis of MΦs infected with nontuberculous mycobacteria, such as MAC and *M. smegmatis*, and the cytokine network concerned with host defense against mycobacterial infection, focusing on MΦs.

2. Analyses of immune dynamics in non-tuberculous mycobacterial infections based on pathological findings: Kenji HIBIYA^{1,2}, Masao TATEYAMA¹, Jiro FUJITA¹ (¹Department of Infectious, Respiratory, and Digestive Medicine, Control and Prevention of Infectious Diseases, Faculty of Medicine, University of the Ryukyus, ²School of Dentistry, Matsumoto Dental University)

In *Mycobacterium avium* complex (MAC) lung diseases, there were the infectious type and the host response type. Many

bacteria were observed in the case of fibrocavitary type of pulmonary MAC disease and disseminated MAC disease in AIDS patients. This phenotype demonstrated the exudative response and was considered that infection played a crucial role. Meanwhile, few bacteria were observed in the case of nodular bronchiectatic type of pulmonary MAC disease and the lymph node localized type of immune reconstitution syndrome in AIDS patients. These phenotypes demonstrated the proliferative reaction and were considered that the host response played a crucial role. In the immunological background, Th17 cells or Th2 cells rather than Th1 cells may play a role in the infectious type. In contrast, it was considered that immune response of Th1 cells had a central role in the host response type.

3. Nontuberculous mycobacterial infection and nutrition: Nobuhiko NAGATA (Department of Respiratory Medicine, Fukuoka University Chikushi Hospital)

We evaluated the nutritional state and its relation to the prognosis of nontuberculous mycobacteria (NTM) infected patients cohort registered at National Hospital Organization Omuta Hospital. The cohort showed low BMI, low blood prealbumin concentration, diminished visceral fat volume and diminished dietary uptake of total energy, carbohydrate, protein, and lipid. There is a significant relationship between BMI and the number of involved segments assessed by CT. Deterioration assessed by CT was significantly related to blood prealbumin concentration. Among various nutritional parameters,

BMI and blood prealbumin concentration were considered to have close relationship to clinical pictures of NTM patients.

4. New insights into the pathophysiology and immunological mechanism of hot tub lung: Hisayoshi DAITO (Saitama Medical University International Medical Center)

Mycobacteria have pathogenic potential not only as infectious agents for chronic infections, but also as immunogenic agents for hypersensitivity pneumonitis (HP). To clarify the pathophysiology of mycobacterial HP, we established a mouse model with a clinical isolate of *Mycobacterium avium* from a patient with hot tub lung disease. Our studies suggested that hot tub lung develops via the mycobacterial engagement of Toll-like receptor (TLR) 9-myeloid differentiation factor (MyD) 88 signaling in lung CD11c⁺ cells independent of mycobacterial infectious capacity.

Key words: Immune response, Cytokine, Pathologic analysis, Nutritional status, Hypersensitivity pneumonitis

¹Department of Respiratory Medicine, Fukuoka University Hospital, ²Department of Respiratory Medicine, Tohoku University Graduate School of Medicine

Correspondence to: Masaki Fujita, Department of Respiratory Medicine, Fukuoka University Hospital, 7-45-1, Nanakuma, Jonan-ku, Fukuoka-shi, Fukuoka 814-0180 Japan.
(E-mail: mfujita@fukuoka-u.ac.jp)

—————The 88th Annual Meeting Mini-Symposium—————

EXPANDING THE ROLE OF THE NURSING PROFESSION IN TUBERCULOSIS MEDICAL SERVICES

Chairpersons: ¹Yoko NAGATA and ²Teiko KATO

Abstract Implications of changes in the law regarding the payment system for medical services in 2012 for TB medicine and care include mandatory hospital DOTS, planning and implementing adherence support for patients, patient education, and close cooperation with public-health centers. Nurses are expected to contribute to early diagnosis of TB and treatment completion among high-risk populations by coordinating with the community and relevant organizations. It is also important to clarify roles and establish a network through which necessary information and advice may be sought from specialists. Expanding the role of nursing professions in TB care and medicine is hoped to improve the level of awareness and knowledge among persons involved in TB prevention, care, and medicine.

1. TB control at Hyogo Cancer Center—Collaboration between CNIC and public-health centers in early detection of TB and infection control: Fumi WADA (Hyogo Prefecture Cancer Center)

The level of knowledge regarding TB control among medical personnel has decreased at our center due to a lack of experience. By appointing Certified Nurses in Infection Control (CNICs) as being responsible for infection control, we managed to establish a TB control manual and a clear system for reporting. CNICs play a central role in coordinating with public-health centers to share patient information and discuss contact investigation.

2. Role of a hospital with TB beds in collaborating with the public and the relevant organizations: Teiko KATO (Akita City Hospital)

We conducted a TB education program for the public, relevant organizations, and prisons to increase awareness and knowledge on TB and to eliminate the stigma attached to it. The program covered the general definition of TB, infection control, risk factors, and DOTS. Participants responded to questionnaires before and after the program. Before the program, attitudes towards TB included “TB is a disease of the past” and “TB is a dreadful disease.” After the program, 95% responded that they had better knowledge of TB.

3. Collaboration between hospitals and public-health centers: Hisako HAGIWARA (National Hospital Organization Chiba-East National Hospital)

At our hospital, we collaborate with the public-health centers

through a DOTS conference, which began two years ago. In order to support patients after they are discharged, it is extremely important to assess risk factors for default and to establish support tailored to individual needs. Sharing information and utilization of a common tool for assessment and evaluation is critical in achieving this goal. It is also important to secure a stable living environment for patients so that they can continue their treatment by utilizing social resources.

4. Cooperation in a region with limited TB hospitals: Toshimi IJIMA (Yamanashi Prefecture Kyoto Public-Health Center)

Integration of the TB Prevention Act into the Prevention of Infectious Diseases and Medical Care for Infectious Patients Act has greatly affected TB control policy in Yamanashi Prefecture. Evaluation of the situation highlighted several issues, including differences in assessment methods between hospitals and public-health centers, as well as overlaps in patient education. In 2010, a workshop was thus conducted with a hospital, a public-health center, and an infection control division of the prefectural government to clarify roles and establish common risk assessment and educational tools.

Special speech. Vision of future tuberculosis care in regions: Eriko SHIGETO (National Hospital Organization Higashihiroshima Medical Center)

One of the issues in future TB care is the treatment of TB patients in infection control ward in general hospital, which will also contribute to prevent hospital-acquired infection of TB that sometimes occurs before diagnosis. To ensure proper TB care in these situations, it is required for TB experts to provide information for general hospitals and health care workers about tuberculosis. Strong government commitment is required for restructure of these systems of TB care.

Key words: DOTS conference, Community cooperation, Active case-finding, Health education, Knowledge and attitude

¹The Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association, ²Akita City Hospital

Correspondence to: Yoko Nagata, The Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association, 3-1-24, Matsuyama, Kiyose-shi, Tokyo 204-8533 Japan.
(E-mail: nagata@jata.or.jp)

TREATMENT OF TUBERCULOSIS IN PATIENTS WITH COMORBIDITIES

Chairpersons: ¹Masahiro ABE and ²Akira FUJITA

Abstract Early detection and appropriate treatment are the keys to tuberculosis control. In particular, providing appropriate treatment for tuberculosis in patients with HIV infection, rheumatoid arthritis (RA), chronic hepatic disease, or renal failure necessitating hemodialysis, and taking appropriate measures against adverse reactions to antituberculosis drugs are issues of critical importance.

This mini-symposium, four experts explained the current status of “treatment of tuberculosis in patients with comorbidities” and proposed measures to address these problems.

Dr. Aoki talked about “HIV infection complicated by tuberculosis.” To the next, Dr. Yoshinaga gave a talk on “treatment of tuberculosis in RA patients receiving biological agents.” Further, Dr. Sasaki lectured on “tuberculosis in patients with hepatic disease/impairment”. Lastly, Dr. Takamori gave a lecture on “tuberculosis in patients with renal disease and those on hemodialysis.”

Tuberculosis patients often have some underlying diseases, and adverse reactions caused by antituberculosis drugs, such as hepatic and renal impairments, are matters of concern. I believe that this mini-symposium has provided useful information for physicians engaged in tuberculosis treatment and for many other healthcare professionals as well.

1. HIV infection and Tuberculosis: Takahiro AOKI (AIDS

Clinical Center, National Center for Global Health and Medicine)

HIV infection significantly increases the risk of active tuberculosis (TB) disease. Active TB disease requires prompt initiation of anti-TB treatment. Therapy for active TB disease in HIV-infected patients should follow the general principles guiding treatment for individuals without HIV. Treatment of drug-susceptible TB disease should include a standard regimen. All patients with HIV/TB disease should be given antiretroviral therapy (ART). Important issues related to the use of ART in patients with active TB disease include: (1) when to start ART, (2) drug-drug interactions between rifamycins and some of the currently-used antiretroviral (ARV) agents, (3) the additive toxicities associated with concomitant ARV and TB drug use, and (4) the development of TB-associated IRIS after ART initiation.

2. The influence of biological agents on the incidence of tuberculosis (TB) in Japanese patients with rheumatoid arthritis (RA): Yasuhiko YOSHINAGA (Rheumatic Disease Center, Kurashiki Medical Center)

To evaluate the influences of biological agents on the incidence of TB in Japanese patients with RA, we calculated the standardized incidence ratio (SIR) of TB from the clinical data in the National Database of Rheumatic Disease maintained

by iR-net in Japan (*NinJa*) prospectively and then conducted a comparison with the SIR of TB from the post-marketing survey data on infliximab, etanercept, adalimumab, and tocilizumab in Japan. Among 7,832 RA patients not receiving biological agents, 7 developed TB. The SIR of TB in RA patients not receiving biological agents was 3.98 (95% CI: 1.22–6.74). According to the post-marketing survey on infliximab in 5,000 RA patients, etanercept in 13,894 RA patients, adalimumab in 7,740 RA patients, and tocilizumab in 7,901 RA patients, 14, 10, 9 and 5 cases of TB have been reported, respectively, and the corresponding SIR of TB were 34.4, 8.21, 13.6 and 8.01. The incidence of TB in patients with RA was higher than that of the general population, and the increase was greater with the biological agents, especially anti-TNF antibodies, which also increase the risk of extra-pulmonary TB. We must recognize the risk of TB for at least one year after starting biological agent treatment of patients with RA.

3. Anti-tuberculosis treatment in patients with hepatic disease and those with poor liver function: Yuka SASAKI (Department of Respiratory Medicine, Fukuji Hospital, Japan Anti-Tuberculosis Association)

Hepatotoxicity is known to occur at a high frequency as a side effect of tuberculosis treatment. (1) In this study, 61 patients (14.0%) had hepatotoxicity among 435 patients treated with HRZ+one anti-tuberculosis drug in Fukuji Hospital, and hepatotoxicity was higher in those over age 80 years. The elderly should be treated with appropriate

regimens after adequate examination. (2) Fifty percent of active tuberculosis patients who are positive for HCV antibody develop hepatotoxicity. (3) The outcomes of active tuberculosis patients with liver cirrhosis are not good. The fatality rate was 32%.

4. Tuberculosis and end-stage renal disease necessitating hemodialysis: Mikio TAKAMORI (Department of Pulmonary Medicine, Tokyo Metropolitan Tama Medical Center)

End stage renal failure patients on hemodialysis, especially those with diabetes, are at high risk for tuberculosis infection. The incidence rate of tuberculosis was 2–25 fold higher than the population average among hemodialysis patients. The diagnosis of tuberculosis in these patients is difficult due to lack of respiratory symptoms. IGRAs are useful for diagnosis in these patients. For the management of active tuberculosis patients receiving hemodialysis, treatment with three or four first-line drugs is recommended.

Key words: Tuberculosis, HIV, Rheumatoid arthritis, Hepatic impairment, Chronic renal impairment

¹National Hospital Organization Ehime National Hospital,

²Tokyo Metropolitan Health and Treatment Corporation Tama-Hokubu Medical Center

Correspondence to: Masahiro Abe, National Hospital Organization Ehime Medical Center, 366 Yokogawara, Toon-shi, Ehime 701–0281 Japan. (E-mail: mabe@ehime-nh.go.jp)