

—————Memorial Lecture by the Imamura Award Winner—————

## ANALYSIS OF BACTERIAL FACTORS ASSOCIATED WITH PATHOLOGICAL OR CLINICAL MANIFESTATIONS OF *MYCOBACTERIUM AVIUM* DISEASE BASED ON GENOME ANALYSIS

Kei-ichi UCHIYA

**Abstract** [Background] Infectious disease caused by *Mycobacterium avium* shows diverse pathological and clinical manifestations. This is possibly due to both host factors and bacterial factors, but many questions remain answered regarding these manifestations. [Methods] To assess the relationship between the different pathological and clinical manifestations of *M. avium* disease and bacterial factors, we performed comparative genome analysis using clinical isolates from patients with various symptoms. [Results] We determined the complete genome sequence of the previously unreported *M. avium* strain TH135 isolated from a patient with pulmonary *M. avium* disease, and further demonstrated the presence of a novel plasmid, pMAH135, encoding proteins involved in the pathogenicity and antimicrobial resistance of mycobacteria. Our analysis also showed that *M. avium* strains, which cause pulmonary and disseminated disease, have genetically distinct features, and isolates from patients with pulmonary disease were more resistant to seven antibiotics, including clarithromycin, than isolates from patients with disseminated disease. Comparative genome analysis of 79 *M. avium* strains comprising four subspecies revealed the presence of genetic elements specific to each lineage, which are thought to be acquired via horizontal gene transfer during the evolutionary process. Moreover, the analysis identified potential genetic determinants associated with not only the progression of pulmonary disease but also the host range characteristics of *M. avium*. Notably, this analysis indicated an association between the progression of pulmonary *M. avium* disease and several virulence genes including pMAH135. [Conclusion] These results suggest that bacterial factors play an important role in the diverse pathological and clinical manifestations of *M. avium* disease.

**Key words:** *Mycobacterium avium* disease, Pathological manifestation, Clinical manifestation, Bacterial factors, Genome analysis

## Review Article

## PROSPECTS OF THE MEDICAL CARE SYSTEM FOR TUBERCULOSIS IN JAPAN

Seiya KATO

**Abstract** The incidence of tuberculosis (TB) in Japan has markedly decreased owing to various efforts based on the Tuberculosis Prevention Law. The introduction of a short regimen of rifampicin and pyrazinamide has shortened hospitalization periods. As a result, the required number of TB beds has decreased, and many hospitals removed TB beds altogether. This has caused poor accessibility of TB medical services in many areas. However, the bed occupancy rate for TB is low, and enormous differences can be seen among prefectures.

We estimated the necessary number of hospital beds for TB patients by prefecture using the data from 2017 surveillance data along with the following assumptions: All sputum smear-positive patients are hospitalized. Among sputum smear-negative patients, 30 percent of those aged over 70 years old and 5% of the remaining patients are hospitalized. The final estimate was obtained by multiplying 1.6, as a seasonable variable, to adjust for fluctuations in the number of TB patients based on the time when the above number was calculated.

TB medical care creates a financial deficit in most TB hospitals due to poor bed occupancy rates, unreasonable reimbursement from public health insurance, and additional costs for infection control. As the number of TB patients decreases, it is becoming difficult for hospitals to secure physicians who are experienced with TB medical care, especially in low incidence areas. The medical care system for TB, which is in a critical situation in many prefectures, needs to be restructured.

The following proposals should be implemented for the medical care system in low incidence situations, to improve patient-centered medical care for TB: 1) secure hospital beds for TB patients, 2) shorten hospitalization periods, 3) reconsider the applications of TB beds, model beds, and infectious disease beds for TB patients, 4) maintain the quality of TB medical services, 5) establish a collaboration mechanism for TB work in respective areas.

In order to secure an adequate number of hospital beds, financial deficits need to be resolved by adjusting bed occupancy rates and improving the related income. As the incidence of TB is expected to decrease, the area set up within a ward for TB patients needs to be flexible. Consequently, beds for TB should be in isolation rooms complete with a pre-admittance room. In this way, the room can be used for infectious diseases other than TB. In order to shorten hos-

pitalization periods, a policy amendment should be implemented to facilitate the smooth transfer of non-infectious TB patients to general hospitals or geriatric facilities, and new technology should be developed to evaluate the contagiousness of the patients so that they can be transferred as soon as possible. As needs and social resources for the medical service of TB patients become increasingly diverse, the application of TB beds, model beds, and infectious disease beds for TB patients should be reconsidered. To maintain the quality of medical service, it is necessary to provide training for health care workers and opportunities for interns to experience medical care for TB patients through the collaboration of governments, medical facilities, and educational organizations. It is also important to establish a consulting system for medical service providers at the prefectural level; however, a national-level center may be required in the future as it may be difficult to maintain it at the prefectural level. In order to tackle the above-mentioned challenges, a regional collaboration mechanism should be established. In some prefectures, holding collaboration meetings among hospitals that have TB beds or model beds, university hospitals, core hospitals for infection control, and the government is functioning well and facilitating mutual understanding.

In conclusion, the provision of medical services for TB patients is facing critical situations in many areas. It is necessary to establish a medical service system for TB patients in low incidence situations. In order to realize patient-centered medical care, which requires a sufficient number of hospital beds for various needs of medical care alongside quality service, it is necessary to resolve financial deficits, shorten hospitalization periods, utilize hospital beds beyond their current demarcation, and establish a medical service collaboration mechanism at the regional level.

**Key words:** Tuberculosis, Hospital beds, Low incidence, Medical care system, Regional collaboration

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## HISTORY IN TUBERCULOUS PATHOGENESIS FROM A VIEWPOINT OF PHYSICIAN

Atsuyuki KURASHIMA

**Abstract** Today, research papers on tuberculosis have been developed internationally on an unprecedented scale and depths. Although it is important to clinicians, many of these have not been introduced in a way that clinicians can grasp easily in Japan today. Here, I present the historical overview of the pathogenesis of tuberculosis from the personal appreciation of a physician who is pursuing mycobacterial disease. And I am going to introduce a result of modern tuberculosis research.

Experimental tuberculosis has mainly used rabbits and guinea pigs as animals that can reproduce the pathogenesis of tuberculosis of man that has led to the formation of TB cavities. Today, new methodologies with cutting-edge techniques, such as zebrafish, new pure mice, cynomolgus monkeys, DNA-labeled TB bacilli and PET/CT evaluation etc. are opening up a fundamental understanding of tuberculosis immunity that has not been fully elucidated for example, the

“Koch phenomenon”.

This article is a review that focuses on the pathogenesis of tuberculosis among the special lectures reported at the 94th Annual Meeting of the Japanese Society for Tuberculosis.

**Key words:** Primary complex, Koch phenomenon, Erituberculosis, Delayed type hypersensitivity, Cell mediated immunity, Concurrent infection with tuberculosis

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## CURRENT SITUATION OF FOREIGN-BORN TUBERCULOSIS PATIENTS IN JAPAN — How It Is and How It Should Be on Treating Especially Outpatients —

Kiyoko TAKAYANAGI

**Abstract** The percentage of foreign-born TB patients in Japan is gradually increasing and reached to 10.7% in 2018. There are various demanding factors such as difficulty of communication, drug resistance, instability of social infrastructure, transfer out, returning home country, etc. To complete their treatment domestically take the top priority. Treatment support for them is involved in many aspects, especially we should make patients centered, and there is a greater need for early detection, prevention of infection spread, and completion of treatment. Well-trained medical interpreters have supported our treatment for many years at Center for Health Check and Promotion of Japan Anti-Tuberculosis Association. We have held DOTS meetings for foreigners with staff members of public health center

regularly since 2006 and have various ideas and materials to prevent interruptions of the treatment. We show some tips in treating TB outpatients through our experience.

**Key words:** Tuberculosis, Foreign nationals, Outpatient

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## WHOLE GENOME SEQUENCING AS A PROMISING TOOL FOR EPIDEMIOLOGICAL INVESTIGATIONS OF TUBERCULOSIS

<sup>1,2</sup>Takemasa TAKII

**Abstract** The epidemiologists of tuberculosis are able to obtain huge amount of genotypic information at one time due to the innovation of new sequencing technology. The new technology, whole genome sequencing (WGS), possesses higher ability of analyzing the cluster and linkage associations among the clinical isolates of tuberculosis (TB) than traditional methods like genotyping, RFLP, VNTR and spoligotyping. Furthermore, the WGS analysis is also able to predict drug susceptibility of the isolate against anti-TB drugs. I here review the role of the WGS analysis in epidemiological investigations of tuberculosis.

**Key words:** Tuberculosis, Molecular epidemiology, Whole genome analysis

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## PRESENT STATUS AND PROBLEMS OF TUBERCULOSIS SURVEILLANCE

<sup>1,2</sup>Kenji MATSUMOTO

**Abstract** To clarify the present status and problems of tuberculosis surveillance in tuberculosis control, TB analysis and assessment meeting (TB meeting), which evaluates tuberculosis surveillance in Osaka City, analyzed “the degree of contribution to tuberculosis control”. The purpose of this meeting is to share problems and evaluate tuberculosis control activities. Concerning methods, data on tuberculosis are collected and analyzed, accurate evaluation is performed, and effective measures are taken. The TB meeting consisted of 4 external members specializing in tuberculosis and epidemiology, members of Division of Microbiology, Osaka Institute of Public Health, and physicians and public health nurses in Public Health Office and Public Health and Welfare Centers in 24 wards and others. The major evaluation contents were: 1) Changes in the incidence of tuberculosis: Changes in newly registered tuberculosis cases were evaluated in the entire Osaka City and each of the 24 wards. 2) Topics: Analysis and evaluation of tuberculosis control activities were performed, and advanced topics were provided. 3) Evaluation of newly registered cases: Patient control is performed in the 24 wards. Whether the diagnosis and treatment of each case,

and contact examination were appropriately performed in each ward was determined. Based on changes in the incidence of tuberculosis, the characteristics of each jurisdiction district were clarified, and the direction of control activities was determined. The provision of topics was useful for the planning, evaluation, and revisions of control measures. The case study allowed the evaluation of the consistency of control activities. These results showed the importance of the use of tuberculosis surveillance for tuberculosis control.

**Key words:** TB control, Surveillance, Evaluation, Evidence, Analysis and assessment meeting

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CHARACTERISTICS OF TWO DIFFERENT FORMS OF *MYCOBACTERIUM AVIUM* COMPLEX PULMONARY DISEASE; FIBROCAVITARY AND NODULAR BRONCHIECTATIC DISEASE

Hiroshi MORO and Toshiaki KIKUCHI

**Abstract** Reported poor prognostic factors of *Mycobacterium avium* complex lung disease (MAC-LD) include radiographic findings, undernutrition, anemia and high inflammation test values. To clarify the pathophysiology of MAC-LD, we investigated cytokine profiles in patients with MAC-LD. We analyzed 27 patients with MAC-LD, 6 with the fibrocavitary form and 21 with the nodular bronchiectatic form. Serum C-X-C motif ligand 10 (CXCL-10) concentration was significantly elevated in patients with the fibrocavitary form. CXCL-10 levels correlated with body mass index, serum albumin concentration and high-resolution CT scores. Serum CXCL-10 levels probably reflect the severity of MAC-LD.

**Key words:** Non-tuberculous mycobacterial pulmonary

disease, *Mycobacterium avium* complex pulmonary disease, Fibrocavitary disease, Nodular bronchiectatic disease, CXCL-10

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## PREVENTING TUBERCULOSIS INFECTION IN HEALTHCARE SETTINGS

Naoko SUZUKI

**Abstract** In Japan, in recent years, we have a serious problem of Doctor's Delay of elderly people's diagnosis of tuberculosis (TB), related to the aging of patients receiving emergency medical care. The prevalence of TB in Japanese healthcare workers (HCWs) is generally about twice the same age. National hospital organization, the A hospital is in the central part of Japan and is a national acute hospital with no TB disease bed (600 beds), which is often associated with this issue and latent tuberculosis infection (LTBI) occurs in HCW. Therefore, we analyzed cases of the Doctor's Delay, which occurred in elderly TB and examined the risk of LTBI of HCWs and countermeasures.

We targeted the case (Doctor's Delay) where elderly people aged 65 and over were hospitalized without suspecting TB and subsequently diagnosed with TB, in the acute care hospital from 2016–2017. The subject cases were 15 cases, the average age was 82.7 years old, and the male was 10 cases (67%). The main symptoms of hospitalization were weight loss, body movement difficulty, dizziness, falls, malaise, hematemesia, decreased appetite, lower extremity edema, cough, runny nose, fever, dyspnea, etc. Seven patients were admitted through the emergency department. Six patients used nursing care services before hospitalization. The average number of days in a Doctor's Delay was 35.7 days. In each case, 22 to 92 HCWs were involved in and a total of 800 HCWs were screened for TB contact. There were 236 nurses, 61 physicians, 67 radiologists, 50 therapists and 58 other healthcare professionals. There were two cases showing LTBI was contracted. Three HCWs: an occupational therapist, a nurse, and a pharmacist were diagnosed with LTBI.

The symptoms of elderly tuberculosis patients were not

typical and not always accompanied by fever and prolonged cough symptoms. Furthermore, in the beginning, there were many cases where they were admitted to the emergency first-aid clinic due to falls or sudden weight loss. In acute phase hospitals, it is difficult for all elderly patients to be treated with tuberculosis at an early stage, even if they see respiratory disease specialists. Therefore, it is considered that delays in diagnosis have occurred. More importantly, these elderly people are using nursing care, so there is concern that tuberculosis infection may have occurred in facility users and care workers at nursing homes without physicians.

To prevent tuberculosis infection in medical staff caused by the onset of tuberculosis in the elderly, it is necessary to share information and educate on how to control infection early in the onset of tuberculosis in these elderly people and the risk of infection to medical personnel. The key to preventing LTBI and TB is to consider the possibility of TB in high-risk groups, and make the diagnosis as quickly as possible.

**Key words:** Tuberculosis nosocomial infection, Tuberculosis infection control, Elderly tuberculosis

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EPIDEMIOLOGICAL EVALUATION OF  
THE TERM “TUBERCULOSIS DANGER GROUP” POPULATION  
— A Case Study from Osaka City, Japan —

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**Abstract** [Objective] To assess the epidemiological validity of the concept of “tuberculosis danger group”.

[Methods] Smear positive index patients aged between 20 to 64 years old, who were notified to Osaka City Public Health Center, and their contacts were investigated to calculate the number and rate of secondary index patients by job category. Multiple regression analysis was also conducted to identify potential risk factors for secondary transmission.

[Results] Secondary infection rate was the highest for construction workers (28.2%), followed by physicians and nurses (26.7%). Number of secondary patient per index case was the largest for trainees (1.3), followed by construction workers (1.0).

[Conclusions] Secondary infection rate of jobs such as healthcare workers and service industry workers, which have traditionally been regarded as “danger groups” was not significantly higher than other jobs, while that of construc-

tion workers was higher. Appropriateness of the use of the term “danger group” in prioritizing TB policies should be reconsidered.

**Key words:** Tuberculosis, “Danger group”, Contact investigation

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## A CASE OF PULMONARY *MYCOBACTERIUM XENOPI* INFECTION PRESENTING INTERESTING IMAGING CHANGES

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and Fumio NOMURA

**Abstract** A 68-year-old man was referred to our hospital to undergo surgery for an abdominal aortic aneurysm. Pre-operative computed tomography (CT) revealed a cavitory lesion with an irregularly thick wall in the left upper lung. When we were consulted 3 weeks later, a second CT revealed a new thin-walled cavitory lesion in the right upper lung. Another week later, the cavity had changed to a nodule as revealed by high-level uptake of fluoro-deoxy-glucose by positron emission tomography (PET). The bronchial lavage fluid obtained via bronchoscopy exhibited smear positivity for acid-fast bacteria but the results of polymerase chain reaction for both *Mycobacterium tuberculosis* and *Mycobacterium avium* complex were negative. Two months after the PET study, the nodule in the right lung became a cavity with a thick wall resembling the original lesion in the left upper lung. Subsequently, the acid-fast bacterial culture was positive and identified as *Mycobacterium xenopi* by DNA-DNA hybridization method. Furthermore, *M. xenopi* was also isolated in the patient's sputum specimen, and the patient

was ultimately diagnosed with a pulmonary *M. xenopi* infection. Chemotherapy with rifampicin, ethambutol, and clarithromycin was initiated and levofloxacin was added 10 months later because of an indelible cavitory lesion. The wall thicknesses of both right and left lesions became markedly thinner after 2 years of continuous treatment. The patient subsequently survived successfully without a relapse of the infection for 4 years.

**Key words** : Pulmonary nontuberculous mycobacteriosis, *Mycobacterium xenopi*, Imaging findings, Chemotherapy

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