

## Original Article

CLINICAL ANALYSIS OF *MYCOBACTERIUM ABSCESSUS*  
PULMONARY INFECTION IN OUR HOSPITAL

Yoshihiro KOBASHI and Mikio OKA

**Abstract** [Objective] We analyzed the clinical characteristics of pulmonary infection due to *Mycobacterium abscessus*.

[Materials and Methods] Four cases diagnosed with *M. abscessus* pulmonary infection encountered at Kawasaki Medical School Hospital and affiliated hospitals over the last five years were enrolled in this study. They all satisfied the diagnostic criteria of the Japanese Society for Tuberculosis. The clinical findings in this study were also compared to those of previously reported cases in Japan.

[Results] The average age of the four cases was 56 years (one male and three females). All four cases showed underlying diseases, comprising two cases with malignancy, one with old pulmonary tuberculosis and one with collagen vascular disease receiving immunosuppressive treatment. Three cases were detected based on clinical symptoms, and one was incidentally identified during follow-up for another underlying disease. Laboratory examinations revealed mild or moderate inflammatory responses in three of the four cases, and three of the four were smear-positive for acid-fast bacilli in the clinical specimens (sputum in one and bronchial alveolar lavage fluid in two) microbiologically. The radiological examination revealed that one case showed tuberculosis resembling a cavitary lesion and three showed the small nodular and

bronchiectatic type. The extent of lesions was within the unilateral lung in all cases. Concerning treatment for *M. abscessus* pulmonary infection, combined multi-drug chemotherapy using IPM/cs, AMK, CAM, and LVFX was carried out in three of the four cases, achieving a satisfactory clinical effect. However, one case died due to progression of the underlying disease before the initiation of treatment.

[Conclusion] Although *M. abscessus* pulmonary infection was more frequent in cases with underlying disease, the early, appropriate administration of antibiotics was performed in two of the four cases correctly diagnosed using bronchoscopic procedures, resulting in clinical improvement.

**Key words** : *Mycobacterium abscessus* pulmonary infection

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## The 84th Annual Meeting Invited Lecture

FIGHTING THE TUBERCULOSIS EPIDEMIC IN THE WESTERN PACIFIC REGION:  
CURRENT SITUATION AND CHALLENGES AHEAD

Pieter J. M. van MAAREN

**Abstract** [Introduction] Tuberculosis (TB) remains a major public health problem in the Western Pacific Region. More than 20% of the global burden of TB is found in the Region. In 2007, the latest year for which data is available, there were an estimated 1.9 million incident cases (109 per 100,000 population). Four countries (Cambodia, China, the Philippines and Vietnam) account for 93% of the total estimated incident cases in the Region. Every year an estimated 300 thousand persons die due to TB. The Region is host to an estimated 135,000 multi-drug resistant TB cases, most of which can be found in China.

[TB prevalence and TB mortality] The Regional Stop TB strategy aims to halve the prevalence and mortality rates of 2000 by 2010. Based on current estimates, the TB prevalence declined with 24% between 2000 and 2007, while TB mortality declined with 19% in the same period. Given the current annual decrease in TB prevalence and mortality, it is unlikely that the Region will achieve the 50% reduction by 2010.

[Case finding] Approximately 1.4 million new TB cases were notified in the Region in 2007, of which close to 0.7 million smear-positive cases. Cases from China accounted for 70% of the total notified smear-positive cases. The Regional case detection rate was sustained at 78%. Case detection rates in China, the Lao People's Democratic Republic, Mongolia, the Philippines and Vietnam exceeded the 70% target.

[Treatment outcomes] A total of 92% of the 0.7 million new pulmonary smear-positive cases registered for treatment in 2006 were successfully treated. The treatment success rates exceed the 85% target in all countries with a high burden of TB, except Papua New Guinea where it was reported at 73%.

[Multidrug-resistant TB] In 2007, the proportion of MDR-TB in new TB cases was estimated to be 4%. A total of 135,411 MDR-TB cases was estimated to have occurred in 2007. Based on the overall case management data, 10,231 new patients and 1,596 re-treatment patients were reported with available drug susceptibility testing (DST) results in the Region. Of these, 1% (89/10,231) and 29% (468/1,596) had MDR-TB, respectively. Capacity to detect and treat MDR-TB cases is still very limited in most countries in the Region. Eighteen countries and areas in the Region have conducted drug resistance surveillance (DRS) since 2000, according to the Global Project on Anti-tuberculosis Drug Resistance Surveillance. Among new TB cases, the prevalence of multidrug-resistant TB (MDR-TB) ranged from 0% in Cambodia to 11.1% in the Commonwealth of the Northern Mariana Islands. MDR-TB prevalence among re-treatment cases ranged from 3.1% in Cambodia to 27.5% in Mongolia. In the five countries with a high burden of TB with available data from surveys (Cambodia, China, Mongolia, the Philippines, and Vietnam), MDR-TB prevalence in new cases and re-treatment cases ranged from 0% in Cambodia to 4.9% in China and from 3.1% in Cambodia to 27.5% in Mongolia, respectively. Notably, there were alarming rates of MDR-TB in several provinces in China among both new and re-treatment cases. Increasing numbers of MDR-TB cases are reported from Papua New Guinea.

[TB-HIV co-infection] The overall estimated prevalence of HIV in new TB cases in 2007 was 2.7%. With 8.0% in 2008 compared to 11.8% in 2003, Cambodia shows a declining prevalence of HIV in new TB cases. There was a significant increase in the use of anti-retroviral therapy (ART) in the Region. However, detailed and complete data as well as strong collaboration in HIV and TB management are needed to be able to closely monitor the use of ART and its impact on TB-HIV co-infection in the Region.

[Conclusion] In spite of the substantial progress made in most countries with a high burden of TB, substantial challenges remain in the Region. The rate of decline in TB prevalence and mortality is too low to reach the

50% reduction goal in 2010. It will be necessary to further increase TB case detection and address the emerging spread of drug-resistant TB. The slow response in the most affected countries in the Region is a cause for concern. Strong commitment by national governments and their partners is needed to sustain and further strengthen the current TB control efforts.

## NOVEL DIAGNOSTIC TESTS FOR TUBERCULOSIS INFECTION: THEIR PROBLEMS AND PERSPECTIVES

Chairpersons: <sup>1</sup>Tadayuki AHIKO and <sup>2</sup>Kiminori SUZUKI

**Abstract** Since 2000, the incidence of tuberculosis (TB) has decreased gradually in Japan. However, more than 24 thousand TB patients were newly notified in 2008, and Japan is still classified as an "intermediate burden country". Early identification and treatment of those with latent tuberculosis infection (LTBI), having a high risk to progress to active TB, will decline TB incidence effectively and result in elimination of TB.

The only method for identifying LTBI has been the tuberculin skin test (TST), but TST may give false positive results in BCG-vaccinated people and in those exposed to nontuberculous mycobacteria. New diagnostic tests, called Interferon-Gamma Release Assays (IGRAs), have been recently introduced, in order to improve the specificity of TST. These include the QuantiFERON-TB (QFT) and the T-SPOT.TB tests. The former is available in two formats: QuantiFERON TB-Gold (QFT-G) and a newer version of QFT assay, so-called QuantiFERON-TB Gold In-Tube (QFT-GIT). The T-SPOT.TB test has not been approved yet in Japan.

The Japanese Society for Tuberculosis recommends that QFT tests should be used in all circumstances in which TST is used, including contact investigations and TB screening of healthcare workers. Although the QFT tests are widely utilized, the QFT tests have shown some limitations and problems: limited sensitivity of QFT-G, difficulty in interpretation of data in immuno-suppressed subjects and in children, lack of predictive value for future development of active TB, the inter-laboratory variability and quality assurance. In this symposium, we'll discuss the above mentioned issues and their search for solutions.

1. Quality assurance of QFT and research on improvement of its sensitivity: Nobuyuki HARADA (Immunology Division, Department Mycobacterium Research and Reference, The Research Institute of Tuberculosis)

Since there were some discrepancies of QFT-G results of the same subjects among different laboratories, the quality assurance of QFT-G is thought to be important. We have carried out the quality assurances of QFT-G in 2007 and 2008. Although, approximately half of participants were categorized to be non-acceptable in the first quality assurance, many of those categorized to be non-acceptable became acceptable in the second one. From their results it is conceivable that the introduction of the quality assurance would be effective to improve the test skills. IGRAs including QFT-G are relatively new methods to diagnose TB infection, and the efforts to improve the performance of IGRAs are still under way. A new version of QFT-G (QFT-GIT) is more convenient in the first

step of QFT (i.e. blood culture), and we have shown that QFT-GIT has the higher sensitivity than QFT-G. Another method, T-SPOT.TB based on ELISPOT method, has been shown to be more sensitive than QFT assays. A recent study has demonstrated that measurement of monokines, such as IP-10, along with interferon-gamma (IFN- $\gamma$ ), could improve the sensitivity of QFT to diagnose TB infection. More promising diagnostic methods could be developed in the near future.

2. Application of IGRAs to pediatric TB practice; its usefulness and limitation: Osamu TOKUNAGA, Takeshi MIYANOMAE (Department of Pediatrics, National Hospital Organization Minami-Kyoto National Hospital)

Our study group, named "The Research Group on the Performance of QuantiFERON-TB in Children", has collected data on the performance of QFT in pediatric patients with active TB diseases and TB contact examination cases, and also investigated the usefulness and limitation of QFT in the diagnosis of tuberculosis infection in children.

Although the sensitivity of QFT for pediatric patients with active TB diseases was about 90%, as high as for adult active TB cases, the sensitivity for the diagnosis of latent TB infection in children, especially both in infants and toddlers, was quite low.

Positive QFT results may be useful to confirm TB infection and diagnose active TB disease in children whose radiological findings are compatible with TB disease, but have no bacteriological evidence. On the other hand, negative QFT results should not be used to rule out TB infection in children who had a contact history with contagious TB patients.

3. Performance of QFT for diagnosis of latent TB infection in immunocompromised patients: Haruyuki ARIGA (National Hospital Organization Tokyo National Hospital)

The detection of LTBI in compromised hosts is essential for TB control, but T cell assay might be influenced by the degree of cell-mediated immunosuppression. However, the relationship between immunocompetence and specific IFN- $\gamma$  response in QFT-G is uncertain. Our data indicated that the proportion of positive QFT assay results was found to be positively associated with lymphocyte count. Conversely, indeterminate assay results showed a negative relationship with lymphocyte count. Indeterminate result rates significantly increased in the categories with less than 700 lymphocyte cells/mm<sup>3</sup>. Most markedly, in severe lymphocytopenia with less than 300 cells/mm<sup>3</sup>, the fraction of test with indeterminate result was 37.8%. In patients with impaired cell-mediated immunity or

lymphocytopenia, QFT-G results should be interpreted carefully since false-negative proportion could be increased.

#### 4. QFT-G as a tool for the detection of TB infection among contacts of TB cases: Takashi YOSHIYAMA (Fukujuji Hospital, JATA)

QFT-G has become available for the detection of TB infection among contacts of TB cases in Japan. We would like to discuss the limitations and problems of QFT-G and their solutions.

##### 1) Sensitivity of QFT-G

The meta-analysis has shown the sensitivity of QFT-G to be approximately 80%. However, the reports on the sensitivity of QFT-G for the contacts of TB cases are limited in number, and we reviewed TB cases detected during a follow-up period after contact investigations by the classification of QFT-G results at the time of contact examinations. Among 39 cases detected during a follow-up period, 19 cases were negative with QFT-G at the time of contact examinations. All these cases with negative QFT-G at the time of contact examination were contacts of highly infectious (with high QFT-G positivity among contacts) TB cases.

##### 2) Timing of application of QFT-G

I previously reported that among 8 contacts who became QFT-G positive during a follow-up period, all contacts became positive within 3 months of last contacts before diagnosis, except one pregnant woman, who became QFT-G positive 6 months after the last contacts with TB cases (QFT-G results at

2 months and 5 months were negative). A certain immunological status must be taken into consideration in the timing of its application.

#### 5. Introduction of QFT-G for the nosocomial infection control for health care workers: Hidetoshi IGARI (Division of Control and Treatment of Infectious Diseases, Chiba University Hospital)

At Chiba University Hospital we have met some patients with active TB every year, partly due to their immunocompromised status. I presented a case of contact screening. QFT-G is a useful tool to detect a condition of LTBI in the health care workers. However there is scant evidence to support that the QFT current cut-off value is appropriate for the diagnosis of LTBI. Further study is needed to estimate its efficacy of QFT as an administrative tool for the infection control in health care facilities.

**Key words:** Interferon-gamma release assays, QFT, T-SPOT. TB, Latent tuberculosis infection, Contact investigation

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## IMMUNOSUPPRESSIVE THERAPY AND TUBERCULOSIS

Chairpersons: <sup>1</sup>Kosho YOSHIKAWA and <sup>2</sup>Shuichi YANO

**Abstract** Tuberculosis infection has been involved in host immunity. Diabetes, tumor-bearing patients, AIDS increases the risk of TB infection. And also patients with immunosuppressive therapy has a high risk of developing TB. Japan is a country of moderate TB prevalence yet. Considering the tuberculosis epidemic situation in Japan, risk of developing TB in patients receiving immunosuppressive therapy is high. Tuberculosis incidence state of immunosuppression is not typical, disseminated tuberculosis, and many extrapulmonary tuberculosis. X-ray picture of pulmonary tuberculosis is often different from typical. The tuberculosis incidence in patients

receiving immunosuppressive therapy has a negative impact on the original disease. Early detection of tuberculosis, early treatment is important. But potential effectiveness of treatment for latent TB infection is clear. The patient at high risk of developing tuberculosis is required to make early treatment of latent TB infection.

Through this mini-symposium, member of the Japanese Society for Tuberculosis, along with other specialist physicians, confirmed that it is important that we have established a cooperative system of prevention and early diagnosis and early treatment of tuberculosis.

1. Revolution of treatment with biologics and management of tuberculosis in patients with rheumatoid arthritis: Yoshiya TANAKA, Katsunori SUZUKI, Kazuyoshi SAITO (The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Japan)

Rheumatoid arthritis (RA) is a systemic inflammatory disease that causes significant morbidity and mortality. TNF- $\alpha$  and IL-6 play a pivotal role in the pathological processes of RA through the accumulation of inflammatory cells as well as the self-perpetuation of inflammation, leading to cartilage and bone destruction. The combinational use of biologics targeting TNF- $\alpha$  and methotrexate (MTX) has revolutionized the treatment of RA, producing significant improvements in clinical, radiographic, and functional outcomes that were not previously observed. Post-marketing Surveillance which was conducted to evaluate the safety and effectiveness of infliximab and etanercept in Japan also clarified the safety of the TNF-inhibitors and risk factors involved in the severe adverse effects such as bacterial pneumonia and tuberculosis. Japan College of Rheumatology has recommended that tuberculosis screening before infliximab treatment and prophylactic anti-tuberculosis treatment in the case of a suspected past history of tuberculosis should be performed for subsequent patients. As a consequence, prophylactic administration of antituberculosis drugs was increased, and the number of tuberculosis decreased. Accordingly, prophylaxis before starting biologics and appropriate treatment of severe adverse effects, including bacterial pneumonia, tuberculosis, pneumocystis pneumonia, by physicians have been emerging.

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

To evaluate the influence of anti-TNF therapy on the incidence of TB in Japanese patients with RA, we calculated the standardized incidence ratio (SIR) of TB from the clinical data on National Database of Rheumatic Disease by iR-net in Japan (*NinJa*) prospectively and compared with the SIR of TB from the data of the post-marketing survey of infliximab and etanercept in Japan. Among 7832 RA patients without anti-TNF therapy, 7 patients developed TB. The SIR of TB in RA patients without anti-TNF therapy was 3.98 (95%CI: 1.22–6.74). According to the post-marketing survey of infliximab in

5000 RA patients and etanercept in 13894 RA patients, 14 and 10 cases of TB had reported, the SIR of TB were 21.5 and 5.5, respectively. The incidence of TB in patients with RA was higher than general population, and was increased more by the anti-TNF therapy. We have to recognize the risk of TB when we start anti-TNF therapy to patients with RA.

3. Usefulness and limitations of QuantiFERON-TB Gold in Japanese rheumatoid arthritis patients for estimating latent tuberculosis infection: Shogo BANNO (Division of Rheumatology and Department of Medical Oncology and Immunology, Nagoya City University Graduate School of Medical Science)

We estimated the usefulness of QFT-2G compared with Tuberculin skin test or anti-TBGL antibody. We assessed the sensitivity and specificity of QFT-2G in Japanese rheumatoid arthritis patients with a past history of tuberculosis. Using ROC analysis, the AUC of QFT-2G was significant large. The QFT-G negativity does not exclude the possibility of TB infection because the sensitivity of the test in RA patients is low. The QFT-2G was not affected by the treatment of MTX, and the incidence of indeterminate result was low. It is impossible to confirm the presence of a past history of TB based on the results of QFT-2G alone, which limits its usefulness as a diagnostic tool for evaluation of LTBI.

4. Treatment of latent tuberculosis infection: Fumio YAMAGISHI (Department of Respiratory Diseases, National Hospital Organization Chiba-East National Hospital)

When using infliximab against rheumatoid arthritis, giving an active treatment for latent tuberculosis infection is recommended. That is because the onset of tuberculosis was reduced when a treatment for latent tuberculosis infection was given. In addition, the dosage and the period at administration of INH should follow the treatment standard of tuberculosis.

**Key words:** TNF  $\alpha$  inhibitor, Rheumatoid arthritis, QuantiFERON-TB, Latent tuberculosis infection, INH

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## PREVENTION OF TUBERCULOSIS IN MEDICALLY HIGH-RISKED PATIENTS

Chairpersons: <sup>1</sup>Yuka SASAKI and <sup>2</sup>Emiko TOYOTA

**Abstract** In the last ten years, prevalence rate of tuberculosis have been successfully decreasing under 20/100,000 in Japan and great advance has been brought about in this field; for instance IGRAs (QFT etc) and diagnosis of LTBI. The Japanese Society for Tuberculosis declared statement to perform more active prophylaxis in 2004 but we have still many of compromised patients with TB who could be prevented from getting active tuberculosis. With this symposium, we discussed how to work up actually on this problem in each clinical sites. We should alert physicians participating with medically high-risk patients to recognize the risk of tuberculosis and to promote prevention. In addition, treatment of LTBI should be registered to Public Health Center.

1. A study how to prevent the appearance of active tuberculosis in patients with corticosteroids: Is the state of implementation of medication for LTBI proper?: Masahiro KAWASHIMA (National Hospital Organization Tokyo National Hospital)

The statement for treatment of LTBI by the Japanese Society for Tuberculosis in 2004 gives a concrete description about treatment of LTBI in patients with corticosteroids, but the state of implementation of medication for LTBI in patients with corticosteroids is unclear. 41 cases with active tuberculosis occurred during steroids therapy were studied and at least 15 cases were thought to have been indicative of LTBI retrospectively. Evaluation of risk for TB before and during steroids therapy were insufficient and medication for LTBI were unpracticed. On the other hand, 61 cases who started steroids therapy in our hospital were studied. Examination of sputum, chest-CT scanning, QFT or PPD were performed in most of all patients and then 17 cases were thought to be indication of treatment of LTBI but actually only followed. One patients progressed active TB. Promotion of treatment of LTBI for patients with corticosteroids may leads the decrease of active tuberculosis in those patients.

2. Tuberculosis among patients with rheumatoid arthritis; steroids to anti-TNF $\alpha$ : Tomoshige MATSUMOTO (Osaka Prefectural Medical Center for Respiratory and Allergic Diseases)

Anti-TNF $\alpha$  agents made rheumatoid arthritis remittent effectively but occurrence of TB disease increase as more use of them. We already reported some of problems as follows: 1) diagnosis of LTBI, 2) method and duration for treatment for LTBI not sufficiently established, 3) difficult diagnosis of TB because of atypical figures, 4) paradoxical response, 5) to stop anti-TNF $\alpha$  agents make control of RA difficult for rebound, 6) not established treatment for RA after TB treatment, 7) less professional institutions to treat both RA and TB. Data of over 5000 cases who were treated by Remicade revealed TB did not occur among cases with INH prophylaxis. Furthermore there are possible use of anti-TNF $\alpha$  agent with antituberculous agents. Then it is recommended that screening for TB is necessary before starting anti-TNF $\alpha$  agent and prophylaxis by INH if possible LTBI. We should be careful not to misdiagnose worsening RA by sign of TB or other infectious diseases.

3. A consideration of the prevention from tuberculosis in hemodialysis patients: Takeshi KAWASAKI (National Hospital Organization Chiba-East National Hospital)

Hemodialysis patients have been increasing and aging in Japan, and they are in great danger of tuberculosis. When hemodialysis patients become tuberculosis, there is a possibility of infection to other patients, so the prevention, early detection and treatment for tuberculosis are very important. It became clear by questionnaires that many medical dialysis did not know about the recommendation of treatment for latent tuberculosis infection from the Japanese Society for Tuberculosis. It is important to examine and treat actively for latent tuberculosis infection of hemodialysis patients for the pre-



vention of tuberculosis, and needed to enlighten to medical dialysis.

4. Prevention of active tuberculosis in HIV-infected persons: Akira FUJITA (Tokyo Metropolitan Fuchu Hospital)

The risk for active TB among HIV-infected persons is about from 20 to 200 times higher than among the general population. In Japan which is one of TB middle-burden countries and has BCG vaccination program, interferon-gamma release assay (IGRA) is useful rather than tuberculin skin test for the diagnosis of latent TB infection (LTBI). IGRA for the diagnosis of LTBI is recommended for HIV-infected persons with CD4 positive lymphocyte (CD4+) counts above 50 cells/ $\mu$ L, because our study suggested the sensitivity of QFT-G in the patients with CD4+ below 50 cells/ $\mu$ L may be low. Appropriate TB contact investigation for HIV-infected persons is important. For example, contacts who do not know their HIV-infection status should be advised to take HIV testing in the urban areas with high HIV prevalence rate. A possible correlation between non-adherence to highly active antiretroviral therapy and the risk of active TB development suggests that good adhere to antiretroviral drugs will be able to prevent

active TB in HIV-infected patients.

5. Administration's problems for latent tuberculosis infection (LTBI): Chika SHRAI (Public Health Center of Kobe City)

Clinician is obliged to report medication-required LTBI to Public Health Center, based on the Infectious Diseases Control Law. The Administration is unable to assess measures for TB without these reports. It is mandatory to own significance of LTBI reports and high-risk factors jointly by clinicians and public health facilities. It ought to acknowledge these procedures as essential tactics to eliminate TB through low spread.

**Key words:** Preventive therapy, Medically high risked patients, Treatment of LTBI, QFT

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**Abstract** Although the tuberculosis (TB) incidence rate in Japan reached 19.4 per 100,000 in 2008, the rates among the elderly (65+ yrs) were high, e.g. 29.5 of those aged 64–74 years, 64.2 of those aged 75–84 years and 97.3 of those aged 85 years and over. The trends of incidence rates of elderly TB differed by age group. Since 2000, those aged 65–84 years showed a relatively faster decrease, whereas those aged 85 years and over showed a slower decrease.

The proportion of those aged 65 years and over increased from 36.8% in 1987 to 56.7% in 2008, i.e. an increase of 1.5 times. Especially, the proportion of those aged 80 years and over increased greatly from 7.9% in 1987 to 26.6% in 2008, i.e. an increase of 3.4 times. The proportion of elderly TB differed greatly by prefecture.

According to epidemiological indicators of elderly TB, the proportion of extra-pulmonary TB was larger (24.9%) than that of younger TB patients aged 15–64 years (17.2%). The proportion of bacillary TB among elderly pulmonary TB patients was larger than that of younger pulmonary TB patients, but the proportion of cavitary TB among elderly pulmonary TB patients was smaller than that of younger pulmonary TB patients. The proportion of TB patients having only other symptoms without respiratory symptoms increased with age, e.g. 19.5% of those aged 65–74 years, 23.2% of those aged

75–84 years and 27.5% of those aged 85 and over.

Regarding the delay of case detection among elderly TB patients, the patient's delay tended to be shorter but the doctor's delay was longer. Although most TB patients including elderly TB patients were detected upon visiting a medical institution with some symptoms, in the case of elderly TB more patients were detected as outpatients or inpatients for a disease other than TB.

The prognosis of newly notified TB patients in 2007 was followed up till the end of 2008. Among TB patients aged 65 years and over, 26.4% died within one year and 14.8% died within 3 months. The proportion of death increased with age, and accelerating quickly particularly among those aged 75 years and over.

**Key words:** Tuberculosis, Incidence, Elderly, Age, Trend, Epidemiological indicator, Death, Prefecture

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