Japan, a “medium-burden tuberculosis country”

In the past, the prevalence of tuberculosis (TB) in Japan was so high that it was said to be a national threat (in 1943, the TB death rate was 235 per 100,000 people, 150 times higher than in 2015). Then, after the war, the number of cases dropped rapidly, and for a while it was thought that the epidemic was over. However, in 1996-1997, there was a new outbreak of TB cases, and the prevalence rate began to rise again, and continued to do so for 3 years. Japan declared a “tuberculosis state of emergency” to draw attention to the problem. After that, the number of cases finally began to decrease, but tuberculosis had once again gained attention as a “re-emerging infectious disease”. The current prevalence rate is 14 per 100,000 people (or approx. 1 per 7000 people), many times higher than in other developed countries. As this is about the same rate as it was in America in the 1970s, Japan has been designated a “medium-burden tuberculosis country” (Figure 1).

Figure 1: Prevalence rates of tuberculosis in Japan and other developed countries (All tuberculosis, 2015)
Causes of the TB “re-emergence”

Within this “TB re-emergence”, new problems have surfaced.

1. **Increase in the number of group infections.**
   Among the younger generation, there are many people with no immunity to TB, and late diagnoses and other factors result in increased group infections / infections within hospitals (Figure 2).
   
   - Figure 2: Group Outbreaks: Where does it start? (2003-2014, total cases: 524, cumulative group cases: 710)

   TB group infection is defined as “when a single source of infection spreads tuberculosis to two or more families and 20 or more people”.
   “Social welfare facilities” includes welfare facilities for the elderly, geriatric health service facilities, and facilities for the disabled. “Other” includes places such as restaurants, entertainment facilities, and internet cafes that use an unspecified number of people. Infections that are spread across 2 or more groups are counted multiple times.

2. **Increase in the number of severe cases / severe outbreaks**
   There are cases of patients becoming seriously ill immediately after catching TB, and cases where TB is only diagnosed after reaching a severe stage.
   What’s more, of the patients who are diagnosed with TB and start treatment, 10% will not survive. Among those, half will die within a year of diagnosis (Figure 3).
   
   - Figure 3: Mortality rate of tuberculosis patients over time (1990-2015) (Death within one year of being diagnosed with tuberculosis)
3. **Increase in outbreaks among the elderly**
   Recently, 70% of outbreaks have been among patients who are age 60 and above. The main reason is that many people in this age group were inflected before or after the war, and with the onset of old age, health problems and other factors trigger the latent TB, causing it to become active.

4. **Increase in outbreaks among economically vulnerable members of society**
   Recently, there have been a notable number of outbreaks among those who are in socially vulnerable situations, including the homeless, and those who are unable to take proper care of their health.

5. **The emergence of multidrug-resistant tuberculosis**
Be careful of poorly ventilated locations

The bacterium that causes tuberculosis (TB), mycobacterium tuberculosis, is spread through the air when people who have active tuberculosis cough or sneeze, and other people then breathe in the bacteria (Airborne Infection, Droplet Nuclei Infection). The disease is not spread by holding hands with someone who is infected, or by using the same tableware etc.

Because TB germs released into the air can linger for an extended period in locations with poor air conditioning or ventilation, there have been cases of the disease spreading even when the infected person is no longer present.

Large cities where many people live and work together in close quarters have high risks of infection due to their very nature. Moreover, with the recent increase in homelessness, and the lack of healthcare that accompanies it, combined with an increase in the number of foreign workers from countries with high rates of TB infection, we see a difference in the spread of TB in large cities compared with rural areas (figure 4).
Factors Which Increase the Risk of Becoming Infected

- **Infancy and pubescent children**
  Infants, with their weaker immune systems, can easily succumb to TB if they become infected. These children are at a greater risk of suffering serious complications and thus require special attention.

- **Stress**
  It is believed that stress and irregular lifestyle patterns can also make one more susceptible to TB.

- **Gender Differences**
  Women are more susceptible to the disease before middle age, and men become more susceptible after reaching middle age.

- **Diabetes, Stomach Ulcers, and Other Conditions**
  People with diabetes or stomach ulcers, or those who have had a gastrectomy, are known to be more susceptible to TB. In addition, those with pneumoconiosis, those who have undergone intestinal bypass operations, those undergoing dialysis, or those with hemophilia are also said to be vulnerable.

- **Adrenocortical Hormone Agents, Biological Drugs**
  Anti-cancer drugs and adrenocortical hormone agents (steroids) used to treat asthma, collagen disease, cancer, and other disorders can weaken the immune system and increase the user's risk of contracting TB. People using TNFα inhibitors (biological drugs), currently receiving attention as a treatment for rheumatoid arthritis and other disorders, have also been recognized worldwide as being more susceptible to the disease.

- **AIDS, HIV Infection**
  In Africa and some Asian countries, the presence of populations with weakened immune systems due to HIV, has led to increases in the number of TB infections, and become a serious issue.

- **Hereditary Predisposition**
  Science is gradually uncovering information indicating that resistance to TB is genetically determined.

- **Tobacco and Other Factors**
  Smokers, people who have contracted tuberculosis in the past, people who have not received the BCG vaccination and received positive results from tuberculin tests, people with others close to them who have recently contracted TB, and individuals in similar circumstances are also at a higher risk of contracting the disease.
Early stages of pulmonary tuberculosis present cold-like symptoms.

The symptoms during the early stages of pulmonary tuberculosis are similar to those of a common cold: cough, phlegm, and fever. However, they differ from a common cold in that the symptoms persist for more than 2 weeks, or repeat a cycle of getting better then worse.

- Phlegm secretion
- Lingering cough
- Fatigue
- Persistent slight fever

A persistent cold is a red flag

Even if you think you just have a cold, or perhaps have just smoked too many cigarettes, consult your physician as soon as possible. The disease is easier to manage with early detection, and you are less likely to spread it to the people around you.

Infection does not necessarily lead to the active disease

Even if you are infected with the tuberculosis bacteria, you may not develop the active disease. The immune system of a healthy body will suppress the bacteria after infection. When the body becomes weakened, or its immune functions are compromised due to other illnesses, the suppressed TB bacteria reactivate, potentially causing you to experience disease symptoms.
Figure 5 The development of TB from infection to the active disease

**Infection does not necessarily lead to the active disease**

- **Infection**
  - TB bacteria inhaled into the lung(s) start to proliferate in the lung
  - Proliferation of TB bacteria in the lung is generally inhibited since the human body develops immunity and fights against it

- **Hibernation-like state**
  - TB bacteria enter a hibernation-like state after inhibition of their proliferation by the human body's immune system
  - The TB bacteria can stay inside the body for several decades

- **Active disease breaks out**
  - Endogenous exacerbation
    - Recurrence of TB bacteria proliferation will occur and trigger the active disease when the body's immune system declines due to some other cause
    - This outbreak could happen over one year after the first infection, and occasionally several decades after the first infection

- **Active disease breaks out**
  - Primary infection TB
    - TB bacteria will proliferate and cause disease in cases of poor immunity early in the infection
    - This tends to happen in infants and elderly individuals

Provided by: Tatsuro Mori, President of the Japan National Tuberculosis Association Foundation
Here is an example case displaying a typical course of disease progression for tuberculosis:

Mr. A is in his 60s. He was relatively healthy, and had never had a major illness.

1. **Symptoms**
   He started coughing, and assumed that he had caught a cold. He took some cold medicine that he had on hand. This helped relieve the symptoms a little in 3-4 days, so he just left it at that.

2. **Fever**
   After 2 weeks, he started coughing again. This time, the cough was accompanied by a mild fever of around 37.5°C in the evenings. When he consulted his physician, he was told that his cold had returned, and was prescribed antibiotics, antipyretics, and a cough suppressant.

3. **Blood-tinged phlegm**
   The symptoms eased a little, perhaps due to the medication he was taking, but a week later, he saw some blood in his phlegm, and became concerned. He had a chest X-ray, and his phlegm tested. He was diagnosed with infectious pulmonary tuberculosis (Figure 6-①).

4. **Hospitalization**
   He was immediately admitted to a hospital that had a TB unit, and started on a standard course of treatment. Medication was administered following the “Directly Observed Treatment, Short course (DOTS)” method, whereby the patient was given his medication by a nurse after breakfast every day, along with a cup of water, which he then ingested in front of the nurse (Figure 6-②).

5. **Treatment progress**
   2 months after the start of the treatment, Mr. A tested negative on the bacterial smear test, 3 times in a row. Moreover, the chest X-ray revealed a reduction in shadows, indicating that the treatment had been successful (Figure 6-③).

6. **Discharge**
   A DOTS meeting was held, where the physician and nurse from the hospital, a caseworker, and a regional public health nurse discussed Mr. A’s treatment going forward. It was determined that he could continue his regular treatment as an outpatient. He was then discharged from the hospital and switched to an outpatient treatment program (Figure 6-③).

7. **Outpatient visit**
   As an outpatient, his treatment was reduced to just 2 drugs. He visited the outpatient department on a monthly basis to receive one month’s worth of drugs, which he took daily. His wife marked “administered” on the calendar in his medication logbook, which had been issued by a local public health center. His physician verified and signed it during Mr. A’s monthly visits. The public health nurse, who visited him at home every month, also checked this logbook and signed it, as well as offering words of encouragement (Figure 6-④).

8. **End of treatment**
   4 months of outpatient treatment ended without any major side-effects. When his recovery was confirmed through a chest X-ray during his last appointment, his treatment officially ended (Figure 6-⑤).
Tuberculosis is not a problem for the patient alone.

People who had contact with Mr. A were checked to make sure that they were not infected (a contact investigation).

When Mr. A was admitted to the hospital, a nurse from a public health center visited him to explain his disease and treatment, and also to ask about his activities prior to experiencing symptoms. Based on his response, the local public health center narrowed down the list of potentially infected individuals (his wife, his children's families who had been to visit a few times after the coughing started, friends from a local Go club, etc.). The local public health center contacted these individuals and asked them to get tested. Based on the test results, his wife, while she was asymptomatic, was deemed to be potentially infected, and received preventative treatment. The families of his children were all uninfected. His friends from the Go club all showed no abnormalities on their chest X-rays.
Tuberculosis tests and diagnosis

Tuberculosis is diagnosed using the results of X-rays, microbiological examinations, etc. Currently in Japan, 80% of pulmonary TB is diagnosed through a microbiological examination. (Figure 7)

- Figure 7: Tuberculosis diagnosis flowchart

1. **Incidental finding due to another health condition**
   - X-ray
   - This method is used for mild cases of active TB in its early stages
   - Although a plain radiography method is commonly used, CT scans, which allows visualization of the cross sections of the lung, can also be used
   - X-rays can show signs of diseases such as pneumonia or scarring left after recovering from TB. Therefore, it is difficult to conclude if it is TB by using X-rays alone.

2. **Patient seeks medical care for symptoms of TB**

3. **Health screening**

4. **Tuberculin test and Interferon-Gamma Release Assay (IGRAs)**
   - This method is used to screen for TB infection
   - A Tuberculin test can give a positive result regardless of presence of TB infection for an individual who has previously had a BCG shot. For this reason, a recently-invented method called Interferon Gamma release assay (a blood test) is used for screening

5. **TB bacteria testing**
   - **Smear test:** Phlegm from a patient is smeared on a microscope slide, and TB is detected by drying only the TB bacteria. When this test is positive, the patient can be declared a source of infection.
   - **Cultivation test:** Phlegm from a patient is smeared on a culture medium that allows proliferation of only TB bacteria, and allows detection of proliferated TB bacteria with the naked eye. It takes 8 weeks for the final test result. However, this method is 10 times more sensitive than other smear tests. Lately, liquid culture mediums have been developed to provide a quicker result.

6. **PCR testing:** This method is as sensitive as a cultivation test for TB bacteria detection, and can provide the result within couple of days

7. **Result: TB positive**
   - **Diagnosis confirmed**
   - **Clinical course and pathological exam**
   - **Strong suspicion of TB**

8. **Result: TB negative**
   - **Not TB**
TB can occur in places other than the lungs

The majority of TB cases are of pulmonary tuberculosis (PTB). However, TB can occur in organs other than the lungs. (Figure 8)
Extrapulmonary TB (EPTB) accounts for 20% of all tuberculosis cases.

Figure 8: Parts of the body where non-pulmonary tuberculosis can occur

- Tuberculous meningitis
- Miliary tuberculosis
- Nephrotuberculosis
- Cervical lymph node tuberculosis
- Pulmonary hilar lymph node tuberculosis
- Tuberculous pleuritis
- Articular tuberculosis (Spine etc)

Provided by: Toei Moto, honorary chief of the research institution of Japan Anti-Tuberculosis Association Foundation
Almost all treatment is medicine based.

**Pharmacotherapy**

It is important to continue treatment using the prescribed medication properly. The main medications currently used for treatment are as follows:

1. Rifampicin
2. Isoniazid (hydrazide)
3. Streptomycin
4. Ethambutol
5. Pyrazinamide

The most typical treatment pattern is:
1 + 2 + 4 + 5 (or swap out 4 for 3) for 2 months, and following that, 1 + 2 for 4 months.* In the past, treatment for TB took 2-3 years or longer, but now it can be completed in 6 months (short-term chemotherapy).


**When hospitalization is necessary**

If the patient’s general condition is poor, if the symptoms are severe, or if there are concerns about infecting others around them, hospitalization is necessary. With effective treatment, the bacteria should cease activity after 2-3 months, so even patients who were concerned about infecting others can return home and just visit the hospital periodically to continue treatment as an outpatient.

**When surgery is necessary**

Currently, surgery is seldom performed. However, if medication fails to eliminate the bacteria, then surgery can be considered.
It is said that "there is no better treatment than prevention," but what prevention strategies are available for tuberculosis (TB)? We will consider methods in these three categories.

- **Before infection**: BCG vaccine (vaccination)
- **Following infection**: Treatment of latent TB infection (chemoprophylaxis)
- **When there is a high risk of infection**: Contact investigation

### BCG vaccine (vaccination)

BCG is a vaccine that confers resistance (immunity) against TB in uninfected individuals by injecting a person with an innocuous relative of the tuberculosis bacteria *Mycobacterium tuberculosis*. In Japan, children receive the BCG vaccine before reaching one year of age (ideally at 5-7 months of age). The method of vaccination is a "stamp" injection, which results in 18 small needle marks that appear roughly 6 months after inoculation.

Vaccinated individuals have an 80% lower chance of developing the disease after infection compared to those who are unvaccinated. In infants, TB infections entail a substantial likelihood of severe illnesses such as meningitis, and the BCG vaccine is effective in preventing these outcomes as well. The vaccine is thought to remain effective for 10-15 years.

### Treatment of latent TB infection (chemoprophylaxis)

Those who have recently been infected with the *Mycobacterium tuberculosis* bacterium have a high risk of developing TB within one to two years. Even those who were infected less recently may suffer from a heightened risk of developing TB due to a number of causes (see Tuberculosis symptoms). Drugs that suppress the immune response, which are taken during treatment for numerous diseases, are particularly problematic if you are infected with TB. This state is known as a latent tuberculosis infection, with the *Mycobacterium tuberculosis* bacteria in the body considered to be in a preparatory stage prior to disease onset. Patients at this stage of infection are asked to take a course of TB treatment to kill off the bacteria before they trigger the active disease. This prophylactic treatment was formerly known as chemoprophylaxis, or preventive internal administration, and is thought to reduce the risk of disease onset by about 50-80%.

The tuberculin reaction test is used to diagnose latent TB in infants, and a blood test (QuantiFERON or T-SPOT) is used in older patients. The standard treatment regimen is 6-9 months of isoniazid treatment.
Contact Investigation

If someone is suffering from TB, and especially if that person is releasing Mycobacterium tuberculosis bacteria (i.e., infectious tuberculosis), there is a risk that the bacteria may have infected those nearby. Moreover, if the person showing symptoms of the disease is a child or adolescent, they may have recently acquired the infection from someone else. Therefore, when a person is found to have TB, it is necessary to find those who are also infected or are the source of the infection. The search for and examination of such people is known as a contact investigation, and is an important part of the TB control measures carried out by public health centers. If not done properly, the situation may worsen and lead to mass outbreaks or grave illnesses in infants.

Characteristics of an initial patient indicating that a contact investigation is especially important

1. Patient is releasing large amounts of bacteria (positive smear test)
2. Patient has not been diagnosed in a long time
3. Patient is a child or adolescent (especially in the case of multiple patients)
4. Patient has a rare disease type (e.g., meningitis, middle ear infection, etc.)

Characteristics of a contacted person that indicate a contact investigation is especially important

1. Person is an infant or has reduced immune function due to illness (e.g., AIDS or kidney failure) or treatment (e.g., adrenocortical hormone therapy)
2. Person has been in close contact with the initial patient (e.g., family members or close friends)

Tests and evaluations that are part of a medical exam

1. Evaluation: Assess the extent to which the person under examination has talked with or worked or studied in the same room with the patient since the onset of the illness (the onset of coughing). Possible situations where contact may have occurred include family life, workplace/school activities, clubs, hobbies, and leisure activities.
2. Blood test (QuantiFERON or T-SPOT)/immunodiagnostic tuberculin reaction test: These tests check for TB infection. If it is judged that an infection has occurred, it is necessary to treat the latent TB infection (chemoprophylaxis).
3. Chest X-ray exam: Determine whether an infection has already triggered disease onset. Patients with early-stage TB are most often asymptomatic, and early discovery and treatment is key. For those with high infection risks, this test should be administered repeatedly for about two years after the time when contact with the first patient occurred.

What steps are being taken in Japan to prevent the spread of TB?

Tuberculosis is an important public health issue

In Japan, the Infectious Diseases Control Law stipulates various measures for controlling TB. The following are some measures that relate to TB control in Japan.
• **BCG vaccination**
The government is required by law to work towards the vaccination of all infants. In recent years, nationwide vaccination rates in Japan have reached over 97%.

• **Treatment of a latent TB Infection**
Although only young patients were treated in the past, treatment is now performed on patients of all ages. As with standard TB treatments, in Japan, the cost is covered by public funding.

• **Patient discovery**
Patient discovery may occur during a health checkup or may be triggered by the onset of symptoms. Contact investigations (non-periodic health examinations) occur when medical exams are conducted on those in the vicinity of infected persons in an attempt to find others who may be infected or be experiencing the disease. A breakdown of recent methods for discovering pulmonary tuberculosis patients is as follows (Fig. 9).

Figure 9: Breakdown of methods for discovering tuberculosis patients (data from 14,123 newly enrolled patients with pulmonary tuberculosis in 2015)

- **Patient Support**
Although only young patients were treated in the past, treatment is now performed on patients of all ages. As with standard TB treatments, in Japan the cost is covered by public funding.

  o **Public aid**
  In Japan, TB treatment is subsidized through public health insurance as well as through public funds. This prevents situations where a course of treatment may need to be ended prematurely due to the patient's financial situation, and also makes the government responsible for treatment quality.

  o **The Japanese version of DOTS**
  To ensure that a patient completes his or her treatment in accordance with the doctor's instructions, a patient's doctor coordinates with health centers during the entire duration of the hospitalization/outpatient treatment regimen to help ensure the patient receives the proper treatment.

  o **Quarantine**
  In-hospital quarantine is recommended for patients who are at risk of spreading the disease to others.
• **Surveillance (trend monitoring)**
  Data collection and analysis is carried out continually to determine trends in TB outbreaks and evaluate countermeasures/medical treatments. This information is used to plan further actions.

• **The Japan Anti-Tuberculosis Association and the Stop TB Partnership Japan**
  The Stop TB Partnership Japan was established in November 2007 in cooperation with both public and private sector organizations including the Japan Anti-Tuberculosis Association. The organization serves as a vehicle for maintaining and strengthening coordination in the fight against TB both in Japan and worldwide.
What efforts are being made to fight tuberculosis globally?

Global tuberculosis countermeasures are connected to the eradication of tuberculosis in Japan

Since the development of DOTS, the importance of (TB) countermeasures has been recognized internationally. In today's world, with frequent global travel, the increase of TB in Asia and Africa is not simply "someone else’s problem"; this is why a global effort is being made to formulate new strategies to eradicate the disease.

- In 1993, the World Health Organization (WHO) issued a TB Emergency Declaration, marking it as a global health emergency, and urged developing and developed countries to work together systematically to tackle the problem.

- Recognizing the economic benefit of TB countermeasures using DOTS, the World Bank began granting large-scale financial aid (loans) for TB countermeasures to countries such as China and India.

- With the WHO at their core, several public and private groups and organizations came together to form the Stop TB Partnership, which became a powerful supporter for global TB countermeasure promotion, focusing on developing countries.

- Japan's proposal at the 2000 G8 summit in Okinawa spread awareness of the fact that contagious diseases were preventing developing countries from growing. The Global Fund to Fight Aids, Tuberculosis and Malaria was established under the leadership of the UN, and began providing significant funding to combat these illnesses.
Developing countries in Asia and Africa have especially high numbers of patients

Tuberculosis worldwide

There are 10.4 million new cases of TB per year worldwide, and 1.4 million people have died from TB (chart/figure 10). These numbers have finally started to slowly decrease in the past few years. Developing countries have the highest number of patients. TB is called a "re-emerging infectious disease" because it just won’t go away, and recently, complications such as TB/HIV co-infection and MDR-TB (multidrug-resistant tuberculosis) have become a problem.

* When deaths by TB/HIV co-infection are added to the number given in the chart, yearly deaths come to 390,000 worldwide.

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* HIV positivity not included

WHO: Global Tuberculosis Report 2016
TB spreads in HIV positive patients

HIV is a disease that severely weakens the immune system, and is the biggest risk factor for TB. When HIV began to spread in Africa, the number of TB infections increased too. Additionally, TB countermeasures collapsed in former socialist countries with chaotic social systems; TB cases increased, and malignant (drug-resistant) TB in became a particular problem. Even in developed countries, TB is becoming a problem again due to the effects of HIV, emerging poverty, and infections brought in from counties where TB is rampant.

What is multidrug-resistant tuberculosis?

The TB bacterium *Mycobacterium tuberculosis* can become resistant to TB drugs. Multidrug-resistant tuberculosis (MDR-TB) is a strain of TB that has developed resistance to both Isoniazid and Rifampicin, the two most important drugs currently used to treat TB. MDR-TB has recently been increasing globally (including in Japan), and is the most critical issue surrounding the increase of TB today. Some situations that may lead to the development of MDR-TB are inadequate treatment, irregular drug administration, or drug administration that is suspended before the course is finished. Even after treatment is over and the infection seems to be cured, relapse occurs in around 2-5% of patients\(^1\,^2\). The right side of Figure 11 (Previously treated patients) shows that such patients often have MDR-TB. Unfortunately, however, anyone infected by an MDR-TB patient will also have MDR-TB from the start (First-time patients, Figure 11 left side).

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**Figure 11:** Frequency of MDR-TB in Japan

![Bar Chart](chart.png)

- First-time patients (2,097 Individuals)
  - Others: 8.5%
  - H: 3.1%
  - R: 0.7%
  - S: 5.6%
  - E: 1.3%
  - MDR: 0.4%

- Previously-treated patients (195 Individuals)
  - Others: 20.5%
  - H: 12.3%
  - R: 6.7%
  - S: 12.3%
  - E: 2.6%
  - MDR: 4.1%

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S: Streptomycin  H: Isoniazid  R: Rifampicin  E: Ethambutol  MDR: Multiple drug resistant

Ryoken, IJTLD 19(2), 157-162, 2015
Courses of treatment for MDR-TB patients

When the main drugs used to treat TB, Rifampicin and Isoniazid (Hydrazide), both become ineffective (multidrug-resistant, MDR), TB becomes extremely difficult to treat. Figure 12 shows research on courses of treatment for MDR-TB patients. Several drugs with severe side effects must be used over long periods of time for this treatment to work. In some cases, surgery is also required. Even so, the results are poor: as shown, recovery was confirmed in 62% of cases, but the remaining cases either ended in death or failed to stop the infection.

What is the globally promoted TB treatment system DOTS?

DOTS (Directly Observed Treatment, Short-Course) is a strategy developed by the WHO to ensure that drugs are reliably administered to patients.

With the opinion that international society was taking the TB problem too lightly, Dr. Arata Kochi, who was appointed director of the World Health Organization’s tuberculosis programs in 1989, developed and spread the powerful treatment program known as “DOTS”. This system provides patients in developing countries with a reliable supply of expensive drugs that they could not previously access, and is effective primarily because it requires medical professionals to give the drugs directly to patients and oversee their administration in person. This system has been adopted not only in developing countries, but also in developed countries such as the US, and has become the world’s standard TB treatment method. In Japan too, the Infectious Diseases Control Law stipulates that “The health care center and attending physician must cooperate to support the patient and ensure that the patient follows through with regular drug administration.” Known as the “Japanese DOTS” system, this process provides and confirms drug administration in ways that fit the circumstances of each patient and region (See “Tuberculosis symptoms”).

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