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ROLES OF PUBLIC HEALTH CENTERS (*HOKENJO*) IN TUBERCULOSIS CONTROL IN JAPAN

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ABSTRACT

Public health centers (PHCs, *hokenjo* in Japanese) are local government authorities responsible for public health in Japan. PHCs have an important role in tuberculosis (TB) control. Typically, their responsibilities include 1) the recommendation to admit infectious TB patients to an isolation ward, 2) health checkups with chest X-ray of those in a close contact with infectious TB patients, and 3) public subsidy of medical expenses for TB treatments. Facing the emergence of multi-drug resistant tuberculosis (MDR-TB), the national TB control program was drastically changed; the Japanese version of the Directly Observed Treatment in Short-course (DOTS) strategy was started in 2005. New roles were added to PHCs' responsibilities; 1) active screening of latent TB infection by interferon gamma release assays for those in a close contact with infectious TB patients, 2) community DOTS to promote treatment adherence to outpatients, 3) cohort analysis of outcomes of TB treatment, and 4) national MDR-TB surveillance. These roles are important in preventing MDR-TB and eliminating TB in Japan.

Key Words: public health center, multi-drug resistant tuberculosis, latent tuberculosis infection, DOTS strategy, Infectious Disease Act.

INTRODUCTION

Public health centers (PHCs, *hokenjo* in Japanese) are local authorities executing the public health administration of the Japanese government. The structures and roles of PHCs have rarely been published in the English language. Our previous article simply summarized the structures and roles of PHCs in the course of providing the fundamentals of community health, as described in the Community Health Act (*Chiiki Hoken Hou* in Japanese).[1)]

As briefly described in our previous article, tuberculosis (TB) control is one of the most important roles of PHCs. The incidence rate of TB in Japan was 16.4 per 100,000 in 2011, which was high compared with other developed countries.[2)] Recently, multi-drug resistant tuberculosis (MDR-TB) emerged as a new challenge to TB control.[3,4)] MDR-TB is defined as TB resistant to both isoniazid (INH) and rifampicin (RFP). Since both drugs are highly effective drugs against TB, the resistance to them requires three or four other drugs for treatment, over a much longer period, resulting in higher costs for MDR-TB treatment. The resistance takes place mainly due

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to an inappropriate regimen, irregular or inadequate treatments, as well as infection from patients with MDR-TB.[3,4]

The legal basis for the National Tuberculosis Program (NTP) of Japan was the Tuberculosis Control Act (*Kekkaku Yobou Hou* in Japanese), most recently amended in 2005, in the face of tremendous changes in tuberculosis epidemiology in the last half century.[5] The Act was further incorporated into the Infectious Disease Act (*Kansensho Hou* in Japanese) in 2007.[6] This article describes the roles of PHCs in NTP, mainly based on the Infectious Disease Act, with emphasis on the Japanese version of the Directly Observed Treatment in Short-course (DOTS) strategy.

AGING OF TB PATIENTS IN JAPAN

Compared to the other countries, TB patients in Japan have been growing older alongside the aging of the population. In 2012, 65.2% of smear-positive pulmonary patients were aged 65 years and older, and 37.2% were aged 80 years and older,[2] while globally 59.7% were between 15 to 44 years and only 9.9% were aged 65 years and older.[7]

One reason for the extreme aging of TB patients is the intergenerational gap between very high infection prevalence in the elderly and very low infection prevalence in the younger population. The gap in infection prevalence was caused by rapid and continuous reduction of infection risk after World War II due to the dramatic decrease of the incidence of TB cases in Japan from 590,662 (698.4 per 100,000) in 1951 to 22,681 (17.7 per 100,000) in 2011.[2]

Another reason for the aging of TB patients is rapid aging of the population. Aged people who were mostly infected in the past, and thus more likely to develop the disease due to biological senescence,[8] have been increasing. While only 5% of the Japanese population were aged 65 years or over in 1950, the corresponding percentage was 23% in 2010. The population aged 80 years or over was 8 million (6.4%) in 2010, over 70% of which were estimated to be TB infected in the past.[8]

ACTIVE SCREENING FOR TUBERCULOSIS INFECTION BY PHCs

Tuberculin skin test (TST) was the only test for TB infection approved in Japan, before interferon gamma release assays (IGRAs) for whole blood became available as a diagnostic method of TB infection.[9] IGRAs are not affected by bacillus Calmette–Guérin (BCG) vaccination and most non-TB mycobacterium infections. This difference from TST is an advantage in that it can be used as a more accurate screening method for TB infection in Japan. Another merit of IGRAs is that the assays require only one visit, whereas a TST requires two visits; the first visit for injection of tuberculin and the second visit to measure the size of the skin reaction 48–72 hours after the injection.[9]

In 2007, the Ministry of Health, Labour and Welfare (MHLW) of Japan approved IGRAs as a method to diagnose TB infection, and abandoned age restrictions for latent tuberculosis infection (LTBI) treatment that had limited it to those aged less than 30 years, both in practice covered by health insurance, and for additional subsidies for patients' medical expenses by the Infectious Disease Act. LTBI is defined as those who are infected with *tuberculosis bacilli*, but have no symptoms or signs due to the infection, being different from active TB. Through the introduction of this new technology into health checkups by PHCs for those in a close contact with infectious TB patients, those with LTBI were added to the subjects to be identified under TB control by PHCs.[10]

Although IGRAs cannot distinguish recent infection from past infection, it is effective for identifying recently infected persons among a population with low prevalence of TB. If they are diagnosed as LTBI, PHCs recommend a course of INH medication for 6 to 9 months to prevent the development of symptomatic TB.[11]

In 2007, 2,455 LTBI patients were treated, who were found to be in a close contact with an infectious TB patient by PHCs.[12] The number increased to 7,979 in 2011.[2] Assuming that cumulative incidence rate of active TB from LTBI is 10%[13] and INH provides two thirds of protection against the development of active TB,[14] it is expected that the treatment prevents 533 cases of active TB. Owing to the abandonment of age restrictions, those aged 30 years or over became 68% of treated LTBI patients in 2011.[2] Health checkup by PHCs for those in close contact found also 836 active TB patients in 2011. The detection rate was very high at 3.8 per 1,000 compared to the 0.05 per 1,000 rate found by annual screening of residents by municipalities,[2] although the subjects for screening with chest X-ray changed from those aged 18 years or older to 65 years or older in 2005.

WHO STOP TB STRATEGY

In the 1990's, WHO recommended DOTS: medication under the direct observation of medical staff, for the duration of 6 months.[15] The standard short course regimen consists of the initial phase of 2 months of INH (H), RFP (R), pyrazinamide (PZA or Z) and ethambutol (EB or E) daily, followed by a continuation phase consisting of 4 months of INH and RFP daily (2HRZE/4HR) or 3 days a week (2HRZE/4$(HR)_3$).[15] WHO also recommended the alternative 8 months of regimen consisting of a 6-month continuation phase (2HRZE/6HE) in case that directly observed treatment is not available. Since it was reported that this regimen was associated with a higher rate of failure and relapse, and induced RFP resistance,[15,16] WHO revised the recommendation in 2010 to remove the 2HRZE/6HE treatment regimen.[15]

WHO now recommends supervision and support for all TB patients in order to ensure the completion of treatment for the 6-month standard regimen. The optimal continuation phase regimen is INH and RFP daily, not INH and RFP three days a week. Accordingly, directly observation is a must in case of the latter regimen, because even a one-time skip of medication would result in treatment failure.[11,17]

DOTS is internationally agreed as a strategy for TB control. It stands for Directly Observed Treatment, Short-course, being shorter than one- or two-year courses common in the past. The five components of DOTS (WHO Stop TB Strategy[15]) are as follows:

1. Political commitment with increased and sustained financing
2. Case detection through quality-assured bacteriology
3. Standardized treatment with supervision and patient support
4. An effective drug supply and management system
5. Monitoring and evaluation system and impact measurement

JAPANESE VERSION DOTS STRATEGY

In 1996, the Japanese NTP newly adopted a 6-month regimen (2HRZE/4HR) as a standard, as well as a 9-month regimen (9HRE) adopted before that. In 2000, DOTS was been introduced for the first time in Japan in large cities such as Shinjuku, Kawasaki, Yokohama, and Osaka for homeless and slum residents, resulting in a demonstrable success.[18-21] These results were derived

from active screenings for impoverished populations in metropolitan areas, following DOTS with incentives such as city sponsored apartments and public assistance. To identify the effectiveness of DOTS in general populations, further research will be needed.

In 2003, MHLW announced the Japanese version of the DOTS strategy to all medical professionals. Both PHCs and physicians treating TB patients are responsible for promoting treatment adherence by the Infectious Disease Act. Supervised and supported treatment of the Japanese version of the DOTS strategy is divided into inpatient treatment "hospital DOTS", and outpatient treatment "community DOTS".[22] Most characteristic of the Japanese version DOTS strategy is the inpatient treatment of sputum smear positive pulmonary patients.[18-21]

According to the Infectious Disease Act, sputum smear positive patients must be admitted to a TB isolation ward in a hospital to prevent transmission to others in Japan.[1] Such patients have a large bacillary load, increasing the risk of selecting resistant bacilli. Because the mechanism of resistance is based on spontaneous mutation and selection, adherence to treatment by these patients is essential to prevent drug resistance.[23]

INPATIENT TREATMENT "HOSPITAL DOTS"

In hospital DOTS, as a rule, drug taking by hospitalized patients is to be directly observed during the whole period by hospital staff such as nurses and pharmacists. However, when the hospital staff is convinced of complete adherence to medication, it is possible to change the supervision method for counting and recording the number of empty bags or each dose of anti-TB drugs on the patient's treatment card (*Fukuyaku Techou* in Japanese), which includes the information for each patient necessary for TB control.

Patients treated with the standard chemotherapy over 2 weeks can be discharged from the isolation ward, if they meet the following criteria: (1) free of symptoms (cough, fever, etc.); (2) three different sputum smears are negative for acid-fast bacilli; (3) both physician and PHC in charge are convinced that the patient will adhere to community DOTS after discharge; (4) the patient understands methods to prevent TB infection to others through cough etiquette, disposal of sputum wrapping paper or cloth, or other required methods; and (5) the patient does not live with children who are not vaccinated by BCG, nor with HIV infected persons. To confirm the above points, a meeting is held with hospital staff and PHNs of PHCs before discharge. In addition, the meeting has a role in deciding the frequency, place, method, and supervision for each patient to be discharged. The PHNs meet the patient to inform him/her of the decision, obtain consent, and supervise the patient after discharge.

OUTPATIENT TREATMENT "COMMUNITY DOTS"

Community DOTS is to observe or confirm outpatients' drug taking by several methods, such as direct observation at facility or patient's home, confirmation through checking patient's treatment card or counting empty drug bags and so on.

Generally, TB patients who are sputum smear negative at diagnosis or after inpatient treatment are treated at a clinic. PHNs of PHCs visit his/her home or workplace to assess the patient's background and risk of treatment interruption. Based on the assessment, they decide how to supervise each patient with the assistance of physicians: frequency, place, and method of contact, as well as a supervisor who confirms and supports the patient's medication (*Fukuyaku Shiensha* in Japanese). The treatment supervisor must be assigned for each TB patient with the agreement

Table 1 Risk of treatment interruption and supervision of frequency, place, method and supervisor

Subjects	Risk	Frequency	Method	Supervisor
Homeless people, alcohol or drug dependents, recurrent cases and patients with interruption history	High	Every day	Mandatory visit of patient to a clinic, hospital, pharmacy or public health center, and directly observed drug intake	Medical staff of clinic or hospital, pharmacist of pharmacy, or public health nurse at PHC
Solitary elderly, or institutionalized elderly requiring nursing care, etc	Medium	Once or twice a week	Visit of supervisor to patient' home and confirmation through patient's treatment card or counting empty drug bags	Public health nurse at PHCs
Elderly with families or in facility, etc	Low	Once or twice a month	Confirmation of adherence by telephone calls, FAX or e-mail to patient' family or nursing staff of facility who confirms each dose of drugs with the patient's treatment card or by counting empty drug bags	Patient' family or nursing staff of facility
Employees	Low	Once a month	Confirmation of each dose of drugs through the patient's treatment card or by counting empty drug bags. Patients receive drugs by prescription at pharmacy once a month.	Pharmacist of pharmacy

of the patient. Table 1 shows the method of supervision according to patients' risk.

Physicians usually prescribe anti-TB medication once a month, paying attention to how well patients adhere to the drug regimen. In addition, they have to give instructions on treatment to the patients, warn the patients to visit a clinic in the case of an appointment cancellation, and communicate with PHNs of PHCs.

ADDITIONAL PUBLIC SUBSIDY FOR MEDICAL EXPENSE OF TB

To promote standard treatments and to ensure the completion of medical treatments, additional public subsidy for medical expense of TB is important. Expenses for medication that meet the standard treatment only is subsidized by the Infectious Disease Act established by MHLW. Table 2 shows standard treatments of Japan in 2009.[11] To promote adherence and to ensure an effective blood concentration of drugs,[15,24] medication once a day rather than three times a day is recommended.

Not only a smear test but also a culture test must be conducted for TB patients. According to the standard treatment, if a culture test is positive for TB, a drug susceptibility test (DST) must be conducted, although the conventional DST requires weeks (for liquid media) or months (for solid media). If resistance is found to any drugs, the regimen needs to be reconsidered.

Patients need to apply to PHCs for the TB medical expense public subsidy. To subsidize medical expenses, the Infectious Disease Advisory Committee evaluates whether the doctor's treatment meets the standard criteria. In case that outpatient treatment exceeds 6 months, the patient needs to re-apply every 6 months.

1) Inpatients in TB isolation ward

Medical expenses of patients in a TB isolation ward are basically covered by the public subsidy and health insurance. The covered expenses include the admission fee and treatment fees for concomitant diseases unrelated to TB.

Table 2 Standard treatment regimens for previously untreated patients

		Duration	Intensive phase	Continuous phase
Method A	Standard	6 months*	RFP+NH+PZA+SM (or EB) for 2 months	RFP+INH for 4 months*,**
Method B	Only when PZA cannot be administered ***	9 months *	RFP+INH+SM (or EB) for 2 months	RFP+INH for 7 months*,**

INH: isoniazid, RFP: rifampicin, PZA: pyrazinamide, EB: ethambutol, SM: streptomycin

* The treatment period of continuous phase can be prolonged by 3 months for patients with severe lesions or those with diabetes etc, resulting in 9 months for Method A and 12 months for Method B, in total.

** When drug susceptibility is unknown and symptom improvement is unclear, SM (or EB) is continued until drug susceptibility is identified or clinical improvement is confirmed.

*** Method B is used only when pyrazinamide cannot be administered due to adverse reactions for those such as patients with underlying hepatic disorders or elderly patients aged 80 years or older.

2) Inpatients with TB in general ward and outpatients

Non-infectious TB patients under severe conditions such as miliary TB, meningitis, or severe pleuritis, can be admitted to a general ward. The admission fee is subsidized only in cases of admission due to surgery, such as severe spinal caries. In Japan, health insurance generally covers 70% of medical expense (both inpatient and outpatient care) for those aged less than 70 years, and 90% for those aged 70 years or over. For non-infectious TB patients, the subsidy additionally provides for the rest of the expenses, excluding 5% of total medical expenses, i.e., 25% for those aged less than 70 years and 5% for those aged 70 years or over. The final out-of-pocket payment is 5% of the total medical expense. In cases of lower income persons receiving public assistance, the remaining 5% is covered by the public assistance fund.

REGISTRATION AND TREATMENT MONITERING OF TB PATIENTS

Monitoring treatment and outcome is important.[11] In Japan, PHCs register TB patients based on a doctor's notification. According to the Infectious Disease Act, doctors who diagnose TB patients must report the patient's information, including name, sex, age, address, occupation, disease type and anatomical site, symptoms, bacteriological and radiological findings to the nearby PHC. The documents to be submitted to PHCs are: 1) application form for medical subsidy, with their doctor's medical certificate, by TB patients (or his/her family); 2) notification by the hospital which has accepted the infectious TB patient; and 3) notification of admission and discharge of TB patients by hospital. The patient's adherence is followed up by a supervisor in the Japanese version of DOTS strategy. In the case that TB patients do not apply for a continuance of their medical subsidy after expiration, PHCs inquire of physicians as to treatment outcome.

If necessary, PHCs inquire of the biological laboratory of the hospital as to the results of DST. If TB patients die, PHCs confirm the cause of death by the vital registration system. All medications given, bacteriological response, adverse reaction, and patient's adherence and outcome are recorded to the registration card.

According to the WHO, a cohort is a group of patients diagnosed and registered for treatment during one-quarter of a year, and evaluation of treatment outcome in new pulmonary smear-positive patients is used as a major indicator of program quality.[7] The director, PHNs and other staff of PHCs hold a conference to evaluate treatment outcomes of each cohort (cohort analysis) at the end of every one-quarter of a year.

Table 3 shows definitions of treatment outcomes of cohort analysis.[25] Standards of judgment in Japan are severe compared with that of the WHO.[7] For example, for a patient whose sputum

Table 3 Definition of treatment outcome of newly treated smear positive pulmonary tuberculosis in National Tuberculosis Program (NTP) of Japan and WHO

Outcome	NTP of Japan	WHO
Cure	A patient who was culture-negative in the last month of treatment and on at least two previous occasion	A patient who was sputum smear-negative in the last month of treatment and on at least one previous occasion
Completed	A patient who completed treatment but did not have a negative sputum smear or culture result after 5 month treatment	A patient who completed treatment but did not meet the criteria for cure or failure
Died	A patient who died from any reason during treatment.	A patient who died from any cause during treatment
Failed	A patient whose sputum smear or culture was positive at 5 months or later during treatment.	A patient who has remained sputum smear-positive at month 5 or later during treatment.
Default	A patient whose treatment was interrupted for 2 consecutive months or more, or shorter than 6 or 9 month treatment	A patient whose treatment was interrupted for 2 consecutive months or more.
Transferred out	A patient who has been transferred to another PHC's area	Not defined
Treatment for more than 12 months	Treatment for more than 12 months	Not defined
Not evaluated	Death without treatment, no information on initial treatment regime, unused both INH and RFP at the onset of treatment, or interruption of INH or RFP	A patient whose treatment outcome is not known.
Treatment success	Sum of cured and completed treatments	Sum of cured and completed treatments

The differences in standards of judgment between Japan and the WHO.
1 The bacteriological situation is confirmed not by sputum smear result, but by culture result in Japan.
2 WHO definition of "not evaluated" is "a patient whose treatment outcome is not known".
3 Because this long treatment period is common in Japan, "treatment for more than 12 months" was added to the Japanese definition.

smear is negative and culture positive 5 months or later during treatment, by the standards of Japan the treatment would be rated as a "treatment failure", but by the standards of the WHO it would be rated as a "cure", because a culture test is deemed unnecessary by WHO standards.

PHC BASED NATIONAL TB SURVEILANCE SYSTEM

The National TB Surveillance Center is operated within the Research Institute of Tuberculosis (*Kekkaku Kenkyuujo* in Japanese), a facility of the Japan Anti-tuberculosis Association (*Kekkaku Yoboukai* in Japanese, non-governmental organization). The MHLW of Japan entrusts surveillance to the Research Institute of Tuberculosis. All 490 PHCs[26] in Japan input all necessary information on registered TB patients into a computer at the PHC, from which anonymized data are sent to a central computer in the National TB Surveillance Center. The system was renewed to conform to the Infectious Disease Act in 2007, which enabled automated cohort analysis of all TB patients including DST survey and co-infection of HIV. The National TB Surveillance Center evaluates TB control at the nationwide, prefectural or designated city, and PHCs levels, calculating the TB incidence and MDR rate.

Table 4 shows treatment outcomes of newly treated smear positive pulmonary TB registered in 2007[12] and 2010[2] in Japan. Globally, the treatment success rate for new cases with sputum smear-positive pulmonary TB in the 2010 cohort was 87%, which exceeded the WHO target of 85%.[7] The rate of Japan was 52.0%, much lower than the global rate. The reasons are considered

Table 4 Treatment outcome among newly treated smear positive pulmonary tuberculosis patients registered in 2010 and 2007 in Japan

	2007		2010	
Outcome	N	%	N	%
Total	9,421	100.0	8,242	100.0
Cured	1,589	16.9	1,658	20.1
Completed	2,702	28.7	2,630	31.9
Died	1,729	18.4	1,711	20.8
Failed	93	1.0	61	0.7
Defaulted	474	5.0	235	2.9
Transferred out	297	3.2	248	3.0
Treatment for more than 12 months	1,130	12.0	819	9.9
Not evaluated	1,407	14.9	880	10.7
Treatment success	4,291	45.6	4,288	52.0

mainly: 1) TB patients are older; 37.2% were aged 80 years and over,[2] so the "died" rate was extremely high at 20.8%, compared to other countries; and 2) the standards of judgment in Japan are strict compared with those of the WHO. For example, a patient whose sputum smear is negative and culture positive 5 months or later during treatment, by the standards of Japan the treatment would be rated as a "treatment failure", but by the standards of the WHO it would be rated as a "cure", because a culture test is deemed unnecessary by WHO standards. In another example, patients with interrupted INH due to adverse effects are "cured" by the WHO definition, but "not evaluated" by the standards of Japan. 3) The WHO basically evaluates the outcome 6 months after treatment begins. In Japan, long term treatment of more than 12 months for cases with medical cessation due to adverse effects is common. The standard regimen for elderly patients aged 80 years or over with diabetes is 12 months. The NTP in Japan aimed to bring "failed + defaulted" treatment for new TB cases under 5%. This rate was 6.0% among the 2007 cohort, and decreased to 3.6% among the 2010 cohort, possibly due to improvement in drug adherence.

PREVALENCE OF MDR AND TB PATIENTS CO-INFECTED WITH HIV

In 2012, the WHO estimated that globally 3.7% (95% confidence interval, 2.1–5.2%) of new cases and 20% (13–26%) of previously treated cases had MDR-TB.[7] Less than 4% of new bacteriologically-positive cases and 6% of previously treated cases were tested for MDR-TB worldwide in 2011.[7] The WHO commented that ideally DST should be done for all patients at the start of treatment[17] so that the most appropriate therapy for each individual can be determined. The Global Plan to Stop TB 2011–2015 includes the target that by 2015 all new cases of TB considered at high risk of MDR-TB (estimated at about 20% of all new bacteriologically-positive cases globally) and all previously treated cases should undergo DST[7].

In Japan, the Tuberculosis Research Committee (*Ryoken* in Japanese) has been conducting hospital-based nationwide drug resistance surveys approximately every 5 years; the results showed MDR-TB prevalence decreased 0.8% of new cases, 19.7% of previously treated cases

in 1997,[27] 0.7% and 9.8%, respectively in 2002.[28] In 2007, PHC-based DST surveillance began. The surveillance demonstrated the reduction was 0.6% of new cases and 7.2% of previously treated cases in 2007,[12] 0.5% and 3.3% in 2011, respectively.[2] The initial culture test positive among pulmonary TB patients registered in PHCs increased from 63.8% in 2007 to 79.0% in 2011, and the DST positive among culture-positive pulmonary TB cases increased from 41.8% to 73.7% in the same period. In 2011, there were 17,519 pulmonary TB patients, with 14,425 (82.2%) bacteriological cases confirmed by microscopic smear test, culture or nucleotide acid amplification method, and 8,654 (49.4%) sputum smear positive cases.

Co-infection of TB and HIV is one of the main reasons for emergence of MDR-TB.[3,4] According to the WHO, 1.1 million (13%) of the 8.7 million people who have developed TB worldwide are HIV-positive. Although only TB patients who suspect HIV infection are serologically tested and reported to PHCs, those with HIV among newly notified TB patients were 57 (0.2%) out of 25,254 in 2007[12] and 75 (0.3%) out of 22,681 in 2011,[2] indicating that the prevalence of co-infection of HIV and TB has been gradually increasing. In 2011, there were 1,518 HIV infection cases newly notified to PHCs as per the Infectious Disease Act. The age distribution skewed younger in comparison with that of TB patients. The actual co-infection rate may be higher than the one reported, which was very low compared with the global rate.

The following reasons are considered for the decreasing MDR-TB prevalence:[22,29-32] 1) improvement of adherence due to the Japanese version of the DOTS strategy; 2) promotion of standard treatments; and 3) appropriate modification of treatment regimen based on DST at diagnosis.

CONCLUSIONS

Among the many roles of PHCs described in the Community Health Act in Japan,[1] TB control is one of the most important. MDR-TB prevalence in Japan has been decreasing, for which PHCs seem to play important roles within the Japanese version of the DOTS strategy. To ensure effective implementation of these measures, sufficient numbers of public health professionals knowledgeable about infectious disease control, especially medical doctors, are needed in PHCs. Public health researchers are responsible for advocating the maintenance and extension of the PHC system. This article described new roles of PHCs in TB control of Japan, which will facilitate the exchange of information among their counterparts in other countries.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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