Taiwan Epidemiology Bulletin

March 5 , 2013/ Vol.29 / No.5

Original Article

Treatment of Latent Tuberculosis Infection in Taiwan: the Present and Future

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Abstract

The latent tuberculosis infection (LTBI) refers to the latent period in which the contact has been infected with *Mycobacterium tuberculosis* after exposure but has not yet experienced symptom onset. In Taiwan, the priority groups for LTBI treatment were populations with high risks of LTBI and low risks for developing drug-induced adverse reactions. The national tuberculosis (TB) program for treatment of LTBI among contacts aged younger than 13 years was launched on April 1, 2008. The key to the promotion of treatment is the coordination between the public health and medical systems, and the achievement of treatment depends on the support of the directly observed preventive treatment (DOPT) strategy. The partnership between the public health and medical systems confirmed, promoted, and provided a basis for cooperation. The subsequent treatments were conducted under the strategies of DOPT and copayment subsidized by the government, alongside with the TB case management system. Since April 2012, the TB contacts who (1) age 13 years or older and were born after January 1, 1986, (2) have been exposed to smear-positive and culture-positive TB index cases, and (3) have lived with the index case or had close contact with the index case in the same school or populous institution have been included for LTBI screening. To eradicate TB, we discuss the current management policy for LTBI in the end of the article. There remain many challenges to be faced and dealt with.

Keywords：Latent Tuberculosis Infection, adolescents, campus, outbreak

The old lady who wanted to die when she received the diagnosis of TB

Old lady, “Doc, I am already so old, and after being diagnosed with TB, I really don’t want to live anymore.”

Doc, “TB is a curable disease. It is not the end of world. Don’t be so pessimistic.”
Old lady, “But it is possible that my granddaughter might have been infected by me although she has not yet shown symptoms? What should I do if she really has the same disease as I have? She is my dearest precious and sleeps with me every night. I would not want to live on if I had transmitted TB to her.”

The past treatment strategy for LTBI in Taiwan

Before 2008, stories as such were heard every day, as 15,000 to 16,000 TB cases were confirmed each year resulting in the agonizing elderly, innocent child contacts, panicking parents, and even broken family relationships, which were encountered by most healthcare workers and public health staffs. The most frequently used way for consolation is education: we told the poor elderly, who suffered from the side effects of TB medications, that the communicability of TB is not as high as influenza. Their worries are not necessary. The granddaughter might not have been infected, and we would follow her up with chest X rays; even if she was infected, she could still be free from the disease. The elderly were asked to take their TB medications and to not be unnecessarily concerned.

Previous studies indicate that the clinical disease develops among 10% of all TB contacts who are infected with TB. Among TB contacts younger in age, such as infants, who were in close contact with a patient, such as those in the same household or an environment without adequate ventilations with a patient, or contacts of an index case with a delayed diagnosis who were positive for sputum smear or had chest cavities in radiographs are at higher risk of disease development, the rate is up to 20% among those who are infected. Therefore, the risk of disease development among TB contacts is not as low as we recognized before [1]. The TB incidence rate in Taiwan in 2005 was 72/100,000 person-year (Figure 1). The older age groups

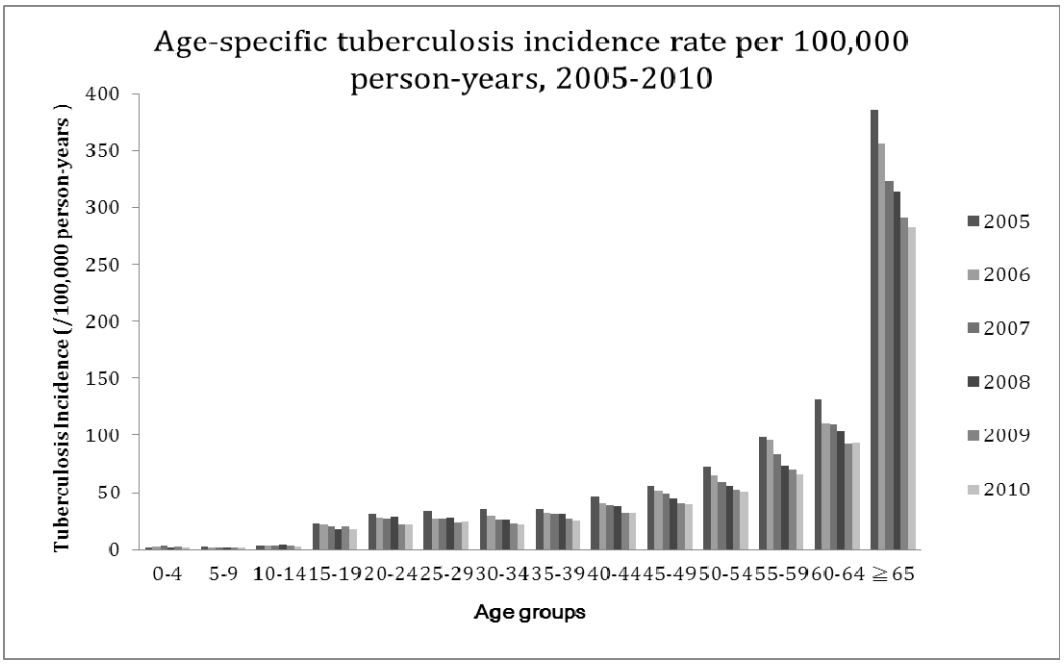

Figure 1. Age-specific tuberculosis incidence rate per 100,000 person-years, 2005-2010
Source: Taiwan CDC. Epidemiology and Control Policy of Tuberculosis in Taiwan. Taiwan CDC, 2012 .

have higher incidence rates. More than half of the TB cases belonged to the older age group aged more than 65 years. If the government is busy dealing with the numerous TB cases, the responsibility of the public health system is to manage the confirmed cases by completing as much treatment as possible with limited resources. For the TB contacts, we could only perform chest radiograph examination and education because of the limited resources. The screening and treatment for LTBI were not included in the TB control strategies at that time.

The latent tuberculosis infection (LTBI) is defined as the latent period in which the contact has been infected with *Mycobacterium tuberculosis* after exposure but has not experienced symptom onset. The latent period in TB could be lifetime or only several months. Before the Taiwan government launched the treatments for LTBI, some pediatricians had provided treatments for LTBI for children before undergoing bone marrow transplantation or chemotherapy according to the recommendations from the American Academy of Pediatrics [2]. Because the boosters for Bacillus Calmette-Guerin (BCG) vaccines were stop among sixth graders in Taiwan since 1997, the factors that affect the results of tuberculin skin test (TST) among the generations born after 1985 are mainly the newborn BCG immunization and the exposure to nontuberculous mycobacteria (NTM) in the environment [3]. Therefore, the use of TST for screening the TB contacts among younger generations is justified. Previously, the Bureau of Chronic Disease Prevention and Cure had used TST to diagnose and provide treatments for LTBI among aboriginal populations with high risks of TB infections. However, the long term effects could not be evaluated because the treatments and follow-ups were not documented at that time. In late 1990s, the Mennonite Christian Hospital surveyed the prevalence of TB infections by TST and provided treatments for LTBI patients in many aboriginal villages [4]. Based on the preliminary analysis of two studies, the positivity of TST is linearly correlated with the age of aboriginal residents with high risks of TB in Taiwan, which indicated that most TB infections occurred during childhood and adolescence. The observation of treatment safety indicated that the side effects were not common while using isoniazid as monotherapy, and no case of alcoholic hepatitis or drug-induced acute exacerbations of chronic hepatitis was reported. The drug compliance was not clear because the DOPT strategy was not applied in the study [5].

In 2005, research mandated by the Taiwan Centers for Disease Control (CDC) analyzed the distribution of TST sizes among BCG-vaccinated children aged between 3 months and 14 years without exposure to TB cases in urban areas, compared with children who had contacts with TB cases [6]. According to the TST reactions from 850 children subjects without TB contact history, the reactions decline gradually after immunization, but the positivity rates increase after the age of 7 years. For children aged 0 to 2 years, the cut-off TST size of 21 mm, combined with analysis in normal distributions, yield the minimal difference in annual infection rates; for those aged 3 to 7 years, the cut-off size is 15 mm and for those aged 8 to 14 years the cut-off size is 12 mm. However, by applying these cut-offs, under the basis of more than 30% of children contacts exposed to smear-positive TB cases in the household should had

been infected, the sensitivity was only 44.5%. The specificity was 89.5% for children without the risks of contracting TB by these cut-offs. To raise the sensitivity of TST to 90% among child contacts in household, the TST size of 10 mm is recommended to be used as the cut-off value of positivity for child contacts in household. Research on child contacts conducted by other countries indicates that the cut-off value of 5 mm yields optimal sensitivity [7], but this cut-off result in over-diagnosis of patients and leads to unnecessary LTBI treatments. Some other countries rather exclude true cases and adopt the cut-off value of 15 mm to treat fewer patients [8]. According to local research in Taiwan mentioned above, children without contact with TB cases should not receive TST because of low specificity. If we must perform the TST due to medical considerations, we should adjust the cut-off value according to the age of the examinees to prevent false positivity. Children who are household contacts of a patient should be screened by using the cut-off size of 10 mm to capture the largest possible number of infected cases.

The development of current strategy and selection of target populations

Based on previous local studies and foreign literature, the priority groups for LTBI treatment in Taiwan were defined as populations with high risks of LTBI and low risks for developing drug-induced adverse reactions. Before the end of 2007, the discussion of LTBI and the selection of target populations by the Tuberculosis Advisory Committee that were done based on a cohort study launched in 2005, which followed generations that had not experienced LTBI treatments for two-years. Although the TB contacts in the younger age groups do not have incidence rates that are as high as those of the older age groups (TB incidence rates in Taiwan increase with age among both TB contacts and non-contacts), for age-specific TB incidence rates, those aged less than 12 years have the highest relative risk, up to 240 times, and those aged more than 65 years have the lowest relative risk, down to 8 times because of high background TB incidence [9]. The relative risk for those aged between 15 and 19 years is about 50 times [10]. The major adverse reaction of isoniazid is hepatotoxicity [11], which increases with age. Many countries use the age of 35 years as the cut-off for treatment warning or upper limit [8]. Besides the drug-induced hepatotoxicity, the 15% carrier rate of hepatitis B in Taiwan and the relatively high carrier rate of hepatitis C in several villages and towns also matter [12]. The generations born after 1985 universally received hepatitis B vaccines after birth, so the carrier rate of hepatitis B dropped significantly among these generations. The populations with low risks for developing drug-induced adverse reactions can be targeted at the generations born after 1985. Therefore, on April 1, 2008, TST was provided universally, for the first time in the history of TB control and prevention, for the child contacts aged less than 13 years. Patients with positive TST were referred to LTBI partner physicians for evaluation of the appropriateness of LTBI treatment. Once the treatment was initiated, the public health team offered DOPT and completed the treatment course.

The supporting measures for the current LTBI treatment strategy in Taiwan and the partnership with medical system

LTBI treatments in many countries are unsatisfactory [13]. The key to the promotion of treatments is the coordination between the public health and medical systems, and the achievement of treatments depends on the support of the DOPT strategy. The partnership between the public health and medical systems confirmed, promoted, and provided a basis for cooperation. The second edition of the Taiwan Guidelines for TB Diagnosis and Treatment, published in 2006 [14], had already provided information on the diagnosis and treatment for LTBI, including the cut-offs of TST sizes for different risk groups and ages. The guidelines also regarded 10 mm as the cut-off size that indicated LTBI for contacts of any age (the standard was set up according to the distribution of TST sizes among indigenous contacts and in South American and European countries where BCG was given). For immunocompromised patients, such as acquired immunodeficiency syndrome (AIDS) patients or patients undergoing immunosuppression, TST size of 5 mm was adopted as the cut-off value of LTBI [15]. The screening and treatments for LTBI among the health workers with recent TB infections, AIDS patients or patients undergoing immunosuppression were also laid out in the guidelines. Since April 2008, Taiwan CDC has held several training sessions on LTBI management of contacts in regional collaborating hospitals and with local public health workers (1). Because of the expansion of subjects for LTBI management, which includes the contacts born after 1985, another 12 training sessions had been held at the end of 2011 and the beginning of 2012. The number of LTBI partner physicians involving in LTBI treatments increased from less than 300 persons in 2008 to more than 600 persons in 2011 (Table). Since the majority of the treatment subjects are child contacts, Taiwan CDC communicates with infectious diseases specialists and chest specialists in the Taiwan Pediatric Association, Infectious Diseases Society of Taiwan, Taiwan Society of Pulmonary and Critical Care Medicine by submitting manuscripts to their publications and doing oral presentations. Valuable suggestions for improvement of the program was provided from front-line health care workers contributed much to the adjustment of the policy itself. The LTBI partner physicians also shared the achievements of TB control and prevention through this process of communication and feedback.

Table. The indicators to evaluate the progress of contact investigation and latent tuberculosis (TB) infection treatment (LTBI)in Taiwan during 2007-2010

Year	Active TB Case Finding among new TB cases (%)	The Average Contacts/ Index Case	LTBI partnerphysicians (persons)	LTBItraining	LTBI Treatment No.
2007	2.2%	3.5	-	-	-
2008	2.6%	5.2	265	6	1440
2009	4.0%	5.7	376	8	2650
2010	4.5%	6.6	420	internet based	3874
2011	6.4%	8.1	541	internet based	4842
2012	Not available	Not available	1025	12	Not available

Source:Taiwan CDC. Epidemiology and Control Policy of Tuberculosis in Taiwan. Taiwan CDC, 2012;P-C Chan, M-Y Chiou, K-F Wang, C-H Yang, C-T Fang. Engaging all TB care providers to implement isoniazid preventive therapy nationwide. Int J Tuberc Lung Dis.2011;11:S295-6. (Poser discussion at 42st IUATLD, Lille, 20111029)

The DOT strategy in public health and the elimination of treatment barriers

Since 2007, the tracing and screening of TB contacts were enhanced and the treatment barriers were reduced by the copayment subsidized by the government. Following the DOTS strategy, all counties and cities in Taiwan, were required to report the numeric public health indices regularly for ranking and contest with one another, in addition to the management of TB cases and contacts. The average numbers of screened contacts for one index case increased from 2.6 in 2006 to 8.1 (Table), and more clusters could be identified. In the past, we can only trace the contacts in these clusters, but now with the experience in LTBI treatments for those aged less than 13 years, we can provide LTBI treatments for those aged between 13 and 25 years to reduce the risks of disease development among the contacts in the clusters in school, which also indirectly gives us information on safety and efficacy of LTBI treatments among this age group. For those contacts who turn into LTBI patients, subsequent treatments are conducted by DOPT strategy, copayment subsidized by the government, and supported by the TB case management. Both the index patients and their contacts therefore share resources, resulting in a collaborative anti-TB atmosphere that encourages them to complete the treatments together.

The monitoring of the outcome and side effects of the treatments

We accumulated valuable indigenous data from the promotion of LTBI treatment policy for those aged less than 13 years [16]. First, the infectivity is not directly correlated with the disease development but TST indurations. Second, the higher the degree of positivity from TST is, the higher the risk of disease development is. The risks increase rapidly if the TST size is larger than 10 mm, and the risks reach a plateau for those with a TST size larger than 15 mm. Third, the LTBI treatments are definitely protective for contacts with positive TST results. Last, under the 85% - 92% coverage of DOTS strategy, the LTBI treatment completion rates among children contacts who were exposed to infectious index cases can reach 87% - 90%. We compared the effects of the policy after one year of promotion to see if the training sessions and the policy promotion at the local levels contributed to the improvement. The proportion of treatments received among TST-positive contacts increased from 61% in 2008 to 75% ($p < 0.001$); the proportion of second TST performed among TST-negative contacts increased from 54% in 2008 to 81% ($p < 0.001$). However, the proportion of individuals receiving treatments among contacts with TST conversion remained high (from 70% to 73%, $p=0.632$). The proportion of second TST performed among TST-positive contacts decreased from 16% to 9% ($p < 0.001$). Among all contacts who initiated treatments and had treatment results, 3.6% of them stopped the treatments because the index cases were excluded from the TB diagnosis, and 4% stopped the treatments because the TB from the index cases was found to be resistant to isoniazid. Comparing the outcomes of disease development among contacts who refused LTBI treatment with those who received it, we found that the treatment reduced 96% of the risk of disease development [17].

The 9-month LTBI treatment course provided in Taiwan is based on the post-hoc analysis of the research conducted by Dr. Comstock in Alaska [18]. Besides, the schedule of treatments follows the suggestions from the American Academy of Pediatrics: in the beginning of the treatment course, the liver function is not routinely assessed except for patients with specific hepatic or renal function impairment, diabetes mellitus, or acquired immunodeficiency., Blood samples are obtained only if drug-related reactions are suspected during the treatment course so that unnecessary blood sampling that reduces the willingness for treatments can be avoided [2]. In this period, 4 patients developed hepatitis with clinical symptoms, which subsided after the treatments stopped. The incidence was 1.3 per 1,000 persons.

The LTBI treatment strategy in the future in Taiwan

The number of national TB reported cases decreased from 16,472 persons in 2005 to 12,600 persons in 2011. Since the launch of the DOTS strategy in 2006, which was supported by the efforts from the local health departments and the cooperation from medical institutions, the incidence rate of TB had decreased from 72.5 persons per 100,000 populations in 2005 to 57.2 persons per 100,000 populations, indicating a 20% reduction. The decreasing trend of the TB incidence rates was also noticed among school age and adolescent populations between 5 and 24 years (Figure 2). Several TB cases in school reported by the media aroused the public's attention and also resulted in the misconception of a worsening TB endemic. Actually, about

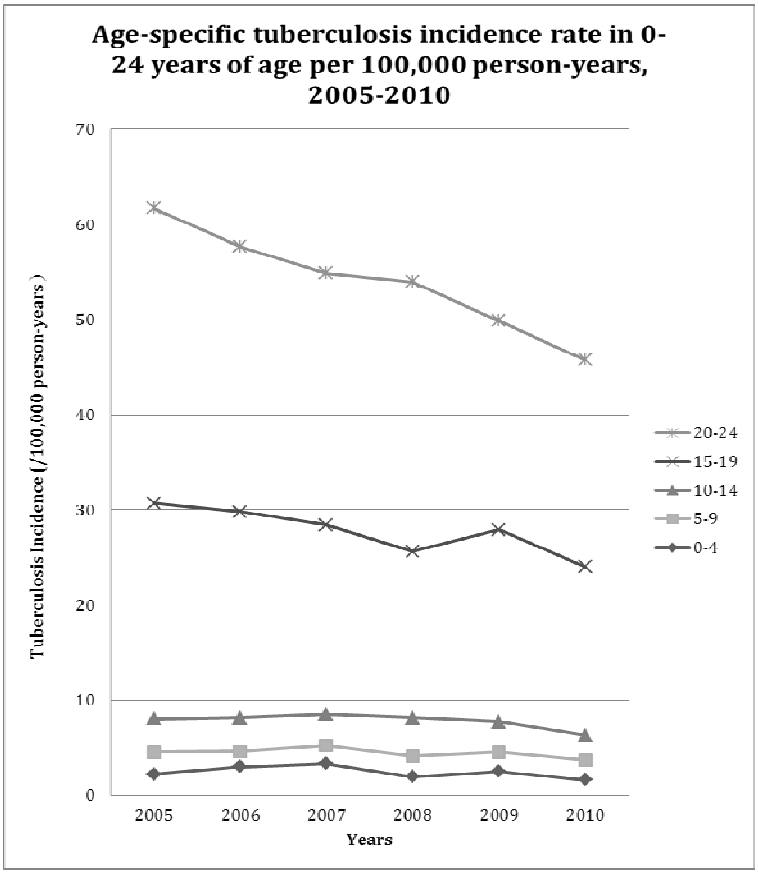

Figure 2. Age-specific tuberculosis incidence rate in 0-24 years of age per 100,000 person-years, 2005-2010

Source: Taiwan CDC. Epidemiology and Control Policy of Tuberculosis in Taiwan. Taiwan CDC, 2012;References

two TB student cases aged more than 13 years were reported each day and only six TB clusters in school were identified every year in the recent two years. This information shows that, through early screening, we should provide early and necessary protective measures, including the LTBI treatments and timely referral of TB cases, to reduce the TB incidence in school. Since April 2012, the contacts aged 13 years or older or born after January 1, 1986, who were exposed to smear-positive and culture-positive index cases and lived with the index cases or in school or a populous institution, have been included in the subjects for LTBI screening.

The high desire for autonomy among adolescents provides an obstacle to the 9-month treatment course and leads to refusal to adopt the DOPT strategy or cessation of treatment. The needs for financial and human resources increase with the extension of treatment populations. It is worth conducting an operational research to see if the drug resistant strains increase significantly when the populations under treatment increase. How is the feasibility of using 3G cellular phones to assist in completing DOT-based treatments among highly autonomic adolescents? Is the short-term but effective treatment regimen containing rifampin as safe as the conventional treatment regimen? Could this regimen play a role in treating LTBI in Taiwan? Could the public health system extend the subjects for screening to those aged less than 35 years if the number of TB cases under control keeps decreasing? At that time, how should the TST combine with other new diagnostic tools to support the screening of subjected needed to be treated? These are the questions and aspects we have to consider for formulating the policy in the future.

The grandmother and the granddaughter who persevered in completing the treatment

Although the granddaughter brought up by the grandmother in the story at the beginning received the diagnosis of LTBI, her physical examination and chest radiograph were normal, which mean that the disease did not develop. The grandmother was concerned about the possible side effects before her granddaughter took the anti-TB medications and questioned about the long, 9-month treatment course. After the physician explained clearly, the grandmother took her granddaughter to the clinic every month and the granddaughter took the medications every day during the 9-month LTBI treatment course. The weight of the granddaughter increased gradually, and she completed the LTBI treatment two months after her grandmother completed her TB treatment. In this period, both of them received the medications delivered by the DOTS workers every day and took the medication without interruptions. During their last clinic visit, the grandmother said gratefully that it was so lucky that her granddaughter could be treated, and her sorrow was thoroughly relieved as their treatment completed.

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Outbreak Investigation Express

The Epidemiologic Investigation on a Case of *Angiostrongylus Cantonensis* Infection in Kaohsiung City, 2012

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Abstract

The definitive hosts of *Angiostrongylus cantonensis* are mainly rodents. The nematode is commonly parasitic in the lungs of mice. Mollusks are the primary intermediate hosts, such as the giant African snails, apple snails, slugs, etc. Human beings are not proper hosts for *A. cantonensis*, but may become infected through ingestion of snails with *A. cantonensis* or food contaminated by the discharge of mucus which contains the third stage larvae of *A. cantonensis*. That is one common pathogen of eosinophilic meningitis. This case was involving a 74-year-old woman with no chronic disease who grew vegetables for living. She had developed symptoms of body aches, headache, abnormal behavior, confusion and trance in turn since June 23, 2012. Medical examination found that the proportions of the eosinophilic leukocytes were as high as 10.5% and 70% in her blood and cerebrospinal fluid, respectively. She was notified as a suspected case of *Angiostrongylus cantonensis* infection on July 23, and was confirmed by the Kaohsiung Medical University on July 27. After receiving supportive treatment, she had recovered and was discharged on July 28. Epidemiologic investigation suggested that the case might have exposed to snail mucus with the third stage larvae of *A. cantonensis* when farmed in the vegetable garden then got infection.

Keywords: *Angiostrongylus cantonensis*, snail, eosinophilic meningitis

The Taiwan Epidemiology Bulletin series of publications is published by Centers for Disease Control, Department of Health, Taiwan (R.O.C.) since Dec 15, 1984.
Publisher : Feng-Yee Chang
Editor-in-Chief : Yi-Chun Wu **Telephone No :** (02) 2395-9825
Executive Editor : Hsin-Yi Wang, Li-Gin Wu **Website :** http://teb.cdc.gov.tw/
Address : No.6, Linshen S. Road, Taipei, Taiwan 100 (R.O.C.)
Suggested Citation :
[Author].[Article title].Taiwan Epidemiol Bull 2013;29:[inclusive page numbers].