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BRIEF REPORT

Activities of the Korean Institute of Tuberculosis

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Abstract
The Korean National Tuberculosis Association (KNTA) set up the Korean Institute of Tuberculosis (KIT) in 1970 to foster research and technical activities pertaining to tuberculosis (TB). The KNTA/KIT had successfully conducted a countrywide TB prevalence survey from 1965 to 1995 at 5-year intervals. The survey results (decline in TB rates) established Korea as a country that had successfully implemented national control programs for TB. The KIT developed the Korea Tuberculosis Surveillance System and the Laboratory Management Information System, both of which were transferred to the Korea Centers for Disease Control and Prevention after its establishment. The KIT functions as a central and supranational reference TB laboratory for microbiological and epidemiological research and provides training and education for health-care workers and medical practitioners. Recently, the KIT has expanded its activities to countries such as Ethiopia, Laos, and Timor-Leste to support TB control and prevention. The KIT will continue to support research activities and provide technical assistance in diagnosing the infection until it is completely eliminated in Korea.

1. Introduction

The Korean National Tuberculosis Association (KNTA) was established on November 6, 1953, to fight against tuberculosis (TB), which was the most serious public health problem during and after the Korean War. The KNTA was formed by the integration of pre-existing organizations such as the Chosun Anti-Tuberculosis Association, Anti-Tuberculosis Association, Missionary Doctor Committee, and Committee for Tuberculosis Prevention (Ministry of Health). At present, the KNTA has 12 branches and four specialized TB clinics known as the Double Cross Clinic.

The KNTA joined *The International Union Against Tuberculosis and Lung Disease* in 1954, and from then onward, it started developing into an international organization.

Since then, the KNTA has successfully conducted seven countrywide TB prevalence surveys from 1965 to 1995 at 5-year intervals and carried out campaigns and active TB case-finding activities, while also providing laboratory services to the national TB control program (NTP) to improve treatment for TB patients and supporting TB-related studies for improving the services of the NTP.

The KNTA decided to set up the Korean Institute of Tuberculosis (KIT) in 1970 to foster TB-related research

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and technical activities. The KIT included a bacteriology department (formerly known as the *Central TB Laboratory Department*), a training department for TB health-care workers, and an epidemiology department (formerly known as the *Medical Department*). Since its inception, the KIT has improved consistently and is now a leading institute for TB research in Korea that provides a scientific basis for TB control.

2. Achievements of the KIT

2.1. Domestic achievements

Under the NTP, the KIT has provided laboratory diagnostic services as well as training and education for health-care workers. In addition, it played an active role in policy development for TB control and eradication before the establishment of the Korea Centers for Disease Control and Prevention (KCDC). The KIT also conducts microbiological, epidemiological, and operational research.

Laboratory diagnosis is essential for the confirmation and treatment of TB. The KIT carried out 2831 microbiological examinations in 1962 and this number increased to 363,089 in 2012, including 9040 cases of drug-susceptibility testing (DST) and 163,121 culture examinations (Table 1) [1]. The KIT has provided laboratory technical support and reagents for microscopic examinations to public health centers in Korea. In addition, the KIT also provides laboratory services to the private sector. The KIT performed 108,706 microbiological examinations for the private sector, including 17,826 cases of DST. The KIT conducted almost two thirds of DST in 2013.

To provide technical support to the NTP, staff at the KIT performed supervisory visiting to public health centers until 2007. The KIT developed and constructed the Korea Tuberculosis Surveillance System and the Tuberculosis Laboratory Management Information System, which were transferred to the KCDC following its establishment. In addition, the KIT operates *web-PACS*, a web-based healthcare service developed by the KIT that supports radiological diagnosis of TB in public health centers. The number of public health centers that participated in the web-PACS was 202 in 2013 and 176,201 radiographic images were read by central and regional reading centers.

The number of research articles published reflects the research activities carried out and scientific achievement. So far, the KIT has published 163 articles in 48 Science Citation Index journals.

2.2. International part

Since 1979, the KIT has been organizing international TB training courses sponsored by the World Health Organization (WHO), the Korea International Cooperation Agency (KOICA), and other organizations. In 1984, the KIT joined as a member of the Tuberculosis Surveillance and Research Unit, which was founded by the WHO and the International Union Against Tuberculosis, and hosted two annual meetings in Korea. A total of 728 health workers, mainly medical doctors, participated in the 73 training courses conducted until 2013 [1].

In 1995, the KIT was designated as a WHO collaborating center and joined with the Supranational Reference Laboratory Network in 1994. The KIT also played a vital role in overseeing quality assurance activities for TB laboratory services and technical support to countries such as Vietnam, China, and the Philippines.

Since 2010, the KIT has expanded its activity globally under the official development assistance (ODA) projects for directly and indirectly supporting TB control and elimination in countries such as Ethiopia, Timor-Leste, Laos, and the Philippines.

3. Current roles and activities

3.1. Laboratory service

The Department of Laboratory Medicine provides microbiological laboratory services for the NTP and quality assurance as the TB reference laboratory in Korea (Table 1).

The KIT and various branches of the KNTA conduct microbiological examinations such as smears, cultures, strain identification, DST for *Mycobacterium tuberculosis*, and nontuberculous mycobacteria detection. In addition, for the rapid diagnosis and identification of drug resistance among the various strains of *Mycobacterium*, the KIT carries out molecular testing methods such as real-time polymerase chain reaction and Xpert MTB/RIF assay (Xpert assay; Cepheid, Sunnyvale, CA). The KIT also produces media for culture, strain differentiation, and DST, and provides the materials to public and private laboratories.

3.2. Research and development

The Department of Research and Development (Taiwan) actively studies molecular epidemiology, maintains data on various *Mycobacterium* species, develops new diagnostic tools for early detection of TB, and carries out other academic studies related to TB.

- *Molecular epidemiology:* Molecular epidemiological studies for TB started out as a laboratory research project in the late 1990s. A database of the various epidemiological study results was established in 2005. The initial purpose of the study was to verify the transmission link among TB patients in schools by DNA typing of the strains. Nowadays, these molecular epidemiological technologies have become an essential part of the investigation on TB outbreaks in Korea. The molecular epidemiology studies helped in identifying the transmission link

Table 1. Accomplishments of laboratory examinations for public health centers (1962−2013).

Year	No. of examination cases	Direct smear microscopy	Culture		DST		Strain identification		Quality control for smear examination	NAAT	DNA Finger printing
			Solid media	Liquid media	Conventional	Molecular	Conventional	Molecular			
1962	2,831	1,462	1,369								
1963	16,157	5,437	4,664		1,233		4,823				
1964	18,973	6,886	6,885		1,744		3,458				
1965	74,146	34,757	30,112		7,079		2,198				
1966	177,120	74,386	71,204		15,114		16,416				
1967	171,898	81,926	76,091		3,448		10,433				
1968	218,631	102,257	93,428		2,339		8,296		12,311		
1969	235,464	106,437	101,212		4,490		11,168		12,157		
1970	236,674	112,828	92,152		2,598		13,915		15,181		
1971	325,301	130,146	117,386		3,192		8,110		66,467		
1972	200,624	70,294	65,353		2,075		6,512		56,390		
1973	280,733	114,322	109,364		4,330		1,793		50,924		
1974	258,419	103,111	98,347		1,133		2,343		53,485		
1975	268,019	117,478	104,491		1,281		2,461		42,308		
1976	287,999	133,835	113,528		3,074		3,771		33,791		
1977	325,713	153,335	134,445		9,876		3,631		24,426		
1978	309,805	141,816	129,998		12,097		1,036		24,858		
1979	314,312	143,229	132,126		10,304		5,230		23,423		
1980	317,886	148,400	136,383		9,895		3,965		19,243		
1981	346,006	147,797	139,365		10,210		3,864		44,770		
1982	333,229	144,155	137,318		10,310		4,231		37,215		
1983	334,248	141,683	136,178		8,121		4,042		44,224		
1984	349,539	148,356	143,686		8,836		4,192		44,469		
1985	401,816	169,063	164,728		7,240		4,290		56,495		
1986	432,281	183,295	178,292		6,162		4,346		60,186		
1987	411,647	173,994	169,868		6,538		4,413		56,884		
1988	365,386	160,337	157,024		4,903		4,376		38,746		
1989	369,626	162,618	159,632		3,554		4,301		39,521		
1990	358,740	159,807	157,606		3,471		4,153		33,703		
1991	353,737	156,313	156,313		3,627		3,960		33,524		
1992	321,877	140,482	140,482		3,224		3,693		33,996		
1993	320,447	137,696	137,696		3,068		4,074		37,913		
1994	294,817	127,372	127,372		2,914		3,417		33,742		
1995	260,902	110,953	110,953		2,852		5,023		31,121		

(*1Continued on next page*)

Table 1 (*Continued*)

Year	No. of examination cases	Direct smear microscopy	Culture		DST		Strain identification		Quality control for smear examination	NAAT	DNA Finger printing
			Solid media	Liquid media	Conventional	Molecular	Conventional	Molecular			
1996	239,508	101,284	101,284		2,483		5,004		29,453		
1997	219,132	89,917	89,917		2,616		4,716		31,966		
1998	220,942	96,558	96,558		2,845		5,451		19,530		
1999	217,976	94,864	94,864		2,771		5,454		20,023		
2000	199,748	87,416	87,416		2,459		5,172		17,285		
2001	191,701	81,640	81,640		2,169		5,063		21,189		
2002	181,202	78,820	78,820		2,105		5,181		16,276		
2003	176,211	83,993	83,993		2,268		5,253		704		
2004	185,620	86,576	86,576		5,200		5,643		1,125		
2005	240,590	113,330	113,330		7,375		5,511		1,044		
2006	271,069	127,209	127,209		6,461	994	6,089		1,210		1,897
2007	320,957	152,522	152,522		6,292	932	5,987		1,174		1,528
2008	318,531	147,455	147,455		5,536	445	5,977		1,139		1,715
2009	328,192	152,089	152,089		5,884	408	7,208	1,302	1,625		1,940
2010	307,367	140,392	140,392	4,209	4,807	2,141	6,526	1,170	1,312		1,453
2011	343,148	154,009	154,009	9,112	5,333	2,916	5,727	1,197	2,407	5796	1,360
2012	363,089	164,478	164,478	9,040	5,275	2,824	6,201	1,283	871	7269	1,370
2013	351,385	159,477	159,477	10,921	4,759	1,567	6,807	1,445	920	4574	1,438
Total	13,971,371	6,158,292	5,947,080	33,282	256,970	12,227	274,904	6,397	1,230,726	17,639	12,701

DST = drug-susceptibility testing; NAAT = Nucleic Acid Amplification Tests.

during a TB outbreak and improved the procedures for the treatment of latent TB infection (LTBI).

The Department of Research and Development has also built a database for *M. tuberculosis* strains using IS6110-based restriction fragment-length polymorphism typing of clinical isolates, which is a gold standard method for strain typing. In addition, the department recently established a database for variable number tandem repeat typing of *M. tuberculosis* strains. The department gives an effort to other countries such as China, Japan, Philippines, Vietnam and Mongolia for establishing a molecular technology like RFLP and VNTR typing. It is expected that the molecular epidemiology research will play a vital role in various aspects of TB control in the future.

- *Korea Mycobacterium Resource Center:* Biospecimens are fundamental for microbiological research. The Korea Mycobacterium Resource Center (KMRC) has collected TB biological specimens from public health centers (*M. tuberculosis* and various nontuberculous mycobacterial strains), during TB outbreaks, from TB patients born outside South Korea, including North Korea defectors, and from various research groups. At present, the center contains more than 20,000 mycobacterial strains, including drug-resistant and nontuberculous mycobacteria (Table 2) [2]. In 2007, the KMRC officially opened a *Mycobacterium* strain bank, and in the same year, it signed a memorandum of understanding with the Korean Collection of Type Culture in the Korea Research Institute of Bioscience and Biotechnology. The KMRC was designated as a national cooperation bank with the National Culture Collection for Pathogens in the KCDC in 2009 and it adopted the ISO 9001 quality management standard to acquire reliability as a biological resource bank. The KMRC has distributed TB resources to many research groups.
- *Exploring useful antigens for the immunological diagnostics of LTBI:* Identifying new antigens for the early diagnosis of LTBI has recently been explored to accelerate TB prevention and control. Until now, tuberculin skin testing (TST) and interferon gamma-releasing assay have been used for the diagnosis of LTBI. The Department of Research and Development has dedicated its efforts to identify new antigens that can be useful for the early diagnosis of LTBI or biomarkers to predict TB progression.
- *Projects supported by external funds:* The KIT also coworks with other academic institutions that are supported by external funds. The projects currently handled by the KIT are as follows: *Study on M. tuberculosis catalase and peroxidase activities and isoniazid resistance*, *Culturing TB bacteria in microfluidic system and verification of possibility in applying DST*. In addition, KIT performs screening of new anti-TB drugs by *in vitro* assessment and also identifies and evaluates useful biomarkers for the diagnosis of LTBI. The Engineering College of Seoul National University has partnered with the KIT for the development of the microfluid system. This system can reduce the period of culture and provide DST results within a few days.

Table 2. Resources in the Korea Mycobacterium Resource Center (2013).

	Resources	No. of strains
NTM	Reference strains (ATCC, JCM, KCTC)	124
	Clinical isolates	330
Mycobacterium tuberculosis		
RFLP	Recurrent TB cases	91
	North Korean patients	220
	Gangwon province and outbreaks	1,919
	The Philippines	138
DST	Pan susceptible	58
	Monodrug resistant	449
	Multidrug resistant	240
	Extensively drug resistant	218
	DST low-level resistant	320
	DST high-level resistant	82
Non-DST	New smear-positive patients from public health centers	11,076
	Drug-resistance surveys among new patients	5,632
	National TB prevalence surveys	270
	Quality assurance program for DST	412
	Strains requested from abroad	1,031
Total		22,610

ATCC = American Type Culture Collection; DST = drug-susceptibility testing; JCM = Japan Collection of Microorganisms; KCTC = Korean Collection for Type Cultures; NTM = nontuberculous mycobacteria; RFLP = restriction fragment length polymorphisms; TB = tuberculosis.

3.3. Domestic cooperation

The KIT has provided technical support and updated training programs for health-care workers. In addition, it provides training programs for newly appointed army doctors and medical officers in public health centers (Table 3) [1]. In Korea, doctors in private and public health centers are recommended to attend these training courses, because such courses help them stay up-to-date on the guidelines for the management, control, and prevention of TB. The KIT has also partnered with educational institutions through the public−private mix collaboration program. This project aims to provide specialized training on TB care and control for nurses from general hospitals. The KIT provides training on TST for nurses participating in epidemiological investigations, because TST is still an important method for contact or outbreak investigations.

Table 3. Annual achievements of domestic training and education.

Year	Participants	Place	Number of training times	Number of trainees
1954–1959	Doctors in general hospitals, medical college, doctors, nurses, radiologists, microscopists, and health-care workers	Unclassified		4,301
1960–1969	Doctors, nurses, laboratory technicians, health-care workers, TB nurse officers, and others	Central	84	2,089
		Local	202	3,786
		Unclassified		2,683
1970–1979	TB medical officers, TB health-care workers, laboratory technicians, TB nurse officers, and others	Central	260	6,721
		Local	406	22,007
1980–1989	TB doctors, directors/officers of public health centers, public medical doctors, other doctors, TB nurse officers, health-care workers, laboratory technicians, and TB volunteers in Korea Catholic Church	Central	121	3,298
		Local	187	5,389
1990–1999	TB doctors, public health doctors, doctors in public health centers in Seoul, TB health-care workers, doctors in national TB hospitals, Doctors in the National Institutes of Health, TB nurse officers, and others	Central	96	4,084
		Local	49	2,392
2000–2009	TB doctors, public health doctors, doctors in public health centers, practitioners, TB health-care workers, and TB nurse officers	Central	199	16,682
		Local	66	3,880
2010–2013	TB doctors, public health doctors, doctors in public health centers, practitioners, TB health-care workers, and TB nurse officers	Central	61	8,942
		Local	53	1,208

Training and education were provided by the Korean Institute of Tuberculosis and the Korean National Tuberculosis Association. TB = tuberculosis.

3.4. Epidemiological investigations

To fight against a public health problem such as TB, it is essential to understand the size of the problem. In this regard, the KIT has conducted various activities and surveys to evaluate the epidemiological status of TB such as prevalence, incidence, and infection rates. The last countrywide prevalence survey was carried out in 1995. Since then, the KIT has analyzed the prevalence rate through the Korean National Health and Nutritional Examination survey, which revealed an age-adjusted prevalence rate of $208/10^5$ (age $\geq$ 15 years) in 2010 [3]. The prevalence rate was $173/10^5$ in 2006 and $98/10^5$ in 2011 based on the analysis of national health screening data [4]. The incidence rate was $117/10^5$ in 2006–2008 and $110/10^5$ in 2008–2010 [5]. Tuberculin surveys were carried out to estimate the prevalence of TB infections and the annual risk of tuberculosis infections in school children and new entrants into military service, who are considered to be vulnerable groups [6,7]. Operational epidemiological studies were also carried out to improve the NTP [8]. A pilot study for the implementation of modified directly-observed treatment projects was also carried out (2012–2013). Drug taking was monitored either directly by health-care workers or indirectly by smart phone or digital pillbox. A total of 546 patients were enrolled for the study from 29 public health centers and 11 private clinics, including a clinic for the homeless [2].

3.5. International cooperation

The international cooperation division is responsible for international fellowship training, technical assistance, and ODA.

- *International fellowship training:* The division has facilitated invitational fellowship training since 1971 in coordination with the WHO. In addition, the division coordinates with various organizations such as the KOICA, the Korea Foundation for International Healthcare, and the Ministry of Health and Welfare in developing countries in providing training as required. Training is provided on improving knowledge about NTP, microbiological examinations (e.g., smear, culture, and DST), and quality assurance. Participants of the KIT cipants of insurance. nations al Heawere health-care workers (doctors, nurses, laboratory technician, radiologists, etc.) come from high TB-burden countries such as Ethiopia, the Philippines, Timor-Leste, Myanmar, Laos, Cambodia, Vietnam.
- *Technical assistance:* Technical assistance was provided to the Philippines and Laos for both the programmatical and technical development of TB laboratory services. In addition, external quality assurance for DST was provided to some countries in accordance with the TB Supranational Reference Laboratory Network's terms of reference.

- *ODA:* Since the Republic of Korea joined the Organization for Economic Cooperation and Development, Development Assistance Committee in 2009, the budget for official development is continuously increasing to fulfill the demands from the international society. The experience with successful NTP activities is shared with the high TB-burden countries through agreements with organizations such as the KOICA. The KIT expects to meet the Millennium Development Goals through the various ODA projects.

At present, two ODA projects have been implemented by the KIT: *Project for TB Prevention and Control in Ethiopia* and *Project for Capacity Building on TB Control in Timor-Leste*.

4. Discussion

The KIT and the KNTA have significantly contributed to the decrease in TB cases in Korea though various activities such as campaigns, systematically supporting the laboratory system, the development of guidelines, active screening of TB with mobile X-ray machines, research, training, and education. However, at present, the environment surrounding the KIT/KNTA is changing. The burden of TB is continuously decreasing due to economic development and various activities undertaken by the NTP. With the development of a health insurance system, many people prefer to visit private health centers than public health centers. In addition, the establishment of the KCDC has changed the role played by the KIT to a great extent. Previous the roles of the KIT such as policy development, operation and management of the surveillance system, epidemiological investigation, and training programs are now handled by the KCDC. Expanding TB control/maintenance activities to other countries that require international assistance, providing assistance to decrease TB burden in North Korea, and strengthening multi-institutional research activities are areas that require further improvements.

As a specialized and unique TB research institution in Korea, the KIT will continue to provide technical support to the NTP and be a linchpin that supports other academic institutions for research until complete elimination of TB in Korea. In addition, the KIT has strong plans to further expand its role globally and to eliminate TB in North Korea. These mottos will help to realize the vision of the KIT—*Leading institute in the world to stop TB*.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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