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    | 1,233 | 4,823                 |                                       |      |                   |
| 1963 | 16,157                   | 5,437                   | 4,664    | 1,744 | 3,458                 |                                       |      |                   |
| 1964 | 18,973                   | 6,886                   | 6,885    | 7,079 | 2,198                 |                                       |      |                   |
| 1965 | 74,146                   | 34,757                  | 30,112   | 15,114 | 16,416               |                                       |      |                   |
| 1966 | 177,120                  | 74,386                  | 71,204   | 16,168 | 12,157               |                                       |      |                   |
| 1967 | 171,898                  | 81,926                  | 76,091   | 10,433 |                     |                                       |      |                   |
| 1968 | 218,631                  | 102,257                 | 93,428   | 12,311 |                     |                                       |      |                   |
| 1969 | 235,464                  | 106,437                 | 101,212  | 12,157 |                     |                                       |      |                   |
| 1970 | 236,674                  | 112,828                 | 92,152   | 15,181 |                     |                                       |      |                   |
| 1971 | 325,301                  | 130,146                 | 117,386  | 66,467 |                     |                                       |      |                   |
| 1972 | 200,624                  | 70,294                  | 65,353   | 56,390 |                     |                                       |      |                   |
| 1973 | 280,733                  | 114,322                 | 109,364  | 50,924 |                     |                                       |      |                   |
| 1974 | 258,419                  | 103,111                 | 98,347   | 53,485 |                     |                                       |      |                   |
| 1975 | 268,019                  | 117,478                 | 104,491  | 42,308 |                     |                                       |      |                   |
| 1976 | 287,999                  | 133,835                 | 113,528  | 33,791 |                     |                                       |      |                   |
| 1977 | 325,713                  | 153,335                 | 134,445  | 24,426 |                     |                                       |      |                   |
| 1978 | 309,805                  | 141,816                 | 129,998  | 24,858 |                     |                                       |      |                   |
| 1979 | 314,312                  | 143,229                 | 132,126  | 33,791 |                     |                                       |      |                   |
| 1980 | 317,886                  | 148,400                 | 136,383  | 19,243 |                     |                                       |      |                   |
| 1981 | 346,006                  | 147,797                 | 139,365  | 44,770 |                     |                                       |      |                   |
| 1982 | 333,229                  | 144,155                 | 137,318  | 37,215 |                     |                                       |      |                   |
| 1983 | 334,248                  | 141,683                 | 136,178  | 44,224 |                     |                                       |      |                   |
| 1984 | 349,539                  | 148,356                 | 143,686  | 44,469 |                     |                                       |      |                   |
| 1985 | 401,816                  | 169,063                 | 164,728  | 56,495 |                     |                                       |      |                   |
| 1986 | 432,281                  | 183,295                 | 178,292  | 60,186 |                     |                                       |      |                   |
| 1987 | 411,647                  | 173,994                 | 169,868  | 56,884 |                     |                                       |      |                   |
| 1988 | 365,386                  | 160,337                 | 157,024  | 38,746 |                     |                                       |      |                   |
| 1989 | 369,626                  | 162,618                 | 159,632  | 39,521 |                     |                                       |      |                   |
| 1990 | 358,740                  | 159,807                 | 157,606  | 33,703 |                     |                                       |      |                   |
| 1991 | 353,737                  | 156,313                 | 156,313  | 33,524 |                     |                                       |      |                   |
| 1992 | 321,877                  | 140,482                 | 140,482  | 33,996 |                     |                                       |      |                   |
| 1993 | 320,447                  | 137,696                 | 137,696  | 37,913 |                     |                                       |      |                   |
| 1994 | 294,817                  | 127,372                 | 127,372  | 33,742 |                     |                                       |      |                   |
| 1995 | 260,902                  | 110,953                 | 110,953  | 31,121 |                     |                                       |      |                   |

(Continued on next page)
| Year | No. of examination cases | Direct smear microscopy | Culture | DST | Strain identification | Quality control for smear examination | NAAT | DNA Finger printing |
|------|--------------------------|-------------------------|---------|-----|-----------------------|---------------------------------------|------|-------------------|
|      |                          |                         |         |     | Conventional          | Molecular                             |      |                   |
|      |                          |                         |         |     | 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             |
| 2010 | 307,367                  | 140,392                 | 140,392 | 4,209 | 2,141                 | 6,526                                 | 1,170| 1,312             |
| 2011 | 343,148                  | 154,009                 | 154,009 | 9,112 | 2,916                 | 5,727                                 | 1,197| 1,438             |
| 2012 | 363,089                  | 164,478                 | 164,478 | 9,040 | 2,824                 | 6,201                                 | 1,283| 1,370             |
| 2013 | 351,385                  | 159,477                 | 159,477 | 10,921| 1,567                 | 6,807                                 | 1,445| 1,438             |
| Total| 13,971,371               | 6,158,292               | 5,947,080 | 33,282| 256,970               | 274,904                               | 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:** Biopsicems 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 Korea 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 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.
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 208/105 (age ≥ 15 years) in 2010 [3]. The prevalence rate was 173/105 in 2006 and 98/105 in 2011 based on the analysis of national health screening data [4]. The incidence rate was 117/105 in 2006 and 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 fellowship training 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.

### 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              |
| 1970–1979 | TB medical officers, TB health-care workers, laboratory technicians, TB nurse officers, and others | Central                             | 260                      | 6,721              |
| 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              |
| 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 | Local                                | 187                      | 5,389              |
| 2000–2009 | TB doctors, public health doctors, doctors in public health centers, practitioners, TB health-care workers, and TB nurse officers | Local                                | 49                       | 2,392              |
| 2010–2013 | TB doctors, public health doctors, doctors in public health centers, practitioners, TB health-care workers, and TB nurse officers | Local                                | 61                       | 8,942              |

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