THIRD ANTI-TUBERCULOSIS DRUG RESISTANCE SURVEY REPORT (2016–2017), MONGOLIA

Ulaanbaatar
2017

NOTE

PREFACE

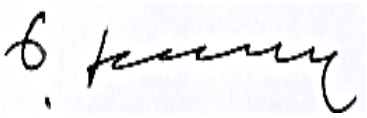
The latest National TB Prevalence Survey has demonstrated that TB prevalence in Mongolia is three times higher than previously estimated by National TB Program and World Health Organization. Furthermore, universally high TB prevalence in all age groups is an indication of active transmission of TB in the country, which calls for revisiting current detection, diagnosis, treatment and follow-up strategies, and implementing large scale control measures. In the recent past drug-resistant TB morbidity and mortality are increasing in Mongolia, which could be related to the weaknesses of NTP management more than to enhanced detection and diagnosis capacity. National anti-tuberculosis drug resistance survey was conducted twice in Mongolia, and it has already been 10 years since the last DRS. Therefore, the Third National Drug Resistance Survey has been successfully completed by TB Research and Surveillance Unit of NCCD, Ministry of Health, World Health Organization and Global Fund-Supported Project on AIDS and TB in 2016-2017.

According to this survey the prevalence of MDR-TB among new and retreatment TB cases is 5.3 and 16.5 percent, respectively. The prevalence among new TB cases is 3.8 times higher compared to the previous survey.

The survey findings have highlighted that the Government of Mongolia needs to pay particular attention to this issue, and implement large scale measures to prevent the spread of primary drug resistance and to enhance infection prevention and control. Growing prevalence of the primary drug-resistant TB could potentially threaten national security, and cause significant damage to human health and the country's economy, if uninterrupted.

TB, for long recognized as a social disease, has greatly affected socio-economic wellbeing and human health, and continues to do so in the 21st century. Therefore, I would like to emphasize the importance of evidence-based sustainable multi-sectoral collaboration and whole-of-society approach in the fight against TB. I hope the findings of the survey will be used in decision making, policy formulation and implementation, and will contribute to enhanced control of drug-resistant TB.

Respectfully,



D. Nyamkhuu, PhD, Assoc. Prof.

General Director of NCCD

ACKNOWLEDGEMENT

Tuberculosis is one of the leading causes of communicable disease morbidity and mortality in Mongolia, which continues to pose significant challenges in prevention and control, and requires enhanced efforts to detect, control and contain the spread of the disease.

I would like to acknowledge staff of the Program Coordination Unit of the Global Fund-Supported Project on AIDS and TB under the leadership of Dr. Oyunbileg A. for providing financial assistance to conduct the current survey, which has updated prevalence estimates for resistance to first line TB drugs, has provided estimates of the prevalence of resistance to second line TB drugs for the first time, has updated information on genetic mutations conferring drug resistance, has assessed anti-TB drug resistance dynamics and patterns, and has provided baseline information for program strengthening.

I would like to sincerely thank Dr. Soe Nyunt-U, WHO Representative in Mongolia and Dr. Narantuya J., WHO officer in charge of HIV and TB for invaluable financial and technical support in conducting the Third National Drug Resistance Survey. Thanks are due to Dr. Norio Yamada, MD, MSc, Head of International Cooperation Department, RIT/JATA, Prof. Satoshi Mitarai, MD, PhD, Head of Bacteriology Division, Mycobacterium Reference Center, RIT/JATA, Dr. Akiko Takaki, PhD, Chief of Mycobacteriology Laboratory, RIT/JATA and Dr. Tetsuhiro Sugamoto, JATA for continued collaboration and technical support in conducting all three rounds of the drug resistance survey, and organizing two mobile seminars on DRS data management, laboratory quality control and data use.

Last, but not least thank you to the members of the Technical Working Group for promptly responding to challenges arising during the course of the survey, the staff of TB Surveillance and Research Unit of the National Center for Communicable Diseases, in particular the staff of the National TB Reference Laboratory under the leadership of Dr. Oyuntuya T. for undertaking the survey field work and analysis, the staff of Aimag and Capital City Departments of Health, District Health Centers and TB Dispensaries for successfully organizing the survey data collection, and the survey participants for their time and contribution.

I would like to wish you all health, happiness and success in your endeavors.

Respectfully,

D. Enkhmandakh, MS, Clinical Prof.

Head of TSRU, NCCD

THIRD ANTI-TUBERCULOSIS DRUG RESISTANCE SURVEY TEAM MEMBERS

INTERNATIONAL CONSULTANTS:

Norio Yamada, MD, MSc	Head of International Cooperation Department, RIT/JATA
Satoshi Mitarai, MD, PhD	Professor/Head, Department of Mycobacterium Reference and Research, RIT/JATA
Akiko Takaki, MD, PhD	Chief of Bacteriology, Department of Mycobacterium Reference and Research, RIT/JATA
Tetsuhiro Sugamoto, MPH	Officer, JATA

SURVEY TEAM:

Principal investigator:

B. Buyankhishig, MD, PhD, Clinical Professor	Monitoring and Evaluation Adviser, TSRU, NCCD

Survey coordinator:

D. Naranzul, MD, PhD	Epidemiologist, NCCD

Survey data manager:

B. Tsolmon, MD	Epidemiologist, NCCD

Survey data operator:

B. Solongo	Data operator

TSRU researchers:

D. Enkhmandakh, MD, MS, Clinical Professor	Head of TSRU, NCCD
D. Gantsetseg, MD, MS	Head of Division, TSRU, NCCD
P. Yanjindulam, MD	TSRU, NCCD
D. Munkhjargal, MD	TSRU, NCCD
D. Otgontsetseg, MD	TSRU, NCCD
P. Nasanjargal, MD	TSRU, NCCD
B. Uranchimeg, MD	Statistician, TSRU, NCCD
B. Nyamdulam, MD	Epidemiologist, NCCD
E. Uyanga	Social worker, TSRU, NCCD
L. Chinzorig, MD	Epidemiologist, TSRU, NCCD
P. Chinbat, MD	TSRU, NCCD
D. Erdenechimeg, MD	Epidemiologist, TSRU, NCCD
D. Dorjmaa, MD	TSRU, NCCD
M. Enkhtuya	Health statistician, TSRU, NCCD

National TB Reference Laboratory team:

T. Oyuntuya, MD, MS	Head of NTRL, NCCD
N. Erdenegerel, MD	Laboratory doctor, NCCD
E. Baasansuren, MD	Laboratory doctor, NCCD
B. Tsetsegtuya, MD, MS	Laboratory doctor, NCCD
Ch. Narantsetseg, MD	Laboratory doctor, NCCD

Sh. Gundsuren, MD, MS	Laboratory doctor, NCCD
Sh. Darisuren	Senior laboratory technician, NCCD
Ch. Tsevelmaa	Laboratory technician, NCCD
B. Bayasgalan	Laboratory technician, NCCD
J. Dolgormaa	Laboratory technician, NCCD
Kh. Munkhgerel	Laboratory technician, NCCD
M. Nyamaa	Laboratory technician, NCCD
O. Budsuren	Laboratory technician, NCCD
E. Jugdermaa	Laboratory technician, NCCD
M. Otgonjargal	Laboratory technician, NCCD
D. Erdenetsetseg	Disinfection technician, NCCD
Ts. Narmandakh	Support staff, NCCD
Ts. Altansukh	Support staff, NCCD
D. Adiyadulam	Janitor, NCCD

Specimen transportation team

Ts. Gankhuu, MD, MS, Clinical Prof.	President, Union of Soum Doctors and Specialists
B. Soninkhuu, MD, MS	Officer, Union of Soum Doctors and Specialists
Ts. Shijirmaa	Officer, Union of Soum Doctors and Specialists

Local survey teams

21 aimags	TB coordinator, doctor, nurse, feldsher and laboratory technician
9 districts of the capital city	TB coordinator, doctor, nurse, feldsher and laboratory technician
Prison Camp No. 429	TB coordinator, doctor, nurse and laboratory technician
"Enerel" Hospital	TB doctor, nurse and laboratory technician
NMHC	Officer in charge

SURVEY IMPLEMENTERS:

Government of Mongolia, Ministry of Health, National Center for Communicable Diseases, TB Surveillance and Research Unit.

Capital City Department of Health, District Health Centers, TB Dispensaries

Aimag Departments of Health, General Hospital, TB Dispensaries

TB hospital of Prison Camp No. 429

"Enerel" Hospital

SPUTUM SPECIMEN TRANSPORTATION:

Union of Soum Doctors and Specialists

SURVEY FINANCING AGENCY:

Global Fund Supported Project on AIDS and TB

World Health Organization

National Center for Communicable Disease

MOBILE SEMINAR ORGANIZERS:

Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association

THIRD ANTI-TUBERCULOSIS DRUG RESISTANCE SURVEY REPORT WRITING TEAM

Report written by:

B. Buyankhishig, MD, PhD, Clinical Prof.	Principal investigator, NCCD
D. Naranzul, MD, PhD	Epidemiologist, Survey coordinator, NCCD
S. Ganzaya, MD, MS	Epidemiologist, Global Fund Supported Project on AIDS and TB
N. Erdenegerel, MD	Laboratory doctor, NTRL, NCCD
B. Tsolmon, MD	Epidemiologist, Survey data manager, NCCD
T. Oyuntuya, MD, MS	Head of NTRL, NCCD
E. Baasansuren, MD	Laboratory doctor, NTRL, NCCD
B. Tsetsegtuya, MD, MS	NTRL, NCCD
D. Munkhjargal, MD	TSRU, NCCD

Data analyzed by:

B. Tsolmon, MD	Epidemiologist, Survey data manager, NCCD
Norio Yamada, MD, MSc	Head of International Cooperation Department, RIT/JATA
Matteo Zignol	Officer, WHO Stop TB, Geneva, Switzerland

Technical support provided by:

J. Narantuya, MD, MPH	Officer in charge of AIDS and TB, WHO Country Office in Mongolia

Translated by:

S. Tugsdelger, MD, MPH	Epidemiologist

Edited by:

D. Davaalkham, MD, PhD, Prof.	Head, Department of Epidemiology and Biostatistics, SPH, MNUMS
N. Naranbat, MD, PhD, Assoc.Prof.	President, Mongolian Anti-Tuberculosis Coalition

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ABBREVIATIONS

AFB	Acid-Fast Bacillus
AIDS	Acquired Immune Deficiency Syndrome
Am	Amikacin
BCG	Bacille de Calmette et Guerin (vaccine for TB)
BDQ	Bedaquiline
Cm	Capreomycin
CXR	Chest X-Ray
DNA	Deoxyribonucleic Acid
DOTS	Directly Observed Treatment, Short Course
DRS	Drug Resistance Survey
DR-TB	Drug-Resistant Tuberculosis
DST	Drug Susceptibility Test
E	Ethambutol
EPTB	Extrapulmonary Tuberculosis
EQA	External Quality Assessment
FGD	Focus Group Discussion
FHC	Family Health Center
H	Isoniazid
HCW	Healthcare Worker
HIV	Human Immunodeficiency Virus
IEC	Information, Education and Communication
Km	Kanamycin
LPA	Line Probe Assay
MATA	Mongolian Anti-Tuberculosis Association
MATC	Mongolian Anti-Tuberculosis Coalition
MDR-TB	Multidrug Resistant Tuberculosis
MFGPA	Mongolian Family Group Practices Association
MNT	Mongolian Tugrik (national currency)
MOFALI	Ministry of Food, Agriculture and Light Industry
MOHS	Ministry of Health and Sports
MORTT	Ministry of Road, Transportation and Tourism
MOTT	Mycobacterium Other Than Tuberculosis
MTB	Mycobacterium Tuberculosis
MTBDR*plus*	Line probe assay for the rapid detection of *Mycobacterium tuberculosis* complex and mutations conferring resistance to rifampin and Isoniazid

MTBDR*sl*	Rapid DNA-based test for detecting specific mutations associated with resistance to fluoroquinolones and second-line injectable drugs in *Mycobacterium tuberculosis* complex
NCCD	National Center for Communicable Diseases
NGO	Non-Governmental Organization
NMHC	National Mental Health Center
NSO	National Statistics Office
NTP	National Tuberculosis Program
NTRL	National Tuberculosis Reference Laboratory
Ofx	Ofloxacin
PCR	Polymerase Chain Reaction
PCU	Program Coordination Unit
PHC	Primary Health Care
PNB	Para-Nitro Benzoic Acid Test
PRC	People's Republic of China
PTB	Pulmonary Tuberculosis
R	Rifampicin
RDTC	Regional Diagnostic and Treatment Center
RIT	Research Institute of Tuberculosis
RR-TB	Rifampicin-Resistant Tuberculosis
S	Streptomycin
SHC	Soum Health Center
SLI	Second-Line Injectable
SOP	Standard Operating Procedure
STI	Sexually Transmitted Infection
STREAM	The Evaluation of a Standardized Treatment Regimen of Anti-Tuberculosis Drugs for Patients with MDR-TB
TB	Tuberculosis
TSRU	Tuberculosis Surveillance and Research Unit
TWG	Technical Working Group
UNDP	United Nations Development Program
USDS	Union of Soum Doctors and Specialists
WHO	World Health Organization
WPR	Western Pacific Region
XDR-TB	Extensively Drug-Resistant Tuberculosis

EXECUTIVE SUMMARY

Backround: Nationwide anti-TB drug resistance survey (DRS) was conducted in 1999 and 2007 in Mongolia. Share of MDR-TB cases among newly notified TB cases increased from 1.0 percent in 1999 to 1.4 percent in 2007, and the share of MDR-TB among previously treated TB cases was 27.5 in 2007. WHO recommends repeating DRS every 5 years in countries with no well-established drug resistance surveillance system.

Goal: The survey aimed at estimating the prevalence of drug-resistant tuberculosis (DR-TB) among pulmonary tuberculosis (PTB) cases, detecting gene mutations conferring drug resistance, and identifying ways to enhance the prevention and control of multi-drug resistant tuberculosis (MDR-TB).

Material and methods: Sampling frame was comprised of all TB diagnostic centers in 21 provinces and 9 districts of Mongolia, including hospital at Prison Camp No. 429, NMHC and "Enerel" hospital for the homeless. The survey population included all new and retreatment sputum smear positive PTB cases notified during the survey data collection period. Sample size was 1220 new sputum smear positive PTB cases. All retreatment TB cases notified during the survey data collection period were included into the study in order to determine the proportion of retreatment TB cases with resistance to anti-TB drugs. All new and retreatment cases, who met the survey inclusion criteria, were interviewed and two sputum specimens were collected from each case.

Once sputum smear positive TB case was diagnosed, sputum specimens were collected before treatment initiation or within 7 days after the treatment commencement. Smear and culture testing was done on all sputum specimens. All smear positive cases were tested for rifampicin and isoniazid resistance using MTBDR*plus* test kit. Positive culture results warranted identification of Mycobacteria. After identification test, first-line DST was done on solid media. Second-line DST using conventional and molecular-based methods (MTBDR*sl*) were done in case multidrug resistance or resistance to rifampicin was present.

Results: Almost all new (92.6%) and retreatment (98.3%) TB cases notified during data collection period participated in the survey. A total of 1175 smear-positive new TB cases participated in the survey, which exceeded the required sample size of 1037 new cases (estimated taking into account potential losses due to specimen quality, and improper storage, transportation and incubation).

Average age of the survey participants was 36.6±14.8 years with the youngest aged 8 years and the oldest aged 89 years. New cases were significantly younger (average age 35.5±14.9 years) compared to retreatment cases (average age 41.0±13.6 years) ($p<0.001$).

Males accounted for 57.1% of new vs. 68.5% of retreatment cases ($p<0.001$). Slightly more than a third (39.3%) of the survey participants were from rural areas and 1.6% – were prisoners, and there was no difference between new and retreatment cases in this regard.

The prevalence of resistance to first-line TB drugs among new cases (31.1%) was significantly lower compared to retreatment cases (41.6%) ($p=0.001$). The prevalence of mono-resistance was similar among new (15.6%) and retreatment (13.9%) TB cases. The prevalence of mono-resistance to streptomycin was highest among both new (8.1%) and retreatment (6.4%) TB cases ($p=0.333$). The prevalence of mono-resistance to isoniazid among new and retreatment TB cases was 7.3 and 6.7 percent, respectively ($p=0.764$). Of 147 poly-resistant TB cases, 132 (90%) were resistant to isoniazid and streptomycin. Poly-resistance was detected in 10.1% of new and 11.2% of retreatment TB cases.

The prevalence of MDR-TB was three times higher among retreatment cases 16.5% [95% CI: 12.2–-21.5] compared to new cases 5.3% [95% CI: 4.1–6.7] (p<0.001). The majority of MDR-TB cases (73.8% (45/61) of new and 77.3% (34/44) of retreatment cases) were resistant to all 4 first-line TB drugs.

The prevalence of rifampicin-resistant TB among retreatment cases (17.9% [95% CI: 13.5–22.3]) was 3.2 times higher than among new cases (5.6% [95% CI: 4.2–6.9)].

There was no significant difference in the prevalence of MDR-TB among new cases according to the place of residence (urban/rural/prison). However, the prevalence of MDR-TB among retreatment cases was significantly higher among prisoners (66.7%) compared to rural (18.4%) or urban (13.5%) cases (p=0.002).

There was no significant difference in the prevalence of MDR-TB with additional resistance to second-line TB drugs among both new (11.5% [95% CI: 4.7–22.2]) and retreatment (9.1% [95% CI: 2.5–21.7]) cases (p=0.693). The prevalence of ofloxacin resistance was highest among both new (9.8%) and retreatment (4.5%) cases (p=0.313). The prevalence of extensively drug-resistant TB (XDR-TB) was 4.9% [95% CI: 1.0–13.7] among new cases.

According to univariate analysis MDR-TB was associated with the history of contact with DR-TB case (OR=2.7 [95% CI: 1.1–6.5], p=0.032) among new cases and with imprisonment (OR=9.0 [95% CI: 1.9–43.1], p=0.006) among retreatment cases.

According to routine TB surveillance data, MDR-TB notification rate increased from 4.6 to 7.7 per 100,000 population between 2007 and 2016 in Mongolia. Similarly, MDR-TB notification rate in prisons increased from 50 to 83.3 per 100,000 population during the same reporting period.

Conclusions

1. The prevalence of TB resistant to first-line drugs was 31.1% [95% CI: 28.5–33.9] among new and 41.6% [95% CI: 35.6–47.7] among retreatment cases in Mongolia. The prevalence of primary DR-TB increased by 68.1% among new cases and decreased by 10.5% among retreatment cases compared to the previous round of DRS.
2. The prevalence of MDR-TB was 5.3% [95% CI: 4.1–6.7] among new and 16.5% [95% CI: 12.2–21.5] among retreatment cases in Mongolia. The prevalence of MDR-TB increased 3.8 times among new cases and decreased 1.7 times among retreatment cases compared to the previous round of DRS.
3. The prevalence of MDR-TB with additional resistance to second-line TB drugs was 10.5% [95% CI: 5.3–18.0].
4. Increased risk of MDR-TB was associated with the history of contact with DR-TB case (OR=2.7 [95% CI: 1.1–6.5], p=0.032) among new cases and with imprisonment (OR=9.0 [95% CI: 1.9–43.1], p=0.006) among retreatment cases.
5. Mutation in rpoB gene was detected in all Rifampicin-resistant strains, and the gene mutation at codon S531L (MUT3) was detected in 84.4% of these strains. Mutation in inhA gene was predominant (83.4%) in strains resistant to Isoniazid only.

CHAPTER I. SURVEY JUSTIFICATION

1.1 Preface

Background information about Mongolia

Geography

Mongolia is located in North-East Asia, and spans 2,392 km from West to East and 1,259 km from North to South occupying a territory of 1,564,116 km^2. The country borders with Russian Federation to the North and People's Republic of China (PRC) to the South with the land border of 8,252.7 km in total. Mongolia is located 1,580 m above the sea level with the highest point Khuiten Uul located 4,374 m above the sea level and the lowest point Khukh Nuur Depression located 532 m above the sea level. Capital City Ulaanbaatar is located 1,350 m above the sea level.[1]

Climate

Mongolia is the country of four seasons with sharp continental climate, low precipitation, and large temperature difference between daily/annual maximum and minimum. Mongolia is a land-locked high altitude country, and as such has a largely colder climate compared to other countries along the same latitude. Average annual temperature is 8.5°C in Gobi Region and –7.8°C in mountainous areas. January is the coldest month with temperature ranging from –31.1°C to –55.3°C, while July is the warmest month with temperature ranging from +28.5°C to +44.0°C. Average annual precipitation is 200-220 mm ranging from 38.4 mm in the Southern parts of the country (Gobi desert) to 389 mm in the Northern parts. Rainy season lasts from June to August, and dry season lasts from November to March. Mongolia has on average 3,000 hours of sunny days annually.[1]

Population

Mongolia had the highest in Asia population growth rate of 2.1–2.5% prior to 1990.[1] As of the end of 2016 the population of the country was 3.1 million inhabitants, which was 2 percent higher compared to the same period of the preceding year. Two-thirds (68.9%) of the population live in urban and 31.1 percent – in rural settings. Capital City Ulaanbaatar is home to 1.4 million people or 46.2 percent of the country's total population. Male-to-female ratio is 97:100, and males account for 49.2 percent of the population, while females – for 50.8 percent. In terms of age structure children under 15 years of age account for 30 percent, adults aged 15-64 years – for 66.2 percent and the elderly above the age of 65 – for 3.8 percent of the population. There were 869.8 thousand households (67.8 percent urban and 32.2 percent rural) with an average of 3.5 persons per household as of 2016. Number of households in Ulaanbaatar City, Khangai, Central, Western and Eastern Regions was 380,800, 171,000, 149,100, 104,200 and 64,700, respectively.[2]

Urbanization is rapidly growing, and industrialization has taken place in the past 40 years contributing to economic growth. Internal migration to Ulaanbaatar City is responsible for growing urbanization.[1]

Poverty

Poverty has decreased in the recent past due to rapid economic growth. As of 2013, the number of working age population was 1.2 million, of whom 92.1 percent were employed and 7.9 percent were unemployed. According to October 2014 data unemployment rate was 6.4% and inflation rate was 12.1% (NSO 2014 b). The number of officially registered unemployed individuals reached its peak in 1994 (75.5 thousand) and decreased twice to 34.2 thousand in 2014.

Poverty assessment based on 2010 Population and Household Census conducted by the National Statistics Office (NSO) of Mongolia jointly with UNDP has demonstrated that poverty was comparatively high in Khovd and Gobi-Altai aimags in the Western Region, and Khuvsgul, Zavkhan and Uvurkhangai aimags in Khangai Region of the country. More than a quarter (27.4%) of the population has consumption below poverty line, and 23.2% or urban and 35.5% of rural population are poor (NSO, 2012). [1]

Medical services

As of 2016, there were 3,500 health organizations in Mongolia, including 13 tertiary healthcare facilities, 5 Regional Diagnostic and Treatment Centers (RDTCs), 16 aimag general hospitals, 12 district general hospitals/health centers, 6 soum general hospitals, 39 inter-soum hospitals, 273 Soum Health Centers (SHCs), 220 Family Health Centers (FHCs), 234 private hospitals 234 and 1,076 private clinics.

Number of healthcare workers (HCWs) in public and private sector was 48,173 in 2016, which was 1.6 percent higher compared to the preceding year. Of HCWs, 93.2 percent were health professionals and 6.8 percent were allied personnel.[2]

Maternal and child health

A total of 75,851 pregnant women attended prenatal care in 2016. Of them, 84.7 percent started antenatal care in the first trimester, 13.8 percent – in the second trimester and 1.5 percent – in the last trimester. Of pregnant women attending antenatal care, 53.4 percent underwent chest X-ray (CXR) examination, and 0.8 percent or 341 women had been diagnosed with active TB.[2]

Population morbidity and mortality

As of 2016, the leading causes of population morbidity were respiratory diseases (1,647.4 per 10,000 population), diseases of digestive system (1,231.4 per 10,000 population), cardiovascular diseases (1,007.6 per 10,000 population), diseases of genito-urinary system (807.6 per 10,000 population) and injuries and poisoning (469.9 per 10,000 population). Cardiovascular diseases, neoplasms and injuries and poisoning remain leading causes of population mortality since 1995.

A total of 16,181 deaths were reported in 2016, which was by 193 cases or 1.2 percent fewer compared to the preceding year. As of 2016, cardiovascular diseases accounted for 33.3 percent, neoplasms – for 25.6 percent, injuries and poisoning – for 15.0 percent, diseases of digestive system – for 7.4 percent, and respiratory diseases – for 4.3 percent of deaths. In total, the above five causes accounted for 85.4 percent of all deaths. [2]

Diabetes:

Diabetes morbidity rate was 78.6 per 10,000 population in 2016, which was by 14.8 more than in the preceding year. The rate was 75.5 per 10,000 males and 82.9 per 10,000 females. In terms of age structure, diabetes morbidity was highest (286.3 per 10,000) in 45–65 year-olds. The rate was relatively high in Central Region (74.5 per 10,000 population), and Darkhan-Uul (146.6), Selenge (76.4), Umnugobi (69.8) and Gobisumber (42.5) aimags. The disease accounted for 48.9 percent of endocrine and metabolic diseases.[2] In recent years the number of patients with TB and diabetes co-morbidity, which results in prolonged cure, poor treatment outcomes and higher relapse rates, is rising worldwide and in Mongolia.

Communicable diseases:

A total of 69,663 cases (or 227.8 per 10,000 population) of 28 types of acute communicable diseases were notified in 2016, which was by 10,263 cases more than in the preceding year. Intestinal

infections accounted for 13.0 percent, respiratory infections – for 62.0 percent, zoonoses – for 0.7 percent, sexually transmitted infections (STIs) – for 21.5 percent, blood-borne infections – for 0.7 percent, and other communicable diseases – for 2.1 percent of all communicable diseases. [2]

Cumulative number of notified HIV/AIDS cases was 225 as of 2016, and all of the cases were sexually transmitted. Of them, 26 cases were notified in 2016, which was by 8 cases more than in the preceding year. The overwhelming majority (81%) of HIV/AIDS cases were males, and 18.0 percent were females. [2]

A total of 277 deaths due to communicable diseases were reported in 2016 including 112 deaths due to TB, 15 deaths due to congenital syphilis, 5 deaths due to viral hepatitis, 132 deaths due to measles, 8 deaths due to HIV/AIDS, 2 deaths due to tick-borne encephalitis, and 1 death due to chicken pox, meningococcal infection and malaria each. [2]

1.2 General Information on TB

TB is one of the infectious diseases re-emerging since 1990s. According to the World Health Organization (WHO) report 9.6 million individuals suffered TB infection and 1.5 million individuals died of TB worldwide in 2014.

During the reporting period 480,000 cases of HIV-TB co-infection were diagnosed, of whom 390,000 cases were estimated to die. Additionally, 480,000 cases of MDR-TB were diagnosed, of whom 190,000 were estimated to die. A total of 46,560 cases of extensively drug-resistant TB (XDR-TB) were registered.

Detection of TB infection among migrants, prisoners, children, the elderly and the vulnerable is challenging, and these populations have limited capacity to overcome the burden of the disease. Although almost all countries provide free TB services, patients often discontinue their treatment due to financial difficulties, which leads to the development of drug resistance.

An estimated 71,000 individuals develop MDR-TB annually in the Western Pacific Region (WPR) of WHO. However, only 16 percent of them are reported, 10 percent are enrolled in treatment, and only 5 percent are successfully treated. Weak health systems, limited accessibility of health services, inadequate coordination mechanisms, drug use and discrimination are the factors behind the re-emergence of TB.

2015 marked the year of radical changes in TB control as the global community has moved from Millennium Development Goals (MDGs) to Sustainable Development Goals (SDGs) and from Stop TB to End TB strategy. Globally TB surveillance systems capable of capturing essential data have been set up within the past 20 years. Nonetheless, it remains vital to further reinforce achievements in TB diagnosis, treatment and prevention.

1.3 Epidemiological Profile of TB in Mongolia

Mongolia has the fourth highest TB rate among 37 countries of WPR. TB is the third most common communicable disease in Mongolia after sexually transmitted infections and viral hepatitis and is the leading cause of mortality among all communicable diseases. TB remains a major challenge for the country's health sector.

Number of newly notified TB cases was 4,045, which accounted for 5.8 percent of all-cause communicable diseases in 2016 in Mongolia. The majority (61.0%) of TB cases or 2,469 cases were notified in Ulaanbaatar. Of newly notified cases, 2,131 (52.7%) had pulmonary TB (PTB) and 1,914 (47.3%) had extrapulmonary TB (EPTB). During the reporting period PTB notification decreased by 230 cases or 2.6 percent, while EPTB notification increased by 5 cases or 2.6 percent compared to 2015.[2]

In terms of age structure, 63.6 percent of newly notified TB cases were aged 15–44 years. Men (53.5%) accounted for slightly more of the newly notified TB cases than women (46.5%). TB mortality rate per 10,000 population increased by 0.01 in 2016 compared to 2015.[2]

According to the mid-term external review of Mongolia's National Stop TB Strategy conducted by WHO jointly with other international partners in 2013, there is an ongoing transmission of TB in the communities and the infection is concentrated among vulnerable population groups.[3]

Half of TB patients are unemployed, and 70 percent have income below sustainable livelihood level. In recent years the number of cases with severe forms of TB, such as MDR-TB and XDR-TB is growing, leaving no room for complacency.[3]

TB puts a severe burden on household and country economy as it requires long and costly treatment often with severe side effects and distress, and leads to temporary (sometimes lifelong) disability and impairment (such as lifelong deafness or hearing impairment) restricting income-generating activities of patients and their caregivers. In terms of potential years of life lost, pulmonary TB ranks third following liver cirrhosis and intrahepatic cholangiocarcinoma according to a Study on Health and Poverty conducted among 15–64 year-olds in Mongolia in 2009.

Treatment of a drug-susceptible TB case lasts for 6–12 months and costs on average 270,000 MNT, while that of an MDR-TB case lasts for 24 months and costs 9.1–17.2 mln MNT depending on the treatment regimen. Costs associated with 24–36 months of treatment of one XDR-TB patient are even greater and amount to 40.9 mln MNT plus more than 140,000 MNT for the treatment of side effects. These costs pose an additional burden on poor households already overburdened with incapacitating disease, which often make social welfare support the only source of income for the patient.

Although 60% of MDR-TB patients can be cured as a result of proper treatment, about 20% continue spreading the infection in the community because of treatment failure or default. Family members of patients with infectious TB have 10 times higher risk of contracting the disease.

The number of household contacts of MDR-TB patients contracting the disease is growing in the past few years, and the fact that 26 of 74 pediatric MDR-TB patients are under five years of age is of particular concern.

The results of the first national TB prevalence survey in Mongolia have demonstrated that the prevalence rates of smear positive and bacteriologically confirmed pulmonary TB were 204 (143.0-265.1) and 559.6 (454.5-664.7) per 100,000 adult population in 2014-2015, respectively. Survey observed prevalence of all forms of TB for all age groups was 757 (620-894) per 100,000 population was 3 times higher than the WHO estimate of all forms of TB at that time.[4]

1.4 Implementation Status of National TB Program in Mongolia

Mongolia as a WHO member state decided to adopt DOTS as the main TB control strategy in 1990. Hence, DOTS was adapted to local needs, and the first National TB Control Program was developed and approved by the Government of Mongolia in 1994 to be implemented until 2000. Since then, sub-programs on TB control in line with WHO policies and local needs were implemented in 2002–2010 and 2010–2015. The latest sub-program is being implemented for the period of 2015–2020.

TB laboratory network in Mongolia

Central (tertiary) level: National TB Reference Laboratory (NTRL) of NCCD performs the following tests: *Mycobacterium* culture on solid medium (Ogawa), *Mycobacterium* culture on liquid medium (MGIT), first-line DST (Solid L-J/Liquid), second-line DST (Solid L-J), microscopic

examination (Ziehl-Neelsen staining, fluorescent microscopy), LPA (molecular genetic method for isoniazid and rifampicin susceptibility testing), loop-mediated isothermal amplification assay (TB-LAMP) for the detection of *M.tuberculosis*, and MTB complex identification tests (niacin test, para-nitrobenzoate assay, Capilia-TB). NTRL provides supportive supervision to TB laboratories in all aimags, the Capital City, Prison Camp No. 429, "Enerel" hospital for the homeless and some soums. It also participates in international and national research.

Sub-national (secondary) level: TB dispensaries in Departments of Health or General Hospitals of 21 aimags perform microscopic examination. Culture testing on solid medium and molecular biologic assay (Xpert MTB/RIF) have been introduced in Dornod and Darkhan-Uul provinces since 2011.

Peripheral (primary) level: Microscopic examination is performed in 3 Soum Health Centers (SHCs) with high population density and TB notification.

International reference laboratory: Research Institute of Tuberculosis (RIT) of Japan serves as a supra-national reference laboratory for Mongolia, provides technical assistance to NTRL, conducts training on culture testing, DST and fluorescent microscopic examination, and provides quality assurance on first and second-line DST.

Table 1. Timeline of DST capacity building at NTRL

№	Type of testing	Year introduced
1	First-line DST on solid medium	1970, 2003
2	Second-line DST on solid medium	2009
3	Molecular detection of resistance to first-line drugs (MTBDR*plus*)	2009
4	First-line DST on *liquid medium* (BACTEC MGIT)	2011
5	Molecular detection of resistance to second-line drugs (MTBDR*sl*)	2013
6	Xpert MTB/RIF	2013
7	Molecular identification of MOTT (Genotype Mycobacterium CM)	2014
8	Molecular identification of MTB complex (Genotype MTBC)	2015

TB laboratory capacity-building

Based on the findings of the first National TB Prevalence Survey it has been decided to scale-up the use of rapid molecular techniques (Xpert MTB/RIF, TB-LAMP) in order to improve TB diagnostic capacity in Ulaanbaatar and to decentralize TB services, and the proposition has been included in the project proposal submitted to the Global Fund for implementation in 2018-2020. TB treatment regimens currently used in Mongolia are shown in the tables below.

Table 2. TB treatment regimen used in 1993-1999 in Mongolia

№	Type of TB case	Intensive phase	Continuation phase
1	New case	2RHZE 2HES	4RH (3rd group 2RH) 10HE
2	TB meningitis	2RHZE	6RH
3	Retreatment case	3RHZES/1RHZE	5RHE

Table 3. Use of fixed-dose combinations (1999-up to date)

№	Type of TB case	Intensive phase	Continuation phase
1	New case	2RHZE	4RH
2	TB meningitis	2 RHZE	10RH
3	Retreatment case	2RHZES/1RHEZ	5RHE

Mongolia has been sustainably using fixed-dose combinations in TB treatment since their introduction in 2000.

MDR-TB management

Mongolia has been successfully implementing the Global Fund-Supported Project on AIDS and TB for more than a decade since 2003, and has made a leap forward in detection, diagnosis and treatment of MDR-TB with the introduction of "DOTS plus" program[5] in 2006. MDR-TB treatment regimen introduced within the framework of the program is shown below.

Table 4. MDR-TB treatment regimen (2006–2010)

№	Case definition	Intensive phase	Continuation phase
1	Confirmed case of MDR-TB	6Z-Km-Ofl-Eth-Cs	12-18Z-Ofl-Eth-Cs

Table 5. MDR-TB treatment regimen (2010–2014)

№	Case definition	Intensive phase	Continuation phase
1	Confirmed case of MDR-TB	8Z-Km-Ofl-Eth-Cs	16Z-Ofl-Eth-Cs

Table 6. MDR-TB treatment regimen (2014–up to date)

№	Case definition	Intensive phase	Continuation phase
1	Confirmed case of MDR-TB	6-8Z-Km/Cm-Lfl-Eto/Pto-Cs/PAS-H*	16-18Z-Lfl-Eto/Pto-Cs/PAS-H*

H* – high dose

Table 7. XDR-TB treatment regimen (2015–up to date)

№	Case definition	Intensive phase	Continuation phase
1	Confirmed case of XDR-TB	6-8Imp-Z-Mfx-Lzd-Cfz-PAS-H*	16Z-Mfx-Lzd-Cfz-PAS-H*

H* – high dose

Treatment of few XDR-TB cases started in 2015 in Mongolia.

Briefly about "STREAM" international multi-center clinical trial in Mongolia

"STREAM" is a clinical trial intended to assess MDR-TB treatment regimens 3-4 times shorter than conventional regimen. The trial is funded by the Clinical Trials Unit at University College London, UK Medical Research Council in a number of countries including Mongolia. The trial is conducted in two phases (2014-2016, 2016-2019) in Mongolia.[6] The trial treatment regimens are shown below.

Table 8. Shortened regimen for MDR-TB treatment (STREAM clinical trial. Stage I, 2014-2016, Stage II 2016.03-2019)

№	MDR-TB treatment regimen	Intensive phase	Continuation phase
1	Standard regimen (A)	8Km(Cm)-Lfx-Cs(PAS)-Eto(Pto)-H-Z	16Lfx-Cs(PAS)-Eto(Pto)-H-Z
2	9-month short regimen (B)	4Km-Cfz-Mfx-Pto-E-H-Z	6Cfz-Mfx-E-Z
3	9-month short regimen (C)	4H-E-Z-Pto-BDQ-Lfx-Cfz (BDQ 3 times a week starting from week 15)	6BDQ-Lfx-Cfz-Z (BDQ 3 times a week)
4	6-month regimen (D)	2Km-H-Z-BDQ-Lfx-Cfz (BDQ and H 3 times a week starting from week 15)	5BDQ-Lfx-Cfz-Z (BDQ 3 times a week)

B = 16 weeks / 24 weeks = 40 weeks, C = 16 weeks / 24 weeks = 40 weeks, D = 8 weeks / 20 weeks = 28 weeks.

1.5 Current Status of Anti-TB Drug Resistance in Mongolia

There is a slight reduction in TB notification in Mongolia. However, the incidence of drug resistant TB, in particular MDR-TB is increasing year on year.

Laboratory diagnosis of MDR-TB in Mongolia dates back to 2003. Since then 1,726 MDR-TB cases have been diagnosed, of whom about 20 percent died while on a waiting list for treatment. Furthermore, the number of defaulted cases or cases in whom treatment failed is increasing steadily. A total of 40 XDR-TB cases have been reported in the country in 2009–2015, of whom 32 cases (or 80 percent) died.

Although 60% of MDR-TB patients can be cured as a result of proper treatment, about 20% continue spreading the infection in the community because of treatment failure or default. In particular, 17.2 percent of MDR-TB patients defaulted, 9.2 percent died and treatment failed in 7.7 percent in 2014.

The number of household contacts of MDR-TB patients contracting the disease is growing in the past few years, and the fact that 26 of 74 pediatric MDR-TB patients are under five years of age is of particular concern. Almost two-thirds (63.1 percent) of MDR-TB patients are notified in Ulaanbaatar, while 36.9 percent – in provinces and 2.6 percent – in prisons. The majority (68.7 percent) of MDR-TB cases is males, and youth aged 15–34 years account for 57.8 percent.[7]

Nationwide anti-TB drug resistance survey (DRS) was conducted in 1999 and 2007 in Mongolia. Share of MDR-TB cases among newly notified TB cases increased from 1.0 percent in 1999 [8,9] to 1.4 percent in 2007, and the share of MDR-TB among previously treated TB cases was 27.5 in 2007 [10] (Table 9).

Table 9. Findings of the National Anti-Tuberculosis Drug Resistance Survey

Drug resistance	1999		2007			
	New	95%CI	New	95%CI	Retreatment	95%CI
Any drug resistance	**29.4%**	**25.2-34.0**	**18.5%**	**15.6-21.7**	**46.5%**	**39.4-53.7**
Isoniazid	15.3%	12.1-19.1	12.6%	10.2-15.5	36.5%	29.8-43.6
Rifampicin	1.2%	0.5-2.9	2.2%	1.2-3.7	31.0%	24.7-37.9
Streptomycin	24.2%	20.3-28.6	11.5%	9.2-14.3	33.5%	27.0-40.5
Ethambutol	1.7%	0.8-3.5	1.7%	0.9-3.1	22.0%	16.5-28.4
MDR-TB	**1%**	**0.38-2.5**	**1.4%**	**0.7-2.7**	**27.5%**	**21.4- 34.2**

WHO recommends repeating DRS every 5 years in countries with no well-established drug resistance surveillance system. The current DRS was conducted in order to monitor trends in drug resistance, identify risk factors, formulate appropriate TB control strategies and strengthen drug-resistance surveillance system.

CHAPTER II. GOAL AND OBJECTIVES

2.1 Goal

To determine the proportion of drug resistant TB among notified PTB cases, to identify genetic mutations associated with TB drug resistance, and to formulate policy recommendations for MDR-TB prevention and control in Mongolia.

2.2 Objectives

- To determine the proportion of new and retreatment TB cases with resistance to first-line anti-tuberculosis drugs
- To determine the proportion of MDR-TB among new and retreatment TB cases
- To determine the proportion of drug resistance to fluoroquinolones and second-line injectable (SLI) agents among patients with resistance to Rifampicin and Isoniazid
- To identify association between multi-drug resistance and some risk factors

2.3 Novelty of research

- The proportion of drug resistant TB among notified TB cases has been determined using internationally recognized modern molecular genetic methods;
- Drug resistance to second-line anti-tuberculosis drugs has been assessed using conventional and molecular genetic methods, and genetic mutations associated with TB drug resistance have been identified.

2.4 Expected Outcomes

- The proportion of cases resistant to first and second-line anti-tuberculosis drugs among new and retreatment TB cases has been determined, and trends in drug resistance over time have been assessed at the national level;
- Associations between MDR-TB and selected risk factors have been evaluated, and policy recommendations for MDR-TB control and prevention have been formulated for the revision of the Stop TB Strategy.

CHAPTER III. SURVEY METHODOLOGY

3.1 Survey Design

The survey used cross-sectional design.

3.2 Sampling Frame and Survey Population

Sampling frame was comprised of all TB diagnostic centers in 21 provinces and 9 districts of Mongolia, including hospital at Prison Camp No. 429, NMHC and "Enerel" hospital for the homeless. Currently, only one microscopy center for TB exists in each province/district. The survey population included all new and retreatment sputum smear positive PTB cases notified during the survey data collection period.

3.3 Sample Size and Sampling Method

Required sample size was calculated using the following formula in accordance with the WHO Guidelines for Surveillance of Drug Resistance in Tuberculosis (2015)[11].

$$n = \frac{N * z^2 * p * (1-p)}{d^2 * (N-1) + z^2 * p * (1-p)}$$

N – total number of new sputum smear positive cases registered in 2015	1,724
z – z-value that corresponds to 95% confidence interval	1.96
d – absolute precision	2%
p – expected proportion of Rifampicin-resistant TB in the target population	2.5%
n – sample size	

Using the above formula the desired sample size of new sputum smear positive PTB cases is estimated at 1,037. If a potential loss of 15% due to inadequate specimen quality, storage, transportation and contamination is incorporated into the sample size calculation, the desired sample size increases to 1,220 new sputum smear positive PTB cases.

All retreatment TB cases notified during the survey data collection period were included into the study in order to determine the proportion of retreatment TB cases with resistance to anti-TB drugs (total number of previously treated smear positive TB cases was 415 in 2015).

A method of 100% sampling of TB units was used, and the number of study subjects to be recruited from each unit was proportional to the number of new sputum smear positive PT cases notified in 2015 (Table 10).

Table 10. Number of new smear-positive TB cases recruited from TB units

№	TB units	Previously treated smear positive TB	New smear positive TB	
			Notified	Sample size
1	Arkhangai	1	14	10
2	Bayan-Ulgii	3	15	11
3	Bayankhongor	1	23	16
4	Bulgan	4	23	16
5	Gobi-Altai	0	14	10
6	Gobisumber	0	5	4
7	Darkhan-Uul	17	89	63
8	Dornogobi	13	37	26
9	Dornod	24	80	57
10	Dundgobi	3	9	6
11	Zavkhan	2	9	6
12	Orkhon	3	62	44
13	Uvurkhangai	4	26	18
14	Umnugobi	1	13	9
15	Sukhbaatar	5	39	28
16	Selenge	18	80	57
17	Tuv	13	50	35
18	Uvs	2	24	17
19	Khovd	1	18	13
20	Khuvsgul	8	31	22
21	Khentii	16	62	44
	Total for provinces	**139**	**723**	**512**
22	Baganuur	1	15	11
23	Bayangol	23	112	79
24	Bayanzurkh	90	226	160
25	Nalaikh	2	24	17
26	Songinokhairkhan	71	246	174
27	Sukhbaatar	13	96	68
28	Khan-Uul	27	109	77
29	Chingeltei	24	117	83
32	“Enerel” Hospital	9	18	13
33	NMHC	0	0	0
30	Bagakhangai	0	2	1
	Total for Ulaanbaatar	**260**	**965**	**683**
31	**Prison Hospital**	16	36	25
	Grand total	**415**	**1,724**	**1,220**

3.4 Case Definitions

TB cases are classified as drug sensitive TB and drug resistant TB according to susceptibility of *M. tuberculosis* to anti-tuberculosis drugs.

- **Drug-susceptible TB:** TB case with no evidence of resistance to any of the anti-TB drugs on DST.
- **Drug-resistant TB:** TB case with evidence of resistance to anti-TB drugs. Drug-resistant TB is classified as follows:
  - **Monoresistance:** Resistance to one first-line anti-TB drug only.
  - **Poly-drug resistance:** Resistance to more than one first-line anti-TB drug (other than both isoniazid and rifampicin).
  - **Multidrug resistance:** Resistance to at least both isoniazid and rifampicin.
  - **Extensively drug resistance:** Resistance to any fluoroquinolone and to at least one of three SLI drugs (Capreomycin, Kanamycin and Amikacin), in addition to multidrug resistance.
  - **Rifampicin resistance:** Resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, whether monoresistance, multidrug resistance, poly-drug resistance or extensive drug resistance.[11,12]

3.5 Laboratory Case Definitions

Sputum smear microscopy:

Table 11. Interpretation of smear test results (WHO recommendation)

Results	ZN 1000X, 1 length =100 fields	FCH 200X, 1 length =20 fields	FCH 400X, 1 length =40 fields
Negative	0 AFB/1 length	0 AFB/1 length	0 AFB/1 length
Confirmation required		1-4 AFB/1 length	1-2 AFB/1 length
Scanty	1-9 AFB/1 length	5-49 AFB/1 length	3-24 AFB/1 length
1+	10-99 AFB/1 length	3-24 AFB in a field	1-6 AFB in a field
2+	1-10 AFB / 1/2 length	25-250 AFB in a field	7-60 AFB in a field
3+	>10 AFB /1/5 length	>250 AFB in a field	>60 AFB in a field

Recording results of primary culture:

Table 12. Interpretation of culture test results (WHO recommendation)

Growth	Results	Niacin test result	Conclusion
None	Negative	NA	Negative MTB complex
1-9 colonies	Record actual number	positive	MTB complex
10-100 colonies	1+	positive	MTB complex
>100-200 colonies	2+	positive	MTB complex

>200 colonies (too many to count or confluent)	3+	positive	MTB complex
Growth mycobacteria other than TB	Positive for other mycobacteria	negative	No MTB complex growth, but positive for other mycobacteria
Contaminated	contaminated	NA	contaminated
ZN+ growth in presence of contamination	Positive MTB and contaminated*	positive	Positive MTB complex and contaminated record and subculturing

*- Culture should be re-inoculated

DST results:

- TB case with evidence of resistance to anti-TB drugs identified on DST using solid media (WHO-recommended "gold standard") is classified as drug-resistant TB irrespective of the findings of molecular genetic testing.

3.6 Survey Inclusion and Exclusion Criteria

Inclusion criteria

- Citizen of Mongolia
- Informed consent provided by individuals themselves, and in case of persons aged 16 or below – additionally, by their parents or surrogate decision-makers
- New sputum smear positive PTB case
- Previously treated sputum smear positive PTB case (after relapse, treatment after loss to follow-up, treatment after failure and others)

Exclusion criteria

- Foreigner
- Informed consent not provided by individuals themselves, and in case of persons aged 16 or below – additionally, by their parents or surrogate decision-makers
- New sputum smear negative PTB case, who is positive on molecular genetic and culture testing
- Clinically diagnosed PTB (sputum smear negative)
- New TB case, who had been on anti-TB medications for more than a week before sputum submission
- EPTB case

CHAPTER IV. SURVEY PROCEDURES

4.1 Recruitment of TB Patients

Upon detection every sputum smear positive TB case was asked to participate in the survey by a TB doctor (trained professional). The following procedures were adhered to:

- A prospective survey participant was informed about the nature and significance of the survey.
- Informed consent form was clearly explained to the patient.
- If the patient consented to participate in the survey and signed the informed consent form, he/she was registered in the survey participant registry, and sputum specimen was collected.

4.2 Questionnaire Interview

Patients, who provided written informed consent to participate in the survey, were registered as survey participants and interviewed by a trained healthcare worker using a specially designed questionnaire. The questionnaire consisted of background information part, and questions about TB symptoms, healthcare seeking behavior, previous and current TB treatment, contact with TB patients, addictive behaviors and lifestyle habits. In case the participant was unable to answer the questions (e.g. due to speech or hearing impairment) a family member or caregiver was interviewed.

4.3 Sputum Sample Collection

Specimen collection procedures

All new and retreatment TB cases, who met the survey inclusion criteria, submitted sputum specimens as per routine procedures. Once sputum smear positive TB case was diagnosed, sputum specimens were collected before treatment initiation or within 7 days after the treatment commencement. Cases, who met the survey inclusion criteria, were registered in the survey registry and bacteriological testing form was completed.

TB laboratory technician of the survey site was responsible for sputum collection, storage, transportation and internal quality control. The survey patients were asked to submit two (spot and morning) sputum specimens. After collecting spot specimen, the patient was given sputum container and clear instructions on how to collect morning sputum. Laboratory technician was responsible for attaching the survey participant's unique barcode to the outside of the sputum container. Physician and laboratory technician checked sputum submission by patients, who met inclusion criteria, against survey participant registry.

4.4 Sputum Sample Storage

Once sputum is collected, the outside of all specimen containers should be checked for contamination and barcode completeness. Then, specimen container shall be placed in a re-sealable plastic bag.

Upon collection sputum specimens were stored in a cold chain (at $+2^0$C to $+8^0$C) away from sunlight, and the cold chain temperatures were monitored three times a day and recorded in a temperature monitor log-book. Sputum specimens were delivered to the NTRL of NCCD from provinces within 5 days and from districts within 3 days from the date of collection**.**

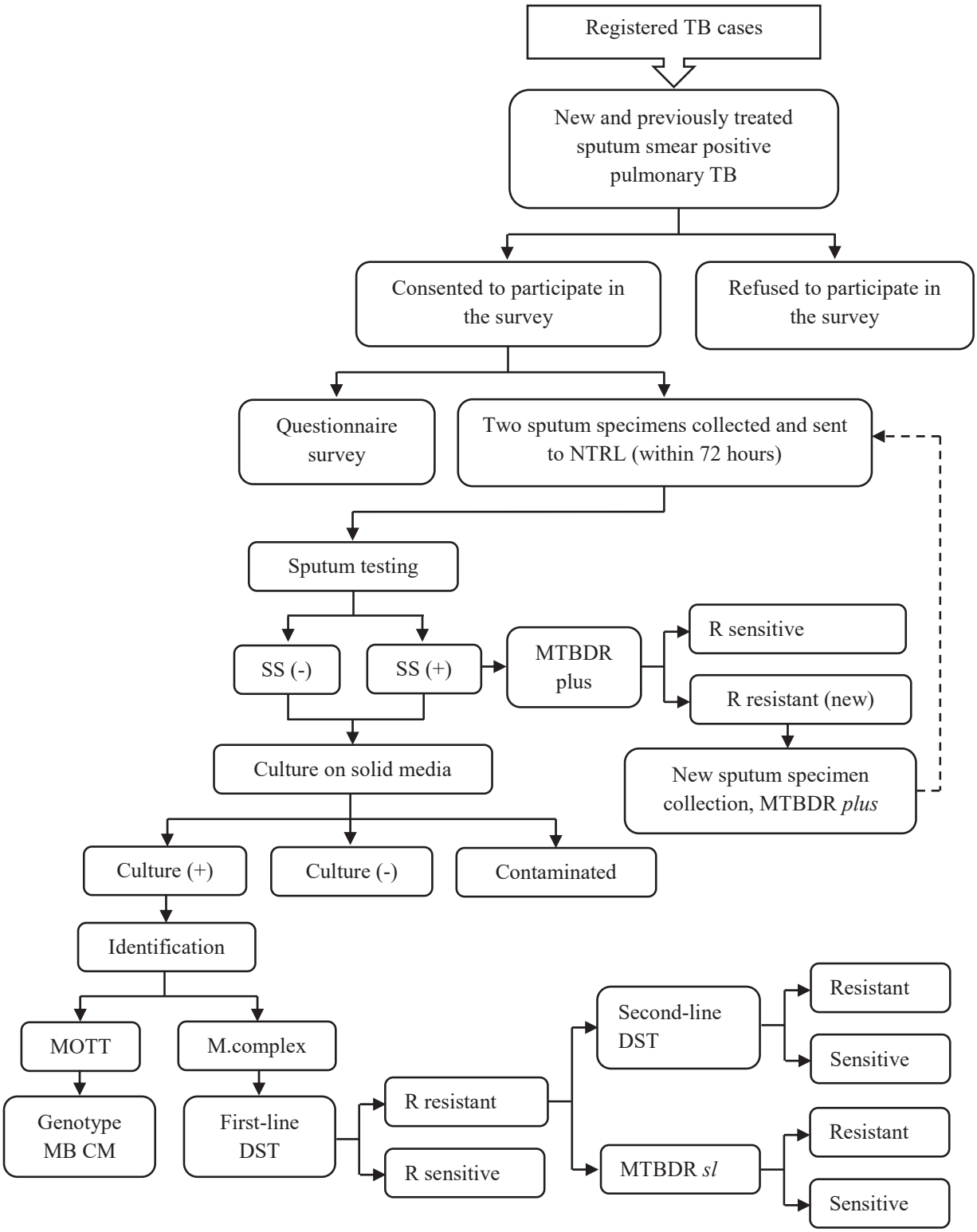

Figure 4. Survey methodology

4.5 Sputum Sample Processing and Transportation

Collected and stored sputum specimens were transported in compliance with WHO/FAO/OIE Guidelines for the Safe Transport of Infectious Substances and Diagnostic Specimens, ICAO/IATA Packaging Instructions 602 and 650, and Order of the Minister of Road, Transportation Tourism of Mongolia № 70 of 2006.[13,14]

A container with sputum specimen in a re-sealable plastic bag was placed upright in a specially labelled cold chain box with ice-packs. Specimens were transported to the NTRL of NCCD ensuring cold chain regime (at +2 ˚C to +8 ˚C). Specimens were transported from sputum collection sites to NTRL 1–3 times a week.

Laboratory technician at NTRL followed the procedures below when receiving transported specimens: checked temperature monitor log-book recordings, checked specimens against Referral Forms, and registered received specimens in a log-book.

Local specimen transporter submitted a proper evidence of transportation costs to the Union of Soum Doctors and Specialists (USDS), implementing agency of a Sub-project on Strengthening Specimen Transportation System. Transportation costs were reimbursed by the sub-project based on the evidence.

4.6 Infection Control and Biosafety Procedures

National and international rules and regulations were strictly observed when transporting infectious and biological materials.

CHAPTER V. LABORATORY PROCEDURES

5.1 Bacteriological Testing

Smear and culture testing was done on all sputum specimens. All smear positive cases were tested for Rifampicin and Isoniazid resistance using MTBDR*plus* test kit. Positive culture results warranted identification of Mycobacteria. After identification test, first-line DST was done on solid media. Second-line DST using conventional and molecular-based methods (MTBDR*sl*) were done in case multidrug resistance or resistance to rifampicin was present.

5.1.1 Sputum Smear Microscopy

All survey TB units performed sputum smear testing.

Sputum smear examinations were done within 2 days after the receipt of a specimen at the NTRL. Smear examination results along with the survey form were handed to data manager within 2 days after smear results became available. Smear microscopy was done on all specimens irrespective of breaches in storage and transportation regimen or duration, but proper notes were made in laboratory log-book.

Laboratory technician at the NTRL prepared sputum smear and examined it using fluorescent (LED) microscope. Results of smear microscopy were recorded in laboratory log-book using sputum smear grading.

Results and interpretation

Smear negative specimens were stained by Ziehl-Neelsen (ZN), and re-checked by laboratory technician. All sputum smears have been stored consecutively by the smear number in special boxes.

5.1.2 Culture examination

Sputum specimens were homogenized and decontaminated by modified Petroff's method, and treated with 4% NaOH. Each processed specimen was inoculated in 2 tubes with 2% Ogawa medium, and cultured at 36±1˚C. Culture results were interpreted according to the WHO recommendations shown below.

Results and interpretation

Culture test results are positive if the growth of colonies is observed on media. The grading is done as follows:

- Negative**:** No bacterial growth
- Scanty: 1–9 colonies grown (the exact number of colonies should be written)
- Positive 1+ : 10–100 colonies
- Positive 2+ :100–200 colonies
- Positive 3+ : more than 200 colonies or bacterial lawn
- Contaminated – both specimens are contaminated

In case of contamination test results were recorded, culture materials were destroyed immediately, and specimens were obtained anew if necessary. Culture results were checked weekly starting from day 21. If there was no growth at the end of week 8, a negative result was reported.

Positive cultures are stored on media containing 15% glycerol (Middle brook 7H9) at

–70 ˚C in accordance with bio-safety rules of procedures at NTRL of NCCD.

5.1.3 Identification of *M. tuberculosis* Complex

The phenotypic identification of mycobacteria was based on comparison of colony morphology and growth temperature. Other identification tests included biochemical and immunno-chromatographic tests.

Niacin test

Cord formation in AFB was used for the initial culture identification. Niacin test is a biochemical test of identification of *M. tuberculosis* complex. Strip tests were used on new cultures with more than 50 colonies grown in solid media for 21–28 days.

Results and interpretation

The specimen was read as negative in case of no coloration, positive – if yellow color was produced, and invalid – if other colors were produced. (SOP-NTRL-T-14 Standard Operating Procedures).

Identification of M. tuberculosis in PNB-containing medium

Pure culture was used for this test in order to prevent false results.

Results and interpretation

- Intensive growth in the presence of PNB and in control medium without PNB indicates the presence of MOTT.
- Growth in the control medium with scanty or no growth in the presence of PNB indicates the presence of M. Tuberculosis complex.
- No growth in both control and PNB-containing medium indicates invalid test, and the test should be repeated (SOP-NTRL-T-14 Standard Operating Procedures)

Identification with Capillia-TB assay

This immuno-chromatographic test was performed on pure cultures grown in solid media for 21–28 days.

Results and interpretation

If a line was observed only on the control reading area the specimen was interpreted to be negative. If a line was observed both on the test and control reading areas the specimen was interpreted to be positive for *M. tuberculosis* complex. An invalid result was obtained if no line was observed. (SOP-NTRL-T-15 Standard Operating Procedures).

Identification of MOTT with molecular biological tests

In case MOTT was identified Genotype Mycobacterium CM (HAIN LifeScience, GmbH, Germany) was used. This is a test system for genetic identification of M. tuberculosis complex and 24 of the most common MOTT species from cultivated samples. If the Genotype Mycobacterium CM findings indicate the presence of other TB species Genotype Mycobacterium AS test was performed.

Results and interpretation

M. fortuitum: *Mycobacterium fortuitum*, *M. abscessus*: *Mycobacterium abscessus*, *M. chelonae*: *Mycobacterium chelonae*, *M. intracellulare*: *Mycobacterium intracellulare*, *M. avium*:

Mycobacterium avium, *M. kansasii*: *Mycobacterium kansasii*, *M. flavescens*: *Mycobacterium flavescens*, *M. gordonae*: *Mycobacterium gordonae*, *M. haemophilum*: *Mycobacterium haemophilum*, *M. simiae*: *Mycobacterium simiae*, *M. intermedium*: *Mycobacterium intermedium*, *M. malmoense*: *Mycobacterium malmoense*, *M. interjectum*: *Mycobacterium interjectum*, *M. tuberculosis* complex: *Mycobacterium tuberculosis* complex, other mycobacterium species, *M. paratuberculosis*, *M. gastri*, *M. genavense*, *M. heckeshornense*, *M. lentiflavum*, *M. marinum*, *M. mucogenicum*, *M. nebraskense*, *M. neoaurum*, *M. nonchromogenicum*, *M. paraffinicum*, *M. peregrinum M. septicum*, *M. sphagni*, *M. szulgai*, *M. scrofulaceum*, *M. triplex*, *M. ulcerans*, *M. xenopi*.

5.1.4 Drug Susceptibility Testing

DST was performed only at the NTRL using mature culture grown for 28 days or continuous culture added to fresh medium within 1–2 weeks prior to testing.

5.1.5 DST on Solid Media

DST results were assessed after 3–4 weeks of cultivation in case more than 100 colonies had grown in drug-free medium diluted to10^{-2}, and more than 50 colonies in medium diluted to 10^{-4}. No growth at week 6 indicated drug susceptibility. Drug concentration was 0.2 μg for isoniazid, 40 μg for rifampicin, 2.0 μg for ethambutol and 4.0 μg for streptomycin.

Results and interpretation

Test results were interpreted as resistant or sensitive to each specific drug. Number of colonies on drug-free medium was counted, and if the growth on drug-containing medium was less than 1% of the count the case was reported as "susceptible". If the growth on drug-containing medium was more than 1% of the count the case was reported as "resistant".

5.1.6 Second Line DST on Solid Media

Second-line DST on solid media was performed if resistance to Rifampicin was detected. DST results were assessed after 3–4 weeks of cultivation in case more than 100 colonies had grown in drug-free medium diluted to 10^{-2}, and more than 50 colonies in medium diluted to 10^{-4}. No growth at week 6 indicated drug susceptibility. Drug concentration was 40 μg for amikacin, 40 μg for capreomycin, 30 μg for kanamycin and 2.0 μg for ofloxacin.

Results and interpretation

Test results were interpreted as resistant or sensitive to each specific drug. Number of colonies on drug-free medium was counted, and if the growth on drug-containing medium was less than 1% of the count the case was reported as "susceptible". If the growth on drug-containing medium was more than 1% of the count the case was reported as "resistant".

5.1.7 Molecular Genetic Methods for First Line DST

Molecular line probe assay using MTBDRplus test kit (HAIN LifeScience, GmbH, Germany) allow for rapid detection of resistance to isoniazid and rifampicin (MDR-TB) in patient specimens and culture isolates.

Evaluation of the test results was done using the manufacturer's interpretation chart. The test was performed in accordance with standard operating procedures (SOP-NTRL-T-16). The test was performed on smear positive cases.

Results and interpretation

Test results shall be interpreted as resistant or susceptible to isoniazid and rifampicin, or invalid.

The test will be performed on sputum samples prior to inoculation on culture medium. If MDR-TB or rifampicin resistance is detected in sputum samples from anew case, additional sputum specimen should be collected and re-tested. The final decision is made based on the results of the second test, and both specimens should be cultured and tested for drug resistance.

5.1.8 Molecular Genetic Methods for Second Line DST

Molecular line probe assay using **MTBDR*sl*** test kit (HAIN LifeScience, GmbH, Germany) allows for rapid detection of resistance to fluoroquinolones and/or SLIs (XDR-TB) in specimens and culture isolates from patients with rifampicin resistance. Evaluation of the test results was done using the manufacturer's interpretation chart. The test was performed in accordance with standard operating procedures (SOP-NTRL-T-16).

Results and interpretation

Test results shall be interpreted as resistant or susceptible to fluoroquinolones and/or SLIs, or invalid.

Feedback of laboratory test results

NTRL of NCCD prepared monthly and annual reports of sputum specimen quality, contamination, and smear and culture testing, and delivered the reports to the survey data manager on a regular basis.

5.2 Laboratory Infection Control Procedures

Laboratory safety and infection control regimen was strictly followed.

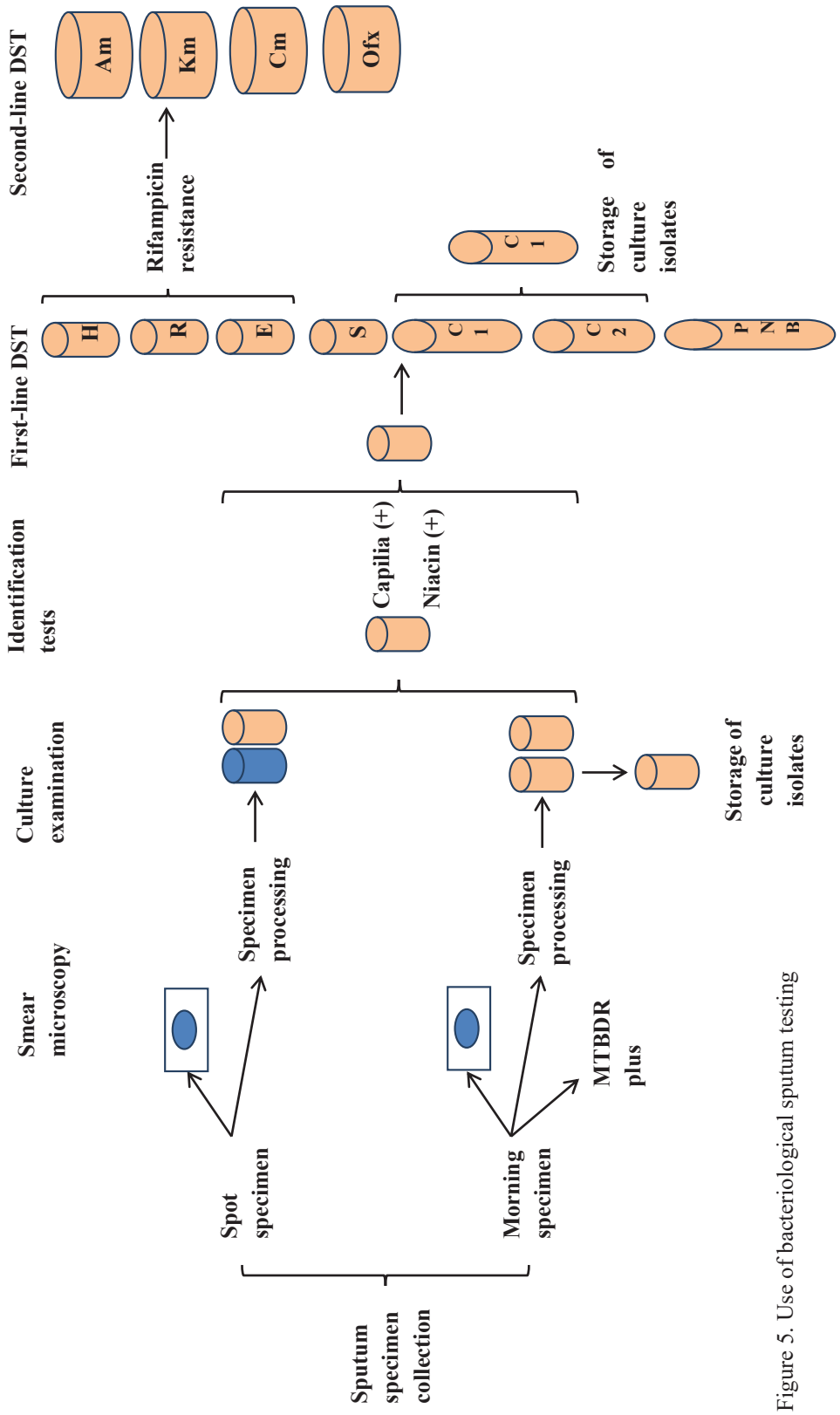

Figure 5. Use of bacteriological sputum testing

Figure 2. Use of bacteriological examination

CHAPTER VI. DATA MANAGEMENT AND ANALYSIS

6.1 Data Management

All survey documents were received by data manager for processing and entry (Figure 3). Survey questionnaires and bacteriological testing forms were double-entered for enhancing data quality. Data analysis was completed using STATA13/SE software. TB doctors and specialists were trained on the importance of checking the completeness of the survey questionnaires and bacteriological testing forms in order to ensure comprehensive data was available for the analysis.

Smear positive case, which consented to participate in the survey was registered in the Survey Participants Registry (Form 2).

Use of barcoding

Each participant was assigned a unique identification number, which was recorded on a barcode. First three digits of the barcode corresponded to TB unit, and last three digits – to a participant number. Barcodes were printed prior to data collection on a special sticker paper and distributed to the TB units. Fifteen barcodes per participant were printed and used on all survey forms, specimen containers and plastic bags.

In order to ensure confidentiality participant name was recorded only on "Informed Consent Form" (Form 1) and "Survey Participants Registry" (Form 2). No name was recorded on other forms.

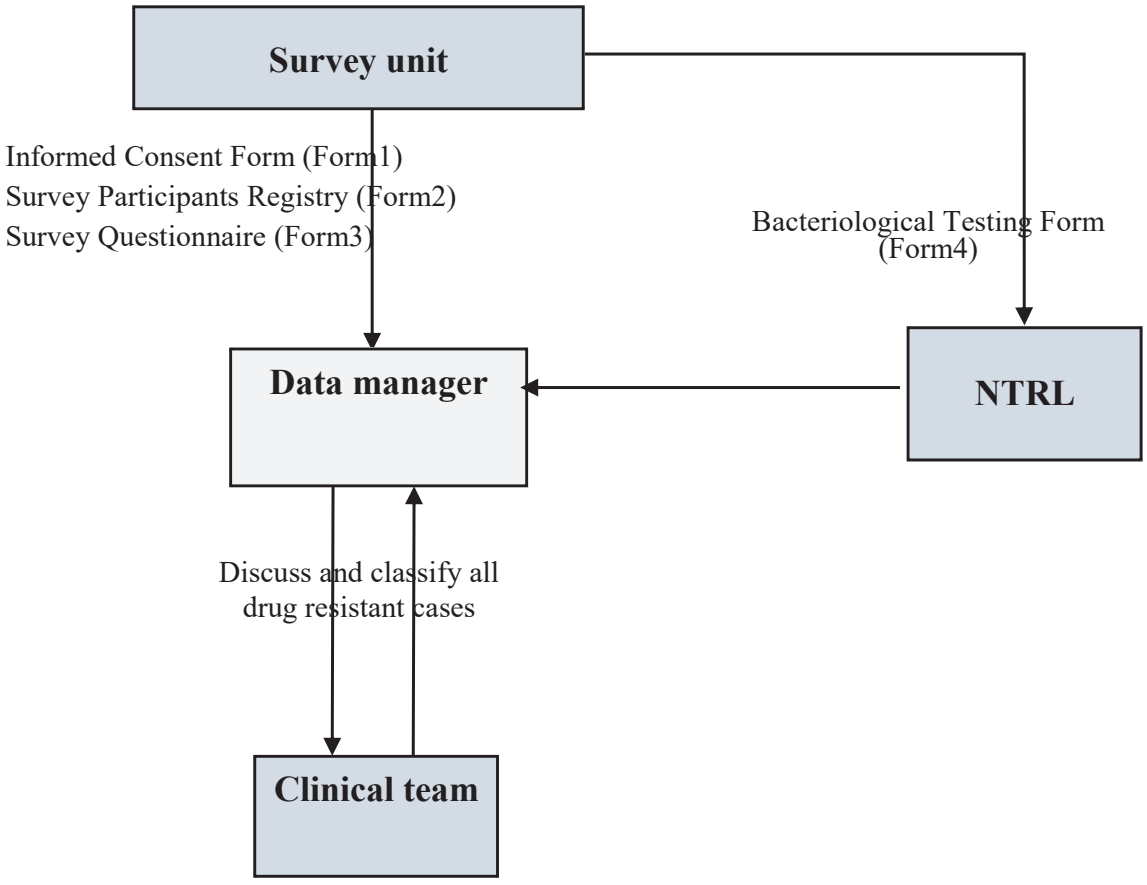

Figure* 3. *Survey data flow

6.2 Database Management

Database was developed using MS Access software after data collection tools (forms) were finalized.

The database consisted of the following parts:

1. Survey questionnaire
2. Bacteriological testing form
3. Participant registry
4. Drug resistant TB case registry (casebook)

Data manager prepared a list of cases with drug-resistant TB, and filed it separately.

6.3 Data Collection and Storage

Provincial and district TB coordinators (trained doctors and specialists) were responsible for data management at their TB units and ensured timely and safe transfer of data to NCCD. They also oversaw the quality and completeness of the survey forms.

Data manager was responsible for receiving all survey forms and checking their number against the number of specimens received. Data manager was also responsible for filing and preparing the survey forms for entry into the database.

6.4 Information Security

Originals of completed survey questionnaires, consent forms, participant registries and bacteriological testing forms have been securely stored in a locked room at the TSRU of NCCD. Database has been backed-up every week and prior to making any changes (such as double entry or data editing).

6.5 Data Analysis and Reporting

Data manager monitored the notification of drug resistant TB cases and their management on a weekly basis. The survey data analysis and preliminary report writing were completed within 8 months after reaching the target sample size and completing sputum specimen collection.

Descriptive analysis of the general characteristics of the survey participants such as age, gender, place of residence, socio-economic characteristics and selected risk factors have been performed.

The following analyses were carried out in accordance with the survey objectives:

- Resistance to first-line anti-TB drugs among new TB cases according to individual drugs as well as their combinations.
- Resistance to first-line anti-TB drugs among retreatment TB cases according to individual drugs as well as their combinations.
- Proportion of MDR-TB cases among new TB cases.
- Proportion of MDR-TB cases among retreatment TB cases.
- Proportion of cases resistant to fluoroquinolones and SLIs among TB cases resistant to rifampicin.
- Associations between MDR-TB and selected risk factors.
- Findings of the survey were compared to the findings of the previous national drug resistance surveys as well as similar studies in other countries.

Multiple imputation of missing values was performed to calculate proportions of patients with drug resistance. Proportions of DR-TB cases were calculated as a point estimate with 95% confidence interval (95%CI). Associations between categorical variables were assessed using Pearson's chi square test when the distribution of variables was normal. P-value less than 0.05 indicated statistically significant difference. Associations between MDR-TB and selected risk factors were assessed using uni- and multivariate regression analyses.

Data analysis was performed using STATA 13/SE software (Stata Corp, College Station, Texas, US).

6.5 Dissemination of Survey Findings

A seminar to discuss preliminary findings of the survey was organized 6 months after reaching the target sample size and completing sputum specimen collection. Detailed survey findings will be disseminated at national consultative meetings and research gatherings for comments and suggestions regarding further analysis.

Official survey report will be disseminated at national and international research conferences. The survey findings will be published in national and international journals.

6.6 Data Collection Forms

The following data collection forms were designed specifically for the survey purposes:

Table 13. Survey data collection forms

Form	Content	User
Form 1 – Informed Consent Form	Patient name, address, telephone number, researcher's name and signature	Trained doctor at TB unit
Form 2 – Survey Participants' Registry	Survey participant's name, age, gender, civil registration number, address, specimen submission date, smear results, patients classification, barcode	Trained doctor at TB unit
Form 3 – Survey Questionnaire	Barcode, demographic information, symptoms, history of the past and current disease, risk factors	Trained doctor or nurse at TB unit
Form 4 – Bacteriological Testing Form	Name of TB unit sending the specimen, participant's barcode, civil registration number, specimen quality, specimen submission date, NTRL number, date of specimen receipt, smear results, MTBDR plus results, culture results, identification test results, results of DST in solid media, MTBDR*sl* results	Lab technician at TB unit Lab technician receiving specimens Lab doctor or technician performing test
Form 5 – Laboratory Log Book	Lab number, date of specimen receipt, barcode, smear results, culture results, identification test results, DST cultivation date, results of MTBDR*plus* and MTBDR*sl*, results of DST for HRES and second-line drugs, dates of lab results, notes	Lab doctor or technician at NTRL
Form 6 – Informed Consent Form (for FGD)	FGD participant name, signature, facilitator's name, telephone number	FGD facilitator

CHAPTER VII. CASE MANAGEMENT

7.1 Case Registration and Reporting

New and retreatment smear positive TB cases were registered by local TB units using "TB Patient Registration Form TB-1". The patient was provided with information about the survey, consent for participation in the survey shall be sought, and consenting patients shall be registered in the Survey Participants' Registry.

Previous TB treatment history of every survey participant was checked in the integrated database of TSRD of NCCD, tubis.mn electronic registry, TB dispensary registry and other relevant information sources. Notes regarding previous TB treatment history were made on the questionnaire and testing form, and sent to NTRL together with sputum specimen.

MDR-TB doctor of TSRD re-checked the participant's previous TB treatment history in the integrated database of TSRD, and made relevant notes in a log-book.

Smear and MTBDR*plus* test results performed at NTRL were reported to data manager as soon as the results became available.

If in a patient with negative smear result, and negative or contaminated culture result smear testing at Month 2 after the start of the treatment was positive, then DST was performed, but such a case was not included in the survey. Laboratory test results were noted on Bacteriological Testing Forms and sent back to TB units by mail or with a person delivering next batch of specimens from the field.

TB unit doctor, who received test results was responsible for registering drug-resistant cases in "Drug-resistant TB Patient Registration Form DR-TB-03", and excluded such cases from "TB Patient Registration Form TB-1". Cases with confirmed DR-TB were reported quarterly to TSRU using reporting forms approved by the Order of Health Minister No. 450.

7.2 Treatment

Drug sensitive TB cases were treated according to treatment guidelines for drug susceptible TB. Confirmed DR-TB cases TB cases were treated according to treatment guidelines for DR-TB. Case reports of DR-TB patients together with necessary laboratory test results were discussed by medical consilium, and treatment started within 14 days. Treatment side effects were managed in compliance with the treatment instructions approved by the Order of Health Minister № 319.

7.3 Treatment Outcome Monitoring

Treatment progress and outcomes were regularly discussed and monitored by DR-TB medical consilium.

CHAPTER VIII. SURVEY LOGISTICS

8.1 Technical Working Group

A Technical Working Group (TWG) responsible for providing technical guidance for the conduct of the National DRS was established by the Order of the Minister of Health.

TWG was comprised of representative of MOH, NCCD, Program Coordination Unit (PCU) of the Global Fund Supported Projects and USDS. TWG was responsible for developing the survey protocol, submitting the protocol to the NCCD Research Committee and Medical Ethics Committee of MOH for approval, conducting trainings and providing technical assistance to TB units in survey conduct.

8.2 Roles and Responsibilties of the Survey Collaborators

National Center for Communicable Diseases

- Coordinate daily activities of the survey
- Ensure the availability of necessary laboratory supplies and equipment for the survey
- Develop the survey protocol and methods, seek technical input of the WHO experts, submit the protocol to TWG, and conduct the survey in accordance with international standards
- Submit the protocol to the Medical Ethics Committee of MOH for approval, and submit the survey report at the end of the survey
- Develop training programs and manuals, and conduct trainings for researchers
- Collaborate with WHO and other international consultants and facilitate the implementation of their recommendations
- Liaise with relevant local officials at TB units (prior to and during the course of the survey conduct) to ensure smooth conduct of the survey
- Develop a detailed survey plan, submit the plan to MOH for approval, and provide technical assistance for the survey conduct
- Improve data collection tools and survey procedures based on pilot testing of the survey protocol, and plan the timing of the survey commencement
- Supervise the survey data collection in TB units, and provide necessary technical support and guidance
- Review and compile survey data and reports on a daily basis
- Resolve any issues arising during the survey preparation or the course of the survey
- Data entry, cleaning, storage, analysis, report writing, and dissemination of the survey results

Aimag/Capital City Departments of Health, District Health Centers

- Coordinate the survey activities in the catchment area
- Ensure full participation of the local target population in the survey
- Comply with the survey protocol and SOPs
- Ensure timely transportation of sputum specimens collected in accordance with the survey protocol to NTRL of NCCD

Global Fund Supported Project

Funding:

- Procure and supply necessary laboratory supplies, test kits and equipment for the survey based on NTRL requests
- Provide in a timely manner necessary funding based on requests from the NCCD survey team
- Provide budget for External Quality Assurance (EQA)

Monitoring and evaluation

- Conduct monitoring visits to the survey units
- Monitor and evaluate the operations of the NCCD survey team
- Cover monitoring and evaluation costs

Other:

- Participate in TWG meetings and provide support in implementing its decisions
- Collaborate with WHO consultants and provide support in implementing their recommendations

World Health Organization

Technical support was provided in the following areas

- Development of the survey protocol
- Laboratory performance of bacteriological testing
- EQA of DST
- Data management, analysis and processing
- Participation in international conferences
- Dissemination of the survey findings
- Publication of the survey results

Funding:

- Development and editing of the survey protocol

Other:

- Participate in TWG meetings and provide support in implementing its decisions
- Collaborate with WHO consultants and provide support in implementing their recommendations

8.3 Roles and Responsibilities of the Survey Team Members

Table 14. Affiliations, roles and responsibilities of the survey team members

Position	Roles and responsibilities
Head of TSRU and NTP Manager, NCCD	• Oversee the survey logistics • Review weekly survey reports and monitor the survey performance • Resolve issues related to the survey arrangement, human resources, funding and other aspects
Head of Examination and Supervision Department, TSRU, NCCD	• Balance the workload of the researchers • Ensure participation of researchers in trainings • Provide supportive supervision and technical support to provincial and district TB units, Hospital at Prison Camp № 429 and "Enerel" hospital • Organize medical consilium to discuss treatment regimens for DR-TB patients diagnosed within the framework of the survey • Provide technical support in supervising the treatment of DR-TB patients • Assess and report treatment outcomes of DR-TB patients • Present information on case management of diagnosed patients at Monday TSRU meetings
Head of NTRL, TSRU, NCCD	• Order, receive and ensure the availability of laboratory supplies and equipment for the survey • Provide TB laboratories in provinces, districts, Hospital at Prison Camp № 429 and "Enerel" hospital with necessary supplies • Train laboratory staff for the survey • Develop laboratory procedures part of the survey protocol and data collection tools • Collaborate with WHO consultants and implement their recommendations • Check and receive specimens from TB units (quantity, integrity, cold chain regimen, supporting documents) • Perform smear, LPA and culture testing • Perform DST • Ensure compliance with laboratory infection control measures • Complete laboratory testing forms and submit them to the survey data manager on a daily basis • Develop training program for the survey researchers and facilitate trainings • Participate in external and internal laboratory quality assurance programs • Participate in data analysis and report writing • Produce and submit to the survey coordinator monthly and quarterly activity reports

Position	Roles and responsibilities
Survey coordinator, TSRU, NCCD	• Coordinate daily survey logistics • Develop the survey protocol • Organize TWG meetings • Submit the survey methodology to the NCCD Research Committee for review and approval • Submit the survey methodology to the MOH Medical Ethics Committee for review and approval • Collaborate with WHO consultants • Develop training program for the survey researchers and conduct trainings • Facilitate trainings for the survey researchers • Develop data collection plan • Develop terms of reference and budget estimations for the survey activities • Produce and submit to relevant agencies monthly, quarterly and annual activity reports • Ensure timely reporting of any issues that arise during the course of the survey to the management and collaborators • Participate in data analysis and report writing
Principal investigator	• Edit the survey protocol • Participate in TWG meetings • Assist in the submission of the survey methodology to the NCCD Research Committee for review and approval • Assist in the submission of the survey methodology to the MOH Medical Ethics Committee for review and approval • Collaborate with WHO consultants • Facilitate trainings for the survey researchers • Serve as a member of the survey clinical team • Assist in resolving any issues that arise during the course of the survey • Participate in data analysis and report writing

Position	Roles and responsibilities
Data manager, epidemiologist of TSRU, NCCD	• Develop the survey protocol and data collection tools • Collaborate with WHO consultants • Prepare data entry templates for the survey questionnaire and laboratory results • Develop an integrated survey database • Enter survey questionnaires and laboratory test results (smear, LPA culture, identification, etc.) on a daily basis • Develop an integrated case book and maintain it on a daily basis • Receive test results from NTRL on a daily basis, enter the results into an integrated database, and report to an officer in charge of MDR-TB of TSRU • Ensure the validity of double entered data • Oversee data storage procedures • Check data for accuracy, identify and rectify system errors, and produce data management reports on a regular basis • Develop SOPs in accordance with the survey protocol • Develop training program for the survey researchers and facilitate trainings • Lead data analysis and report writing • Develop and print barcodes to be used in the survey • Produce and submit to the survey coordinator monthly, quarterly and annual activity reports
Officer in charge of specimen transportation sub-project, TSRU, NCCD	• Serve as a survey assistant • Participate in the development of the survey protocol • Receive sputum specimens delivered by local TB unit officers and check the following documents for completeness: ✓ Informed consent form ✓ Questionnaire ✓ Proof of sputum specimen transportation costs • Reimburse specimen transportation costs to local TB units on a monthly basis, and submit financial reports to PCU of the Global Fund Supported Projects • Check questionnaires from the field for completeness and hand them over to data manager • Deliver laboratory test results to provincial and district TB coordinators, and TB doctors of Hospital at Prison Camp № 429 and "Enerel" Hospital • Archive completed survey questionnaires, informed consent forms and other related materials • Produce financial reports of the survey activities and submit them to relevant authorities • Produce and submit to the survey coordinator monthly, quarterly and annual activity reports • Keep TWG meeting minutes

Position	Roles and responsibilities
Officer in charge of MDR-TB, TSRU, NCCD	• Develop chapter on case management of the survey protocol • Maintain an integrated registry of DR-TB cases identified within the framework of the survey • Provide within 2 days reports about detected DR-TB cases to provincial and district TB coordinators, TB doctor of "Enerel" Hospital and Deputy Director in Charge of Medical Services of Hospital at Prison Camp № 429 electronically and by the phone • Ensure detected DR-TB cases are discussed by medical consilium within 2 weeks • Commence treatment of DR-TB cases based on the medical consilium decision • Regularly monitor intensive and continuation phases of TB treatment • Monitor the management of treatment side effects, and provide technical support to local doctors • Assess treatment outcomes of DR-TB cases identified within the framework of the survey, and write and disseminate assessment reports • Produce and submit to the survey coordinator monthly, quarterly and annual activity reports
TB pharmacologist, Pharmacology Department of NCCD	• Ensure uninterrupted supply of drugs for the treatment of DR-TB cases identified within the framework of the survey • Forecast and ensure uninterrupted supply of drugs for the management of treatment side effects • Produce and submit to the Head of TSRU monthly, quarterly and annual drug stock and supply reports

Position	Roles and responsibilities
Provincial and district TB coordinators Deputy Director in Charge of Medical Services of Hospital at Prison Camp № 429 TB doctor of "Enerel" Hospital	• Detect smear positive TB cases • Collect sputum specimens from new and previously treated smear positive TB cases prior to treatment commencement • Deliver sputum specimens together with reporting forms to NTRL of NCCD within 2 days of collection from districts, and within 3 days from provinces in compliance with cold chain requirements • Inform NTRL of NCCD by phone about dispatch of specimens • Obtain informed consent and completed questionnaires from the survey participants, and dispatch them together with sputum specimens • Check and validate the history of previous TB treatment of the detected cases (via integrated NCCD registry, tubis.mn electronic registry, TB clinic registry etc.) • Solicit laboratory test results of transported specimens from the officer in charge of MDR-TB of TSRU on a weekly basis • Manage cases based on laboratory test results • Submit necessary materials of detected DR-TB cases to medical consilium for discussion and treatment decision • Monitor treatment process in accordance with the guidelines • Assess patient treatment outcomes • Conduct contact tracing and examination • Produce and submit to TSRU monthly, quarterly and annual reports

8.4 Laboratory Supplies and Equipment

Laboratory supplies and equipment for the survey were procured with the funding from the Global Fund Supported Project on AIDS and TB.

8.5 Human Resource Management

The survey was conducted by the staff of TSRU and NTRL of NCCD without recruiting additional human resources.

8.6 Financing

The survey was conducted with the financial support from the Global Fund Supported Project on AIDS and TB, and WHO.

8.7 WHO Technical Support and Collaboration

WHO provided technical assistance in survey protocol development, data analysis, report writing, publishing the survey results and presenting the findings at international conferences.

8.8 Monitoring and Evaluation

Internal and external monitoring and evaluation of the survey was undertaken.

8.8.1 Internal Monitoring and Evaluation

- A team consisting of the representatives of Examination and Supervision Department and NTRL of TSRU, NCCD conducted on-site supportive supervision visits to selected TB units.
- Provincial and district TB coordinators were responsible for daily monitoring of the survey activities at TB units.
- Survey coordinator, data manager and TSRU advisers conducted supportive supervision visits to oversee patient recruitment, questionnaire administration, and specimen collection, storage and transportation in districts and provinces.

8.8.2 External Review (mid-term)

External review of the survey was conducted by experts from WHO and Department of Mycobacterium Reference and Research in RIT/JATA. External review team assessed the survey data management and conducted laboratory EQA.

CHAPTER IX. SURVEY PREPARATORY WORK

9.1 Training of Researchers

Researchers were trained according to pre-approved training program and plan before the survey commencement. Trainings for central survey team researchers were conducted.

TB coordinators, TB doctors and laboratory technicians from 21 provinces, 9 districts, Hospital at Prison Camp № 429 and "Enerel" Hospital were trained in survey methods, patient recruitment procedures, obtaining informed consent, questionnaire administration, specimen collection, storage and transportation, patient treatment, treatment supervision, and other relevant aspects of the survey.

Official letters from the General Director of NCCD soliciting support in conducting the survey will be send to authorized officials in 21 provinces, 9 districts, Hospital at Prison Camp № 429 and "Enerel" Hospital.

Training program for local survey teams and researchers from TSRU of NCCD covered the following topics:

Module A: General introduction of the National Anti-TB Drug Resistance Survey: This module included topics such as rationale for the survey, survey design, methods, and roles and responsibilities of researchers. The module for local teams additionally included information on data collection and management procedures.

Module B: NTRL procedures: This module was designed for training all staff of NTRL, and focused on technical aspects of sputum smear, culture, and identification and HAIN tests. It also included information on management and organization of laboratory operations during the survey; procedures for receiving, storing, processing and testing of specimens; data collection forms; internal and external quality assurance; infection control measures, and reporting of test results. The Head and advisers of NTRL facilitated trainings using this module.

Module C: Procedures at provincial and district TB units: This module was designed for training local TB coordinators, TB doctors and laboratory technicians, and included technical guidance on patient selection, registration, informed consent, questionnaire administration, sputum specimen collection, storage and transportation, feedback of test results, patient treatment, and treatment supervision. It also included information on working arrangements for the survey at provincial / district TB dispensaries, Hospital at Prison Camp № 429 and "Enerel" Hospital.

The survey coordinator, data manager and Head of NTRL facilitated trainings using this module.

Module D: Survey arrangements, coordination and monitoring and evaluation: This module was designed for training the central survey team and clinical team.

This module included information on survey logistics, solutions to common issues and challenges, monitoring and evaluation, reporting requirements, and communication and collaboration between team members.

Module E: Data entry, cleaning, storage and checking: This module was designed for training staff responsible for data management and data entry operators, and included topics such as data management logistics, data validation, entry and storage. The training was organized as hands-on session using the survey databases, and was facilitated by the survey data manager.

Module F: Survey registration, ethical aspects, questionnaire administration: This module was designed for training all researchers, and was intended to improve researchers' skills to abide by

ethical norms, to administer questionnaire and to recruit survey participants. The training included lectures and workshop sessions, and was facilitated by the survey coordinator and data manager.

Module H: Specimen collection, storage and transportation: This module was designed for training staff responsible for specimen collection, and included information on specimen collection techniques, specimen packaging, labeling, registration, storage and transportation, cold chain regimen, infection control measures, and procedures for handing-over the specimens to NTRL staff. It also included information on on-site quality control. The training was facilitated by the Head of NTRL and officer in charge of specimen transportation sub-project.

CHAPTER X. QUALITY CONTROL

10.1 Internal Laboratory Quality Control

10.1.1 Quality Control of Smear Microscopy

- *Daily control:* To check the quality of dye prepared in-house, one sputum smear of known high AFB positivity (2+) or positive control, and two smears of known AFB negativity or negative control were stained.
- *Checking the quality of a new batch of stain:* Every new batch of stain was checked by staining two positive (2+) and two negative controls.
- All smears were stored in special boxes and clearly marked. Positive smears were read by a second technician.
- "Blinded quality control method" was used for internal quality control. Laboratory technician stored the survey sputum smears in the order of identification numbers in special boxes. Identification numbers of damaged smears have been recorded.
- *Sampling of smears for quality control:* All positive smears and 10% of negative smears were randomly chosen for blinded cross re-checking. The analyst re-checked the smears without knowing the initial test results. In case of discrepancy an external analyst read the slides. Quality of laboratory testing was assessed using positive percent agreement, negative percent agreement, and false positive and false negative rates. Errors were classified as minor or major.

10.1.2 Quality Control of Culture Medium

- The quality of culture medium was checked after coagulating and cooling down the medium. The medium should not have excess water and should not change its color. The color changed if coagulated at excessively high temperature. Formation of holes and bubbles on the surface of the medium was an indication of poor coagulation. Low coagulator temperature easily damages and liquefies the medium.
- In order to check the sterility, samples of culture medium were incubated at 35–37°C for 24–48 hours. If there was no growth on the medium it was considered sterile.

10.1.3 Niacin Test

- Strip tests were checked for expiry date, storage conditions and proper labeling.
- Previously isolated *M. tuberculosis* species were used as a positive control, and *M. terrae* standard species or distilled water – as a negative control.

10.1.4 Internal Quality Control of DST

- Drug-containing medium was checked using H37Rv standard culture.
- Checking the purity of culture: culture colonies in solid medium were checked.

10.1.5 Internal Quality Control of Molecular Genetic Methods for DST

- New batches of test kits were checked using H37Rv standard culture.
- Distilled water was used as a negative control.

10.2 External Quality Assurance

External quality assessment was performed by Supra-national reference laboratory/RIT (Japan), which has been involved in external quality assessment of NTRL of NCCD since 2006.

- Supra-national reference laboratory/RIT (Japan) sent 2015 proficiency tests to NTRL of NCCD. The NTRL completed proficiency tests, and sent them back to RIT, which assessed the NTRL performance and reported the results in writing. The performance of the NTRL of NCCD was assessed based on sensitivity and specificity of proficiency tests for Isoniazid, Rifampicin and second-line TB drugs
- Laboratory expert from Mycobacterial Laboratory of RIT (Japan) undertook external quality assessment once during the survey.
- At the end of the survey the NTRL isolated DNA from all rifampicin resistant *M. tuberculosis* species and 5% of strains susceptible to all first-line drugs, and sent to the Department of Mycoabcterium Reference and Research of RIT (Japan) for identification of mutations conferring drug resistance.
- Supra-national reference laboratory/RIT (Japan) conducted laboratory tests, compared the results with the NTRL results, and submitted test results and official reports to the NTRL of NCCD.

EQA for DST

Proficiency test: Supra-national reference laboratory/RIT (Japan) sent 2015 proficiency tests to NTRL of NCCD. Conventional DST on solid media was performed to identify resistance to isoniazid, rifampicin, ethambutol, streptomycin, kanamycin, amikacin, capreomycin and ofloxacin, and molecular biologic tests were performed to identify genetic mutations conferring resistance to first- and second-line drugs. There were no false positive or false negative results, and the testing sensitivity and specificity were 100% or satisfactory. However, sensitivity of proficiency test was 92% for streptomycin and 63% for ethambutol, and specificity for these two drugs was 100%.

Table 15. External proficiency testing results, 2015

	H 0.2 **µg**/ml	R 40 **µg**/ml	S 4 **µg**/ml	E 2 **µg**/ml	KM 30 **µg**/ml	AM 30 **µg**/ml	CM 30 **µg**/ml	OFL 30 **µg**/ml
Resistant	19	19	11	10	9	9	9	10
False resistant	0	0	0	0	0	0	0	0
Susceptible	6	6	13	9	16	16	16	15
False susceptible	0	0	1	6	0	0	0	0
Total	**25**	**25**	**25**	**25**	**25**	**25**	**25**	**25**
Sensitivity	100%	100%	92%	63%	100%	100%	100%	100%
Specificity	100%	100%	100%	100.0%	100%	100%	100%	100%
Predictive value of resistance	100%	100%	100%	100.0%	100%	100%	100%	100%
Predictive value of susceptibility	100%	100%	93%	60.0%	100%	100%	100%	100%
Effectiveness	100%	100%	96%	76.0%	100%	100%	100%	100%
Kappa coefficient	1.000	1.000	0.920	0.545	1.000	1.000	1.000	1.000

Validation: NTRL has isolated genomic DNA from 110 Rifampicin-resistant strains and 50 strains susceptible to all first-line drugs, and sent them to Supra-national reference laboratory/ RIT (Japan) for validation through the identification of gene mutations conferring drug resistance. Agreement was also very good when another validation method was used.

Rifampicin: Agreement of rifampicin resistance and susceptibility between NTRL of NCCD and Supra-national reference laboratory/RIT (Japan) was 100%, and no false resistant or false susceptible results were obtained.

Drug: Rifampicin

		NTRL of NCCD		Sensitivity	100%
		Resistant	Susceptible	Specificity	100%
RIT/JATA	Resistant	38	0	Predictive value of resistance	100%
	Susceptible	0	50	Predictive value of susceptibility	100%
Total		**38**	**50**	Effectiveness	100%
				kappa coefficient	100%

Isoniazid: Agreement of rifampicin resistance between NTRL of NCCD and Supra-national reference laboratory/RIT (Japan) was 100%. C–15T gene mutation conferring isoniazid resistance was identified by Supra-national reference laboratory/RIT (Japan) in one strain identified by NTRL of NCCD as susceptible to isoniazid. Therefore, test specificity was 97% and specificity was 100%.

Drug: Isoniazid

		NTRL of NCCD		Sensitivity	97%
		Resistant	Susceptible	Specificity	100%
RIT/JATA	Resistant	38	1	Predictive value of resistance	100%
	Susceptible	0	49	Predictive value of susceptibility	99%
Total		**38**	**50**	Effectiveness	99%
				kappa coefficient	98%

CHAPTER XI. FINDINGS

11.1. Survey Summary

The survey data was collected during 12-month period between Feb 01, 2016 and Jan 31, 2017. During the data collection period 1664 sputum smear-positive PTB cases were detected in aimags, districts, Prison Hospital and "Enerel" Hospital, of whom 1321 cases were new. A total of 1560 (93.8%) cases consented to participate in the survey and re-submitted sputum specimen. Of the consented cases, 1223 (or 92.6% of all new cases) were new TB cases, and 337 (or 98.3% of all retreatment cases) were retreatment TB cases.

The survey participation rate was 90.1% in aimags with Bayan-Ulgii aimag having the lowest rate (54.2%). The corresponding rate in Ulaanbaatar City was 96.2% with Nalaikh District (77.8%) and NMHC (0%) having the lowest rate (Table 17). Participation of new cases was 88.1% in aimags and 95.6% in Ulaanbaatar. Nationwide 92.6% of all notified new cases and 98.3% of all notified retreatment cases participated in the survey. Required sample size was estimated at 1037 new cases (without taking into account losses due to specimen quality, storage, transportation and cultivation), and the actual number of new cases submitting sputum specimen for the survey was 1175.

Table 16. Selected demographic characteristics of the survey participants

Characteristics	Total	Participated	Coverage	P-value
Total	**1664**	**1560**	**93.8%**	
Treatment history				<0.001
New	1321	1223	92.6%	
Retreatment	343	337	98.3%	
Age groups				0.205
0-14	18	16	88.9%	
15-24	398	363	91.2%	
25-34	453	431	95.1%	
35-44	286	273	95.5%	
45-54	295	276	93.6%	
55-64	130	121	93.1%	
65+	84	80	95.2%	
Gender				0.747
Male	985	925	93.9%	
Female	679	635	93.5%	
Place of residence				<0.001
Rural	687	619	90.1%	
Urban	928	892	96.1%	
Prison Hospital	27	27	100%	
"Enerel" Hospital	22	22	100%	
Region				0.139
Central	1293	1216	94.0%	
Eastern	152	144	94.7%	
Khangai	158	147	93.0%	
Western	61	53	86.9%	

Table 17. Number of survey participants, by TB dispensaries

TB unit	Notified during the survey period			Participated in the survey			Survey coverage (percent)		
	New	ReTx*	Total	New	ReTx	Total	New	ReTx	Total
Arkhangai	17	2	**19**	15	1	**16**	88.2	50.0	**84.2**
Bayan-Ulgii	11	0	**11**	6	0	**6**	54.5	0.0	**54.5**
Bayankhongor	11	2	**13**	11	2	**13**	100	100	**100**
Bulgan	9	4	**13**	9	4	**13**	100	100	**100**
Gobi-Altai	6	1	**7**	6	1	**7**	100	100	**100**
Gobisumber	12	0	**12**	9	0	**9**	75.0	0.0	**75.0**
Darkhan-Uul	87	25	**112**	51	25	**76**	58.6	100	**67.9**
Dornogobi	27	6	**33**	27	6	**33**	100	100	**100**
Dornod	58	16	**74**	58	16	**74**	100	100	**100**
Dundgobi	9	2	**11**	7	2	**9**	77.8	100	**81.8**
Zavkhan	11	3	**14**	11	3	**14**	100	100	**100**
Orkhon	49	6	**55**	45	6	**51**	91.8	100	**92.7**
Uvurkhangai	10	2	**12**	10	2	**12**	100	100	**100**
Umnugobi	9	2	**11**	9	2	**11**	100	100	**100**
Sukhbaatar	37	6	**43**	30	5	**35**	81.1	83.3	**81.4**
Selenge	66	29	**95**	66	29	**95**	100	100	**100**
Tuv	28	14	**42**	28	14	**42**	100	100	**100**
Uvs	20	3	**23**	16	3	**19**	80.0	100	**82.6**
Khovd	13	3	**16**	11	2	**13**	84.6	66.7	**81.3**
Khuvsgul	30	6	**36**	30	6	**36**	100	100	**100**
Khentii	28	7	**35**	28	7	**35**	100	100	**100**
Aimag total	**548**	**139**	**687**	**483**	**136**	**619**	**88.1**	**97.8**	**90.1**
Baganuur	4	3	**7**	4	3	**7**	100	100	**100**
Bayangol	66	11	**77**	55	11	**66**	83.3	100	**85.7**
Bayanzurkh	176	41	**217**	176	41	**217**	100	100	**100**
Nalaikh	29	7	**36**	23	5	**28**	79.3	71.4	**77.8**
Songinokhairkhan	195	54	**249**	195	54	**249**	100	100	**100**
Sukhbaatar	75	18	**93**	64	17	**81**	85.3	94.4	**87.1**
Khan-Uul	97	21	**118**	93	21	**114**	95.9	100	**96.6**
Chingeltei	98	31	**129**	98	31	**129**	100	100	**100**
Bagakhangai	1	0	**1**	1	0	**1**	100	0.0	**100**
“Enerel” Hospital	13	9	**22**	13	9	**22**	100	100	**100**
NMHC	1	0	**1**	0	0	**0**	0.0	0.0	**0.0**
UB total	**755**	**195**	**950**	**722**	**192**	**914**	**95.6**	**98.5**	**96.2**
Prison Hospital	18	9	**27**	18	9	**27**	100	100	**100**
Grand total	**1321**	**343**	**1664**	**1223**	**337**	**1560**	**92.6**	**98.3**	**93.8**

*ReTx – Retreatment

Although there was no difference in participation by age, gender or region, differences were observed with respect to previous TB treatment history and place of residence (Table 16).

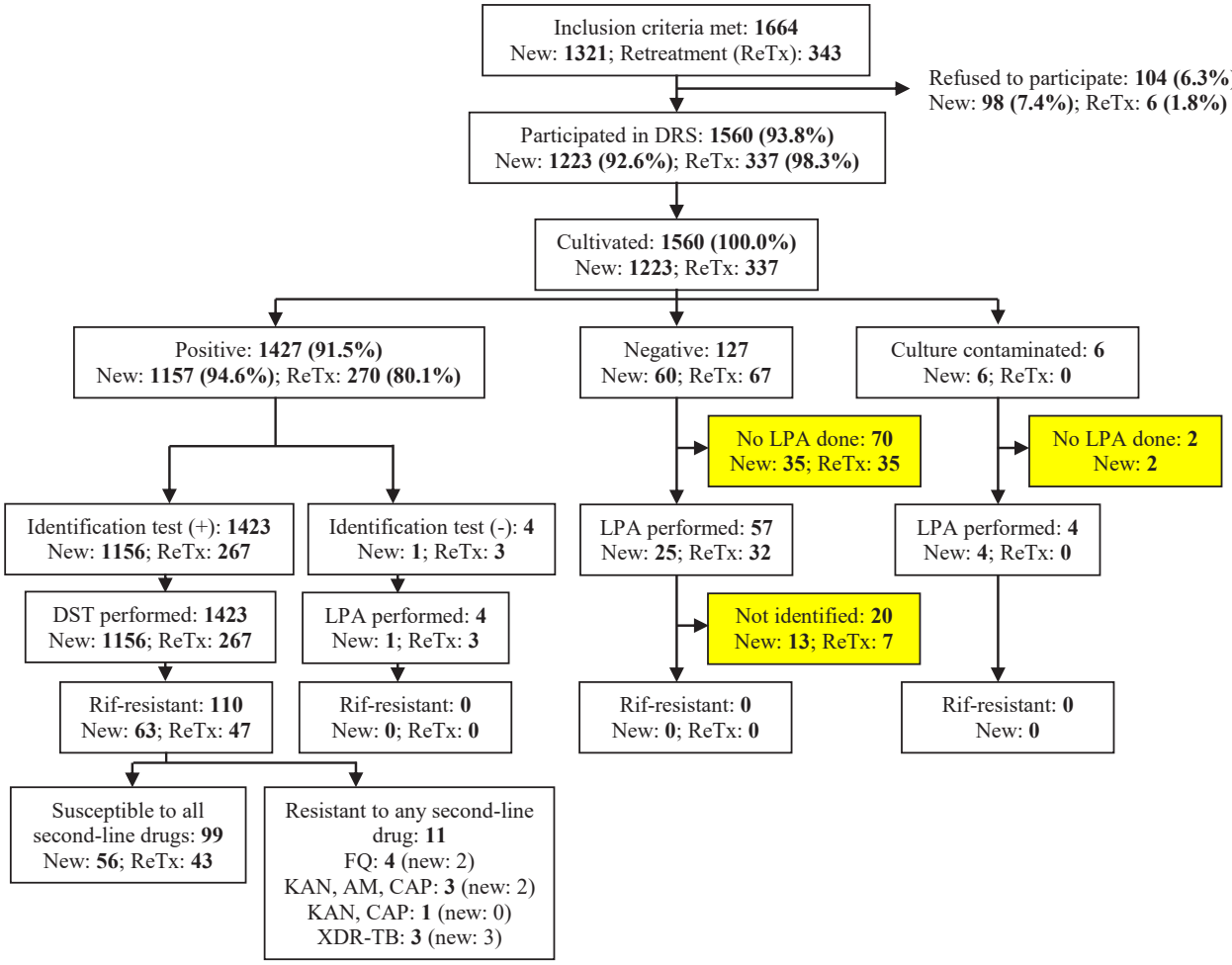

Figure 4. Survey summary

Of 1560 survey participants, 127 (60 new and 67 retreatment) cases had negative culture results. Seventy (35 new and 35 retreatment) cases with negative culture results were excluded from the survey data analysis because no LPA was performed on their sputum specimens. However, LPA was performed on sputum specimens of 57 (25 new and 32 retreatment) cases with negative culture results, and 20 (13 new and 7 retreatment) of them were excluded from data analysis because no MTB was detected (Figure 4).

In total, 90 cases were excluded from the survey, and data analysis was performed on 1470 (1175 new and 295 retreatment) cases. Although culture was contaminated for 6 cases, LPA was performed on 4 of them allowing the detection of Isoniazid and Rifampicin resistance. In other words, first-line DST results were missing for 2 cases with culture contamination.

11.2. General Characteristics of Survey Participants

Demographic and selected social characteristics of the survey participants are shown in Table 18 and Table 19. Average age of the participants was 36.6 ± 14.8 years ranging from 8 to 89 years. New cases (average age 35.5 ± 14.9 years) were younger than retreatment cases (average age 41.0 ± 13.6 years) ($p<0.001$).

Males accounted for slightly more of retreatment cases (68.5%) compared to new cases (57.1%) ($p<0.001$). Overall, 39.3% of the survey participants were from rural areas and 1.6% - from prisons, and there was no difference in place of residence between new and retreatment cases.

Table 18. General profile of the survey participants

Characteristics	New		Retreatment		Total	
	N	%	N	%	N	%
Total	**1175**	**100**	**295**	**100**	**1470**	**100**
Age group						
<15	12	1.0	1	0.3	**13**	**0.9**
15-24	310	26.4	36	12.2	**346**	**23.5**
25-34	342	29.1	69	23.4	**411**	**28.0**
35-44	196	16.7	65	22.0	**261**	**17.8**
45-54	175	14.9	80	27.1	**255**	**17.3**
55-64	82	7.0	31	10.5	**113**	**7.7**
>65	58	4.9	13	4.4	**71**	**4.8**
Gender						
Male	671	57.1	202	68.5	**873**	**59.4**
Female	504	42.9	93	31.5	**597**	**40.6**
Place of residence						
Urban	698	59.4	171	58.0	**869**	**59.1**
Rural	460	39.1	117	39.7	**577**	**39.3**
Prison	17	1.4	7	2.4	**24**	**1.6**
Education						
None	25	2.1	14	4.7	**39**	**2.7**
Primary	83	7.1	18	6.1	**101**	**6.9**
Incomplete secondary	239	20.3	77	26.1	**316**	**21.5**
Completed secondary	496	42.2	122	41.4	**618**	**42.0**
Vocational	67	5.7	15	5.1	**82**	**5.6**
University/college	242	20.6	48	16.3	**290**	**19.7**
Unknown	23	2.0	1	0.3	**24**	**1.6**
Employment status						
Employed	320	27.2	57	19.3	**377**	**25.6**
Unemployed	267	22.7	102	34.6	**369**	**25.1**
School student	58	4.9	2	0.7	**60**	**4.1**
University/college student	124	10.6	13	4.4	**137**	**9.3**
Retired	98	8.3	33	11.2	**131**	**8.9**
Disabled	67	5.7	42	14.2	**109**	**7.4**
Housewife	70	6.0	11	3.7	**81**	**5.5**
Other	164	14.0	32	10.8	**196**	**13.3**
Unknown	7	0.6	3	1.0	**10**	**0.7**

Of the survey participants, 19.7% had university/college education and 42.0% had completed secondary education. Patients with no formal education accounted for 2.1% of new and 4.7% of retreatment TB cases.

Less than a third of both new (27.2%) and retreatment (19.3%) TB cases were employed. Proportion of the disabled was higher among retreatment (14.2%) compared to new (5.7%) cases.

Table 19. General profile of the survey participants (continued)

Characteristics	New		Retreatment		Total	
	N	%	N	%	N	%
Total	**1175**	**100**	**295**	**100**	**1470**	**100**
History of contact with DR-TB						
Yes	50	4.3	20	6.8	**70**	**4.8**
No	1109	94.4	270	91.5	**1379**	**93.8**
Unknown	16	1.4	5	1.7	**21**	**1.4**
Type of housing						
Gher	401	34.1	110	37.3	**511**	**34.8**
House	446	38.0	110	37.3	**556**	**37.8**
Apartment	269	22.9	53	18.0	**322**	**21.9**
Dormitory	41	3.5	11	3.7	**52**	**3.5**
Dwelling not suited for human living	5	0.4	4	1.4	**9**	**0.6**
Other	7	0.6	3	1.0	**10**	**0.7**
Unknown	6	0.5	4	1.4	**10**	**0.7**
Monthly household income						
> 944,153 MNT*	203	17.3	40	13.6	**243**	**16.5**
< 944,153 MNT	897	76.3	219	74.2	**1116**	**75.9**
Unknown	75	6.4	36	12.2	**111**	**7.6**
Smoking						
None	645	54.9	123	41.7	**768**	**52.2**
Quit smoking	104	8.9	30	10.2	**134**	**9.1**
Sometimes	58	4.9	28	9.5	**86**	**5.9**
Daily	363	30.9	112	38.0	**475**	**32.3**
Unknown	5	0.4	2	0.7	**7**	**0.5**
Alcohol consumption						
None	632	53.8	122	41.4	**754**	**51.3**
Once a month or fewer	358	30.5	87	29.5	**445**	**30.3**
2-4 times a year	105	8.9	49	16.6	**154**	**10.5**
2-3 times a week	40	3.4	16	5.4	**56**	**3.8**
More than 4 times a week	32	2.7	19	6.4	**51**	**3.5**
Unknown	8	0.7	2	0.7	**10**	**0.7**

**Source: National Statistical Office, 2016*

History of contact with DR-TB patient was reported by 4.3% of new and 6.8% of retreatment TB cases (p=0.170). The majority of the survey participants lived in gher districts. There was no difference in monthly household income of new vs. retreatment cases (p=0.255). A half of the participants responded they never smoked or used alcohol.

11.3. Main Indicators of Laboratory Microscopy

11.3.1. Sputum Smear Testing

Sputum smear testing was done using fluorescent microscope as per survey protocol. There were 1462 (93.7%) smear-positive and 98 (6.3%) smear-negative cases. Proportion of smear-negative cases was relatively high (14.8%) among patients from prison hospital (Table 20).

Table 20. Smear test results, number of cases

Place of residence	Smear-positive		Smear negative		Total
	N	%	N	%	N
Prison	23	85.2	4	14.8	27
Aimag	564	91.1	55	8.9	619
Ulaanbaatar city	875	95.7	39	4.3	914
Total	**1462**	**93.7**	**98**	**6.3**	**1560**

11.3.2. Culture examination

A total of 3100 specimens were inoculated into two tubes with solid culture media each. There were 1427 (91.5%) were culture positive, 127 (8.1%) – culture negative, and 6 (0.4%) – culture contaminated cases (Table 21). Average cultivation period was 27.1 days for smear-positive and 36.3 days for smear-negative cases.

Table 21. Culture test results, number of cases

Place of residence	Culture positive		Culture negative		Total	
	N	%	N	%	N	%
Prison	24	88.9	3	11.1	27	100
Aimag	553	89.6	64	10.4	619	100
Ulaanbaatar city	850	93.4	60	6.6	914	100
Total	**1427**	**91.5**	**127**	**8.1**	**1560**	**100**

On average, 94.5% of smear-positive cases were also culture-positive. The corresponding positive concordance rate was 96.2% among new and 85.1% among retreatment cases and remained stable for the duration of the survey. Culture contamination rate also remained stable.

Culture contamination rate was 1.2% of inoculated tubes, which was similar to the contamination rate of routine culture testing performed at NTRL. There was no statistically significant difference in culture contamination according to the place of residence (rural, urban, prison) (Figure 5).

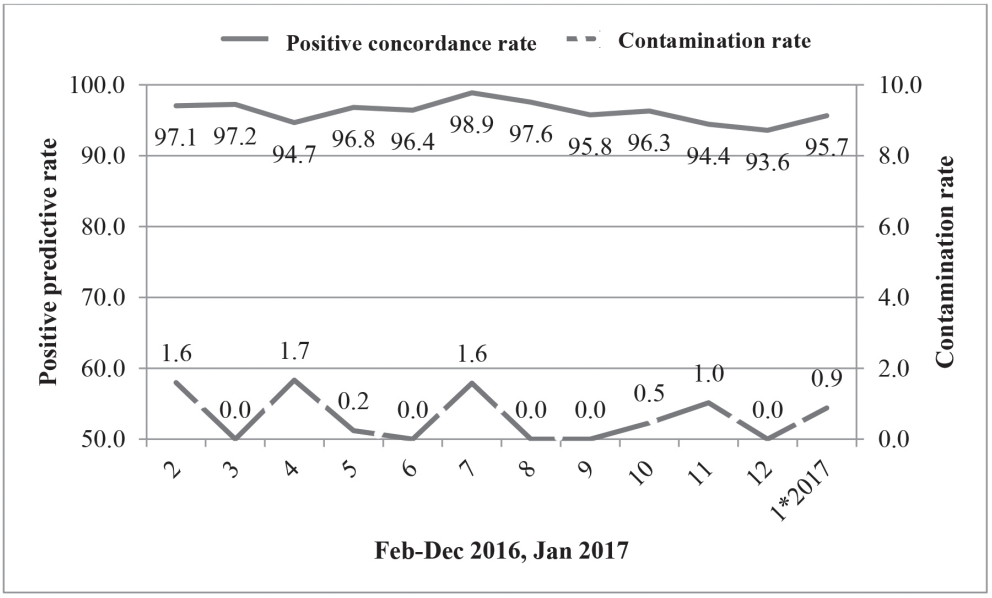

Figure 5. Quality indicators of culture examination, by months

Table 22. Correlation between sputum smear and culture test results

Smear test result	Culture test result						Total
	Negative	**Scanty positive**	**1+**	**2+**	**3+**	**Contaminated**	
Negative	56	29	9	2	0	2	98
Scanty positive	39	22	92	47	12	1	213
1+	30	28	176	303	177	2	716
2+	2	5	36	146	151	1	341
3+	0	4	10	57	121	0	192
Total	**127**	**88**	**323**	**555**	**461**	**6**	**1560**

Of 98 smear-negative cases, 40 (40.8%) were culture-positive. There was a delay in seeking medical care as demonstrated by the fact that highly positive (2+; 3+) culture and smear test results were obtained for 1016 (65.1%) and 533 (34.1%) TB cases, respectively. In other words, PTB cases could be transmitting the infection for quite some time before being diagnosed.

11.3.3 MTB Identification

No MOTT was identified in all isolated 1,427 cultures.

Identification was done using Niacin test on 69.4% (990/1427) and Capillia-TB test on 30.6% (437/1427) of isolated cultures. *M. tuberculosis* complex was identified in 99.7% (1423/1427) of cultures, and 4 cultures were Capillia-TB negative (Figure 6).

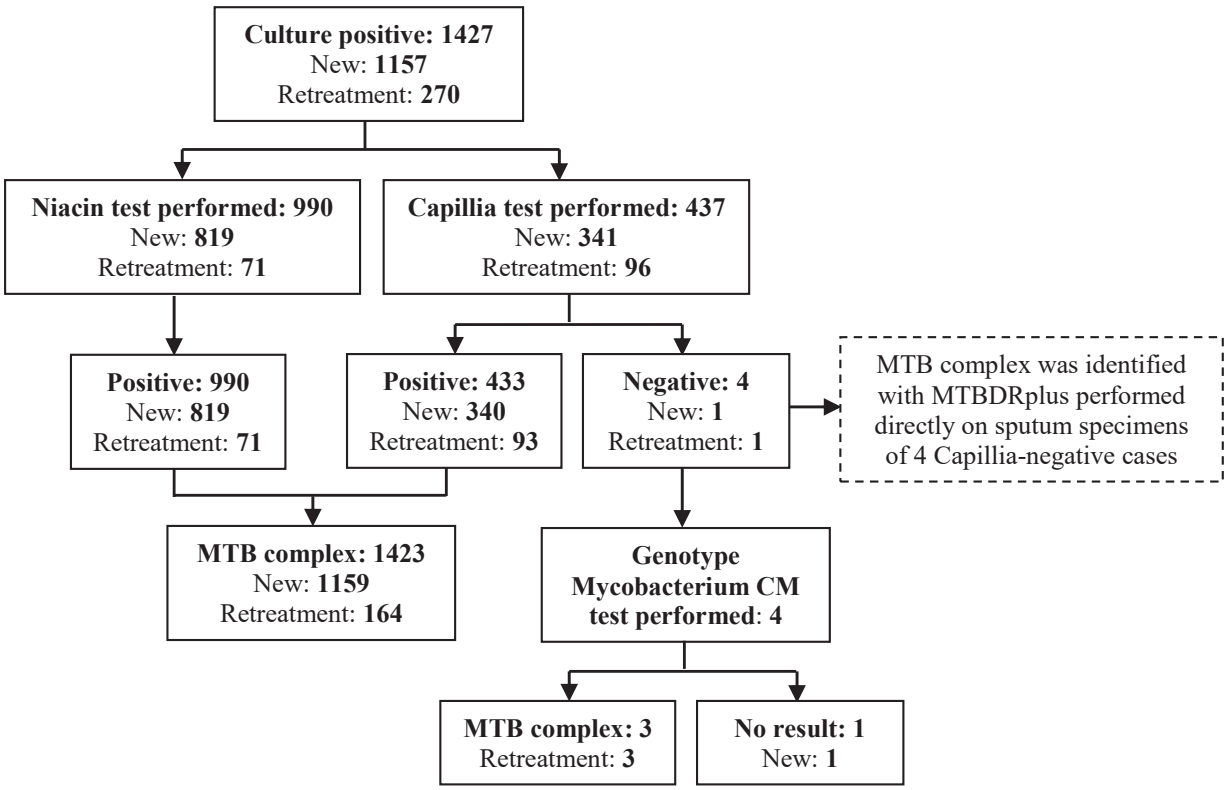

Figure 6. M.tuberculosis complex identification results

MTB complex was identified with MTBDR*plus* test performed directly on sputum specimens of 4 cases with negative identification test results. This test identifies MPB64 antigen of *M. tuberculosis* complex; therefore, it can be negative in case there is mutation in this gene. Identification with

Genotype Mycobacterium CM test confirmed the presence of *M. tuberculosis* complex in 3 of these 4 cultures. These 4 cultures have been sent to RIT (Japan) for full genome sequencing.

11.3.4 DST Results

First-line DST

Gene mutations conferring drug resistance were identified in 1488 (1488/1560 or 95.4%) smear and culture-positive cases using Genotype MTBDR*plus* test, and DST on solid media was performed on 1423 Capillia-TB positive cultures (Table 23).

Table 23. Susceptibility to first-line TB drugs

Test results	Genotype MTBDR*plus*		Conventional method	
	N	%	N	%
Susceptible	1,116	75.0 (72.7–77.1)	952	66.9 (64.4–69.3)
Resistant	350	23.5 (21.4–25.7)	471	33.1 (30.7–35.6)
Monoresistance	241	16.2 (14.4–18.2)	215	15.1 (13.3–17.1)
Polyresistance	0	-	146	10.3(8.8–11.9)
MDR-TB/Rif-resistant	109	7.3 (6.0–9.2)	110	7.7 (6.4–9.2)
Undetermined	22	1.5	-	-
Total	**1488 (100%)**		**1423 (100%)**	

Genotype MTBDRplus test results:

Three quarters (1116/1488 or 75.0%) of cases were susceptible to rifampicin and isoniazid, while 0.3% (5/1488) of cases were resistant to rifampicin only, 16.2% (241/1488) of cases were resistant to isoniazid only, and 7% (104/1488) of cases were resistant to both rifampicin and isoniazid. Overall, drug resistance was detected in 23.5% (350/1488) of cases (Table 24).

Table 24. Resistance to first-line TB drugs

MTBDR*plus* test results	N	%
Susceptible to rifampicin and isoniazid	1116	75.0 (72.7–77.1)
Monoresistance to isoniazid	241	16.2 (14.4–18.2)
Monoresistance to rifampicin	5	0.3 (0.2–0.8)
Resistance to isoniazid and rifampicin	104	7.0 (5.8–8.4)
Undetermined	22	1.5 (1.0–2.2)
Total	**1488**	**100**

Mutations conferring drug resistance were identified in 350 resistant strains. In 31.1% (109) of strains rifampicin-resistance was conferred by mutation in *rpoB* gene. Resistance to isoniazid was conferred by mutation in *katG, inhA,* and both *inhA, katG* genes in 27.0% (93/345), 72.8% (251/345) and 0.3% (1/345) of resistant strains. Mutation in *inhA* gene was predominant (83.4%) in strains resistant to isoniazid only, while mutations in *katG* (51.0%) and *inhA* (48.1%) genes were detected at a similar rate in strains resistant to both rifampicin and isoniazid (Table 25).

Table 25. Prevalence of genetic mutations conferring resistance to isoniazid

Mutation detected	Isoniazid resistant	Resistant to both isoniazid and rifampicin	Total
	N (%)	**N (%)**	**N (%)**
inhA gene mutation	201 (83.4)	50 (48.1)	251 (72.8)
KatG gene mutation	40 (16.6)	53 (51.0)	93 (27.0)
inhA and ***KatG*** gene mutation	-	1 (1.0)	1 (0.3)
Total	**241 (100)**	**104 (100)**	**345 (100%)**

In terms of location of mutations conferring drug resistance, mutation in rpoB gene conferring resistance to rifampicin was detected mainly at codon S531L (MUT3), mutations in *inhA* and *katG* genes conferring resistance to isoniazid were detected predominantly at codons C–15T (MUT1) and S315T (MUT1), respectively (Table 26).

Table 26. Genetic mutations conferring drug resistance, their location and presentation

Gene	Codon	N (%) of strains	Mutation presentation	Substitution/ Mutation	N (%) of strains
Rifampicin resistance (109)					
rpoB WT1	505–509	109 (100)		F505L	-
				T508A	-
				S509T	-
rpoB WT2	510–513	109 (100)		E510H	-
				L511P	-
rpoB WT2 /WT3	510–517	109 (100)		Q513L	-
				Q513P	-
				del514-516	-
rpoB WT3/WT4	513–519	82 (75.2)	*rpoB* MUT1	D516V	1 (0.9)
				D516Y	-
				del515	-
rpoB WT4/WT5	516–522	109 (100)		del518[a]	-
				N518I	-
rpoB WT5/WT6	518–525	109 (100)		S522L	-
				S522Q	-
rpoB WT7	526–529	103 (94.5)	*rpoB* MUT2A	H526Y	2 (1.8)
			rpoB MUT2B	H526D	4 (3.7)
				H526R	-
				H526P[a]	-
				H526Q[a]	-
				H526N/H526L	-
				H526S /H526C	-
rpoB WT8	530-533	12 (11.0)	*rpoB* MUT3	S531L	92 (84.4)
				S531Q[a]	-
				S531W	-
				L533P	-

Gene	Codon	N (%) of strains	Mutation presentation	Substitution/ Mutation	N (%) of strains
Isoniazid resistance (345)					
katG WT	315	155 (44.9)	*katG* MUT1	S315T1	92 (26.6)
			katG MUT2	S315T2	-
inhA WT1	15	99 (28.7)	*inhA* MUT1	C–15T	247 (71.6)
	16		*inhA* MUT2	A–16G	-
inhA WT2	8	339 (98.2)	*inhA* MUT3A	T–8C	5 (1.4)
			inhA MUT3B	T–8A	1 (0.3)

[a]-This is a rare mutation, which cannot be detected in vitro.

Results of DST on solid media

According to DST on solid media 66.7% (952/1423) of cases were susceptible to all anti-TB drugs, 15.1% (215/1423) had monoresistance, 10.2% (146/1423) had polyresistance, and 7.7% (110/1423) had MDR-TB.

Table 27. Findings related to resistance to first-line TB drugs

Type of drug resistance	Test results		
	N	%	95%CI
Susceptible	**952**	**66.9**	**64.4–69.3**
Drug resistant	**471**	**33.1**	**30.7–35.6**
Monoresistant	**215**	**15.1**	**13.3–17.1**
Isoniazid	102	7.2	5.9–8.6
Streptomycin	113	7.9	6.6–9.5
Polyresistant	**146**	**10.3**	**8.8–11.9**
Ethambutol+Streptomycin	1	0.1	0.01–0.4
Isoniazid+Ethambutol	1	0.1	0.01–0.4
Isoniazid+Streptomycin	132	9.3	7.8–10.9
Isoniazid+Ethambutol+Streptomycin	12	0.8	0.5–1.5
Multidrug resistant	**110**	**7.7**	**6.4–9.2**
Rifampicin resistant	4	0.3	0.1–0.7
Rifampicin+Isoniazid	4	0.3	0.1–0.7
Rifampicin+Ethambutol	1	0.1	0.01–0.4
Rifampicin+Isoniazid+Streptomycin	21	1.5	1.0–2.2
Rifampicin+ Isoniazid+Ethambutol	1	0.1	0.01–0.4
Rifampicin+Isoniazid +Ethambutol+Streptomycin	79	5.6	4.5–6.9
Total	**1423**	**100**	**-**

Second-line DST

Resistance to second-line anti-TB drugs was assessed on 110 strains with MDR-TB or monoresistance to rifampicin using conventional DST on solid media and Genotype MTBDR*sl* test. Of these strains, 90.0% (99/110) were susceptible to fluoroquinolone and SLI drugs, 2.7% (3/110) had XDR-TB, 7.3% (8/110) had pre-XDR or monoresistance to either fluoroquinolone (3.6% or 4/110) or SLI drugs (3.6% or 4/110) (Table 28).

Table 28. Findings related to resistance to second-line TB drugs

Test results	Genotype MTBDRplus		Conventional method	
	N	%	N	%
Susceptible to Fluoroquinolone and SLIs	99	90.0 (83.0–94.3)	99	90.0 (83.0–94.3)
Pre-XDR	8	7.3 (3.7–13.7)	8	7.3 (3.7–13.7)
Resistance to fluoroquinolone	4	3.6 (1.4–9.0)	4	3.6 (1.4–9.0)
Resistance to kanamycin, capreomycin, amikacin	3	2.7 (0.9–7.7)	3	2.7 (0.9–7.7)
Resistance to kanamycin, capreomycin	-	–	1	0.9 (0.2–5.0)
Low level resistance to kanamycin	1	0.9 (0.2–5.0)	–	–
XDR-TB (Resistance to fluoroquinolone, SLIs)	3	2.7 (0.9–7.7)	3	2.7 (0.9–7.7)
Total	**110**	**100**	**110**	**100**

Resistance to second-line anti-TB drugs was detected in 11 strains. Mutation in *gyrA* gene at codon A90V (MUT1) was mainly responsible for fluoroquinolone-resistance. Resistance to injectable anti-TB drugs (kanamycin, amikacin, capreomycin) was conferred by *rrs* gene at codon A1401G (MUT1), and low level resistance to kanamycin was conferred by *eis* gene at codon C−14T (MUT1) (Table 29).

Table 29. Genetic mutations conferring resistance to second-line TB drugs and their location

Gene conferring resistance	Amino acid location	Mutation presentation	Mutation	N (%) detected	Type of drug resistance
gyrA WT1		-	G88A G88C	-	Fluoroquinolone
gyrA WT2		*gyrA* MUT1	A90V	3 (2.7)	
		gyrA MUT2	S91P	-	
gyrA WT3		*gyrA* MUT3A	D94A	2 (1.8)	
		gyrA MUT3B	D94N D94Y	1 (0.9)	
		gyrA MUT3C	D94G	1 (0.9)	
		gyrA MUT3D	D94H[1)]	-	
gyrB WT		*gyrB* MUT1	N538D	-	
		gyrB MUT2	E540V	-	
rrs WT1	1401	*rrs* MUT1	A1401G	6 (5.4)	Kanamycin, Amikacin, Capreomycin
	1402	-	C1402T	-	Kanamycin, Capreomycin, Viomycin
rrs WT2	1484	*rrs* MUT2	G1484T	-	Kanamycin, Amikacin, Capreomycin, Viomycin
eis WT1		-	G−37T	-	Low level resistance to Kanamycin
eis WT2		*eis* MUT1	C−14T	1 (0.9)	
		-	C−12T	-	
		-	G−10A		
eis WT3		-	C−2A	-	

11.4. Objective 1: Prevalence of resistance to first-line TB drugs among new and retreatment cases

11.4.1. Prevalence of resistance to first-line TB drugs

Prevalence of resistance to first-line anti-TB drugs among new and retreatment cases is shown in Table 30 by individual drugs and in Table 32 by demographic characteristics. Resistance to first-line anti-TB drugs was more prevalent among retreatment (41.6%) compared to new (31.1%) TB cases (p=0.001).

Prevalence of isoniazid resistance was 22.5% among new and 34.1% among retreatment TB cases (p<0.001). Prevalence of rifampicin-resistant TB was significantly higher among retreatment (17.6%) compared to new (5.5%) cases (p<0.001). Similarly, ethambutol resistance was more common among retreatment (13.1%) than new (5.1%) cases (p<0.001). Prevalence of streptomycin resistance was the highest (23.3% among new and 33.7% among retreatment cases) (p<0.001).

There was no significant difference in the prevalence of monoresistant TB among new (15.6%) and retreatment (13.9%) cases. Monoresistance to streptomycin was most common (8.1% among new and 6.4% among retreatment cases) (p=0.333). Prevalence of monoresistance to isoniazid among new and retreatment TB cases was 7.3 and 6.7 percent, respectively (p=0.764).

Polyresistant TB was detected in 147 cases, of whom 132 (90%) were resistant to isoniazid and streptomycin. Prevalence of polyresistance among new and retreatment cases was 10.1 and 11.2 percent, respectively.

Prevalence of MDR-TB was 16.5% (95% CI: 12.2–21.5) among retreatment cases, which was 3 times higher than among new cases (5.3% [95% CI: 4.1–6.7]) (p<0.001). The majority of MDR-TB cases (73.8% or 45/61 of new and 77.3% or 34/44 of retreatment cases) were resistant to all 4 first-line anti-TB drugs.

LPA was performed on sputum specimens of 41 (16 new and 25 retreatment) culture-negative cases, and isoniazid resistance was detected in 5 (1 new and 4 retreatment) cases. None of these cases were resistant to rifampicin. If these cases are taken into the account the prevalence of Isoniazid resistance is estimated at 22.3% (95% CI: 20.0–24.8) among new and 32.6% (95% CI: 27.4–38.2) among retreatment TB cases.

Weighted prevalence of TB resistant to first-line anti-TB drugs among new and retreatment cases (n=1,423) is shown in Table 32 by demographic characteristics and in Table 33 by individual drugs. There was no significant difference in resistance to first-line drugs among new TB cases by age, gender or place of residence.

Table 30. Prevalence of TB resistant to first-line drugs

Drug resistance	New (n=1156)		Retreatment (n=267)		Total (n=1423)	
	N	Prevalence (%), 95% CI	N	Prevalence (%), 95% CI	N	Prevalence (%), 95% CI
Susceptible to all drugs	**796**	**68.9 (66.0–71.5)**	**156**	**58.4 (52.2–64.4)**	**952**	**66.9 (64.4–69.3)**
Any drug resistance	**360**	**31.1 (28.5–33.9)**	**111**	**41.6 (35.6–47.7)**	**471**	**33.1 (30.6–35.6)**
Isoniazid (H)	262	22.5 (20.2–25.1)	91	34.1 (28.4–40.1)	**352**	**24.7 (22.5–27.1)**
Rifampicin (R)	63	5.5 (4.2–6.9)	47	17.6 (13.2–22.7)	**110**	**7.7 (6.4–9.2)**
Ethambutol (E)	59	5.1 (3.9–6.5)	35	13.1 (9.3–17.8)	**94**	**6.6 (5.3–8.0)**
Streptomycin (S)	269	23.3 (20.9–25.8)	90	33.7 (28.1–39.7)	**359**	**25.2 (23.0–27.6)**
Monoresistance	**180**	**15.6 (13.5–17.8)**	**37**	**13.9 (9.9–18.6)**	**217**	**15.2 (13.4–17.2)**
Isoniazid (H)	84	7.3 (5.8–8.9)	18	6.7 (4.0–10.4)	**102**	**7.2 (5.9–8.6)**
Rifampicin (R)	2	0.2 (0.02–0.6)	2	0.7 (0.09–2.7)	**4**	**0.3 (0.07–0.7)**
Ethambutol (E)	0	0	0	0	**0**	**0**
Streptomycin (S)	94	8.1 (6.6–9.9)	17	6.4 (3.8–10.0)	**111**	**7.8 (6.5–9.3)**
Polyresistance	**117**	**10.1 (8.4–12.0)**	**30**	**11.2 (7.7–15.7)**	**147**	**10.3 (8.8–12.0)**
HE	1	0.08 (0.02–0.5)	0	0	**1**	**0.07 (0.02–0.4)**
HS	104	9.0 (7.4–10.8)	28	10.5 (7.1–14.8)	**132**	**9.3 (7.8–10.9)**
ES	1	0.08 (0.02–0.5)	0	0	**1**	**0.07 (0.02–0.4)**
HES	11	1.0 (0.5–1.7)	1	0.4 (0.009–2.1)	**12**	**0.8 (0.4–1.5)**
RE	0	0	0	0	**0**	**0**
RS	0	0	1	0.4 (0.009–2.1)	**1**	**0.07 (0.02–0.4)**
RES	0	0	0	0	**0**	**0**
MDR-TB	**61**	**5.3 (4.1–6.7)**	**44**	**16.5 (12.2–21.5)**	**105**	**7.4 (6.1–8.9)**
HR	3	0.3 (0.05–0.8)	1	0.4 (0.009–2.0)	**4**	**0.3 (0.07–0.7)**
HRE	1	0.08 (0.02–0.5)	0	0	**1**	**0.07 (0.02–0.4)**
HRS	12	1.0 (0.5–1.8)	9	3.4 (1.6–6.3)	**21**	**1.4 (0.9–2.2)**
HRES	45	3.9 (2.9–5.2)	34	12.7 (9.0–17.3)	**79**	**5.6 (4.4–6.9)**

Table 31. Results of LPA performed on culture-negative sputum specimens

Drug resistance	New (n=16)		Retreatment (n=25)	
	N	%	N	%
Isoniazid resistance	1	6.3	4	16.0
Rifampicin resistance	0	0	0	0
MDR-TB	0	0	0	0

Prevalence of TB resistant to all first-line drugs is shown in Table 31 by demographic characteristics. There was no difference in the prevalence of drug-susceptible TB by gender and place of residence. However, the prevalence among new cases was different by age groups, and was lowest in 35–44 year-olds (61.9%) and highest in 25-34 year-olds (75.1%).

Table 32. Prevalence of resistance to first-line TB drugs among new cases (n=1,156), selected demographic characteristics (weighted)

Characteristics	Isoniazid resistance		Rifampicin resistance		Ethambutol resistance		Streptomycin resistance	
	N	Prevalence (%), 95% CI	N	Prevalence (%), 95% CI	N	Prevalence (%), 95% CI	N	Prevalence (%), 95% CI
Total	**262**	**22.3 (20.0–24.8)**	**63**	**5.4 (4.2–6.8)**	**59**	**5.0 (3.9–6.5)**	**269**	**23.2 (20.9–25.7)**
Age groups								
<15	4	34.1 (13.5–63.3)	0	0	0	0	3	25.7 (8.6–56.2)
15–24	67	21.8 (17.5–26.8)	24	7.7 (5.2–11.3)	23	7.4 (4.9–10.9)	76	24.6 (20.0–29.7)
25–34	63	18.7 (14.8–23.2)	13	4.0 (2.3–6.7)	14	4.2 (2.5–7.0)	61	18.4 (14.5–22.9)
35–44	57	28.7 (22.8–35.5)	11	5.5 (3.1–9.7)	10	5.1 (2.8–9.3)	56	28.8 (22.8–35.6)
45–54	46	26.1 (20.1–33.1)	9	5.1 (2.7–9.6)	8	4.5 (2.2–8.7)	42	24.1 (18.3–31.0)
55–64	17	21.0 (13.4–31.2)	4	5.0 (1.9–12.9)	3	3.7 (0.3–10.8)	15	19.0 (11.7–29.2)
>65	8	13.0 (6.6–24.1)	2	3.3 (0.8–12.3)	1	1.8 (0.3–11.8)	16	28.4 (18.1–41.6)
Gender								
Male	142	21.2 (18.2–24.5)	32	4.9 (3.4–6.8)	25	3.8 (2.6–5.6)	147	22.2 (19.2–25.6)
Female	120	23.9 (20.3–27.8)	31	6.1 (4.3–8.5)	34	6.8 (4.9–9.3)*	122	24.6 (21.0–28.6)
Place of residence								
Rural	104	22.6 (18.9–26.6)	28	6.0 (4.2–8.6)	24	5.2 (3.5–7.7)	106	23.4 (19.7–27.6)
Urban	154	22.1 (19.2–25.4)	35	5.1 (3.7–7.0)	35	5.1 (3.7–7.0)	157	22.7 (19.7–26.0)
Prison	4	23.5 (9.1–48.6)	0	0.0	0	0	6	23.2 (20.9–25.7)

* $p<0.05$

Table 33. Prevalence of resistance to first-line TB drugs among retreatment cases (n=267), selected demographic characteristics (weighted)

Characteristics	Isoniazid resistance		Rifampicin resistance		Ethambutol resistance		Streptomycin resistance	
	N	Prevalence (%), 95% CI	N	Prevalence (%), 95% CI	N	Prevalence (%), 95% CI	N	Prevalence (%), 95% CI
Total	**91**	**32.6 (27.4–38.2)**	**47**	**16.2 (12.4–21.0)**	**35**	**13.3 (6.7–18.0)**	**90**	**33.8 (28.3–39.8)**
Age groups								
<15	0	0	0	0	0	0	0	0
15–24	5	13.5 (5.7–28.8)	3	8.2 (2.6–22.6)	2	6.8 (1.7–23.6)	6	20.3 (9.3–38.6)
25–34	24	37.9 (27.1–50.0)	12	17.9 (10.4–29.1)	10	15.2 (8.3–26.1)	23	35.4 (24.7–47.7)
35–44	20	33.3 (22.9–45.7)	9	14.0 (7.4–24.9)	5	8.9 (3.7–19.9)	18	30.4 (19.9–43.5)
45–54	26	34.1 (24.5–45.3)	14	18.1 (11.0–28.3)	11	15.6 (8.8–26.2)	29	40.9 (30.0–52.7)
55–64	13	42.1 (26.1–60.0)	8	25.8 (13.4–43.9)	6	20.9 (9.6–39.6)	12	41.8 (25.4–60.2)
>65	3	22.8 (7.4–52.0)	1	8.1 (1.1–40.7)	1	8.7 (1.2–42.9)	2	16.6 (4.2–47.9)
Gender								
Male	69	37.2 (30.4–44.4)	35	17.5 (12.8–23.5)	26	14.0 (9.6–19.8)	66	35.4 (28.8–35.4)
Female	22	28.1 (19.2–39.0)	12	13.5 (7.8–22.3)	9	11.7 (6.2–21.1)	24	30.3 (21.1–41.3)
Place of residence								
Rural	39	38.7 (29.3–48.6)	20	17.8 (11.8–26.1)	15	15.2 (9.3–23.7)	34	33.9 (25.2–43.7)
Urban	48	30.1 (23.4–37.8)	23	13.1 (8.8–19.0)	17	10.4 (6.5–16.1)	52	32.3 (25.5–40.0)
Prison	4	66.7 (26.6–91.7)*	4	57.1 (22.8–85.7)*	3	50.0 (16.7–83.4)*	4	66.7 (26.6–91.7)

* $p<0.05$

Table 34. Prevalence of drug-susceptible and drug-resistant TB, by age, gender and place of residence

Characteristics	Total	Susceptible to all drugs		Resistant to any drug		P value
		N	%	N	%	
Total	**1423**	**952**	**66.9**	**471**	**33.1**	
Age groups						0.017
<15	**13**	9	**69.2**	4	**30.8**	
15–24	**337**	234	**69.4**	103	**30.6**	
25–34	**400**	289	**72.3**	111	**27.8**	
35–44	**252**	155	**61.5**	97	**38.5**	
45–54	**245**	146	**59.6**	99	**40.4**	
55–64	**110**	74	**67.3**	36	**32.7**	
>65	**66**	45	**68.2**	21	**31.8**	
Gender						0.908
Male	**849**	569	**67.0**	280	**33.0**	
Female	**574**	383	**66.7**	191	**33.3**	
Place of residence						0.184
Rural	**550**	356	**64.7**	194	**35.3**	
Urban	**850**	583	**68.6**	267	**31.4**	
Prison	**23**	13	**56.5**	10	**43.5**	
New TB case	**1156**	**796**	**67.7**	**360**	**30.6**	
Age groups						0.028
<15	**12**	8	**66.7**	4	**33.3**	
15–24	**308**	213	**69.2**	95	**30.8**	
25–34	**334**	251	**75.1**	83	**24.9**	
35–44	**194**	120	**61.9**	74	**38.1**	
45–54	**173**	109	**63.0**	64	**37.0**	
55–64	**81**	59	**72.8**	22	**27.2**	
>65	**54**	36	**66.7**	18	**33.3**	
Gender						0.337
Male	663	464	**70.0**	199	**30.0**	
Female	493	332	**67.3**	161	**32.7**	
Place of residence						0.630
Rural	448	302	**67.4**	146	**32.6**	
Urban	691	483	**69.9**	208	**30.1**	
Prison	17	11	**64.7**	6	**35.3**	
Retreatment TB case	**267**	**156**	**52.9**	**111**	**37.6**	
Age groups						0.368
<15	**1**	1	**100.0**	0	**0.0**	
15–24	**29**	21	**72.4**	8	**27.6**	
25–34	**66**	38	**57.6**	28	**42.4**	
35–44	**58**	35	**60.3**	23	**39.7**	
45–54	**72**	37	**51.4**	35	**48.6**	
55–64	**29**	15	**51.7**	14	**48.3**	
>65	**12**	9	**75.0**	3	**25.0**	

Gender						0.321
Male	**186**	105	**56.5**	81	**43.5**	
Female	**81**	51	**63.0**	30	**37.0**	
Place of residence						0.127
Rural	**102**	54	**52.9**	48	**47.1**	
Urban	**159**	100	**62.9**	59	**37.1**	
Prison	**6**	2	**33.3**	4	**66.7**	

Outcome of the last treatment of retreatment TB cases is shown in Table 35. Of retreatment TB cases, 78% were treated successfully (cured or completed treatment), 14.9% were lost to follow-up, and 7.1% failed. Of 171 cases from Ulaanbaatar City, 74.9% were treated successfully and 19.3% were lost to follow-up.

Table 35. Outcome of the previous treatment, by place of residence

Place of residence	Outcome of the previous treatment			Total
	Treated successfully	Lost to follow-up	Failure	
Rural	96 (82.1)	10 (8.5)	11 (9.4)	**117 (100)**
Ulaanbaatar	128 (74.9)	33 (19.3)	10 (5.8)	**171 (100)**
Prison	6 (85.7)	1 (14.3)	0 (0)	**7 (100)**
Total	**230 (78.0)**	**44 (14.9)**	**21 (7.1)**	**295 (100)**

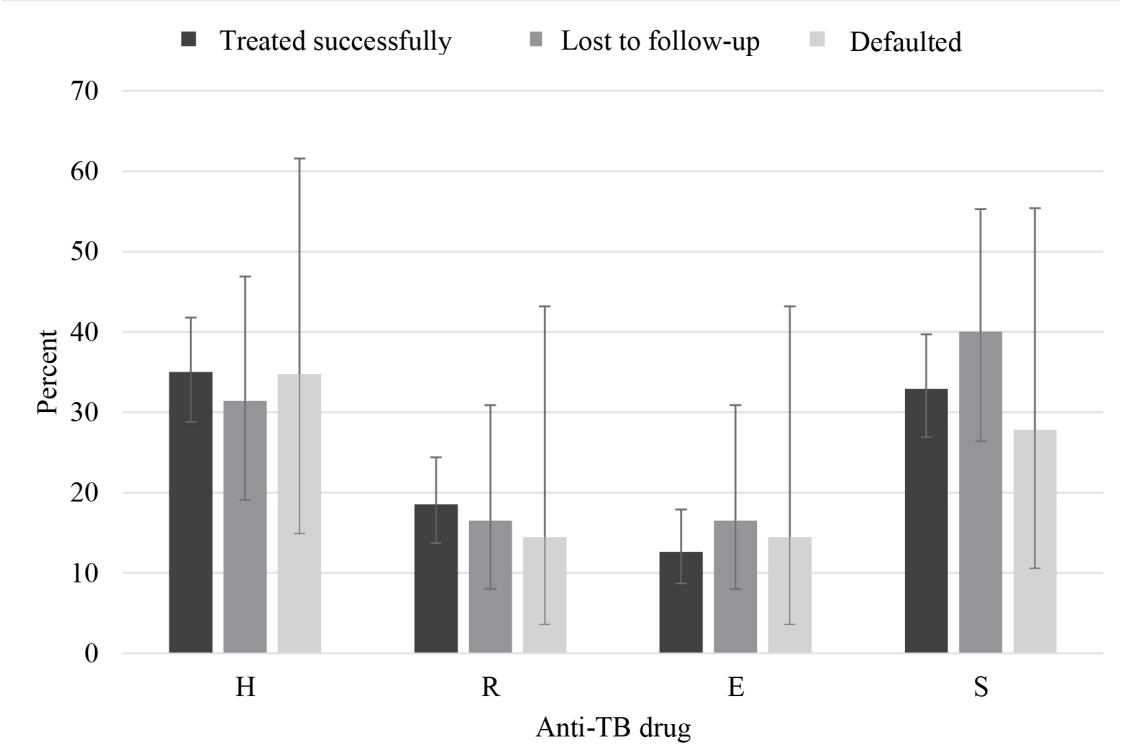

Figure 7. Resistance to first-line drugs among retreatment TB cases according to the previous treatment outcome

11.4.2 Estimation of the Prevalence of Rifampicin Resistance

Missing data

For the purposes of data analysis "ice -- Multiple imputation by the MICE system of chained equations" command was used for the imputation of missing rifampicin susceptibility data for 106 cases with no DST results (including 104 non-participants and 2 culture contamination cases).

Prevalence of rifampicin-resistant TB was 5.6% (95% CI: 4.2–6.9) among new and 17.9% (95% CI: 13.5–22.3) among retreatment cases.

Table 36. Proportion of cases with unknown rifampicin susceptibility and association with selected variables

	Total	Unknown rifampicin susceptibility	Proportion of missing data	Association
Total	**1642**	**176**	**10.7%**	
Treatment history				
New	1307	135	10.3%	Ref.
Retreatment	335	41	12.2%	1.2 (0.8–1.8); p=0.314
Age groups				
0–14	17	4	23.5%	3.4 (1.1–11.6); p=0.041
15–24	395	50	12.7%	1.6 (1.0–2.8); p=0.060
25–34	447	38	8.5%	1.1 (0.6–1.8); p=0.848
35–44	284	23	8.1%	Ref.
45–54	290	35	12.1%	1.6 (0.9–2.7); p=0.117
55–64	127	14	11.0%	1.4 (0.7–2.8); p=0.340
65+	82	12	14.6%	1.9 (0.9–4.1); p=0.080
Gender				
Male	975	104	10.7%	Ref.
Female	667	72	10.8%	1.0 (0.7–1.4); p=0.934
Place of residence				
Rural	676	101	14.9%	3.6 (0.5–27.7); p=0.205
Urban	918	72	7.8%	1.8 (0.5–13.5); p=0.573
Prison	26	2	7.7%	1.8 (0.1–20.7); p=0.657
"Enerel"	22	1	4.5%	Ref.
Region				
Central	1277	131	10.3%	Ref.
Eastern	148	16	10.8%	1.0 (0.6–1.8); p=0.834
Khangai	156	19	12.2%	1.2 (0.7–2.0); p=0.460
Western	61	10	16.4%	1.7 (0.9–3.5); p=0.132

Table 37. Prevalence of Rifampicin-resistant TB, by type of imputation *model*

Imputation model	New			Retreatment		
	Total	Prevalence	95% CI	Total	Prevalence	95% CI
Individual sampling – unweighted	1156	5.5	4.2 – 6.9	267	17.6	13.2 – 22.7
Individual sampling – only new cases weighted	1156	5.5	4.3 – 6.9	–	–	–
Imputation model 1 (age, gender, treatment history, place of residence) - unweighted	1273	5.6	4.2 – 6.9	**301**	**17.9**	**13.5 – 22.3**
Imputation model 1 (age, gender, treatment history, place of residence) – only new cases weighted	**1273**	**5.6**	**4.2 – 6.9**	–	–	–
Imputation model 2 (age, gender, treatment history, place of residence) - unweighted	1273	5.5	4.2 – 6.9	301	18.1	13.3 – 22.8
Imputation model 2 (age, gender, treatment history, place of residence) – only new cases weighted	1273	5.5	4.2 – 6.9	–	–	–

11.5 Objective 2: Prevalence of MDR-TB among New and Retreatment Cases

Prevalence of MDR-TB among new and retreatment cases is shown in Table 38 and Table 39, respectively, by demographic characteristics. MDR-TB prevalence was 7.4% (95% CI: 6.1-8.9) overall, 5.3% (95% CI: 4.1-6.7) among new TB cases and 16.5% (95% CI: 12.2-21.5) among retreatment TB cases. The prevalence of MDR-TB among retreatment cases was 3 times higher compared to new cases ($p<0.001$).

There was no difference in MDR-TB prevalence among new cases by place of residence (urban, rural, prison), but among retreatment cases it was significantly higher in prisons (66.7%) compared to rural (18.4%) or urban (13.5%) settings ($p=0.002$).

Table 38. Prevalence of MDR-TB, by demographic characteristics (weighted)

Characteristics	Total	MDR-TB	Prevalence (%), 95% CI	P value
Total	**1423**	**105**	**7.4 (6.1–8.9)**	
Treatment history				<0.001
New	1156	61	5.3 (4.1–6.7)	
Retreatment	267	44	16.5 (12.2–21.5)	
Age groups				0.594
<15	13	0	0	
15-24	337	26	7.6 (5.3–11.0)	
25-34	400	24	6.3 (4.2–9.2)	
35-44	252	20	8.0 (5.2–12.1)	
45-54	245	21	8.6 (5.7–12.9)	
55-64	110	11	10.4 (5.8–17.9)	
>65	66	3	4.5 (1.4–13.0)	
Gender				0.221
Male	849	64	7.7 (6.0–9.7)	
Female	574	41	7.2 (5.4–9.7)	
Place of residence				0.107
Rural	550	44	8.1 (6.1–10.8)	
Urban	850	57	6.7 (5.2–8.6)	
Prison	23	4	17.4 (6.7–38.3)	

Number of MDR-TB cases and its prevalence rate by administrative units are shown in Figure 7 and Figure 8. The prevalence is relatively high in administrative units located along the railway such as Dornogobi, Tuv, Darkhan-Uul, Orkhon and Selenge aimags and Ulaanbaatar City, as well as in Gobi-Altai and Arkhangai aimags.

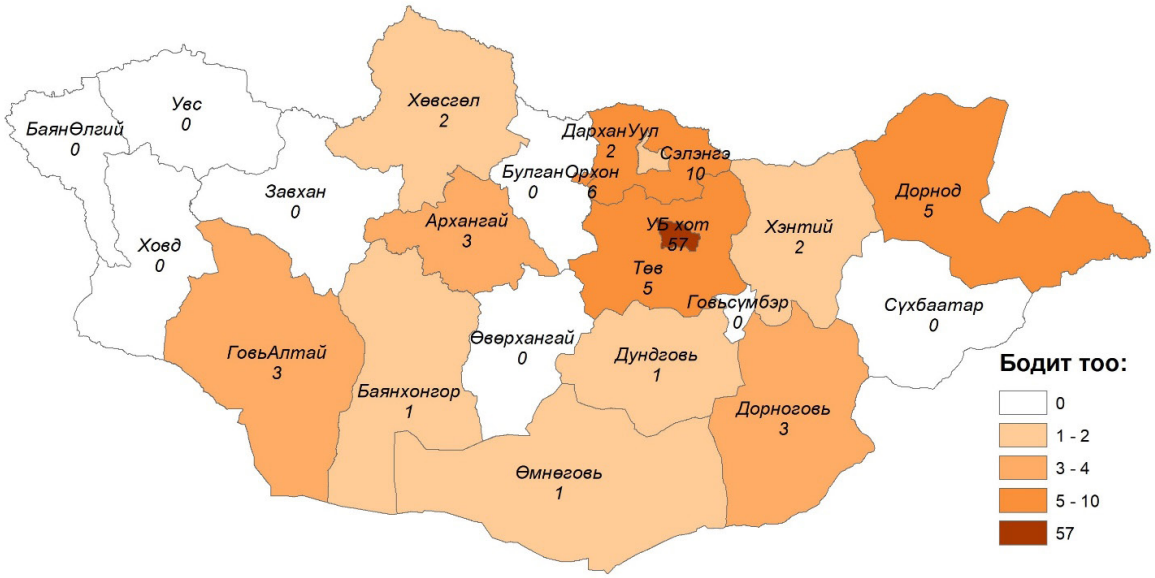

Figure 8. Number of MDR-TB cases, by aimags

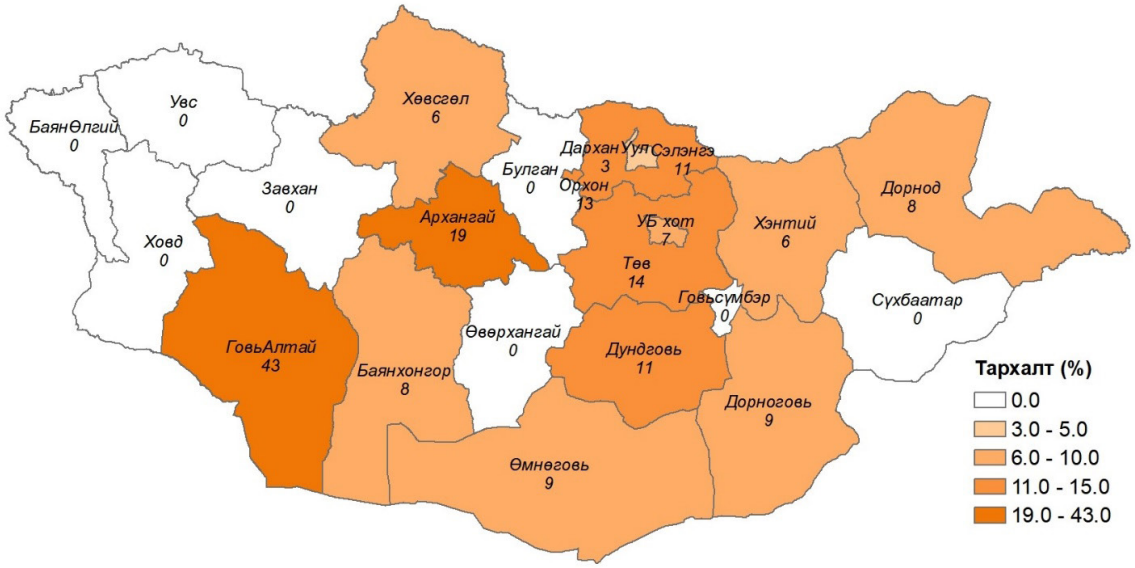

Figure 9. Prevalence of MDR-TB, by aimags

Table 39. Prevalence of MDR-TB among new and retreatment cases, by demographic characteristics

Characteristics	New				Retreatment			
	Total	MDR-TB	Prevalence (%), 95% CI	P value	Total	MDR-TB	Prevalence (%), 95% CI	P value
Total	**1156**	**61**	**5.3 (4.1–6.7)**		**267**	**44**	**16.5 (12.2–21.95**	
Age groups				0.401				0.493
<15	12	0	0		1	0	0	
15–24	308	24	7.7 (5.2–11.3)		29	2	6.8 (1.7–23.6)	
25–34	334	13	4.0 (2.4–6.9)		66	11	17.2 (9.8–28.6)	
35–44	194	11	5.5 (3.1–9.7)		58	9	15.6 (8.3–27.5)	
45–54	173	8	4.5 (2.2–8.7)		72	13	18.6 (11.1–29.5)	
55–64	81	3	4.0 (1.3–12.0)		29	8	27.6 (14.3–46.4)	
>65	54	2	3.5 (0.8–12.9)		12	1	8.7 (1.2–42.9)	
Gender				0.221				0.297
Male	663	30	4.6 (3.2–6.5)		186	34	18.4 (13.4–24.7)	
Female	493	31	6.2 (4.4–8.7)		81	10	13.1 (7.2–22.7)	
Place of residence				0.537				0.002
Rural	448	26	5.7 (3.9–8.3)		102	18	18.4 (11.9–27.4)	
Urban	691	35	5.1 (3.7–7.1)		159	22	13.5 (9.0–19.7)	
Prison	17	0	0.0		6	4	66.7 (26.6–91.7)	
Education				0.502				0.042
None	24	2	7.9 (2.0–26.7)		13	4	33.2 (13.1–62.0)	
Primary	81	2	2.5 (0.6–9.4)		17	4	22.6 (8.6–47.5)	
Incomplete secondary	234	17	7.5 (4.7–11.8)		70	18	26.2 (17.2–38.0)	
Completed secondary	492	22	4.4 (2.9–6.7)		107	13	12.3 (7.2–20.1)	
Vocational	67	4	6.3 (2.4–15.6)		15	0	0.0	
University/college	236	12	4.8 (2.8–8.3)		44	5	11.5 (4.8–25.0)	
Unknown	22	2	8.7 (2.2–29.1)		1	0	0.0	
Employment status				0.083				0.825
Employed	447	23	5.3 (3.5–7.9)		93	14	15.2 (9.2–24.1)	
Unemployed	139	7	5.0 (2.4–10.1)		55	7	16.0 (8.5–43.2)	
School student	58	7	11.9 (5.8–23.0)		2	0	0.0	

Characteristics	New				Retreatment			
	Total	MDR-TB	Prevalence (%), 95% CI	P value	Total	MDR-TB	Prevalence (%), 95% CI	P value
University/college student	122	9	7.4 (3.9–13.7)		10	2	20.7 (5.2–55.6)	
Retired	94	1	1.0 (0.1–6.5)		31	7	22.4 (11.0–40.3)	
Disabled	65	5	7.1 (3.0–16.1)		34	4	12.5 (4.8–29.1)	
Housewife	69	1	1.4 (0.2–9.4)		11	1	8.7 (1.2–43.1)	
Other	162	8	4.9 (2.5–9.5)		31	9	24.5 (12.2–43.2)	
Marital status				0.331				0.696
Single	447	29	6.5 (4.6–9.3)		84	16	19.4 (12.2–29.5)	
Married	631	30	4.7 (3.3–6.6)		143	23	16.7 (11.3–23.9)	
Divorced/Separated	46	2	5.0 (1.2–18.2)		28	3	9.8 (3.1–26.7)	
Widowed	32	0	0.0		12	2	17.6 (4.4–49.7)	
DR–TB contact				0.170				0.874
Yes	50	6	11.0 (5.0–22.7)		18	4	20.6 (7.8–44.3)	
No	1090	54	5.0 (3.8–6.4)		244	39	16.4 (12.2–21.7)	
Unknown	16	1	7.3 (1.0–37.6)		5	1	21.0 (2.8–70.7)	
Type of housing				0.759				0.828
Gher	396	23	5.5 (3.6–8.6)		101	17	17.7 (11.2–26.6)	
House	439	20	4.6 (3.0–7.1)		98	19	19.5 (12.7–28.6)	
Apartment	262	16	6.1 (3.8–9.7)		46	5	10.7 (4.5–23.3)	
Dormitory	41	1	2.3 (0.3–14.8)		11	1	10.4 (1.4–47.9)	
Dwelling not suited for human living	5	0	0.0		4	1	20.3 (2.5–71.5)	
Other	7	0	0.0		3	0	0.0	
Unknown	6	1	14.1 (1.9–58.7)		4	1	25.1 (3.3–76.7)	
Monthly household income				0.902				0.425
> 944,153.00	198	11	5.4 (3.0–9.5)		36	4	11.4 (4.3–27.0)	
< 944,153.00	883	46	5.2 (3.9–6.8)		198	33	16.8 (12.2–22.8)	
Unknown	75	4	5.2 (4.0–6.7)		33	7	1.2 (9.0–38.9)	

11.6 Objective 3: Prevalence of resistance to fluoroquinolone and second-line injectables among TB cases with isoniazid and rifampicin resistance

Prevalence of resistance to second-line anti-TB drugs among MDR-TB cases is shown in Table 40. Of 105 MDR-TB cases, 89.5% (95% CI: 82.0-94.7) were susceptible to all second-line anti-TB drugs. The corresponding rates for new and retreatment cases were 88.5% (95% CI: 77.8-95.3) and 90.9% (95% CI: 78.3-97.5), respectively.

Prevalence of resistance to second-line anti-TB drugs among new and retreatment MDR-TB cases was 11.5% (95% CI: 4.7-22.2) and 9.1% (95% CI: 2.5-21.7), respectively (p=0.693). Resistance to ofloxacin was most commonly found among new (9.8%) and retreatment (4.5%) cases (p=0.313). Prevalence of capreomycin resistance among new and retreatment cases was 6.6 and 4.5 percent, respectively (p=0.661).

Prevalence of XDR-TB among new TB cases was 4.9% (95% CI: 1.0-13.7). All 3 XDR-TB cases were resistant to all second-line anti-TB drugs (AM, KM, CM, OFL). No XDR-TB was detected among retreatment cases. Eight cases with pre-XDR were detected, of which 4 were new TB cases.

Table 40. Prevalence of resistance to second-line drugs among TB cases resistant to isoniazid and rifampicin

Drug resistance	New		Retreatment		Total	
	Total	Prevalence (%), 95% CI	Total	Prevalence (%), 95% CI	Total	Prevalence (%), 95% CI
Total	**61**		**44**		**105**	
Susceptible to all drugs	54	88.5 (77.8–95.3)	40	90.9 (78.3–97.5)	94	89.5 (82.0–94.7)
Resistance to any drug	**7**	**11.5 (4.7–22.2)**	**4**	**9.1 (2.5–21.7)**	**11**	**10.5 (5.3–18.0)**
AM	5	8.2 (2.7–18.1)	1	2.3 (0.5–12.0)	6	5.7 (2.1–12.0)
KM	4	6.6 (1.8–15.9)	2	4.5 (0.6–15.5)	6	5.7 (2.1–12.0)
CM	5	8.2 (3.5–18.1)	2	4.5 (0.6–15.5)	7	6.7 (2.7–13.3)
OFL	6	9.8 (3.7–20.2)	2	4.5 (0.6–15.5)	8	7.6 (3.3–14.5)
Monoresistance	**2**	**3.3 (0.4–11.3)**	**2**	4.5 (0.6–15.5)	**4**	**3.8 (1.0–9.5)**
AM	0	0	0	0	0	0
KM	0	0	0	0	0	0
CM	0	0	0	0	0	0
OFL	2	3.3 (0.4–11.3)	2	4.5 (0.6–15.5)	4	3.8 (1.0–9.5)
XDR-TB	**3**	**4.9 (1.0–13.7)**	**0**	**0**	**3**	**2.9 (0.6–8.1)**
AM KM CM OFL	3	4.9 (1.0–13.7)	0	0	3	2.9 (0.6–8.1)
Pre-XDR	**4**	**6.6 (1.8–15.9)**	**4**	**9.1 (2.5–21.7)**	**8**	**7.6 (3.3–14.5)**
AM KM CM	2	3.3 (0.4–11.3)	1	2.3 (0.5–12.0)	3	2.9 (0.6–8.1)
KM CP	0	0	1	2.3 (0.5–12.0)	1	1.0 (0.02–5.2)
OFL	2	3.3 (0.4–11.3)	2	4.5 (0.6–15.5)	4	1.8 (1.0–9.5)

11.7 Objective 4: Association between MDR-TB and Selected Risk Factors

Association between MDR-TB and the following risk factors was assessed: age, gender, place of residence, education, history of contact with DR-TB case, smoking, alcohol consumption, history of contact with TB case, history of imprisonment, history of surgical intervention, BCG vaccination

scar, history of preventive treatment, history of any treatment prior to diagnosis, diabetes, income below average, and outcome of the previous TB treatment. The analysis was done using logistic regression for new and retreatment cases separately.

Univariate analysis revealed an association between MDR-TB among new cases and history of contact with DR-TB case (OR=2.7 [95% CI: 1.1–6.5], p=0.032) (Table 41).

Similarly, only "being a prisoner" was associated with MDR-TB among retreatment cases (OR=9.0 [95% CI: 1.9–43.1], p=0.006). In other words, odds of having MDR-TB among retreatment cases diagnosed at prison hospital was 9 times higher compared to urban retreatment cases (Table 42).

Table 41. Univariate analysis of risk factors affecting MDR-TB prevalence among new cases

Characteristics	Total	MDR-TB	Prevalence (%)	OR, 95% CI	P value
Total	**1173**	**61**	**5.2**		
Age groups					
<15	12	0	0.0	-	
15-24	309	24	7.8	2.1 (1.1–4.3)	0.032
25-34	342	13	3.8	Ref	
35-44	196	11	5.6	1.5 (0.7–3.4)	0.330
45-54	175	8	4.6	1.2 (0.5–3.0)	0.675
55-64	82	3	3.7	1.0 (0.3–3.5)	0.951
>65	57	2	3.5	0.9 (0.2–4.2)	0.914
Gender					
Male	670	30	4.5	0.7 (0.4–1.2)	0.200
Female	503	31	6.2	Ref	
Place of residence					
Rural	460	26	5.7	1.1 (0.7–1.9)	0.643
Urban	696	35	5.0	Ref	
Prison	17	0	0.0	–	
Education					
None	25	2	8.0	1.7 (0.4–7.9)	0.520
Primary	83	2	2.4	0.5 (0.1–2.1)	0.334
Incomplete secondary	239	17	7.1	1.5 (0.7–3.1)	0.323
Completed secondary	495	22	4.4	0.9 (0.4–1.8)	0.755
Vocational	67	4	6.0	1.2 (0.4–3.9)	0.741
University/college	242	12	5.0	Ref	
Unknown	22	2	-	–	
History of contact with DR-TB					
Yes	50	6	12.0	2.7 (1.1–6.5)	0.032
No	1107	54	4.9	Ref	
Unknown	16	1	-	-	
Smoking					
None	644	41	6.4	Ref	
Quit smoking	104	3	2.9	0.4 (0.1–1.4)	0.173
Sometimes	58	2	3.4	0.5 (0.1–2.2)	0.383

Characteristics	Total	MDR-TB	Prevalence (%)	OR, 95% CI	P value
Daily	362	14	3.9	0.6 (0.3–1.1)	0.098
Unknown	5	1	-	-	
Alcohol consumption					
None	630	38	6.0	Ref	
Once a month or less	358	15	4.2	0.7 (0.4–1.3)	0.219
2-4 times a month	105	3	2.9	0.5 (0.1–1.5)	0.200
2-3 times a week	40	3	7.5	1.3 (0.4–4.3)	0.708
4 or more times a week	32	1	3.1	0.5 (0.1–3.8)	0.504
Unknown	8	1	-	-	
Household contact with TB					
Yes	224	15	6.7	1.4 (0.8–2.6)	0.264
No	944	46	4.9	Ref	
Unknown	**5**	0	-	-	
History of imprisonment					
Yes	26	1	3.8	0.7 (0.1–5.4)	0.745
No	1115	59	5.3	Ref	
Unknown	32	1	-	-	
History of surgical intervention					
Yes	1115	14	1.3	0.7 (0.4–1.3)	0.288
No	332	46	13.9	Ref	
Unknown	23	2	-		
BCG vaccine scar present					
Yes	881	47	5.3	1.1 (0.6–1.9)	0.875
No	275	14	5.1	Ref	
Unknown	17	0	-		
History of preventive treatment with Isoniazid					
Yes	6	1	16.7	3.7 (0.4–31.9)	0.239
No	1141	59	5.2	Ref	
Unknown	26	1	-		
History of any treatment prior to diagnosis					
Yes	444	27	6.1	1.3 (0.8–2.1)	0.358
No	704	34	4.8	Ref	
Unknown	25	0	-		
Diabetes					
Yes	85	6	7.1	1.4 (0.6-3.4)	0.439
No	1058	54	5.1	Ref	
Unknown	30	1	-		
Monthly household income					
> 944,153.00	203	11	5.4	Ref	
< 944,153.00	895	46	5.1	0.9 (0.5-1.9)	0.871
Unknown	75	4	-		

Table 42. Univariate analysis of risk factors affecting MDR-TB prevalence among retreatment cases

Characteristics	Total	MDR-TB	Prevalence (%)	OR, 95% CI	P value
Total	**295**	**44**	**14.9**		
Age groups					
<15	1	0	-	-	
15-24	36	2	5.6	Ref	
25-34	69	11	15.9	3.2 (0.7–15.4)	0.143
35-44	65	9	13.8	2.7 (0.6–13.4)	0.215
45-54	80	13	16.3	3.2 (0.7–15.5)	0.130
55-64	31	8	25.8	5.9 (1.2–30.4)	0.033
>65	13	1	7.7	1.4 (0.1–17.0)	0.784
Gender					
Male	202	34	16.8	1.7 (0.8–3.6)	0.177
Female	93	10	10.8	Ref	
Place of residence					
Rural	117	18	15.4	1.2 (0.6–2.4)	
Urban	171	22	12.9	Ref	0.544
Prison	7	4	57.1	9.0 (1.9–43.1)	0.006
Education					
None	14	4	28.6	3.4 (0.8–15.2)	0.103
Primary	18	4	22.2	2.5 (0.6–10.4)	0.223
Incomplete secondary	77	18	23.4	2.6 (0.9–7.6)	0.076
Completed secondary	122	13	10.7	1.0 (0.3–3.1)	0.964
Vocational	15	0	-	-	
University/college	48	5	10.4	Ref	
Unknown	1	0	-	-	
History of contact with DR-TB					
Yes	20	4	20.0	1.5 (0.5–4.7)	0.502
No	270	39	14.4	Ref	
Unknown	5	1	-	-	
Smoking					
None	123	18	14.6	Ref	
Quit smoking	30	6	20.0	1.5 (0.5–4.1)	0.471
Sometimes	28	3	10.7	0.7 (0.2–2.6)	0.590
Daily	112	16	14.3	1.0 (0.5–2.0)	0.940
Unknown	2	1	-	-	
Alcohol consumption					
None	122	21	17.2	Ref	
Once a month or less	87	12	13.8	0.8 (0.4–1.7)	0.505
2-4 times a month	49	6	12.2	0.7 (0.3–1.8)	0.423
2-3 times a week	16	3	18.8	1.1 (0.3–4.2)	0.879
4 or more times a week	19	1	5.3	0.3 (0.03–2.1)	0.211
Unknown	2	1	-	-	

Characteristics	Total	MDR-TB	Prevalence (%)	OR, 95% CI	P value
Household contact with TB					
Yes	79	8	10.1	0.6 (0.2–1.3)	0.167
No	211	36	17.1	Ref	
Unknown	5	0	-	-	
History of imprisonment					
Yes	11	2	18.2	1.4 (0.3–6.6)	0.691
No	273	38	13.9	Ref	
Unknown	11	4	-	-	
History of surgical intervention					
Yes	77	9	11.7	0.7 (0.3–1.5)	0.357
No	212	34	16.0	Ref	
Unknown	6	1	-		
BCG vaccine scar present					
Yes	233	33	14.2	0.8 (0.4–1.6)	0.483
No	56	9	16.1	Ref	
Unknown	6	2	-		
History of preventive treatment with Isoniazid					
Yes	11	2	18.2	1.3 (0.3–6.3)	0.739
No	275	40	14.5	Ref	
Unknown	9	2	-		
History of any treatment prior to diagnosis					
Yes	99	12	12.1	0.7 (0.3–1.4)	0.299
No	191	32	16.8	Ref	
Unknown	5	0	-		
Diabetes					
Yes	26	4	15.4	1.1 (0.4–3.3)	0.910
No	261	38	14.6	Ref	
Unknown	8	2	-		
Monthly household income					
> 944,153.00	40	4	10.0	Ref	
< 944,153.00	219	33	15.1	1.6 (0.5–4.8)	0.403
Unknown	36	7	-		
Outcome of the previous treatment					
Treated successfully	230	35	15.2	Ref	
Defaulted	44	7	15.9	1.1 (0.4–2.6)	0.907
Treatment failure	21	2	9.5	0.6 (0.1–2.6)	0.486

11.8 Comparison to the Previous Two Surveys

National DRS was conducted in 1999, 2007 and 2016–2017 in Mongolia. The first 1999 survey assessed the prevalence of drug resistance among new smear-positive PTB cases only. According to this survey MDR-TB prevalence among new cases was 1%.[8,9] The second 2007 survey demonstrated that MDR-TB prevalence was 1.4% among new and 27.5% among retreatment cases.[10]

The current third survey was conducted 10 years after the second survey, and has demonstrated that MDR-TB prevalence increased 3.8 times among new cases (5.3%), but decreased 1.7 times among retreatment cases (16.5%) (Table 43).

According to 2016 DRS, 31.1% of MTB isolates from new PTB patients were resistant to any anti-TB drug, 22.5% – to isoniazid, 5.5% – to rifampicin and 23.3% – to streptomycin. Thus, the prevalence of primary DR-TB increased in 2016 compared to 2007.

Table 43. Findings of the National Anti-Tuberculosis Drug Resistance Survey in Mongolia

Drug resistance	1999	2007		2016	
	New	New	Retreatment	New	Retreatment
Proportion of DR-TB cases	**29.4%**	**18.5%**	**46.5%**	**31.1%**	**41.6%**
Isoniazid	15.3%	12.6%	36.5%	22.5%	34.1%
Rifampicin	1.2%	2.2%	31.0%	5.5%	17.6%
Streptomycin	24.2%	11.5%	33.5%	23.3%	33.7%
Ethambutol	1.7%	1.7%	22.0%	5.1%	13.1%
Proportion of MDR-TB cases	**1%**	**1.4%**	**27.5%**	**5.3%**	**16.5%**

This is an alarming finding, which warrants large scale measures to prevent the spread of MDR-TB and strengthening of infection prevention and control. Rapid increase in the prevalence of primary MDR-TB could potentially threaten national security, and cause significant damage to human health and the country's economy, if uninterrupted.

Drug resistance among retreatment TB cases reached 41.6%, which was 10.5% less than in 2007. In particular, resistance to isoniazid (34.1%), rifampicin (17.6%) and ethambutol (13.1%) decreased, but resistance to streptomycin (33.7%) remained high. Decline in drug resistance, especially resistance to the most important first-line drugs (isoniazid, rifampicin and ethambutol) among retreatment cases is a sign of progress in controlling healthcare-related acquired drug resistance (Table 44).

Table 44. Prevalence of TB resistant to first-line drugs, by year of DRS

Drug resistance	1999	2007	2016
Susceptibility to all drugs (%) 95% CI	70.6	74.9% (71.9–77.8)	66.9 (64.4–69.3)
New TB case: Prevalence of DR-TB (%) 95% CI	29.4 (25.2–34.0)	18.5% (15.7–21.6)	31.1 (28.5–33.9)
Retreatment TB case: Prevalence of DR-TB (%) 95% CI	–	46.5 (39.4–53.7)	41.6 (35.6–47.7)
Overall prevalence (%) 95% CI		25.1 (22.2–28.1)	33.1 (30.6–35.6)

Although drug resistance among retreatment TB cases declined according to 2016 DRS, the prevalence of DR-TB overall and among new TB cases increased posing significant threat to public health.

Resistance to isoniazid, ethambutol, rifampicin and streptomycin among new TB cases increased compared to the previous two rounds of DRS in Mongolia. However, among retreatment cases resistance to isoniazid (34.1%), rifampicin (17.6%) and ethambutol (13.1%) decreased, and resistance to streptomycin (33.7%) remained stable (Figure 10, Figure 11).

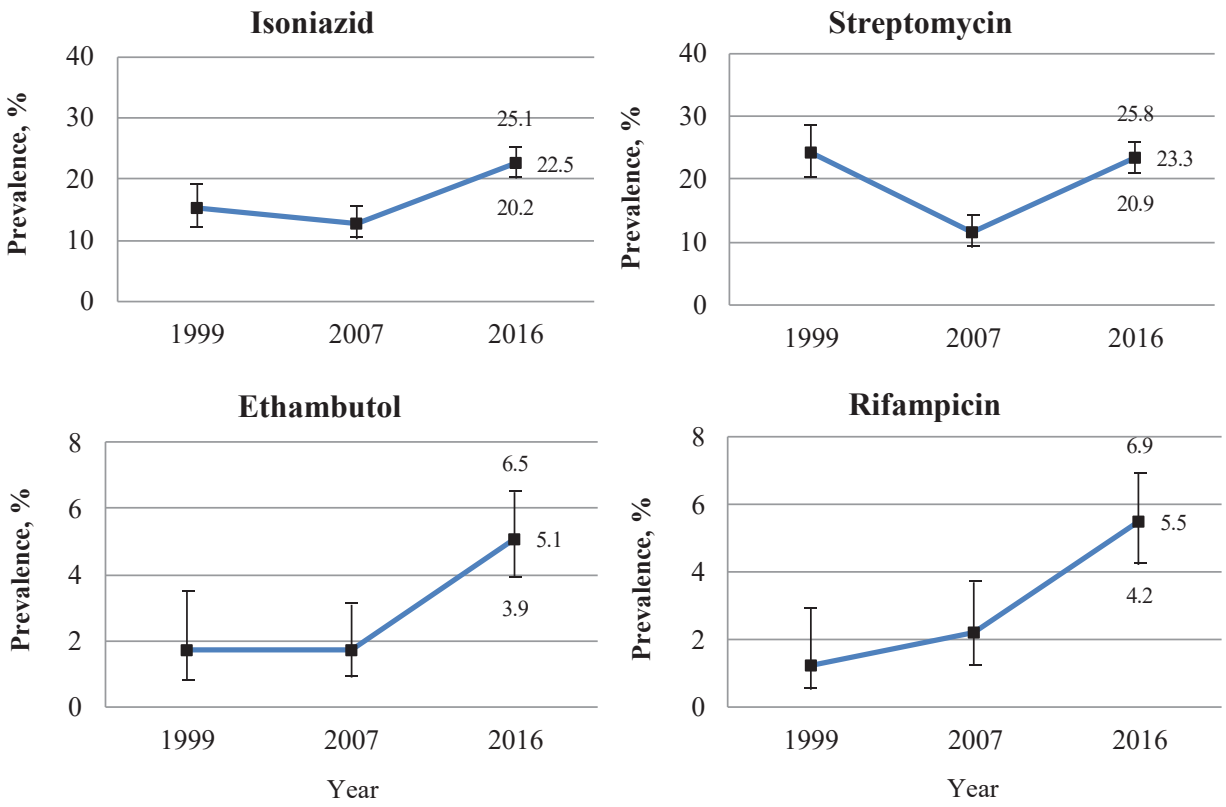

Figure 10. Trends in resistance to first-line drugs among new TB cases

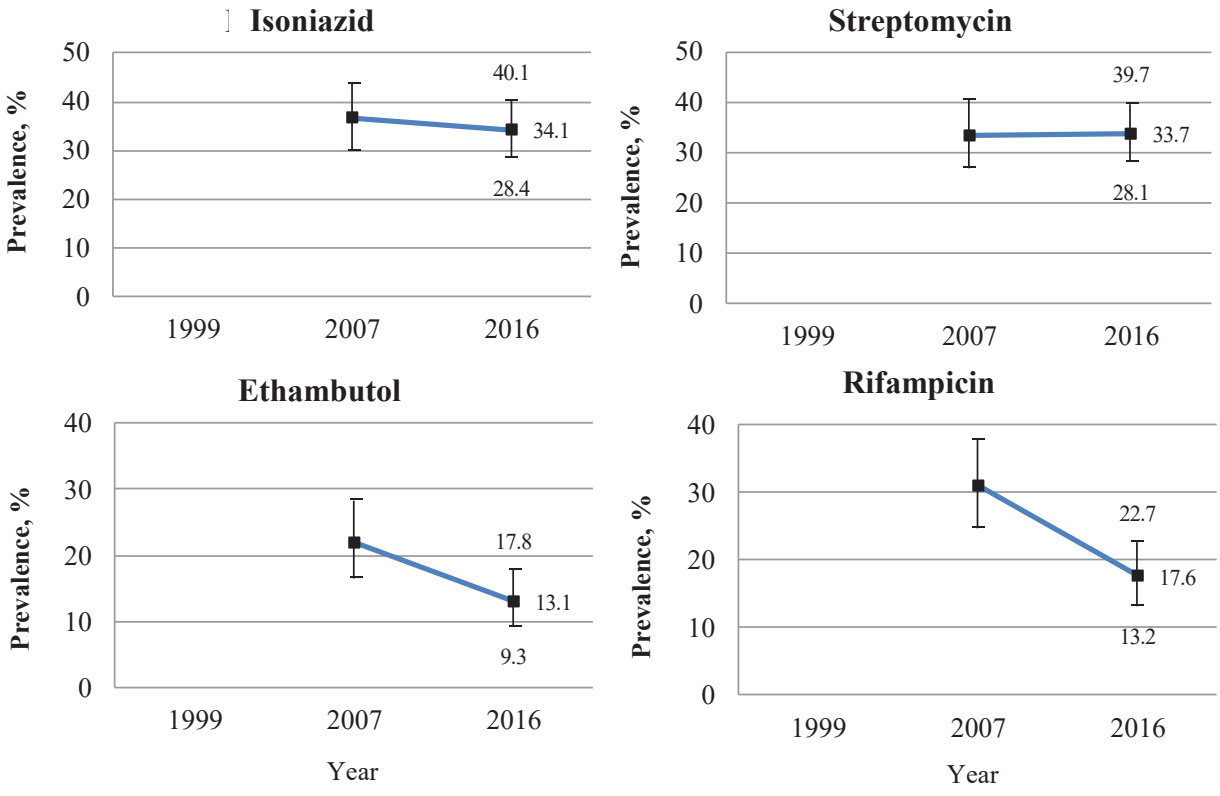

Figure 11. Trends in resistance to first-line drugs among retreatment TB cases

Table 45. Prevalence of MDR-TB, by year of DRS

Drug resistance	1999	2007			2016		
	New	New	Retreatment	Total	New	Retreatment	Total
MDR-TB	1.0 (0.4–2.5)	1.4 (0.7–2.7)	27.5 (21.4– 34.2)	7.5 (5.9–9.6)	5.3 (4.1–6.7)	16.5 (12.2–21.5	7.4 (6.1–8.9)
HR	0.2 (0.0–1.4)	0.2 (0.01–1.0)	5.6 (1.1–6.4)	0.8 (0.4–1.8)	0.3 (0.05–0.7)	0.4 (0.009–2.0)	0.3 (0.07–0.7)
HRE	0.0	0.2 (0.01–1.0)	4.3 (0.6–5.0)	0.6 (0.2–1.5)	0.08 (0.02–0.5)	0	0.07 (0.02–0.4)
HRS	0.2 (0.0–1.4)	0.5 (0.1–1.5)	5.0 (2.4–9.0)	1.5 (0.9–2.7)	1.0 (0.5–1.8)	3.4 (1.6–6.3)	1.4 (0.9–2.2)
HRES	0.5 (0.1–1.8)	0.6 (0.2–1.7)	17.5 (12.5– 23.5)	4.6 (3.3–6.3)	3.9 (2.9–5.2)	12.7 (9.0–17.3)	5.6 (4.4–6.9)

MDR-TB prevalence increased among new, but decreased among retreatment cases. In particular, HR-resistance remained stable among new TB cases, but decreased sharply from 5.6% in 2007 to 0.4% in 2016 among retreatment cases.

Prevalence of TB resistant to 4 main anti-TB drugs (HRES) among new cases increased from 0.5% to 3.9%. This could be due to inadequate treatment monitoring when using fixed-dose combinations in TB treatment. Among retreatment cases the prevalence of resistance to HRES was 12.7% (95% CI: 9.0–17.3) and resistance to HRS was 3.4% (95% CI: 1.6–6.3), which was lower than in 2007. Resistance to four main anti-TB drugs (HRES) increased sharply among new cases posing a significant challenge in TB treatment (Table 45).

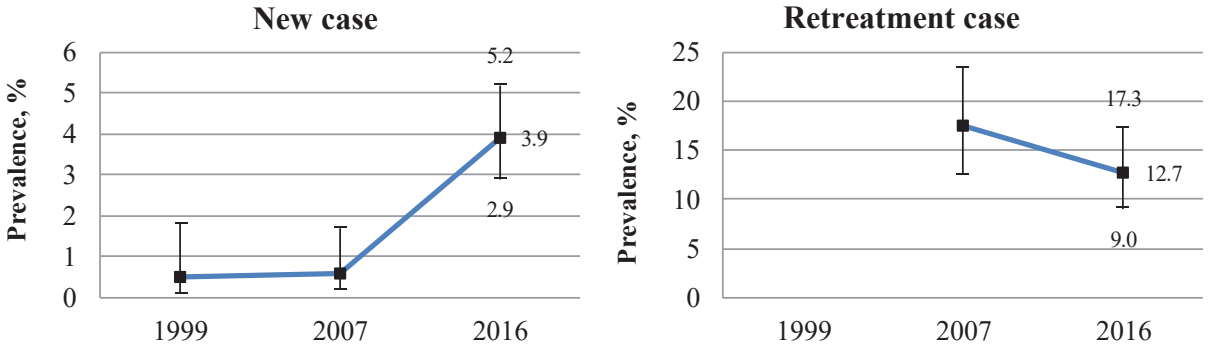

Figure 12. Trends in resistance to all first-line drugs (HRES) according to case classification

Prevalence of TB resistant to all first-line drugs (HRES) increased among new and decreased among retreatment cases (Figure 12).

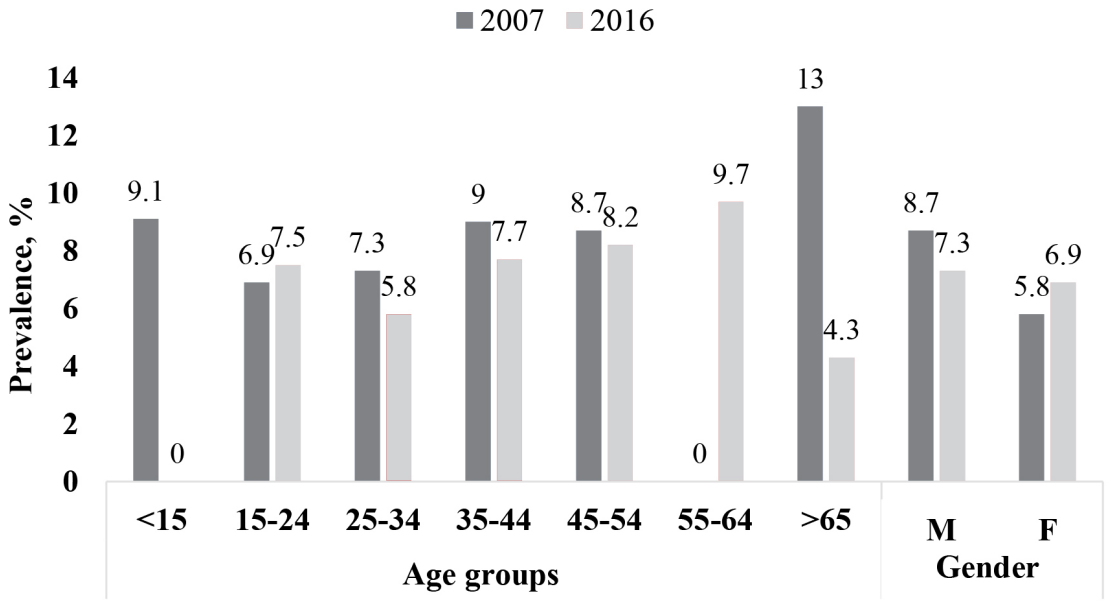

Figure 13. Comparison of age and gender-specific MDR-TB prevalence to 2007 DRS findings

MDR-TB prevalence decreased in under-15 and above 65 age groups, but increased in 15–24 and 55–64 year-olds compared to 2007. There was a slight increase in females as well (Figure 13). Prevalence of DR-TB among new cases was 32.5% in rural areas, 30.3% in Ulaanbaatar City and 35.3% in prisons, which was an increase compared to the previous two rounds of DRS. The corresponding prevalence among retreatment cases was 48.6% in rural areas and 37.7% in Ulaanbaatar City, which was 5.2–4.8% less compared to the previous DRS rounds. However, the prevalence of DR-TB among retreatment cases in prisons was 66.7%, which was almost twice as high as in 2007 (35.3%) (Table 46).

Table 46. Prevalence of drug-resistant TB in Mongolia, by place of residence

Place of residence	1999	2007		2016	
	New (%) 95% CI	New (%) 95% CI	Retreatment (%) 95% CI	New (%) 95% CI	Retreatment (%) 95% CI
Rural	29.6 (25.6–35.1)	19.2 (14.8–24.3)	53.8 (43.0–64.4)	32.5 (28.2–37.1)	48.6 (38.7–58.5)
Ulaanbaatar	28.6 (20.6–38.2)	16.9 (13.1–21.1)	42.5 (32.9–52.4)	30.3 (26.8–33.9)	37.7 (30.0–46.0)
Prison Hospital	–	30.0 (6.7–65.2)	0	35.3 (14.2–61.7)	66.7 (22.2–95.7)
"Enerel" Hospital	–	100.0 (2.5–100.0)	100.0 (2.5–100.0)	16.6 (2.0–48.4)	33.3 (7.5–70.1)

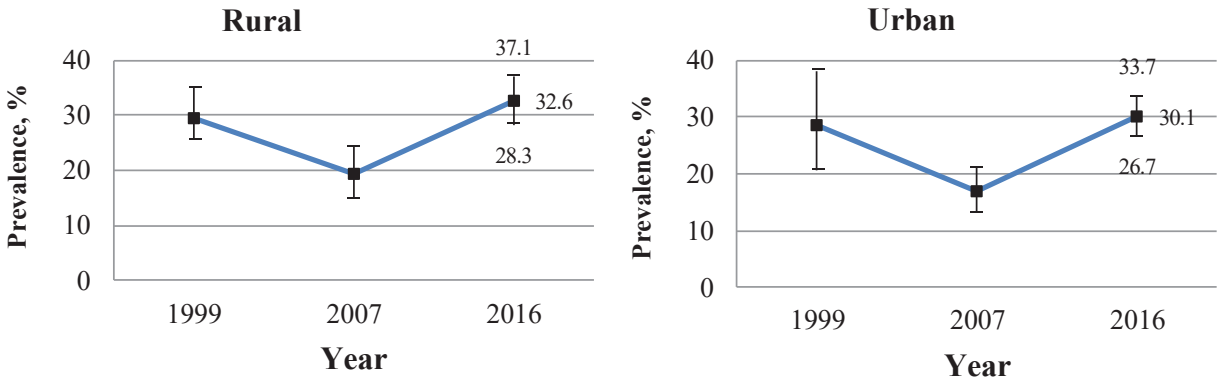

Figure 14. Trends in prevalence of DR-TB among new cases, by place of residence

Prevalence of DR-TB among new cases increased both in rural and urban settings (Figure 14).

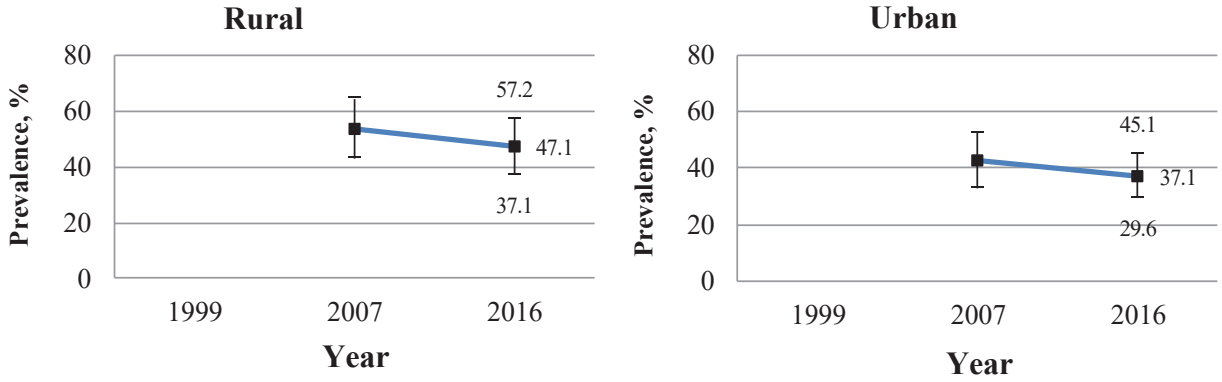

Figure 15. Trends in prevalence of DR-TB among retreatment cases, by place of residence

Prevalence of DR-TB among retreatment cases decreased both in rural and urban settings (Figure 15).

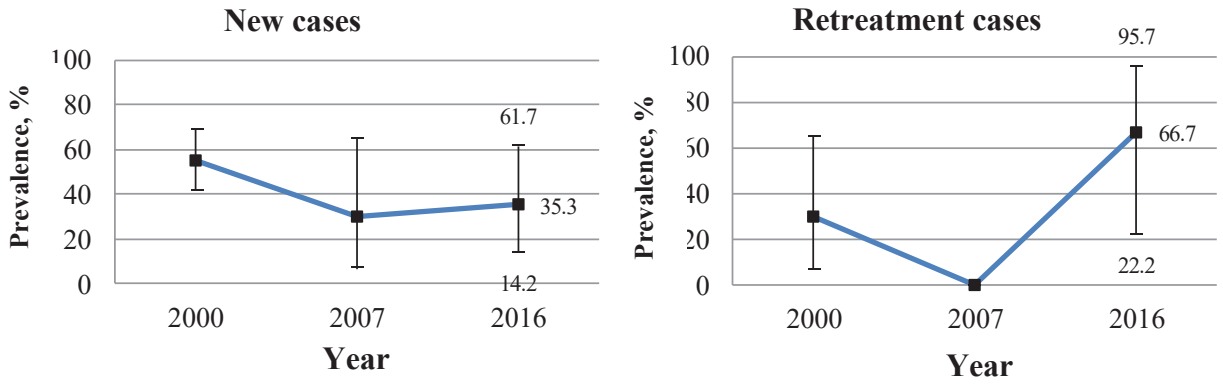

Figure 16. Trends in prevalence of DR-TB among prisoners according to case classification

In prisons the prevalence of DR-TB among new cases decreased compared to 2000, but increased compared to 2007 DRS. However, the prevalence among retreatment cases increased sharply (Figure 16).

11.9. Comparison to Similar Surveys Conducted in Other Countries

Some of the findings of the Third National DRS (2016-2017) in Mongolia were compared to surveillance data and findings of similar studies conducted in other countries and regions.

Table 47. Estimated incidence of MDR and Rifampicin-resistant TB in 2015 in 30 countries with high burden of MDR-TB, by WHO regions, globally and in Mongolia

Countries and regions	MDR/RR-TB* estimation among new cases %		MDR/RR-TB estimation among retreatment cases %	
	Point estimate	95% CI	Point estimate	95% CI
Countries with high burden of MDR/RR-TB	4.3	2.7–5.8	22	14–31
Africa	3.0	1.2–4.9	15	7.5–22
America	2.9	1.6–4.2	12	7.3–17
Mediterranean	4.1	3.0–5.1	17	12–23
Europe	16	11–20	48	42–53
South East Asia	2.6	2.3–3.0	17	15–19
Western Pacific	5.1	3.0–7.2	26	23–30
Global	**3.9**	**2.7–5.1**	**21**	**15–28**
Mongolia (2017)	**5.6**	**4.2–6.9**	**17.9**	**13.5 – 22.3**

Notes: *MDR/RR-TB: Multi-drug and Rifampicin-resistant TB

Estimated prevalence of MDR/RR-TB among new and retreatment cases in 30 countries with high burden of MDR-TB and 6 regions of WHO as presented in WHO Global TB Report-2016 are shown in Table 47 above. [15]

The prevalence of MDR/RR-TB among new cases was 5.6% (95% CI: 4.2–6.9) in 2016 in Mongolia, which was higher than the prevalence of 4.3% (95% CI: 2.7–5.8) in 30 high-burden countries and 3.9% (95% CI: 2.7–5.1) globally. The rate was close to MDR-TB prevalence rate of 5.1% (95% CI: 3.0–7.2) in WPR.

The prevalence of MDR/RR-TB among retreatment cases was 17.9% (95% CI: 13.5–22.3) in 2016 in Mongolia, which was lower compared to 30 high burden countries (22% [95% CI: 14–31]), global average (21% [95% CI: 15–28]) and WPR (26% [95% CI: 23–30]), and similar to MDR-TB prevalence in Africa (15% [95% CI: 7.5–22]), America (12% [95% CI: 7.3–17]), the Mediterranean (17% [95% CI: 12–23]) and South East Asia (17% [95% CI: 15–19]). [15]

The prevalence of MDR/RR-TB among new and retreatment cases in 2016 in Mongolia was less than in WHO European Region (Table 47).

According to the Third National DRS in Mongolia the prevalence of TB resistant to any anti-TB drug among new cases was 31.1% (95% CI: 28.5–33.9) and MDR-TB prevalence among new cases was 5.3% (95% CI: 4.1–6.7), which was similar to the corresponding prevalence in neighboring PRC (34.2% [95% CI: 30.9–37.6] and 5.7% [95% CI: 4.5–7.0], respectively). [16,17] In contrast, the prevalence of TB resistant to any anti-TB drug among retreatment cases was 41.6 (95% CI: 35.6–47.7) or 1.3 times lower than in PRC (54.5% [95% CI: 49.6–59.4]), and MDR-TB prevalence among retreatment cases was 16.5% (95% CI: 12.2–21.5) or 1.6 times lower than in PRC (25.6% [95% CI: 21.5–29.8]). [16,17]

In Mongolia the prevalence of MDR-TB among new and retreatment cases was 4.4 and 3 times lower than in Russian Federation (23.1% among new and 48.6% among retreatment cases), respectively. [18]

Similarly, the prevalence of MDR-TB among new and retreatment cases in Mongolia was 4.3 and 3.3 times lower than in Kazakhstan (22.9% among new and 55.0% among retreatment cases), respectively (Table 48). [18]

Table 48. Comparison to findings of DRS conducted in other countries

№	Countries	Prevalence among new TB cases % (95% CI)		Prevalence among retreatment TB cases % (95% CI)	
		Any drug resistance	MDR-TB	Any drug resistance	MDR-TB
1	India*	21% (19.3–23.4)	2.4% (1.6–3.1)	46.3 (43.1–49.2)	17.4% (15.0–19.7)
2	Philippines	17.4% (15.8-19.2)	1.9% (1.41-2.71)	43.6% (36.4 - 51.2)	21.4% (15.6 - 28.7)
3	Indonesia	17.1% (14.8–19.3)	1.8% (1.0–2.6)	34.3% (22.9–45.7)	17.1% (8.1–26.2])
4	Bangladesh	12.3% (9.3–16.1)	1.4% (0.7–2.5)	43.2% (37.1–49.5)	28.5% (23.5–34.1)
5	Uzbekistan	47.4% (41.9-52.9)	23.2%(17.8-29.5)	82.0% (71.6-89.1)	62.0% (52.5-70.7)
6	Azerbaijan	42.0%	13.0%	61%	28.0%
7	Vietnam†	26.3% (22.5–30.4)	1.8% (1.0–3.3)	62.9% (51.4–73.1)	23.2% (13.6–36.8)
8	Vietnam	32.7% (29.1–36.5)	4.0% (2.5–5.4)	54.2% (44.3–63.7)	23.3% (16.7–29.9)
8	Uganda	10.3% (8.40–12.30)	1.40% (0.6–2.2)	25.9% (18.1–34.8)	12.1% (6.80–19.40)
9	Somali	14.4% (10.3–18.5)	5.2% (2.8–7.5)	53.8% (36.8–70.9)	40.8% (24.7–57.0)
10	Belorussia	55.8% (47.9–63.6)	35.3% (27.7–42.8)	82.4% (73.1–91.6)	76.5% (66.1–86.8)
11	Pakistan	26.8 % (24.1–30.2)	3.7% (2.5–5.0)	44.3% (37.5–51.3)	18.1% (13.0–23.4)
12	Russian Federation		23.1%		48.6%
13	Kazakhstan		22.9%		55.0%
14	PRC‡	24.3% (14.8– 42.1)	5.4% (2.1 – 10.4)	51.8% (27.5 – 67.5)	25.6% (11.7 – 36.8)
15	PRC˚	34.2% (30.9 - 37.6)	5.7% (4.5-7.0)	54.5% (49.6-59.4)	25.6% (21.5-29.8)
16	Mongolia (2016)	31.1% (28.5-33.9)	5.3 % (4.1-6.7)	41.6% (35.6-47.7)	16.5% (12.2-21.5)

Notes: *Gujarat State of India, †South Vietnam, ‡survey conducted in 10 states of PRC, ˚national survey conducted in PRC

Extremely high prevalence of DR-TB in three neighboring countries with strong economic and business ties with Mongolia calls for establishing joint surveillance and response system for the prevention of MDR-TB importation and spread. Population movement between these countries is rising as a result of growing tourism, student exchange and trade in the last decade.

The prevalence of TB resistant to any anti-TB drug among new cases in Mongolia (31.1% [95% CI: 28.5–33.9]) was higher than in Asian countries such as Indonesia (17.1% [95% CI: 14.8–19.3]),[19] Philippines (17.4% [95% CI: 15.8–19.2])[20] and India (21% [95% CI: 19.3–23.4]).[21] Similarly, the prevalence of MDR-TB among new cases in the country was 1.3-3.7 times higher compared to Bangladesh (1.4% [95% CI: 0.7–2.5]),[22] Indonesia (1.8% [95% CI: 1.0–2.6]),[19] Philippines (1.9% [95% CI: 1.41–2.71]), [20] India (2.4% [95% CI: 1.6–3.1])[21] and Vietnam (4.0% [95% CI: 2.5–5.4]).[23,24] Mongolia had lower MDR-TB prevalence among new cases (5.3% [95% CI: 4.1-6.7]) compared to Former Soviet Union republics such as Azerbaijan (13.0%),[18] Uzbekistan (23.2% [95% CI: 17.8–29.5]),[25] and Belorussia (35.3% [95% CI: 27.7–42.8]).[26]

CHAPTER XII. DISCUSSION

New wave of antibiotic resistance

Since late 1990s the WHO has drawn global attention to the threat of antibiotic resistance as it takes the world to the pre-antibiotic era with unstoppable progress of infectious diseases, and has urged Member States to recognize drug-resistant infections as new infections. The WHO Global Strategy for Containment of Antimicrobial Resistance was adopted in 2001, and the summary report on progress made in implementing the Strategy was considered at the Sixty-eighth World Health Assembly in May 2015, which adopted a Global Action Plan on Antimicrobial Resistance to enhance the control of antimicrobial resistance.[27]

There is an urgent need to develop and implement a National Program on Control of Resistance to Anti-TB Drugs in Mongolia. Failure to do so could result in considerable human and socio-economic losses in the nearest future as demonstrated by the findings of this survey.

Damage caused by resistance to anti-TB drugs

According to TSRU (NCCD) data treatment of a drug-susceptible TB case lasts for 6-12 months and costs on average 270,000 MNT, while that of an MDR-TB case lasts for 24 months and costs 9.1-17.2 mln MNT depending on the treatment regimen.

Costs associated with 24-month treatment of one XDR-TB patient are even greater and amount to 41 mln MNT plus about 200,000 MNT for the treatment of side effects. MDR and XDR-TB puts a severe burden on household and country economy as they require long and costly treatment often with severe side effects and distress, and lead to temporary (sometimes lifelong) disability and impairment (such as lifelong deafness or hearing impairment) restricting income-generating activities of patients and their caregivers.

In MDR and XDR-TB patients MTB is shed for 3.5–4 months after treatment initiation on average. Such a prolonged infectiousness of these patients poses significant challenges in interrupting chain of infection transmission in communities. Therefore, it is important to strengthen the surveillance of anti-TB drug resistance and scale-up prevention measures.

Prevalence of TB in Mongolia

According to the First National TB Prevalence Survey in Mongolia the prevalence of smear-positive and bacteriologically-confirmed PTB among adults was 204 (95% CI: 143.0–265.1) and 559.6 (95% CI: 454.5–664.7) per 100,000 population in 2014–2015. This was three times as high as previously estimated. Another alarming finding was that prevalence of smear-positive TB was three times higher than the corresponding notification rate.

The prevalence of smear-negative, but culture-positive TB (340 [95% CI: 273–407] per 100,000 population) was higher compared to smear-positive TB (204 [95% CI: 143–265] per 100,000 population). The prevalence survey has demonstrated that sputum smear testing alone can only detect one-third of bacteriologically-confirmed TB. Therefore, it is vital to revise TB detection strategy in Mongolia with the due consideration of local conditions.

The prevalence of bacteriologically-confirmed TB was highest in 15–34 and ≥55 age groups. Universally high prevalence of TB in all age groups and all strata suggests active TB transmission in communities in Mongolia. [4]

Prevalence of TB resistant to first line drugs

According to 2016 DRS the prevalence of resistance to first-line anti-TB drugs was higher among retreatment (41.6%) compared to new (31.1%) TB cases (p=0.001). Resistance to Isoniazid

was detected in 22.5% of new and 34.1% of retreatment TB cases (p<0.001). Similarly, resistance to Rifampicin was significantly higher among retreatment (17.6%) than new (5.5%) TB cases (p<0.001). Resistance to ethambutol was also more common among retreatment (13.1%) compared to new (5.1%) TB cases (p<0.001). Streptomycin-resistance was detected most commonly among both new (23.3%) and retreatment (33.7%) cases (p<0.001).

Resistance to isoniazid, rifampicin, ethambutol and streptomycin was high especially among retreatment cases. In particular, resistance to rifampicin among retreatment cases was three times higher compared to new cases.

There was no significant difference in the prevalence of TB resistant to first-line drugs among new (15.6%) and retreatment (13.9%) cases.

MDR-TB prevalence among retreatment cases was 16.5% (95% CI: 12.2–21.5) or three times more than among new (5.3% [95% CI: 4.1–6.7]) cases (p<0.001). The overwhelming majority of MDR-TB cases among both new (73.8%) and retreatment (77.3%) cases were resistant to 4 first-line anti-TB drugs.

The fact that three-quarters of MDR-TB cases were resistant to 4 first-line anti-TB drugs could be due to inadequate treatment monitoring and active transmission of primary MDR-TB in the community.

This is also a likely consequence of inadequate treatment monitoring and weak program management when using fixed-dose combinations in TB treatment.

Increase in TB resistant to most effective and affordable four main anti-TB drugs (HRES) poses a significant challenge in TB treatment in the future.

Lack of statistically significant difference in resistance to first-line drugs by age, gender and place of residence is a sign of widespread high prevalence of drug resistance in the community.

Three times higher prevalence of rifampicin resistance among retreatment vs. new TB cases could be due to poor monitoring and management of directly observed TB treatment.

There was no difference in the prevalence of MDR-TB among new cases by place of residence (urban, rural or prison), but the prevalence among retreatment cases was considerably high in prisons (66.7%). Therefore, enhancing treatment monitoring and infection control in prisons is vital.

According to univariate analysis MDR-TB was associated with the history of contact with DR-TB case. Therefore, it is important to strengthen monitoring of DOTS and contact tracing, and early detection of DR-TB.

In terms of the outcome of the last treatment 78% of the previously treated TB cases was treated successfully (cured, treatment completed), 14.9% was lost to follow-up and 7.1% failed treatment. Of 171 retreatment cases from Ulaanbaatar, 74.9% was treated successfully and 19.3% was lost to follow-up. This is a clear consequence of inadequate DOTS monitoring and a prerequisite of DR-TB transmission.

Prevalence of TB resistant to second line drugs

Prevalence of resistance to second-line anti-TB drugs was not assessed in the previous two rounds of DRS in Mongolia. The current survey found that 89.5% (95% CI: 82.0–94.7) of Rifampicin-resistant TB cases was susceptible to second-line anti-TB drugs. The corresponding rate for new cases was 88.5% (95% CI: 77.8–95.3) and for retreatment cases was 90.9% (95% CI: 78.3–97.5).

There was no significant difference in the prevalence of TB resistant to second-line drugs among new (11.5%) vs. retreatment (9.1) cases.

Prevalence of XDR-TB among new cases was 4.9% (95% CI: 1.0–13.7), and all XDR-TB cases were resistant to AM, KM, CM and OFL. No case of XDR-TB was detected among retreatment cases. It is quite alarming that all XDR-TB cases have been detected among new TB cases.

Second-line anti-TB drugs are the last resort wide-spectrum antibiotics. Therefore, their extensive use for the treatment of pneumonia, genito-urinary diseases and following major surgeries, and over-the-counter sales should be discontinued.

There is an urgent need to develop and implement national policy on use and stock-piling of anti-TB drugs in Mongolia.

Risk factors

Univariate analysis revealed an association between MDR-TB among new cases and history of contact with DR-TB case (OR=2.7 [95% CI: 1.1–6.5], p=0.032).

According to 2016 report of TSRU (NCCD), 185 (10.4%) TB cases were detected among household contacts of MDR-TB patients in 2006-2016. Proportion of the diseased among household contacts of MDR-TB patients was 2.5 times higher compared to household contacts of drug-susceptible TB patients (4.1%). Therefore, enhancing measures to break the chain of TB transmission through tracing of household and other close contacts of TB index case, early detection of infectious TB and direct observation of every dose of treatment is necessary.

According to univariate analysis MDR-TB was associated with imprisonment (OR=9.0 [95% CI: 1.9–43.1], p=0.006) among retreatment cases. In other words, odds of MDR-TB were 9 times higher among prisoners compared to urban TB cases.

According to N. Naranbat et al. (2000) the prevalence of primary DR-TB among prisoners was 55.4% or by 26% more than in the general population, and MDR-TB prevalence was 16.1% or 16.1 times more than in the general population.

According to routine TB surveillance report (2011–2015) cure rate of smear-positive new PTB cases in prisons decreased from 80.6% in 2013 to 65.2% in 2015, and treatment failure increased from 6.5% to 34.8% during the same period. This is likely to be related to inadequate treatment monitoring and infection control.

Poor hygiene conditions, including inadequate ventilation, natural lighting and overcrowding in prisons coupled with malnutrition, emotional distress and lack of healthcare services create favorable conditions for the transmission of respiratory diseases, particularly TB.

Comparison to previous rounds of DRS in Mongolia

National DRS was conducted in 1999, 2007 and 2016 in Mongolia. The 1999 DRS assessed the prevalence of drug resistance among new smear-positive PTB cases only, and the prevalence of MDR-TB was 1% among new TB cases. The 2007 DRS found that the prevalence of MDR-TB was 1.4% among new and 27.5% among retreatment cases.

The current third national DRS was conducted a decade after the second survey, and detected MDR-TB in 5.3% of new and 16.5% of retreatment TB cases. Thus, the prevalence of MDR-TB increased 3.8 times among new, but decreased 1.7 times among retreatment cases.

Compared to 2007 primary resistance to anti-TB drugs increased in 2016, and the prevalence of resistance to any anti-TB drug was 31.1%, to Isoniazid – 22.5%, to Rifampicin– 5.5% and to Streptomycin – 23.3% among new PTB cases.

Prevalence of DR-TB among retreatment cases decreased by 10.5% to 41.6% in 2016 compared to the previous DRS. Particularly, prevalence of resistance to isoniazid (34.1%), rifampicin (17.6%) and ethambutol (13.1%) decreased, but resistance to streptomycin (33.7%) remained high. Decrease in drug resistance among retreatment cases could be attributed to better treatment monitoring by healthcare workers.

MDR-TB prevalence is increasing among new, but decreasing among retreatment TB cases as demonstrated by three rounds of DRS in Mongolia.

Prevalence of TB resistant to four main first-line drugs (HRES) increased from 0.5% to 3.9% among new cases possibly due to poor monitoring of treatment with fixed-dose combinations. Among retreatment cases the prevalence of resistance to HRES decreased to 12.7% (9.0–17.3) and the prevalence of resistance to HRS decreased to 3.4% (1.6–6.3) in 2016 compared to 2007. Sharp increase in the prevalence of resistance to four main anti-TB drugs (HRES) among new cases could potentially pose significant challenges in TB treatment in the nearest future.

Compared to 2007 DRS the prevalence of MDR-TB declined in under-15 and above 65 age groups, and increased in 15–24 and 55–64 year-olds. It also increased in females by 3.1%. Prevalence of DR-TB among retreatment cases in prisons increased almost twice to 66.7% in 2016 compared to 35.3% in 2007.

According to routine TB surveillance data, MDR-TB notification rate increased from 4.6 to 7.7 per 100,000 population between 2007 and 2016 in Mongolia. Similarly, MDR-TB notification rate in prisons increased from 50 to 83.3 per 100,000 population during the same reporting period.

Prevalence of DR-TB among prisoners and retreatment cases increased compared to 2007. It is crucial to improve TB detection, infection control, DOTS monitoring and hygiene conditions in prison.

Comparison to performance of laboratory EQA in 2006 and 2016

NTRL has participated in RIT-JATA EQA to test proficiency for 1st line DST since 2006, and for 2nd line DST since 2009. Specificity and sensitivity of DST has been rated as "satisfactory".

Results of DST proficiency testing in 2006 and 2016, when the national DRS were conducted, are shown below. Specificity and sensitivity of DST for isoniazid and rifampicin were 100% in both survey years. Sensitivity of DST for ethambutol was 100% in both survey years, while its specificity was 70% in 2006 and 66.7% in 2016. Sensitivity of DST for streptomycin was 93% in 2006 and 100% in 2016, while its specificity was 93% in 2006 and 73.3% in 2016.

Drugs	Sensitivity		Specificity	
	2006	2016	2006	2016
Isoniazid	100%	100%	100%	100%
Rifampicin	100%	100%	100%	100%
Ethombutal	100%	100%	70%	66.7%
Streptomycin	93%	100%	93%	73.3%

Why DR-TB is increasing in Mongolia?

According to TB care guidelines, which were effective at the time of this survey (Order of Health Minister No.319 of 2014), DST was performed if TB case failed treatment with first-line anti-TB drugs, was previously treated for TB, defaulted, relapsed, had close contact with DR-TB case, or had HIV co-infection.

In other words, new TB patients with primary drug resistance underwent DST only after failure of treatment with first-line anti-TB drugs. This resulted in treatment delay and prolonged infectiousness of these patients. In summary, not performing DST on all new TB cases contributed to late diagnosis and treatment of DR-TB.

Mid-term review of the National TB Prevention and Control Strategy (2010–2015) was undertaken jointly with WHO experts in 2013. According to the review, about 2700 smear-positive TB cases were diagnosed annually, and treatment was commenced in only about 2000 (~75%) cases in the same year due to the need for repeated testing in some cases and treatment evasion in the majority of cases (20-25%). Failure to treat all laboratory-confirmed TB cases is one of the main causes for continued transmission of infection on the community.

According to 2016 TSRU (NCCD) report 80.6% of cases were cured, 4.0% completed treatment, 2.3% died, 8.1% failed and 5.1% defaulted. Mortality due to TB increased by 26 cases compared to the previous year.

TB surveillance report for 2011-2015 demonstrated that the number of relapsed and retreatment cases increased year on year from 220 (4.6%) in 2013 to 415 (8.4%) in 2015. A total of 1,192 relapsed TB cases were notified during 2010-2014, and treatment outcome data was available for 1,153 cases. Of the latter, 58.2% were cured, 13.8% completed treatment, 5.6% died, 17.8% failed, 4.3% defaulted and 0.3% were transferred to another facility. During the reporting period 725 cases were retreated after previous treatment failure or default, and treatment outcome data was available for 706 of these cases. Of the latter, 42.7% were cured, 27.5% completed treatment, 5.0% died, 12.2% failed, 10.6% were lost to follow-up and 1.5% were transferred. The above data demonstrates low cure rate and high rates of mortality, treatment failure, default and loss to follow-up among relapsed and retreatment TB cases.

High rates of treatment failure and default on one hand, and delayed diagnosis of DR-TB on the other increase the risk of infection transmission in the community.

The current national survey detected 533 (34.1%) cases with high infectiousness grade (2+; 3+) on smear testing, which was yet another sign of delays in diagnosis and increased risk of infection transmission in the community.

According to data for the past 6 years number of patients disabled as a result of TB, particularly the number of the severely (>70%) disabled, is increasing. In 2016, 274 persons died due to TB, which was more than in the previous year. Of these cases, 159 (58%) died at the hospital, 95 (34.7%) – at home and 20 (7.3%) – in other places or due to injuries. These data indicate that there are delays in TB diagnosis and lack of access to health services for complicated cases, which are often highly infectious.

Laboratory diagnosis of MDR-TB in Mongolia dates back to 2003, and its treatment – to 2006. Since then 2201 MDR-TB cases have been diagnosed, of whom 1683 (76.4%) commenced treatment, 324 (14.7%) died while on a waiting list for treatment, and 194 (8.8%) refused treatment.

According to TB surveillance report (2011–2015) 44.8% of MDR-TB cases had HRES resistance, 3.5% had HRE resistance, 15.7% had HRS resistance, 20.9% had HR resistance, and 11.1% had R resistance.

Increased prevalence of DR-TB is a result of improved laboratory capacity on one hand, and increased active transmission of infection in the community on the other.

Retrospective analysis of new TB cases, who underwent treatment in 2010–2011, has demonstrated that 35% of cases with first-line drug treatment failure had MDR-TB, and 59% of these treatment failure cases were resistant to all first-line anti-TB drugs (including Streptomycin).

MDR-TB treatment success rate was 64% in 2008 and increased to 67.5% in 2016 in Mongolia. However, sputum conversion rate at Month 6 of MDR-TB treatment declined from 80% in 2006 to 65.2% in 2016, and loss to follow-up increased from 4% to 13.6% fuelling the risk of transmission of primary DR-TB in the community.

Laboratory capacity to perform second-line DST was established in 2009 in Mongolia. Since then, 44 XDR-TB cases have been diagnosed, and as of 2015, 75% of them or 33 cases died and 5 patients have commenced treatment. The current survey has detected XDR-TB among new TB cases only.

Laboratory capacity for DST has been improving gradually with the introduction of first-line DST on solid media in 1970 (turnaround time – 2 months), second-line DST on solid media in 2009 (turnaround time – 2 months), molecular biological MTBDR*plus* assay for first-line DST (turnaround time – 2–3 days), first-line DST on liquid media (BACTEC MGIT) in 2011 (turnaround time – 2–3 weeks), and molecular biological MTBDR*sl* assay for second-line DST in 2013 (turnaround time – 2–3 days). This capacity currently exists only at the national level (NTRL of NCCD).

Delays in seeking medical attention, weak program management and inadequate laboratory capacity contribute to delays in TB diagnosis and treatment, and risk of DR-TB transmission is fuelled by inadequate treatment monitoring.

High prevalence of TB resistant to all 4 main first-line anti-TB drugs in Mongolia could be related to weak capacity to detect, diagnose and treat DR-TB until very recently, which has resulted in the establishment of endemic transmission of the disease, and to the introduction of fixed dose combinations in TB treatment (HR combination since 1996 and HRES combination since 1999). Despite satisfactory TB treatment success rate in the past 2 decades, treatment failure, refusal and default contributed to the transmission of MDR-TB. For instance, 96 (51%) of 188 MDR-TB cases diagnosed in 2003-2006 died before treatment commencement while still on the waiting list.

MDR-TB diagnosis and treatment services were introduced in 2006 in accordance with the Order of Health Minister No. 176 of Jun 06, 2006 without building proper infrastructure in terms of human resources, and infection prevention and control systems. This has resulted in added workload of aimag and district TB dispensaries and has affected the quality of services.

High prevalence of TB resistant to all first-line drugs is a result of poor program management, DOTS supervision and infection control measures.

The findings of the survey have highlighted the importance of introduction and scaling-up of simple molecular technologies such as XpertMTB/RIF and LPA, improving early detection of DR-TB and containing infection transmission.

Delay in diagnosis and drug resistance are the main factors preventing containment of TB transmission and mortality. Introduction of Xpert MTB/RIF recommended by WHO is crucial for early diagnosis of TB, particularly smear-negative and DR-TB. XpertMTB/RIF has been introduced since October 2013 in Mongolia, and currently is performed at NTRL of NCCD, RDTC in Dornod aimag, Darkhan-Uul aimag general hospital and prison hospital. It is planned to scale-up XpertMTB/RIF testing to provinces with high TB notification and districts of Ulaanbaatar within the framework of the Global Fund-Supported Project to be implemented in 2018–2020.

Availability of TB services in rural settings and prisons needs to be improved. Particular attention should be paid to strengthening and ensuring sustainability of an already established specimen transportation system.

Prevalence of drug resistance among retreatment TB cases

It has already been more than a decade since the introduction of MDR-TB treatment in compliance with the WHO-recommended standard regimen in 2006 in Mongolia. Since then, laboratory capacity has been strengthened at the national level with the support of the Global Fund, MDR-TB outpatient treatment posts have been established in TB dispensaries of aimags and districts with high TB burden, infection prevention and control systems have been upgraded in NCCD, prison hospital and general hospital TB wards in selected aimags, and healthcare providers have been trained in MDR-TB management.

During this period 3 ministerial orders have been issued to guide DR-TB detection, diagnosis and treatment (Order of Health Minister No. 176 of 2006 on Implementing MDR-TB Prevention and Control Measures, Order of Health Minister No. 397 of 2009 on Approval of TB Diagnosis and Treatment Guidelines, and Order of Health Minister No. 319 of 2014 on Approval of Instructions for TB Care).

According to the above orders DST is performed in the following cases: (1) positive smear test result at Month 2 (3) of treatment with first-line drugs or at Month 5 of treatment with second-line drugs; (2) smear-positive case, who did not complete previous anti-TB treatment with first or second-line drugs; (3) relapse after treatment with first or second-line drugs; (4) TB case treated for more than 1 month if (a) treatment regimen is unknown, (b) smear conversion of an initially smear-negative case during the course of the treatment, or (c) case remaining smear-negative after treatment default for more than 2 months; (5) chronic smear-positive case; (6) TB case detected among family members or other close contacts of DR-TB patient; and (7) TB-HIV co-infection. This policy has implications for early detection and timely management of DR-TB among patients on TB treatment. For instance, according to TB surveillance report (2011–2015) cure rate of relapsed TB cases increased from 55% in 2010 to 58% in 2014, while mortality and treatment failure decreased 2.7 times (mortality decreased from 9.0% to 3.5%, and treatment failure declined from 20.0% to 7.4% between 2010 and 2014). Early detection of drug resistance among retreatment TB cases has likely contributed to such improvements in treatment outcomes. Unfortunately, treatment default among relapsed TB cases almost tripled from 2.4% in 2010 to 6.7% in 2014.

DOTS Plus sub-program has been implemented since 2006, and has contributed to the decline of DR-TB prevalence among retreatment cases through the introduction of drug susceptibility testing of suspected DR-TB cases.

The evidence above demonstrates that TB control and prevention measures in the country tend to target diagnostic and treatment services provided to TB patients in healthcare facilities, while neglecting public health aspects of population-based prevention, early detection and communication. On the other hand, current human resources, service infrastructure and organization are falling short of providing high quality, accessible services to contain the spread of DR-TB.

Mutations conferring drug resistance in MTB species isolated in Mongolia

Study of gene mutations conferring drug resistance in 109 MTB species and 41 smear-positive specimens of 150 MDR-TB cases diagnosed in 2009–2010 found rpoB gene mutation at codon S531L (MUT3) in 83.3% of multi-drug resistant strains, and mutation in *inhA* gene in 64.3% of Isoniazid-resistant strains.

Mutation in *rpoB* gene at codon S531L (MUT3) was found in 91.3% (21/23) of Rifampicin-resistant strains, and mutation in *inhA* gene was found in 67.2% (43/64) of Isoniazid-resistant strains isolated from TB cases detected by the National TB Prevalence Survey (2015-2016).

In a study conducted in South Africa 70.5% of Rifampicin-resistant strains had mutation in *rpoB* gene at codon S531L, and 64.1% of isoniazid-resistant strains had mutation in *katG* gene. In Ethiopia 82.4% of mutation in *rpoB* gene was detected at codon S531L, and 90.2% of isoniazid-resistant strains had *katG* gene mutation. According to study of MTB species isolated in 1996–2001 in Russia, Isoniazid-resistance was conferred by mutation in *katG* gene at codon S315T in 93.6% of strains. Similarly, mutation in *katG* gene was detected in 94.3% of Isoniazid-resistant strains in China.

In our study mutation in rpoB gene was detected in all rifampicin-resistant strains, and the gene mutation at codon S531L (MUT3) was detected in 84.4% (92/109) of these strains, which was similar to the studies above. However, isoniazid-resistance was conferred mainly by mutation in *inhA* gene, which was different from the findings of studies conducted in other countries, but similar to the study conducted in Mongolia earlier.

Mutations in *inhA* gene confer low-level resistance to isoniazid, while katG mutations confer high-level isoniazid resistance. Predominance of *inhA* mutations in Mongolia according to the current and previous studies supports the use of high-dose Isoniazid in the treatment regimen of isoniazid-resistant cases.

Mutations in *rpoB* gene at codon S531L (MUT3) conferring resistance to rifampicin and *inhA* gene mutations at codon C–15T (MUT1) conferring resistance to isoniazid were predominant according to our study.

Comparison of DR-TB prevalence in Mongolia to neighboring and other countries

Globally, MDR-TB prevalence among new TB cases is 3.9% (95% CI: 2.7–5.1) and among retreatment TB cases is 21% (95% CI: 15–28) (Global TB report, 2016). Mongolia is a part of the WPR, where the prevalence of MDR-TB among new cases is 30% higher and among retreatment cases 23% higher than the global average.[15]

Russian Federation, PRC and India account for almost half (45%) of all MDR-TB cases in the world, and are among 30 high TB burden countries.

In Russian Federation an estimated prevalence of MDR-TB among new cases is 22% and among retreatment cases is 53%, and incidence of MDR-TB is 42 per 100,000 population. The corresponding rates in PRC are 6.6%, 30% and 5.1 per 100,000 population, respectively.

According to Mongolia's Third National DRS the prevalence of resistance to any anti-TB drug was 31.1% (95% CI: 28.5–33.9) and that of MDR-TB was 5.3% (95% CI: 4.1–6.7) among new TB cases, which was similar to corresponding rates of 34.2% (95% CI: 30.9–37.6) and 5.7% (95% CI: 4.5–7.0) in neighboring PRC, respectively. However, the prevalence of resistance to any anti-TB drug among retreatment cases was 41.6% (95% CI: 35.6–47.7), which was 1.3 times lower than in PRC (54.5% [95% CI: 49.6-59.4]). Similarly, MDR-TB prevalence among retreatment cases was 16.5% (95% CI: 12.2–21.5) or 1.6 times less than in PRC (25.6% [95% CI: 21.5–29.8]).

In neighboring Russian Federation the prevalence of MDR-TB is 23.1% among new and 48.6% among retreatment cases, which is 4.4 and 3 times higher than in Mongolia, respectively.

Similarly, the prevalence of MDR-TB among new and retreatment cases in Mongolia was 4.3 and 3.3 times lower than in Kazakhstan (22.9% among new and 55.0% among retreatment cases), respectively.

The prevalence of resistance to first-line anti-TB drugs among retreatment cases in Mongolia is much lower compared to neighboring countries, which could be due to more effective DOTS implementation in public health sector and almost nonexistent private sector in TB care.

N. Naranbat et al. (1999) found that MTB Beijing type mutation was predominant (64.2%) especially in species resistant to Ethambutol and Rifampicin.

According to B. Buyankhishig et al. (2007) 97.8% of multi-drug resistant MTB strains in Mongolia had Beijing type mutation, and a hypothesis regarding the existence of a more resistant and highly infectious strain was proposed.

G. Ulziijargal et al. (2012) found that MDR-TB in Mongolia was mainly caused by Beijing type MTB resistant to all first-line anti-TB drugs. According to this study 88% of multi-drug resistant MTB strains in Mongolia had Beijing type mutation and MTB belonging to family LAM, Haarlem and NEW1 was detected in few cases. Beijing type MTB is also commonly found among drug susceptible and resistant MTB strains isolated from neighboring Inner Mongolia (PRC) and Southern parts of Russia. A recent study has established that Beijing strains originated in the Northern parts of China, and could potentially rapidly develop drug resistance and spread globally. The study has also identified a number of new MIRU not detected previously elsewhere. One of the underlying causes of this could be an endemic strain, which has been spread in Mongolia or imported from neighboring countries via Trans-Siberian railway connection. It has been noted that it is difficult to establish the origin and transmission pathway of the strain in the absence of more detailed molecular testing data.

Mongolia is located between two "hot spots" with high prevalence of DR-TB in the world. The country has close social and economic ties to its neighbors, and citizens of Mongolia can travel freely to neighboring China and Russia without visa for up to 30 days.

The prevalence of TB resistant to any anti-TB drug among new cases in Mongolia (31.1% [95% CI: 28.5-33.9]) was higher than in Asian countries such as Indonesia (17.1% [95% CI: 14.8–19.3]), Philippines (17.4% [95% CI: 15.8–19.2]) and India (21% [95% CI: 19.3–23.4]). Similarly, the prevalence of MDR-TB among new cases in the country was 1.3–3.7 times higher compared to Bangladesh (1.4% [95% CI: 0.7–2.5]), Indonesia (1.8% [95% CI: 1.0–2.6]), Philippines (1.9% [95% CI: 1.41–2.71]), India (2.4% [95% CI: 1.6–3.1]) and Vietnam (4.0% [95% CI: 2.5–5.4]).

Mongolia had lower MDR-TB prevalence among new cases (5.3% [95% CI: 4.1–6.7]) compared to Former Soviet Union republics such as Azerbaijan (13.0%), Uzbekistan (23.2% [95% CI: 17.8–29.5]) and Belorussia (35.3% [95% CI: 27.7–42.8]).

Based on the evidence above the following causes of active transmission of DR-TB in Mongolia can be identified: (1) delays in seeking medical attention for TB-related symptoms, (2) current policy does not require performing DST in newly diagnosed TB cases, (3) long DST turnaround time of 2 months, (4) delays in treatment commencement following laboratory confirmation of diagnosis, (5) 15-20% of laboratory-confirmed TB cases are lost to follow-up before treatment commencement, (6) high rates of treatment failure, loss to follow-up and death due to weak management of DOTS, (7) inadequate infection prevention and control in healthcare facilities, and (8) weak program management.

In addition to the above internal factors there is a multitude of external risk factors, such as high prevalence of DR-TB in neighboring countries, and growing transmission of highly virulent and rapidly evolving drug resistant Beijing type MTB. Therefore, it is important to conduct in-depth molecular biological studies to establish origin, transmission pathways and full genome sequence of drug resistant MTB strains.

XDR-TB case study

Three cases of XDR-TB have been detected by this survey, and a brief description of the cases is presented below. Materials of medical consilium comprised of aimag/district TB dispensary staff

and physicians of MDR-TB ward of NCCD, NTRL database and additional information provided by patient families via telephone have been used additionally. Information regarding clinical management of these three cases is presented as of August 23, 2017.

Case 1

Background information: Patient 32 years old, male. Place of residence: Songinokhairkhan district of Ulaanbaatar City. Number of household members: 4 (wife and 2 children). Employed at a state-owned company.

Contacts: No TB is notified among household members or close relatives.

History of previous TB treatment: None.

Bacteriological testing and DST: Feb 24, 2016 – sputum smear (+), Feb 29 – HR-resistant (MTBDR*plus*), Mar 28 – culture (++), May 18 – HRES-resistant (DST on solid media), May 25 – XDR-TB (MTBDR*sl*), Jul 18 – resistant to Ofl, Am, Km, Cm (second-line DST on solid media).

CXR: Infiltration shadows in both lungs.

Treatment: Feb 22, 2016 – commencement of treatment with first-line anti-TB drugs. Jun 30 – medical consilium of NCCD made a decision to commence XDR-TB treatment (regimen: Imp 2.0, Mfx 400 mg, Z1600, Lzd600, Cfz100, Amx/Clv-625*2, H900) with the diagnosis "Infiltrating TB in upper lobe of right lung, disintegration phase. AFB (+), resistance to HRES+FLQ, Am/Cm". Body weight: 74 kg. Jul 4 – admitted to MDR-TB ward of NCCD. Oct 27 – discharged from hospital following sputum and culture conversion after 110 days of treatment, and transferred to Songinokhairkhan District TB Dispensary for follow-up treatment. Jan 10, 2017 – medical consilium decided to discontinue Imp from treatment regimen.

Case 1. Bacteriological testing for treatment monitoring

Test/ Month	0	1	2	3	4	5	6	7	8	9	10	11	12	13
Smear	+	++	+	-	+ -	-	-	+ -	-	-	+ -	+ -	-	-
Culture	+	-	+	-	-	-	-	-	-	-	-	-		

Discussion: Case 1 has primary XDR-TB. Treatment regimen has been adjusted based on DST using rapid and conventional methods.

Results of bacteriological testing for treatment monitoring demonstrate that the patient converted to smear-negative status at Month 5 of treatment, but converted back to smear-positive status at Months 7, 10 and 11. This highlights the importance of improving direct observation of treatment administration, monitoring of treatment side effects, and making adjustments to treatment regimen as necessary.

Case 2

Background information: Patient 18 years old, male. Place of residence: Khan-Uul district of Ulaanbaatar City. Number of household members: 4 (parents and younger sibling). Graduated from Khan-Uul district secondary school No.18. Spent considerable time in PC game centers. Was admitted to university, but dropped out, unemployed.

Contacts: No TB is notified among household members or close relatives.

History of previous TB treatment: None.

Bacteriological testing and DST: Aug 2, 2016 – smear (++), Aug 3 – HR-resistant (MTBDR*plus*), Aug 30 – culture (+++), Feb 1, 2017 – XDR-TB (MTBDR*sl*), Feb 6 – HRES-resistant (DST on solid media), Jul 6 – resistant to Ofl, Am, Km, Cm (second-line DST on solid media).

CXR: Infiltration shadows, caverns with thick walls in apices of both lungs.

Treatment: Jul 29, 2016 – treatment with first-line drugs commenced, Aug 25 – MDR-TB treatment commenced based on bacteriological test results. Feb 16, 2017 – medical consilium of NCCD made a decision to commence XDR-TB treatment (regimen: Cm 750 mg, Z1600 mg, Mfx400, Pto500, Cfz100, PAS8.0, H600) with the diagnosis "Fibrous-cavernous lung TB, infiltration phase. AFB (+), resistance to H, R, Am/Cm, FLQ", and the treatment commenced on Feb 22. Body weight: 48 kg. Jul 2, 2017 – underwent lobectomy in Surgery Ward of TB Clinic, NCCD. Jul 27 – medical consilium of NCCD made a decision to discharge and transfer the patient to district TB dispensary for follow-up treatment.

Case 2. Bacteriological testing for treatment monitoring

Test/ Month	0	1	2	3	4	5	6	7	8	9	10	11	12	13
Smear	++	+++	++	+	-	+-	-	+	+-	-	+	+-	-	-
Culture	+++	++	++	+	7к	6к	+	+	+	+	+	+		

Discussion: Case 2 has primary XDR-TB, and has been diagnosed late. Treatment regimen has been adjusted based on DST using rapid and conventional methods.

Underwent lobectomy at NCCD because of slow smear and culture conversion. Discharged from hospital after smear conversion. Although last 2 consecutive smear tests were negative there was no evidence of culture conversion. Therefore, the patient should be given thorough instructions regarding infection prevention and control at home, and household and other close contacts of the patient should undergo regular examinations and testing. On the other hand, it is crucial to improve direct observation of treatment administration, monitor treatment side effects, and make adjustments to treatment regimen as necessary. There is a high risk of treatment failure in case of inadequate treatment monitoring.

Case 3

Background information: Patient 22 years old, female. Place of residence: Selenge aimag. Number of household members: 4 (mother, son, nephew). Lived in a rented apartment in Ulaanbaatar City for 2 years prior to being diagnosed with TB, and worked as a salesmen in a 24-hour grocery store.

Contacts: Brother was diagnosed with TB in 2000 and cured.

History of previous TB treatment: None.

Bacteriological testing and DST: Oct 12, 2016 – sputum smear (++), Oct 13 – HR-resistance (MTBDR*plus*), Nov 11 – culture (++), Nov 11 – XDR-TB (MTBDR*sl*), Mar 6, 2017 – HRES-resistant (DST on solid media), Jul 6 – resistant to Ofl, Am, Km, Cm (second-line DST on solid media).

CXR: Indurated foci in right lung. Cavernous shadow in upper quadrant and high contrast shadow in lower quadrant of left lung.

Treatment: Oct 6, 2016 – treatment with first-line drugs commenced. Nov 3 – medical consilium of NCCD made a decision to commence MDR-TB treatment (regimen: Z1600, Km0.75, Lfx750 mg, Eto500, Cs500, H600), which lasted for 13 days. Nov 16 – medical consilium of NCCD made a decision to commence XDR-TB treatment (regimen: Cm750, Z1600, Cfz100, Pto500 mg, Cs500,

Mfx400, H600) with the diagnosis "Fibrous-cavernous TB in left lung, disintegration phase. AFB (+), resistance to HR, FLQ, Am/Cm", and the treatment commenced on Nov 17. Patient was hospitalized in MDR-TB ward of NCCD for 62 days, discharged on Jan 5, 2017 based on patient's request, and transferred to Selenge aimag TB dispensary for follow-up treatment. Mar 9, 2017 – treatment regimen changed. Aug 8, 2017 – medical consilium made a decision to discontinue Mrp from treatment regimen.

Case 3. Bacteriological testing for treatment monitoring

Test/ Month	0	1	2	3	4	5	6	7	8	9	10	11
Smear	++	+++	++	+++	-	+	+++	++	++	+	++	+
Culture	++	+++	+++	+++	++	+	++	++	+	++	++	

Discussion: Case 3 has primary XDR-TB, and has been diagnosed late. Treatment regimen has been adjusted based on DST using rapid and conventional methods. However, treatment is not effective, ***it is almost clear that the treatment is failing***. Patient discharge from the hospital was not justified because there is no evidence of smear and culture conversion, and the case is highly likely to transmit the infection in the community.

It is crucial to exert efforts on the part of healthcare providers, the case and her family members to continue inpatient treatment of the case under close monitoring of treatment effectiveness and side effects. The case remains smear and culture-positive, putting her close contacts at risk of contracting XDR-TB. The case should be isolated, and provided with palliative care in case of treatment failure.

CHAPTER XIII. CONCLUSIONS AND RECOMMENDATIONS

1. The prevalence of TB resistant to first-line drugs was 31.1% [95% CI: 28.5–33.9] among new and 41.6% [95% CI: 35.6–47.7] among retreatment cases in Mongolia. The prevalence of primary DR-TB increased by 68.1% among new cases and decreased by 10.5% among retreatment cases compared to the previous round of DRS.
2. The prevalence of MDR-TB was 5.3% [95% CI: 4.1–6.7] among new and 16.5% [95% CI: 12.2–21.5] among retreatment cases in Mongolia. The prevalence of MDR-TB increased 3.8 times among new cases and decreased 1.7 times among retreatment cases compared to the previous round of DRS.
3. The prevalence of MDR-TB with additional resistance to second-line TB drugs was 10.5% [95% CI: 5.3–18.0].
4. Increased risk of MDR-TB was associated with the history of contact with DR-TB case (OR=2.7 [95% CI: 1.1–6.5], p=0.032) among new cases and with imprisonment (OR=9.0 [95% CI: 1.9–43.1], p=0.006) among retreatment cases.
5. Mutation in rpoB gene was detected in all Rifampicin-resistant strains, and the gene mutation at codon S531L (MUT3) was detected in 84.4% of these strains. Mutation in inhA gene was predominant (83.4%) in strains resistant to Isoniazid only.

RECOMMENDATIONS

The main strategy for breaking the chain of transmission of DR-TB in the community is to detect cases early, to initiate treatment without delay, and to ensure strict adherence to treatment regimen. In Mongolia TB is diagnosed by smear microscopy in aimag and district TB dispensaries. However, National TB Prevalence Survey (2014–2015) has demonstrated that TB notification rate was 34%. According to TB surveillance reports Mongolia has reached regional and international targets of treatment success rate, which is currently above 85% among new TB cases, and about 60% among MDR-TB patients in the country.

Evidence above highlights the importance of improving TB detection in the community. Improved case detection will result in increased demand for TB treatment, including MDR-TB treatment. Therefore, it is important to build human resource and service capacity for TB.

The following recommendations for strengthening TB control in Mongolia are proposed taking into account the findings of the current survey, TB morbidity, DR-TB prevalence, and existing treatment and diagnostic capacity.

To improve policy and legal environment

- To develop and implement an independent National Program on TB Prevention and Control separately from the currently effective integrated National Program on Communicable Disease Prevention and Control
- To develop and endorse a Law on TB Infection Control (to discourage treatment refusal and default in individuals with infectious forms of TB)
- To develop and implement national policy on use and stock-piling of anti-TB drugs in Mongolia (discontinue extensive use of second-line anti-TB drugs for the treatment of pneumonia, genito-urinary diseases and following major surgeries, and their over-the-counter sales)
- To assess workload and capacity of human resources providing TB care, and to ensure staff numbers are adequate for effective implementation of NTP by providing necessary budget, incentives and other social benefits
- To enforce the implementation of the Order of Health Minister No. A/306 of 2017 on "Measures to Improve TB Services" at all levels of healthcare system
- To submit the survey findings to MOH Advisory Committee on TB for discussion and formulation of policy recommendations

To improve DR-TB detection

- To introduce WHO-endorsed highly sensitive rapid diagnostic tests such as Xpert MTB/RIF in health services at all levels, and to ensure uninterrupted supply of laboratory human resources and reagents.
- To enhance early detection and cost effectiveness of active TB case finding in high risk groups by using digital chest X-ray (CXR) examination and highly sensitive rapid molecular tests such as Xpert MTB/RIF.
- To perform DST on all new and retreatment PTB cases prior to treatment initiation using rapid molecular techniques, and to use DST results in case management.
- To enhance tracing and management of household and close contacts of TB cases with the following treatment outcomes: failure, lost to follow-up, died or refused treatment.

- To improve the accessibility of TB care in rural areas through strengthening an already established specimen transportation system and increasing the frequency, quality and efficiency of specimen transportation especially from rural areas and prisons.

To strengthen DR-TB treatment and follow-up

- To develop TB human resource development policy, and to standardize the number of TB patients per doctor.
- To improve management with first-line anti-TB drugs, and to ensure seamless effective treatment through scaling-up treatment and follow-up based on primary health care (PHC) and communities.

To prevent and halt DR-TB transmission

- To enhance management of the National TB Program (NTP) and Directly Observed Treatment with Short-Course chemotherapy (DOTS).
- To reduce the risk of TB transmission by assessing the risk of loss to follow-up prior to treatment initiation, implementing measures to prevent such loss, and systematically assessing causes of treatment failure, loss to follow-up and treatment refusal on a case-by-case basis.
- To advance the quality of DOTS (especially at TB wards, dispensaries, PHC centers, prisons, "Enerel" hospital for the homeless and NMHC) in order to prevent the transmission of primary DR-TB (especially MDR-TB and XDR-TB).
- To improve TB detection and prevention by strengthening collaboration and coordination with other health programs and projects, and integrating TB care into all outreach programs (e.g. immunization, maternal and child health care, HIV/AIDS outreach, diabetes screening, mental health care).
- To establish local support groups comprised of representatives of health sector, police, social welfare, education sector, local government, employers and non-governmental organizations (NGOs), which will be responsible for implementing targeted measures to improve treatment adherence among defaulted patients.
- To establish palliative services for terminally ill patients with XDR-TB or untreatable chronic TB in order to prevent infection transmission to household members and others.
- To establish TB transmission patterns based on molecular epidemiological survey

To strengthen DR-TB surveillance system

- To maintain and regularly update web-based DST database (tubis.mn) at NTRL; thus, ensuring timely access to patients' DST results for TB doctors.
- To ensure laboratories with Xpert MTB/RIF equipment regularly upload DST results into the web-based DST database.
- To strengthen drug resistance surveillance among new and retreatment TB cases.

To scale-up information, education and communication

- To enhance advocacy for high level decision-makers at all levels (national, subnational, local) in order to put TB high on health sector agenda and to secure political support for TB prevention and control

- To implement systematic IEC activities for the general public on proper use of antibiotics
- To ensure sustainability of routine IEC activities for the general public on TB prevention
- To scale-up IEC activities for employers
- To reduce delays in diagnosis by increasing public awareness about TB signs and symptoms, and implementing routine IEC activities through different mass media channels
- To enhance healthcare worker skills to provide counseling and IEC to TB patients and their families
- To prevent TB transmission in the community by improving the quality of counseling for patients who defaulted, refused treatment or lost to follow-up

To strengthen DR-TB control in prisons

- To improve early detection of TB through systematic active case finding among prisoners
- To strengthen specimen transportation system in prisons
- To enhance the quality of DOTS and to ensure direct observation of each treatment dose
- To enhance infection prevention and control measures in TB Hospital of Prison Camp No. 429
- To revise Joint Order of the Minister of Health, Minister of Defense, and Minister of Justice No. 307/276/312 of 2002 on "Scaling-up TB Prevention and Control"

Priorities for further studies and assessments

- Full genome sequencing of MTB isolated within the framework of the 1st, 2nd and 3rd National DRS in Mongolia.
- Assessment of DOTS Plus sub-program implemented since 2006.
- Conduct 4th DRS in 2022 in case routine DST of all TB cases is not introduced (or in case DST is performed in less than 95% of new PTB cases annually).

CHAPTER XIV. STRENGTHS OF THE SURVEY

Methodology of the 3rd DRS in Mongolia was developed based on 2015 WHO Guidelines for Surveillance of Drug Resistance in Tuberculosis. The survey protocol was reviewed and approved by Ethics Committee of MOH, Scientific Committee of NCCD and WHO WPR Office.

WHO and RIT/JATA provided technical assistance throughout the survey and participated in EQA for laboratory testing and data management. Relevant decision-makers and national and local researchers were trained, and data collection was organized in accordance with the approved methodology.

The Global Fund-Supported Project on AIDS and TB provided financial support for the survey. Sputum specimens were transported from data collection units using specimen transportation system established by the project and managed by USDS.

Use of WHO methodology and contemporary molecular testing technology in the current DRS has enabled accurate estimation of the magnitude of DR-TB in Mongolia. The findings of this 3rd National DRS in Mongolia have been compared to the previous two rounds of DRS as well as similar studies conducted in other countries.

The quality of the current survey was measured using quality indicators such as coverage, participation rate, percent completing questionnaire survey, sputum submission rate, contamination rate and EQA indicators, and according to these indicators the quality of the survey was rated as satisfactory. WHO and RIT/JATA provided support in data management and analysis.

PI, Survey Coordinator and Data Manager participated in WHO Workshop on DRS Data Analysis in Geneva, which has been crucial for data analysis, dissemination of the survey findings and comparisons across countries.

In summary, the current study has updated prevalence estimates of resistance to first-line anti-TB drugs, has established prevalence of resistance to second-line anti-TB drugs, has updated information on mutations conferring drug resistance, and provided evidence for revising and improving current DR-TB detection, diagnosis and treatment strategies in Mongolia.

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