Public Health Action

International Union Against Tuberculosis and Lung Disease
Health solutions for the poor

VOL 3 NO 4 PUBLISHED 21 DECEMBER 2013

Countrywide audit of multidrug-resistant tuberculosis and treatment outcomes in Mongolia

S. Ganzaya,[1] N. Naranbat,[2] K. Bissell,[3] R. Zachariah[4]

http://dx.doi.org/10.5588/pha.13.0052

Setting: Eighteen treatment units for multidrug-resistant tuberculosis (MDR-TB) in Mongolia.

Objective: To determine the total number of MDR-TB cases detected, their resistance patterns, the proportion and characteristics of cases starting treatment, the delay between diagnosis and treatment initiation, and the relation between treatment outcomes and drug resistance.

Design: Retrospective cohort study using routine programme data.

Results: Of 268 MDR-TB cases detected, 168 (63%) were resistant to HRES, 59 (22%) to HRS, 34 (13%) to HR and 7 (3%) to HRE. Of the 268 MDR-TB patients, 139 (52%) started treatment: 69 (50%) were secondary and/or university students, 35 (25%) were unemployed, 24 (17%) were currently employed and 14 (8%) retired, disabled or status was unrecorded. The median time from MDR-TB diagnosis to treatment initiation was 137 days (IQR 43–218). The treatment success rate was 69%; 9% failed treatment, which may indicate extensively drug-resistant TB (XDR-TB) or pre-XDR-TB.

Conclusion: Close to seven in 10 patients in Mongolia had a successful treatment outcome, which is encouraging. Specific problems included the high proportion of students, about half of all diagnosed patients accessed treatment and there was an unacceptable delay of 4 months to treatment. These issues need to be addressed.

Mongolia (population: 2.7 million) ranks fourth among the high tuberculosis (TB) burden countries in the World Health Organization (WHO) Western Pacific Region.[1] TB is the third most common communicable disease in Mongolia after sexually transmitted infections (STIs) and viral hepatitis, and is the leading cause of mortality among all communicable diseases.[2]

The annual TB notification rate is 145 per 100000 population. Treatment success for new smear-positive TB cases has been over 85% since 2000, and reached 88% in 2012. However, failure rates have been increasing, and reached 7.1% in 2012.[2] This may indicate the existence of multidrug-resistant tuberculosis (MDR-TB) among new cases. MDR-TB is caused by strains of *Mycobacterium tuberculosis* that are resistant to at least isoniazid (H, INH) and rifampicin (R, RMP). The emergence of MDR-TB is threatening Mongolia's progress in controlling TB. In 2007, a drug resistance survey showed that 1.4% of new TB cases and 28% of retreatment TB cases had MDR-TB.[3] Between 2006 and 2012, a total of 1171 MDR-TB cases were diagnosed. A drug resistance survey in 2007 showed a rate of any drug resistance of 7.5% (95% confidence interval [CI] 5.9–9.5), with respectively 1.4% (95%CI 0.7–1.6) and 27.5% (95%CI 21.8–34.1) among patients with and without a history of treatment. The MDR-TB case detection rate among retreatment cases was 68% of that estimated (129 notified/170 estimated), and is >200% of that estimated among new cases (56 notified/33 estimated), according to the 2007 drug resistance survey, questioning the accuracy of the 2007 estimates today.

Mongolia started implementing programmatic management of drug-resistant TB in 2006, and revised its national TB guidelines in 2009 to include the management of both drug-susceptible and -resistant TB.[4] Attempts have since been made to scale up access to MDR-TB treatment, supported by international institutions such as the Green Light Committee (providing drugs and technical assistance) and the Global Fund to Fight AIDS, Tuberculosis and Malaria. There are several operational challenges to MDR-TB management. Diagnosis is difficult and is possible only in the capital city, incurring delays of several months; access to drugs and treatment is limited to centralised health facilities, and treatment is long (18–24 months) and involves many drugs. In addition, public road networks are poor and public transport is expensive; 39% of the rural population lives under the poverty line. Thus, although Mongolia is scaling up MDR-TB treatment, a number of barriers are likely to affect the time taken to initiate treatment and treatment outcomes. From the first ever countrywide study in Mongolia, we report on 1) the total number of MDR-TB cases detected and their resistance patterns, 2) the proportion starting treatment and the delay between diagnosis and treatment initiation, 3) characteristics of those starting treatment, and 4) the relation between treatment outcomes and drug resistance.

METHODS

Design

This was a retrospective cohort study using routine programme data.

Study setting and population

The study was conducted in Mongolia, a landlocked country in Central Asia, between July 2012 and June 2013. It included all patients diagnosed with laboratory-confirmed MDR-TB between January 2009 and June 2010. The National TB Reference Laboratory (NTRL) and the 18 health facilities that manage TB, including MDR-TB cases, were included. The National Center for Communicable Diseases (NCCD) is the central agency

AFFILIATIONS
1 Global Fund-supported Project on AIDS and TB, Ministry of Health, Ulaanbaatar, Mongolia
2 TB Coalition, Ulaanbaatar, Mongolia
3 International Union Against Tuberculosis and Lung Disease, Paris, France
4 Médecins Sans Frontières, Brussels Operational Centre, Luxembourg

CORRESPONDENCE
Ganzaya Sukhbaatar
Regence Residence-16 #203
Olympic Street
Sukhbaatar District 1st Khoroo
Ulaanbaatar, Mongolia
Tel: (+976) 7713 1328
Fax: (+976) 7713 9732
e-mail: ganzaya@aids.mn

ACKNOWLEDGEMENTS
This research was supported through an operational research course that was jointly developed and run by the Centre for Operational Research, International Union Against Tuberculosis and Lung Disease, Paris, France; The Union South-East Asia Regional Office, New Delhi, India; and the Operational Research Unit (LUXOR), Médecins Sans Frontières, Brussels-Luxembourg.
Additional support for running the course was provided by the Center for International Health, University of Bergen, Bergen, Norway.
Funding for the course was from an anonymous donor and the Department for International Development, London, UK.
Conflict of interest: none declared.

KEY WORDS
MDR-TB; drug-resistant pattern; Mongolia

Received 24 July 2013
Accepted 12 November 2013

PHA 2013; 3(4): 333–336
© 2013 The Union

responsible for the overall coordination of the implementation of the national Stop TB strategy. TB services are provided free of charge. Mongolia has a low prevalence of human immunodeficiency virus (HIV), with an HIV infection rate of <0.1% among adults and of 0.06% among the 78% of TB cases tested for HIV in 2012. There are very few cases of TB-HIV co-infection in Mongolia (0.31/100 000).

Diagnosis and management of MDR-TB

MDR-TB diagnosis

Sputum specimens are collected from patients presumed to have MDR-TB (Table 1) at district dispensaries in Ulaanbaatar, provincial dispensaries and sub-provincial facilities. All specimens are transported to the NTRL for culture and drug susceptibility testing (DST) against INH, RMP, ethambutol (E, EMB) and streptomycin (S, SM). Culture is performed using solid (Ogawa) medium. Species identification was performed using conventional methods: morphology, *p*-nitrobenzoic acid and the niacin test. DST was performed using the Löwenstein-Jensen proportion method for first-line drugs. Conventional culture and DST are the main diagnostic tools for patients thought to have drug-resistant TB. The GenoType® MTBDRplus test (Hain Lifescience, Nehren, Germany) and line-probe assay are currently being used at NRTL, but were not available for this study. DST against second-line drugs is performed only for patients who do not respond well to the MDR-TB regimen.

The NRTL is the only laboratory that performs diagnostic culture and DST in the country; quality assurance is provided by its supranational laboratory and the Research Institute of Tuberculosis, Tokyo, Japan. External quality assurance results in 2011 showed high efficiency and excellent performance.[5] After a turnaround of 4–5 months, the laboratory result is recorded in the laboratory register and relayed by the TB Department epidemiologist to the district or province dispensary TB coordinator by telephone, and, in turn, to the sub-province manager. An official paper-based result follows with the culture results.

Treatment

Once MDR-TB is confirmed, staff from the district or provincial dispensary contact the patient and enter the data into the Category 4 MDR-TB Register. MDR-TB treatment is standardised using a regimen comprising kanamycin (KM), capreomycin (CPM), ofloxacin, levofloxacin, ethionamide, prothionamide, cycloserine (CS), and para-aminosalicylic acid (PAS). The drugs are selected by the case management committee of the NCCD, and treatment is administered according to national guidelines (Table 2).[4] Side effects are monitored clinically. In the case of KM resistance or ototoxicity, CPM is used. In the case of CS intolerance, PAS is added to the regimen. Treatment is generally initiated in the MDR-TB ward. The patient is admitted to the ward and receives treatment for at least 2 months after culture conversion, after which the patient is transferred to the district or provincial dispensary for continuation of treatment for a period of at least 18 months until completion.

TABLE 1 Mongolia NTP case definitions for presumptive MDR-TB and MDR-TB

Presumptive MDR-TB
- Non-converters: patients who remain sputum smear-positive at month 2 of treatment (Category 1 or 2 regimens)
- Failures: patients who remain sputum smear-positive by month 5 on Category 1 and 2 regimens
- Return after default: patients who return to treatment sputum smear-positive after interruption of Category 1 and Category 2 treatment
- Relapse while on first or second-line treatment
- Other: includes the following cases who have been on anti-tuberculosis treatment for at least 1 month:
  - Previous treatment regimen is unclear or sputum smear is negative
  - Sputum smear is negative at the beginning of treatment, but turned positive in the course of treatment
  - Sputum smear is negative after interrupting treatment for ⩾2 months
  - Chronic cases with positive sputum smear
  - Cases with TB-HIV co-infection
  - Contacts of MDR-TB cases

NTP = National Tuberculosis Programme; MDR-TB = multidrug-resistant tuberculosis; HIV = human immunodeficiency virus.

TABLE 2 Treatment regimens for MDR-TB in Mongolia

Drug resistance pattern	Treatment regimen
HR	ZESKmOfxEth
HRE	ZSKmOfxEthCs
HRS	ZEKmOfxEthCs
HRES	ZKmOfxEthCs

MDR-TB = multidrug-resistant tuberculosis; H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol; S = streptomycin; Km = kanamycin; Ofx = ofloxacin; Eth = ethionamide; Cs = cycloserine.

Follow-up and treatment outcomes

Sputum is transported to the NTRL for follow-up smear and culture on a monthly basis during the intensive phase and every 2 months thereafter.[4] If serious drug reactions or complications are encountered, the district or province TB Coordinator presents the case to the NCCD case management committee for consensus management. Patients are given incentives such as transport allowances and free ancillary drugs. MDR-TB treatment outcomes are standardised per national guidelines,[4] which are adapted from the 2008 WHO guidelines[6] (Table 3).

Data and analysis

For all confirmed MDR-TB cases, socio-demographic data were collected from the laboratory register. For those enrolled for MDR-TB treatment, data were collected from MDR-TB treatment cards and the laboratory register, and included variables related to disease characteristics, time taken to enrolment on treatment, treatment outcomes and drug resistance patterns. Data were collected

TABLE 3 Mongolia NTP definitions for MDR-TB treatment outcomes

Cured: patient in the final 12 months of treatment, culture performed every 30 days, of which the last five consecutive results are negative, or 3–4 consecutive negative cultures and no clinical symptoms

Treatment completed: anti-tuberculosis treatment completed and patient is culture-negative at the end of treatment. However, less than five cultures are performed in the final 12 months of treatment or the patient has 3–4 consecutive negative cultures, but with persistent clinical symptoms or there is extra-pulmonary TB

Died: patient who dies for any reason during the course of MDR-TB treatment

Defaulted (lost to follow up): patient whose treatment was interrupted for ⩾2 months

Failed: of the last three consecutive cultures, one or more are positive

Transfer out: patient has moved to another province or district during the course of treatment

NTP = National Tuberculosis Programme; MDR-TB = multidrug-resistant tuberculosis.

into a structured proforma and then double-entered, validated and analysed using EpiData version 3.1 (EpiData Association, Odense, Denmark). Further validation was performed by cross-checking between the laboratory register, the MDR-TB register, patient cards and specific medical history cards available in the MDR-TB ward of the NCCD.

Ethics

Ethics approval was obtained from the Ethics Advisory Group of the International Union Against Tuberculosis and Lung Disease, Paris, France, and the NCCD, Ulaanbaatar, Mongolia.

RESULTS

MDR-TB patients and their resistance patterns

Of 268 patients diagnosed with MDR-TB in Mongolia, 168 (63%) were resistant to HRES, 59 (22%) to HRS, 34 (13%) to HR and 7 (3%) to HRE.

Proportion initiating treatment and time from diagnosis to treatment initiation

Among the 268 MDR-TB patients, 137 (51%) were male and 52% were aged 25–34 years. A total of 139 (52%) patients were started on treatment. Reasons for non-initiation of treatment were not available at this stage, as our analysis was based on routine laboratory data and patient treatment cards. The median time from MDR-TB diagnosis to treatment initiation was 137 days (interquartile range [IQR] 43–218).

Characteristics of MDR-TB patients starting treatment

Of those who started treatment, 70/139 (50%) were male, 30.2% were aged in the 15–24 year age group, and 28.1% were in the 25–34 year age group. There were 138 cases of pulmonary TB and one of extra-pulmonary TB; 69 (50%) were secondary school and/or university students, 32 (23%) were unemployed, 24 (17%) currently employed and 14 (10%) were retired, disabled or status was unrecorded. A TB contact history was mentioned by 66 (48%) patients. There were 79 (57%) cases with WHO Category 2 failure, 37 (27%) with Category 1 failure, 11 (8%) relapses, 10 (7%) with new TB (contacts of MDR-TB) and two with 'other'.

Relation between treatment outcome and drug resistance patterns

Table 4 shows the treatment outcomes by drug resistance pattern. TB treatment success (cured and treatment completed) was 69%. There was a trend towards decreasing treatment success associated with an increasing number of drugs to which the patient was resistant, although this was not statistically significant. Failure on MDR-TB treatment was 9%.

DISCUSSION

In this first countrywide study of MDR-TB in Mongolia, we found that half of all patients placed on treatment were secondary and/or university students. Nearly seven in 10 patients had a successful treatment outcome, which is encouraging. The treatment success rate of 69% in Mongolia is better than that found in a recent meta-analysis of outcome data from 9153 MDR-TB patients from 32 sites worldwide, which reported a mean success rate of only 54%.[7]

However, there are a number of caveats to our study. First, only about half of all diagnosed MDR-TB patients managed to start MDR-TB treatment and there was a median delay of over 4 months between diagnosis and treatment initiation. In Mongolia, the rate of reported deaths before treatment among MDR-TB patients is about 34%.[8] Our reported outcomes thus do not include the upstream impact of delayed treatment initiation on death and loss to follow-up. In addition, those who started treatment are likely to have had a survival benefit. Treatment outcomes are likely to be much worse if, as recently recommended by the WHO,[9] diagnosed MDR-TB patients are used as the denominator for assessing programme performance.

The strengths of this study are that we used countrywide data and our findings are thus representative of the situation in Mongolia. Data were carefully validated using patient cards and registers, and are thus robust. We adhered to STROBE (Strengthening the Reporting of Observational Studies in Epidemiology)[10] guidelines, including ethics considerations.[11] One important limitation is that we do not have information on what happened to patients who were diagnosed with MDR-TB but were not enrolled on treatment. From a public health perspective, such patients are at high risk of death and transmission of resistant TB. Of additional concern is the 9% failure rate, which may be an early warning of pre-XDR (extensively drug-resistant) or XDR-TB. Further research on these two issues is needed.

The 2009 World Health Assembly resolved that at least 75% of all notified MDR-TB cases should have a successful treatment outcome by 2015.[12] Like many other countries, Mongolia thus needs to accelerate progress toward early diagnosis and access to treatment. Ways forward include moving to more rapid MDR-TB diagnostic technology. This is already being done with the introduction of culture on liquid medium in 2011. The Mongolian NTRL now has the capacity to perform smear, culture, species identification and first-line DST using solid media. However, the NTRL can perform only conventional solid culture, bio-chemical identification and solid DST. The possibility of using Xpert® MTB/RIF technology (Cepheid, Sunnyvale, CA, USA) also needs to be explored, as this allows diagnosis to be decentralised. The delays in diagnosis and treatment initiation highlight an urgent need for uptake of molecular techniques for MDR-TB testing. Measures to

TABLE 4 MDR-TB treatment outcomes in relation to drug resistance patterns, Mongolia, January 2009–June 2010

Drug resistance pattern	Total	Cured *n* (%)	Completed *n* (%)	Failure *n* (%)	Lost to follow-up *n* (%)	Transferred out *n* (%)	Died *n* (%)	Treatment ongoing *n* (%)	Not recorded *n* (%)
HR	31	20 (65)	4 (13)	—	2 (6)	1 (3)	—	3 (10)	1 (10)
HRE	1	—	—	—	—	—	1 (100)	—	—
HRS	31	18 (58)	4 (13)	4 (13)	2 (6)	—	1 (3)	2 (6)	—
HRES	76	44 (59)	6 (8)	8 (11)	7 (9)	—	7 (9)	1 (1)	2 (3)
Total	139	82 (59)	14 (10)	12 (9)	11 (8)	1 (1)	9 (7)	6 (4)	3 (2)

MDR-TB = multidrug-resistant tuberculosis; H = isoniazid; R = rifampicin; E = ethambutol; S = streptomycin.

decentralise MDR-TB treatment to a larger number of facilities are also urgently needed, and this is now underway in eight provinces. Community awareness and involvement also needs to be enhanced and this issue has been taken on board.

A specific problem is the high proportion of students with MDR-TB. Although this maybe an indication of community transmission, or relatively better access, schools can be a hot spot for TB transmission. The very cold climate, closed windows and congested dormitories in residential schools may be partially responsible. Urgent measures are needed to investigate this issue further.

In conclusion, the first countrywide audit of MDR-TB management in Mongolia is encouraging but highlights a number of areas that need specific attention, including the need to ensure earlier access to treatment.

References

1 Weezenbeek K, Hiatt T, Bergstrom K, et al. Report of midterm external review of the National Stop TB Strategy 2010–2015. Geneva, Switzerland: World Health Organization, 2013.
2 Mongolian Tuberculosis Programme. Annual report of the National Tuberculosis Programme. Ulaanbaatar, Mongolia: National Centre for Communicable Disease, 2012.
3 Buyankhishig B, Naranbat N, Mitarai S, Rieder H L. Nationwide survey of anti-tuberculosis drug resistance in Mongolia. Int J Tuberc Lung Dis 2011; 15: 1201–1205.
4 Ministry of Health Mongolia. Mongolia national guidelines on TB care and services. Ulaanbaatar, Mongolia: Ministry of Health Mongolia, 2009.
5 Mitarai S. Mission report: performance of the National Tuberculosis Reference Laboratory of Mongolia. Tokyo, Japan: Supranational Laboratory, Research Institute of Tuberculosis, 2012.
6 World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. WHO/HTM/TB/2008.402. Geneva, Switzerland: WHO, 2008.
7 Ahuja S D, Ashkin D, Avendano M, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLOS Med 2012; 9: e1001300.
8 Naranzul D, Gantsetseg D, Tsolmon B. Surveillance report of MDR-TB in Mongolia. Ulaanbaatar, Mongolia: National Center for Communicable Diseases, 2011.
9 World Health Organization. Definitions and reporting framework for tuberculosis 2013 revision. WHO/HTM/TB/2013.2. Geneva, Switzerland: WHO, 2013.
10 Von Elm E, Altman D G, Egger M, Pocock S J, Gotzsche P C, Vandenbroucke J P. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement; guidelines for reporting observational studies. Lancet 2007; 370: 1453–1457.
11 Edginton M, Enarson D, Zachariah R, et al. Why ethics is indispensable for good-quality operational research. Public Health Action 2012; 2: 21–22.
12 World Health Organization. World Health Assembly resolution on prevention and control of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis. WHA62/2009/REC/1. Geneva, Switzerland: WHO, 2009. http://apps.who.int/gb/ebwha/pdf_files/WHA62-REC1/WHA62_REC1-en.pdf Accessed December 2013.
13 Boehme C C, Nicol M P, Nabeta P, et al. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. Lancet 2011; 2: 1495–1505.

Contexte : Dix-huit unités de traitement de la tuberculose multirésistante (TB-MR) en Mongolie.
Objectif : Déterminer le nombre total de cas de TB-MR détectés et leur profil de résistance, la proportion et les caractéristiques des cas en début de traitement, le délai entre le diagnostic et la mise en route du traitement, ainsi que la relation entre le résultat du traitement et la résistance aux médicaments.
Schéma : Etude de cohorte rétrospective basée sur les données de routine du programme.
Résultats : Les cas résistants étaient au nombre de 168 (63%) pour l'association HRES, 59 (22%) pour HRS, 34 (13%) pour HR et 7 (3%) pour HRE. Sur les 268 patients porteurs d'une TB-MR, 139 (52%) ont débuté leur traitement. 69 (50%) étaient des lycéens ou des étudiants, 35 (25%) étaient sans emploi, 24 (17%) avaient un travail et 14 (8%) étaient retraités, invalides ou non enregistrés. La durée médiane entre le diagnostic et la mise en œuvre du traitement était de 137 jours (IQR 43–218). Le taux de réussite du traitement était de 69% ; les 9% d'échec pourraient correspondre à une tuberculose ultrarésistante (TB-XDR) ou pré-XDR.
Conclusion : Près de sept patients atteints de TB-MR sur 10 en Mongolie ont été traités avec succès, ce qui est encourageant. Les problèmes particuliers constatés sont la proportion élevée d'étudiants, le fait que seulement la moitié des patients diagnostiqués aient eu accès au traitement et le délai inacceptable de 4 mois entre le diagnostic et le traitement. Ces problèmes doivent être résolus.

Marco de referencia: Dieciocho unidades de tratamiento de la tuberculosis multidrogorresistente (TB-MDR) en Mongolia.
Objetivo: Determinar el número total de casos de TB-MDR detectados y el perfil de resistencia, la proporción de casos que iniciaron tratamiento y sus características, el retraso entre el diagnóstico y el comienzo del tratamiento y la relación entre los desenlaces terapéuticos y la resistencia a los medicamentos.
Método: Fue este un estudio de cohortes retrospectivo a partir de los datos corrientes del programa.
Resultados: Se observaron 168 casos de resistencia a HRES (63%), 59 casos resistentes a HRE (22%), 34 casos de resistencia a HR (13%) y 7 casos resistentes a HRE (3%). De los 268 pacientes con diagnóstico de TB-MDR, 139 comenzaron el tratamiento (52%). Sesenta y nueve pacientes eran estudiantes de secundaria o universitarios (50%), 35 pacientes estaban desempleados (25%), 24 tenían un empleo (17%) y 14 pacientes eran jubilados, minusválidos o no contaban con definición en los registros (8%). La mediana del lapso entre el establecimiento del diagnóstico de TB-MDR y el comienzo del tratamiento fue 137 días (IQR 43–218). La tasa de éxito terapéutico fue 69% y se observó 9% de casos con fracaso terapéutico, que pueden corresponder a casos de tuberculosis extremadamente drogorresistente (TB-XDR) o a una alarma temprana de casos pre-XDR.
Conclusión: Cerca de siete de cada 10 pacientes en Mongolia alcanzaron un desenlace terapéutico favorable, lo cual augura buenas perspectivas. Los problemas específicos observados fueron una alta proporción de estudiantes, solo cerca de la mitad de los pacientes con diagnóstico establecido accedieron al tratamiento y se observó un retraso inaceptable del tratamiento de 4 meses. Es importante aportar respuestas a estas dificultades.

Public Health Action (PHA) The voice for operational research.
Published by The Union (www.theunion.org), PHA provides a platform to fulfil its mission, 'Health solutions for the poor'. PHA publishes high-quality scientific research that provides new knowledge to improve the accessibility, equity, quality and efficiency of health systems and services.

e-ISSN 2220-8372
Editor-in-Chief: Donald A Enarson, MD, Canada
Contact: pha@theunion.org
PHA website: http://www.theunion.org/index.php/en/journals/pha
Article submission: http://mc.manuscriptcentral.com/pha