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Prevalence of and risk factors for resistance to second-line drugs in people with multidrug-resistant tuberculosis in eight countries: a prospective cohort study

Tracy Dalton,
Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, Atlanta, GA, USA

Peter Cegielski,
Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, Atlanta, GA, USA

Somsak Akksilp,
Office of Disease Prevention and Control Region 7, Ubon Ratchatani, Thailand

Luis Asencios,
National Tuberculosis Reference Laboratory, Lima, Peru

Janice Campos Caoili,
Tropical Disease Foundation, Manila, Philippines

Sang-Nae Cho,
International Tuberculosis Research Center, Masan and Yonsei University College of Medicine, Seoul, South Korea

Vladislav V Erokhin,
Central Tuberculosis Research Institute, Russian Academy of Medical Sciences, Moscow, Russian Federation

Julia Ershova,
Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, Atlanta, GA, USA

Correspondence to: Dr Tracy Dalton, Centers for Disease Control and Prevention, 1600 Clifton Road Northeast, Mailstop F08, Atlanta, GA 30333, USA, tldalton@cdc.gov.

Contributors

PC and Katherine Tan designed the initial study proposal. TD, PC, JCC, JE, Alison Taylor, Katherine Tan, EK, CK, Melanie Wolfgang, Carmen Contreras, and Joey Lancaster contributed to the study design, database development, data collection, monitoring, training, data analysis, and data interpretation. TD and Lois Diem did the drug-susceptibility testing at the Centers for Disease Control and Prevention. Michael Chen provided statistical consultation. SA, JCC, MTG, BYK, HJK, KK,VL, GVV, MAY, Rattanawadee Akkslip, Wanpen Wattanaamornkiet, Jaime Bayona, Carmen Contreras, Seonyoung Min, Tatiana Khorosheva, Elena Kyryanova, Thelma Tupasi, Ingrida Sture, Tiina Kummik, Tatiana Kuznetsova, and Tatiana Somova were responsible for patients' enrolment and treatment at the study centres. LA, LEV, Wanlaya Sitti, Sofia Andreevskaya, Larisa Chernousova, Elea Larionova, Tatyana Smirnova, Alena Vorobyeva, Isdore Shamputa, Jeanette Brand, Eunjin Cho, Seok Yong Eum, Hyun Kyung Kwak, Jongseok Lee, Evgenia Nemtsova, Grace Egos, Chang-ki Kim, Inga Norvaisa, Girts Skenders, Klavdia Levina, Gloria Yale, Gustavo Pariona, Carmen Suarez, and Eddy Valencia were responsible for local laboratory testing and shipping cultures to the Centers for Disease Control and Prevention. All authors contributed to data collection, study coordination, and critical revision of the paper.

Conflicts of interest

We declare that we have no conflicts of interest.

Ma Tarcela Gler,
Tropical Disease Foundation, Manila, Philippines

Boris Y Kazennyy,
Orel Oblast Tuberculosis Dispensary, Orel, Russian Federation

Hee Jin Kim,
Korean Institute of Tuberculosis, Seoul, South Korea

Kai Kliiman,
Tartu University Hospital, Tartu, Estonia

Ekaterina Kurbatova,
Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, Atlanta, GA, USA

Charlotte Kvasnovsky,
Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, Atlanta, GA, USA

Vaira Leimane,
State Agency, Infectology Centre of Latvia, Tuberculosis and Lung Disease Clinic, Riga, Latvia

Martie van der Walt,
Medical Research Council, Pretoria, South Africa

Laura E Via,
National Institute for Allergy and Infectious Disease, National Institutes of Health, Bethesda, MD, USA

Grigory V Volchenkov,
Vladimir Oblast Tuberculosis Dispensary, Vladimir, Russian Federation

Martin A Yagui,
National Institute of Health, Lima, Peru

Hyungseok Kang,
National Masan Tuberculosis Hospital, Masan, South Korea

Global PETTS Investigators

Summary

Background—The prevalence of extensively drug-resistant (XDR) tuberculosis is increasing due to the expanded use of second-line drugs in people with multidrug-resistant (MDR) disease. We prospectively assessed resistance to second-line antituberculosis drugs in eight countries.

Methods—From Jan 1, 2005, to Dec 31, 2008, we enrolled consecutive adults with locally confirmed pulmonary MDR tuberculosis at the start of second-line treatment in Estonia, Latvia, Peru, Philippines, Russia, South Africa, South Korea, and Thailand. Drug-susceptibility testing for study purposes was done centrally at the Centers for Disease Control and Prevention for 11 first-line and second-line drugs. We compared the results with clinical and epidemiological data to identify risk factors for resistance to second-line drugs and XDR tuberculosis.

Findings—Among 1278 patients, 43·7% showed resistance to at least one second-line drug, 20·0% to at least one second-line injectable drug, and 12·9% to at least one fluoroquinolone. 6·7% of patients had XDR tuberculosis (range across study sites 0·8–15·2%). Previous treatment with second-line drugs was consistently the strongest risk factor for resistance to these drugs, which increased the risk of XDR tuberculosis by more than four times. Fluoroquinolone resistance and XDR tuberculosis were more frequent in women than in men. Unemployment, alcohol abuse, and smoking were associated with resistance to second-line injectable drugs across countries. Other risk factors differed between drugs and countries.

Interpretation—Previous treatment with second-line drugs is a strong, consistent risk factor for resistance to these drugs, including XDR tuberculosis. Representative drug-susceptibility results could guide in-country policies for laboratory capacity and diagnostic strategies.

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Introduction

Multidrug-resistant (MDR) tuberculosis, defined as tuberculosis caused by *Mycobacterium tuberculosis* resistant to at least isoniazid and rifampicin, accounts for 3·6–4·8% of incident cases of tuberculosis worldwide—around 440 000 new cases in 2008.[1,2] In 2000, the Green Light Committee was formed within the Stop TB Partnership and WHO to increase access to high-quality, second-line antituberculosis drugs at low prices, to prevent additional drug resistance, and to contribute evidence for policy development. By 2011, 255 project applications to the Green Light Committee had been approved that covered more than 130 000 patients with MDR tuberculosis.[3,4]

The global emergence of extensively drug-resistant (XDR) tuberculosis heralds the advent of widespread, virtually untreatable tuberculosis.[2,5] XDR tuberculosis is defined as disease caused by *M tuberculosis* strains resistant to at least isoniazid, rifamipicin, and one or more drugs within each of the two most important groups of second-line antituberculosis drugs (fluoroquinolones and injectable drugs).[5,6] XDR tuberculosis has been reported in 77 countries, but precise prevalence is unclear. Only two of 27 high-burden MDR tuberculosis countries routinely test for resistance to second-line drugs.[2]

After an epidemic of XDR tuberculosis in South Africa, the South Africa Medical Research Council convened an emergency consultation in August, 2006, that outlined a global strategy to combat this form of disease.[7,8] This strategy was refined in October, 2006, by the WHO Global Task Force on XDR-TB and disseminated widely.[7,8] The strategy underscored the urgent need to quantify the extent of XDR tuberculosis with population-based data.[7,8] Limited laboratory capacity and inconsistent procedures for testing have hindered understanding of resistance to second-line drugs.[2,9]

Shortly before these events, we launched a multinational, epidemiological study of MDR tuberculosis, the Preserving Effective TB Treatment Study (PETTS). It focused on the risk factors for and frequency and consequences of acquired resistance to second-line drugs in

people with MDR tuberculosis. In view of the emergence of XDR tuberculosis, we expanded PETTS in November, 2005, to include additional study sites and participants to provide poulation-based data on the prevalence of second-line-drug resistance in patients with MDR tuberculosis. Here we report the findings of the expanded study in eight countries.

Methods

Participants

The PETTS proposal was presented at an open meeting of the International Working Group on MDR tuberculosis in October, 2003, and included an open invitation to centres to participate. Clinical centres in nine countries (Estonia, Latvia, Peru, the Philippines, Russia, South Africa, South Korea, Taiwan, and Thailand) volunteered to participate. The drug-susceptibility data for Taiwan were not available at the time of data analysis and, therefore, were not included in this report (figure). Health-care professionals at these sites provide care for nearly all patients with MDR tuberculosis within their jurisdictions: nationwide in Estonia and Latvia; in two districts in Lima, Peru (Lima Ciudad and Lima Este); in two oblasts (territories) of Russia (Orel and Vladimir oblasts); in greater Manila in the Philippines; in four provinces of South Africa (Eastern Cape, KwaZulu Natal, Mpumalanga, and Northwest); in the two main referral centres for MDR tuberculosis in South Korea (National Masan Tuberculosis Hospital, Masan, and Korean Institute of Tuberculosis, Seoul); and in four provinces in northeast Thailand (Sakon Nakon, Srisaket, Ubon Ratchathani, and Yasothon). In the participating countries, WHO estimated that the prevalence of MDR tuberculosis among patients never previously treated for tuberculosis was 1·7–18·0%, and among previously treated patients was 6·7–46·0%.[10] Estonia, Latvia, Peru, the Philippines, and Russia were running projects approved by the Green Light Committee at the time of the study. South Africa, South Korea, and Thailand had not submitted project applications to the Green Light Committee before entering the study and, therefore, were deemed non-Green Light Committee countries. All countries had well established tuberculosis programmes, including strategies for MDR tuberculosis, when PETTS started. The study protocol was approved by ethics committees in every participating country and by the Centers for Disease Control and Prevention (CDC) in the USA.

Study population

Adults within the catchment areas with locally confirmed, pulmonary MDR tuberculosis who started treatment with second-line drugs between Jan 1, 2005, and Dec 31, 2008, were eligible for inclusion. Patients must have received treatment with second-line drugs for at least 30 days, had a baseline mycobacterial culture from sputum collected within 30 days before or after the start of second-line treatment, had at least one follow-up positive culture from sputum collected at least 30 days after the baseline sample, and periodically had samples shipped to CDC, Atlanta, GA, USA, for drug-susceptibility testing. Exclusion criteria were age younger than 18 years, current imprisonment, and pregnancy. After November, 2005, we dropped the requirement for the positive follow-up culture and stratified the analysis according to whether a follow-up isolate was available. Estonia, Latvia, South Africa, and Masan, South Korea, stayed with the two-culture protocol because of their primary interest in acquired drug resistance, but otherwise collected the same data as

other regions. South Africa did not enrol patients previously treated for MDR tuberculosis. All patients gave written informed consent.

Procedures

Demographic, socioeconomic, and clinical data were recorded for each patient by trained personnel, including details of previous and current treatments, surgery, hospital admissions, comorbidities (particularly HIV-1 infection), local microbiology results, baseline chest radiography results, and final treatment outcomes. Cases were classified according to previous treatment and related outcomes. Data abstracted from medical and laboratory records were double entered locally into a customised database (Epilnfo, version 3.3.2). Duplicate databases were compared electronically and discrepancies were resolved from primary sources. Data collection and data entry were supervised by a team of coordinators at country, regional, and international levels for quality assurance and completeness (TD, PC, JCC, JE, MTG, KK, EK, CK, and Melanie Wolfgang, CDC, Atlanta, GA, USA, Carmen Contreras, Socios en Salud Sucursal, Lima, Peru, and Joey Lancaster, Medical Research Council, Pretoria, South Africa).

Baseline sputum specimens were tested locally with culture for *M tuberculosis* complex and for susceptibility to at least isoniazid and rifampicin. Duplicate cultures were inoculated from the same specimens for study purposes. Microbiological methods differed by site, but all laboratories used internationally recommended media and methods.[11,12] Follow-up sputum samples were collected and cultured monthly for the duration of the patient's treatment for MDR tuberculosis. Duplicates of positive baseline and follow-up cultures were batched and shipped to CDC.

Upon receipt at CDC, isolates were grown in 5 mL Middlebrook 7H9 broth with polysorbate 80 (Remel, Lenexa, KS, USA) at 37°C until the turbidity reached roughly a McFarland 1·0 standard.

Baseline isolates were tested for drug susceptibility at CDC, according to the Clinical Laboratory Standards Institute standard,[11] by the indirect agar proportion method that uses Middlebrook 7H10 agar (BD), supplemented individually with the following drugs: isoniazid 0·2 μg/mL, rifampicin 1·0 μg/mL, ethambutol 5·0 μg/mL, streptomycin 2·0 μg/mL, ofloxacin 2·0 μg/mL, ciprofloxacin 2·0 μg/mL, kanamycin 5·0 μg/mL, capreomycin 10·0 μg/mL, amikacin 4·0 μg/mL, aminosalicylic acid 2·0 μg/mL, and ethionamide 10·0 μg/mL. Resistance was reported when the proportion of growth on drug-containing medium was at least 1% of that on drug-free medium. Contamination was defined as colony morphology inconsistent with *M tuberculosis* or growth of fungus.

Statistical analysis

All statistical analyses were done with SAS (version 9.2). The incidence of resistance amplification was estimated a priori to be 10–30%.[13,14] Therefore, we used the χ^2 test for independent groups and applied the Power and Sample Size Calculation (version 2.0) to calculate group sizes, with an assumed relative risk of at least 2·0 for resistance amplification in non-Green Light Committee sites (exposed) compared with Green Light Committee projects (unexposed). To achieve 80% power with 95% CI, we estimated that we

would need to enrol the following numbers of patients per group, by amplification rate in Green Light Committee sites: 435 at 5%; 199 at 10%; 120 at 15%; and 81 at 20%. Although the primary analysis was stratified by sites to determine an aggregated (pooled) estimate of relative risk, sites were offered the opportunity to increase their own sample size to enhance the precision of site-specific outcome measures.

Drug-susceptibility results were analysed as dependent variables, and clinical, epidemiological, and microbiological information about each patient as independent variables. We analysed risk factors for and prevalence of resistance to each drug separately and in the following groups: four first-line drugs (isoniazid, rifampicin, ethambutol, and streptomycin); at least one second-line fluoroquinolone (ofloxacin or ciprofloxacin); at least one second-line injectable drug (kanamycin, capreomycin, and amikacin); all second-line injectable drugs; any second-line drug; at least one other oral second-line drug (aminosalicylic acid or ethionamide); and combinations for XDR tuberculosis. Each drug and combination represents a separate analysis of risk factors. In this report we focus on resistance to any fluoroquinolone, any second-line injectable drug, any other oral second-line drug, and risk of XDR tuberculosis.

For continuous variables we calculated means and SDs, medians with ranges and IQRs, and specified percentiles. For categorical data, we tabulated two-way frequency distributions for each characteristic versus each drug-susceptibility result, and used Pearson's χ^2 statistic or Fisher's exact test to test significance, as appropriate. For ordinal variables, the p values for trend were based on the Mantel-Haenszel χ^2 test. For continuous variables, we compared two groups with Student's *t* test if the data were normally distributed with at least 30 observations per group; otherwise, we used the Wilcoxon's rank sum test. For analyses that involved more than two groups, we used one-way analysis of variance and the Kruskal-Wallis test. Site-specific selection fractions were calculated as the number of patients enrolled divided by total number patients eligible during the enrolment period. Statistical comparisons across countries were based on data weighted by the reciprocal of the selection fraction.[15,16]

We took p values of 0·05 or less to be significant, and those of 0·001 or less to be highly significant. We report actual numbers and percentages for descriptions of patients' characteristics and drug resistance for each country, and weighted numbers and percentages for results from statistical analyses of risk factors across sites.

To assess whether the prevalence of drug resistance and relations with risk factors and drug-susceptibility results differed in the two sampling protocols, we stratified the analysis by whether a follow-up positive culture was available or not. We used the Breslow-Day test for homogeneity to determine whether relative-risk estimates across strata were significantly different from each other.[15]

Role of the funding source

The US Agency for International Development had no role in the design, implementation, analysis, and interpretation of results. CDC Division of Tuberculosis Elimination led the study design, training for data collection and monitoring, data analysis, data interpretation,

and writing of the report. Other sponsors had no roles in these activities. The corresponding author had full access to the data in the study and had final responsibility for the decision to submit for publication.

Results

Of 3034 eligible patients, 1782 (58·7%) were enrolled (figure). The most common reasons for patients not to be enrolled were no positive follow-up culture, no consent, previous treatment with second-line drugs for MDR tuberculosis, and staff turnover, although exact numbers for the different reasons are not available. Baseline isolates were not shipped to CDC for 242 (13·5%) patients. The centres in Estonia, Latvia, South Africa, and Masan, South Korea, maintained the original follow-up culture protocol throughout the study. Of the 1540 baseline isolates received and recovered successfully at CDC, MDR tuberculosis was confirmed in 1278 (83·0%, figure, table 1).

The characteristics of patients with MDR tuberculosis isolates assessed at CDC are shown in table 1. In every country, more patients were male than female. The highest proportion of patients were in the 25–44-year age group, and the overall median age was 37 years (range 18–81). Social characteristics of patients differed between countries. Unemployment was lowest in Thailand and highest in South Africa. History of imprisonment was lowest in South Korea and highest in Russia. Homelessness was uncommon, but reached 12·0% in Latvia and 17·4% in Estonia. Alcohol abuse varied widely (range 11 [2·8%] of 397 to 64 [64·0%] of 100), as did tobacco use (range 0 to 40 [87·0%] of 46). Patients infected with HIV were enrolled in all countries except the Philippines and South Korea, where HIV testing was not routine but those tested were negative. 145 (86·3%) of 168 patients with HIV infections lived in South Africa. In Estonia, Latvia, Russia, South Africa, and Masan, South Korea, most patients were in hospital at the time of enrolment, but in the other countries very few had been admitted. 1199 (93·8%) of 1278 patients had a history of tuberculosis, with percentages ranging from 47·8% to 100·0% across countries. Of the 1199 patients, most (70·6%) had had one or two previous tuberculosis episodes. 1186 (92·8%) of 1278 patients had received first-line antituberculosis drugs before the study. By contrast, only 195 (15·3%) had received second-line drugs, with the lowest percentage being 2·7% in South Africa and the highest 53·5% in South Korea.

The prevalence of resistance varied substantially between countries (table 2). 625 (49·0%) of 1278 *M tuberculosis* isolates were resistant to ethambutol and streptomycin as well as isoniazid and rifampicin. Resistance to any second-line drug was 43·7% and ranged from 33·3% in Thailand to 62·0% in Latvia. The prevalence of resistance to fluoroquinolones was 12·9% and was lowest in the Philippines and highest in South Korea. Resistance to at least one second-line injectable drug was 20·0% overall, with the lower prevalence being in the Philippines and the highest in Latvia. Resistance to all three second-line injectable drugs was significantly more frequent in the Eastern Cape province, South Africa, than in the other South African provinces (65 [48·9%] of 133 *vs* 10 [6·3%] of 160, p<0·0001). Resistance to other oral second-line drugs was seen in all countries, with the aggregate prevalence being 27·1% (range 13·0–38·0%). XDR tuberculosis was seen in 86 (6·7%) of 1278 patients

overall, and was least prevalent in the Philippines and most prevalent in South Korea (table 2).

Findings for potential risk factors are shown in tables 3-6. The strongest, most-consistent risk factor was previous treatment for MDR tuberculosis with any second-line drug, and the risk remained significant when fluoroquinolones, second-line injectable drugs and other oral second-line drugs were assessed separately. Resistance to fluoroquinolones and second-line injectable drugs and XDR tuberculosis, but not resistance to other oral second-line drugs, were significantly less prevalent in countries with than in those without Green Light Committee approved projects. This difference was due to the very low prevalence of resistance to second-line drugs in the Philippines, which had the largest Green Light Committee project. Being in hospital at the time of enrolment was a strong risk factor for resistance to fluoroquinolones and second-line injectable drugs, and for XDR tuberculosis, but not for resistance to other oral second-line drugs. Other, risk factors differed between drugs and countries (tables 3-6). For instance, fluoroquinolone resistance and XDR tuberculosis were more frequent in women than in men. Patients with HIV infection had significantly less fluoroquinolone resistance than those not infected with HIV. Cavitary lung disease nearly doubled the risk of resistance to second-line injectable agents. Other risk factors for resistance to second-line injectable drugs included unemployment, a history of imprisonment, alcohol abuse, and tobacco use (table 4).

Little difference was seen between patients with one or at least two positive cultures in terms of association of specific risks with specific drug resistance.

Discussion

This large, prospective study of resistance to second-line drugs for MDR tuberculosis shows comprehensively that the prevalence of resistance is high (43·7%), and that the risk of XDR tuberculosis (6·7%) in the eight countries studied is worrying.

The prevalence of drug resistance correlates with the time that second-line drugs have been available in each country. They had been available for 10 years or less in Thailand (7 years), the Philippines (9 years), and Peru (10 years), and these countries had the lowest rates of resistance. By contrast, South Korea and Russia had the longest histories of availability (more than 20 years) and the highest rates of resistance. Other practices, including criteria for treatment, admission to hospital, directly observed therapy, and drug procurement, should be assessed to find out whether they affect resistance rates.

WHO data showed that 5·4% of patients with MDR tuberculosis had XDR tuberculosis.[2] In our population, 6·7% had XDR tuberculosis. This higher rate might be due at least partly to differences in laboratory procedures. We tested all three second-line injectable agents for this study, but most countries test one or two, which could underestimate the burden of XDR tuberculosis. The same may be said for fluoroquinolones.

The prevalence values we found show some differences from and similarities to country-specific surveillance data from WHO. Fluoroquinolone resistance was 26·1% in Estonia, 14·0% in Latvia, and 12·6% in South Africa, and 30·6%, 15·6%, and 14·2% in WHO data.

For XDR tuberculosis, however, although the rates for South Africa are similar (10·6% *vs* 10·5%), those for Estonia and Latvia were lower in our study (6·5% *vs* 12·5% and 8·0% *vs* 14·8%, respectively).[2] Thus, prevalence of resistance to second-line drugs in the three countries was not likely to be artificially increased because of the two-culture criterion. Another study of MDR tuberculosis in Estonia showed a similar rate of 5·2% for XDR tuberculosis.[17]

Few studies have been done of resistance to second-line drugs, probably because of low capacity for laboratory testing.[1] Previous studies have reported prevalence of 23% in South Korea and of 6% in Peru for XDR tuberculosis among patients with MDR tuberculosis treated at tertiary referral hospitals.[6,18] In these countries we showed 15% and 6% prevalence, respectively. A study done in Thailand before XDR tuberculosis was defined found that 9% of patients with MDR tuberculosis had resistance to a fluoroquinolone and 5% to kanamycin.[19] These values are similar to those in our study.

Previous treatment for MDR tuberculosis with a second-line drug was the strongest risk factor for resistance, which is consistent with previous reports.[6,20] Patients being in hospital at enrolment was also strongly associated with resistance, possibly because of nosocomial transmission or disease severity. Women had greater prevalence of fluoroquinolone resistance than men, and thereby greater risk of XDR tuberculosis, which is consistent with the findings of a study done in South Korea.[6] By contrast, HIV-infected patients were less likely than other patients to have resistance to fluoroquinolones, but in other studies HIV infection has been a strong risk factor for XDR tuberculosis.[20] Unlike fluoroquinolones, resistance to second-line injectables was associated with social factors, including imprisonment, unemployment, alcohol abuse, and smoking. Social factors should be taken into account in the management of tuberculosis.

PETTS had important limitations. The prospective gathering of data under programmatic conditions led to some variability between sites in the information available. Differences in demographic, social, and clinical risk factors might be related to the extent of missing data for specific variables. Data collection was based on medical records, where some features are not routinely recorded and we could not acquire the data. However, of the variables that applied to all patients, only six had more than 10% of data missing. Data from Masan, South Korea, were extracted from a separate study that was being done in collaboration with the US National Institutes of Health and, therefore, we used their data collection instrument, which included all variables except years of education and number of children.[6] When we expanded the enrolment criteria in November 2005, Estonia, Latvia, and Masan, South Korea, were close to their enrolment targets and maintained the original protocol of requiring a second positive culture per patient. South Africa began enrolling patients with one culture, but only shipped samples for those with a second positive culture to CDC. The rest of the sites changed protocols and required only a baseline positive culture. This difference might have contributed to country-specific differences. The patients tested might not have been representative of the larger populations of adults with pulmonary MDR tuberculosis in the study countries to the extent that the prevalence of drug resistance among enrolled patients differed from that in patients who were not enrolled. We could not assess how representative our patient cohorts were because we did not collect demographic and

medical information for eligible patients who were not enrolled. The enrolment rates at some centres were low owing to circumstances not related to the study, such as changes in personnel. Finally, the results are not generalisable to the world as a whole because India and China—the countries with the highest numbers of tuberculosis cases—did not participate. India and China had pilot projects for MDR tuberculosis approved by the Green Light Committee, but not until 3 and 4 years, respectively, after PETTS started. Population-based data on resistance to second-line drugs in these two countries are limited. In China's 2007 national drug resistance survey, 27·4% (95% CI 23·1–32·1) of cases of MDR tuberculosis tested for resistance to second-line drugs showed fluoroquinolone resistance and 7·2% of patients (4·9–10·2) had XDR tuberculosis.[2] In India, a 2006 population-based survey of tuberculosis drug resistance in Gujarat State reported fluoroquinolone resistance in 24·1% of cases (18·5–30·3) and XDR tuberculosis in 3·2% (1·2–6·6).[2] In both surveys, fluoroquinolone resistance was near the high end of the range of values in our study. The prevalence of XDR tuberculosis in China was slightly higher than the average value in our study, but in Gujarat State, India, it was similar to the lower values in our study. Other reports from China and India have been based on retrospective reviews of cases at specialised tuberculosis referral centres that happened to have drug-susceptibility results for second-line drugs and are not representative of the general population.[21-24]

As a large, multicentre, collaborative study, PETTS also has strengths. All drug-susceptibility testing was done in one reference laboratory with standard, quality-controlled methods, which eliminated variability intrinsic to phenotypic testing in multiple laboratories. Additionally, the study was designed to provide data within defined criteria that were representative for the populations served by the participating programmes. Five of the participating countries had projects approved by the Green Light Committee in place at the time of the study and, therefore, were representative of other countries with approved projects. Of the countries without approved projects, one was a high-income and two were upper-middle-income countries and would not be representative of the worldwide situation, especially for low-income countries. Nevertheless, our country-specific results can be extrapolated to guide in-country policy for laboratory capacity and for designing effective treatment recommendations for MDR tuberculosis.

PETTS continues, and follow-up isolates are being tested to investigate the frequency of and risk factors for acquired resistance to second-line drugs in patients with MDR tuberculosis. The effect of the Green Light Committee initiative in combating acquired resistance to second-line drugs, the timing of acquired resistance, and the role of specific genetic mutations in different regions of the world are also being assessed.

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*: Global PETTS Investigators and coauthors

Rattanawadee Akksilp, Wanlaya Sitti, and Wanpen Wattanaamornkiet, Office of Disease Prevention and Control Region 7, Ubon Ratchatani, Thailand; Sofia N Andreevskaya, Larisa N Chernousova, Olga V Demikhova, Elena E Larionova, Tatyana G Smirnova, Irina A Vasilieva, and Alena V Vorobyeva, Central Tuberculosis Research Institute, Russian Academy of Medical Sciences, Moscow, Russian Federation; Clifton E Barry III, Ying Cai, and Isdore C Shamputa, National Institute for Allergy and Infectious Disease, National Institutes of Health, Bethesda, MD, USA; Jaime Bayona and Carmen Contreras, Socios en Salud Sucursal, Lima, Peru; Cesar Bonilla and Oswaldo Jave, Ministry of Health, National TB Strategy, Lima, Peru; Jeannette Brand, Joey Lancaster, and Ronel Odendaal, Medical Research Council, Pretoria, South Africa; Michael P Chen, Lois Diem, Beverly Metchock, Kathrine Tan, Allison Taylor and Melanie Wolfgang, Centers for Disease Control and Prevention, Division of TB Elimination, Atlanta, GA, USA; Eunjin Cho, Seok Yong Eum, Hyun Kyung Kwak, Jiim Lee, Jongseok Lee, and Seonyeong Min, International Tuberculosis Research Center, Masan and Yonsei University College of Medicine, Seoul, South Korea; Irina Degtyareva, Evgenia S Nemtsova, Tatiana Khorosheva, and Elena V Kyryanova, Orel Oblast Tuberculosis Dispensary, Orel, Russian Federation; Grace Egos, Ma Therese C Perez, and Thelma Tupasi, Tropical Disease Foundation, Manila, Philippines; Soo Hee Hwang, National Masan Tuberculosis Hospital, Masan, South Korea; Chang-ki Kim, Su Young Kim, and Hee Jeong Lee, Korean Institute of Tuberculosis, Seoul, South Korea; Liga Kuksa, Inga Norvaisha, Girts Skenders, and Ingrida Sture, State Agency, Infectology Centre of Latvia, Tuberculosis and Lung Disease Clinic, Riga, Latvia; Tiina Kummik, Tartu University Hospital, Tartu, Estonia; Tatiana Kuznetsova and Tatiana Somova, Vladimir Oblast Tuberculosis Dispensary, Vladimir, Russian Federation; Klavdia Levina, North Estonia Regional Hospital, Tallinn, Estonia; Gustavo Pariona and Gloria Yale, Lima City Health District Reference Laboratory, Lima, Peru; Carmen Suarez, Lima East Health District Reference Laboratory, Lima, Peru; Eddy Valencia, National Tuberculosis Reference Laboratory, Lima, Peru; and Piret Viiklepp, National Tuberculosis Registry, National Institute for Health Development, Tallinn, Estonia.

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Panel: Research in context

Systematic review

We searched PubMed with the search term "(tuberculosis OR TB) AND (extensive drug resistance OR XDR OR second-line drug resistance OR fluoroquinolone resistance OR kanamycin resistance OR amikacin resistance OR capreomycin resistance) AND (epidemiology OR prevalence OR risk factors)". The search identified 568 publications. Of these, 85 articles contained original data on the epidemiology of drug-resistant tuberculosis, including information on resistance to second-line drugs. The remainder were reviews, editorials, letters, studies focused on treatment and treatment outcomes, phylogenetic and transmission studies, and case reports or small case series.

Interpretation

Of 85 articles on the epidemiology of resistance to second-line drugs, 60 were retrospective reviews based on medical records or laboratory records at tertiary referral hospitals, specialised tuberculosis hospitals, and mycobacteriology reference laboratories, and data had been recorded previously for other purposes. Thus, they reflected highly selected groups of patients and did not represent the general population. Seven reports based on national or multinational surveillance systems included little information about risk factors because they were limited to routinely captured data. With one exception, South Korea, susceptibility testing for second-line drugs is not done routinely, and, therefore, resistance data are not routinely captured by surveillance systems. 16 studies focused on specific classes of second-line drugs (usually fluoroquinolones) or on extensively drug-resistant tuberculosis, but did not assess individual drugs. Seven publications focused narrowly on specific groups such as prisoners, miners, health-care workers, people with HIV infection, and migrants and another seven phylogenetic analyses focused on transmission dynamics, including contact investigations, and on molecular characterisation of specific DNA mutations associated with phenotypic resistance to specific individual drugs. These 85 papers represented little geographical overlap with our study— 72 (85%) reported data from countries or regions not included in this study, and design limitations in ten of the remaining 13 reports meant little population crossover. Thus, our report adds prospective, population-based data from many locations not previously studied that include detailed information on risk factors related to resistance to individual drugs as well as drug combinations, according to centralised laboratory testing.

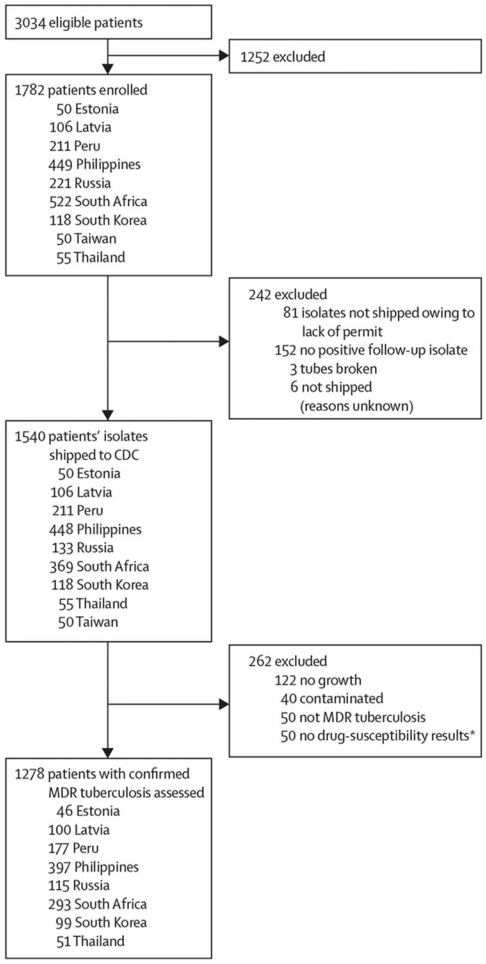

Figure: Study profile

CDC=Centers for Disease Control and Prevention. MDR=multidrug-resistant. *All from Taiwan.

Table 1:

Characteristics of patients with confirmed MDR tuberculosis

	Number of patients per country (%)								Total (n=1278)
	Estonia (n=46)	Latvia (n=100)	Peru (n=177)	Philippines (n=397)	Russia (n=115)	South Africa (n=293)	South Korea (n=99)	Thailand (n=51)	
Sex									
Male	36 (78·3%)	70 (70·0%)	104 (58·8%)	241 (60·7%)	96 (83·5%)	163 (55·6%)	76 (76·8%)	33 (64·7%)	819 (64·1%)
Female	10 (21·7%)	30 (30·0%)	73 (41·2%)	156 (39·3%)	19 (16·5%)	130 (44·4%)	23 (23·2%)	18 (35·3%)	459 (35·9%)
Age group (years)									
18–24	2 (4·4%)	2 (2·0%)	67 (37·9%)	55 (13·9%)	14 (12·2%)	39 (13·3%)	7 (7·1%)	4 (7·8%)	190 (14·9%)
25–44	19 (41·3%)	47 (47·0%)	89 (50·3%)	210 (52·9%)	57 (49·6%)	191 (65·2%)	51 (51·5%)	25 (49·0%)	689 (53·9%)
45–64	22 (47·8%)	46 (46·0%)	16 (9·0%)	128 (32·2%)	37 (32·2%)	63 (21·5%)	35 (35·4%)	19 (37·3%)	366 (28·6%)
≥65	3 (6·5%)	5 (5·0%)	5 (2·8%)	4 (1·0%)	7 (6·1%)	0	6 (6·1%)	3 (5·9%)	33 (2·6%)
Marital status									
Never married	13 (28·3%)	25 (25·0%)	99 (55·9%)	111 (28·0%)	30 (26·1%)	166 (56·7%)	15 (15·2%)	7 (13·7%)	466 (36·5%)
Currently married or cohabitating	17 (36·9%)	40 (40·0%)	59 (33·3%)	255 (64·2%)	45 (39·1%)	64 (21·8%)	23 (23·2%)	38 (74·5%)	541 (42·3%)
Previously married	15 (32·6%)	35 (35·0%)	18 (10·2%)	31 (7·8%)	39 (33·9%)	17 (5·8%)	7 (7·1%)	6 (11·8%)	168 (13·1%)
Data missing	1 (2·2%)	0	1 (0·6%)	0	1 (0·9%)	46 (15·7%)	54 (54·6%)	0	103 (8·1%)
Education									
Primary or less	15 (32·6%)	19 (19·0%)	17 (9·6%)	67 (16·9%)	17 (14·8%)	91 (31·1%)	24 (24·2%)	37 (72·6%)	287 (22·5%)
Secondary	13 (28·3%)	41 (41·0%)	110 (62·2%)	164 (41·3%)	48 (41·7%)	115 (39·3%)	46 (46·5%)	9 (17·7%)	546 (42·7%)
Postsecondary	18 (39·1%)	40 (40·0%)	50 (28·2%)	166 (41·8%)	50 (43·5%)	11 (3·8%)	29 (29·3%)	5 (9·8%)	369 (28·9%)
Data missing	0	0	0	0	0	76 (25·9%)	0	0	76 (6·0%)
Occupational risk									
Yes	3 (6·52%)	4 (4·0%)	9 (5·08%)	11 (2·8%)	7 (6·1%)	18 (6·1%)	0	3 (5·9%)	55 (4·3%)
No	41 (89·1%)	96 (96·0%)	167 (94·4%)	386 (97·2%)	108 (93·9%)	208 (71%)	48 (48·5%)	48 (94·1%)	1102 (86·2%)
Data missing	2 (4·35%)	0	1 (0·56%)	0	0	67 (22·9%)	51 (51·5%)	0	121 (9·5%)
Employment status									
Employed	13 (28·3%)	35 (35·0%)	51 (28·8%)	274 (69·0%)	27 (23·5%)	71 (24·2%)	67 (67·7%)	43 (84·3%)	581 (45·5%)
Unemployed	19 (41·3%)	47 (47·0%)	75 (42·4%)	67 (16·9%)	60 (52·2%)	198 (67·6%)	23 (23·2%)	8 (15·7%)	497 (38·9%)
Other	14 (30·4%)	18 (18·0%)	50 (28·2%)	56 (14·1%)	28 (24·3%)	20 (6·8%)	8 (8·1%)	0	194 (15·2%)
Data missing	0	0	1 (0·6%)	0	0	4 (1·4%)	1 (1·0%)	0	6 (0·5%)

	Number of patients per country (%)								Total (n=1278)
	Estonia (n=46)	Latvia (n=100)	Peru (n=177)	Philippines (n=397)	Russia (n=115)	South Africa (n=293)	South Korea (n=99)	Thailand (n=51)	
History of imprisonment									
Yes	8 (17·4%)	20 (20·0%)	6 (3·4%)	7 (1·8%)	30 (26·1%)	16 (5·5%)	1 (1·0%)	6 (11·8%)	94 (7·4%)
Data missing	0	0	7 (4·0%)	2 (0·5%)	0	138 (47·1%)	51 (51·5%)	0	198 (15·5%)
History of homelessness									
Yes	8 (17·4%)	12 (12·0%)	2 (1·1%)	4 (1·0%)	5 (4·4%)	5 (1·7%)	0	0	36 (2·8%)
Data missing	0	0	0	2 (0·5%)	0	100 (34·1%)	51 (51·5%)	0	153 (12·0%)
Alcohol abuse									
Yes	28 (60·9%)	64 (64·0%)	11 (6·2%)	11 (2·8%)	38 (33·0%)	45 (15·4%)	13 (13·1%)	3 (5·9%)	213 (16·7%)
Data missing	0	0	2 (1·1%)	1 (0·3%)	0	55 (18·8%)	1 (1·0%)	0	59 (4·6%)
Current smoker									
Yes	40 (87·0%)	70 (70·0%)	0 (0%)	9 (2·3%)	94 (81·7%)	52 (17·8%)	36 (36·4%)	6 (11·8%)	307 (24·0%)
Data missing	0	1 (1·0%)	1 (0·6%)	1 (0·3%)	0	14 (4·8%)	0	0	17 (1·3%)
HIV infection									
Yes	2 (4·4%)	3 (3·0%)	6 (3·4%)	0	5 (4·4%)	145 (49·5%)	0	7 (13·7%)	168 (13·2%)
Unknown or data missing	2 (4·4%)	0	0	396 (99·8%)	0	24 (8·2%)	45 (45·5%)	1 (2·0%)	468 (36·6%)
Diabetes									
Yes	4 (8·7%)	2 (2·0%)	7 (4·0%)	104 (26·2%)	9 (7·8%)	11 (3·8%)	15 (15·2%)	10 (19·6%)	162 (12·7%)
Unknown or data missing	0	0	0	0	0	4 (1·4%)	1 (1·0%)	0	5 (0·4%)
Contact of tuberculosis case									
Yes	18 (39·1%)	30 (30·0%)	102 (57·6%)	239 (60·2%)	50 (43·5%)	117 (39·9%)	25 (25·3%)	17 (33·3%)	598 (46·8%)
Unknown	13 (28·3%)	2 (2·0%)	0	21 (5·3%)	7 (6·1%)	83 (28·3%)	0	22 (43·1%)	148 (11·6%)
Contact of MDR tuberculosis case									
Yes	11 (23·9%)	28 (28·0%)	41 (23·2%)	56 (14·1%)	20 (17·4%)	26 (8·9%)	3 (3·03%)	2 (3·9%)	187 (14·6%)
Data missing	16 (34·8%)	2 (2·0%)	19 (10·7%)	123 (31·0%)	30 (26·1%)	157 (53·6%)	52 (52·5%)	38 (74·5%)	437 (34·2%)
History of tuberculosis									
Yes	22 (47·8%)	78 (78·0%)	166 (93·8%)	397 (100%)	106 (92·2%)	281 (95·9%)	98 (99·0%)	51 (100·0%)	1199 (93·8%)
Number of episodes									
0	24 (52·2%)	22 (22·0%)	11 (6·21%)	0	9 (7·8%)	12 (4·1%)	1 (1·0%)	0	79 (6·2%)
1	16 (34·8%)	54 (54·0%)	103 (58·2%)	22 (5·5%)	73 (63·5%)	145 (49·5%)	15 (15·2%)	18 (35·3%)	446 (34·9%)
2	4 (8·7%)	22 (22·0%)	45 (25·4%)	153 (38·5%)	24 (20·9%)	98 (33·5%)	30 (30·3%)	24 (47·1%)	400 (31·3%)

	Number of patients per country (%)								Total (n=1278)
	Estonia (n=46)	Latvia (n=100)	Peru (n=177)	Philippines (n=397)	Russia (n=115)	South Africa (n=293)	South Korea (n=99)	Thailand (n=51)	
3	2 (4·4%)	2 (2·0%)	17 (9·6%)	128 (32·2%)	5 (4·4%)	30 (10·2%)	22 (22·2%)	9 (17·7%)	215 (16·8%)
≥24	0	0	1 (0·6%)	94 (23·7%)	4 (3·5%)	8 (2·7%)	31 (31·3%)	0	138 (10·8%)
Treatment									
First-line drugs	20 (43·5%)	76 (76·0%)	165 (93·2%)	397 (100·0%)	105 (91·3%)	281 (95·9%)	91 (91·9%)	51 (100·0%)	1186 (92·8%)
Second-line drugs	8 (17·4%)	21 (21·0%)	21 (11·9%)	54 (13·6%)	27 (23·5%)	8 (2·7%)	53 (53·5%)	3 (5·9%)	195 (15·3%)
Fluoroquinolones*	4 (8·7%)	14 (14·0%)	21 (11·9%)	53 (13·4%)	19 (16·5%)	8 (2·7%)	44 (44·4%)	3 (5·9%)	166 (13·0%)
Second-line injectable drugs	4 (8·7%)	18 (18·0%)	19 (10·7%)	8 (2·0%)	20 (17·4%)	8 (2·7%)	21 (21·2%)	1 (2·0%)	99 (7·8%)
Other oral second-line drugs	7 (15·2%)	16 (16·0%)	20 (11·3%)	2 (0·5%)	20 (17·4%)	8 (2·7%)	51 (51·5%)	1 (2·0%)	125 (9·8%)
Data missing	0	0	0	0	0	0	1 (1·0%)	0	1 (0·1%)
First treatment for MDR tuberculosis									
Yes	39 (84·8%)	88 (88·0%)	157 (88·7%)	391 (98·5%)	109 (94·8%)	282 (96·3%)	33 (33·3%)	50 (98·0%)	1149 (89·9%)
Data missing	1 (2·2%)	0	0	0	2 (1·7%)	0	52 (52·5%)	0	55 (4·3%)
In hospital at enrolment									
Yes	38 (82·6%)	100 (100·0%)	1 (0·6%)	57 (14·4%)	114 (99·1%)	293 (100·0%)	51 (51·5%)	5 (9·8%)	659 (51·6%)
Cavitary disease on chest radiograph									
Yes, unilateral	26 (56·5%)	55 (55·0%)	60 (33·9%)	125 (31·5%)	62 (53·9%)	113 (38·6%)	22 (22·2%)	22 (43·1%)	485 (38·0%)
Yes, bilateral	14 (30·4%)	35 (35·0%)	19 (10·7%)	74 (18·6%)	27 (23·5%)	79 (27·0%)	10 (10·1%)	12 (23·5%)	270 (21·2)
Unknown or data missing	0	0	15 (8·5%)	7 (1·8%)	0	0	41 (41·4%)	0	63 (4·9%)
Positive sputum-smear test at enrolment									
Yes	34 (73·9%)	75 (75·0%)	116 (65·5%)	380 (95·7%)	68 (59·1%)	282 (96·3%)	85 (85·9%)	44 (86·3%)	1084 (84·8%)
Data missing	0	0	31 (17·5%)	1 (0·3%)	0	1 (0·3%)	1 (1·0%)	2 (3·9%)	36 (2·8%)

MDR=multidrug-resistant. *Ciprofloxacin, ofloxacin, lomefloxacin, levofloxacin, and moxifloxacin.

Table 2:

Drug resistance at baseline

	Number of patients per country (%)								Total
	Estonia (n=46)	Latvia (n=100)	Peru (n=177)	Philippines (n=397)	Russia (n=115)	South Africa (n=293)	South Korea (n=99)	Thailand (n=51)	
First-line drugs									
Ethambutol	41 (89·1%)	65 (65·0%)	92 (52·0%)	308 (77·6%)	62 (53·9%)	177 (60·4%)	57 (57·6%)	24 (47·1%)	826 (64·6%)
Streptomycin	46 (100·0%)	96 (96·0%)	99 (55·9%)	239 (60·4%)	110 (96·5%)	210 (71·7%)	46 (46·5%)	35 (68·6%)	881 (69·0%)
Four first-line drugs *	41 (89·1%)	65 (65·0%)	62 (35·0%)	205 (51·8%)	61 (53·5%)	142 (48·5%)	30 (30·3%)	19 (37·3%)	625 (49·0%)
Second-line drugs									
Any second-line drug	24 (52·2%)	62 (62·0%)	60 (33·9%)	153 (38·5%)	63 (54·8%)	131 (44·7%)	49 (49·5%)	17 (33·3%)	559 (43·7%)
At least one fluoroquinolone	12 (26·1%)	14 (14·0%)	16 (9·0%)	28 (7·1%)	21 (18·3%)	37 (12·6%)	32 (32·3%)	5 (9·8%)	165 (12·9%)
Injectable drugs									
Kanamycin	13 (28·3%)	42 (42·0%)	30 (17·0%)	7 (1·8%)	38 (33·0%)	80 (27·3%)	23 (23·2%)	4 (7’8%)	237 (18·5%)
Amikacin	11 (23·9%)	35 (35·0%)	31 (17·5%)	7 (1·8%)	19 (16·5%)	80 (27·3%)	18 (18·2%)	4 (7·8%)	205 (16·0%)
Capreomycin	2 (4·4%)	15 (15·0%)	30 (17·0%)	1 (0·3%)	8 (7·0%)	79 (27·7%)	14 (14·1%)	3 (5·9%)	152 (12·0%)
At least one	14 (30·4%)	47 (47·0%)	34 (19·2%)	8 (2·0%)	40 (34·8%)	84 (28·7%)	23 (23·2%)	5 (9·8%)	255 (20·0%)
All	2 (4·35%)	9 (9·0%)	26 (14·7%)	1 (0·3%)	6 (5·2%)	75 (25·6%)	13 (13·1%)	2 (3·9%)	134 (10·5%)
Other oral second-line drugs									
Ethionamide	5 (10·9%)	23 (23·0%)	13 (7’3%)	121 (30·5%)	16 (13·9%)	50 (17·1%)	11 (11·1%)	10 (19·6%)	249 (19·5%)
Aminosalicylic acid	2 (4·4%)	24 (24·0%)	23 (13·0%)	8 (2·0%)	18 (15·7%)	23 (7’9%)	34 (34·3%)	5 (9·8%)	137 (10·7%)
At least one	6 (13·0%)	38 (38·0%)	34 (19·2%)	125 (31·5%)	30 (26·1%)	64 (21·8%)	36 (36·4%)	13 (25·5%)	346 (27·1%)
XDR tuberculosis	3 (6·5%)	8 (8·0%)	11 (6·2%)	3 (0·8%)	13 (11·3%)	31 (10·6%)	15 (15·2%)	2 (3·9%)	86 (6·7%)

XDR=extensively drug-resistant. *Isoniazid, rifampicin, ethambutol, and streptomycin.

Table 3:

Risk factors for resistance to fluoroquinolones at baseline *

	Weighted frequency of resistance†	Weighted percentage for resistance (95% CI)†	p value	Risk ratio (95% CI)
Green Light Committee approval				
Yes	191	12·0 (9·4–14·5)	0·01	0·68 (0·50–0·91)
No	183	17·8 (13·9–21·6)	..	..
Sex				
Male	202	12·0 (9·6–14·5)	0·0072	0·66 (0·49–0·89)
Female	172	18·2 (14·2–22·3)	..	..
History of imprisonment				
Yes	28	12·1 (5·0–19·2)	0·80	0·92 (0·50–1·71)
No	248	13·1 (10·6–15·5)	..	..
Unemployed				
Yes	167	14·6 (11·1–18·0)	0·49	1·13 (0·80–1·58)
No	140	12·9 (9·8–16·1)	..	..
Current alcohol abuse				
Yes	87	14·9 (9·6–20·2)	0·49	1·15 (0·77–1·71)
No	242	13·0 (10·7–15·3)	..	..
Current tobacco use				
Yes	131	16·5 (12·1–21·0)	0·09	1·33 (0·96–1·85)
No	222	12·4 (10·1–14·8)	..	..
HIV infection				
Yes	42	10·0 (5·2–14·8)	0·03	0·57 (0·34–0·96)
No	264	17·5 (14·3–20·8)	..	..
First time treated for MDR tuberculosis				
No	62	37·0 (24·6–49·4)	<0·0001	3·33 (2·27–4·89)
Yes	256	11·1 (9·1–13·1)	..	..
In hospital at enrolment				
Yes	291	16·9 (13·9–20·0)	<0·0001	1·84 (1·35–2·50)
No	83	9·2 (6·9–11·5)	..	..
Pulmonary radiographic abnormality				
Unilateral	60	13·4 (8·5–18·3)	0·64	0·91 (0·61–1·36)
Bilateral	314	14·7 (12·3–17·2)	..	..
Cavitary disease on chest radiograph				
Unilateral	159	15·3 (11·7–18·9)	0·12	1·34 (0·92–1·95)
Bilateral	71	11·9 (7·6–16·2)	0·85	1·04 (0·66–1·67)
No cavity	95	11·4 (8·1–14·7)	..	..
Sputum-smear test results at enrolment				
Positive	302	13·6 (11·3–15·8)	0·08	0·68 (0·45–1·3)
Negative	66	19·9 (12·3–27·4)	..	..

	Weighted frequency of resistance†	Weighted percentage for resistance (95% CI)†	p value	Risk ratio (95% CI)
Previous treatment with second-line injectable drugs				
Yes	100	40·8 (30·1–51·4)	<0·0001	3·68 (2·67–5·07)
No	240	11·1 (9·0–13·1)	..	..
Previous treatment with fluoroquinolones				
Yes	134	38·7 (30·5–46·9)	<0·0001	3·89 (2·89–5·23)
No	205	10·0 (7·9–12·0)	..	..
Previous treatment with another oral second-line drug				
Yes	108	35·8 (26·7–44·9)	<0·0001	3·27 (2·38–4·49)
No	231	11·0 (8·9–13·1)	..	..
Previous treatment with a third-line drug				
Yes	32	62·6 (41·7–83·5	<0·0001	4–81 (3·31–6·98)
No	307	13·0 (10·8–15·2)	..	..

MDR=multidrug-resistan. *Age, marital status, education, occupation risk, homelessness, contact with a tuberculosis or MDR tuberculosis patient, previous surgery for tuberculosis, diabetes mellitus, and comorbidities were not significantly associated with fluoroquinolone resistance (p>0·1; data not shown). †Site-specific sampling weights were calculated as the total number of eligible cases during the enrolment period divided by the number of patients enrolled.

Table 4:

Risk factors for resistance to second-line injectable drugs at baseline *

	Weighted frequency of resistance†	Weighted percentage for resistance (95% CI)†	p value	Risk ratio (95% CI)
Green Light Committee approval				
Yes	372	23·4 (19·9–26·9)	0·03	0·79 (0·63–0·98)
No	307	29·8 (25·1–34·4)	..	..
Sex				
Male	418	24·9 (21·4–28·3)	0·33	0·90 (0·72–1·12)
Female	261	27·8 (23·0–32·5)	..	..
History of imprisonment				
Yes	108	46·7 (35·5–58·0)	<0·0001	1·94 (1·47–2·55)
No	458	24·1 (21·0–27·2)	..	..
Unemployed				
Yes	368	32·0 (27·4–36·6)	0·0001	1·60 (1·25–2·04)
No	216	20·0 (16·1–23·9)	..	..
Current alcohol abuse				
Yes	248	42·5 (35·2–49·9)	<0·0001	2·08 (1·66–2·60)
No	381	20·4 (17·5–23·3)	..	..
Current tobacco use				
Yes	296	37·4 (31·4–43·5)	<0·0001	1·84 (1·48–2·28)
No	364	20·4 (17·4–23·4)	..	..
HIV infection				
Yes	147	35·0 (27·3–42·6)	0·76	1·04 (0·81–1·34)
No	507	33·6 (29·5–37·7)	..	..
First time treated for MDR tuberculosis				
No	67	40·3 (27·5–53·1)	0·0076	1·66 (1·18–2·33)
Yes	562	24·3 (21·4–27·2)	..	..
In hospital at enrolment				
Yes	596	34·7 (30·8–38·7)	<0·0001	3·80 (2·86–5·04)
No	83	9·1 (6·8–11·5)	..	..
Pulmonary radiographic abnormality				
Unilateral	89	19·8 (13·9–25·7)	0·04	0·73 (0·53–1·00)
Bilateral	583	27·3 (24·2–30·5)	..	..
Cavitary disesae				
Unilateral	321	30·8 (26·1–35·6)	<0·0001	1·82 (1·37–2·43)
Bilateral	173	29·0 (22·6–35·4)	0·0012	1·72 (1·24–2·38)
No cavity	141	16·9 (12·9–20·9)	..	..
Sputum-smear test result at enrolment				
Positive	566	254 (22·4–28·4)	0·15	0·80 (0·59–1·07)
Negative	105	31·8 (23·2–40·4)	..	..

	Weighted frequency of resistance†	Weighted percentage for resistance (95% CI)†	p value	Risk ratio (95% CI)
Previous treatment with second-line injectable drugs				
Yes	110	44·9 (34·2–55·6)	<0·0001	1·95 (1·49–2·56)
No	499	23·0 (20·1–25·9)	..	..
Previous treatment with fluoroquinolones				
Yes	124	35·8 (27·–44·1)	0·0031	1·53 (1·17–1·99)
No	485	23·5 (20·5–26·5)	..	..
Previous treatment with another oral second-line drug				
Yes	128	42·3 (32·9–51·8)	<0·0001	1·86 (1·43–2·41)
No	480	22·8 (19·9–25·7)	..	..
Previous treatment with a third-line drug				
Yes	26	50·1 (28·3–71·9)	0·0096	2·03 (1·29–3·19)
No	583	24·7 (21·9–27·6)	..	..

MDR=multidrug-resistant. *Age, marital status, education, occupation risk, homelessness, contact with a tuberculosis or MDR tuberculosis patient, previous surgery for tuberculosis, diabetes mellitus, and comorbidities were not significantly associated with resistance to second-line injectable drugs (diabetes mellitus p=0·02, other characteristics p>0·1; data not shown). †Site-specific sampling weights were calculated as the total number of eligible cases during the enrolment period divided by the number of patients enrolled.

Table 5:

Risk factors for extensively drug-resistant tuberculosis at baseline *

	Weighted frequency of resistance†	Weighted percentage for resistance (95% CI)†	p value	Risk ratio (95% CI)
Green Light Committee approval				
Yes	87	5·5 (3·6–7·4)	0·0002	0·45 (0·29–0·69)
No	126	12·3 (8·9–15·6)	..	..
Sex				
Male	96	5·7 (3·9–7·5)	0·0002	0·46 (0·30–0·70)
Female	118	12·5 (8·9–16·1)	..	..
History of imprisonment				
Yes	20	8·7 (2·7–14·6)	0·57	1·24 (0·59–2·61)
No	132	7·0 (5·1–8·9)	..	..
Unemployed				
Yes	110	9·5 (6·6–12·4)	0·10	1·48 (0·92–2·37)
No	70	6·5 (4·1–8·8)	..	..
Current alcohol abuse				
Yes	54	9·3 (4·8–13·7)	0·35	1·30 (0·75–2·23)
No	133	7·1 (5·3–9·0)	..	..
Current tobacco use				
Yes	71	9·0 (5·5–12·5)	0·47	1·19 (0·74–1·91)
No	135	7·5 (5·6–9·5)	..	..
HIV infection				
Yes	39	9·3 (4·7–13·9)	0·61	0·87 (0·50–1·51)
No	161	10·7 (8·0–13·4)	..	..
First time treated for MDR tuberculosis				
No	38	23·0 (11·4–34·6)	<0·0001	3·66 (2·08–6·43)
Yes	145	6·3 (4·7–7·9)	..	..
In hospital at enrolment				
Yes	185	10·8 (8·2–13·3)	<0·0001	3·36 (2·03–5·57)
No	29	3·2 (1·8–4·6)	..	..
Pulmonary radiographic abnormality				
Unilateral	31	6·9 (3·3–10·6)	0·47	0·81 (0·45–1·44)
Bilateral	183	8·6 (6·6–10·6)	..	..
Cavitary disease				
Unilateral	89	8·6 (5·7–11·4)	0·26	1·36 (0·80–2·33)
Bilateral	46	7·6 (4·0–11·3)	0·55	1·22 (0·64–2·30)
No Cavity	53	6·3 (3·7–8·9)	..	..
Sputum-smear test result at enrolment				
Positive	173	7·8 (6·0–9·6)	0·16	0·66 (0·37–1·18)
Negative	39	11·8 (5·5–18·1)	..	..

	Weighted frequency of resistance†	Weighted percentage for resistance (95% CI)†	p value	Risk ratio (95% CI)
Previous treatment with second-line injectable drugs				
Yes	69	28·3 (18·3–38·4)	<0·0001	4·75 (3·05–7·42)
No	129	6·0 (4·4–7·5)	..	..
Previous treatment with fluoroquinolones				
Yes	82	23·7 (16·1–31·3)	<0·0001	4·21 (2·73–6·49)
No	116	5·6 (4·0–7·2)	..	..
Previous treatment with another oral second-line drug				
Yes	73	24·1 (15·7–32·4)	<0·0001	4·05 (2·60–6·31)
No	125	5·9 (4·3–7·6)	..	..
Previous treatment with a third-line drug				
Yes	16	32·2 (11·8–52·6)	<0·0001	4·18 (2·13–8·21)
No	182	7·7 (5·9–9·5)	..	..

MDR=multidrug-resistant. *Age, marital status, education, occupation risk, homelessness, contact with a tuberculosis or MDR tuberculosis patient, previous surgery for tuberculosis, diabetes mellitus, and comorbidities were not significantly associated with extensively drug-resistant tuberculosis (p>0·1; data not shown). †Site-specific sampling weights were calculated as the total number of eligible cases during the enrolment period divided by the number of patients enrolled.

Table 6:

Risk factors for resistance to other oral second-line drugs at baseline*

	Weighted frequency of resistance†	Weighted percentage for resistance (95% CI)†	p value	Risk ratio (95% CI)
Green Light Committee approval				
Yes	467	29·3 (25·8–32·9)	0·11	1·18 (0·96–1·45)
No	257	24·9 (20·7–29·1)	..	..
Sex				
Male	494	29·4 (25·9–32·9)	0·08	1·20 (0·97–1·48)
Female	230	24·4 (20·2–28·7)	..	..
History of imprisonment				
Yes	67	29·0 (18·3–39·8)	0·63	1·10 (0·75–1·62)
No	500	26·4 (23·3–29·4)	..	..
Unemployed				
Yes	285	24·9 (20·7–29·0)	0·17	0·86 (0·69–1·07)
No	312	29·0 (24·9–33·1)	..	..
Current alcohol abuse				
Yes	156	26·7 (20·1–33·4)	0·78	0·96 (0·73–1·26)
No	518	27·8 (24·8–30·8)	..	..
Current tobacco use				
Yes	229	29·0 (23·3–34·7)	0·50	1·08 (0·86–1·36)
No	478	26·8 (23·8–29·9)	..	..
HIV infection				
Yes	95	22·6 (16·0–29·2)	0·22	0·82 (0·59–1·13)
No	417	27·6 (23·8–31·5)	..	..
First time treated for MDR tuberculosis				
No	62	37·0 (24·5–49·6)	0·06	1·44 (1·01–2·06)
Yes	592	25·7 (22·9–28·4)	..	..
In hospital at enrolment				
Yes	485	28·2 (24·5–31·9)	0·48	1·07 (0·89–1·29)
No	239	26·4 (22·9–29·9)	..	..
Pulmonary radiographic abnormality				
Unilateral	108	24·1 (17·8–30·3)	0·24	0·85 (0·64–1·12)
Bilateral	605	28·4 (25·3–31·4)	..	..
Cavitary disease				
Unilateral	265	25·5 (21·2–29·8)	0·95	0·99 (0·78–1·26)
Bilateral	179	30·0 (23·8–36·1)	0·26	1·17 (0·89–1·52)
None	215	25·7 (21·4–30·0)	..	..
Sputum-smear test results at enrolment				
Positive	624	28·0 (25·1–30·9)	0·58	1·10 (0·78–1·54)
Negative	84	25·5 (17·3–33·6)	..	..

	Weighted frequency of resistance†	Weighted percentage for resistance (95% CI)†	p value	Risk ratio (95% CI)
Previous treatment with second-line injectable drugs				
Yes	105	42·8 (32·1–53·5)	0·0013	1·63 (1·24–2·13)
No	570	26·3 (23·5·29·2)	..	..
Previous treatment with fluoroquinolones				
Yes	142	40·9 (32·6–49·2)	0·0003	1·58 (1·26–2·00)
No	533	25·8 (22·9–28·8)	..	
Previous treatment with another oral second-line drug				
Yes	136	44·8 (35·4–54·3)	<0·0001	1·75 (1·38–2·22)
No	539	25·6 (22·7–28·4)	..	..
Previous treatment with a third-line drug				
Yes	32	62·8 (43·2–82·5)	0·0001	2·31 (1·66–3·21)
No	643	27·2 (24·4–30·0)	..	..

MDR=multidrug-resistant. *Age, marital status, education, occupation risk, homelessness, contact with a tuberculosis or MDR tuberculosis patient, previous surgery for tuberculosis, diabetes mellitus, and comorbidities were not significantly associated with resistance to other oral second-line drugs (diabetes mellitus p=0·06, other characteristics p>0·1; data not shown). †Site-specific sampling weights were calculated as the total number of eligible cases during the enrolment period divided by the number of patients enrolled.