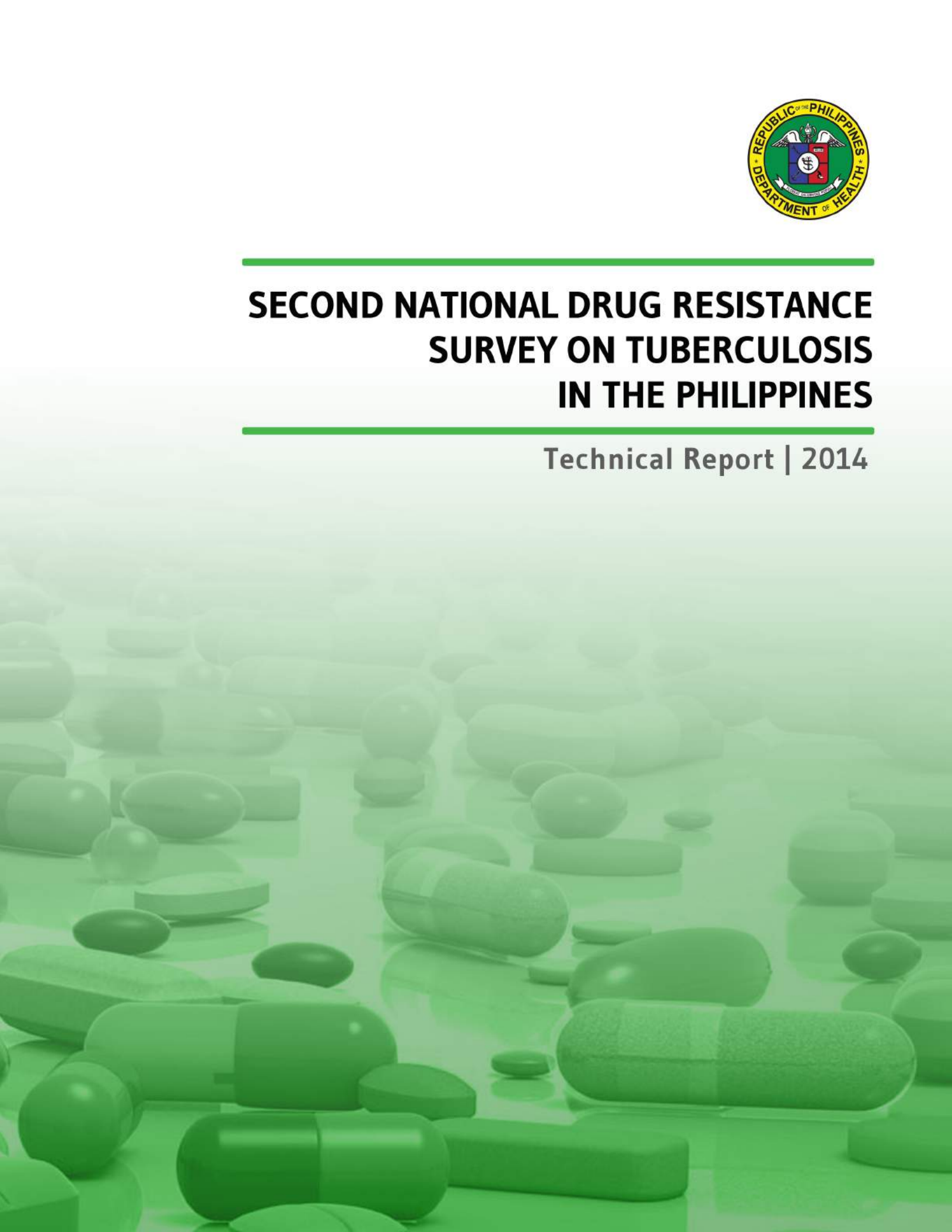
SECOND NATIONAL DRUG RESISTANCE SURVEY ON TUBERCULOSIS IN THE PHILIPPINES

Technical Report | 2014



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INTRODUCTION

Tuberculosis, or TB, is a contagious disease caused by *Mycobacterium tuberculosis* which most frequently targets the lungs. The bacteria can be transmitted from person to person by droplet nuclei from the throat and lungs of people with TB. The latest global report of World Health Organization (WHO) in 2012 put estimates of new TB cases at 8.6 million and 1.3 million deaths.

Most cases of tuberculosis are curable, allowing an effective strategy to control the spread of TB to be implemented. Individuals with infectious TB are treated with a full course of the correct dosage of anti-TB medicines that includes isoniazid, rifampicin, pyrazinamide, streptomycin and ethambutol. Due to a lengthy treatment course of 6 to 8 months, WHO recommends a supervised treatment strategy to ensure a regular and uninterrupted intake of medicine called directly-observed treatment, short-course (DOTS). The DOTS strategy is not simply concerned with patient treatment only but is a management strategy for public health systems that incorporates case-detection through high quality bacteriology, standardized short-course chemotherapy, ensuring patient adherence to treatment, adequate drug supply, and monitoring system for program supervision and evaluation, and very importantly, political commitment. A global strategy anchored on these had enabled countries, especially the high-burden ones, to improve their TB control programs by increasing detection and cure rates and obtaining greater political commitment.

Major obstacles remain in the efforts to achieving global TB control targets. Multiple drug resistance TB (MDR-TB) is one of them. MDR-TB is defined as a form of drug-resistant TB due to a M. Tuberculosis resistant to at least both isoniazid and rifampicin, the two most powerful anti-TB drugs. Treatment for MDR-TB is longer than the usual course, using more expensive second-line drugs that have more side effects. MDR-TB management is included in the new and comprehensive Stop TB strategy. An even more serious threat is the emergence of extensively-drug resistant TB (XDR-TB) in patients who are infected with MDR-TB and resistant also to any of the fluoroquinolones and any injectable anti-TB drugs.

The assessment of the spread of anti-TB drug resistance has thus become a necessary component of the global fight to stop TB. Since 1994, the WHO, IUATLD (The Union) and other partners have spearheaded the Global Project on Anti-tuberculosis Drug Resistance Surveillance (The Global Project). This partnership assists countries in planning the expansion of MDR-TB management using accurate data on national prevalence and patterns of drug resistance. It supports National Reference Laboratories in countries in the conduct of national surveillance for drug resistance using properly selected representative samples of adequate size, data collection and analysis which delineates between new and previously treated cases and internationally accepted methodology and quality control of drug testing. The standardization of these procedures for national surveillance allows global level evaluation of the magnitude and trends in anti-tuberculosis drug resistance. Through these surveys, the growing global burden of MDR-TB has been documented, and in recent years, also the spread of XDR-TB (WHO Global Report 2013).

The Philippines is one of the 22 high burden countries for tuberculosis. In 2012, there were approximately 450,000 cases with 23,000 deaths. This corresponded to 461 existing cases of TB and 24 deaths per 100,000 population in the country. Incident cases of TB were counted at 265 per 100,000 population (WHO Global Report 2013).

Programmatic management of multi-drug resistant TB was started in 1999 by the Tropical Disease Foundation (TDF) through the TDF – Makati Medical Center (MMC) DOTS Clinic. In 2003, the Philippines received funding support from the Gobal Fund to Fight AIDS, TB and Malaria (GFATM) with the TDF as principal recipient to treat MDR-TB cases. First covering the National Capital Region, additional treatment centers were set-up. Local government units (LGUs) and other partners were then engaged by working with the Center for Health Development (CHD) and other partners by referring MDR-TB suspects to the treatment centers. These LGUs were also expected to provide continuing MDR-TB care. Significantly, the National TB Reference Laboratory (NTRL) was designated as the lead agency in the establishment of a laboratory network in the Philippines. In 2008, the National Implementing Guidelines for the Programmatic Management of Drug-Resistant TB (PMDT) was signed by the Secretary of Health. The principal recipient designation by GFATM was transferred from the TDF to Philippine Business for Social Progress (PBSP) in 2010 and necessary adjustments were implemented. There are 44 PMDT facilities in the country located in 16 regions (Lofranco, unpublished report).

The Philippines conducted its first National Drug Resistance Survey in 2004 employing the recommended procedures of the WHO and The Union (Philippine Nationwide Tuberculosis Drug Resistance Survey Team [PNTDRST], 2009). In this survey they reported that the prevalences of the different forms of anti-TB drug resistance were high. Resistance to any drug was 20.40% in new TB cases and 38.80% in previously treated TB cases. Multi-drug resistant TB prevalence was 3.80% and 20.90%, respectively, among the two groups of TB patients.

Funded by the Global Fund Project "Sustaining TB Control and Ensuring Universal Access to Comprehensive Quality TB Care", the 2nd National Drug Resistance Survey (DRS) started in 2011 and was completed in 2012. This report presents the results of this study.

ACKNOWLEDGEMENT

The Department of Health – Infectious Diseases Office – National TB Control Program (NTP) and the RITM - National TB Reference Laboratory (NTRL) wishes to express its heartfelt gratitude to the following organizations and individuals for the invaluable contribution during the conduct of the 2nd Drug Resistance Survey for the Philippine National TB Program:

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NTRL LABORATORY RESEARCH TEAM
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To our local consultant to the DRS, Dr. Jesus Sarol Jr. and to the international consultant and supra- national TB laboratory, Research Institute of Tuberculosis – Japan Anti-Tuberculosis Association Dr. Akira Shimouchi, Dr. Satoshi Mitarai, Dr. Akihiro Ohkado, Dr. Norio Yamada

To the international partners and their in-country representatives and/or projects, particularly The Global Fund to Fight AIDS, Tuberculosis, and Malaria (TGFATM), United States Agency for International Development (USAID), and World Health Organization (WHO);

To the in- country partners and their representatives from Centers for Health Development, Provinces and Cities, Rural Health Units;

To the TB Laboratory Network, particularly the Treatment Centers, Satellite Treatment Centers, Culture Centers, and Microscopy Centers.

The development and publication of this DRS report were supported by The Global Fund to Fight AIDS, Tuberculosis, and Malaria (GF – TB) through the Philippine Business for Social Progress.

OBJECTIVES OF THE 2ND NATIONAL DRUG RESISTANCE SURVEY

The main objectives of the 2nd National DRS are as follows:

To determine the national prevalence of resistance to 4 major anti-TB drugs (HRES) among new and previously treated patients

To determine the prevalence of multi-drug resistant TB among new and previously treated patients

Other objectives for the survey are:

To determine the proportions and patterns of drug resistance to fluoroquinolones and second-line injectable agents among strains with confirmed resistance to INH and Rifampicin

To evaluate associations between drug resistance and age, sex, and urban-rural residence and other selected risk factors.

SAMPLING DESIGN: MODIFIED TWO-STAGE SAMPLING DESIGN

DESCRIPTION

The sampling design was a modified two-stage cluster sampling design that generally followed the recommended sampling design as described in the guidelines for drug resistance surveillance by the World Health Organization (WHO, 2009). All known DOTS facilities in the country were listed and formed into clusters. A cluster was defined as a single DOTS facility, which can be a rural health unit (RHU), health center, hospital, jail treatment center or public-private mix DOTS clinic (PPMD), that registered TB patients for treatment using the recommended DOTS strategy, or a group of geographically adjacent DOTS facilities such that each cluster had an expected minimum total number (150) of new smear-positive TB cases based on the 2009 NTP case-finding report of the facilities. Clusters were first selected with probabilities proportionate to size, where size was the expected number of new smear-positive TB patients. Within a selected cluster, new smear-positive TB patients and previously-treated TB cases with new episode of treatment were recruited sequentially. Those who agreed to participate in the survey were taken into the study.

STUDY POPULATIONS

The 2nd National DRS aimed to measure drug resistance among newly registered episodes of TB. There were two populations of interest in this survey: new smear-positive TB cases and previously treated TB cases. The latter included relapses, failures, return after default (RAD) and other retreatment cases (unknown outcome of previous treatment, and/or retreatment of smear-negative pulmonary TB or bacteriologically negative extrapulmonary disease).

INCLUSION/EXCLUSION CRITERIA

The inclusion criteria for patients were the following:

a. sputum AFB smear-positive pulmonary TB case
b. newly registered episode of TB detected during the specified time for data collection in the DOTS facilities included in the sample
c. at least 15 years of age
d. provided informed consent

TB patients who were smear-negative, extra-pulmonary cases, those with on-going treatment during the time of data colletion and those younger than 15 years of age were excluded from the study.

SAMPLE SIZE

The targeted sample size was obtained as follows. The expected proportion was 4.40%, which was the estimated prevalence of resistance to rifampicin using the data from the 2004 National DRS (corrected for sampling weights). The design effect derived from the previous survey was 1.20. The expected losses was pegged at 15%. The expected population of new smear-positive TB patients was approximately 90,000 cases. It was assumed then that it would be similar to the reported total number in the 2009 NTP Report of DOTS facilities in the country. Given these values, the resulting sample size requirement was 2815 new smear-positive TB cases.

For the other study population of interest, all previously-treated patients under a new episode of TB treatment were invited in the selected clusters. The recruitment of these patients was opened while the recruitment of new smear-positive patients in the same facilities was being completed.

Sixty (60) clusters were included in this survey. The targeted sample size per cluster was 47 new smear-positive patients to reach the total sample size requirement. This sample size already allowed for possible losses due to several reasons related with the complex process of determining patient eligibility, transmission of specimens and documents and laboratory proccessing and encoding of results. However, considerable variation in the actual number of patients included per cluster in the analysis resulted. Many clusters did not have adequate number of patients while the others exceeded the required number to be recruited. Many reasons were cited for these occurrences. For practical purposes, the sampling frame used the listing of TB cases per cluster in 2009. These numbers of patients per cluster could have changed drastically in the clusters in 2011. Actually all clusters were able to recruit at least 48 patients for the combined new and previously treated patients. Patients were recruited into the study once their smear-positive status was known. However, there was still uncertainty in determining whether a smear-positive patient would satisfy the inclusion/exclusion criteria until after the interview of the patient was accomplished, testing of the sputum samples were completed and the determination of the classification of a patient as new or previously treated patient was finally established after review of the interview proceedings and clinical records. The patient could withdraw from the study, fail to provide adequate sputum samples, have culture tests that were contaminated or did not grow, or have susceptibility testing that did not give interpretable results (unreadable or too few colonies). In some clusters, the number of losses varied in magnitude across clusters. The final number of patients in the analysis were severely reduced in some clusters. Other DOTS facilities acted conservatively and recruited more patients which was allowed. This resulted in some clusters exceeding the targetted sample size even to a considerable degree.

SAMPLING OF NEW SMEAR-POSITIVE TB PATIENTS

Essentially the 2012 National DRS employed a two-stage cluster sampling design where clusters were chosen with probabilities proportional to size (PPS sampling). Within a selected cluster, TB patients who qualified for the study were included sequentially as they came to the centers for treatment.

For this survey, a case-finding report of all health center facilities that registered TB patients for treatment was prepared by the National TB Control Program (NTP).

These facilities all implemented the DOTS strategy in TB treatment and prevention, hence, collectively these are referred to here as 'DOTS facilities'. These included rural health units (RHUs), health centers (HCs), hospitals, jail treatment centers and public-private mix DOTS (PPMD) facilities. The NTP report provided the number of new and old smear-positive TB cases per health center facility in 2009. DOTS facilities that registered large numbers of new smear-positive TB cases were individually considered a cluster. On the other hand, many DOTS facilities were 'small' in the sense that these had very few registered new smear-positive TB patients. For this reason, adjacent small DOTS facilities within a province were lumped together into clusters such that each cluster had approximately 150 or more new smear-positive TB cases. The considerations in lumping together small DOTS facilities into clusters were taken in this order: 1) belonged to the same interlocal health zones (ILHZs); 2) belonged to the same congressional district; 3) within specified geographical boundaries; 4) within same province; and 5) within same region. Even RHUs that reported zero (0) new cases of smear-positive TB in 2009 were included in the cluster in accordance with these considerations. There were very few exceptions where the clusters had less than 150 expected new smear positive TB cases.

A listing of the clusters formed using the above considerations was then prepared as the sampling frame for the clusters. The provinces of Basilan and Batanes were not included in the list. No report of smear-positive TB cases for 2009 was available for Basilan at the time of sample selection. While Batanes had zero reported smear-positive TB cases in 2009, the logistical difficulty in collecting, sending and testing specimens for purposes of the DRS was too great, thus impractical to include in the sampling frame.

To implement the PPS sampling design, besides each cluster in the list, the total number of new smear-positive TB cases in the DOTS facilities belonging to each cluster was attached.

An additional column was created containing the respective cumulative total of new smear-positive TB patients starting from the first cluster in the list. Upon completing the sampling frame, a sample of 60 clusters was chosen with probabilities proportional to size, where size was the total number of new smear-positive TB cases in 2009 for all DOTS facilities belonging to the cluster .

New smear-positive TB cases in the cluster who agreed to participate were included sequentially in the survey. The recruitment of new smear positive cases ceased for the cluster once the required number of 47 patients was reached. The expected total number of new smear positive TB cases that were to be recruited for this study was 2820.

SAMPLING OF PREVIOUSLY TREATED TB CASES

The clusters randomly chosen for the recruitment of new smear-positive TB cases were also the source of sampling of previously treated TB cases. Within each cluster, all previously treated TB cases who qualified for the study and provided informed consent during the specified data collection period were included in the sample.

DATA COLLECTION

ENROLMENT OF PATIENTS

After the clusters to be included in the survey were identified, preparation of the DOTS facilities was done. These included enlisting the support of these facilities in informing prospective subjects. Staff of these facilities were also invited for an orientation training on the procedures of the DRS.

The training focused on the interview of patients, collection of sputum samples, decontamination, inoculation, storage, transport of inoculated media, and proper recording of the forms.

Patients were recruited from the sample DOTS facilities. These health facilities, like all DOTS facilities nationwide, implemented standardized management protocols and guidelines for TB cure and prevention as described in the Manual of Procedures (DOH 2005) developed by the National TB Control Program (NTP) in cooperation with local and international key stakeholders and partners. Patients who presented with TB symptoms that included cough for two or more weeks, with or without fever, chest and/or back pains not referable to any musculo-skeletal disorders, hemoptysis or recurrent blood-streaked sputum, significant weight loss and other symptoms, such as sweating, fatigue, body malaise, shortness of breath were considered suspects for TB. These patients were motivated by the DOTS facility staff to undergo direct sputum smear microscopy (DSSM) testing.

Patients were instructed to return to the health facility for the results of the microscopy testing. The appropriate intervention under the NTP Manual of Procedures was provided to the patients depending on the results of the microscopy testing. If this patient was positive by DSSM, he/she was given a TB patient category based on previous history of treatment (new, relapse, treatment failure, return-after default, transfer-in and other TB patient). The attending health care provider of the TB patient invited the eligible patient to join the DRS. An interested patient was then referred to the DRS-trained staff who determined patient eligibility, oriented the patient about the DRS procedures and obtained informed consent.

PATIENT INTERVIEW

The DRS-trained doctor or nurse conducted a detailed interview of the patient to complete the Case Report Form. The interview established the accurate classification of the patient as to being new smear-positive TB or previously treated TB case, where the latter is further subdivided into relapse, failure, return after default (RAD) and other retreatment cases (unknown outcome of previous treatment, and/or retreatment of smear negative pulmonary TB or bacteriologically negative extrapulmonary disease). Patients were asked about their past and present illness related to tuberculosis and show past clinical records if available.

The definition of the different classification of TB patients is as follows:

New case – a patient who has never had treatment for TB or who has taken anti-TB drugs for less than one month

Relapse – a patient previously treated for TB, who has been declared cured or treatment completed, and is diagnosed with bacteriologically positive (smear or culture) TB

Treatment failure – a patient who, while on treatment, is sputum smear-positive at five months or later during the course of treatment

Return after default (RAD) – a patient who returns to treatment with positive bacteriology (smear or culture), following interruption of treatment for two months or more

Other retreatment case – all new episodes of TB case that do not fit the above definitions. This includes patients who were previously treated but the outcomeof their previous treatment is unknown and/or who have returned to treatment with smear-negative pulmonary TB or bacteriologically negative extrapulmonary disease.

Previously treated case – a newly registered episode of TB in a patient who is any of the following: relapse, treatment failure, return after default or other retreatment case.

Aside from the clinical history, data on selected risk factors were collected by the interviewer. These risk factors included history of diabetes, smoking, alcohol use, drug use, previous HIV testing and contacts with other TB patients in the household. Diabetes history was obtained only through interview.

SPUTUM COLLECTION AND PROCESSING

TB patients who joined the DRS were asked for consent to use their sputum samples previously submitted for the DSSM. If these samples were no longer viable for inoculation for drug susceptibility testing (DST), the patients were requested to submit two additional fresh sputum specimens prior to initiation of TB treatment. These were inoculated by the medical technologist/microscopist and labeled with the bar-coded stickers. The inoculated tubes were then sent to the Regional Culture Center.

CULTURE AND DRUG SUSCEPTIBILITY TESTING

Mycobacterium tuberculosis were isolated from the two inoculated specimens from smear- positive TB patients using the modified Ogawa method. At NTRL, M. tuberculosis colonies were identified and differentiated from other mycobacteria on the basis of growth characteristics, morphology and rapid speciation TB antigen test.

Drug susceptibility testing on the isolates then followed. DST was performed using the Löwenstein-Jensen (LJ) proportion method. The critical proportion of resistance was 1% for all drugs, and the critical concentrations were 0.20mcg/ml for INH, 4mcg/ml for SM, 40mcg/ml for RFP, and 2mcg/ml for EMB. Strains that were resistant to any of the four drugs were designated as having "any resistance." Strains resistant to at least both INH and RFP were defined as having multi-drug resistance (MDR). Susceptibility testing for second line drugs (Levofloxacin, Kanamycin, Amikacin and Capreomycin) were performed for strains resistant to both INH and RFP. Critical concentrations for second line drugs were: Levofloxacin 1.00 mcg/ml, Kanamycin 30.00 mcg/ml, Amikacin 40.00 mcg/ml and Capreomycin 40.00 mcg/ml. Strains with resistance to INH and RFP plus additional resistance to a fluoroquinolone and a second-line injectable drug is defined as having extensively drug resistant TB (XDR-TB).

DATA PROCESSING AND ANALYSIS

All accomplished DRS data forms were sent to the Department of Epidemiology and Biostatistics (DEBS) of the Research Institute for Tropical Medicine. Forms were checked for completeness and errors. Data were encoded using a data entry program in MS Acccess. These files were then converted into STATA databases for statistical analysis.

Observations were weighted using the inverse of the probabilities of selection of the observations in the estimation of the parameters of interest. The weights were calculated using the formula:

$$w_i = \frac{47}{n_i} * \frac{1}{(\frac{60 * N_i}{N})(\frac{47}{N_i})}$$

where wi = weight of an individual
n_i = actual sample size in the cluster
N_i = size of the cluster, represented by the number of TB cases in the cluster in 2009, and
N = total number of TB cases in all clusters in 2009
Since cluster sampling was employed, the design was considered in the calculation of the standard errors and confidence intervals of the estimates.

The prevalence of resistance to individual drugs and to different combinations of drugs were derived separately for new TB cases and previously treated TB cases. Multidrug resistance (MDR-TB) was defined as resistance to at least both rifampicin and isoniazid. The prevalence of resistance was estimated using a weighted approach using the inverse sampling probabilities as weights. Other methods of estimation such as unweighted analysis, a meta-analytic approach where each cluster is considered a separate study, and different approaches to variance estimation such as robust estimation and Random Effects (RE) were also applied for comparison of approaches.

Comparisons of these proportions based on sex, age groups, history of diabetes, smoking, alcohol drinking, drug use and presence/absence of other TB patients in the household were evaluated. Odds ratios were computed to assess the strength of the associations of these variables to drug resistance. Logistic regression was likewise employed to assess the association of each of these variable controlling for the effect of potential confounders.

The extent of missing data, especially on the results of the drug susceptibility testing, was assessed. The percent of missing DST among eligible patients was determined across categories of patient characteristics such as sex, age, urban-rural classification, weight, presence/absence of haemoptysis, AFB smear result, alcohol use, smoking, presence/absence of diabetes, having another TB patient in the household and previous TB treatment. Comparisons were assessed for statistical significance using standard Chi-square tests.

Missing data imputation was carried out on the data using multiple imputation by chained equations (Royston 2005). In this approach, several data sets containing different versions of imputed values of missing data were created. The risk factors sex, age, weight, hemoptysis, smear result, alcohol use, smoking, diabetes and presence of another TB patient in the household variables were included in the model for imputation. All were included even if any of them did not correlate to MDR-TB or with the missingness of the data. The statistical analysis was then performed on each of these imputed data sets. The results were then combined to derive a single set.

Data analysis was performed using Stata Ver 10.1. In particular, the SVY module and estimation commands were utilized since this module is appropriate for data obtained from cluster sampling designs. The progarm ICE was used for multiple missing data imputation.

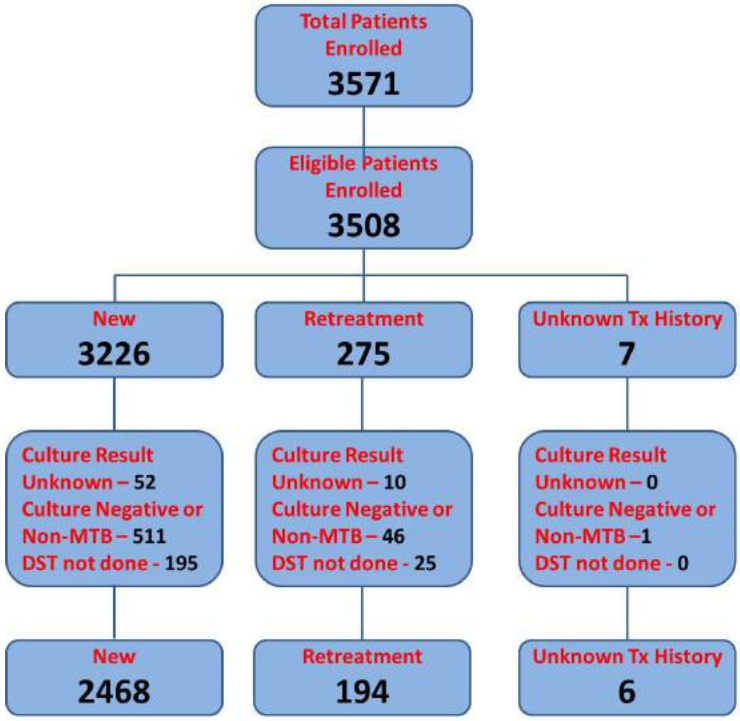
RESULTS

Recruitment of subjects and specimen collection started in September 2011 and ended in December 2012. A total of 3571 patients were enrolled, of which, sixty-three did not pass eligibility: 40 does not have data on age, 20 were <15 years old and 3 had been in treatment for at least one month.

Among the 3508 eligible participants, 3226 were new cases, 275 were retreatment cases and 7 were with unknown treatment history. Still, several participants were excluded because of the following reasons: (a) unknown culture result [52 among new cases and 10 among retreatment cases]; (b) culture negative or Non-MTB [511 among new cases; 46 among retreatment cases; and 1 among those with unknown treatment history]; and (c) DST not done [195 among new cases and 25 among retreatment cases].

In total, there were only 2668 patients available for analysis. These included 2468 new TB cases, 194 retreatment cases and 6 with unknown treatment history.

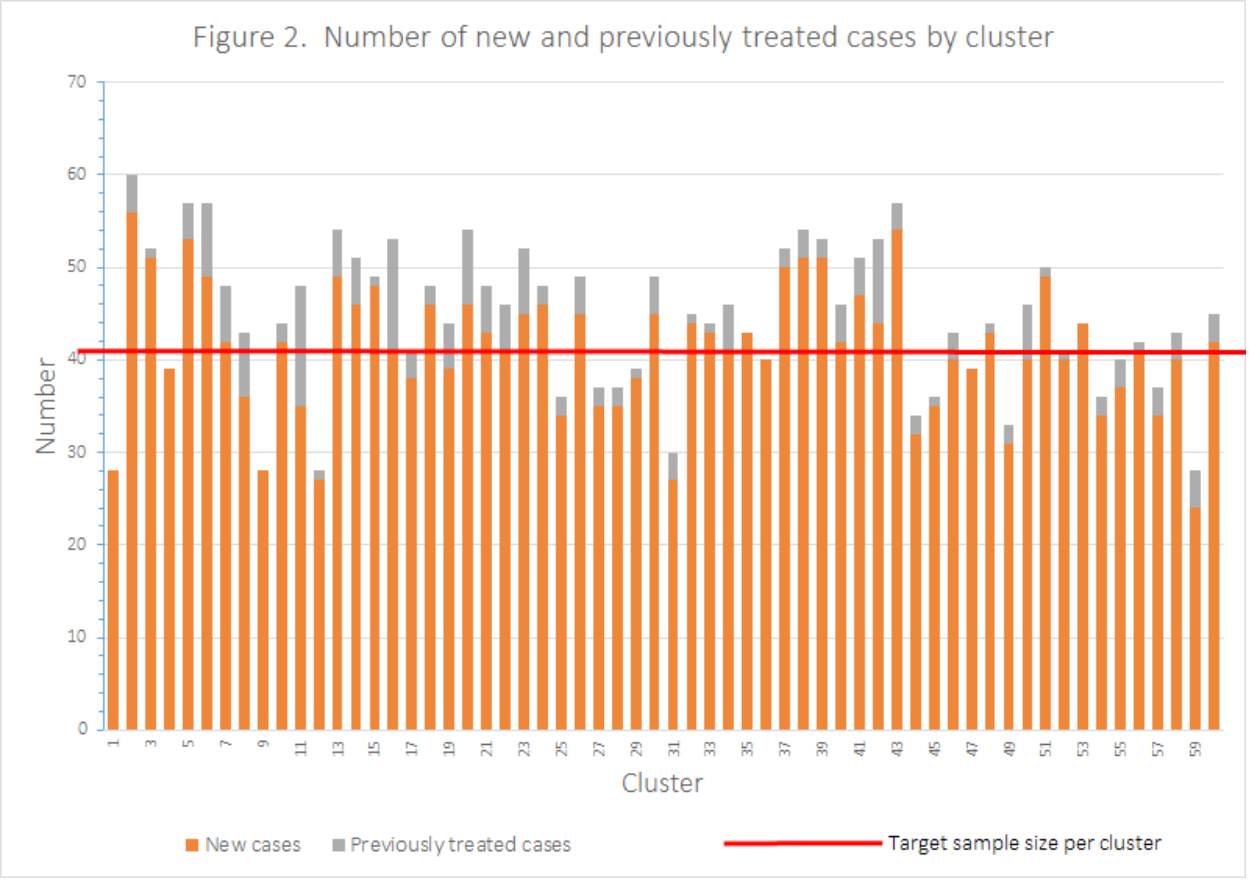
Figure 1. Breakdown of the number of TB patients enrolled in the National Drug Resistance Survey, Philippines, 2012



Our targeted sample size is 2448 excluding the expected losses. The actual size is 2468 which attained the target. However, the numbers of new and previously treated TB cases by cluster show wide variation in these numbers across clusters (Figure 2). The minimum cluster sample size in the analysis was 24 patients while the highest was 56 patients. Eighteen clusters failed to reach the desired minimum sample size of 41 per cluster (removing adjustment of 15% loss) while 14 clusters exceeded the target number by a considerable amount of greater than or equal to 50. This clearly deviated from that intended by the sampling design to achieve equal probabilities of the units by having equal sizes per cluster.

The demographic profile of patients is shown in Table 1. The ages of the patients ranged from 15 to 88 years with a mean and standard deviation of 41.30 and 14.90 years, respectively. The new cases of TB has a lower mean age, x=41.00 (sd=14.90) years as compared to the previously treated cases, x=44.80 (sd=13.8) years, t=3.89, p=0.0001. There were nearly 3 male TB patients for every female patient in both groups. Around two-thirds of patients (67.54%) were seen in rural areas. This percentage was slightly higher among the new cases than in the previously treated cases (x^2=3.09, p=0.079).

Figure 2. Number of new and previously treated cases by cluster



Information on the occupation of the large proportion (38.43%) of the patients was missing. Among that available, the occupational group with the highest proportion among the two groups of patients were the laborers and unskilled workers (19.80%). Among the new cases, farmers, forestry workers and fishermen (16.00%) comprised the next biggest group while in the previously treated group, this percentage (6.70%) was not similarly high.

Table 1. Demographic profile of TB patients, National Drug Resistance Survey, Philippines, 2012

Demographic Profile	New Patients		Previously Treated Patients		Combined	
	N = 2468		N = 194		N = 2662	
	No.	%	No.	%	No.	%
AGEGROUP						
≤ 19	167	6.77	4	2.06	171	6.42
20 – 29	508	20.58	31	15.98	539	20.25
30 – 39	508	20.58	41	21.13	549	20.62
40 – 49	562	22.77	59	30.41	621	23.33
50 – 59	443	17.95	40	20.62	483	18.14
≥ 60	280	11.35	19	9.79	299	11.23
SEX						
Male	1824	73.91	148	76.29	1972	74.08
Female	644	26.09	46	23.71	690	25.92
AREA						
Rural	1678	67.99	120	61.86	1798	67.54
Urban	790	32.01	74	38.14	864	32.46
OCCUPATION						
None	104	4.21	9	4.64	113	4.24
Students	87	3.53	4	2.06	91	3.42
Laborers and Unskilled Workers	486	19.69	41	21.13	527	19.8
Farmers, Forestry Workers and Fishermen	395	16	13	6.7	408	15.33
Plant and machine Operators and Assemblers	158	6.4	10	5.15	168	6.31
Trades and Related Workers	99	4.01	15	7.73	114	4.28
Service Workers and Shop and Market Sales Workers	87	3.53	9	4.64	96	3.61
Inmates	51	2.07	5	2.58	56	2.1
Technicians and Associate Professionals	21	0.85	0	0	21	0.79
Clerks	14	0.57	0	0	14	0.53
Professionals	12	0.49	1	0.52	13	0.49
Officials of Government and Special-Interest Organizations, Corporate Executives, Managers, Managing Proprietors and Supervisors	8	0.32	1	0.52	9	0.34
Special Occupation	9	0.36	0	0	9	0.34
Unknown	937	37.97	86	44.33	1023	38.43

PREVALENCE OF DRUG RESISTANCE

Table 2 shows the prevalence of resistance to first-line anti-TB drugs among TB patients. Resistance to any of the drugs was very common among the previously treated cases. This group had consistently far higher rates of resistance to anti-TB drugs than the new cases of tuberculosis. Among the latter group, resistance to any one of the four drugs, isoniazid, rifampicin, ethambutol and streptomycin was 17.47% (95%CI: 15.85%-19.21%). The previously treated cases had almost 2.50 times higher percentage of resistance to any of the drugs at 43.61% (95%CI: 36.35%-51.17%), $x^2_{df=1}$=77.5, p<0.0001. As for individual drugs, the difference in the prevalence of resistance between the two groups of patients was most pronounced with rifampicin. The percentage of previously treated cases who were resistant to rifampicin was 26.45% (95%CI: 20.35%-33.60%), compared to only 2.43% (95%CI: 1.75%-3.37%) among the new cases. The difference in proportion of resistance to ethambutol was also very significant, 12.76% (95%CI: 8.25%-19.21%) among previously treated cases versus 1.57% (95%CI: 1.11%-2.20%) among new TB cases.

Monoresistance to specific anti-TB drugs was also higher in the previously treated group. Monoresistance was found in 18.89% (95%CI: 13.75%-25.39%), compared to 13.34% (95%CI: 12.09%-14.70%) of new cases. This difference was statistically significant ($x^2_{df=1}$=4.8, p=0.0291). Resistance to isoniazid was the most common form of monoresistance in the two groups, 13.08% in the previously treated cases and 10.26% in the new cases.

It is worth noting that the prevalence of monoresistance to a specific drug was disproportionately lower than that of having any resistance to that particular drug. For example, the proportion of having any resistance to isoniazid was 36.56%, compared to only 13.08% for monoresistance to isoniazid among previously treated cases. For rifampicin, monoresistance was only 3.80% compared to 26.45% for any resistance with rifampicin in the same group of patients. The comparisons among the new cases showed similar ratios of monoresistance prevalence to any resistance prevalence to a specific drug. These results indicate that having resistance to two or more anti-TB drugs was far more common than monoresistance to a particular drug for both new and previously treated patients.

Multidrug resistance (MDR-TB) as defined by resistance at least to both isoniazid and rifampicin was present in 1.96% (95%CI: 1.41%-2.71%) of new cases, but among the previously treated cases, this prevalence was more than 10 times higher (21.40%, 95%CI: 15.59%-28.66%). MDR-TB without additional resistance to either ethambutol or streptomycin (8.35% in previously treated and 0.86% in new cases) was slightly more common than having additional resistance with ethambutol (4.14% and 0.51%) or streptomycin (2.58% and 0.20%) or both (6.34% and 0.39%), respectively, for previously treated and new cases of TB.

Polyresistance prevalence was quite low among the previously treated cases (3.32%, 95%CI: 1.34%-8.00%) but relatively higher among the new cases (2.25%, 95%CI: 1.75%-2.88%) as compared to multidrug resistance prevalence.

No extensively drug resistant cases were detected. Also, no fluoroquinolone resistant cases were seen, while only 6 cases with resistance to second line injectable anti-TB drugs were detected.

Table 2. Prevalence of resistance to first-line and second-line anti-TB drugs among TB patients, National Drug Resistance Survey, Philippines, 2012

Drug Resistance	New Patients n = 2468			Previously Treated Patients n = 194			Combined n = 2662		
	N	%	95% CI	n	%	95% CI	n	%	95% CI
Susceptible	2034	82.53	80.79 - 84.15	108	56.39	48.83 - 63.65	2142	80.67	78.78 - 82.42
Any resistance to:									
Isoniazid (H)	350	14.06	12.60 - 15.65	72	36.56	29.38 - 44.39	422	15.66	14.04 - 17.44
Rifampicin (R)	61	2.43	1.75 - 3.37	52	26.45	20.35 - 33.60	113	4.15	3.20 - 5.35
Ethambutol (E)	38	1.57	1.11 - 2.20	25	12.76	8.25 - 19.21	63	2.36	1.77 - 3.16
Streptomycin (S)	130	5.22	4.20 - 6.46	25	12.44	8.06 - 18.73	155	5.73	4.71 - 6.96
Total any resistance	434	17.47	15.85 - 19.21	86	43.61	36.35 - 51.17	520	19.33	17.58 - 21.22
Monoresistance									
Isoniazid only	250	10.04	8.84 - 11.39	26	13.08	8.67 - 19.26	276	10.26	9.02 - 11.65
Rifampicin only	9	0.36	0.18 - 0.75	8	3.8	1.70 - 8.27	17	0.61	0.34 - 1.09
Ethambutol only	3	0.14	0.04 - 0.45	0	0		3	0.13	0.00 - 0.42
Streptomycin only	69	2.79	2.18 - 3.56	4	2.01	0.75 - 5.29	73	2.74	2.17 - 3.44
Total Monoresistance	331	13.34	12.09 - 14.70	38	18.89	13.75 - 25.39	369	13.74	12.44 - 15.15
Multi-drug Resistance									
H + R	22	0.86	0.53 - 1.39	16	8.35	4.67 - 14.50	38	1.39	0.89 - 2.18
H + R + E	12	0.51	0.26 - 0.98	8	4.14	2.10 - 7.97	20	0.76	0.47 - 1.24
H + R + S	5	0.2	0.09 - 0.48	5	2.58	0.97 - 6.67	10	0.37	0.19 - 0.75
H + R + E + S	10	0.39	0.19 - 0.78	13	6.34	2.88 - 13.39	23	0.81	0.42 - 1.56
Total MDR	49	1.96	1.41 - 2.71	42	21.4	15.59 - 28.66	91	3.35	2.53 - 4.41
Polyresistance (other than MDR)									
H + E	8	0.33	0.17 - 0.65	1	0.56	0.08 - 4.03	9	0.35	0.19 - 0.65
H + S	40	1.6	1.15 - 2.22	2	1.04	0.26 - 4.05	42	1.56	1.14 - 2.14
H + E + S	3	0.12	0.04 - 0.37	1	0.48	0.07 - 3.36	4	0.14	0.00 - 0.38
R + E	0	0		2	1.04	0.26 - 4.05	2	0.09	0.02 - 0.37
R + S	1	0.04	0.00 - 0.27	0	0		1	0.03	0.00 - 0.25
R + E + S	2	0.07	0.02 - 0.30	0	0		2	0.07	0.02 - 0.28
E + S	0	0		0	0		0	0	
Total Polyresistance (other than MDR)	54	2.17	1.66 - 2.83	6	3.32	1.34 - 8.00	60	2.25	1.75 - 2.88
Extensively Drug Resistant TB (XDR-TB)									
SLD (Injectables)	4	8.16	2.29-19.60	2	4.76	0.58-16.16	6	6.89	2.46-13.80
Fluoroquinolone	0	0		0	0		0	0	

The prevalences of any resistance to anti-TB drugs and MDR-TB according to sex, age and urban-rural classification of residence of patients are shown in Table 3.

There were only small differences in the prevalence of any resistance between male and female patients and between urban and rural patients for both new and previously treated cases. Across age groups, no trend in prevalences of any resistance was seen for both types of patients.

Table 3. Prevalence of any and multi-drug resistance among TB patients, National Drug Resistance Survey, Philippines, 2012

	New Patients			Previously Treated Patients			Combined		
	n	%	95% CI	n	%	95% CI	n	%	95% CI
ANY RESISTANCE	**434**			**86**			**520**		
Sex									
Female	115	17.69	14.66 - 21.18	20	43.4	28.39 - 59.72	135	19.36	16.08 - 23.11
Male	319	17.37	15.40 - 19.53	66	43.69	34.41 - 53.43	385	19.31	17.24 - 21.56
		$x^2_{df=1}$=0.04, p=0.833			$x^2_{df=1}$=0.02, p=0.894				
Age									
≤ 19	31	17.96	12.51 – 25.09	4	100		35	19.7	13.97 – 27.05
20 – 29	100	19.67	16.55 – 23.22	16	50.11	32.39 – 67.80	116	21.42	18.49 – 24.66
30 – 39	77	15.11	12.31 – 18.42	15	35.43	20.52 – 53.83	92	16.58	13.69 – 19.94
40 – 49	103	18.11	14.76 – 22.02	32	53.3	38.56 – 67.49	135	21.43	17.90 – 25.44
50 – 59	81	18.1	14.37 – 22.53	10	25.52	14.11 – 41.69	91	18.7	15.25 – 22.72
≥ 60	42	15.06	11.60 – 19.33	9	46.86	26.43 – 68.39	51	16.99	13.72 – 20.85
		$x^2_{df=5}$=5.38, p=0.372			$x^2_{df=4}$=15.16, p=0.010				
Setting									
Rural	296	17.27	14.43 - 20.54	54	43.27	30.70 - 56.76	350	19.42	16.47 - 22.75
Urban	138	17.54	15.57 - 19.71	32	43.84	34.23 - 53.94	170	19.27	17.14 - 21.60
		$x^2_{df=1}$=0.01, p=0.917			$x^2_{df=1}$=0.06, p=0.811				
MDR	**49**			**42**			**91**		
Sex									
Female	11	1.73	0.91 - 3.28	13	28.95	17.34 - 44.18	24	3.5	2.21 - 5.51
Male	38	2.04	1.48 - 2.80	29	18.97	12.28 - 28.14	67	3.28	2.40 - 4.47
		$x^2_{df=1}$=0.34, p=0.557			$x^2_{df=1}$=1.55, p=0.213				
Age									
≤ 19	5	2.91	1.26 – 6.57	2	48.06	2.29 – 97.34	7	3.87	1.97 – 7.48
20 – 29	11	2.26	1.30 – 3.90	9	29.17	16.53 – 46.15	20	3.8	2.48 – 5.80
30 – 39	12	2.32	1.28 – 4.16	8	18.85	9.99 – 32.71	20	3.51	2.25 – 5.45
40 – 49	12	2.05	1.10 – 3.81	16	26.39	15.78 – 40.69	28	4.35	2.80 – 6.70
50 – 59	6	1.32	0.61 – 2.82	3	7.66	2.38 – 22.00	9	1.83	0.86 – 3.84
≥ 60	3	1	0.32 – 3.04	4	20.75	7.15 – 47.09	7	2.2	1.07 – 4.45
		$x^2_{df=5}$=3.50, p=0.623			$x^2_{df=4}$=8.77, p=0.119				
Setting									
Rural	29	2.47	1.54 - 3.95	26	21.1	12.49 - 33.39	55	4.01	2.66 - 6.01
Urban	20	1.7	1.09 - 2.65	16	21.44	13.91 - 21.56	36	3	2.04 - 4.40
		$x^2_{df=1}$=1.78, p=0.182			$x^2_{df=1}$=0.00, p=0.994				

For MDR, there appeared a slightly higher prevalence of MDR among the male new cases (2.04/1,000) compared to the female new cases (1.73/1,000). The reverse is seen among the previously treated cases where female patients (28.95/1,000) had higher prevalence than male patients (18.97/1,000). The prevalence of MDR-TB appeared to decrease at the higher age groups in both patients. However, these trends were not

found to be statistically significant (=6.71, p=0.243 for new cases, =4.52, p=0.341 for previously treated cases, using chi-square test for trends which is not the same as the chi-square test of homogeneity in Table 3). Prevalence of MDR-TB among rural patients seemed higher at 2.47/1000 compared to 1.70/1000 among urban patients. However, again this was not statistically significant (=1.78, p=0.182). No difference was found in the prevalence of urban and rural patients among those with previous treatment of TB (=0.00, p=0.994).

RISK FACTORS FOR ANY RESISTANCE AND MULTIDRUG RESISTANCE

The association of any drug and multidrug resistance of patients with sex, age, weight, hemoptysis, smear result, alcohol use, smoking, diabetes and presence of another TB patient in the household were examined using logistic regression analysis. This was done separately for new TB cases and previously treated TB patients.

No significant association was found between any resistance to anti-TB drugs and the above variables for new cases and previously treated patients (Tables 4 and 5). All odds ratios had ranged between 0.50 to 2.00, and their confidence intervals included the null value of 1.00.

For MDR-TB, only one variable, having/not having diabetes mellitus was significantly associated among new cases (Table 6). These patients with diabetes mellitus were twice more likely (OR=2.20, 95%CI: 1.03-4.67, p=0.041) to be multidrug resistant than patients without diabetes. Similarly, only diabetes mellitus was signficantly associated with MDR status among patients with previous TB treatment (Table 7). The odds of being MDR among previously treated patients with diabetes mellitus were 2.6 times (95%CI: 1.26-5.53, p=0.011) as that among the same type of patients without diabetes mellitus.

Table 4. Univariate analysis of association of factors to any drug resistance among new TB patients, National Drug Resistance Survey, Philippines, 2012

Factors		Any Resistance				
	n*	n	%	OR	95%CI	p-value
Sex						
Female	644	115	17.9			
Male	1824	319	17.5	0.98	0.74 – 1.29	0.874
Missing Values	0					
Age						
≤ 19	136	31	17.96			
20 – 29	408	100	19.67	1.12	0.71 – 1.77	0.627
30 – 39	431	77	15.11	0.81	0.49 – 1.36	0.424
40 – 49	459	103	18.11	1.01	0.60 – 1.69	0.969
50 – 59	362	81	18.1	1.01	0.60 – 1.71	0.972
≥ 60	238	42	15.06	0.81	0.47 – 1.39	0.439
Missing Values	434					
Setting						
Urban	790	138	17.5			
Rural	1,678	296	17.6	1.02	0.79 - 1.32	0.881
Missing Values	0					
Weight at presentation						
>50 kg	834	130	15.6			
<51kg	1,621	299	18.5	1.2	0.96 - 1.51	0.808
Missing Values	13					
Haemoptysis						
No	1,544	269	17.4			
Yes	920	164	17.8	1.04	0.82 - 1.30	0.756
Missing Values	4					
Smear 2+ or more						
No	1,299	232	17.9			
Yes	869	150	17.3	0.96	0.73 - 1.27	0.778
Missing Values	300					
Alcohol use						
Less than daily	2,025	362	17.9			
Daily	434	71	16.4	0.9	0.66 – 1.22	0.486
Missing Values	9					
Ever smoked						
No	912	169	18.5			
Yes	1,550	264	17	0.91	0.73 - 1.14	0.402
Missing Values	6					
Diabetes mellitus						
No	1,917	343	17.9			
Yes	200	43	21.5	1.22	0.84 – 1.79	0.29
Missing Values	351					
TB among HH members						
No	1,735	311	17.9			
Yes	728	123	16.9	0.94	0.72 - 1.23	0.644
Missing Values	5					

*due to missing values, the total number for analysis of each variables differs

Table 5. Univariate analysis of association of factors to any drug resistance among previously treated TB patients, National Drug Resistance Survey, Philippines, 2012

Factors		Any Resistance				
	N	N	%	OR	95%CI	p-value
Sex						
Female	46	20	43.5			
Male	148	66	44.6	1.01	0.45 – 2.28	0.977
Age						
≤ 29	35	20	55.26			
30 – 39	41	15	35.43	0.44	0.15 – 1.28	0.13
40 – 49	59	32	53.3	0.72	0.46 - 1.87	0.823
50 – 59	40	10	25.52	0.28	0.10 – 0.79	0.017
≥ 60	19	9	46.86	0.71	0.25 – 2.04	0.522
Setting						
Urban	74	32	43.2			
Rural	120	54	45	1.02	0.52 – 2.00	0.944
Weight at presentation						
>50 kg	66	33	50			
<51kg	127	53	41.7	0.75	0.40 - 1.42	0.376
Haemoptysis						
No	123	58	47.2			
Yes	71	28	39.4	0.75	0.44 - 1.26	0.27
Smear 2+ or more						
No	105	46	43.8			
Yes	80	37	46.3	1.11	0.54 – 2.26	0.771
Alcohol use						
Less than daily	165	70	42.4			
Daily	29	16	55.2	1.6	0.81 – 3.16	0.173
Ever smoked						
No	69	35	50.7			
Yes	125	51	40.8	0.68	0.36 - 1.28	0.225
Diabetes mellitus						
No	152	69	45.4			
Yes	25	12	48	1.07	0.49 – 2.34	0.855
TB among HH members						
No	120	50	41.7			
Yes	74	36	48.7	1.36	0.78 - 2.36	0.276

Table 6. Univariate analysis of association of factors to MDR-TB among new TB patients, National Drug Resistance Survey, Philippines, 2012

Factors		MDR				
	N	N	%	OR	95%CI	p-value
Sex						
Female	644	11	1.71			
Male	1824	38	2.08	1.18	0.63 – 2.19	0.602
Age						
≤ 19	167	5	2.91			
20 – 29	508	11	2.26	0.77	0.29 – 2.04	0.595
30 – 39	508	12	2.32	0.79	0.28 – 2.23	0.653
40 – 49	562	12	2.05	0.7	0.24 – 2.01	0.5
50 – 59	443	6	1.32	0.44	0.13 – 1.50	0.187
≥ 60	280	3	1	0.34	0.08 – 1.41	0.133
Setting						
Urban	790	20	2.53			
Rural	1,678	29	1.73	0.68	0.35 - 1.32	0.251
Weight at presentation						
>50 kg	834	17	2.04			
<51kg	1,621	32	1.97	0.94	0.57 - 1.54	0.808
Haemoptysis						
No	1,544	31	2.01			
Yes	920	17	1.85	0.94	0.51 - 1.71	0.825
Smear 2+ or more						
No	1,299	28	2.16			
Yes	869	16	1.84	0.89	0.44 - 1.78	0.733
Alcohol use						
Less than daily	2,025	39	1.93			
Daily	434	10	2.3	1.21	0.63 - 2.30	0.562
Ever smoked						
No	912	21	2.3			
Yes	1,550	28	1.81	0.77	0.43 - 1.37	0.36
Diabetes						
No	1,917	35	1.83			
Yes	200	8	4	2.2	1.03 - 4.67	0.041
TB among HH members						
No	1,735	36	2.07			
Yes	728	13	1.79	0.83	0.41 - 1.66	0.588

Table 7. Univariate analysis of association of factors to MDR-TB among previously treated TB patients, National Drug Resistance Survey, Philippines, 2012

Factors	MDR					
	N	N	%	OR	95%CI	p-value
Sex						
Female	46	13	28.3			
Male	148	29	19.6	0.57	0.24 – 1.39	0.213
Age						
≤ 29	35	11	31.13			
30 – 39	41	8	18.85	0.51	0.19 – 1.36	0.175
40 – 49	59	16	26.39	0.79	0.35 – 1.80	0.574
50 – 59	40	3	7.66	0.18	0.05 – 0.64	0.009
≥ 60	19	4	20.75	0.58	0.15 – 2.20	0.415
Setting						
Urban	74	16	21.6			
Rural	120	26	21.7	0.4	0.46 – 2.25	0.959
Weight at presentation						
>50 kg	66	16	24.2			
<51kg	127	26	20.5	0.85	0.43 - 1.67	0.63
Haemoptysis						
No	123	30	24.4			
Yes	71	12	16.9	0.66	0.32 - 1.33	0.234
Smear 2+ or more						
No	105	20	19.1			
Yes	80	20	25	1.43	0.66 – 3.10	0.354
Alcohol use						
Less than daily	165	34	20.6			
Daily	29	8	27.6	1.42	0.60 – 3.33	0.419
Ever smoked						
No	69	16	23.2			
Yes	125	26	20.8	0.85	0.44 - 1.67	0.64
Diabetes mellitus						
No	152	29	19.1			
Yes	25	10	40	2.64	1.26 – 5.53	0.011
TB among HH members						
No	120	25	20.8			
Yes	74	17	23	1.18	0.52 - 2.66	0.683

MISSING DATA

As described earlier, several patients who were eligible were excluded in the analysis due to missing information on DST. Two hundred twenty (220) had no information on DST which were imputed using multiple imputation by chained equation (MIC). The percentage with missing DST was determined for each category of sex, age group, urban-rural classification, weight, presence/absence of haemoptysis, AFB smear result, alcohol use, smoking, presence/absence of diabetes mellitus, having another TB patient in the household and previous TB treatment. Table 8 shows the proportion of missing DST data seemed to increase slightly as patient get older (=13.41, p=0.020). There were 11% missing DST for the oldest group of patients, twice more than the 5% missing in the youngest age group. In between, the missing percentages were in graduated levels as the age group went higher except for the 30-39 age group. Those who had previous treatment were more likely to have missing DST (11.40%) than new patients (7.3%) (=4.81, p=0.028). The percentage with missing DST results did not significantly differ across categories of the other variables (p>0.05).

Multiple imputation was done to the missing data using the ICE program in STATA (Royston 2005). The listed risk factors in Table 5 namely sex, age, weight, hemoptysis, smear result, alcohol use, smoking, diabetes and presence of another TB patient in the household variables were included in the model for imputation even if these were not all correlated to MDR-TB and with missingness of information. The prevalences of resistance to specific drugs, any resistance and MDR TB were re-estimated with the imputed data. The results are shown in Tables 9 and 10. There was slight adjustment upwards in several estimated prevalences of resistance with the imputed data. For instance, prevalence of any resistance and MDR TB among new cases shifted to 2.02/1,000 from 1.96/1,000 patients and to 18.85/1,000 from 14.47/1,000 patients, respectively. Among previously treated patients, the prevalence of any resistance increased to 45.42/1,000 from 43.46/1,000 patients after data imputation. However, not all prevalences increased after imputation. The prevalence of MDR-TB among previously treated patients decreased to 20.35/1,000 from 21.40/1,000 patients. In all these results, the adjustments in estimates after multiple imputation was integrated were not that substantial.

Table 8. Assessment of the completeness of data on DST results for Isoniazid and Rifampicin, National Drug Resistance Survey, Philippines, 2012

Factors	Missing Data for DST on Isoniazid and Rifampicin		Complete Data for DST on Isoniazid and Rifampicin		p-value
	No.	%	No.	%	
Sex					
Female	62	8.23	691	91.77	0.459
Male	158	7.4	1977	92.6	
Age					
≤ 19	9	5	171	95	0.02
20 – 29	31	5.42	541	94.58	
30 – 39	49	8.18	550	91.82	
40 – 49	46	6.88	623	93.12	
50 – 59	48	9.04	483	90.96	
≥ 60	37	10.98	300	89.02	
Setting					
Rural	157	8.02	1801	91.98	0.239
Urban	63	6.77	867	93.23	
Weight at presentation					
>50 kg	278	23.54	903	76.46	0.692
<51kg	557	24.14	1750	75.86	
Unknown	5	25	15	75	
Haemoptysis					
No	127	7.06	1671	92.94	0.273
Yes	93	8.57	992	91.43	
Unknown	0	0	5	100	
Smear 2+ or more					
No	114	7.5	1406	92.5	0.969
Yes	80	7.74	953	92.26	
Unknown	26	7.76	309	92.24	
Alcohol use					
Less than daily	174	7.35	2194	92.65	0.297
Daily	44	8.66	464	91.34	
Unknown	2	16.67	10	83.33	
Ever smoked					
No	86	8.05	982	91.95	0.685
Yes	133	7.34	1679	92.66	
Unknown	1	12.5	7	87.5	
Diabetes mellitus					
No	161	7.21	2072	92.79	0.202
Yes	19	7.76	226	92.24	
Unknown	40	9.76	370	90.24	
TB among HH members					
No	160	7.93	1858	92.07	0.48
Yes	59	6.84	804	93.16	
Unknown	1	14.29	6	85.71	
Previous anti-TB treatment					
No	195	7.32	2468	92.68	0.07
Yes	25	11.42	194	88.58	
Unknown	0	0	6	100	

Table 9. Prevalence of resistance to first-line anti-TB drugs among TB patients with imputed values, National Drug Resistance Survey, Philippines, 2012

Drug Resistance	New n = 3226			Retreatment n = 282			Total n = 3508		
	No.	%	95% CI	No.	%	95% CI	No.	%	95% CI
Susceptible	2583	80.15	78.32 - 81.85	152	54.58	48.15 - 60.86	2735	78.15	76.17 - 80.01
Any resistance to:									
Isoniazid (I)	469	14.41	12.87 - 16.10	101	35.26	28.92 - 42.17	570	16.04	14.33 - 17.91
Rifampicin (R)	95	2.96	2.19 - 3.97	70	24.48	19.07 - 30.83	165	4.64	3.62 - 5.92
Ethambutol (E)	84	2.68	1.95 - 3.68	38	13.37	9.46 - 18.58	122	3.52	2.68 - 4.61
Streptomycin (S)	206	6.43	5.22 - 7.88	37	12.98	9.22 - 17.99	243	6.94	5.73 - 8.37
Total any resistance	643	19.85	18.15 - 21.68	130	45.42	39.14 - 51.85	773	21.85	19.99 - 23.83
Monoresistance									
Isoniazid only	332	10.15	8.92 - 11.52	37	12.69	9.05 - 17.50	369	10.34	9.08 - 11.76
Rifampicin only	25	0.78	0.47 - 1.31	10	3.34	1.63 - 6.74	35	0.98	0.63 - 1.54
Ethambutol only	21	0.64	0.39 - 1.07	6	2.13	0.95 - 4.68	27	0.76	0.49 - 1.18
Streptomycin only	109	3.39	2.65 - 4.33	8	2.88	1.48 - 5.52	117	3.35	2.65 - 4.22
Total Monoresistance	487	14.96	13.66 - 16.37	61	21.03	16.58 - 26.30	548	15.44	1.41 - 16.88
Multi-drug Resistance									
H + R	33	1.01	0.66 - 1.53	29	10.24	6.79 - 15.15	62	1.73	1.21 - 2.47
H + R + E	13	0.42	0.23 - 0.80	8	2.88	1.46 - 5.59	21	0.62	0.38 - 0.99
H + R + S	7	0.22	0.11 - 0.46	5	1.82	0.68 - 4.80	12	0.35	0.19 - 0.64
H + R + E + S	12	0.37	0.20 - 0.68	16	5.42	2.50 - 11.36	28	0.76	0.42 - 1.40
Total MDR	65	2.02	1.46 - 2.80	58	20.35	15.35 - 26.48	123	3.46	2.65 - 4.50
Polyresistance (other than MDR)									
H + E	13	0.42	0.23 - 0.75	1	0.39	0.05 - 2.84	14	0.42	0.24 - 0.72
H + S	50	1.53	1.16 - 2.01	3	1.09	0.36 - 3.31	53	1.5	1.13 - 1.98
H + E + S	9	0.3	0.12 - 0.71	2	0.74	0.18 - 2.99	11	0.33	0.16 - 0.70
R + E	0	0		2	0.79	0.19 - 3.26	2	0.06	0.02 - 0.25
R + S	3	0.09	0.03 - 0.28	0			3	0.08	0.03 - 0.26
R + E + S	2	0.06	0.01 - 0.24	0			2	0.05	0.01 - 0.22
E + S	14	0.47	0.20 - 1.08	3	1.03	0.33 - 3.20	17	0.52	0.25 - 1.05
Total Polyresistance (other than MDR)	91	2.86	2.21 - 3.71	11	4.04	2.20 - 7.30	102	2.96	2.27 - 3.85

Table 10. Prevalence of any and multi-drug resistance among TB patients with imputed values, National Drug Resistance Survey, Philippines, 2012

	New Patients			Previously Treated Patients			Combined		
	n	%	95% CI	n	%	95% CI	n	%	95% CI
ANY RESISTANCE	**643**			**130**			**773**		
Sex									
Female	177	19.81	16.91 - 23.06	27	41.04	27.61 - 55.95	204	21.25	18.12 - 24.75
Male	466	19.87	17.92 - 21.97	103	46.76	39.45 - 54.22	569	22.07	20.00 - 24.29
Age									
≤ 19	50	23.39	17.11 – 31.11	5	100		55	25.09	18.79 – 36.25
20 – 29	146	22.14	18.76 – 25.92	21	51.87	37.98 – 65.49	167	23.81	20.62 – 27.32
30 – 39	115	17.48	14.78 – 20.57	22	39.02	24.70 – 55.52	137	19.06	16.28 – 22.18
40 – 49	145	19.74	16.94 – 22.87	41	48.85	37.53 – 60.28	186	22.64	19.53 – 26.08
50 – 59	117	20.21	16.66 – 24.30	24	36.99	26.08 – 49.42	141	21.84	18.22 – 25.96
≥ 60	70	17.76	14.27 – 21.89	17	47.06	31.38 – 63.33	87	20.13	16.61 – 24.19
Setting									
Urban	204	20.33	17.33 - 23.70	38	40.3	30.75 - 50.65	242	21.98	18.99 - 25.30
Rural	439	19.62	17.62 - 21.80	92	48.11	39.64 - 56.70	531	21.78	19.51 - 24.24
MDR	**65**			**58**			**123**		
Sex									
Female	15	1.73	1.00 - 2.97	16	24.86	14.68 - 38.89	31	3.3	2.18 - 4.96
Male	50	2.13	1.55 - 2.92	42	18.97	13.17 - 26.56	92	3.51	2.64 - 4.66
Age									
≤ 19	5	2.29	0.99 – 5.23	2	37.08	3.33 – 90.98	7	3.06	1.55 – 5.99
20 – 29	16	2.56	1.49 – 4.37	11	28.01	16.40 – 43.55	27	4	2.63 – 6.02
30 – 39	15	2.26	1.27 – 3.99	11	19.75	11.04 – 32.80	26	3.54	2.31 – 5.39
40 – 49	14	1.88	1.07 – 3.29	18	21.66	13.40 – 33.08	32	3.85	2.55 – 5.77
50 – 59	10	1.73	0.87 – 3.41	10	15.35	8.34 – 26.55	20	3.05	1.83 – 5.05
≥ 60	5	1.27	0.54 – 2.99	6	16.04	6.86 – 33.14	11	2.47	1.43 – 4.24
Setting									
Urban	28	2.77	1.70 - 4.51	17	17.66	10.28 - 28.66	45	4.01	2.65 - 6.01
Rural	37	1.66	1.08 - 2.55	41	21.77	15.27 - 30.05	78	3.19	2.24 - 4.53

Table 11. Comparison of the prevalence of drug resistance between 2004 and 2012 surveys

	New Patients		Previously Treated Patients		Combined	
	%	95% CI	%	95% CI	%	95% CI
Any resistance						
2012 survey	17.47	15.85 - 19.21	43.61	36.35 - 51.17	19.33	17.58 - 21.22
2004 survey	20.4	18.10 – 22.90	38.8	27.80 – 51.10	22.2	19.70 – 24.90
MDR						
2012 survey	1.96	1.41 - 2.71	21.4	15.59 - 28.66	3.35	2.53 - 4.41
2004 survey	3.8	2.60 – 5.50	20.9	13.00 – 32.00	5.7	4.30 – 7.50

DISCUSSION

Before discussing the implications of the results of the 2nd National Drug Resistance Survey, we first point out some concerns related to the quality of the data. Firstly, the design of the study called for equal number of patients eligible for testing to be recruited per cluster hoping to achieve equal probabilities of inclusion per patient under the PPS sampling design. This was not followed for those stated reasons as has been provided earlier in the methodology.

The problem of unequal distribution of sample sizes per cluster was further compounded by the occurrence of missing DST results. The resulting wide variation in cluster sample sizes was as low as 24 patients to as high as 56 patients in one cluster (Figure 2). In this study, the potential bias due to this problem was minimized by employing a weighted analysis with missing data imputation using chain equations (Royston 2005). Clusters were weighted equally regardless of the number of patients included in a cluster while missing values were imputed by an iterative process based on known values of the patients' sex, age, weight, hemoptysis, smear result, alcohol use, smoking, diabetes and presence of another TB patient in the household.

After accounting for missing values, there were only very minor changes in the prevalence estimates of MDR-TB. For new cases, the prevalence was 2% (95% CI: 1.40% – 2.70%) with no adjustment for missing values. With adjustment, this became 2% (95% CI: 1.50% – 2.80%). Among the previously treated cases, the estimate changed from 21.40% (95%CI: 15.60%-28.70%) to 21.60% (95%CI: 20.40%-26.50%) after adjustment for missing values. The closeness of the two resulting estimates could be attributed to the following. The equations in the missing data imputation algorithm had used as input variables sex, age, weight, hemoptysis, smear result, alcohol use, smoking, diabetes and presence of another TB patient in the household. Among these, only diabetes was found to be significantly associated with MDR-TB in both new (Table 6) and previously treated cases (Table 7). Furthermore, the percent with missing DST values was found to be uncorrelated with sex, weight, hemoptysis, smear result, alcohol use, smoking, diabetes and presence of another TB patient in the household (Table 8). The association with sex, which the only variable significantly associated, was not strong. The ratio of proportion of missing DST among the extreme age groups was only 2.20 (11% for ≥60 years vs 5% for ≤19 years).

A further examination of the missing data patterns per cluster was done. For each cluster, the recruited sample size, the percent of contamination, no growth, non-availability of DST result and MDR-TB rate were obtained. A simple correlation analysis was done on these variables. The data and results are presented in the Appendix. The results show that the pattern of contamination, no growth, and MDR-TB rates did not correlate with sample size per cluster ($p \geq 0.20$). However, there was marginally

significant correlations of contamination rate and non-growth rate with MDR-TB, r=-0.25, p=0.0534 and r=-0.23, p=0.0820, respectively. This meant that the higher the contamination and non-growth rate, the lower the MDR-TB rate in the cluster. Additionally, contamination rate correlated positively with non-growth rate suggesting that clusters with high contamination tended to have high non-growth rates. Taking these correlations together, this would lead to an underestimation of the over-all MDR-TB rates.

The second survey was conducted using the same sampling design as the first DRS (Philippine Nationwide Tuberculosis Drug Resistance Survey Team [PNTDRST 2009]). This would facilitate the comparison of the results of the two surveys. In the following comparisons, all 2004 values were taken from the PNTDRST 2009 report. The age and sex profiles of the two surveys are very similar. There is a higher proportion of rural TB patients in this survey, 67%, compared to 56% in the previous one. This difference is not problematic since there is no association shown between the prevalence of drug resistance and urban-rural residence among new and previously treated patients in this study (Table 3).

Compared to the 3.80% (95% CI: 2.60%-5.50%) prevalence of MDR-TB among new TB patients in 2004, the rate is lower 1.96% (95% CI: 1.41%-2.71%) in this study. The reduction in the prevalence of MDR-TB seemed to be attributed to the reduction in the prevalence rate for rifampicin resistance from 4.30% in 2004 to 2.40% in 2012. Isoniazid resistance had an insignficant increase from 13.3% to 14% in those years. There is also a consistent decline for streptomycin resistance which went down from 12% to 5.20% and ethambutol from 4.30% to 1.60% in 2004 and 2012, respectively.
The Philippine MDR-TB rate among new TB patients in 2012 compared favorably against global estimates of MDR-TB in 2008, which is at 3.60% (95% CI: 3.00-4.40) (WHO, 2010). This figure was obtained by combining available MDR-TB rates from 114 country reports.

The prevalence among previously treated TB patients show only minimal changes, 21.30% (95% CI: 15.50%-28.70%) in this study compared to 20.90% (95% CI: 13.00% – 32.00%) in 2004. Drug specific changes in resistance were all not significant as indicated by large overlaps in the respective confidence intervals for 2004 and 2012.

As has been discussed earlier, the reduction in the MDR-TB rates for newly diagnosed cases could be partially due to the pattern of missing data in the study. Another reason could be related to the manner the recent survey was conducted. Learning from the lessons gathered from the 2004 survey, problems with quality of the patient data, specifically related to their prior treatment experience, were minimized through intensified emphasis during training in data collection. In the previous study, the problems of misclassification were more likely in the direction of previously treated cases being labled as new cases. If these problems had actually occurred with considerable frequency in the 2004 survey, this would have contributed to higher rates of MDR-TB among the newly diagnosed cases and lower rates in the previously treated cases. Thus, misclassification bias could have possibly contributed to the lowering of the MDR-TB rates among new cases in 2012.
However, the 50% reduction in the MDR-TB rate among incident TB cases could not be entirely attributed to the problem of missing data nor to misclassification bias. There were only weak and marginally significant correlations of the contamination rate and non-growth rate with MDR-TB. Misclassification bias in 2004 was also unlikely to create a big dent in the results since quality procedures and strict review of the data were also observed in 2004 even if an improvement in quality could have actually been achieved in the 2012 survey.

A stronger argument for the reduction of the prevalence of MDR-TB among new cases would be to attribute this to the efforts of the National TB Control Program and other

stakeholders involved in the prevention and control of TB in the Philippines. Since 2004, the Philippines has sustained high rates of case detection from 73% to 75%, cure rates from 80% to 83% and success rates 85% to 89% (Vianzon 2011). High case detection, cure and success rates would not only reduce the pool of TB patients but more so the numbers of defaulters under DOTS treatment. This would lead to less sources of transmission for new cases of MDR-TB in the population. The consistency of the country's high performance in terms of these indicators points to the extensive and effective efforts contributed by the government and its many partners in the private sector as the main forces in the reduction of MDR-TB in the Philippines.

The lowering MDR-TB among new cases could also be attributed to the sustained economic progress that the country has gone through in the past several years. The Philippines gross domestic product (GDP) growth by an average of 5.0% annually from 2004 to 2011 (International Monetary Fund, 2012). This could have lead, not only to improved government health service delivery, but also to the decrease in the public's exposure to other risk factors of TB like poor health education, unhealthy attitudes and practices, over-crowding, unsanitary living environments, low access to health care, poor nutrition, and the like.

The study also looked into the association of possible risk factors such as sex, age, weight, hemoptysis, smear result, alcohol use, smoking, diabetes and presence of another TB patient in the household with MDR-TB. This knowledge could be used to form the bases of better drug-resistance prevention and control programs. It found none except for diabetes and previous TB treatment (Tables 6 and 7). Studies on MDR-TB from other countries have not actually identified any of the risk factors studied as particularly critical inputs to the prevention and control program for MDR-TB in their respective populations (WHO, 2010).

CONCLUSION AND RECOMMENDATIONS

The results show that the rate of MDR-TB among new cases was 1.96% (95% CI: 1.41%-2.71%) and 21.40% (95%CI: 15.59%-28.66%) among previously treated TB patients. There has been a 50% reduction in the MDR-TB rate among new TB cases in 2012 survey compared with that in 2004 and apparently no change in the prevalence of MDR-TB among previously treated cases.

The wide difference in the prevalence of MDR-TB among previously treated and new incident cases of TB patients indicate that prior exposure to TB treatment is clearly the most significant risk factor for drug resistance. The default rate of patients undergoing DOTS treatment should be kept in check, as much as possible reduced to 0 percent if spread of MDR-TB is to be controlled. The consistent high case detection rates of above 70% and cure rates and success rates above 80% experienced by the country under the current NTP is laudable, however, these indicators need to be pushed further upwards.

For the next survey, there should be closer supervision and better coordination in the recruitment of TB patients and processing of forms and sputum specimens between the research staff and the health workers. The improvement of timeliness of submission of forms and deliveries of specimens could be looked into to reduce the occurrence of wide discrepancies in the sample sizes per cluster and of lost or wasted specimens. A thorough review of the experiences from the two previous drug resistance surveys should be done prior to embarking on a new one.

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APPENDIX

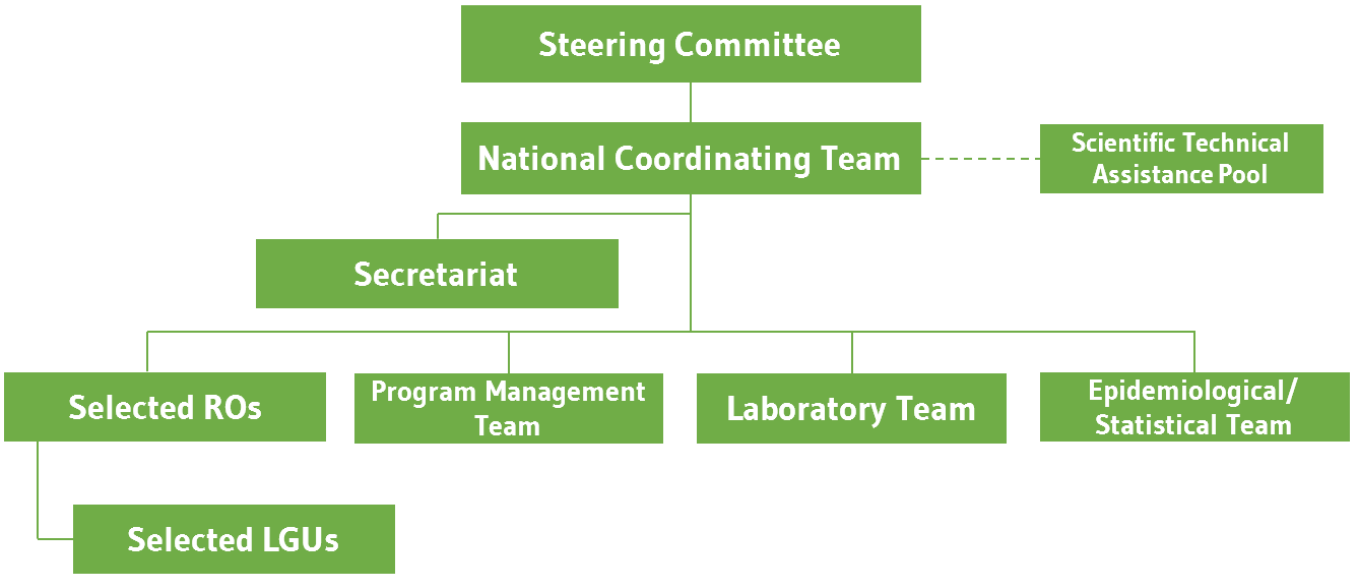
SECOND NATIONAL TB DRUG RESISTANCE SURVEY (DRS) TEAM

The National Coordinating Committee (NCC) was responsible in planning, monitoring, and ensuring the implementation of the approved protocol and workplan of the 2nd DRS project.

The following are the key project staff:

Chairman, Steering Committee (SC)	Dr. Enrique Tayag
Co-Chairman, Steering Committee	Dr. Remigio Olveda Dr. Eduardo Janairo
Chairman, National Coordinating Committee (NCC)	Dr. Noel Macalalad
Lead, Program Management Team	Dr. Rosalind Vianzon
Lead, Laboratory Team	Ms. Cristina Villarico
Lead, Epidemiological/Statistical Team (EST)	Dr. Veronica Tallo
The Scientific Technical Assistance Pool (STAP)	Dr. Jaime Montoya Dr. Jesus Sarol, Jr. Dr. Adelwisa Ortega Dr. Arthur Lagos Dr. Mariquita Mantala Dr. Norio Yamada Dr. Satoshi Mitarai Mr. Eric Camacho
Operations Manager, DRS Secretariat	Dr. Ma. Cecilia G. Ama

Organizational Structure of the 2nd TB Drug Resistance Survey (DRS) Team



The Team is composed of the following:

1. The Steering Committee (SC) provided the oversight and direction to the project implementation according to its approved workplan;

2. The National Coordinating Committee (NCC) planned, monitored, and ensured the implementation of the workplan. The NCC has three component, namely:
    a. Program Management Team planned the DRS project together with other teams, conducted training of doctors and nurses on patient interview, patient registration, infection prevention and control of tuberculosis (IPCT) and counseling, facilitated LGU advocacy and plans and manages the pilot test.
    b. Laboratory Team conducted laboratory training for medical technologists, managed all logistics (laboratory and non-laboratory), conducted monitoring and evaluation of laboratory aspects of the implementation and performs Quality Assurance (local and international by Supranational Reference Laboratories).
    c. Epidemiology/Statistical Team (EST) developed Data Management System Tools, conducted data analysis and performed data quality audit

3. The Scientific Technical Assistance Pool (STAP) provided scientific and technical advice to the NCC;

4. The DRS Secretariat coordinated the day to day implementation of the project to the NCC, facilitated contracting of consultants by PBSP, provided administrative, logistics and technical backstopping to SC, NCC, and DRS Operation Team, managed DRS events, maintained records and documentation, and facilitated communication and coordination among stakeholders;

5. Selected Center for Health Development (CHDs) trained and monitored the activity in coordination with the NCC;

6. Selected Local Government Units implemented the activity at their level.

Correlation of percentage of contamination, no growth, no DST and MDR-TB rate (number below each refers to statistical significance)

	Cluster size	Percent contaminated	Percent no growth	Percent with no DST	MDR-TB rate
Cluster size	1				
Percent contaminated	0.0959	1			
	0.4661				
Percent no growth	-0.0937	0.3038	1		
	0.4764	0.0183			
Percent with no DST	0.1153	0.1827	0.3246	1	
	0.3803	0.1623	0.0114		
MDR-TB rate	0.169	-0.2506	-0.2264	-0.207	1
	0.1967	0.0534	0.082	0.1125	

Comparison of Prevalences Using Different Methods of Estimation

	New Cases		Previously treated cases	
Estimation Procedure	**Point Estimate (%)**	**95% Confidence Interval (%)**	**Point Estimate (%)**	**95% Confidence Interval (%)**
Simple unweighted estimation	2	1.5 – 2.6	21.6	16.1 – 28.1
Fixed-effects model	2.1	1.4 – 2.7	20.7	14.3 – 27.0
Standard logistic regression	2	1.5 – 2.5	19.4	15.0 – 23.7
Robust variance estimation	2	1.4 – 2.7	19.4	14.1 – 24.6
Random effects logistic regression	1.6	1.0 – 2.1	16.4	11.1 – 21.6
Weighted logistic regression model	2	1.4 – 2.7	19.2	14.0 – 24.4
Weighted robust variance logistic regression	2	1.3 – 2.6	19.7	13.7 – 25.8

Missing Value Information per Cluster

Cluster	Number eligible	No not contaminated	No of contaminated	Percent contaminated	No with growth	No of no growth	Percent no growth	Number with MTB	Without DST	With DST	Percent with DST	Negative MDR-TB	Positive MDR-TB	Percent with MDR
1	48	42	6	12.5	39	9	18.75	33	5	28	15.15	27	1	3.57
2	69	68	1	1.45	63	6	8.7	62	2	60	3.23	55	5	8.33
3	64	63	1	1.56	59	5	7.81	58	6	52	10.34	47	5	9.62
4	55	51	4	7.27	45	10	18.18	41	2	39	4.88	38	1	2.56
5	69	67	2	2.9	62	7	10.14	60	3	57	5	56	1	1.75
6	69	66	3	4.35	62	7	10.14	59	2	57	3.39	50	7	12.28
7	58	55	3	5.17	55	3	5.17	52	4	48	7.69	45	3	6.25
8	53	50	3	5.66	47	6	11.32	44	1	43	2.27	39	4	9.3
9	48	42	6	12.5	39	9	18.75	33	4	29	12.12	29	0	0
10	57	55	2	3.51	53	4	7.02	51	7	44	13.73	41	3	6.82
11	59	58	1	1.69	54	5	8.47	53	4	49	7.55	43	6	12.24
12	43	41	2	4.65	32	11	25.58	30	2	28	6.67	28	0	0
13	62	60	2	3.23	56	6	9.68	54	0	54	0	53	1	1.85
14	55	54	1	1.82	54	1	1.82	53	2	51	3.77	49	2	3.92
15	54	53	1	1.85	53	1	1.85	52	3	49	5.77	47	2	4.08
16	63	63	0	0	58	5	7.94	58	5	53	8.62	48	5	9.43
17	52	52	0	0	46	6	11.54	46	5	41	10.87	40	1	2.44
18	56	55	1	1.79	50	6	10.71	49	1	48	2.04	46	2	4.17
19	52	52	0	0	45	7	13.46	45	1	44	2.22	42	2	4.55
20	59	59	0	0	56	3	5.08	56	1	55	1.79	55	0	0
21	56	56	0	0	53	3	5.36	53	5	48	9.43	47	1	2.08
22	52	51	1	1.92	50	2	3.85	49	3	46	6.12	44	2	4.35
23	56	56	0	0	53	3	5.36	53	1	52	1.89	47	5	9.62
24	55	54	1	1.82	49	6	10.91	48	0	48	0	46	2	4.17
25	41	38	3	7.32	40	1	2.44	37	1	36	2.7	36	0	0
26	62	56	6	9.68	56	6	9.68	50	1	49	2	49	0	0
27	53	48	5	9.43	42	11	20.75	37	0	37	0	35	2	5.41
28	51	49	2	3.92	40	11	21.57	38	1	37	2.63	37	0	0
29	56	51	5	8.93	47	9	16.07	42	3	39	7.14	39	0	0
30	68	60	8	11.76	60	8	11.76	52	3	49	5.77	49	0	0

Missing Value Information per Cluster

Cluster	Number eligible	No not contaminated	No of contaminated	Percent contaminated	No with growth	No of no growth	Percent no growth	Number with MTB	Without DST	With DST	Percent with DST	Negative MDR-TB	Positive MDR-TB	Percent with MDR
31	56	52	4	7.14	40	16	28.57	36	6	30	16.67	30	0	0
32	59	57	2	3.39	51	8	13.56	49	4	45	8.16	44	1	2.22
33	49	48	1	2.04	46	3	6.12	45	1	44	2.22	43	1	2.27
34	56	54	2	3.57	52	4	7.14	50	4	46	8	45	1	2.17
35	49	47	2	4.08	46	3	6.12	44	1	43	2.27	43	0	0
36	50	49	1	2	45	5	10	44	4	40	9.09	40	0	0
37	72	69	3	4.17	63	9	12.5	60	8	52	13.33	52	0	0
38	65	65	0	0	60	5	7.69	60	6	54	10	53	1	1.85
39	62	62	0	0	60	2	3.23	60	6	54	10	54	0	0
40	55	51	4	7.27	54	1	1.82	50	3	47	6	45	2	4.26
41	63	61	2	3.17	56	7	11.11	54	3	51	5.56	46	5	9.8
42	63	61	2	3.17	58	5	7.94	56	3	53	5.36	51	2	3.77
43	71	66	5	7.04	70	1	1.41	65	8	57	12.31	56	1	1.75
44	68	53	15	22.06	57	11	16.18	42	10	32	23.81	34	0	0
45	53	52	1	1.89	44	9	16.98	43	8	35	18.6	35	1	2.78
46	50	49	1	2	50	0	0	49	6	43	12.24	42	1	2.33
47	49	46	3	6.12	43	6	12.24	40	1	39	2.5	39	0	0
48	58	56	2	3.45	50	8	13.79	48	4	44	8.33	42	2	4.55
49	52	52	0	0	40	12	23.08	40	7	33	17.5	32	1	3.03
50	53	52	1	1.89	52	1	1.89	51	5	46	9.8	41	5	10.87
51	62	59	3	4.84	57	5	8.06	54	4	50	7.41	50	0	0
52	52	52	0	0	47	5	9.62	47	6	41	12.77	41	0	0
53	55	52	3	5.45	51	4	7.27	48	3	45	6.25	45	0	0
54	49	49	0	0	40	9	18.37	40	4	36	10	35	1	2.78
55	51	49	2	3.92	45	6	11.76	43	3	40	6.98	40	0	0
56	67	63	4	5.97	52	15	22.39	48	6	42	12.5	42	0	0
57	55	55	0	0	46	9	16.36	46	9	37	19.57	37	0	0
58	59	53	6	10.17	52	7	11.86	46	4	42	8.7	43	0	0
59	59	54	5	8.47	37	22	37.29	32	4	28	12.5	27	1	3.57
60	54	49	5	9.26	51	3	5.56	46	1	45	2.17	42	3	6.67