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Possible Risk Factors for Multidrug-Resistant Tuberculosis Infection in the Philippines

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Walden University
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Abstract

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MA Ed., University of the City of Manila, 1995

BS, University of the Philippines, 1987

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

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Public Health

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Abstract

Multidrug-resistant Mycobacterium tuberculosis (MDR-TB) is a leading cause of morbidity and mortality in the Philippines. The purpose of this study was to gain knowledge about the relationship between potential risk factors and MDR-TB. Risk factors (the independent variables) for MDR-TB (the dependent variable) include previous TB treatment, infection with HIV, exposure to patients with drug-susceptible TB/MDR-TB, delays in diagnosis and treatment, employment status, smoking, imprisonment, alcohol abuse, and poor compliance with TB treatment regimens. The study was based on the epidemiological approach to causal inference work. A case-control study design was used wherein a quantitative method was applied in data analysis to assess the strength of the pre-identified possible risk factor(s) association to MDR-TB infection. Data were collected using survey questionnaires that were administered to patients ($N = 172$) from health centers in Leyte, San Mateo Rizal, and San Lazaro. Hypotheses were tested using chi-square analysis, Fisher's exact test, and an odd ratio. Drug-susceptible TB respondents who smoked on a daily basis were 3 times more likely (95% CI 1.021-13.341, OR 3.69) to develop an MDR-TB infection than were other respondents. Respondents who did not comply with the anti-TB treatment regimen were 9 times more likely (95% CI 2.104-43.059, OR 9.519) to develop an MDR-TB infection than other respondents. Health care providers may be able to use study findings to develop programs to help drug-susceptible TB patients stop smoking and better comply with treatment regimens designed to prevent MDR-TB infection, resulting, potentially, in improved public health outcomes for patients.

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Dedication

This study is dedicated to my late father Attorney Molovon A. Azores Sr. whom I promised that I would further my education when I come to America. Equally to is my beloved dearest late mother Lourdes Pasagui Azores a proficient school administrator, for her unwavering love, support, and prayers for her eight children. My dearest sister, Dr. Rowena Azores Mendoza, who is like a mother to her younger siblings, for being a source of inspiration and role model. My beloved sisters, Romelda Azores, Rhodetta Azores Tondo, Atty Rhodora Azores Lina and Dr. Ronahlee Azores Asuncion. My elder brothers Reuel P. Azores and Rhoderick P. Azores for the supports and inspirations. To my ever loving niece Dr. Faith Marie Azores Bolotaolo, the memories we had when you're a baby for we grew up together in my sister's house.

Finally, this work is likewise dedicated to my wife Rowena K. Azores and my beloved twin daughters Rhoslyn K. Azores and Raizel K. Azores for the unwavering support in my pursuit of knowledge; that this humble endeavor may inspire them to pursue higher education as well.

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I am profoundly grateful for the professionalism, dedication, the great wealth of knowledge, support, patience, constructive criticism and advice of Dr. Donald Goodwin Dr.PH., my adviser, and committee chair. The encouragement and suggestions provided by Dr. Michelle Shipp MD, Dr.PH., and Dr. Peter B. Anderson, Ph, D., FSSSS., Vasileios Margaritis, PhD, MSc, DDS.,members of my committee. Dr. Tammy L. Root, Ph.D., Walden University Academic Research Coordinator, School of Health Sciences for helping me constitutes my dissertation committee. Dr. Leilani Endicott, Ph.D., of the Walden University Institutional Review Board Chair and Director, Office of Research Ethics and Compliance for the review of my research proposal and approval granted to conduct the study.

To my sisters including Jane Palacay, Dr Leonita P. Azores, and brother-in-law especially Dr. Eric Mendoza, for the unwavering encouragement and assistance. My wife Rowena Lynn K. Azores and my beloved twin daughters Rhoslyn and Raizel K. Azores for understanding with me especially in times when I cannot have dinner with you or drive to a place that you wanted to visit since I was busy with the course work, and reading journals for my research work.

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Chapter 1: Introduction to the Study

Introduction

Data from the World Health Organization **(**WHO, 2013a) show that, in 2012, 8.6 million people globally were infected with tuberculosis (TB), and 1.3 million died of the disease. Low- and middle-income countries accounted for 95% of TB deaths (WHO, 2013a). More people are dying of the disease with the emergence and proliferation of multidrug resistant–tuberculosis bacteria (MDR-TB; WHO, 2013a).

In 1994, epidemiologists began to monitor drug-resistant TB through WHO's Global Project on Anti-Tuberculosis Drug Resistance Surveillance (Zignol et.al, 2012). The project goal is to assess epidemiological trends of the disease . Data collected and analyzed from 127 countries, representing 66% of WHO's 193 member states, show that 0-28.9% of TB cases in 2007-2010 were multidrug resistant (Zignol et.al, 2012). Enrollment for MDR-TB treatment increased from 2009 to 2012 and is projected to further increase by 2015 (see Figure 1).

In response to the aforementioned findings, public health experts from WHO developed a six-point strategy as part of the Global Plan to Stop TB program (WHO, 2014e). The program's primary goal is to reduce the global burden of the TB disease by 2015 (WHO, 2014e). The continued evolution of the TB causing organism strain to be antibiotic-resistant could potentially hamper the realization of the Global Plan to Stop TB program.

Several factors have been observed towards a successful treatment of MDR-TB infection. Among which are manipulation of the medicine to suit the pediatric patient,

some patients are experiencing adverse effect of the medicine since its more toxic, 2 years or longer treatment period, daily injections for 6 months and much more expensive (TB Alliance, 2013). The longer treatment period can cause side effects which result in poor adherence to the treatment regimen (TB Alliance, 2013). As a consequence, the disease becomes more difficult and costly to treat each time a patient does not complete his or her course of drugs (TB Alliance, 2013).

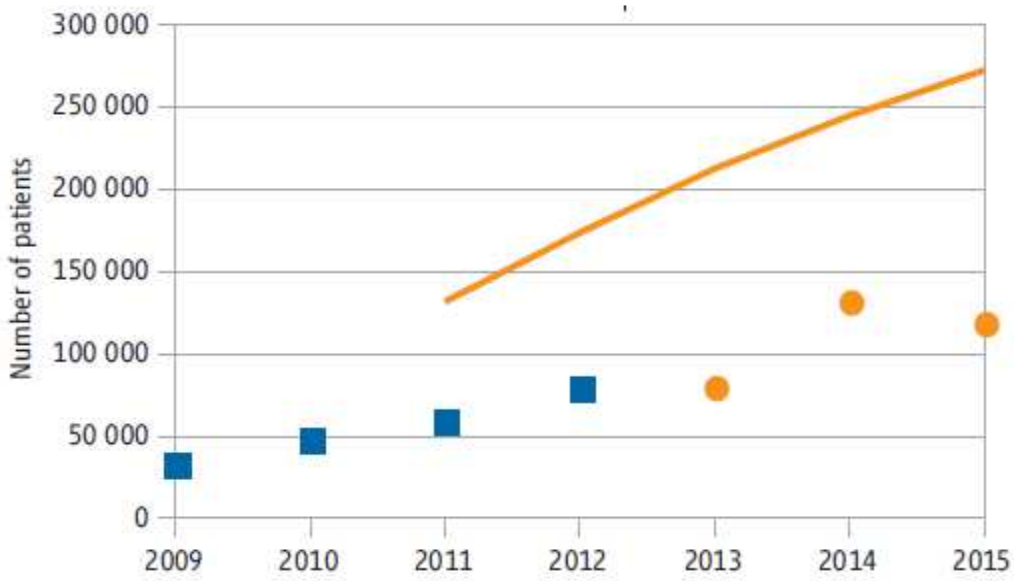


Figure 1. Drug susceptibility testing coverage among new cases and enrollment in MDR-TB treatment compared with the targets in the Global Plan to Stop TB, 2011–2015. Lines indicate the planned targets; blue squares, the situation in 2009–2012, and orange circles, the projected enrollments in 2013–2015. Data on projected enrollments in 2015 were incomplete. Adapted from Global Tuberculosis Report 2013, page 52. Copyright 2013by the World Health Organization.

Epidemiologists are concerned about the rise in MDR-TB cases globally and poor treatment outcomes. The number of cases reported has tripled between 2007-2010 (WHO, 2013a). In the 2010 profile, only 48% or so of MDR-TB patients in the cohort had

successfully completed treatment (WHO, 2013a). Twenty-eight percent of cases were reported as lost to follow-up or had no outcome information (WHO, 2013a; see Figure 2).

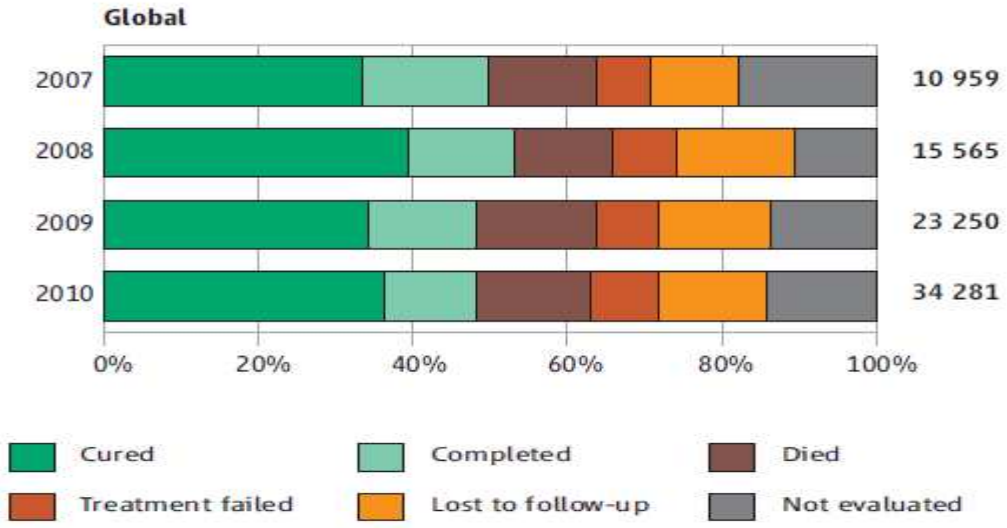


Figure 2. Global treatment outcomes for patients diagnosed with MDR-TB by WHO, 2007–2010 cohorts.The total numbers of cases with outcome data are shown beside each bar. Adapted from Global Tuberculosis Report 2013, page 57. Copyright 2013 by the World Health Organization.

Understanding the risk factors related to the onset of a disease is very critical in epidemic prevention. The information obtained in the primary prevention stage is of greatest value before the biological onset of illness. The persistent increase in the prevalence rate of TB, specifically MDR-TB continues to concern among public health practitioners (WHO, 2013a).

Background

The high global death rate of TB is due to the presence of the pathogenic causative agent *Mycobacterium tuberculosis* (Mtb), according to researchers (National Institute of Allergy and Infectious Diseases [NIAID], 2010). This organism is aerobic and rod-shaped

and is present in people with active TB (NIAID, 2010). It can remain dormant for years without causing any TB disease symptoms (latent TB) but may eventually become active TB (NIAID, 2010).

Mtb is a very resilient phototrophic organism. The bacterium can adapt to changes such as nutrient deprivation, hypoxia, and various exogenous stress conditions throughout the course of infection (Cook et al., 2009). The ability of the organism to adapt to environmental changes is due to the presence of complex regulatory networks and signals that result in temporal gene expression coupled with metabolic and energetic changes (Cook et al., 2009). The front line drugs against Mtb infection are isoniazid and rifampicin. In cases of MDR-TB infection, however, the bacterium is resistant to isoniazid or rifampicin (XDR-TB; WHO, 2014b). When the Mtb bacterium strain is resistant to ofloxacin or moxifloxacin or other second-line drugs, the disease is classified as extensively drug-resistant tuberculosis (XDR-TB; WHO, 2014b).

Historical Perspective of TB

The rich history of tuberculosis dates back to the Stone Age. Around 460 BC, Hippocrates called the disease “phthisis.” In modern times, the disease began to be called TB (Mackenzie, 2012). It reached the Americas well before Columbus (Mackenzie, 2012). After 1600, TB became pandemic and rampaged throughout Europe. TB caused a quarter of all deaths by the 1800s (Mackenzie, 2012). DNA analysis of ancient human remains obtained from southern Germany (1400–1800 AD), Hungary (600–1700 AD), and Egypt (3500–500 BC) revealed high frequencies of TB in all time periods (Zink, 2007).

Observers became optimistic about eradicating TB after Robert Koch discovered and stained the causal organism in 1882 (NIAID, 2010). This was followed 60 years later by the discovery of antibiotics such as streptomycin (1943), isoniazid (1951), pyrazinamide and cycloserine (1952), ethionamide(1956), rifampin (1957), and ethambutol (1962; Keshavjee & Farmer, 2012). The influx of anti-TB drugs in the market has allowed the *Mtb* organism to adapt in the form of a mutation conferring resistance to it (Keshavjee & Farmer, 2012). Thus, epidemiologists monitored anti-TB drug resistance in Britain from 1955-1956 and in the United States from 1965-1968 (Keshavjee & Farmer, 2012). In a 2000-2004 study on *Mtb* isolates, researchers at Supranational Reference Laboratories concluded that the presence of XDR-TB throughout different world regions resulted from improper treatment of MDR-TB infection (Shah et al., 2007). The surge in MDR-TB infection has been attributed to the increasing resistance of the *Mtb* organism to more than one anti-TB drug (NIAID, 2010).

Risk Factors for MDR-TB Infection

Risk factors for the development of MDR-TB infection vary considerably depending on the population studied, the reason for the research investigation, and the methodology that is applied. In a retrospective study conducted in South West Nigeria among pulmonary TB patients with MDR-TB, of the 88 respondents, 55 were resistant to at least one antibiotic against Mtb (Daniela & Osmanb, 2011). Resistance was showed to be associated with previous history of anti-TB treatment (Daniela & Osmanb, 2011). Data revealed that age (OR = 0.86 [95% CI 0.35-2.13]; $p = 0.72$) and gender (OR = 1.24 [95% CI 0.49-3.14]; $p = 0.62$) were not significantly associated with drug resistance (Daniela &

Osmanb, 2011). The authors recommended conducting a national TB drug resistance survey specific to South West, Nigeria. The primary aim of the survey was to determine the actual burden and risk factors associated with drug resistance to TB (Daniela & Osmanb, 2011).

Previous history of anti-TB treatment was identified as a risk factor for MDR-TB infection in a study conducted in the Republic of Georgia. The study was performed from July 2005 to May 2006. Previous TB treatment and female gender were identified as risk factors of MDR-TB (Lomtadze et al., 2009). The identification of the female gender as an MDR-TB risk factor contrasted Daniela and Osmanb's (2011) findings wherein gender was found to be associated to MDR-TB infection.

In Belarus, a nationwide survey to assess the prevalence of MDR-TB and to investigate associated risk factors was conducted from 2010 to 2011. Possible risk factors associated with the development of MDR-TB in the study were age, country of birth, TB treatment history, the level of education, living conditions, household size, employment status, history of imprisonment, alcohol consumption, history of smoking and HIV status (Skrahina et al., 2013). Previous TB treatment was found to be the strongest risk factor followed by HIV infection, age, history of imprisonment, disability sufficient to prevent work, alcohol abuse and smoking (Skrahina et al., 2013).

Residents living in the old urban areas in Vietnam and is infected with the Beijing genotype of Mtb bacteria and is infected with HIV is an associated risk factors for MDR-TB infection in a study performed in Hanoi, Vietnam (Hang et.al. 2013). The researchers recommended that careful monitoring be undertaken in areas with a high proportion of the

Beijing strain of Mtb and HIV infection to avoid transmission of MDR-TB (Hang et.al. 2013). However, no clear association between time and geographic location of MDR-TB and HIV infection was observed in a metaanalysis study performed by Suchindran, Brouwer, and Van Rie (2009). The researchers aimed to determine if HIV infection is a risk factor for the MDR-TB infection (Suchindran, Brouwer, and Van Rie (2009). The researchers were not able to demonstrate an overall association between MDR-TB and HIV or acquired MDR-TB and HIV. These data suggest that HIV infection is associated with primary MDR-TB infection. The researchers recommended that other studies be conducted to better clarify the relationship between MDR-TB and HIV for all regions of the world (Suchindran et. al., 2009).

Ricks et al. (2012) studied the possible risk factors for the development of MDR-TB in Namibia using 117 confirmed cases of MDR-TB. The authors found that risk factors associated with the MDR-TB infection were previous hospitalization (OR 1.9, 95% CI 1.1–3.5) and contact with a household member with MDR-TB (OR 5.1, 95% CI 2.1–12.5). These studies show that there is no clear understanding of the risk factors that can be associated with MDR-TB infection for it may vary with the socio, cultural, demographic and economic conditions prevailing in a country.

Problem Statement

In a study completed as part of the Tuberculosis Profile of the Philippines, 2003–2011, Vianzon, Garfin, Lagos, and Belena (2013) found that 98.9% of the 379,390 diagnosed cases were pulmonary TB. Further, TB was found to be the sixth leading cause of morbidity and mortality in the Philippines. The country has one of the highest numbers

of MDR-TB cases and ranks as ninth among the 22 highest TB-burden countries in the world (Vianzon, Garfin, Lagos, and Belena, 2013). The emergence of MDR-TB poses a serious threat to TB control in developing countries like the Philippines. Besides being difficult and expensive to treat, the disease requires a longer period of treatment. The Tuberculosis financing profile of the Philippines showed that for 2016 the Philippine Department of Health requires $104 million US dollars to operate the TB prevention and control program. However, only 21% of the required program cost will be provided by the government, 41% international grants, while 38% was unfunded (WHO, 2014a). Further, data showed that in the Philippines, 4% of all new TB cases have MDR-TB, and 4.6% of all drug-resistant TB cases have XDR-TB (WHO, 2014a).

I performed a query in the WHO interactive database on the treatment outcomes of MDR-TB cases in the Philippines. Figure 3 shows that only 49% of the reported MDR-TB cases in 2013 were successfully treated. The figure also shows that 12% died, 1% failed treatment, 29% were lost to follow-up, and 8% were not evaluated (WHO, 2014c).

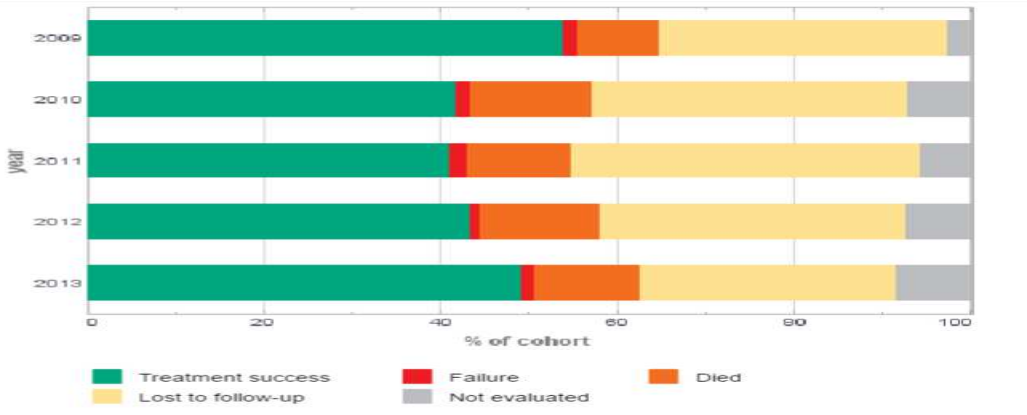


Figure 3. Indicators of diagnosis, notification, and treatment of multidrug-resistant TB, by region or country and year Adapted from Diagnosis, Notification and Treatment of Rifampicin Resistant TB (MDR-RR TB). From Interactive tuberculosis data visualizations World Health Organization.

The Philippines Department of Health Tuberculosis Control program approved the conduct of the study for there is no study at the present that identify national and geographically relevant risk factors for MDR-TB infection in the Philippines. The identification of risk factors is critical for TB disease prevention and control, especially in the Philippines where public health resources are limited. A person who is identified as having an increased risk for diseases can participate in laboratory testing and receive treatment prioritization. Early treatment may minimize the detrimental biological, psychological and social effects TB disease.

Nature of the Study

The study followed the quantitative methodology and used a case-control design. The control subjects were selected among patients with drug-susceptible Tuberculosis, and the cases were patients with clinically confirmed MDR-TB. The study subjects were patients who have been clinically confirmed to be MDR-TB positive. MDR-TB infection is the dependent variable of the study wherein the condition already occurred to patients. The study l used a semi-structured questionnaire to collect relevant information from enrolled participants.

The quantitative analysis aimed to assess if there is a statistically significant relationship between each identified risk factor and the MDR-TB infection. If no statistically significant causal relationship is established, the specific risk factors will not be considered as direct risk factors (Porta, 2014).

Research Questions and Hypotheses

I sought to answer the following research question: Is there an association between MDR-TB infection and the following possible risk factors: previous TB treatment, infection with human immunodeficiency virus, exposure to a drug-susceptible TB/MDR-TB patient, delay in diagnosis and treatment, employment status, smoking, imprisonment, alcohol abuse, and compliance with TB treatment regimen. I tested the following hypotheses:

$H_0$1*:* MDR-TB infection is not associated with any of the following possible risk factors as determined by the standardized questionnaire: (a) previous TB treatment; (b) infection with human immunodeficiency virus; (c) exposure to drug-susceptible TB/MDR-TB; (d) delayed in diagnosis and treatment; (e) employment status; (f) smoking; (g) imprisonment; (h) alcohol abuse and (i) compliance with drug-susceptible TB treatment regimen.

$H_1$1: MDR-TB infection is associated with one or more of the following possible risk factors as determined by the standardized questionnaire: (a) previous TB treatment; (b) infection with Human Immunodeficiency Virus; (c) exposure to drug-susceptible TB/MDR-TB; (d) delayed in diagnosis and treatment; (e) employment status; (f) smoking; (g) imprisonment; (h) alcohol abuse and (i) compliance with drug-susceptible TB treatment regimen.

Purpose of the Study

In this study, I assessed the strength of association between identified risk factors and the development of the MDR-TB infection in the Philippines. Specifically, I examined

whether the following factors are causally associated with MDR-TB infection: (a) previous TB treatment, (b) infection with HIV, (c) exposure to a drug-susceptible TB/MDR-TB patient, (d) delay in diagnosis and treatment, (e) employment status, (f) smoking, (g) imprisonment, (h) alcohol abuse, and (i) compliance with TB treatment regimen. Findings may inform efforts by public health professionals and other stakeholders in the community to develop effective proactive intervention programs to enhance MDR-TB prevention in the Philippines.

Theoretical Foundation

This study is anchored in the epidemiological theory of John Snow. He pioneered the epidemiological approach to causal inference work with an emphasis on the evaluation of preventive, ameliorative, and curative interventions (Fine et al., 2013). The theory provided an understanding of the agent, the environment and host as a framework for the dynamics of disease transmission.

Snow's epidemiological approach started during the outbreak of cholera epidemic in London which occurred in 1831–1832 and in 1848–1849 where he used skilled reasoning, graphs, and maps to demonstrate the impact of presumed *Vibrio cholera* contaminated water coming from the Broad Street pump. The ideas from the epidemiological study of Dr. Snow were published in his book *On the Mode of Communication of Cholera* in 1855 which later was republished as a classic work in epidemiology, resulting in lasting recognition of his work (Frerichs, 2009).

Definitions

I have defined the following terms to clarify the terms and variables I used in my investigation:

Acquired resistance: Patients diagnose with TB and taking the anti-tuberculosis drug and subsequently acquire resistance (WHO, 2009).

Cured: Patients that completed the course of anti-tuberculosis treatment and laboratory analysis from 5 consecutive sputum cultures demonstrated the absence of the *Mtb* (WHO, 2009).

Efflux mechanism: The movement of the antibiotic compound out of the cell (Machado et al., 2012).

Efflux pumps inhibitors: Compounds such as thioridazine, chlorpromazine, and verapamil that prevents the movement of antibiotic out of the cell (Machado et al., 2012).

Failed treatment: Patient demonstrated viable *Mtb* from sputum culture despite the 12-month antituberculosis therapy (WHO, 2009).

Multidrug resistant tuberculosis: a condition wherein the strain of Mycobacterium tuberculosis is resistant to at least isoniazid and rifampicin (Zignol et al., 2012).

New case: Patients who denied during direct questioning having had any prior anti-tuberculosis treatment for up to one month (WHO, 2009).

Recurrence of TB after treatment: Reinfection of antibiotic resistant *Mtb* organism after treatment from MDR-TB.

Possible risk factor(s): Variables in the study such as previous TB treatment, infection with human immunodeficiency virus, exposure to drug susceptible TB/MDR-TB

patient, delay in diagnosis and treatment, demographics (e.g., age and gender), social factors (e.g., smoking, imprisonment, unemployment, and alcohol abuse), and recurrence of TB after treatment.

Preferential social mixing: Individual that chooses to associate with others that have similar HIV-status and lower average CD4 counts among HIV-seropositive individuals (Sergeev, Colijn, Murray, & Cohen, 2012).

Previously treated: Patients upon direct questioning admit having been treated for TB for 1 month or more (WHO, 2009).

Primary resistance: Patients who have been previously treated for TB but with resistance to one or more anti-tuberculosis drug (WHO, 2009).

Treatment regimen: Use of MDR-TB - HRZES (H-Isoniazid 300mg, R-Rifampicin 450mg, Z-Pyrazinamide 1g, E-Ethambutol 800mg, S-Streptpmycin1g) for the first 2 months, then HRZE for the third month during the intensive phase (Department of Health Government of the Philippines, 2003).

Treatment regimen survey: A type of survey that aims to measure first-line and/or second-line drug resistance among a group of selected patients who cannot be considered representative of a patient population (WHO, 2009).

Limitations and Assumptions of the Study

My interactions with study subjects are one of the limitations of the study. In addition due to the archipelagic location of the country, study participants will be limited in number and may potentially affect the generalizability of the study results. Study participants were obtained from the different Department of Health - National

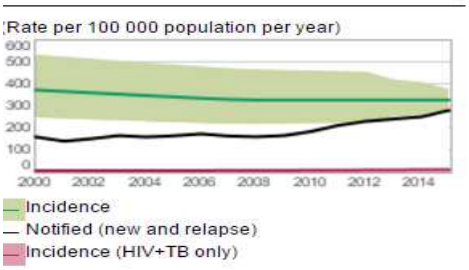
Tuberculosis Control Program treatment centers/hospitals in the country such as San Lazaro Hospital and various town health center in the province of Leyte and Rizal. Specifically in the towns of San Mateo, Burauen, Dagami, Tanauan, Capoocan, Cariga and Barugo. Medical records in the Philippines, especially in some clinics/hospitals located outside the capital city, are paper based. Access and completeness of medical records provided a limitation in the verification of patient data and consequently in the enrollment of cases. Patients from clinics/hospitals where medical record data are not complete were considered for enrollment in the study. This lead to potential selection bias, where more participants from urban areas are enrolled in the study. Another limitation of the study was that since data collection was through the use of the questionnaires with regards to the respondents past events, recall bias was potentially introduced which in most cases items in the questionnaire were left unanswered. The researcher requested respondents to answer unanswered questions during the final review of the questionnaire. However, in most cases, they refuse to provide an answer which was respected by the researcher. The high rate of unanswered questions provided bias to the study test results; thus study conclusion cannot be applied to the general population.

The assumption of the study is that the laboratory-confirmed study respondents with MDR-TB are correct and reliable based on the input from the clinician, including the assumption that the study respondents will provide information to the best of their ability.

Significance of the Study

Identifying country specific relevant risk factors of MDR-TB infection that are reflective of the socio, cultural, economic, and demographic conditions in the area may help prevent the proliferation of the disease. The identification of risk factors can provide guidance to health care professionals in the identification of high-risk patients, thus increasing the effectiveness of MDR-TB prevention program in the Philippines. It is hoped that the results of the study will provide public health officials an additional basis for programmatic priority planning and policy decision making in the practice of public health. Also, the study can perhaps aid public health practitioners to identify the risk differences which can help prioritize resource allocation for the surveillance, control, and prevention of MDR-TB. The data that were generated from this study may have a potential impact on public health educators and help them educate the general public on the modifiable risk factor(s) to prevent if not decrease MDR-TB infection. This study hopes to fill in the gap in the literature for no studies have been done on MDR-TB risk factors in the Philippines.

As shown in the graphs below, the incidence rate of TB in the Philippines continue to decline from the year 2000 to 2014 and with a success treatment rate of 49%. (Figure 4).



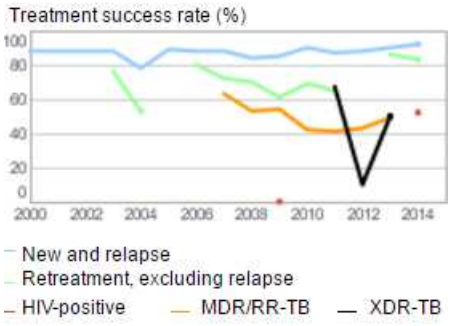


Figure 4. Incidence rate of TB in the Philippines from the year 2000 to 2014 Adopted from: Tuberculosis Country Profiles (WHO, 2014a).

The identification of risk factors for MDR-TB infection will lead into early treatment prioritization and prevent the proliferation of TB disease in the community. In a collaborative study by Bishai, Bishai and Bishai (2010), the researchers concluded that in populations with low prevalence of drug-susceptible TB, a greater proportion of MDR-TB case detection accompanied with compliance with directly observed treatment, short-course (DOTS) is crucial to prevent TB epidemic. The emergence of a new *Mtb* strains and MDR-TB infection development could trigger an increase in TB prevalence rate in a population that lost herd immunity. The study was performed through a computer simulation of MDR-TB epidemics (Bishai et al., 2010). DOTS were developed by WHO, as the most cost-effective strategy to stop the spread of TB. The treatment program is based on five elements such as collaborative sustained effort from the government, case detection, standardized treatment, regular, uninterrupted drug supply and a standardized recording and reporting system for assessment of treatment result (World Health Organization, 2014b).

Importance for Social Change

The result of the study hopes to benefit the members of the community for it can be used by public health practitioners as a basis in educating the population on risk factors associated with the probability of MDR-TB infection that is relevant to the geographic location. Geographically relevant risk factors may be significant for it may allow members of the community to easily recognize and modify the situation so as to lessen the risk of disease infection and ultimately reduce morbidity due to TB and MDR-TB.

The Philippines is considered a developing country where there are limited resources. The reduction in MDR-TB transmission would result in reduced health care costs as a consequence of decreased hospitalization admission of patients with MDR-TB. Those limited resources can then be channeled to augment other needed health care services for the population. Also, a decrease in MDR-TB transmission will lead to a reduction in the bacterial reservoir within the community at large. Because the treatment of the MDR-TB infection is expensive, knowledge of the risk factors associated with the infection may prevent the disease occurrence in a family member and avert the burden of its associated cost.

Health care providers will be able to prioritize diagnosis and treatment based on risk factors knowledge which can save time, financial resources and most importantly prevent further damage to patient's organ due to early detection and most effective treatment. Another social impact of the study will be that it may help bring equity to the underserved group especially that in most cases patients with tuberculosis belongs to economically deprived segments of society.

Summary

The Philippines MDR-TB infection ranks as ninth among the 22 highest TB-burden countries in the world (Vianzon, Garfin, Lagos, and Belena, 2013). With limited resources identifying the probable risk factors associated with MDR-TB infection needed for patient early treatment prioritization and decrease the proliferation of the disease in the community. The purpose of this study is to assessed the strength of association between identified risk factors and the development of the MDR-TB infection in the Philippines. Specifically, I examined whether the following factors are causally associated with MDR-TB infection: (a) previous TB treatment, (b) infection with HIV, (c) exposure to a drug-susceptible TB/MDR-TB patient, (d) delay in diagnosis and treatment, (e) employment status, (f) smoking, (g) imprisonment, (h) alcohol abuse, and (i) compliance with TB treatment regimen. I conducted survey questionaire as primary instrument in obtaining data from the study participants.

Chapter 2 of this research include the literature on TB pathogen MDR-TB, characteristics, modes of transmission, pathogenesis of the bacterium; the organism's evolution from antibiotic susceptible to multidrug resistant, mechanism for drug resistance,morbidity, mortality, and health cost are described in addition to clinical presentation, signs, and symptoms to better understand the health impact of MDR-TB infection. In addition, chapter 2 also provided MDR-TB geographic distribution, manifestation, drug resistance, prevention, and control from published epidemiological studies and the state of TB and MDR-TB epidemiology in the Philippines. Chapter 3 is an

explination of the methods used to gather and interpret the data. Chapter 4 is a report of the data and Chapter 5 is the interpretation of those data.

Chapter 2: Literature Review

Introduction

The Philippines is a developing country and has one of the highest numbers of MDR-TB cases and ranks as ninth among the 22 highest TB-burden countries in the world (Vianzon, Garfin, Lagos, and Belena, 2013). The emergence of MDR-TB infection poses a serious threat to TB control program of the Philippines government. MDR-TB infection requires a longer period of treatment, and a result could consume the resources of the TB control program. The study assessed the strength of association between identified risk factors and the development of the MDR-TB infection in the Philippines. Specifically, I examined whether the following factors are causally associated with MDR-TB infection: (a) previous TB treatment, (b) infection with HIV, (c) exposure to a drug-susceptible TB/MDR-TB patient, (d) delay in diagnosis and treatment, (e) employment status, (f) smoking, (g) imprisonment, (h) alcohol abuse, and (i) compliance with TB treatment regimen.

In this chapter, I provided a brief description and background of the TB pathogen MDR-TB. The discussion includes the characteristics, modes of transmission, and pathogenesis of the bacterium; the organism's evolution from antibiotic susceptible to multidrug resistant; and the mechanism involve for drug resistance. Morbidity, mortality, and health cost are described in addition to clinical presentation, signs, and symptoms to better understand the health impact of MDR-TB infection. I discussed current research studies on risk factors of MDR-TB infection which served as background of the study hypothesis.

A discussion of MDR-TB geographic distribution, manifestation, drug resistance, prevention, and control from published epidemiological studies are also presented. These studies also provide the framework for my methodology. The section on the state of TB and MDR-TB epidemiology in the Philippines was also discussed.

Literature Search Strategy

I used PubMed and Academic Search Premier databases to identify relevant published research studies. Research from WHO and the journals *New England Journal of Medicine*, *Emerging Infectious Diseases*, *Clinical Infectious Disease*, and *Journal of Infectious Diseases* were used in the review of related literature. The research terms used were multidrug resistance tuberculosis, Mycobacterium tuberculosis (*Mtb*), antibiotic resistance, TB in the Philippines, and TB risk factors. Published studies from 2009 to 2014 were reviewed. The basis for the selection of published literature review inclusion are those that discussed MDR-TB, tuberculosis, mycobacterium tuberculosis (*Mtb*), antibiotic resistance, prevention and control, TB in the Philippines, TB epidemiology, disease geographic distribution, prevention, control, clinical presentation, and risk factors methodologies.

Pathogenic Characteristics of Mycobacterium Tuberculosis

General morphological characteristics of Mtb include being rod-shaped or tubercle bacilli, slender, nonmotile, and appearing bent or curved (Gengenbacher & Kaufmann, 2012; Ahmad, 2011). The organism has an impermeable and thick cell walls or capsule. The cell wall is composed of peptidoglycans, polysaccharides, unusual glycolipids, and lipids. The lipids are made of a long chain of fatty acids, such as mycolic acid

(Gengenbacher & Kaufmann, 2012; Ahmad, 2011). The organism belongs to the mycobacterium genus and is known to be an opportunistic pathogen due to its ability to survive in various types of environment (Cook et al., 2009).

Gengenbacher and Kaufmann (2012) found out that the ability of the *Mtb* organism to become dormant in a nonreplicating state is due to low metabolic activity. Dormancy in the nonreplicating state allows phenotypic drug resistance of Mtb. These findings above were corroborated by Bret, Demetriadou, and Zahrt (2011), who found that the *Mtb* organism adapts to changes in the granulomatous lesions environment. The changes could be due to low-oxygen tension, nutrient depletion, reactive oxygen and nitrogen species, altered pH, toxic lipid moieties, and cell wall/cell membrane-perturbing agents. The adaptation is made possible through transcriptional reprogramming. In transcriptional reprogramming, the original genetic expression that would not allow the *Mtb* organism to survive in the unfavorable environmental condition leads to the development of a variety of regulatory factors (Bret et al. 2011). Among these factors are 11 complete two-component signal transduction systems (TCSSs), several orphaned response regulators (RRs), and sensor kinases (SKs) (Bret et al. 2011; Forrellad et al. 2013). Virulence genes develop that contain the code for the virulence factor protein molecule which allows the *Mtb* organism to survive in the form of positive response to the host immune reaction (Forrellad et al. 2013).

An important characteristic of this infectious agent of tuberculosis is that the organism does not require specific nutritional substances for normal metabolism and reproduction. The ability of the *Mtb* organism to survive in various types of nutritional

substances provides ease of growth, proliferation and infection (Gouzy et al. 2013). The flexible catabolic pathways allow multiple carbon and energy sources utilization from the infected person to play a critical part in the mycobacterial physiology and virulence that place TB disease as one of the global leading causes of morbidity and mortality (Gouzy et al. 2013).

Furthermore, when bacteria infect the human body, the macrophage (a type of white blood cell) engulfs and digests the microbe (phagocytosis) and initiates adaptive immunity in conjunction with lymphocytes (Meena & Rajni, 2010). Mtb uses the macrophage for its replication through various survival mechanisms, which then allows the macrophage to remain available to host the pathogenic organism (Meena and Rajni, 2010). The survival mechanism could be through inhibition of phagosome harboring the Mtb with a lysosome, acidification of the phagosome, protection from oxidative radicals, TACO protein on the phagosome, and expression of virulence proteins in the PE-PGRS family (Meena & Rajni, 2010). These *Mtb* survival strategies are comprehensively described by Gengenbacher and Kaufmann (2012), who contend that the survival success of *Mtb* is based on three capacities, which are first reprogramming of macrophages after primary infection /phagocytosis in order to prevent its own destruction initiating the formation of well-organized granulomas, second comprising different immune cells to create a confined environment for the host–pathogen standoff; and third the capability to shut down its own central metabolism, terminate replication and thereby transit into a stage of dormancy rendering itself extremely resistant to host defense and drug treatment (Gengenbacher & Kaufmann, 2012, p. 514).

Meanwhile, one third of the global human population harbors *Mtb* in dormant form (Guptaa, Kaula, Tsolakib, Kishoreb, & Bhakta, 2011). Considering this figure, public health professionals should underscore the importance of addressing the issue on how to prevent *Mtb* infection. WHO data showed that 1.3 million died from the disease in 2013, of which 320,000 were HIV-positive individuals as a result of comorbidity (World Health Organization (WHO, 2013a).

Modes of Transmission of Mycobacterium Tuberculosis

The mode of transmission for MDR-TB strains is the same to that of drug-susceptible *Mtb* organism strains. The primary mode of transmission of *Mtb* is through inhalation of the tubercle bacilli that is present in the microscopic droplets from an active TB infected person (Versalovic et al. 2011). The microscopic droplets of 1-5 micron in size, once exhaled, easily mix with air circulation until a susceptible person inhales the droplet nuclei (Versalovic et al. 2011). The expulsion of the microscopic droplets can also potentially occur when an active TB-infected person coughs, sneezes, speaks, sings, or laughs (NIAID, 2010a). However, not all persons exposed to microscopic droplets containing Mtb bacilli develop tuberculosis. In fact, the risk of developing active TB disease is only 10% for a person with a latent infection which is accelerated to 10-15% per year to progression for patients with HIV (WHO, 2014d; Versalovic et al., 2011; Ritacco et al., 2012).

Understanding disease transmission is one of the tenets of the science of epidemiology. The proliferation of TB in a population can be prevented by understanding the mode of transmission which can then be the foundation for the conceptualization and

development of appropriate, correct proactive infection control measures. TB bacilli can also be transmitted in a workplace as demonstrated in a study by Jonsson, Kan, Berggren and Bruchfeld (2013).The researchers applied restriction fragment length polymorphism technique to cluster the *M. tuberculosis.* The isolated organism was from healthcare workers who develop TB within ten months after the death of an HIV-positive patient with pulmonary tuberculosis. Study results showed that there was a correlation between the number of working hours and risk of acquiring tuberculosis infection and disease. Jonsson et al., (2013) recommended that healthcare workers should undergo screening for latent TB as a baseline reference in case of future contact-tracing after an accidental exposure. The aforementioned study exemplifies the occupational transmission modality and is also present among dental hygienist. TB infection occurred among dental hygienist after working for several months with patients coming from countries in which TB is endemic (Merte, Kroll, Collins, and Melnick, 2014).

Though social interaction has shown to contribute the transmission of *Mtb*, physicochemical environmental parameters likewise play a role in the proliferation of the microscopic droplets that contain the *Mtb* bacilli. The observed cause of the seasonal rise of tuberculosis during winter is crowding. This was affirmed by a study performed from 1993 to 2004 in the Netherlands (n = 4,746) using autocorrelation function plots and spectral analysis. The researchers found out that the increased transmission of TB during winter time is unlikely to be the only cause of the seasonal peak in TB notifications (Soetens, Boshuizen, and Altes, 2013).

Whenever human overcrowding occurred due to limited space; the situation is a potential, excellent ground for *Mtb* proliferation especially when an infected person in the group coughs. López et.al, (2013) performed a study to evaluate the use of cough-generated aerosols of *M. tuberculosis* to predict recent transmission. Multivariable logistic regression analysis with cluster adjustment was applied to analyze predictors of new infection among patients with pulmonary TB. The respondents of the study underwent a standard evaluation and collection of cough aerosol cultures of M. tuberculosis. The study data revealed that household contacts of patients with TB who produced high aerosols (≥10 CFU) were more likely to have a new infection compared with contacts of TB patients with low-aerosol (1-9 CFU). , Patients with a high TB aerosol contact was the only predictor of new M. tuberculosis infection in unadjusted and adjusted analyses. The importance of identifying the reservoir of TB transmission within the community deserves increased focus. This could be done by intensive household contact tracing to attain an effective disease transmission reduction (Kompala, Shenoi, and Friedland, 2013).

In the continental United States, about a fifth of MDR-TB cases can be linked to transmission within the country. The disease reservoir is infected person who already acquired TB before entry into the country (Moonan et al., 2013).The data from this case finding study showed that 20 (22%) of these individuals developed MDR-TB as a result of the transmission within the country. The researchers found out that 38 (41%) were deemed to have reactivation of disease. However 14 (15%) respondents had a known previous episode of tuberculosis outside the USA; five individuals (5%) had documented the

treatment of the previous episode, and nine cases (10%) insufficient evidence to definitively classify reason for disease transmission (Moonan et al., 2013).

It is then apparent that there is a need to fully understand the risk factor for communicable disease transmission to develop a disease transmission control program like those geared for MDR-TB. Such program could be community-based treatment. Community-based treatment program offers important advantages over the hospital or clinic-based care not only in cost and effectiveness. It allows rapid identification of infectious cases especially in drug-resistant cases, followed by effective and fully supervised treatment (Nardell and Dharmadhikari, 2010).

The study by López et al., (2013) suggested that *Mtb* transmission is better predicted in cough aerosols than sputum smear microscopy or culture. Close and frequent proximity to TB-infected persons that coughs are an excellent mode of *Mtb* transmission. The finding above is further corroborated in a study by Kopeć et al., (2012). The researchers studied 35 family households in Poland using spoligotyping and the mycobacterial interspersed repetitive unit-variable-number of tandem repeat (MIRU-VNTR) typing. Results of the study demonstrated that out of 78 patients, 49 (63%) of the infection was attributed to intra-household transmission. The finding clearly supports the study conclusion of López et al., (2013) that household setting is an important reservoir of *Mtb* transmission.

DRUG-RESISTANT TUBERCULOSIS

History of drug resistance

Tuberculosis has almost threatened the very existence of humanity in the biosphere. Since the time, immemorial this white plague has caused the loss of millions of lives. The discovery and development of streptomycin in 1944 paved the way for the treatment of TB infected person. The treatment was considered as the first world drug trial involving randomization of study participants (Keshavjee and Farmer 2012). However, resistance to the first anti-tubercular drug became apparent as shown by some patients with relapse. Laboratory tests showed that the bacilli from the sputum of that patient were resistant to streptomycin due to a mutation in the 16S ribosomal DNA (rrs) and the S12 ribosomal protein gene (rpsL). The resistance was attributed to the drug mechanism target of disrupting the bacterial protein synthesis (Goldberg, Siliciano, and Jacobs, 2012).

Since then, research on new antitubercular medication has lead to the development of isoniazid, pyrazinamide, cycloserine, ethionamide, rifampin, and ethambutol. Drug resistance always threatened the effectiveness of the monotherapy due to *Mtb* selective mutation (Keshavjee and Farmer 2012). Antibiotics currently available for TB treatment act differently on *Mtb*. As shown in Figure 5, the synthesis of *Mtb* cell wall is inhibited by isoniazid and ethambutol. Rifampin inhibits the synthesis of RNA and pyrazinamide antibiotics prevent the microbial growth by disrupting the plasma membrane and energy metabolism (NIAID, 2012b).

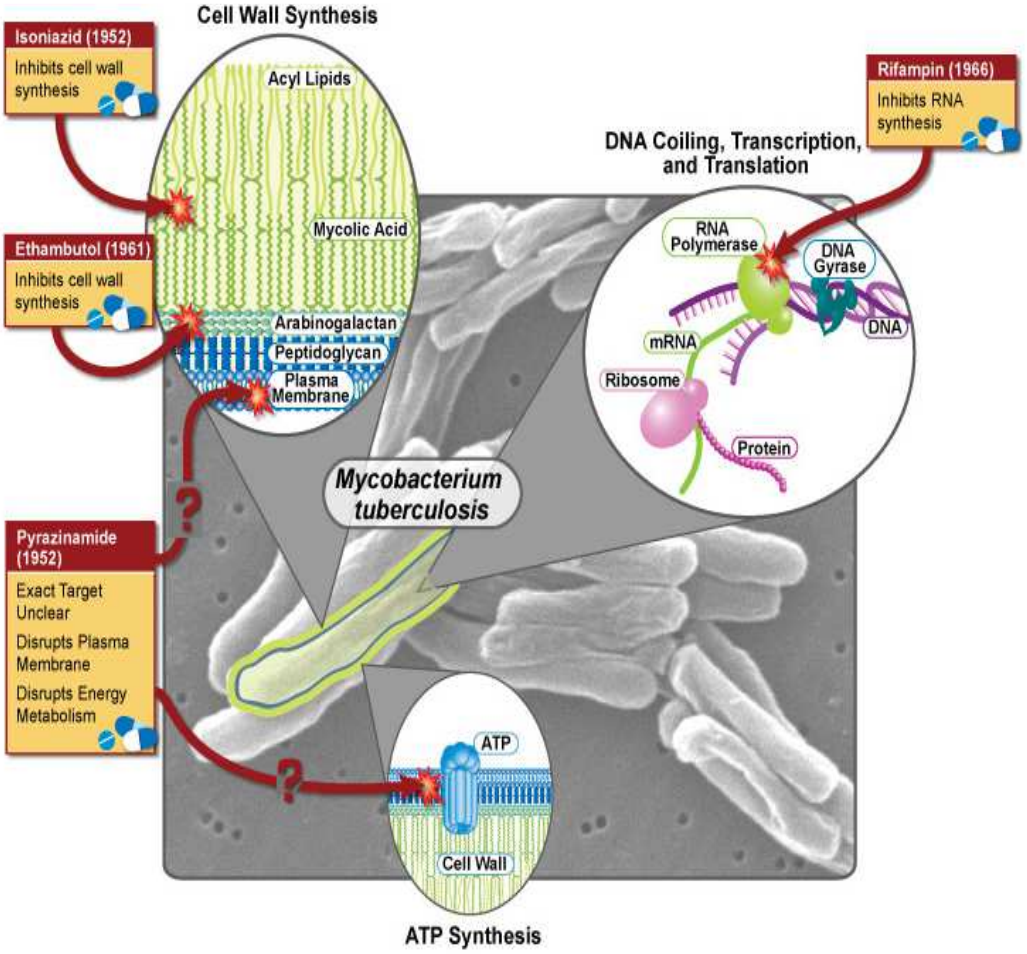


Figure 5. First-Line Treatment of Tuberculosis for Drug-Sensitive TB. Courtesy National Institute of Allergy and Infectious Diseases. Adopted from: NIAID, (2012b).

Recognizing the potential for antibiotic resistance, combining anti-TB drugs or multiple drug chemotherapy became the standard of treatment specially that drug resistance has received increased attention in the early of 1990's since TB became a co-morbidity of Human immunodeficiency virus- immunodeficiency syndrome (HIV-AIDs).A typical example was the study on modeling the dynamic relationship between HIV and the risk of drug-resistant tuberculosis by Sergeev, Colijn, Murray, and Cohen

(2012). The researchers concluded that the rise in HIV could increase the prevalence of MDR-TB in populations due to preferential social mixing among individuals.

Classification of Drug Resistance

The emergence of MDR-TB undermines the effort of the World Health Organization through the Millennium Development Goals (MDGs) and by the Stop TB Partnership. The programs aim to reduce by 50% TB prevalence and death rates towards the end of 2015 and to eliminate TB as a public health problem by 2050 (WHO, 2014e). The current epidemiological standard for MDR-TB classification is provided in the World Health Organization Guidelines for surveillance of drug resistance in tuberculosis – 4th ed. The treatment regimen survey aims to determine the predominant source and pattern of MDR-TB. The source of the classification provides a clear definition of patient's registration groups by the history of previous treatment. The classifications are a new case, previously treated case, primary resistance, acquired resistance, cured and failed (WHO, 2009).

Mechanism of Drug Resistance

The mechanism of *Mtb* drug resistance has been studied using molecular genetics approach. Understanding the mechanism involved in drug- resistance is critical in the development of new anti-TB medicine besides the fact that the presence of drug resistance *Mtb* compounds the problem of eliminating TB. *Mtb* drug resistance could be intrinsic/natural or acquired. The natural presence of an unusual structure of the mycolic acid-containing cell wall allows a low permeability of chemotherapeutic compounds such as antibiotics on top of the role of efflux mechanism (Da Silva and Palomino, 2011). This was further substantiated by an in vitro induction study that aimed to investigate the

mechanism by which resistance towards isoniazid develops and how overexpression of efflux pumps favors mutations development in isoniazid targets (Machado et al., 2012). The aforementioned study applied a prolonged serial exposure of *Mtb* strains to the critical concentration of isoniazid. The study revealed that susceptible and rifampicin mono-resistant strains once exposed to this concentration become resistant to isoniazid after three weeks, and that resistance observed for the majority of these strains could be reduced using efflux pumps inhibitors due to overexpression efflux pump genes. Machado et al., (2012) further provided justification that intrinsic or natural resistance, as exemplified by the efflux, pumps mechanism allows the maintenance of an isoniazid-resistant population in a sub-optimally treated patient.

The repeated and inappropriate use of antibiotic is a major cause of acquired antibiotic resistance. The resistance may also develop as a result of chromosomal mutations wherein the number of chromosomes or the bacterial structure is changed or through horizontal gene transfer that involves the alteration of the original genetic code (Smith, Wolff, & Nguyen, 2013). The chromosomal mutation was examined by Georghiou et al., 2012. The researcher made use of published studies to determine *Mtb* mutations association with resistance to Amikacin (AMK), Kanamycin (KAN), Capreomycin (CAP) antibiotics. Further, the researchers also characterize the diversity and frequency of mutations as well as describe the strength of the association between specific mutations and phenotypic resistance in global populations. The researchers found out that genes rrs A1401G mutation were present in the majority of AMK, KAN, and CAP resistant *Mtb* strains, but was also found in 7% of CAP susceptible strains (Georghiou et

al., 2012). Isoniazid and Rifampicin are the common first line of drug in the treatment of tuberculosis. The *Mtb* genes involved in acquired antibiotic resistance to isoniazid are *katG*, *inh*A, *ndh*, and *ahpC* which function for prodrug activation, drug target, and activity modulation and resistance marker respectively. Likewise, *rpoB* gene reacts on drug target and is involved in rifampicin resistance (Smith, Wolff, &Nguyen, 2013)

Epidemiology of Drug Resistance Tuberculosis

The MDR-TB infection has spread globally. This was observed since the introduction of the first anti-tuberculosis drug streptomycin in 1944. Microbial culture of patients that underwent relapse of the disease showed resistance to the antibiotic (Keshavjee, and Farmer, 2012). WHO in 1994 initiated the Global Project on Anti-Tuberculosis Drug Resistance Surveillance. The program systematically collected and analyzed data from 114 countries WHO, 2010a). The 2010 surveillance data of countries (see Table 1) that reported first-line anti-TB drug resistance show the highest level of resistance is in Europe. A total of 44 countries or 83% reported first-line anti-TB drug resistance out of 53 European countries monitored. South-East- Asia where the Philippines is located, ranks third with six countries out of 11 (55%) reporting first-line anti-TB drug resistance. In this year alone, the global proportion of MDR-TB among new TB cases reported ranged from 0-28.3% (WHO, 2010a).

Table 1

Number of Countries Reporting Data on Resistance to First-Line Anti-TB drugs by WHO Region

WHO region (no. of countries)	No. of countries reporting first-line anti-TB drug resistance (%)
African (46)	22 (48)
Americas (35)	20 (57)
Eastern Mediterranean (21)	8 (38)
European (53)	44 (83)
South-East Asia (11)	6 (55)
Western Pacific (27)	14 (52)
Total (193)	**114 (59)**

Note. Republished from Multidrug and extensively drug-resistant TB (M/XDR-TB) 2010 Global Report on Surveillance and Response. Copyright 2010 by the World Health Organization.

The proliferation of this disease especially MDR-TB is of grave concern to public health for it transcends borders, thus potentially undermines if not reverses the achievement of TB control and eradication led by WHO. Moreover, the treatment of MDR-TB is difficult and complex when compared to that of drug-susceptible TB. It takes up to two years, involving daily injections of very toxic medicine for six months, and is significantly more expensive. The cost associated with MDR-TB treatment imposes a significant challenge to the government health care system and especially to vulnerable low income families (Tuberculosis Alliance, 2014). Besides the social stigma associated with the disease that destroys families, the productivity loss attributable to TB is 4 to 7 percent of the Gross Domestic Product (Tuberculosis Alliance, 2014).

It is within this framework that the National Strategy for Combating Antibiotic Resistant Bacteria was initiated last September 2014 by the United States Government.

The initiative is a bold step to slow the global public health threat of antibiotic-resistant bacteria typical of which is MDR-TB. The initiative will be achieved in collaboration with the international communities among which is the Trans-Atlantic Taskforce on Antimicrobial Resistance and WHO Global Action Plan for Antimicrobial Resistance. The first two goals of the plan were to: (1) slow the emergence of resistant bacteria and prevent the spread of resistant infections, (2) strengthen National One-Health surveillance efforts to combat resistance (U.S. Government – White House, 2014). Antibiotic resistance is a threat to public health and the economy. In the United States of the 9,588 TB cases reported in 2013, it was estimated that 1-2% has MDR-TB. The treatment cost per case based on the 2010 dollar value is $134,000(U.S. Government – White House, 2014).

Geographical prevalence of MDR-TB transcends country's economic and health care system condition. The drug resistant organism could easily be introduced and proliferate from one country to another especially now a day that people can easily travel because of the modern mode of transportation. The most recent global surveillance data, as shown in Figure 6, percent of new MDR-TB cases in some parts of the former Soviet Union have reached 18 percent, and in the Philippines, the percent of new cases is at 3 to 5.9 percent (WHO, 2013a). More than 80% of those who contracted MDR-TB in North America and Europe died; today the disease is now common in India and China.

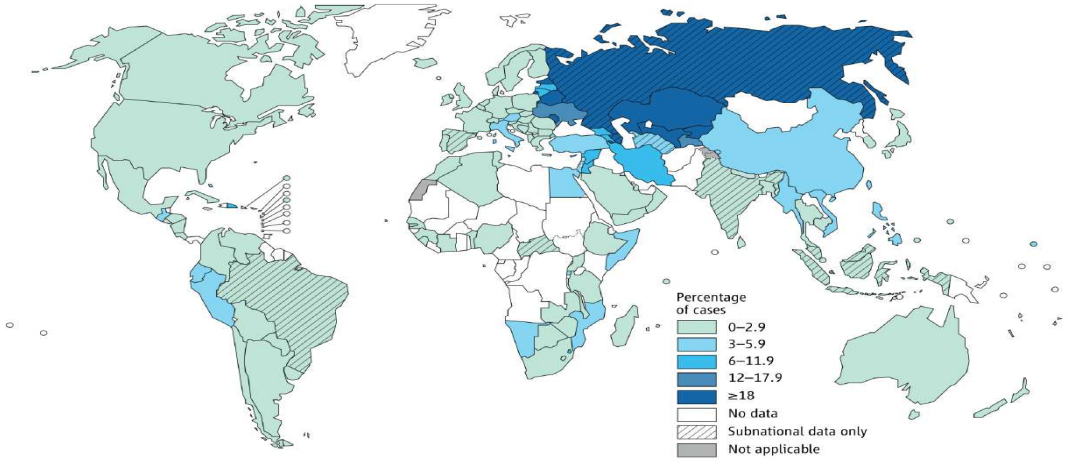


Figure 6. Percentage of new TB cases with MDR-TB, 1994-2012. Adapted from: WHO, (2013)

MDR-TB affects a person of any age, and one of the most MDR-TB vulnerable population groups are children under 15 years of age. The World Health Organization drug resistance surveillance data between 1994 and 2011 were analyzed to test the association between MDR-TB and age group by Zignol et al. (2013) using odds ratios derived by logistic regression. The odd ratio of MDR-TB in children compared to adults varies between countries. In Germany, Namibia, South Africa, the UK and the USA, children <15 years appear to be at significantly higher risk for MDR-TB. The researchers concluded that of the risk of MDR-TB in children and adults are similar in many settings. This finding was later supported by a recent study that aimed to quantify the global incidence of MDR-TB disease in children (Jenkins et al., 2014). Results of the study data after statistical analysis showed that the risk of MDR-TB was nearly identical to children and adults since both groups are exposed to the same local risk. In this meta-analysis study, the researchers considered 3,403 published research studies, of which only 97 studies met inclusion criteria. Statistical calculation of the risk estimated around 1,000,000

(95% Confidence Interval: 938,000 –1,055,000) children developed TB disease in 2010, among whom approximately 32,000 (95% Confidence Interval: 26,000 – 39,000) had MDR-TB (Jenkins, et al, 2014).

RISK FACTORS FOR MDR-TB AND METHODS USED IN THE STUDY

Identification of risk factors is critical since it serves as the foundation for the development of disease prevention and control strategy program. Because of their fundamental role, the identified risk factors should be a result of scientifically based evidence of causality (Porta, 2014). Health risk factors related to MDR-TB increase the chance of getting the disease; nevertheless, it does not imply that the person exposed to such identified risk factors will develop the disease. What is significant to know if preventive care was received after exposure to the risk factor. Preventive care has demonstrated to be very valuable in early disease detection and infection proliferation control among the population especially for a transmittable disease like MDR-TB.

Various risk factors for MDR-TB have been identified depending on the intent of the study and respondents geographical location. Risk factors for the MDR-TB infection are influenced by sociobehavioural, demographic, and economic condition prevailing in the study area coupled with the respondent's current health condition. In a meta-analysis study done by Zhao, Li, Zhang, Wang and Liu (2012), evaluation and analysis of 16 studies obtained from PubMed and Chinese BioMedical databases was performed. MDR-TB was significantly associated with poor quality of Directly Observed Treatment Short-course, poor treatment adherence, previous treatment, poverty, and age. The findings were a result of selected published articles that were independently reviewed following certain

inclusion criteria, and the data were analyzed using Review Manager Software. In a similar study done in the eastern part of China, the case-control study design was utilized to determine the risk factors for MDR-TB among previously TB treated patients. Pre-identified TB patients resistant to at least isoniazid and rifampin were classified as cases, and those, who are susceptible to the TB drug, were under the control group. Multivariate analysis of data showed that the risk factor associated with MDR-TB is the previous treatment of TB (Chen et al., 2013). The treatment course for TB sometimes takes a longer period providing a great chance for the patient to comply poorly with the prescribed treatment regimen. Liu et al. (2013) conducted a similar study in Northeastern China. One of the inclusion criteria in the study was that the sputum collected from the respondent should show positive for the presence of *Mtb* bacteria in addition to being a resident of Lianyungang City. Besides the laboratory report, other data were obtained from personal information, physical examinations, present illness, TB-related complaints, previous medical history, family history and the purified protein derivative test (skin test) result (Liu et al.,2013). The data were obtained through interview and review of respondents' medical records (Liu et al., 2013). Using SPSS version 13.0 data were stored and analyzed to determine the probable association between selected factors. The odds ratios and 95% confidence intervals from an unconditional logistic regression model with $P < 0.05$ based on a two-sided test was applied as the criterion for significance (Liu et al., 2013). The researcher found a similar result that previous treatment classified as the first treatment of more than eight months and more than three prior episodes of anti-TB treatment was an important risk factor for the MDR-TB infection.

Van der Wef, Langendam, Huitric and Manissero (2012) performed a meta-analysis of studies published from the database in MEDLINE and EMBASE on drug resistance after inappropriate TB treatment. The study aimed to assess the evidence that inappropriately following the prescribed tuberculosis treatment regimen is a risk factor for the development of MDR-TB. The researchers found out that there was not enough evidence that MDR-TB development is caused by inadequate treatment. One of the studies that were reviewed showed a 27 fold increase of developing MDR-TB in patients who failed treatment when compared to those patients that observed appropriate treatment regimen (Van der Werf et al., 2012). What is significant in studies done by Zhao, et. al., (2012) and Chen et al. (2013) was that their results underscore the importance of a high-quality standard antibiotic treatment and a strict follow-up of patients to ensure adherence to the prescribed regimen. This is done to avoid possible mutation or evolution of the organism into drug-resistant strain otherwise exposure to TB treatment becomes a risk factor for the development of drug-resistant organisms.

In addition to poor quality of previous TB treatment, gender, and age other contributing risk factors for MDR-TB were also ascertained by Rifat et al. (2014). MDR-TB patients, who are the subject of the study, were randomly selected from government hospitals located in urban and rural areas of Bangladesh. The researchers applied the case-control study design wherein the drug-susceptible TB patients (N = 750) are in the control group while the MDR-TB patients (N = 250) are the cases. All recruited study respondents were of confirmed diagnosis for MDR-TB. A face-to-face interview using a structured questionnaire, and clinical record reviews were conducted to obtain socio-demographic

information to develop the database. The questionnaire was designed to obtain data on possible risk factor association on predictors such as the previous history of TB treatment, gender, age group, education, occupation, smoking status, substance misuse and presence of type-2 diabetes. Data was analyzed using unadjusted and multivariable logistic regressions. Results of the study showed similar strong association (Odd Ratio 716.6, 95% Confidence Interval 282.1-1820.8) of previous TB treatment history with that conducted by Liu et al. (2013). Previous TB treatment history was predominant (98%) among MDR-TB patient respondents in this study compared to drug-susceptible TB patients (6.4%). Other risk factors associated with MDR-TB infections in the following decreasing order of association are; age, education, service, business as occupation, service and business as occupation and type 2 diabetes (Rifat et al., 2014).

Type 2 diabetes is not the only identified comorbid illness identified as the risk factor associated to MDR-TB but also the presence of Human Immunodeficiency Virus (HIV) infection. Skrahina et al. (2013) conducted a survey study in Belarus wherein one of the study aim is to ascertain the risk factor for MDR-TB proliferation in the country. Respondents of the study were not classified between cases and control. The two sputum samples submitted by respondents were subjected to acid-fast direct microscopy examination, and the other was cultured to determine drug resistance or susceptibility. Proper treatment was provided to the respondents. Structured questionnaire interview was applied to gather information on sociobehavioural, treatment history, demographic characteristics, education, living and employment conditions, history of imprisonment, use of alcohol, smoking and HIV infection (Skrahina et al., 2013). Data analysis generated

from the EpiInfo software package version 3.5.1 wherein all the information were stored and statistically subjected to Pearson X^2 to compare categorical variable. Analyses showed that previous treatment history was the number one risk factor for MDR-TB infection. The Odds Ratio was 6.1; 95% Confidence Interval: 4.8–7. This was followed by the presence of HIV infection with Odds Ratio: 2.2; 95% Confidence Interval: 1.4–3.5 (Skrahina et al., 2013). The researchers considered the possible risk factor to be associated with the MDR-TB infection if the P-value is <0.05. Statistical analysis revealed that in Belarus, the risk factors for the MDR-TB infection are age < 35 years, history of imprisonment, disability sufficient to prevent work, alcohol abuse and smoking (Skrahina et al.,2013).The result of the study perhaps indicates that the convergence of HIV and MDR-TB infections is of great public health concern. This requires a stronger collaboration between the two disease control programs and most importantly acceleration of TB resistance detection and improvement to treatment adherence.

HIV as a risk factor for the MDR-TB infection was found to be similarly correlated in a study done in Hanoi, the capital of Viet Nam (Hang et al., 2013). Clinical and epidemiological information were collected by the researchers in this study from 506 newly diagnosed patients with sputum smear- and culture-positive TB. Data were subjected to adjusted odds ratio analysis to determine risk factors degree of correlation to drug resistance. Interesting in this study was that the researchers aimed to understand the risk factor associated with TB drugs (isoniazid, rifampicin streptomycin, and ethambutol) resistance and multi-drug resistance from the *Mtb.* TB drug resistance test was performed on isolates cultured from respondent's sputum. Study result showed that risk factors

associated with isoniazid resistance include living in old urban areas, the presence of the Beijing genotype, and clustered strains. Patient with the Beijing genotype strain of *Mtb* is resistant to streptomycin (Adjusted Odds Ratio: 2.10, 95% Confidence Interval; 1.29–3.40). Moreover, HIV co-infection was found to be associated with rifampicin resistance and MDR-TB (Hang et al., 2013). The researchers of the study concluded that *Mtb* drug-resistant strains could be avoided based on the result of drug susceptibility, coupled with monitoring to ensure treatment prescription adherence.

The identification of risk factors can also be studied following a descriptive case series study design, wherein data are obtained through structured interview and abstraction of treatment record from patient (Pant et al., 2009). In this study, the data was gathered within eight months period from respondents in a DOTS-Plus clinic at Bhim Hospital, Bhairahawa. The study did not have a case-control. However, the authors found out that the primary risk factors for MDR-TB are previous TB treatment followed by male sex, poverty, migration to India, illiteracy, and smoking (Pant et al., 2009).

The literature review showed that varying study design and data gathering strategy could be applied to determine the risk factor of MDR-TB. Terlikbayeva et al., (2012) applied correlational and descriptive analyses to determine the MDR-TB risk factor and its temporal and spatial distribution in Kazakhstan. This study considered social, economic and environmental factors as possible determinants of drug-susceptible TB and the MDR-TB infection. Specifically, the researcher analyzed the TB surveillance data from the National Institute of Geography (NIG) and the National Tuberculosis Program (NTP). The analysis centers on the possible association of MDR-TB infection of alcohol use,

vulnerable group, the presence of diabetes, drug use, jail history, migration status, TB treatment history, occupation, exposure to TB patient, and if recent mother. The data were subjected to descriptive statistical analysis using Microsoft Excel 2010 and SAD 9.2. Thou correlation analysis was not applied in this study; the researchers found out that most study respondents with the MDR-TB infection had previous contact with the patient with drug-susceptible TB or MDR-TB (Terlikbayeva et al., 2012). In addition, the study demonstrated that MDR-TB cases increase in Kazakhstan as the prevalence rate of drug-susceptible TB decrease thereby threaten the gain in the TB control program.

The proliferation of MDR-TB within the household or community as a result of social interaction, behavior, demographic and health conditions has been observed in studies. Cohen et al., (2011) using spoligotyping and 24-loci mycobacterial interspersed repetitive unit–variable number tandem repeat to classify isolates from 101 households in Lima, Peru wherein >1 MDR-TB patient received treatment from 1996–2004. The primary purpose of the study was to estimate the frequency of multiple introductions of MDR-TB into households. The researcher made use of genetic marker to track *Mtb* organism. Data showed ≥ 10% of households are re-infected with the same MDR-TB strain, and 4% are from different MDR-TB strains. Interestingly the proliferation of MDR-TB in a community could be brought about by migrants who have been exposed to resistant *Mtb* strains, and possibly inadequate TB treatment (Bojorquez et al., 2013). This was the findings of Bojorquez et al., (2013) wherein data from Mexico's National TB Drug Resistance Survey (2008-2009) was subjected to multivariate analysis. Factors associated with MDRTB are previous anti-tuberculosis treatment, Mexico-born TB

patients in California and those born elsewhere had greater odds of MDR-TB infection compared with patients who were born in the US (Bojorquez et al., 2013).

CLINICAL PRESENTATION OF TB AND MDR-TB

There is no difference in the clinical presentation of MDR-TB with that of drug-susceptible TB. A bad cough that last three weeks or longer, pain in the chest, coughing with blood or sputum (phlegm from deep inside the lungs), weakness or fatigue, weight loss, no appetite, chills, fever, sweating at night are the general symptoms of the disease (CDC, 2012). Other respiratory symptoms may include shortness of breath, chest pains, and hemoptysis (WHO, 2010b).

To rule out the possibility that a patient may be infected, various diagnostic tests are available. Some active TB-infected patient' do not exhibit respiratory symptoms thus the application of chest x-ray is a valuable tool to identify the presence of pulmonary lesions that may indicate the presence of the disease. However, the most definitive means of diagnosis are through culture collection from three-morning sputa. Culture collection of *Mtb* bacteria is considered the “gold standard” for TB diagnosis (WHO, 2010b). On the other hand, patients with latent TB infection can be tested using tuberculin skin testing as indicated by 5 mm induration two to three days after intradermal injection of *M. tuberculosis* antigens (Konstantinos, 2010). Clinical symptoms of TB vary especially those with extra-pulmonary TB located in lymph nodes, kidney, bones, and brains making it difficult for diagnosis and monitoring treatment progress (Zhang et al., 2011).

Since symptoms of MDR-TB and drug-susceptible TB are not different this, becomes difficult for clinicians to diagnose and prescribe the appropriate chemotherapy

without a definitive identification and characterization of the organism collected from the patient sputum. The Food and Drug Administration (FDA) permitted marketing of the Xpert MTB/RIF assay instrument (Cepheid, Sunnyvale, California) to detect DNA of the *Mtb* complex (MTBC).The instrument can determine genetic mutations associated with resistance to rifampin (RMP) in unprocessed sputum and concentrated sputum sediments. Test results generated by the instrument in conjunction with clinical, radiographic, and other laboratory findings will provide clinicians a comprehensive assessment in the diagnosis of pulmonary tuberculosis (CDC, 2013).

TUBERCULOSIS IN THE PHILIPPINES

The Philippines with a developing economy located in the south-eastern part of Asia composed of 7,107 islands. Based on the 2010 population census data, there are 92.3 million Filipinos (Vianzon et al., 2013). Based on 2010 national data the Gross Domestic Product grew by 7.3%. The geographical location of the country is along the Pacific Ring of Fire and typhoon belt. A significant number of people are displaced and killed due to several natural disasters that occurred in the country (WHO Western Pacific Region, 2014). Natural disasters are some of the risks that hinder the steady rate of Philippines development; thus the significant proportion of the population remain poor (WHO Western Pacific Region, n.d.a). Other health-related risk factors cited by the WHO Western Pacific Region are air pollution, water pollution, poor sanitation and unhygienic practices and solid waste mismanagement. Further, low-income families living in isolated areas are faced with difficulties going to health centers and schools due to inadequate infrastructure and economic condition. The HIV prevalence in the Philippines though

under 0.1% is rapidly expanding due to men who have sex with men, and injection drug users. Besides Tuberculosis, other diseases prevalent in the country are malaria, dengue, filariasis, leptospirosis, other diarrheal diseases, and some soil-transmitted helminths (WHO Western Pacific Region, n.d.). The diseases above are endemic nationwide. Smokers comprise 28.3% of the adult population based on 2009 Global Adult Survey conducted in the country.

TB mortality remains high at 27 per 100,000 populations. TB disease is the sixth leading cause of morbidity and mortality in the Philippines. The country is ninth out of the 22 highest TB-burden countries (WHO, 2014f). The TB disease-causing organism was classified as Manila family of *Mtb* and is a group of clonal isolates seen throughout the Pacific Basin (Frink et al., 2011). TB case notification rate in the Philippines of positive smear cases from 2003 to 2011was highest in 2006 per 100,000 and experienced a decline from 2007 to 2008. An increase observed from 2009 to 2011 but a little below the 2006 case notification rate (Vianzon et al., 2013). The awareness about the disease is present, but the level of understanding of what causes the disease, how it is transmitted, and the importance of completing the prescribed treatment is small (PhilPact, 2010-2015).

A literature review of published studies showed a possible gap of MDR-TB risk factor association studies in the country. One such study is a nationwide survey conducted in the Philippines with respondents enrolled from June 2003 to November 2004 following population-proportionate cluster sampling. The study primary purpose was to determine the national level of MDR-TB prevalence against the isoniazid, rifampicin, ethambutol and streptomycin (Philippine Nationwide Tuberculosis Drug Resistance Survey Team,

2009). The study was conducted for 17 months. The demographic characteristics obtained are; age, gender, place of residence (Philippine Nationwide Tuberculosis Drug Resistance Survey Team, 2009). This comprehensive study made use of the Epi Info Version3 software for data storage and in the determination of drug resistance prevalence. What is remarkable in the study was that previously treated cases had 38.8% resistance to the four drug identified. The percentage resistance is higher to the 20.4% resistance from not treated or new cases throughout the country (Philippine Nationwide Tuberculosis Drug Resistance Survey Team, 2009). In addition, most of the respondents, that has been previously treated, were resistant to isoniazid followed by rifampicin, streptomycin and least resistant to ethambutol (Philippine Nationwide Tuberculosis Drug Resistance Survey Team, 2009).

On the other hand, isoniazid was still observed as the antibiotic of primary resistance for new cases followed by streptomycin, rifampicin, and ethambutol (Philippine Nationwide Tuberculosis Drug Resistance Survey Team, 2009). Remarkably the findings, where *Mtb* was most frequent drug resistant to isoniazid, was concurred in a study that was done on wider year coverage from 2003-2008. The later study found out that among new TB cases, most drug resistance pattern is isoniazid and rifampicin. The anti TB drug resistance pattern in the country was primarily isoniazid followed by rifampicin with fluoroquinolones (Gler, Guilatco, Guray & Tupasi, 2012). The findings from the studies above are of great concern to a public health practitioner. Clinicians' selection for antibiotic to treat the disease will be limited. Antibiotic susceptibility testing, to determine

the most effective drug that will eliminate the pathogenic organism, will add burden to patients.

The treatment of TB provides an additional economic burden on the country's health care system. Fitzpatrick, & Floyd (2012) reported that treatment cost of TB patient in the Philippines is $US3, 613. The country a gross national income as of 2003 data is only US$1, 080. MDR-TB treatment cost is more expensive since the drug used for treatment is considerably higher than drug-susceptible TB cases. Nevertheless, the overall cost of MDR-TB treatment in the Philippines is still lower when compared to other European countries (Loddenkemper, Sotgiu & Mitnick, 2012).

Significantly the transmission of this communicable disease in the Philippines does not necessarily occur directly from the patient living in close proximity in the same household but rather frequently is community-based (Sia et al., 2013). The rapid proliferation of the disease not only affects the lungs but as well the eyes that add a burden to the patient and decreases economic productivity. Seven out of the 103 pulmonary TB patients in the Philippines (6.8% prevalence: 95% CI 2.78% to 13.5%) showed signs of ocular inflammation and lesions (Lara, and Ocampo Jr, 2013).

TB treatment in the Philippines is provided free of charge in government hospitals. This does not include another incendiary cost such as transportation to clinic or hospitals, food, etc. Besides other cost associated with treatment, socio-ecological barriers to treatment can be a factor for the disease to spread within the community. Among which are the quality of healthcare services provided, shame associated with TB and familial

responsibility accompanying during the treatment period (Hua, Loob, Wincha, &. Surkana, 2011).

The need to control if not stop the proliferation of the disease does not center only on the detrimental effect on the physiological health of the infected person but likewise on the mental health brought about by depression. In a cross-sectional survey conducted among pulmonary TB-infected patient that live in Tondo, Manila Philippines16.8% out of the 561 respondents manifested depressive state (Masumoto et al., 2014). The Philippines government recognizes the detrimental effect of TB to health and the economic burden that the disease brought about to patient and society as a whole. TB Control Program was initiated in the Philippines following guidelines provided by the World Health Organization in which free treatment is provided through Directly Observed Treatment, Short-course (DOTS). The treatment program is managed by the National TB Control Program (NTP) of the Department of Health which develops policies and plan. The program was implemented in a devolved system down to the lowest structure of government starting from the national, regional, provincial, municipal and finally Barangay level through a standardized reporting system (Vianzon et al., 2013). However, because of budgetary requirements electronic surveillance to develop a central data system is not yet fully implemented in the country; thus most clinical case record can be obtained through identified DOTS centers. Because of MDR-TB threatens the gains achieved in drug-susceptible TB control program through DOTS; the public-private partnership was forged, and the incorporation of MDR-TB services into the NTP was required by the Department of Health (Quelapio et al., 2010).

Chapter 3: Research Method

The study objective was to assess the strength of the association between possible risk factors and development of the MDR-TB infection. Possible risk factors (the independent variables) that were considered in this study were (a) previous TB treatment, (b) HIV infection, (c) exposure to a drug-susceptible TB/MDR-TB patient, (d) delayed diagnosis and treatment, (e) employment status, (f) smoking, (g) imprisonment, (h) alcohol abuse, and (i) compliance with drug-susceptible TB treatment regimens. I hope that study results provide a basis for public health professionals and other community stakeholders to develop effective and proactive intervention programs to enhance the prevention of MDR-TB in the Philippines.

In this Chapter, I provide an overview of the research design I used, which includes specific details regarding the method, study population, sample, and sampling strategies. The relationships between the study variables are also explained in this chapter. Furthermore, I provide a presentation of the statistical treatment of data and ethical considerations regarding protection of study participants.

Research Design and Rationale

The study applied a quantitative method to assess the strength of the preidentified possible risk factor(s) associated with MDR-TB infection. The data that e collected was assessed to provide evidence of causality. Specifically, case-control design was used in the study. The study subjects were patients who had been clinically confirmed to be MDR-TB positive. MDR-TB infection was the dependent variable of the study.

The control subjects were selected among patients with drug-susceptible TB and clinically confirmed patients with MDR-TB are the cases. Age, gender, and education of control subjects were matched with cases to minimize the effect of confounding. The survey questionnaire is the primary instrument for obtaining data from study participants. Prior research studies performed by Chen et al. (2013) and Rifat et al., (2014) demonstrated that relevant potential risk factors for MDR-TB infection in a particular geographic location could be well studied using a case-control design. I identified risk factor variables to use as independent variables based on the literature I reviewed in Chapter 2.

Settings and Samples

The control and possible eradication of MDR-TB in the Philippines is managed by the Department of Health National - Center for Disease Prevention and Control through the National TB Control Programme (NTP). The central NTP team develops policies, standards, and plans and offers guidance for regional, provincial, municipal, and Barangay levels of government. The primary purpose is to ensure standardized routine treatment of patients through the Directly Observed Treatment, Short-course (DOTS) at designated facilities to control the proliferation of the disease (Vianzon et al., 2013).

Based on geographical location and accessibility of clinics and hospitals, I recruited target survey respondents from Programmatic Management of Drug-Resistant (PMDT) TB clinics and hospitals and drug-susceptible respondents from town health centers that provide DOTS as designated by the National Tuberculosis Program to treat MDR-TB and drug-susceptible TB patients. Most of the 2,618 MDR-TB patients

nationwide are treated in PMDT clinics located in metro Manila (Philippine Business for Social Progress, 2013). One of the PMDT centers is the San Lazaro Hospital, which is located in Manila. A municipal health clinic from the town of San Mateo, Rizal, was also a source of MDR-TB cases, and most of the controls were recruited from the different towns of the province of Leyte such as Burauen, Dagami, Tanauan, Barugo, Capoocan, and Carigara. Leyte is part of Region VIII in the Eastern Visayas Island, which is my home region.

Population Inclusion and Exclusion Criteria

The primary inclusion criteria of the respondents in the case group was that the respondent's has a documented medical record that M. tuberculosis was detected in patient's sputum, and the microbial strain is resistant to either isoniazid or rifampicin. Bacterial resistance to antibiotic is determined through drug susceptibility testing (Philippine Department of Health -National TB Control Program, 2014). The primary inclusion criterion for the control group was that the respondent has a confirmed documented medical record indicating the identification of Mtb from the patient's sputum. However, microscopic sputum examination for the presence of Mtb may affect the performance characteristics of the control due to potential unrecognition of drug resistant Mtb. This was demonstrated in a study performed by Singh (2014) wherein the sputum microscopy was observed to be less sensitive and specific (61.54%, 96.57%) when compared to Cartridge Based Nucleic Acid Amplification test for Mtb (82.69%, 98.29%) in the same 227 patients. To be eligible, study participants must have checked the agree to participate box in the Study Information and Participation Consent form. MDR-TB and

drug-susceptible TB patients' medical records were not accessed and the patients not enrolled if the agree to participate box was not checked.

Main Study Procedure

Consent from the clinic head was obtained from each PMDT treatment center or drug-susceptible TB treatment centers identified (Appendix A). Upon the approval of the PMDT treatment center or TB treatment center administrator, the Study Information, and Participation Consent that's translated in Filipino language were offered to potential study recruits. To ensure that potential respondent understands the study, I provided an individual study orientation in which he/she can freely ask questions and was provided ample time approximately 1 hour to make a decision. Alternatively, I facilitated a small group study orientation to allow those who might want to participate to self-select, in which they can freely ask questions and were provided ample time approximately 1 hour to make a decision. When a recruit volunteered to be a study participant and has signed the informed consent, I assigned a study identification number following a standardized nomenclature to each study participant. The identification system start's with the first letters of the clinic name, followed by a patient number and Co for control or Ca for the case as defined in the study. If the patient ID is, SLHP05Ca meant the respondents came from San Lazaro Hospital, patient number five and was classified under the case group having diagnosed to be infected with MDR-TB. A password protected Excel central database was created with the identity of th*e* respondents. The study identification number was written on the questionnaire and the clinical record data extraction form. Each questionnaire and the medical extraction form were placed inside an envelope. Then the

questionnaire that is in the Filipino language was offered to each participant that signed the Study Information and Participation Consent Form. The respondents answered the questionnaire in an area designated by the facility. The respondents handed over the envelope with the answered questionnaire to the researcher for review and storage. I provided a list of the patient to the clinic/hospital and the envelope with the respondent's clinical record extraction form. Clinic/Hospital was requested to review the patient clinical record to verify whether the patient is either a laboratory confirmed MDR-TB or a laboratory-confirmed Drug-Susceptible TB, and the most recent HIV test result (if available) and was documented in the Respondents – Clinical Record Extraction Form (Appendix B).

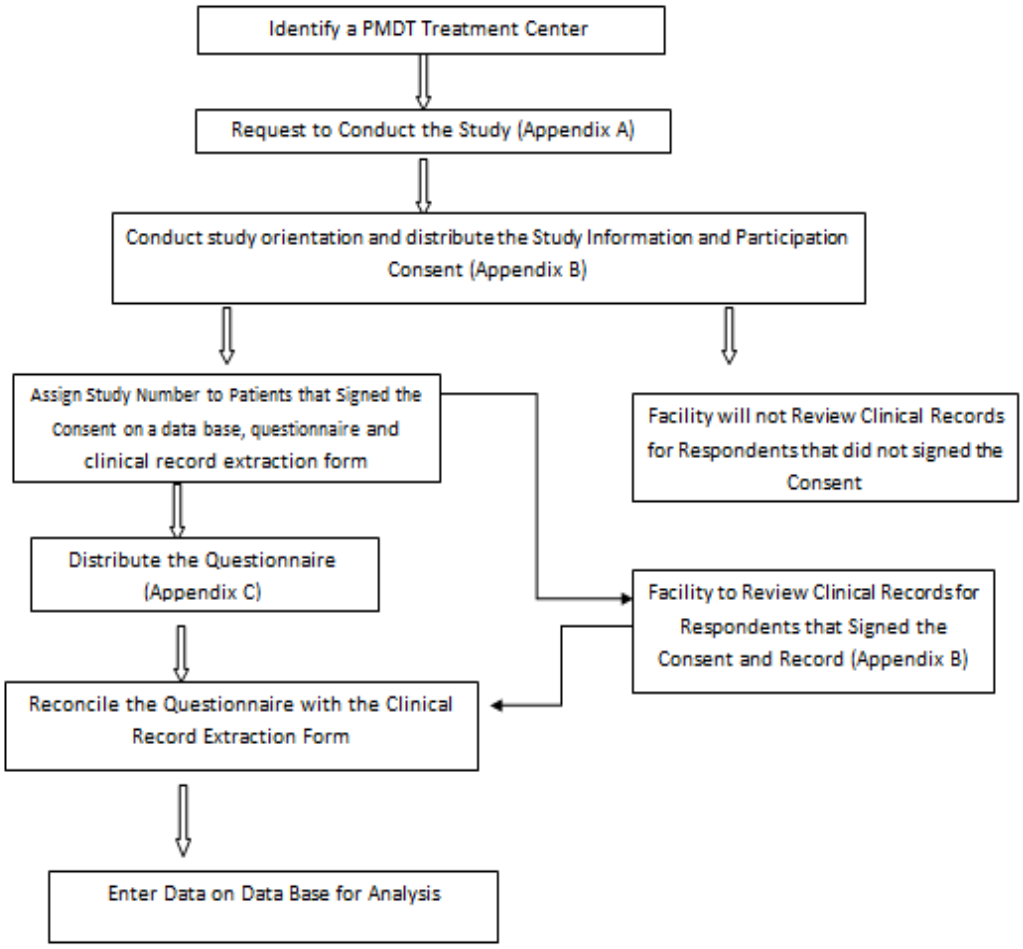


Figure 7. Schematic diagram of the Main Study Procedure

Sample Size Selection

Given the need for the researcher to be personally present during interaction with the study subjects, due to the geographical location of the Philippines and accessibility; the I planned to administer the questionnaire to 50 MDR-TB patients and 50 drug-susceptible TB patients. However, to determine the ideal sample size, a priori power analysis based on chi-square test of independence was conducted to determine the minimum sample size required for this study using Gpower 3.1.9.2. Assuming a moderate

effect size (Cohen's w = 0.3) and a significance level of 0.05, the minimum sample size required to detect a significant effect with 80% power is 108. Thus, 54 control subjects among patients with drug-susceptible Tuberculosis, and 54 cases among patients with clinically confirmed MDR-TB was the ideal sample size in this study.

Data Base Development and Analysis

The study assessed the strength of the association between the identified possible risk factors and MDR-TB infection in the Philippines. Specifically, the study examined whether the following independent variables are associated with MDR-TB infection: (a) previous TB treatment; (b) infected with Human Immunodeficiency Virus; (c) exposure to drug-susceptible TB/MDR-TB patient; (d) delayed diagnosis and treatment; (e) employment status; (f) smoking; (g) imprisonment; (h) alcohol abuse and (i) compliance with drug-susceptible TB treatment regimen.

This study attempted to answer the null hypothesis that the MDR-TB infection is not associated with any of the following possible risk factors as determined by the questionnaire: (a) previous TB treatment; (b) infection with Human Immunodeficiency Virus; (c) exposure to drug-susceptible TB/MDR-TB; (d) delayed in diagnosis and treatment; (e) employment status; (f) smoking; (g) imprisonment; (h) alcohol abuse and (i) compliance with drug-susceptible TB treatment regimen. In addition the alternative hypothesis in this study is: MDR-TB infection associated with one or more of the following possible risk factors as determined by the standardized questionnaire: (a) previous TB treatment; (b) infection with Human Immunodeficiency Virus; (c) exposure to drug-susceptible TB/MDR-TB; (d) delayed in diagnosis and treatment; (e) employment

status; (f) smoking; (g) imprisonment; (h) alcohol abuse and (i) compliance with drug-susceptible TB treatment regimen.

Quality Control of Data

To ensure quality control of data obtained through the following steps were strictly followed:

1. Checked and reviewed the questionnaire that was translated into the Filipino language before the study recruit leaves for missing, incomplete or inconsistency of information data.
2. Consistency checked on each questionnaire to determine logic or compatibility of the answer to related questions.
3. A questionnaire with incomplete information or inconsistent information was returned before the study recruit leaves to clarify with the study respondents if the question was understood.
4. Study respondents were not required to change the answer to the question if he/she does not like to do so.
5. Each questionnaire was evaluated against the corresponding clinical record to ensure the respondents satisfy the inclusion criteria.

Data was entered immediately in the database and validated. All completed questionnaire was kept in a secured file.

Database Development and Management

The database was developed by the researcher that contains the independent (possible risk factors) and dependent (outcome) variables under consideration in this

study. Respondents in the database were identified through the pre-assigned study identification number by the investigator. Questionnaire of study respondents with not more than three missing data or inconsistent answer was used in the development of the database. All questions on the questionnaires were pre-coded as shown in Table 2 to facilitate database development and statistical analysis.

Quality control check of data entry was done at each stage of data entry through verification and cross matching of the response entry of the respondents, linkage of study participant study number to the entered data, correct classification of the respondents (i.e. case or control) and hospital or clinic source of the respondents. All data entered was reviewed and verified to ensure its accuracy before the start of the analysis.

Table 2

Measurement Level and Coding for Independent Variables

Variable	Information source	Variable type	Measurement level and coding
Previous TB treatment	B.10-12	Independent	Categorical 1 = Isoniazid (INH) 2 = Ethambutol (EMB) 3 = Rifampicin (RIF) 4 = Pyrazinamide (PZA) 5 = Others 6 = Not answered
Human immunodeficiency virus infection	D.24-25	Independent	Categorical

Continuation Table 2

			1 = yes 2 = No 3 = Not answered
Exposure to drug-susceptible TB/MDR-TB patient			Categorical
	A.1-4	Independent	1 = yes 2 = No 3 = Don't Know 4 = Not answered
Delayed diagnosis and treatment			Categorical
	A.6-8	Independent	0 = 1 week or less 1 = 2 weeks 2 = 3 Weeks 3 = A month 4 = Greater than 1 month 5 = I don't remember 6 = No answer
Employment status	5	Independent	Categorical 1 = Unemployed 2 = Employed 3 = Retired 4 = Not answered
Smoking	F.31-35	Independent	Categorical 1 = Occasionally 2 = Daily 3 = Not answered
Imprisonment	E.27-28	Independent	Categorical 1 = yes 2 = No 3 = Not answered

Continuation Table 2

Alcohol use	G.36-38	Independent	Categorical 1 = Occasional only 2 = Once a week 3 = Every day 4 = Not answered
Compliance with drug susceptible TB treatment regimen	B.13-17	Independent	Categorical 1 = yes 2 = No 3 = Not answered

Data Analysis

Statistical Package for the Social Sciences (SPSS) software (IBM Corporation, 2014) was utilized to facilitate statistical analysis. Description of cases and controls was performed by comparing the study respondent's socio-demographic and clinical risk factors as shown in the table below.

Table 3

Case and Control group socio-demographic and clinical risk factors Comparative

Risk Factors	All Respondents N =	MDR-TB	Drug-Susceptible TB	P value
a) Previous TB Treatment Isoniazid (INH) Ethambutol (EMB) Rifampicin (RIF) Pyrazinamide (PZA) Others Not answered				

Continuation Table 3

(b) Human Immunodeficiency Virus Infection	
Yes	
No	
Not answered	
(c) Exposure to drug-Susceptible TB/MDR-TB patient	
Yes	
No	
Don't Know	
Not answered	
(d) Delayed diagnosis and treatment	
One week or less	
Two weeks	
3 Weeks	
4 weeks	
Greater than 1 month	
I don't remember	
No answer	
(e) Employment status	
Unemployed	
Employed	
Retired	
Not answered	
(f) Smoking	
Occasionally	
Daily	
Not answered	
(g) Imprisonment	
Yes	
No	
Not answered	

Continuation Table 3

(h) Alcohol Use	
Occasional only	
Once a week	
Every day	
Not answered	
(i) Compliance with drug susceptible TB treatment regimen	
Yes	
No	
Not answered	

Comparative Descriptive Analysis

Each of the categorical independent variables was tested to assess the statistical significance of the association with the dependent variable through the application of the chi-square test. A t-test was applied for the independent interval variable. The alpha level was 0.05, such that when $p < 0.05$ it was considered indicative of a statistically significant association with the dependent variable. To address the research question and determine which of the hypothesis is acceptable, the independent variables or risk factors that have a statistically significant association were further analyzed following the odds ratios.

Participants and Data Protection

Approval to conduct the research was obtained from the Walden University Institutional Review Board. Ethical issues required by IRB were strictly observed in the research process. The researcher does not have any personal biases relative to the study that could jeopardize its scientific objectivity; or any conflicts of interest relevant to the

research. To ensure confidentiality of participant's data information the following steps were followed:

1. Participation in the study is voluntary in nature.
2. Study respondents consent was obtained through an informed consent process and signing of the Study Information and Participation Consent form translated in the Filipino language.
3. Study participants were only identified in the questionnaire through Study ID Number.
4. The master database in Excel format was not linked the Study Number to the Name of the respondents and was secured through a password accessible only by the researcher.
5. Study records/files were stored in a secured manner for 5-yrs and then destroyed.
6. The data was presented only in aggregated form; no patient identifiers were included in any reports of results.
7. Written permission was obtained from appropriate authority to access the data needed for the study.
8. A two page summary of the study results was provided to each hospital/clinic from where the study respondents were obtained which will be posted in hospital/clinic public bulletin board. The Philippines Department of Health and the World Health Organization's Regional Office for the Western Pacific (located in Manila, Philippines), and the Philippine Tuberculosis Society

will also be provided with the two-page summary result. If invited to present the study power point presentation will be utilized.

9. I followed the rules required by the hospital/clinic administration during the conduct of the research study.

The study commenced following the stated methodology of data collection and database development, which was approved by the Walden University Institutional Review Board (IRB).

Chapter 4: Results

The analysis performed is presented in this chapter in order to find out if there is an association between MDR-TB infection and the following possible risk factors: previous TB treatment, infection with HIV, exposure to an unknown TB patient, delay in TB diagnosis and treatment, employment status, smoking, imprisonment, alcohol abuse, and/or compliance with the TB treatment regimen.

Chapter 4 will start with the comparative descriptive demographics for Cases and Control patients. Univariate and bivariate analysis of possible risk factors are described in each section.

Data Collection

Data used in the analyses were gathered from MDR-TB and drug-susceptible TB infected respondents using a questionnaire (see Appendix C) that I developed. The informed consent and questionnaire were translated into Filipino language or Tagalog by the Department of Filipino and Philippine Literature of the College of Arts and Letters, University of the Philippines (see Appendix D and E). Permission to conduct the research (see Appendix F) was obtained from the Philippine government administered health center through the Disease Prevention and Control Bureau of the Department of Health (DOH). The study was approved since the research topic is consistent with the research agenda of Philippines DOH's TB program.

Study respondents for the Control group (drug-susceptible TB patients) were recruited from health centers in the towns of Burauen, Tanauan, Capoocan, Barugo, Dagami, and Carigara all located in the province of Leyte in Region VIII (Eastern

Visayas). Approval from the person-in-charge at each health center or TB program was obtained (see Appendix G, H, I, J, K, and L). For some of the MDR-TB patients, I secured the town mayor's consent was secured first because the Mayor's Office also administers town health centers. I performed the administration of the questionnaire in November 2015.

Data for the cases were collected from the town of San Mateo's Programmatic Management of Drug-Resistant TB Health Center. The town is located in the province of Rizal in Region IV-A. Approval from the person-in-charge at each health center or TB program was obtained (see Appendix M). Most study participants within the Cases group were voluntarily recruited from San Lazaro Hospital in March 2016. The San Lazaro Hospital Ethics Review Board endorsed the study (see Appendix N).

The respondent's identification system was applied so that critical information of participants is not present in the questionnaire and in line with Walden University IRB-approved research protocol described in Chapter 3. Data were collected and entered into a database. It was originally proposed that only questionnaires with fewer than three unanswered items would be considered in the database development. However, this would only provide 35 respondents for Control and 43 for Cases, which would not meet the minimum of 54 respondents for each group. To avoid selection bias all the 172 respondents (Control = 93 and Cases = 79) were included in the database development. Inclusion of the entire respondents in the data base development provides a better understanding and documented justification as to the weakness of the study. In addition, such process provided the foundation for improvements and modifications that will be

stated in the recommendation section of the study in case a similar study is conducted in the future by another researcher. The statistical analyses were performed using statistics described in chapter 3, with the aid of Statistical Package for the Social Sciences (SPSS) software.

Descriptive Epidemiology

In this section, I summarize the demographic profiles of Cases and Controls patients. Sociodemographic characteristics include age, gender, place of birth, education, employment status, and source of income.

Distribution of Controls and Cases. A total of 172 TB patients were recruited. The study population is not representative of all MDT-TB and drug-susceptible TB patients in the country. The Controls group had 93 respondents who were recruited from the different health centers and who voluntarily accepted to answer the study questionnaire. In this group, 44.1% respondents were from the town of Burauen. This is followed by lesser percentages from the towns of Dagami (16.1%), Carigara and Capoocan (12.9%), Tanauan (7.5%), and Barugo (6.5%). The Cases group was composed of 79 respondents. Most (88.6%) of the respondents came from the PMDT section of San Lazaro Hospital, which was selected as a study site because it is one of the DOH hospitals that has been designated to treat MDR-TB. The other respondents were from the health clinics of San Mateo, Rizal (3.8%), Barugo and Dagami (2.5%), and Tanauan and Capoocan (1.3%).

The Philippines, being an archipelago, is generally divided into the three large islands of Luzon, Visayas, and Mindanao. Based on the last population census, which was

conducted in August 2015, Luzon had a population of 57, 470, 097; Visayas, 19,373, 431; and Mindanao, 24,135, 775 (Philippine Statistics Authority, 2015). Inquiry with the Philippine National TB Control Program Management Office revealed that the MDR-TB risk factors that were considered in this study are not obtained as part of data collection on the subnational incidence rate of TB.

The health centers from which Control respondents were recruited are located in the province of Leyte, which is part of the Eastern Visayas region of the Philippines. Most of the respondents in Controls reside in the province of Leyte, 80.1%. Among these respondents, 14.9% were born in Mindanao 4.6% in Luzon. All 79 members of the Cases group answered the question regarding place of birth; 87 of the 93 members of the Control group did so. However, 64.6% of respondents in Cases were born in Luzon, which is where San Lazaro Hospital is located. Some respondents from Cases were born in Mindanao (5.1 %) and Visayas (30.4%). A chi-square test showed a statistically significant difference ($p < 0.0001$) between Cases and Controls regarding place of birth.

Gender. There were 104 male and 68 female respondents. There were 33 (35%) females and 60 (65%) males in the Controls, group and 35 (44%) females and 44 (56%) males in the Cases group. More male respondents was recruited for Controls (60) as compared to Cases (44). There is only a difference of two female respondents between the two study groups. A chi-square test showed that there is no significant difference ($p > 0.05$) between gender distribution or gender profile of the Control and Cases.

Educational Attainment. Comparison of the Cases and Controls respondents educational attainment showed a difference between the two groups. The Cases are

generally more educated having more respondents completed high school and college education. The prevailing educational attainment of the respondents from the Control group is elementary education. The difference in the education profile between Cases and Controls is statistically significant when the Bonferrono correction was applied (p = 0.006) at two levels of education attainment which are elementary and high school.

Table 4

Educational Attainment for Controls and Cases

Educational Attainment	Controls (n = 93)		Cases (n = 79)		Chi square	p value
	Frequency	Percent	Frequency	Percent		
None	6	6.5	2	2.5	1.48	0.22
Elementary	70	75.3	33	41.8	19.95	0.00
High School	0	0	20	25.3	26.64	0.00
College and Masters[a]	17	18.3	24	30.4	3.44	0.06

Note: Pearson Chi-Square, $X^2 = 36.567$
Degree of freedom = 7
Bonferroni's adjustment $p < 0.006$
[a] In the Cases the data for College & Masters were aggregated for this analysis since only 1respondent has a Master's Degree and 0 from Controls.

Table 4 showed that most respondents in the Control group had completed elementary education (75.3%), followed by college degree (18.3%), some did not complete elementary education (6.5%). Out of the 79 respondents with MDR-TB infection 2.5% did not complete elementary education which is generally provided free by the Philippine government. Most of the respondents in the Cases completed elementary education (41.8%) followed by college and master's degree (30.4%). The respondents in the Cases group that completed high school education is 25.3%, and those that did not complete the free elementary education is 2.5%.

Age Profile. Table 5 and Figure 8, show that in the Control group the respondent's age, ranged from 18 to 89 years old (Mean = 50.8, Std. Dev = 17.4). The male respondent's minimum and maximum age are 18 and 80 years old respectively with a Mean of 49.7 and Standard Deviation of 16.2. The female respondent's minimum and maximum age are 19 and 86 respectively, with a Mean of 52.9 and Standard Deviation of 19.3. The t- test showed that there is no statistical difference (p = value 0.25, t = 0.8373, df = 91) among the female and male respondents age in the Control group.

The male respondents in the Cases had a minimum and maximum ages of 18 and 71 respectively, with a Mean of 43.1 and Standard Deviation of 13.6. However, among the females, 19 and 63 are the minimum and maximum ages respectively. The Mean age is 35.7 with a Standard Deviation of 12.8. Statistical analysis showed that there is a difference (p = value 0.02, t = 2.4602, df = 77) among the female and male respondents in the Case group with females statistically significantly younger than the males.

It was observed that MDR-TB respondents are of younger age compared to Drug Susceptible TB (Table 5 and Figure 8). The Cases are younger with a Mean age of 39.8 while the Control is 50.8 (t-test, $p<0.001$).

Table 5

Age Distribution of Controls and Cases

Age Group (years)	Controls (*n* = 93)		Cases (*n* = 79)	
	Percent	Cumulative Percent	Percent	Cumulative Percent
18-23	7.5	7.5	13.9	13.9
24-29	5.4	12.9	13.9	27.8
30-35	9.7	22.6	16.5	44.3

Continuation Table 5

36-41	9.7	32.3	11.4	55.7
42-47	11.8	44.1	13.9	69.6
48-53	10.8	54.8	12.7	82.3
54-59	10.8	65.6	10.1	92.4
60-65	12.9	78.5	3.8	96.2
66-71	7.5	86	3.8	100
72-77	7.5	93.5		
78-83	5.4	98.9		
84-89	1.1	100		
Summary	Mean: 50.8	Std. Dev: 17.3	Mean: 39.8	*Std. Dev*: 13.7

Note: t test = 4.5817
95% CI of 6.29 - 15.81
p-value = < 0.001
Statistically significant difference in the age profile of the Controls and Cases.

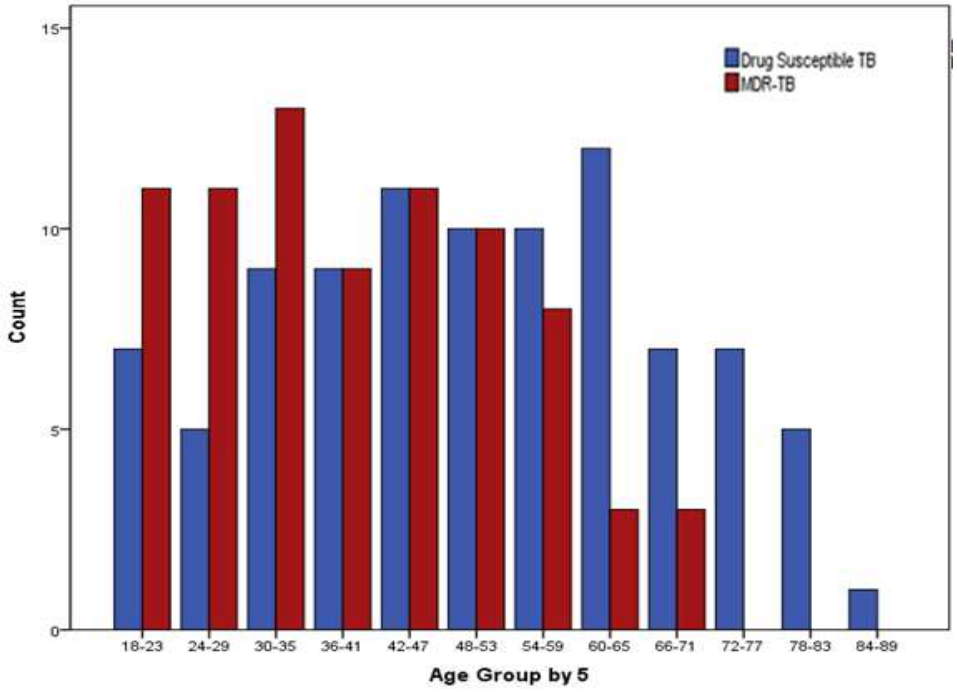


Figure 8. Age of Cases and Controls
Note: Drug Susceptible TB Mean Age = 50.8
Std. Dev. = 17.3
MDR-TB Mean Age = 39.8
Std. Dev. = 13.7

Employment Status and Sources of Livelihood. High unemployment was observed in both Cases and Controls, most of the 93 Controls reported being unemployed and retired (79.6%) and only 18.3% employed (Table 6). However, in the Cases the unemployed and retired is 82.3% with the employed 17.7%. Two Controls did not disclose their employment status. There is no statistically significant difference in employment status between the Control and Cases ($p > 0.88$). Two respondents that did not indicate their employment status were not included in the analysis.

Table 6

Employment Status of Controls and Cases

Employment Status	Controls (n = 93)		Cases (n = 79)	
	Frequency	Percentage	Frequency	Percentage
Unemployed and Retired[a]	74	79.6	65	82.3
Employed	17	18.3	14	17.7
No Answer	2	2.2	0	0

Note: t test = 0.1581
95% CI of -77.28-86.61
p-value = >0.88

Data analysis showed only 17 Control and 14 Cases (18.0% of 172 study subjects overall who provided employment information -- see Table 7) had full time source of livelihood. The primary reasons for unemployment among Controls are health condition and unavailability of employment opportunities in the area.

Only 31 study subjects provided employment income information (14 Cases and 17 Controls). Most of the employed Cases (35.7%) as shown in Table 7 work for various jobs (i.e. furniture working, laborer, a pedicab driver, campaign staff, electrician, sales lady, taxi driver and vendor) as source of livelihood. However, one Case did not disclose

the source of livelihood. Fishing/Farming is the predominant source of livelihood among the employed Controls (52.9%) while Driver (28.6%) and Employment Income (28.6) were most common among the Cases. The probable reason Fishing/Farming is the predominant source of livelihood among the respondents in the Controls, is that the towns in Leyte where the respondents were recruited are either coastal or agricultural area. Driver and Employment income is the predominant livelihood of the Cases because the majority of the respondents were from San Lazaro Hospital. The hospital is located in Manila, a highly populated urban area, and the capital city. Thus this employment profile is consistent with that setting.

Table 7

Controls and Cases that Provided Employment Information

Sources of Livelihood	Control (n = 17)		Cases (n= 14)	
	Frequency	Percent	Frequency	Percent
Business/Employment Income	2	11.8	4	28.6
Fishing/Farming	9	52.9	1	7.1
Driver	0	0	4	28.6
Others	6	35.3	5	35.7

Note: Pearson Chi-Square, $X^2 = 11.460$
Degree of freedom = 7
p-value = 0.12
Others include: Furniture Making, Laborer, Painter, Pedicab Driver, Campaign Staff, Electrician, Sales Lady, Taxi Driver, and Vendor

The result of the Pearson Chi-Square test indicates there is no statistically significant difference between the ages of the respondents in the Controls and Cases relative to their employment status (Table 8). Among the Controls, only 17 respondents are employed; five were between ages 48 to 53. This could be attributed to their health

conditions and unavailability of job opportunity in the area where the Control respondents reside. The data in Table 8 revealed that of the total 14 respondents who are employed in the Case group; six were between ages 18-35. This could be attributed as well to their health conditions and unavailability of job opportunity in the area where the Cases respondents reside.

To compare the age of controls and cases in relation to employment status, raw data for age was utilized to perform the t test. The t test results indicated the following conclusions: the mean age of employed and unemployed respondents is not statistically different from both Controls and Cases, and the mean age of Cases is lower than the mean age of Controls for both employed and unemployed.

Table 8

Comparative Age Group Distribution Between Controls and Cases in Relation to Employment Status

Age (years)	Controls[a,c]		Cases[b,d]	
	Unemployed[e] (n = 72)	Employed[f] (n = 17)	Unemployed[e] (n = 60)	Employed[f] (n = 14)
18-23	7	0	10	1
24-29	5	0	8	3
30-35	8	1	10	2
36-41	7	2	**7**	**2**
42-47	10	1	6	4
48-53	4	5	8	1
54-59	8	2	8	0
60-65	8	3	2	0
66-71	6	1	1	1
72-77	5	1		

continuation Table 8

78-83	4	1		
Mean Age	48.8	55.4	38.9	38.9
St.Dev Age	17.8	12.7	13.5	12.7

Note:

[a] Relationship of Age to Employment status of Controls
Pearson Chi-Square, $X^2 = 12.326$
Degree of freedom = 10
p - value= 0.26

[b] Relationship of Age to Employment status of Cases
Pearson Chi-Square, $X^2 = 0.99$
Degree of freedom = 8
p - value = 0.42

[c] Comparison of Age between Unemployed and Employed Controls
t = 1.43
df = 87
CI= -15.68 to 2.56
p - value = 0.16

[d] Comparison of Age between Unemployed and Employed Cases
t = 0.007
df = 72
CI= - 7.93 to 7.88
p - value= 0.99

[e] Comparison of Age between Unemployed Cases and Controls
t = 3.622
df = 130
CI= 4.35 to 15.43
p - value = 0.001

[f] Comparison of Age between Employed Cases and Controls
t = 3.579
df = 29
CI= 7.04 to 25.81
p - value= 0.001

Hypothesis Testing

The research question in the study is to find out if there is an association between MDR-TB infection and the following possible risk factors: Previous TB Treatment, Infected with Human Immunodeficiency Virus, exposure to drug-susceptible TB/MDR-

TB patient, delayed in diagnosis and treatment, employment status, smoking, imprisonment, alcohol abuse, and compliance with TB treatment regimen.

The null hypothesis (H_0) and alternative hypothesis (H_1) were formulated to objectively identify which of these possible risk factors are associated with MDR-TB infection. The 0.05 alpha or pre-set level of statistical significance was used to which all the p-values were compared to determine whether or not to reject the null hypothesis.

Analysis of probable risk factors for Multi-Drug Resistant TB infection was done consistent with the Case-Control design. The Cases are respondents with MDR-TB and Controls are the respondents with Drug Susceptible TB. Comparison of these risk factors was made between Cases and Controls.

Table 9 shows the results of the assessment whether there is an association of the pre-identified potential risk factors in this study to MDR-TB infection. Chi Square test was used for risk factors with large cell sizes, i.e. Previous TB treatment, Delayed Diagnosis, Exposure to Drug Susceptible TB/MDR-TB patient, Smoking, Compliance with drug susceptible TB treatment regimen and Employment Status. Fisher exact test was used for risk factors with small cell sizes or whose expected values are less than 5, i.e. HIV, Imprisonment and Alcohol Use. Though it is desirable not to have missing data; missing data are almost present in all quantitative studies (Dong and Peng 2013, Zhu, Ibrahim and Tang 2014). The most prevalent reason for incomplete data is item non-response. This would mean that incomplete information collected from a respondent in which case in this study was; refusal of the respondent to provide information in the questionnaire due to personal reasons, which was respected by the researcher. In this study

missing data was handled following list wise deletion (where the study subject's record was excluded from analysis if an essential data element was missing). This means that complete analysis was performed on answered risk factor while excluding those that were not answered. This approach of dealing with missing data reduced the sample size available for analysis, but provided an unbiased parameter estimate (Dong and Peng, 2013).

Table 9

Candidate Risk Factors p value Between Cases and Controls

Risk Factors	All Respondents	MDR-TB	Drug Susceptible TB	P value	
				Chi-Square Test	Fisher Exact Test
a) Previous TB Treatment	N = 62	n = 26	n = 36		
Isoniazid (INH) + Ethambutol (EMB)- Baseline	5 (8.06)	2 (7.69)	3 (8.33)	0.3	
Rifampicin (RIF)	47 (75.81)	22 (84.64)	25 (69.44)		
Pyrazinamide (PZA)	10 (16.13)	2 (7.69)	8 (22.22)		
(b) Human Immunodeficiency Virus infection	N = 120	n = 73	n = 47		
Yes	4 (3.33)	4 (5.48)	0 (0.00)		0.15
No	116 (96.67)	69 (94.52)	47 (100.00)		
(c) Exposure to drug-susceptible TB/MDR-TB Patient	N = 102	n = 42	n = 60		
Yes	52 (50.98)	26 (61.9)	26 (43.33)	0.33	
No	50 (49.02)	16 (38.1)	34 (56.67)		
(d) Delayed diagnosis and treatment	N = 109	n = 44	n = 65		
One week or less - Baseline	26 (23.85)	11 (25.00)	15 (23.08)		
Two weeks	27 (24.77)	12 (27.27)	15 (23.08)	0.91	
3 - 4 Weeks	17 (15.60)	7 (15.91)	10 (15.38)		
Greater than 1 month	39 (35.78)	14 (31.82)	25 (38.46)		

Continuation Table 9

(e) Smoking					
Occasionally	14 (21.21)	4 (11.43)	10 (32.26)	0.04*	
Daily	52 (78.79)	31 (88.57)	21 (67.74)		

Continuation Table 9

(f) Imprisonment [h]	N = 153	n = 66	n = 87		
Yes	10 (6.54)	5 (7.58)	5 (5.75)		0.75
No	143 (93.46)	61 (92.42)	82 (94.25)		
(g) Compliance with drug susceptible TB treatment regimen	N = 127	n = 70	n = 57		
Yes	107 (84.25)	52 (74.29)	55 (96.49)	0.001*	
No	20 (15.75)	18 (25.71)	2 (3.51)		
(h) Alcohol Use	N = 102	n = 42	n = 60		
Occasional Only + Once a week	94 (92.16)	37 (88.1)	57 (95.0)		0.27
Everyday	8 (7.84)	5 (11.90)	3 (5.00)		
(i) Employment Status	N = 170	n = 79	n = 91		
Unemployed + Retired	139 (81.76)	65 (82.28)	74 (81.32)	0.87	
Employed	31 (18.24)	14 (17.72)	17 (18.68)		

Notes:

* Statistically significant, p – value < 0.05.

[a] 1respondent from Controls and 0 from Cases that answered; others were excluded from the Chi Square test calculation.

[b] Multiple responses (42 from Cases and 0 from Controls) were not included in the calculation. 67 respondents did not answer the question on previous TB treatment.

[c] 52 respondents did not answer the question on HIV testing.

[d] 70 respondents did not answer the question on exposure to Drug-susceptible TB/MDR-TB patient.

[e] The "Don't remember response" excluded 9 (Cases) and 10 (Controls) from the Chi Square test calculation. 44 respondents did

not answer the question of delayed diagnosis and treatment.

[f] Combined the 3weeks and 4 weeks in the calculation for Chi Square, since no (0) respondent from Control was delayed in diagnosis and treatment for 3 weeks.

[g] 106 respondents did not answer the question on smoking.

[h] 19 respondents did not answer the question on imprisonment.

[i] 45 respondents did not answer the question on Compliance with drug susceptible TB treatment regimen.

[j] 70 respondents did not answer the question on alcohol use.

[k] 2 respondents from Controls did not provide employment status information.

The Chi-Square test results as shown in Table 9 revealed that previous TB treatment with p-value of 0.30 is not a significant risk factor for MDR-TB infection. The 68 respondents that did not answer on previous TB treatment question were not included in the calculation. The 42 Cases with multiple responses to the question (previous TB treatment) and 0 from Controls is consistent with the Cases having been previously treated for Drug susceptible TB. Multiple responses were also not included in the analysis since this is only selected by Cases and not by Controls. TB treatment in the Philippines is provided by the Department of Health free of charge through the various town health centers and government hospitals. The drug treatment formulation could be fixed-dose combination (HR-Isoniazid and Rifampicin, HRE-Isonizid, Rifampicin and Ethmbutol, HRZE- Isonizid, Rifampicin, Pyrazinamide and Ethmbutol) or single drug formulation which could be either as tablet, syrup or injectable (Streptomycin) form (Philippine Department of Health- Manual of Procedures for the National TB Control Program, 2013).

HIV as a risk factor for MDR-TB infection is shown not to be statistically significant ($p = 0.15$). The 52 respondents that did not indicate in the questionnaire if they have been tested for HIV were not included in the calculation. Data showed that in the study population, 4 from Cases were found to be HIV positive compared to 69 which are HIV negative. The HIV data was confirmed by the healthcare provider through the Clinical Record Extraction Form designed for this study. The 52 respondents that did not indicate if they have been tested for HIV were confirmed by the health care provider. HIV testing for TB patient is generally not required in the Philippines. To be tested for

HIV the TB patient should be 15 years old and above and either live in pre-identified high priority for HIV or belong to a high-risk clinical groups. This policy is anchored on the fact that laboratory testing services are centralized in urban areas, inadequate logistics and death rate is not high in TB-HIV target areas (Philippines Department of Health-National TB Control Program, 2014). Refer to page 85 for further discussion of this issue.

Exposure to Drug-susceptible TB/MDR-TB patient as a risk factor for MDR-TB infection is shown in Table 9 as not statistically significant (p - value = 0.33). Survey showed that in Cases, the exposure to Drug-susceptible TB/MDR-TB infected person was described by Cases as being from friends with once in a while contact (7), house mate with every month contact (14), house mate with once in a month contact (3) and work place with once in a while contact (2). Among Controls, exposure to Drug-susceptible TB/MDR-TB patient was described by Controls as being from: house mate with every month contact (4) and with once in while contact (10), friend with once in while contact (5), work place with once in a while contact (4), cockfighting arena with once in a while contact (1), store with once in a while contact (1), and 1 respondent did provide the source and frequency of contact to the person with TB that might have cause the respondent to get infected with the disease. As shown in Table 10, a total of 52 respondents answered yes to the TB/MDR-TB contact or exposure question while 50 respondents answered no. However out of the 172 respondents in the study, 70 respondents did not answer the questions on Exposure to Drug-susceptible TB/MDR-TB patient; making it susceptible to possible bias. Delayed diagnosis and treatment as a risk

factor for MDR-TB infection as shown in Table 9 is not statistically significant (p = 0.91). It was observed that most of the respondents (35.78%) sought medical diagnosis and treatment after more than a month of experiencing the signs and symptoms of TB. This finding is reflective of the Department of Health -National TB Control Program, updated 2010-2016 Philippine Plan of Action to Control Tuberculosis wherein it states that the TB smear-positivity rate is only 15% nationally, with a wide variance of over 30% from the test results provided by the various Local Government Unit Health Centers. The report attributed the low national TB smear-positivity rate due to lack of TB symptoms awareness, unwillingness to provide sputum for *M. tuberculosis* diagnosis, and most likely case findings, in general, is not yet as rigorous compared to other countries because of resource limitation. The Philippines TB smear-positivity rate is lower compared to a smear positivity meta –analysis study done among pediatric and adult TB patient wherein pediatric TB cases, the TB smear-positivity rate of 6.8% and 52.0% among adult TB cases in 14 countries (Kunkel et al., 2016). One potential reason cited why the smear-positivity rate is low in the Philippines was that the standardized staining protocols are not available at the peripheral level resulting in variable practices that impact on overall smear quality and results in addition to the not fully functional quality assurance system for smear microscopy (Philippines Department of Health -National TB Control Program, 2014). The key to TB control is early detection before it progresses into the contiguous state. One of the limitations of the direct smear using the sputum was that it could not detect the presence of paucibacillary TB. The presence of paucibacillary

bacteria is below the detection limit in direct smear test, this lead into a smear-negative result among pediatric, extra pulmonary tuberculosis (Restrepo; et.al, 2006).

Among the 44 Cases who answered the question (if they seek immediate medical help upon experiencing TB infection symptoms) only 8 indicated the reasons while 36 did not answer the question. The reasons respondents provided for not immediately seeking medical attention are: no money for transportation (1), ashamed of the infection (1), works (2), No budget or money (4). A total of 65 Controls answered the question. However only 8 indicated the reasons why they did not seek immediate medical help. The reasons given were: did not mind the symptoms (1), don't know of TB symptoms (1), forgetfulness (1), financial (2), no money for transportation (1), going to die anyway (1), and don't know that coughing is one of the TB infection symptoms (1).

Smoking was found to be associated with MDR-TB infection as shown in Table 9 ($p = 0.04$). Data indicated that the null hypothesis which is smoking is not a risk factor for MDR-TB infection is rejected. However, Bonferroni correction was not performed because there is no risk of type 1 error (rejecting the null when the null is, in fact, true) since there were only two categories of comparison on the frequency of smoking which is occasionally and daily (Lesack and Naughler, 2011).

The total study population that reported being a smoker before TB infection was 66. Some respondents smoke daily (52 respondents), while some on an occasional basis (14 respondents). Data showed that out of the 93 Cases, and 79 Controls in the study population, 58 and 48 respectively did not answer the question if they are smoking before infected with TB.

A total of 10 respondents in the study population reported having been imprisoned while 143 did not experience imprisonment. The SPSS results for imprisonment (Table 9) as a potential risk factor candidate for MDR-TB infection, showed that it is statistically not significant ($p = 0.75$).

Compliance with drug susceptible TB treatment regimen as a risk factor is associated with MDR-TB infection ($p = 0.001$). Data indicated that the null hypothesis which is compliance with drug susceptible TB treatment regimen is not a risk factor for MDR-TB infection is rejected. However, Bonferroni correction was not performed because there is no risk of type 1 error (rejecting the null when the null is, in fac,t true) since there were only two categories of comparison which are yes and no (Lesack and Naughler, 2011). A total of 107 respondents both from Cases (52) and Controls (55) reported complying with the TB treatment regimen which is administered through the DOT (Directly Observed Therapy). It was observed that out of the 172 total study respondents, 45 (9 Cases, 36 Controls) did not answer on compliance with TB treatment regimen. However, 18 MDR-TB respondents did not previously follow the drug susceptible TB treatment regimen for various reasons. Five did not indicate the reasons for not following the TB treatment regimen while 13 gave the following reasons: work schedule (1), financial (1), drug side effect (1), feel lazy (2), shy for people to know about the infection(1) , was told by the doctor to stop for a reason that the respondent don't remember (1), health care provider not strict(1), vomited blood after 5 months(1), no money (1), no more coughing(1), still feel ok (1) and feels ok after taking some of the

treatment (1). Thought TB infection is gone and cannot sleep were the reasons cited by two Control respondents for not complying with the treatment regimen.

The Fisher Exact test result for alcohol use ($p = 0.27$) and Chi-square test result for employment status ($p = 0.87$) (Table 9) as a potential risk factor candidate for MDR-TB infection showed not statistically-significant. Data showed that more respondents from Controls (43) drink alcohol occasionally than the Cases (27). More respondent in the study population (139) are either unemployed or retired when compared to those who are employed (31).

This study aimed to determine if the identified risk factors were associated with MDR-TB infection. The association was measured using Odds Ratio (OR) in which the precision is estimated by the value of the 95% Confidence Interval (CI). Thus if the OR between Cases and Controls groups is 1, this indicated that there was no difference between the two groups relative to the risk factors under consideration. However, if the OR is > 1, this indicates that the risk factor under consideration affects an increase in Cases rather than Control, and vice versa if the OR is < 1. If the CI is narrow, OR is more precise when compared to a CI value that is broader (Szumilas, 2010).

A validation of the Chi Square statistical results was performed using the Odds Ratio (Table 10) which is the ideal statistical test for Case Control design. Results showed that the OR values and Chi-Square test results are consistent with each other, that is, possible risk factors deemed significant based on the Chi Square test have OR 95% CI which do not contain 1.

Table 10

Candidate Risk Factors Odd Ratio to MDR-TB Infection

Risk Factors	Odds Ratio	95% CI	
		Lower	Upper
a) Previous TB Treatment [a]			
Isoniazid (INH) + Ethambutol (EMB) – Baseline			
Rifampicin (RIF)	1.32	0.202	8.639
Pyrazinamide (PZA)	0.375	0.035	3.999
(b) Human Immunodeficiency Virus infection			
Yes – Baseline	0	0	0
No			
(c) Exposure to drug-susceptible TB/MDR-TB Patient			
Yes – Baseline	0.471	0.21	1.053
No			
(d) Delayed diagnosis and treatment [b]			
One week or less - Baseline			
Two weeks	1.091	0.368	3.235
3 - 4 Weeks [c]	0.955	0.276	3.299
Greater than 1 month	0.764	0.276	2.11
(e) Smoking [d]			
Occasionally – Baseline	3.69*	1.021	13.341
Daily			
(f) Imprisonment			
Yes – Baseline	0.744	0.206	2.684
No			
(g) Compliance with drug susceptible TB treatment Regimen[e]			
Yes – Baseline	9.519*	2.104	43.059
No			
(h) Alcohol Use			
Occasional Only + Once a Week – Baseline	2.568	0.579	11.392
Everyday			

Continuation Table 10

(i) Employment Status			
Unemployed + Retired – Baseline	0.938	0.429	2.049
Employed			

Notes: * Significant in Chi-Square p value < 0.05

[a] 1 respondent from Controls and 0 from Cases that answered Other was excluded from the Odds Ratio calculation.

[b] The Don't remember response 9 (Cases) and 10 (Controls) were excluded from the Odds Ratio calculation.

[c] Combined the 3weeks and 4 weeks in the Odds Ratio, since no (0) respondent from Control was delayed in diagnosis and treatment for 3 weeks.

[d] Drug Susceptible TB patients who are daily smokers is 3.69 x more likely to have MDR-TB infection than occasional smokers. The OR is statistically greater than 1 because the 95% CI does not contain 1.

[e] Drug Susceptible TB patient who does not comply with the treatment regimen is 9.519 x more likely to have MDR-TB infection than those who comply with the Drug Susceptible TB Treatment Regimen. The OR is statistically greater than 1 because the 95% CI does not contain 1.

Based on the Chi-Square test in Table 9, the 2 significant risk factors for MDR-TB infection were: Smoking (p - value = 0.04) and Compliance with drug susceptible TB treatment regimen (p - value = 0.001). The same two risk factors as shown in Table 10 have 95% confidence interval not containing 1, i.e. Smoking (1.021, 13.341) and Compliance with drug susceptible TB treatment regimen (2.104, 43.059).Drug susceptible TB patient who are daily smokers (OR 3.69) are three times more likely to develop a MDR-TB infection than those who smoke occasionally. Additionally, respondents who did not comply with or adhere to drug susceptible TB treatment regimen (OR 9.519) are nine times more likely to develop a MDR-TB infection than those who regularly follow the treatment for drug susceptible TB infection.

Summary

This research attempted to answer the research questions (s) if there is association between MDR-TB infection and the following possible risk factors: (a) previous TB treatment, (b) infection with Human Immunodeficiency Virus, (c) exposure to TB patient, (d) delayed TB diagnosis and treatment, (e) smoking, (f) imprisonment, (g) compliance with the TB treatment regimen, (h) alcohol abuse, and (i) employment status. The data presented in this chapter using Chi Square test was applied to risk factors with large cell sizes, i.e. Previous TB treatment, Delayed Diagnosis, Exposure to Drug Susceptible TB/MDR-TB patient, Smoking, Compliance with drug susceptible TB treatment regimen and Employment Status. Further, Fisher exact test was used for risk factors with small cell sizes or whose expected values are less than 5, i.e. HIV, Imprisonment and Alcohol Use.

Given the data collected from the study, results showed that smoking and compliance with drug susceptible TB treatment regimen are the potential risk factors associated with MDR-TB infection. The data in this study indicated that drug susceptible TB respondents who do not comply with anti TB treatment regimen are nine times more likely to develop MDR-TB when compared to those who regularly follow the treatment regimen. Further, it was also found out from the analysis of the data that drug susceptible TB respondents who smoke on a daily basis is three times more likely to develop a MDR-TB infection. It is reasonable that smoking is a risk factor for MDR-TB infection, because one of the general adverse effects of smoking to the body includes inflammation and which impairs immune function (Center for Disease Control and Prevention (2014).

The ability to fight infectious disease such as MDR-TB of a person with impaired immune system is compromised or entirely absent. Data in the study indicated that risk factors such as previous TB treatment, infection with Human Immunodeficiency Virus, exposure to TB patient, delayed TB diagnosis and treatment, imprisonment, alcohol abuse, and employment status were not associated with MDR-TB infection. Discussions, recommendations, potential social implications as well as the recommendations for further research are discussed in Chapter 5.

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction

The purpose of this quantitative study was to find out if there is an association between MDR-TB infection and the following possible risk factors: (a) previous TB treatment, (b) infection with HIV, (c) exposure to a TB patient, (d) delayed TB diagnosis and treatment, (e) smoking, (f) imprisonment, (g) compliance with the TB treatment regimen,(h) alcohol abuse, and (i)employment status. The study was anchored in the epidemiological theory of John Snow. He pioneered the epidemiological approach to causal inference work with an emphasis on the evaluation of preventive, ameliorative, and curative interventions (Fine et al., 2013). The theory provided an understanding of the agent, the environment, and the host as a framework for the dynamics of disease transmission.

A case-control design was followed, wherein MDR-TB respondents were assigned to one group (Cases) and drug-susceptible TB respondents to another group (Controls). Data were obtained using a self-administered survey questionnaire that I designed for the study. The questionnaires included demographic information and risk factors sections. Controls and Cases were selected based on the eligibility criteria mentioned in Chapter 3. They voluntarily participated in the study.

Members of the Controls group were from towns of Burauen, Dagami, Carigara, Capoocan, Tanuan and Baguro. The towns are located in the Visayas region of the Philippines. The majority (88.6%) of the Cases were from the PMDT section of San Lazaro Hospital, which is one of the hospitals designated by the Philippine Department of

Health hospitals to treat MDR-TB patients. Some of the Cases respondents were recruited from the health clinics of San Mateo, Rizal, Barugo and Dagami, and Tanauan and Capoocan.

It was originally proposed that only questionnaires with less than three unanswered items would be considered in the database development. However, because of logistic problems in obtaining more respondents, potential selections bias, and to better provide justification as to the weakness of the study, all answers from the 172 study respondents (93 Controls and 79 Cases) were included in the analyses.

Statistical analysis using chi-square and Fisher Exact tests and Odd Ratio were performed. Complete data analysis was performed concerning risk factors. The results of the multiple regression analysis show that smoking and compliance with drug susceptible anti TB treatment regimen were associated with MDR-TB infection. Drug susceptible TB respondents who smoke daily are three times (OR 3.690) more likely to develop a MDR-TB infection. Similarly, drug-susceptible TB respondents who do not comply with the treatment regimen are nine times (OR 9.519) more likely to develop a MDR-TB infection. Risk factors such as previous TB treatment, infection with HIV, exposure to TB patient, delayed TB diagnosis and treatment, imprisonment, smoking, alcohol abuse, and employment status were not associated with MDR-TB infection (see Table 10).

Interpretation of the Findings

Data in this study suggest that the type of anti TB drug that the respondents had been previously taking is not a significant risk factor ($p = 0.30$) for MDR-TB infection. Conversely, as discussed in Chapter 4, Mtb drug resistance to anti-TB medicine was

identified among patients with relapse treatment to Streptomycin in 1944 (Keshavjee & Farmer 2012). The drug resistance was attributed to the disruption of the drug mechanism target for bacterial protein synthesis (Goldberg, Siliciano, & Jacobs, 2012). WHO in 1994 initiated the Global Project on Anti-Tuberculosis Drug Resistance Surveillance to track the prevalence of Streptomycin resistance. Project developers systematically collected and analyzed data from 114 countries that reported first-line anti-TB drug resistance (WHO, 2009). WHO data showed that the highest level of anti-TB drug resistance is in Europe (WHO, 2010)

From the biological mechanism aspect, one has to consider the ability of the organism to develop mutation or evolution, if the TB patient is taking substandard, falsified anti-tuberculosis drugs, and failure to follow the prescribed treatment regimen. The presence of substandard, falsified first line anti-tuberculosis drugs such as isoniazid and rifampicin is present in Africa (10.1%), India (10.1%) and other middle-income countries (3.9%; Bate et.al, 2013). The Philippines Food and Drug Administration detected in 2012 a substandard first line anti TB drug that was part of the fixed dose combination procured from a local manufacturer (Philippine Department of Health - National TB Control Program, 2014).

To avoid possible mutation or evolution of the *Mtb* organism into a drug-resistant strain, Zhao et. al. (2012) and Chen et al. (2013) underscored the importance of a high-quality standard antibiotic treatment and a strict follow-up to ensure adherence by patients to the prescribed regimen. Though DOTS is implemented in the Philippines, the Joint Program Review observed that in some areas of the country irregular treatment

increased the risk of drug resistenace (Philippine Department of Health -National TB Control Program, 2014).

The 172 respondents in this study, only 104 and 68 respondents answered and did not answered respectively, the question on previous TB treatment,which may have biased the study findings. The Chi-square test showed that there is no statistical significance difference ($p = 0.89$) between the Cases and Controls of the respondents that answer the question in relation to previous TB treatment. The researcher expected the respondents from the Controls to select no as an answer in the questionnaire especially for first time diagnosed with Drug Susceptible TB. However, some respondents refused to answer the questions despite the explanation provided by the researcher during the review of the questionnaire. As a matter of ethical consideration refusal of the respondents to provide an answer to an item in the questionnaire was profoundly respected by the researcher. The aforementioned finding is not similar to the studies performed by Daniela and Osmand (2011), and Skrahina et. al., (2013), wherein previous TB treatment is a risk factor for MDR-TB infection in a study done in South West Nigeria and Belarus respectively.

An immunocompromised patient such as those with HIV is highly susceptible to TB infection which results in TB being a common comorbidity of HIV infection. To better manage coinfection, WHO requires that key populations have the same access to tuberculosis (TB) prevention, screening and treatment services as other populations at risk of or living with HIV (WHO, 2016). In the Philippines HIV testing among TB patient is required among patient above 15 years old, living in pre-identified priority

areas and belong to high risk group (Philippines Department of Health-National TB Control Program, 2014). The aforementioned PDOH policy is not aligned with the WHO guidelines regarding routine HIV testing of all persons diagnosed with TB, and testing all HIV-infected persons for evidence of *Mtb* infection. In this study,out of 172 respondents only 120 provided HIV statsus and it was found that HIV infection was not associated with MDR-TB infection. This could be attributed to the fact that most of the Control respondents were from the different towns of Leyte (Eastern Visayas) which is not listed as one of the Philippines Department of Health (PDOH) HIV testing priority areas. The respondents in the Cases reside from the different parts of Metropolitan Manila which are a PDOH priority area for HIV testing besides being infected with MDR-TB (a high priority itself). The Updated 2010-2016 Philippine Plan of Action to Control Tuberculosis recommended strengthening the HIV diagnosis among TB patient even if the death rate is not high in TB-HIV target areas (Philippine Department of Health - National TB Control Program, 2014). HIV testing among TB patient is not a requirement for all TB patients. This is consistent with the WHO Western Pacific Region data (Figure 9); wherein in 2014 out of 250,000 newly registered TB cases only 50,000 were tested for HIV despite being one of the fastest-growing HIV epidemics in the world (World Health Organization Western Pacific Region, Philippines– Country profiles on HIV/AIDS, n.d.b)

*Figure 9***.** HIV Testing Among Newly Registered TB Patient in the Philippines in 2013 and 2014. Adopted from: World Health Organization Western Pacific Region, Philippines– Country profiles on HIV/AIDS (n.d.b).

The general mode of MDR-TB and Drug Susceptible TB transmission is through inhalation of the *Mtb* tubercle bacilli that is present in the microscopic droplets from an active TB infected person's which are expulsed by coughing, sneezing, speaking, singing, or laughing (Versaalovic et al., 2011;National Institute of Allergy and Infectious Diseases,2010). Analysis of the data obtained from this study, found that self-reported exposure to drug-susceptible TB/MDR-TB patient was not a risk factor for MDR-TB infection ($p = 0.07$); however out of the 172 respondents, only 102 answered the question on exposure to drug-susceptible TB/MDR-TB patient. Results of the Chi-square test revealed no statistical difference ($p = 0.95$) between those respondents in the Cases and Controls that provided answers to the questions relative to exposure to drug-susceptible TB/MDR-TB patient. Conversely, following the scientific evidence of TB diseases transmission, it is clear that exposure to drug-susceptible TB/MDR-TB is a risk factor. This was found out in a study conducted in Kazakhstan where most study respondents with MDR-TB infection had previous contact with the patient with drug-susceptible TB or MDR-TB (Terlikbayeva et al., 2012).

In the Philippines diagnosis and treatment of TB is provided free by the government through various government hospitals and municipal health centers. It was found out in this study that though delayed diagnosis and treatment (from the onset of TB symptoms) is not associated with MDR-TB infection; 38.78% of the respondents sought medical help after more than one month of experiencing the signs and symptoms of the disease. The primary reason patients shared is financial constraint for one has to spend for the transportation in going to health centers. Most of the study respondents from the Controls reside in far flung areas of the town where the Municipal Health care provider is stationed. Going to the clinic requires a tremendous task of sacrifice especially if the area (Barrio) that the patient live does not have an accessible road. Some patients told the researcher that they would rather spend their money to buy rice (a basic staple food in the Philippines) rather than to pay for the transportation for in this manner more family member will benefit. Delay to a timely care seeking was attributed to stigma to the diseases, lack of proximity to health centers and treatment partners and the perceived high cost of TB treatment (Philippine Department of Health -National TB Control Program, 2014).

The predisposition of an infectious communicable disease should not only be evaluated and assessed from a biological perspective but equally important is from the various socio cultural, economic, behavioral factors that may have triggered an increase in disease susceptibility (Berkman, L. F. & Kawachi, I., 2005). Smoking, imprisonment, compliance with drug susceptible TB treatment regimen, alcohol use, and employment

status were among the various socio cultural, economic, behavioral factors considered in this study.

Smoking harms nearly every organ of the body thereby diminished the overall health condition of the person (Butov et al, 2015). In this study, smoking was associated with MDR-TB infection ($p = 0.04$). The researcher noted a low turnout response, wherein only 65 out of 172 respondents provided an answer to the smoking questions. The Chi-square test showed no statistical difference ($p = 0.45$) between those respondents in the Cases and Controls that provided an answer to the question relative to smoking. It can also be inferred from the data in the study that smoking is a generic risk factor for lung disease (i.e. Drug Susceptible TB, MDR-TB). The association of smoking as a risk factor to lung disease is scientifically explained in a study performed in Kharkiv region of Ukraine by Butov, Kuzhko, Makeeva, and Butova, (2015). They found out that smoking leads to mutation of the PM-T-330 gene IL-2 heterozygous type gene that produces white blood cells which are part of the body's natural response to microbial infection.

Besides smoking, compliance with drug susceptible TB treatment regimen was also found to be associated with MRD-TB infection ($p = 0.001$). Chi-square test showed that there is a high statistically significant difference ($p = 0.001$) found between Cases and Control respondents that provided an answer relative to compliance with drug susceptible TB treatment regimen. Despite the implementation of DOTS program by the Philippines Department of Health, per the treatment outcome of 2011 new smear positive cohort the default rate is 4% (Philippines Department of Health -National TB Control Program, 2014). In a study by Smith, Wolff & Nguyen (2013) and Georghiou et al.

(2012); noncompliance to the required TB treatment regimen such as repeated and inappropriate use of antibiotic is a major cause of *Mtb* chromosomal mutation, which then acquires antibiotic resistance specifically to the first line of drug treatment against TB. Chromosomal mutation through horizontal gene transfer alters the original genetic code due to repeated and inappropriate use of antibiotic (Smith, Wolff, & Nguyen, 2013). The use and misuse of antibiotic in which case not following the prescribe TB treatment regimen accelerate the emergence of drug resistant organism strain (WHO, 2015b). Microorganism resistance to antibiotic is a threat to public health. Daniela and Osmand (2011), and Skrahina et. al., (2013) identified in their respective study that history of previous anti-TB treatment is a risk factor for MDR-TB infection. In the Philippines despite the best effort of the Philippine Department of Health to provide free health care services to TB patients and the general population; difficulty in accessing the health care facilities is one of the primary reasons for not following the prescribed treatment. Most of the respondents live in remote areas that going to the town health centers is a big financial and physical sacrifice. Some patients will have to walk miles or ride on a non-motorize boat to reach the town health center. Among the reasons cited by the respondents for not following the TB treatment regimen is the unavailability of the medicine every time they went to health centers. This is confirmed in the report of the Philippines Department of Health -National TB Control Program (2014) wherein medicine procurement challenges are encountered among which are: non-availability of a source for Streptomycin and medicine requested shelf life of 18 months is too short for the manufacturer to provide to the National Tuberculosis Control Program. The reasons

cited by the respondents for not following the TB treatment regimen are: feeling better in the middle of the treatment period, forgetfulness, and side effects of the medicine. The stated reasons are not just confined to the Philippines. Economic barrier and easy access to health which is affected by social and political factors are some of the commonly given reasons why TB globally are still either not diagnosed, or their cases are not reported and can also have a negative impact on treatment adherence (WHO,2015a).

Limitations of the Study

Understanding MDR-TB infection risk factors is very critical in epidemic prevention. The increase in the prevalence rate of MDR-TB infection is of great concern among public health practitioners (Zignol et al., 2012). This study was able to established that in as far as the geographical area in the Philippines where the study was conducted; smoking is a risk factor for MDR-TB infection which is similar to the study conducted by Skrahina et al., (2013) in Belarus and Pant et al., (2009) done in a DOTS-Plus clinic at Bhim Hospital, Bhairahawa . In addition, this study also found out that non-compliance to drug susceptible TB treatment regimen is likewise a risk factors to MDR-TB infection. The finding is a kin to findings of the study conducted by Terlikbayeva et al., (2012) in Kazakhstan and in China by Chen et al., (2013). Smith, Wolff & Nguyen (2013) and Georghiou et al. (2012) in their respective study concluded that noncompliance to the required TB treatment regimen such as repeated and inappropriate use of antibiotic is a major cause of *Mtb* chromosomal mutation.

This research study was able to bring-in together the research constructs in order to understand the possible risk factors of MDR-TB infection in the Philippines. Once the

researcher completed this study there were several aspects that were manifested which forms the limitations to this study and includes the following:

1. The study population is not a representative of the population in the Philippines with Drug Susceptible TB and MDR-TB infection; thus results cannot be extrapolated to the general Philippine population. Participants of this study were from limited geographic areas which are the town health centers located in Leyte, San Mateo Rizal and patients from the PMDT section of San Lazaro Hospital. The limited geographic study area where the study population was recruited poses a threat to the external validity which limits the generalizability of the study results (Creswell, 2009; Babbie, 2007). Therefore, the risk factors associated to MDR-TB infection that was identified in this study could not be applied in some parts of the country.

2. Limited time, and logistical challenges when working without supporting resources (Supplemental staff from within the PDOH). Supporting resource through the use of PDOH staff from the different area of the country could have expanded the geographic area of the study and allow more respondents to participate in the survey. Confirmation of this research should plan for an expanded set of support resources to enable a representative study to be conducted.

3. The questionnaire was not piloted and evaluated within the target population. Questionnaire pilot study followed by evaluation is very critical to discover the discrepancy and is very important in the standardization of the study instrument (Nachmias and Nachmias, 2008).

4. Not all the 172 respondents provided answer to all items in the questionnaire which may have biased the statistical test results. Further, the number of MDR-TB and Drug Susceptible TB respondents were not equal. An equal number of respondents could present a more careful interpretation existing between the variable (Babbie, 2007).

5. The data in the study was obtained through questionnaire that is written in Pilipino which is the national language of the country. This may have limited the number of respondents since even with free elementary education some potential study respondents cannot read and understand Pilipino thus were not able to be part of the study. Understanding the question is very important in survey research in order to provide accurate retrospective data. The questionnaire could have been written in the respondent's dialect so that it is easier and friendlier to the respondents, and could provide a more accurate answer.

6. Multivariate regression analysis could was not performed because of the limited sample size in the study.

Recommendations

The primordial reason why the study was approve by the Philippine Department of Health specifically the National Tuberculosis Control Program was that the topic was in the research agenda of the TB program. Though the conclusion of the study cannot be generally applied in the country because of the limited number of respondents and geographical area covered, however the results of the study can provide baseline information in case a similar nationwide study is conducted by the Philippine Department

of Health. Based on the result of the data analysis gathered from this study, the following are the suggested refinements in order to increase enrollment to the study which will minimize unanswered questions and prevent the increase of MDR-TB infection in the country.

1. Standardize the questionnaire so that the measuring instrument is most appropriate and therefore measures what the study intend to know. In the original proposal, this was part of Phase 1, however, due to the interest of time and geographical location of the study area this was not pursued.
2. The questionnaire should be written in various dialects spoken by the respondents in the area.
3. Obtain assistance from the staff of the health clinic to accommodate large number respondents. Though it has to be noted that the original proposal called for this, but the IRB insisted that the investigator not to utilize support staff in data collection.
4. Data should be collected following a face-to-face interview using the structured questionnaire instead of traditional paper and pencil self-administration.
5. Request assistance from the PDOH staff to facilitate medical record reviews, help with data collection/survey administration/data computerization) to enable inclusion of a much larger representative sample of Pilipino with TB/MDR-TB cases from around the Philippines.
6. Execute a pilot study to evaluate and assess that the aforementioned suggested refinements have improved the response rate, the completion rate, and reduced significantly the amount of missing information (unanswered questions).

7. HIV testing to TB patient in the Philippines is required among patient above 15 years old, living in pre-identified priority areas and belong to high risk group (Philippines Department of Health-National TB Control Program, 2014). The aforementioned PDOH policy is not aligned with the WHO guidelines regarding routine HIV testing of all persons diagnosed with TB, and testing all HIV-infected persons for evidence of *Mtb* infection. I recommend revising current PDOH policy on HIV testing to completely follow the WHO recommendation to prevent premature death of HIV infected person from dying of TB, and avert the dissemination of TB (especially MDR-TB) in the process.
8. It was found out in this study that one of the reasons cited by the respondents for not following the TB treatment regimen is the unavailability of the medicine every time they went to health centers. This is confirmed in the report of the Philippines Department of Health -National TB Control Program (2014) wherein medicine procurement challenges are encountered. The researcher propose that there should be a regular supply of anti TB medicine to various towns' health centers to make certain that DOTS is strictly implemented.
9. Evaluate current system of anti TB medicine delivery to health centers to ensure sustainable supply and ultimately improve patient compliance to treatment.

Implication for Social Change

Tuberculosis is the leading cause of morbidity and mortality in the Philippines Vianzon, Garfin, Lagos, and Belena (2013). On the global scale, the country is the ninth out of the 22 highest TB-burden countries and has one of the highest burdens of MDR-

TB (WHO, 2014a). The emergence of MDR-TB poses a serious threat to TB control in developing countries; besides being difficult and expensive to treat, the disease requires a longer period of treatment. WHO interactive database on the treatment outcomes of MDR-TB cases in the Philippines showed that only 42% of the reported MDR-TB cases in 2010 were successfully treated, 14% died, 2% failed treatment, 36% were lost to follow-up, and 7% were not evaluated (WHO, 2014a).

There is no study in the Philippines on the risk factors of MDR-TB. The Philippine Department of Health through the National Tuberculosis Control Program agreed to approve the conduct of the study since the topic is on the research agenda of the TB program. This study can help inform the planning of future nationwide MDR-TB research through the lessons learned as discuss in the recommendation section of this chapter.

The findings could contribute to positive social change in that they will provide information to individual, TB Control program Director, and health care providers that could help develop programs for drug susceptible TB to stop smoking and comply with the anti TB drug treatment regimen to prevent MDR-TB infection. Further, the result of the study can promote positive social change in that knowing the risk factor can provide guidance to health workers in the identification of high-risk patients for MDR-TB infection. The recognition of potential MDR-TB infected patient may help improve TB case findings considering that the patient could potentially infect immediate members of the family or person that he/she was in contact and which may result in increase of the current national TB smear-positivity rate. Understanding the risk factors related to the

onset of a disease is very critical in epidemic prevention. The persistent increase in the prevalence rate of TB specifically MDR-TB (Zignol et al., 2012) continued to raise concern among public health practitioners. The result of the study can guide in the early identification of MDR-TB infection and treatment which will minimize the detrimental biological, psychological and social effects of the disease.

Another positive social change in the study was that the researcher was able to interact various TB Health Care Providers especially the personnel in the National Tuberculosis Control Program of the Department of Health, Member of the Ethics Committee of San Lazaro Hospital, PMDT Center of San Lazaro Hospital and Staff of the different Towns Health Care Centers. The study provided an opportunity for the researcher to interact with the different TB patients who were very candid and friendly in sharing their thoughts about their current health conditions.

Conclusion

The primary goal of public health practitioner is to prevent the proliferation of MDR-TB in the community. One method that is employed is through case finding using risk factor. As such appreciating, the risk factors related to human infection of MDR-TB is critical in case finding. Understanding the potential risk factor associated to MDR-TB was consistent with the epidemiological theory of John Snow that was applied in this study. He theorized that the cause of communicable disease can be determined using a case-control study design to assess associations between potential risk factors (independent variables) and the outcome (MDR-TB, the dependent variable) (Frerichs, 2009).

Multidrug-resistant *Mycobacterium tuberculosis* accounts for 4.0% of all new cases of TB in the Philippines (WHO, 2013a). Despite such high percentage rate of MDR-TB infection in the Philippines, there is no study done that determine the possible risk factors that contribute to the continued increase of MDR-TB infection in the country. It is for this reason that the Philippine Department of Health through the National Tuberculosis Control Program approved that the study be conducted for the subject of the study is part of the NTP research agenda as well.

This research investigated the possible risk factors that are associated with MDR-TB infection. The risk factors that were considered are: (a) previous TB treatment, (b) infection with Human Immunodeficiency Virus, (c) exposure to TB patient, (d) delayed TB diagnosis and treatment, (e) smoking, (f) imprisonment, (g) compliance with the TB treatment regimen,(h) alcohol abuse, and (i)employment status.

Results were used to answer the research questions which established that drug susceptible TB who smoke on a daily basis are three times likely to develop MDRT TB infection. Further, data in this study indicated that drug susceptible TB patient is nine times more likely to develop a MDR-TB infection if the anti TB treatment regimen is not complied.

There are some limitations to this study that need to be taken into consideration and that could contribute further to literature. Among the limitations was the geographical location of the study area which limits the generalizability of the study results. Another important limitation was to standardize the questionnaire, translate the questions into various dialects, administer through face to face interview by the staff of

the health clinic to accommodate large number respondents and minimize unanswered questions.

The results of this study can add to the literature on MDR-TB infection in the Philippines and as a bench mark for further studies that will be conducted by NTP on the national level. The MDR-TB infection is a preventable disease. Education, health guidance and counselling coupled with effective treatments through strict adherence to DOTS are the keys to decreasing its prevalence.

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Appendix A: Request to Conduct Research

Name of the Clinic/Hospital Administrator
Address of the Clinic/Hospital

Dear Sir/Madam

This letter serves to request for your permission to conduct survey research on drug susceptible TB and MDR-TB patients in your clinic/hospital/organization. I am presently a Ph.D.in Public Health student at Walden University in the United States of America. The title of my study is: "*Possible Risk Factors of Multi-Drug Resistant Tuberculosis Infection Prevention in the Philippines"*. The proposed study will assess the strength of association between several possible risk factors and the MDR-TB infection. The research is done to fulfill the dissertation research requirement of the degree.

Once permission is granted by your good office the following procedure will be followed.

1. The researcher will provide to prospective study recruits the Study Information and Participation Consent (in Filipino Language) and orientation discussion where they are free to ask questions about the study and will be given ample time around an hour to decide.

2. Once potential recruits volunteer consented in the study the researcher will assign a study ID Number which will be entered in the data base, questionnaire and respondent's - clinical record extraction form.

3. The questionnaire that is in Filipino language will be placed inside an envelope and distributed to respondents. The respondents will answer the questionnaire in an area designated by your facility.

4. The respondents will hand over the envelope with the answered questionnaire to the researcher for review and storage.

5. The researcher will provide a list of patient to the clinic/hospital and the envelope with the respondents clinical record extraction form.

6. Clinic/Hospital will be requested to review the patient clinical record to verify whether the patient is either a laboratory confirmed MDR-TB or a laboratory confirmed Drug Susceptible TB, and the most recent HIV test result (if available)

and will be documented in the RESPONDENT'S - CLINICAL RECORD EXTRACTION FORM.

7. The researcher will develop a data base for analysis to answer the research questions.

Findings of the study can be shared to interested parties such as supporting study participants, the supporting TB Centers, the Philippines DOH, and WHO.

No clinical test will be administered to patients who volunteered to be in the study, nor will they be paid or receive any gifts for the participation in the study. It is hoped that the research findings may help prevent others from developing MDR-TB.

The researcher's Dissertation Committee and Walden University's Institutional Review Board (IRB) (identified below) will assure that ethical principles are adhered to throughout the conduct of this research.

Donald Goodwin, DrPH,
Dissertation Committee Chair
Email [redacted]

IRB@waldenu.edu
Walden University
Research Participant Advocate

I hope that my request shall meet your favorable consideration

Yours Faithfully

Molovon P. Azores Jr.
Investigator
Student Ph.D. Public Health
College of Health Sciences
Walden University
E-mail: [redacted

Appendix B: Respondents Clinical Record Extraction Form

Treatment Center: _____

Respondent's Study ID No. _____

A. Drug Susceptibility Testing (DST) Result

_____ No Resistance/Sensitive to Antibiotic

_____ Resistance to Antibiotic

M. tuberculosis/culture has been found resistance to:

_____ Isoniazid (INH) _____ Rifampicin (RIF)
_____ Ethambutol (EMB) _____ Pyrazinamide (PZA)
_____ Others

B. Type of AIDS Test performed (if available): _____

C. HIV test result:

_____Positive _____ Negative

Date Tested: _____

Documented by: _____ Date: _____

Appendix C: Questionnaire

Respondent's Study ID No. _____

MDR-TB: _____ Non-MDR TB: _____

DEMOGRAPHIC INFORMATION

Instruction: Please check the appropriate answer.

1. Gender:
   Male ___ Female: ___ No Answer: _____
2. Age: _____
3. Place of Birth: ____ Luzon _____ Visayas _____ Mindanao
4. What is your highest level of education?
   None: _____ Elementary: _____ High school: _____
   College: _____ Master's: _____ Doctorate: _____
5. What is your employment status?

   Unemployed: _____ Employed: _____
   Retired: _____
6. What is your main source of income?
   Fishing/Farming _____ Employment income _____
   Business enterprise _____ Property Rental _____
   Others, please specify _____

RISK FACTORS INFORMATION

A. Previous exposure to drug susceptible TB/MDR-TB patient, delayed diagnosis and treatment

1. Do you know if you had been in contact or exposed to someone with TB before you got the disease?
   Yes ___ No __ Don't Know ___

2. If "No" or "Don't Know" please skip to Q5.
   If yes where?
   Home ____ Work-place ____ Friends ____ Prison
   ____ Others please specify_____
3. How often were you in contact with someone with TB?
   _____ Occasionally _____ Monthly ___less than Monthly

4. How long had you been in contact with someone with TB before you were diagnosed with TB?
   Less than 2 months _____ 2 to 6 months _____
   More than 6 months ____

5. Please check the symptoms that you had been experiencing before you were diagnosed as having TB.

____ Cough that lasted 3 weeks or longer ____ Pain in the chest
____ Coughing up blood or sputum ____Weakness
____ Fatigue ____ Weight loss
____ No appetite ____ Chills
____ Fever _____Sweating at night
____ Shortness of breath

6. Did you immediately visit a doctor or seek medical help?
   Yes ____ No _____
   If "No", skip to Q8.

7. If yes, How long did it take to visit a doctor?
   One week or less _____ Two weeks _____ 3 Weeks _____
   A month _____ Greater than 1 month_____
   I don't remember _____
8. If you did not seek medical help immediately, why?

Please state: _____

B. <u>Previous TB treatment and compliance with treatment regimen</u>

9. Is this your first time to have TB?
   Yes _____ No _____

   If "Yes", skip to Section D.

10. Have you previously received TB treatment?
    No ____ Yes _____
    If "No", skip to Section C.

11. Do you remember the drug prescribed to you?
    Yes ____ No ____
    If "No", skip to Q13.

12. If yes please, please check the drug prescribed to you by the Doctor.
    _____ Isoniazid (INH) _____ Rifampicin (RIF)
    _____ Ethambutol (EMB) _____ Pyrazinamide (PZA)
    _____ Others
13. Was your treatment supervised by Directly Observed Treatment Short (DOTS) course personnel?
    Yes _____ No _____
14. Did you follow the prescribed treatment regimen?
    Yes _____ No _____
15. Why did you not follow the prescribed treatment regimen? Please specify
    _____

16. Did you complete the treatment?

Yes _____ No _____

If no, why did you stop the treatment? Please specify

_____

C. Human Immunodeficiency Virus

18. Have you been tested for HIV infection?

Yes ____ No ____

19. Have you been told by your doctor that you have HIV?

Yes _____ No ___

20. What month and year were you diagnosed to have HIV _____

21. Were you treated with HIV? _____ Yes No_____

22. If so please check the medicine you took for HIV.

	Agenerase (amprenavir)		Combivir (AZT + 3TC)
	Complera (Truvada + Edurant)		Crixivan (indinavir)
	Edurant (rilpivirine)		Emtriva (emtricitabine)
	Epivir (lamivudine, "3TC")		Fortovase (saquinavir)
	Fuzeon (enfuvirtide)		Hivid (zalcitabine, "ddC")
	Invirase (saquinavir)		Kaletra (lopinavir)
	Lexiva (fosamprenavir)		Norvir (ritonavir)
	Rescriptor (delavirdine)		Retrovir (zidovudine, "AZT")
	Reyataz (atazanavir)		Stribild (Emtriva + Viread + elvitegravir)
	Sustiva (efavirenz		Tivicay (dolutegravir)
	Triumeg (dolutegravir + abacavir + lamivudine)		Trizivir (AZT/3TC/abacavir)
	Truvada (Emtriva + Viread)		Tybost (cobicistat)
	Videx (didanosine, "ddI")		Viracept (nelfinavir)
	Viramune (nevirapine)		Viread (tenofovir)
	Vitekta (elvitegravir)		Zerit (stavudine, "d4T")
	Ziagen (abacavir)	others (please specify)	

D. Imprisonment

23. Have you been in prison?

Yes _____ No _____

24. If yes, what year you went out of prison? _____

E. Smoking

25. Have you ever smoked cigarettes?
    Yes ____ No _____
26. At what age did you start smoking cigarettes? _____
27. Do you still smoke cigarettes at present?
    Yes _____ No _____
28. Do you smoke cigarettes daily or occasionally?
    Daily _____ Occasionally ____
29. How many cigarettes do you consume?
    Less than 1 pack a week _____ 1 pack a week _____
    2 to 3 pack a week _____ More than 3 pack a week _____
    Don't know occasional only _____
30. Did you stop smoking? _____
31. At what age did you stop smoking? _____

F. Alcohol Consumption

32. Do you drink alcohol?
    Yes ____ No _____
33. What type of alcoholic drink do you usually take?
    Beer _____ Wine _____ Liquor/Spirit _____
    Locally made alcohol drink (i.e. tuba, lambanog) _____
34. How often did you drink beer, wine, liquor/spirit or any locally made alcoholic drink (i.e. tuba, lambanog)?

    Every day ____ Once a week _____ Occasional only _____

Appendix D: Translation Validation Form for Study Information and Consent Form

DEPARMENT OF FILIPINO AND PHILIPPINE LITERATURE
College of Arts and Letters
University of the Philippines, Diliman
Quezon City

TRANSLATION VALIDATION FORM

Original Document Title: TB Infection and TB Drug Resistance in the Philippines

Original Document Version/Date: Sept 15 , 2015

Specify language of Original Document: English

Translated Document Version/Date: October 6, 2015

Specify language of Translated Document: Filipino

Translator:

I, **Jimmuel C. Naval,** Ph. D, a professor of language and creative writing have translated and edited the Original Document into Filipino Language. I certify that the translated version of the documents/questionnaire have reviewed thoroughly and are referenced.

Signed: _____ Date: OCT 1 2015

Appendix E: Study Questionnaire Translated into Tagalog

PALATANUNGAN/QUESTIONAIRE

Numero ng ID sa Pag-aaral ng Respondent/Kalahok _____

MDR-TB: _____ Non-MDR TB: _____

MGA IMPORMASYONG PANGDEMOGRAPIYA

Panuto: Lagyan ng tsek ang angkop na sagot.

1. Kasarian : Lalaki _____Babae_____ walang sagot_____
2. Edad: _____
3. Lugar ng Kapanganakan: _____Luzon _____Visayas _____Mindanao
4. Ano ang pinakamataas na antas ng edukasyon na inyong narating?

   Wala : _____ Elementarya _____Mataas na Paaralan
   Kolehiyo _____ Master's _____ Doktorado _____

5. Ano ang inyong istatus pantrabaho?

   Walang trabaho: _____ May trabaho: _____ Retirado _____

6. Ano ang pangunahing pinagkakakitaan?

   Pangingisda/Pagsasaka _____ Kita sa Pamamasukan/empleyo_____
   Negosyo _____ Pagpapaupa ng ari-arian _____
   Iba pa, tukuyin _____

IMPORMASYON KAUGNAY NG MGA SALIK NA PANGANIB

A. Pagkakaroon ng kontak sa mga pasyenteng may TB at Pagkaantala ng Diagnosis at Paggamot ditto.

1. Alam mo ba kung may pagkakataon na nagkaroon ka ng kontak o ng kasama na may TB bago ka pa nagkaroon ng sakit na ito?

   Oo _____ Hindi _____ Hindi alam_____
   Kung Hindi o Hindi alam, lumundag na sa T5.

2. Kung Oo, saan?

   Tahanan _____ Lugar Trabaho_____ Kaibigan_____
   Piitan_____ Iba pa, mangyaring tukuyin _____

3. Gaano ka kadalas nagkakaroon ng kontak sa taong may TB?

   _____Paminsan-minsan _____Buwan-buwan _____ walang isang buwan

4. Gaano ka na katagal may kontak sa taong may TB bago ang diagnosis na ikaw ay may TB?

   Kulang 2 buwan_____ 2-6 na buwan _____
   Higit sa 6 na buwan _____

5. Lagyan ng tsek ang mga simptomas na iyong naranasan bago ang diagnosis na mayroon kang TB?

   _____Pag-ubo na tumatagal ng 3 linggo o mas matagal pa _____Pananakit ng dibdib

_____Pag-ubo na may lumalabas na dugo o sa sputum _____Panghihina
_____Pagkapagod _____Pagbaba ng timbang
_____Walang gana sa pagkain
_____Pangingiki/pagkaranas ng panlalamig ng katawan
_____Lagnat _____Pamamawis sa gabi _____Paghabol ng hininga

6. Kagyat ka bang bumisita sa doktor o humingi ng tulong medikal?
Oo____ Hindi____

Kung Hindi, lumundag na sa T8.

7. Kung Oo, gaano katagal bago ka sumangguni sa doktor?

isang linggo o wala pang isang linggo_____
dalawang linggo _____
Isang buwan _____
higit sa 1 buwan _____
Hindi ko na maalala _____

8. Kung hindi ka humingi ng kagyat na tulong medikal, bakit?

Mangyaring sabihin: _____

B. Dating Paggamot sa TB at Pagsunod sa mga Hinihingi ng Paggamot

9. Ito ba ang unang pagkakataon na nagkaroon ka ng TB?

Oo_____Hindi_____

Kung oo, lumundag na sa Seksiyon D.

10. Dati ka na bang nakapagpagamot para sa TB?

Hindi _____Oo _____

Kung hindi, lumundag na sa Seksiyon C.

11. Natatandaan mo ba ang inihatol na gamot sa iyo?\

Oo_____ Hindi _____

Kung Hindi lumundag sa T13.

12. Kung oo, lagyan ng tsek ang gamot na inihatol ng doktor sa iyo.

_____Isoniazd (INH) _____Rifampicin (RIF)
_____Ethambutol (EMB) _____Pyrazinamide (PZA)

13. Ang inyo bang paggamot ay nasa ilalim ng superbisyon ng kawani ng Directly Observed Treatment Short (DOTS)?
Oo _____ Hindi____

14. Sinunod mo ba ang itinakdang proseso paggamot?

Oo _____ Hindi_____

15. Bakit hindi mo sinunod ang itinakdang proseso ng paggamot? Mangyaring banggitin _____

16. Kinumpleto mo ba ang gamutan? Oo ____ Hindi ____

17. Kung Hindi, bakit mo itinigil ang paggamot? Mangyaring banggitin _____

C. Human Immunodeficiency Virus Infection

18. Kayo ba ay nasuri na para sa HIV infection?
Oo_____ Hindi _____

19. Naipaalam na ba ng inyong doktok na ikaw ay may HIV?
Oo _____Hindi _____
20. Anong buwan at taon kayo nabigyan ng diagnosis na kayo ay may HIV? _____

21. Kayo ba ay nagamot para sa HIV _____Oo _____Hindi

22. Kung Oo, lagyan tsek ang gamot na inyong ginamit para sa HIV.

Agenerase (amprenavir)		Combivir (AZT + 3TC)
Complera (Truvada + Edurant)		Crixivan (indinavir)
Edurant (rilpivirine)		Emtriva (emtricitabine)
Epivir (lamivudine, "3TC")		Fortovase (saquinavir)
Fuzeon (enfuvirtide)		Hivid (zalcitabine, "ddC")
Invirase (saquinavir)		Kaletra (lopinavir)
Lexiva (fosamprenavir)		Norvir (ritonavir)
Rescriptor (delavirdine)		Retrovir (zidovudine, "AZT")
Reyataz (atazanavir)		Stribild (Emtriva + Viread + elvitegravir)
Sustiva (efavirenz		Tivicay (dolutegravir)
Triumeg (dolutegravir + abacavir + lamivudine)		Trizivir (AZT/3TC/abacavir)
Truvada (Emtriva + Viread)		Tybost (cobicistat)
Videx (didanosine, "ddI")		Viracept (nelfinavir)
Viramune (nevirapine)		Viread (tenofovir)
Vitekta (elvitegravir)		Zerit (stavudine, "d4T")
Ziagen (abacavir)	Iba pa, Bang-gitin)	

D. Pagkakapiit

23. Ikaw ba ay nakulong na sa bilangguan?
    Oo_____Hindi _____

24. Kung oo, anong taon ka nakalaya? _____

E. Paninigarilyo

25. Nasubukan mo na bang manigarilyo?
    Oo _____ Hindi _____

26. Anong edad ka nagsimulang manigarilyo? _____

27. Nagsisigarilyo ka pa rin ba hanggang sa kasalukuyan?
    Oo_____ Hindi_____

28. Nagsisigarilyo ka ba araw-araw o paminsan-minsan lamang ?
    Araw-araw _____ Paminsan-minsan _____

29. Ilang sigarilyo ang nauubos mo?
    Kulang isang kaha sa isang linggo____ 1 kaha sa bawat linggo_____
    2-3 kaha sa isang linggo _____
    mahigit sa 3 kaha sa isang linggo____
    hindi alam, paminsan-minsan lamang_____

30. Tumigil ka na bang manigarilyo? _____

31. Anong edad ka tumigil manigarilyo? _____

F. Pag-inom ng Alak

32. Umiinom ka ba ng alak? Oo _____ Hindi _____

33. Anong uri ng inuming may alkohol ang iyong iniinom?

    Beer____ Wine _____ Liquor/Spirit _____
    lokal na inuming may alcohol (hal. tuba, lambanog) _____

34. Gaano ka kadalas uminom ng beer, wine, liquor/spirit o lokal na inuming may alkohol halimbawa. tuba, lambanog)?

    Araw-araw_____minsan isang linggo _____ paminsan-minsan lamang _____

Appendix F: Permission to Conduct the Study from the Philippines Department of Health

Republic of the Philippines
Department of Health
DISEASE PREVENTION AND CONTROL BUREAU

October 19, 2015

MOLOVON P. AZORES JR.
Student Ph.D. Public Health

Dear **Mr. Azores**:

As discussed with Dr. Rosalind Vianzon, the Division Chief of Infectious Diseases for Prevention and Control Division, we agreed on the conduct of your study for the topic is in the research agenda of the TB Program. Based on the protocol that you have sent, a questionnaire will be used and no other diagnostics or invasive procedure will be done.

Furthermore, we would also request the following from you:

1. Coordinate with the DOH Regional offices where the study will be done to inform them of the conduct of the study
2. Ask permission from the Head of the facilities that will be involved in the study
3. Provide the Program a final copy of the study for us to know the findings and the recommendations made.

Thank you and we look forward for the successful conduct of your study.

Very truly yours,

Anna Marie Celina G. Garfin

ANNA MARIE CELINA G. GARFIN, MD
OIC-NTP Coordinator

Appendix G: Approval to Conduct the Study from Burauen, Leyte Health Center

REQUEST TO CONDUCT RESEARCH

AIMAE GRACE L. CAGARA
NURSE II
RURAL HEALTH UNIT – BURAUEN
BURAUEN, LEYTE

This letter serves to request that I be allowed to conduct survey research on drug susceptible TB and MDR-TB patients in various hospitals in the Philippines. In addition to this letter I will also send the same to hospital/clinic administrator. I am presently a Ph.D in Public Health student at Walden University in the United States of America. The title of my study is: "*Possible Risk Factors of Multi-Drug Resistant Tuberculosis Infection Prevention in the Philippines*". The proposed study will assess the strength of association between several possible risk factors and the MDR-TB infection. The research is to fulfill the dissertation research requirement of the degree.

Once permission is granted by your good office the following procedure will be followed.

1. The researcher will provide to prospective study recruits the Study Information and Participation Consent (in Filipino Language) and orientation discussion where they are free to ask questions about the study and will be given ample time around an hour to decide.
2. Once potential recruits sign a consent to be a participant in the study the researcher will assign a study ID Number which will be entered in the data base, questionnaire and respondent's - clinical record extraction form.
3. The questionnaire that is in Filipino language will be placed inside an envelope and distributed to respondents. The respondents will answer the questionnaire in an area designated by your facility where the patients can complete the questionnaire in privacy..
4. The respondents will hand over the envelope with the answered questionnaire to the researcher for review prior to safe/private storage.
5. The researcher will provide a list of patient names to the clinic/hospital and an envelope containing the respondent's clinical record extraction form which needs to be used to extract key information from the medical record.
6. Clinic/Hospital will be requested to review the patient clinical record to verify whether the patient is either a laboratory confirmed MDR-TB or a laboratory confirmed Drug Susceptible TB, and the most recent HIV test result (if available) to be documented in the RESPONDENT'S - CLINICAL RECORD EXTRACTION FORM and returned in a sealed envelope to the researcher.
7. The researcher will develop a deidentified data base (using only the Study ID to link records) for analysis to answer the research questions.

Findings of the study will be shared to interested parties such as supporting study participants, the supporting TB Centers, the Philippines DOH, and WHO.

No clinical test will be administered to patients who volunteered to be in the study, nor will they be paid or receive any gifts for the participation in the study. It is hoped that the research findings may help in the planning of interventions designed to prevent others from developing MDR-TB.

The researcher's Dissertation Committee and Walden University's Institutional Review Board (IRB) (identified below) will review and approve the research protocol and its implementation to assure that ethical principles are adhered to throughout the conduct of this research.

Donald Goodwin, DrPH,
Dissertation Committee Chair
[redacted]
IRB@waldenu.edu
Walden University
Research Participant Advocate

I hope that my request shall meet your favorable consideration

Yours Faithfully

Molefon P. Azores Jr.
Investigator
Student Ph.D. Public Health
College of Health Sciences
Walden University
E-mail: [redacted]

OKAY TO CONDUCT SURVEY
RESEARCH ON DRUG SUSCEPTIBLE TB
AND MDR-TB PATIENTS

AIMAE GRACE L. CAGARA, RN
NURSE II
RHU – BURAUEN

Appendix H: Approval to Conduct the Study from Tanauan, Leyte Health Center

REQUEST TO CONDUCT RESEARCH

Dr Arlene Santo
Municipal Health Officer
Tanauan, Leyte
Region VIII
Philippines Department of Health

This letter serves to request that I be allowed to conduct survey research on drug susceptible TB and MDR-TB patients in your hospital/clinic. I am presently a Ph.D.in Public Health student at Walden University in the United States of America. The title of my study is: "*Possible Risk Factors of Multi-Drug Resistant Tuberculosis Infection Prevention in the Philippines*". The proposed study will assess the strength of association between several possible risk factors and the MDR-TB infection. The research is to fulfil the dissertation research requirement of the degree.

Once permission is granted by your good office the following procedure will be followed.

1. The researcher will provide to prospective study recruits the Study Information and Participation Consent (in Filipino Language) and orientation discussion where they are free to ask questions about the study and will be given ample time around an hour to decide.
2. Once potential recruits sign a consent to be a participant in the study the researcher will assign a study ID Number which will be entered in the data base, questionnaire and respondent's - clinical record extraction form.
3. The questionnaire that is in Filipino language will be placed inside an envelope and distributed to respondents. The respondents will answer the questionnaire in an area designated by your facility where the patients can complete the questionnaire in privacy..
4. The respondents will hand over the envelope with the answered questionnaire to the researcher for review prior to safe/private storage.
5. The researcher will provide a list of patient names to the clinic/hospital and an envelope containing the respondents' clinical record extraction form which needs to be used to extract key information from the medical record.
6. Clinic/Hospital will be requested to review the patient clinical record to verify whether the patient is either a laboratory confirmed MDR-TB or a laboratory confirmed Drug Susceptible TB, and the most recent HIV test result (if available) to be documented in the RESPONDENT'S - CLINICAL RECORD EXTRACTION FORM and returned in a sealed envelope to the researcher.
7. The researcher will develop a de-identified data base (using only the Study ID to link records) for analysis to answer the research questions

Findings of the study will be shared to interested parties such as supporting study participants, the supporting TB Centers, the Philippines DOH, and WHO.

No clinical test will be administered to patients who volunteered to be in the study, nor will they be paid or receive any gifts for the participation in the study. It is hoped that the research findings may help in the planning of interventions designed to prevent others from developing MDR-TB.

The researcher's Dissertation Committee and Walden University's Institutional Review Board (IRB) (identified below) will review and approve the research protocol and its implementation to assure that ethical principles are adhered to throughout the conduct of this research.

Donald Goodwin, DrPH,
Dissertation Committee Chair
Email [redacted]

IRB@waldenu.edu
Walden University
Research Participant Advocate

I hope that my request shall meet your favorable consideration

Yours Faithfully,

Molovon P. Azores Jr.
Investigator
Student Ph.D. Public Health
College of Health Sciences
Walden University
E-mail [redacted]

Appendix I: Approval to Conduct the Study from Capoocan, Leyte Health Center

REQUEST TO CONDUCT RESEARCH

HON. FEDERICO H. CAROLINO, SR.
MUNICIPAL MAYOR
CAPOOCAN LEYTE

This letter serves to request that I be allowed to conduct survey research on drug susceptible TB and MDR-TB patients in various hospitals in the Philippines. In addition to this letter I will also send the same to hospital/clinic administrator. I am presently a Ph.D.in Public Health student at Walden University in the United States of America. The title of my study is: "*Possible Risk Factors of Multi-Drug Resistant Tuberculosis Infection Prevention in the Philippines*". The proposed study will assess the strength of association between several possible risk factors and the MDR-TB infection. The research is to fulfill the dissertation research requirement of the degree.

Once permission is granted by your good office the following procedure will be followed.

1. The researcher will provide to prospective study recruits the Study Information and Participation Consent (in Filipino Language) and orientation discussion where they are free to ask questions about the study and will be given ample time around an hour to decide.
2. Once potential recruits sign a consent to be a participant in the study the researcher will assign a study ID Number which will be entered in the data base, questionnaire and respondent's - clinical record extraction form.
3. The questionnaire that is in Filipino language will be placed inside an envelope and distributed to respondents. The respondents will answer the questionnaire in an area designated by your facility where the patients can complete the questionnaire in privacy..
4. The respondents will hand over the envelope with the answered questionnaire to the researcher for review prior to safe/private storage.
5. The researcher will provide a list of patient names to the clinic/hospital and an envelope containing the respondent's clinical record extraction form which needs to be used to extract key information from the medical record.
6. Clinic/Hospital will be requested to review the patient clinical record to verify whether the patient is either a laboratory confirmed MDR-TB or a laboratory confirmed Drug Susceptible TB, and the most recent HIV test result (if available) to be documented in the RESPONDENT'S - CLINICAL RECORD EXTRACTION FORM and returned in a sealed envelope to the researcher.
7. The researcher will develop a deidentified data base (using only the Study ID to link records) for analysis to answer the research questions.

Findings of the study will be shared to interested parties such as supporting study participants, the supporting TB Centers, the Philippines DOH, and WHO.

No clinical test will be administered to patients who volunteered to be in the study, nor will they be paid or receive any gifts for the participation in the study. It is hoped that the research findings may help in the planning of interventions designed to prevent others from developing MDR-TB.

The researcher's Dissertation Committee and Walden University's Institutional Review Board (IRB) (identified below) will review and approve the research protocol and its implementation to assure that ethical principles are adhered to throughout the conduct of this research.

Donald Goodwin, DrPH,
Dissertation Committee Chair
Email [redacted]

IRB@waldenu.edu
Walden University
Research Participant Advocate

I hope that my request shall meet your favorable consideration

Yours Faithfully
Molonjon P. Flores Jr.
Investigator
Student Ph.D. Public Health
College of Health Sciences
Walden University
E-mail [redacted]

APPROVED:
[redacted]
MUNICIPAL CH. CAROLINO
NURSE II
for NOV. 12, 2015 A.M.

Approved 10/12/2015
FEDERICO H. CAROLINO, SR.
MUN. MAYOR
Capoocan, Leyte

Appendix J; Approval to Conduct the Study from Barugo, Leyte Health Center

REQUEST TO CONDUCT RESEARCH

Hon. Alden Avestruz
Municipal Mayor
Barugo, Leyte

Attn: Dra. Lourdes A. Calzita
MHO - Barugo Leyte

This letter serves to request that I be allowed to conduct survey research on drug susceptible TB and MDR-TB patients in various hospitals in the Philippines. In addition to this letter I will also send the same to hospital/clinic administrator. I am presently a Ph.D.in Public Health student at Walden University in the United States of America. The title of my study is: "*Possible Risk Factors of Multi-Drug Resistant Tuberculosis Infection Prevention in the Philippines*". The proposed study will assess the strength of association between several possible risk factors and the MDR-TB infection. The research is to fulfill the dissertation research requirement of the degree.

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1. The researcher will provide to prospective study recruits the Study Information and Participation Consent (in Filipino Language) and orientation discussion where they are free to ask questions about the study and will be given ample time around an hour to decide.
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3. The questionnaire that is in Filipino language will be placed inside an envelope and distributed to respondents. The respondents will answer the questionnaire in an area designated by your facility where the patients can complete the questionnaire in privacy..
4. The respondents will hand over the envelope with the answered questionnaire to the researcher for review prior to safe/private storage.
5. The researcher will provide a list of patient names to the clinic/hospital and an envelope containing the respondent's clinical record extraction form which needs to be used to extract key information from the medical record.
6. Clinic/Hospital will be requested to review the patient clinical record to verify whether the patient is either a laboratory confirmed MDR-TB or a laboratory confirmed Drug Susceptible TB, and the most recent HIV test result (if available) to be documented in the RESPONDENT'S - CLINICAL RECORD EXTRACTION FORM and returned in a sealed envelope to the researcher.
7. The researcher will develop a deidentified data base (using only the Study ID to link records) for analysis to answer the research questions.

- MDR - TB patients

Findings [illegible] ... ly participants,
the support [illegible]

No clinical [illegible] ... dy, nor will they
be paid or [illegible] ... research
findings m[illegible] ... in developing
MDR-TB.

The researcher's Dissertation Committee and Walden University's Institutional Review Board (IRB) (identified below) will review and approve the research protocol and its implementation to assure that ethical principles are adhered to throughout the conduct of this research.

Donald Goodwin, DrPH,
Dissertation Committee Chair
Email: [redacted]

[illegible]
Walden University
Research Participant Advocate

I hope that my request shall meet your favorable consideration.

Yours Faithfully

[illegible] Jr.
Investigator
Student Ph.D. Public Health
College of Health Sciences
Walden University
E-mail: [redacted]

APPROVED:

Approved:

MUNICIPAL HEALTH OFFICER

Appendix K; Approval to Conduct the Study from Dagami, Leyte Health Center

REQUEST TO CONDUCT RESEARCH

NEMIA YEBRON - SANGRANO
MUNICIPAL HEALTH OFFICER
LGU - DAGAMI, LEYTE

This letter serves to request that I be allowed to conduct survey research on drug susceptible TB and MDR-TB patients in various hospitals in the Philippines. In addition to this letter I will also send the same to hospital/clinic administrator. I am presently a Ph.D.in Public Health student at Walden University in the United States of America. The title of my study is: "*Possible Risk Factors of Multi-Drug Resistant Tuberculosis Infection Prevention in the Philippines*". The proposed study will assess the strength of association between several possible risk factors and the MDR-TB infection. The research is to fulfill the dissertation research requirement of the degree.

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4. The respondents will hand over the envelope with the answered questionnaire to the researcher for review prior to safe/private storage.
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7. The researcher will develop a deidentified data base (using only the Study ID to link records) for analysis to answer the research questions.

Findings of the study will be shared to interested parties such as supporting study participants, the supporting TB Centers, the Philippines DOH, and WHO.

No clinical test will be administered to patients who volunteered to be in the study, nor will they be paid or receive any gifts for the participation in the study. It is hoped that the research findings may help in the planning of interventions designed to prevent others from developing MDR-TB.

The researcher's Dissertation Committee and Walden University's Institutional Review Board (IRB) (identified below) will review and approve the research protocol and its implementation to assure that ethical principles are adhered to throughout the conduct of this research.

Donald Goodwin, DrPH,
Dissertation Committee Chair
Email: [redacted]

IRB@waldenu.edu
Walden University
Research Participant Advocate

I hope that my request shall meet your favorable consideration

Yours Faithfully
Molonjon P. Flores Jr.
Investigator
Student Ph.D. Public Health
College of Health Sciences
Walden University
E-mail: [redacted]

Permission is hereby granted on your request to conduct research in our municipality.

Signature
NEMIA YEBRON - SANGRANO, MD, MPH
Municipal Health Officer

Appendix L; Approval to Conduct the Study from Carigara, Leyte Health Center

REQUEST TO CONDUCT RESEARCH

MA. BELLA V. PROFETANA, M.D, FPAMS
MHO
CARIGARA, LEYTE

This letter serves to request that I be allowed to conduct survey research on drug susceptible TB and MDR-TB patients in various hospitals in the Philippines. In addition to this letter I will also send the same to hospital/clinic administrator. I am presently a Ph.D.in Public Health student at Walden University in the United States of America. The title of my study is: "*Possible Risk Factors of Multi-Drug Resistant Tuberculosis Infection Prevention In the Philippines*". The proposed study will assess the strength of association between several possible risk factors and the MDR-TB infection. The research is to fulfill the dissertation research requirement of the degree.

Once permission is granted by your good office the following procedure will be followed.

1. The researcher will provide to prospective study recruits the Study Information and Participation Consent (in Filipino Language) and orientation discussion where they are free to ask questions about the study and will be given ample time around an hour to decide.
2. Once potential recruits sign a consent to be a participant in the study the researcher will assign a study ID Number which will be entered in the data base, questionnaire and respondent's - clinical record extraction form.
3. The questionnaire that is in Filipino language will be placed inside an envelope and distributed to respondents. The respondents will answer the questionnaire in an area designated by your facility where the patients can complete the questionnaire in privacy..
4. The respondents will hand over the envelope with the answered questionnaire to the researcher for review prior to safe/private storage.
5. The researcher will provide a list of patient names to the clinic/hospital and an envelope containing the respondent's clinical record extraction form which needs to be used to extract key information from the medical record.
6. Clinic/Hospital will be requested to review the patient clinical record to verify whether the patient is either a laboratory confirmed MDR-TB or a laboratory confirmed Drug Susceptible TB, and the most recent HIV test result (if available) to be documented in the RESPONDENT'S - CLINICAL RECORD EXTRACTION FORM and returned in a sealed envelope to the researcher.
7. The researcher will develop a deidentified data base (using only the Study ID to link records) for analysis to answer the research questions.

Findings of the study will be shared to interested parties such as supporting study participants, the supporting TB Centers, the Philippines DOH, and WHO.

No clinical test will be administered to patients who volunteered to be in the study, nor will they be paid or receive any gifts for the participation in the study. It is hoped that the research findings may help in the planning of interventions designed to prevent others from developing MDR-TB.

The researcher's Dissertation Committee and Walden University's Institutional Review Board (IRB) (identified below) will review and approve the research protocol and its implementation to assure that ethical principles are adhered to throughout the conduct of this research.

Donald Goodwin, DrPH,
Dissertation Committee Chair
Email [redacted]

IRB@waldenu.edu
Walden University
Research Participant Advocate

I hope that my request shall meet your favorable consideration

Yours Faithfully

Molorgon P. Azores Jr.
Investigator
Student Ph.D. Public Health
College of Health Sciences
Walden University
E-mail [redacted]

Edna A. Buñahs
Medical Technologist II

Approved: 10/12/15

w/ but no MDR-TB cases

MA BELLA V. PROFETANA, MD., FPAMS
MHO - CARIGARA LEYTE

patients will come Nov. 18, 2015 - pm

Appendix M; Approval to Conduct the Study from San Mateo, Rizal Health Center

REQUEST TO CONDUCT RESEARCH

Ruby M. Dorona, RN
Public Nurse
Coordinator
San Mateo Rizal

This letter serves to request that I be allowed to conduct survey research on drug susceptible TB and MDR-TB patients in various hospitals in the Philippines. In addition to this letter I will also send the same to hospital/clinic administrator. I am presently a Ph.D.in Public Health student at Walden University in the United States of America. The title of my study is: "*Possible Risk Factors of Multi-Drug Resistant Tuberculosis Infection Prevention in the Philippines*". The proposed study will assess the strength of association between several possible risk factors and the MDR-TB infection. The research is to fulfill the dissertation research requirement of the degree.

Once permission is granted by your good office the following procedure will be followed.

1. The researcher will provide to prospective study recruits the Study Information and Participation Consent (in Filipino Language) and orientation discussion where they are free to ask questions about the study and will be given ample time around an hour to decide.
2. Once potential recruits sign a consent to be a participant in the study the researcher will assign a study ID Number which will be entered in the data base, questionnaire and respondent's - clinical record extraction form.
3. The questionnaire that is in Filipino language will be placed inside an envelope and distributed to respondents. The respondents will answer the questionnaire in an area designated by your facility where the patients can complete the questionnaire in privacy..
4. The respondents will hand over the envelope with the answered questionnaire to the researcher for review prior to safe/private storage.
5. The researcher will provide a list of patient names to the clinic/hospital and an envelope containing the respondent's clinical record extraction form which needs to be used to extract key information from the medical record.
6. Clinic/Hospital will be requested to review the patient clinical record to verify whether the patient is either a laboratory confirmed MDR-TB or a laboratory confirmed Drug Susceptible TB, and the most recent HIV test result (if available) to be documented in the RESPONDENT'S - CLINICAL RECORD EXTRACTION FORM and returned in a sealed envelope to the researcher.
7. The researcher will develop a deidentified data base (using only the Study ID to link records) for analysis to answer the research questions.

(Nov 12-27, 2015.)
permitted by
Ruby M. Dorona, RN
Public Nurse
Coordinator

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Findings of the study will be shared to interested parties such as supporting study participants, the supporting TB Centers, the Philippines DOH, and WHO.

No clinical test will be administered to patients who volunteered to be in the study, nor will they be paid or receive any gifts for the participation in the study. It is hoped that the research findings may help in the planning of interventions designed to prevent others from developing MDR-TB.

The researcher's Dissertation Committee and Walden University's Institutional Review Board (IRB) (identified below) will review and approve the research protocol and its implementation to assure that ethical principles are adhered to throughout the conduct of this research.

Donald Goodwin, DrPH,
Dissertation Committee Chair
Email [redacted]

IRB@waldenu.edu
Walden University
Research Participant Advocate

I hope that my request shall meet your favorable consideration

Yours Faithfully

Molofon P. Azores Jr.
Investigator
Student Ph.D. Public Health
College of Health Sciences
Walden University
E-mail: [redacted]

Appendix N: Approval to Conduct the Study from San Lazaro Hospital

Republic of the Philippines
Department of Health
SAN LAZARO HOSPITAL
Manila, Philippines

ENDORSEMENT OF RESEARCH PROTOCOL

Date : March 22, 2016

For : **WINSTON S. GO, MD, MHA**
Medical Center Chief II
San Lazaro Hospital

Subject: Endorsement of Research Protocol reviewed and approved by SLH Research and Ethics Review Committee:

" Possible Risk Factors of Multi-Drug Resistant Tuberculosis Infection Prevention in the Philippines"
Molovon P. Azores, Jr.
College of Health, Walden University

Please find attached final revision of research protocol for your approval and implementation of the research study.

Truly yours,

Elizabeth Freda O. Telan, MD, PhD
Chair, RERC

Approved as Recommended:

Winston S. Go, MD, MHA
Medical Center Chief II