

Serrano, Grace Kathleen T. et al.

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Tuberculosis and Diabetes Mellitus Control and Care: A Rapid Situational Analysis for Planning a Coordinated Program Response

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Philippine Institute for Development Studies
Surian sa mga Pag-aaral Pangkaunlaran ng Pilipinas

Tuberculosis and Diabetes Mellitus Control
and Care: A Rapid Situational Analysis for
Planning a Coordinated Program Response

Emmanuel S. Baja et al.

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For comments, suggestions or further inquiries please contact:

The Research Information Staff, Philippine Institute for Development Studies

5th Floor, NEDA sa Makati Building, 106 Amorsolo Street, Legaspi Village, Makati City, Philippines

Tel Nos: (63-2) 8942584 and 8935705; Fax No: (63-2) 8939589; E-mail: publications@pids.gov.ph

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Final Report
July 10, 2014

**Tuberculosis and Diabetes Mellitus Control and Care:
A Rapid Situational Analysis for Planning a Coordinated Program
Response**

*A project supported by the Department of Health, Philippines,
and the Philippine Institute for Development Studies*

Project Team:

Emmanuel S. Baja
(Principal Investigator)
Mary Ann D. Lansang,
Marissa M. Alejandria
Nina Castillo-Carandang
(Co-investigators)
Jill R. Itable
(Research Associate)
Grace Kathleen Serrano
(Research Assistant)

*(1) Dept. of Clinical Epidemiology & Section of Infectious Diseases/Dept. of Medicine
University of the Philippines Manila – College of Medicine*

(2) Institute of Clinical Epidemiology, UP Manila National Institutes of Health

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Acronyms and Abbreviations

2H PP	2 hour postprandial blood glucose
AFB	acid-fast bacilli
aHR	adjusted hazards ratio
ASEAN	Association of Southeast Asian Nations
BIRDEM	Bangladesh Institute for Research and Rehabilitation for Diabetes, Endocrine and Metabolic Disorders
CI	confidence interval
CIDA	Canadian International Development Agency
CXR	chest xray
DDO	Degenerative Diseases Office
DM	diabetes mellitus
DOH	Department Of Health
DOTS	Directly Observed Treatment Short-Course
DPCB	Disease Prevention and Control Bureau)
DPP-4 inhibitors	antidiabetic, dipeptidyl peptidase-4 inhibitors
E	ethambutol
ETB or EPTB	extra pulmonary tuberculosis
FBS	fasting blood sugar
FBG	fasting blood glucose
FGD	focus group discussion
GF	Global Fund
GI	gastrointestinal
H	isoniazid
HbA1c	glycated hemoglobin
HERDIN	Health Research and Development Information Network
HIV	human immunodeficiency virus
HMO	health maintenance organization
IDS	infectious disease subspecialty
IUATLD	International Union Against Tuberculosis and Lung Disease
KAP	knowledge attitudes practices
LGU	local government unit
MeSH	Medical Subject Headings
NCR	National Capital Region
NGO	non government organization
NTP	National TB Control Program
NTPS	National TB Prevalence Survey
OGTT	oral glucose tolerance test
OPD	outpatient department
OR	odds ratio

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PCR	polymerase chain reaction
PEN	Package of Essential Non-communicable Diseases
PGH	Philippine General Hospital
PhilPACT	Philippine Plan of Action to Control Tuberculosis
PPD test	Purified Protein Derivative skin test
PTB	pulmonary tuberculosis
PubMed	free search engine accessing primarily the MEDLINE database of references and abstracts on life sciences and biomedical topics
R	rifampicin
RBG	random blood glucose
RBS	random blood sugar
RHU	rural health unit
RNTP	Revised National Tuberculosis Control Program
RR	relative risk
S	streptomycin
SMBG	self monitoring of blood glucose
TB	tuberculosis
UPMREB	University of the Philippines Manila Review Ethics Board
WHO	World Health Organization
Z	pyrazinamide

Final Report

Abstract

Tuberculosis (TB) remains one of the leading killers among bacterial diseases worldwide. In the Philippines, the prevalence of culture-positive TB is estimated to be 5 per 1000 and that for sputum smear-positive pulmonary TB is 2 per 1000 based on the 2007 National Prevalence Survey. In addition, the prevalence of metabolic syndrome among Filipinos is 5% or approximately 5 million people have diabetes (DM) in the Philippines. With the Philippines being endemic for TB, compounded by an upward trend of DM, there is a need to jointly address this tandem disease interaction. This study aims to mount a coordinated response to TB/DM with the following expectations: 1) improve the case detection rate for TB, 2) facilitate early management among patients, and 3) prevent a significant number of severe disease and deaths. A mixed methods are used to achieve the objectives including a systematic review and gray literature to estimate the magnitude of co-morbidity with TB and DM, records review specifically medical records on clinical charts of patients, cross-sectional survey on knowledge, attitudes and practices of health care providers on TB/DM screening and care, focus group discussions comprising of program managers and technical advisors of the National Tuberculosis Program, and costing exercise on bidirectional screening of TB in diabetic patients and vice-versa. Given the government's commitment to the nationwide control of TB, the under-explored frontier of TB among diabetic patients can be among the stretch goals towards increased case detection, management and prevention efforts. Likewise, the increasing prevalence of diabetes in the country and the associated risk of TB transmission in a TB-endemic population suggest the need for raising awareness on the need for TB screening. However, there is a body of programmatic and operational research questions to answer before an integrated approach to bidirectional screening can actually be implemented.

Keywords: tuberculosis, diabetes mellitus, coordinated program response

Executive Summary

Tuberculosis (TB) remains one of the leading killers among bacterial diseases worldwide. In 2012, around 8.6 million new cases were diagnosed and 1.3 million people died globally. In the Philippines, the prevalence and incidence of TB were 450,000 and 260,000, respectively, and the estimated TB mortality was 23,000 (WHO, 2013). In addition, the prevalence of culture-positive TB is estimated to be 4.9/1000 (95% CI 3.8, 6.1) and that for sputum smear-positive PTB is 2/1000 (95%CI 1.2, 2.7) based on the 2007 National Prevalence Survey (Tupasi et al., 2009). The country ranks seventh among the 22 high-burden countries that account for 80% of the global TB burden and ranks second in Asia. On the other hand, the National Nutrition Surveys show an increasing trend in the prevalence of diabetes mellitus (DM) from 3.4% in 2003 to 4.8% in 2008 (Acuin C and Duante C, 2009), which translates to about 5 million Filipinos having the disease. With the Philippines being endemic for TB, compounded by an upward trend of diabetes, there is a need to jointly address this tandem disease interaction.

There is currently a paucity of local data on the prevalence of TB in diabetic patients and vice-versa, mostly limited to clinical case series on TB and DM patients, but not on the double burden from these two diseases. However, there is an ongoing research study* to screen for TB among patients with diabetes, which is reportedly encountering problems in patient recruitment (personal communication, C. Roa). The original 2010-2016 Philippine Plan of Action to Control Tuberculosis (PhilPACT) does not address the TB – DM tandem, even as it cites the need to strengthen the need for better integration of another tandem, TB and HIV (DOH, 2010).

*Involves screening for TB among DM patients in 4 hospitals in the National Capital Region; funded by the World Health Organization (WHO) and the Canadian International Development Agency-sponsored “CATCH TB Project” of the Dept. of Health.

*Involves screening for TB among DM patients in 4 hospitals in the National Capital Region; funded

On the other hand, the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD) underscored the “serious and growing challenge” from the double burden of disease and developed a collaborative framework for care and control of these two diseases, including the need for joint surveillance, coordinated referral and management systems, and a joint research agenda (WHO, 2011).

Mounting a coordinated response to TB/DM is expected to: (1) improve the case detection rate for TB in the Philippines, currently plateauing at a little over 70% for new smear positive cases and 82% for all forms of TB; (2) facilitate early management among these patients; and (3) prevent a significant number of severe disease and deaths. We conducted a rapid situational analysis that could contribute to a programmatic response to TB/DM in the Philippines, identify opportunities as well as barriers to a collaborative approach, and provide recommendations for further implementation research on TB/DM control and care. This policy-oriented research complements, rather than duplicates, the primary data collection efforts being done under the ongoing WHO/CIDA/DOH-sponsored study.

Objectives

The general objective of the study was to contribute to a coordinated program response to TB/DM in the Philippines through a rapid situational analysis. Furthermore, the study had six specific objectives including: (1) to estimate the magnitude of the joint disease burden from TB and DM in the Philippines and in Asia; (2) to describe available collaborative TB/DM initiatives in the Philippines; (3) to investigate the knowledge, attitudes and practices of health care providers; (4) to identify opportunities and barriers for mounting collaborative TB/DM activities; (5) to conduct a cost analysis for bidirectional screening of TB and DM (TB screening among

DM patients, and vice versa); and (6) to identify research gaps that could guide planning and implementation of TB/DM collaborative initiatives.

Methodology

A mixed methods approach was used to address the objectives of the study. These mixed methods included (1) Desk review: a systematic review of published as well as gray literature was conducted in order to estimate the magnitude of co-morbidity with TB and DM; (2) Records review: medical records review was done on clinical charts of patients seen at two TB-DOTs clinics and two diabetic clinics in 2012; (3) Cross-sectional survey on knowledge, attitudes and practices (KAP) of health care providers on TB/DM screening and care: purposive sampling of physicians taking care of TB, DM and TB/DM was done through questionnaires distributed at conventions and meetings; (4) Focus group discussions (FGDs): FGDs were held for the OIC-program manager of the NTP together with the technical advisor of NTP, and the medical officer of the WHO country office and the staff of the Degenerative Diseases Office of the DOH Disease Prevention and Control Bureau (DPCB); and (5) Costing exercise: costing of bidirectional screening of TB in diabetic patients and vice-versa were done using the desk review, records reviews data and cost estimates for diabetes and TB screening tests.

Results

Desk Review

Thirty-one local and international studies on DM-TB co-infection were identified. There were 10 prospective, 8 retrospective, and 5 cross-sectional studies (total of 23 studies) that looked only at DM among TB patients; 5 prospective, 1 retrospective and 1 cross-sectional studies (total of 7 studies) that looked at TB among DM patients; and 1 prospective study that

looked at both DM among TB patients and TB among DM patients. The prevalence of DM among TB patients ranged from 4.0% to 44.0%, while the prevalence of TB among DM patients ranged from 10 per 100,000 to 11,900 per 100,000.

Records Review on the TB/DM Double Burden

A total of 270 clinical charts of patients from DM clinics and TB-DOTS clinics of a hospital seen in 2012 were retrieved and reviewed for the study. In the TB-DOTS clinics, 10/97 (10.3%) of the patients had both DM and TB, while in the DM clinics, 27/173 (15.6%) of the patients had both TB and DM.

For patients with diabetes mellitus, 51/156 (33%) were recently diagnosed within a year; 55% had diabetes for more than 4-5 years ago; and 27% were diagnosed with DM at the age of 35 to 44 years old. Thirty-nine percent of the patients had no presenting symptoms but were diagnosed by screening while 30% presented symptoms of a DM complication. For TB patients, 77/97 (79%) were recently diagnosed within a year; 10% had TB for more than 4-5 years ago, and 32% were diagnosed with TB at the age of < 25 years old. The patients had the following presenting symptoms at the TB DOTS clinics: weight loss (55%), fever (36%), cough (29%), and with cough for ≥ 2 weeks (24%).

In TB-DOTS clinics, chest x-ray (CXR) and at least two smears for acid fast bacilli (AFB) were the top two tests used to screen or diagnose TB. The top two tests used in DM clinics to screen or diagnose TB were also CXR and at least two AFB smears. In addition, more than half of the patients at the TB-DOTS clinics had other tests done (56%) including CT scan and biopsy. For DM diagnostic/screening tests, fasting blood sugar (FBS) determination was the

most frequently ordered test in both the TB-DOTS and DM clinics, followed by 2-hour oral glucose tolerance test (OGTT) and HbA1c test.

Knowledge, Attitudes, and Practices (KAP) on the TB/DM Double Burden

A total of 196 physicians participated in the survey. Sixty percent of the participants were female, and 54.7% graduated from medical school between 2000-2009. There were 88.6% from the field of Internal Medicine, and 43.9% practice in the National Capital Region.

Majority of the participants were able to correctly answer questions on symptoms seen and diagnostic tests used for tuberculosis and diabetes. However, less than half of the respondents were able to correctly answer questions regarding the prevalence of and the risk of acquiring TB, DM and the combination of these two diseases.

More than 70% of participants had favorable perceptions about the NTP and the DOTS program. In addition, more than 70% of the participants also agreed that screening for diabetes should be done in patients with tuberculosis; similarly, that tuberculosis screening should be performed for patients with diabetes. Around 50% of participants agreed to the statements implying difficulties in treating patients with the combined TB and DM.

Focus Group Discussions on the TB/DM Double Burden

FGDs were conducted with three of the Degenerative Diseases Office (DDO) staff members and on a separate venue, with three of the National TB Control Program (NTP) members. The epidemiology and screening of DM in TB and TB in DM were discussed. They were also asked about their insights on collaborative activities related to the control and management of TB and DM.

DM in TB

The DDO members considered DM in TB not much of a public health problem in the Philippines. Similarly, the staff of NTP, did not consider DM in TB as an extensive problem. The DDO staff recognized the importance of screening DM among patients with TB but they expressed the need to for a pilot study to consider the feasibility of screening at the RHU level since the caseload is heavy in these facilities. One of the suggestions they offered was to do screening if the patient has risk factors for DM. On the other hand, a NTP participant did not consider screening for DM among patients with TB to be a priority. One of the members feared that this might cause stigma among patients with DM when associated with TB.

TB in DM

The DDO members found it difficult to answer the question on the epidemiology of TB among DM patients. They think this is due to the vertical nature of the different programs. The DDO members opined that screening for TB among diabetic patients is important but not routine. They were aware of the importance of having a holistic approach to patient management but they did not believe that the RHU has the ability and resources to address all of these problems in an integrated manner. Likewise, the NTP staff opined that screening for TB among diabetic patients is important considering that they are more at risk. The NTP staff also thought that it would be feasible to screen for TB among DM patients but there would be difficulty in reaching out to the population of diabetic patients – where/how to find these patients for them to be screened.

For the screening tests, one of the members considered GeneXpert MTB/RIF, a cartridge-based automated test to identify *Mycobacterium tuberculosis* and resistance to rifampicin, as the

most sensitive test. However this would cost around USD 9 (approximately PhP 400) per cartridge, good only for one person. This cost estimate does not include the fee for the technician, capital costs, training, and others. Sputum AFB smear is a lot cheaper: PhP 50 or free in public centers, and PhP 150 in private centers. However, they stated that the sensitivity of this test is low especially among diabetic patients, who are more likely to be smear-negative. A CXR (estimated cost of PhP 200 - 300 per firm) in addition to sputum AFB smears would increase the diagnostic yield. If CXR is not available, they suggested that the healthcare provider should screen for TB signs and symptoms before ordering diagnostic tests.

Collaborative TB/DM activities

The DDO members are not aware of any existing TB/DM initiatives in the Philippines. They thought that it would be difficult to mount such activities because there is still not enough evidence on the combined TB-DM prevalence, which makes budget allocation a low priority. One of the opportunities that they see is the PEN form. If TB would be included in the form, it would serve as an integrated screening checklist. Data from this might help establish the prevalence of TB/DM and therefore make it justifiable to plan and implement TB/DM collaborative activities.

The NTP members also expressed the need for more data on the TB-DM double burden. They emphasized the collaborative TB-DM study headed by Dr. Roa, which is already on the final stage of completion. One of the opportunities that they see for them to do collaborative work with DDO is the proximity of their offices at the Department of Health.

Costing of Bidirectional Screening of TB in Diabetic Patients and Vice-Versa

Prevalence estimates for TB, DM, and TB & DM

The 2013 global TB report of WHO reported that the prevalence estimate for TB in the Philippines (population 97 million) in 2012 was 450,000 in numbers (uncertainty interval 390,000-500,000) or 461 per 100,000 population (uncertainty interval 405-520, WHO, 2013). While the study of Sy and co-workers on the prevalence of metabolic syndrome among Filipinos reported that 5% or approximately 5 million people have diabetes in the Philippines (Sy et al. 2014). As for the TB/DM double burden, results from the review of medical records estimated that the prevalence for TB/DM double burden ranges from 10.3% to 15.6%.

Estimated cost for screening DM and TB

Several DM and TB screening tests were used to compute the cost of bidirectional screening of TB in diabetic patients and vice-versa. Fasting blood sugar (FBS), and two-hour oral glucose tolerance test (2hr OGTT) were included in the costing exercise since these DM tests were the top 2 favored tests for screening DM according to the results from the review of medical records.

The results of the costing exercise revealed that bidirectional screening of TB in diabetic patients and vice-versa would require a huge budget for the screening programs to be implemented especially for screening TB among persons with DM.

Discussion and Recommendations

Our retrospective study suggests that 1 in 10 patients in TB clinics have concomitant DM, while almost 2 in 10 patients seen in DM clinics have concomitant TB. Our records review suggests that the latter (higher) estimate applies to our setting, given that the very low estimate of

0.01% in the literature was found in a setting with low TB prevalence in the general population. In addition, the 2007 National Tuberculosis Prevalence Survey (NTPS) also reported that almost 2 in 10 participants in the survey with DM have PTB, which was in agreement with our retrospective study (Tropical Disease Foundation Inc. and Department of Health, 2008). Moreover, our survey of practicing physicians revealed that one-third saw around 5 – 20 patients with both TB and DM in a month, although the majority saw less than 5 in a month.

We investigated whether symptoms suggestive of TB in DM patients or DM in TB patients would be useful in filtering and reducing the number of patients who need to undergo laboratory-confirmed screening tests. Our records review suggests that clinical symptoms alone would not be sensitive or specific enough to detect concomitant TB or DM.

These findings suggest that there is added value in bidirectional screening for TB and DM, regardless of symptoms. Early detection and treatment of TB will reduce the risk of transmission from untreated patients and morbidities associated with late treatment of TB-DM. Similarly, early detection and good control of DM among TB patients are likely to improve treatment outcomes.

However, there are fundamental issues to consider and some constraints to overcome prior to programmatic bidirectional screening for these two diseases nationwide. The major issues to be considered are:

- I. Costs of bidirectional screening—estimated to be around PhP 68.8 - 137.5 million for one-time FBS screening among prevalent TB cases, and around PhP 1.98 billion for one-time chest x-ray and an additional PhP 3.85 billion for two sputum AFB smears, among diabetic patients. The costs are based on user charges in a government hospital

- and thus include costs for human resources, use of equipment, materials and supplies. If carried out as government-initiated screening programs or if covered by a PhilHealth outpatient benefit package, there will be economies of scale that would significantly drive down costs. As an interim step, rolling out of screening programs could also consider socioeconomic factors in prioritizing screening among those with increased risk of combined diseases, such as urban poor areas, where overcrowding, poor ventilation, smoking and the marketing of cheap but unhealthy ‘fast food’.
- II. Time required in busy outpatient services to carry out the screening tests—this concern was raised at the FGDs, suggesting the need for pilot studies to determine the feasibility of implementing the screening programs in both TB clinics and medical services where diabetic patients are seen. Corollary to this is the need to determine the most cost-effective screening tests for DM and TB as well as the availability and accessibility of these tests in healthcare facilities at various levels.
- III. Awareness building and acceptability of screening tests among patients—as raised in the FGDs, there is still stigma attached to the diagnosis of TB and reluctance to provide sputum (for TB screening) or blood samples (for DM screening), or to undergo a chest x-ray (for TB screening).
- IV. Costs of treatment for diagnosed TB or DM—there will be a significant increase in the TB case detection rate once TB screening among DM patients is rolled out; public services and private-public partnerships must be ready to meet the demand for TB-DOTS services, including quality anti-TB drugs. Similarly, with the expected rise in DM cases detected through screening programs, the government’s Package for

- Essential Non-Communicable Disease Interventions will need to ensure an adequate supply of anti-diabetes drugs and educational materials for diet and lifestyle change.
- V. Creation of an integrated information management system for TB-DM surveillance, control and management—this is needed to address information and research gaps on the magnitude of the TB-DM problem in the country, long-term outcomes, other associated morbidities, best screening tests to use, cost-effectiveness of interventions including bidirectional screening, and other public health issues in prevention and control.
- VI. Collaborative or integrated nature of interventions for TB-DM—in addition to the above information and research gaps, it is not clear at this point whether collaborative arrangements should be made between TB clinics and medical clinics serving DM patients involving inter-clinic referrals, or whether health providers in TB clinics and DM-focused services should be trained to manage both diseases. In the survey of practicing physicians, only 50% of the respondents stated that they referred DM patients with TB to TB-DOTS clinics, preferring to manage both diseases by themselves. However, they recognized the challenges of managing combined TB-DM and the standards that need to be met for directly observed treatment for TB. In the FGDs, the DOH staff acknowledged that there are no existing collaborative activities between the National TB Program and the Degenerative Diseases Office with regard to integrated management of TB-DM, even as they recognized the importance of such, especially in terms of screening for and management of TB among diabetic patients. Some of the reasons for the absence of collaboration stem from the vertical

nature of the programs, even though both communicable and non-communicable disease programs are housed under one Center in the Department of Health.

The above research issues complement the research agenda drawn by international experts on TB and DM (Harries et al. 2010), and which remain relevant and not fully answered today. Of the ten research questions identified by the expert meeting held in November 2009, four were identified as high priority: (i) whether, when and how to screen for TB in patients with DM, and vice versa; (ii) the impact of DM and non-diabetes hyperglycemia on TB treatment outcomes and deaths; (iii) implementation and evaluation of the TB-DOTS model for DM management; and (iv) the development and evaluation of better point-of-care diagnostic and monitoring tests for DM patients.

The results of the ongoing prospective study supported by WHO/CIDA/DOH are much awaited to bolster burden of disease estimates. Similarly, the physician survey and FGDs merely provide a snapshot of the knowledge and practices of healthcare providers and public health programs, but additional studies are needed, including operational research to address the issues raised in Items I – VI above.

In conclusion, our rapid assessment provides additional information to support an integrated approach to the considerable double burden of tuberculosis and diabetes mellitus. Given the government's commitment to the nationwide control of TB, the under-explored frontier of TB among diabetic patients can be among the stretch goals towards increased case detection, management and prevention efforts. Likewise, the increasing prevalence of diabetes in the country and the associated risk of TB transmission in a TB-endemic population suggest the need for raising awareness on the need for TB screening. However, there is a body of

programmatic and operational research questions to answer before an integrated approach to bidirectional screening can actually be implemented.

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Final Report

I. Background and Rationale

Tuberculosis (TB) remains one of the leading killers among bacterial diseases worldwide. In 2012, around 8.6 million new cases were diagnosed and 1.3 million people died.¹ According to a recent systematic review, diabetic patients have three times the risk of contracting TB compared to non-diabetics (95% CI 2.3-4.3).² Other studies report the fraction of TB cases attributable to diabetes mellitus (DM) to be between 15% and 25%.³⁻⁵ Epidemiologic modeling of the burden of these two diseases in India estimated that DM accounts for 14.8% of pulmonary tuberculosis (PTB) and 20.2% of smear positive TB.⁴ Another study from India found that the proportion of diabetic patients among established pulmonary TB cases with no previous history of DM was as high as 40%.⁶

In the Philippines, the prevalence and incidence of TB were 450,000 and 260,000, respectively, and the estimated TB mortality was 23,000.¹ Moreover, the prevalence of culture-positive TB is estimated to be 4.9/1000 (95% CI 3.8, 6.1) and that for sputum smear-positive PTB is 2/1000 (95%CI 1.2, 2.7) based on the 2007 National Prevalence Survey.⁷ The country ranks seventh among the 22 high-burden countries that account for 80% of the global TB burden and ranks second in Asia. On the other hand, the National Nutrition Surveys show an increasing trend in the prevalence of DM from 3.4% in 2003 to 4.8% in 2008⁸, which translates to about 5 million Filipinos having the disease. According to the Philippine Health Statistics 2009, TB (all-forms) is the sixth leading cause of mortality at 25.4/100,000, while DM is the eighth leading cause of deaths at 19.8/100,000.⁹ With the Philippines being endemic for TB, compounded by an upward trend of diabetes, there is a need to jointly address this tandem disease interaction.

There is currently a paucity of local data on the prevalence of TB in diabetic patients and vice-versa, mostly limited to clinical case series on TB and DM patients, but not on the double burden from these two diseases. However, there is an ongoing research study* to screen for TB among patients with diabetes, which is reportedly encountering problems in patient recruitment (personal communication, C. Roa). The initial 2010-2016 Philippine Plan of Action to Control Tuberculosis (PhilPACT) does not address the TB – DM tandem, even as it cites the need to strengthen the need for better integration of another tandem, TB and HIV.¹⁰ On the other hand, the WHO and the IUATLD underscored the “serious and growing challenge” from the double burden of disease and developed a collaborative framework for care and control of these two diseases, including the need for joint surveillance, coordinated referral and management systems, and a joint research agenda.¹¹

Mounting a coordinated response to TB/DM is expected to: (1) improve the case detection rate for TB in the Philippines, currently plateauing at a little over 70% for new smear positive cases and 82% for all forms of TB; (2) facilitate early management among these patients; and (3) prevent a significant number of severe disease and deaths. We conducted a rapid situational analysis that could contribute to a programmatic response to TB/DM in the Philippines, identify opportunities as well as barriers to a collaborative approach, and provide recommendations for further implementation research on TB/DM control and care. This policy-oriented research complements, rather than duplicates, the primary data collection efforts being done under the ongoing WHO//CIDA//DOH-sponsored study.

*Involves screening for TB among DM patients in 4 hospitals in the National Capital Region; funded by the World Health Organization (WHO), and the Canadian International Development Agency-sponsored “Catch TB Project” of the Dept. of Health.

II. General Objective

To contribute to a coordinated program response to TB/DM in the Philippines through a rapid situational analysis.

III. Specific Objectives (SO)

- SO 1: To estimate the magnitude of the joint disease burden from TB and DM in the Philippines and in Asia;
- SO 2: To describe available collaborative TB/DM initiatives in the Philippines;
- SO 3: To investigate the knowledge, attitudes and practices of health care providers;
- SO 4: To identify opportunities and barriers for mounting collaborative TB/DM activities;
- SO 5: To conduct a cost analysis for bidirectional screening of TB and DM (TB screening among DM patients, and vice versa); and
- SO 6: To identify research gaps that could guide planning and implementation of TB/DM collaborative initiatives.

IV. Methodology

1. Desk review

A systematic review of published as well as gray literature was conducted in order to estimate the magnitude of co-morbidity with TB and DM. Search strategy. We searched both PubMed (1966 to December 2013) and HERDIN databases (1966 to December 2013) using the following MeSH and free text terms: tuberculosis, diabetes mellitus, screening, treatment outcomes, Philippines, and Asia. Based on the titles and abstracts, we obtained the full text of English language articles pertinent to the epidemiology, screening, prevention, treatment or control of TB/DM co-morbidity, particularly those related to the Philippines and other Asian

countries. Since a number of pertinent local journals are not indexed in PubMed (e.g., the Philippine Journal of Internal Medicine, the Philippine Journal of Microbiology and Infectious Diseases, the Pediatric Infectious Disease Society of the Philippines Journal, Journal of Pediatric Infectious Diseases, Journal of the ASEAN Federation of Endocrine Societies) we also did a search using Google Scholar and the aforementioned search terms.

Citations in the retrieved journal articles were reviewed to find additional pertinent articles. We also asked local experts on TB and DM control and management about other possible sources of pertinent information, including unpublished technical reports, databases and survey data (see Appendix A for the guide we adopted for critical appraisal of prevalence studies).¹² Information on ongoing collaborative TB/DM initiatives was also obtained from the Department of Health, professional medical societies and local experts (see subsections on the KAP survey and focus group discussions).

All retrieved articles, gray literature and databases were evaluated in terms of the study design, study size and representativeness of study samples, screening/testing methods for TB and/or DM and their validity and reliability, availability of point estimates as well as 95% confidence intervals, and applicability to the Philippine setting. Estimates of TB-DM co-morbidity were analyzed and classified according to the strength of the available evidence.

2. Records review

The desk review of local publications and gray literature was supplemented by a medical records review of clinical charts of patients seen in 2012. After seeking permission to review medical records, information on the presence of TB or DM or TB-DM was

obtained, together with the patient's age, sex, socioeconomic status, age and year of onset of the disease/s if known, staging/classification of the disease/s, types of TB/DM screening/diagnostic tests done, and treatments received. We reviewed the records in the following facilities:

- a) The diabetes clinic of the Out-Patient Department (OPD) at the Philippine General Hospital;
- b) One diabetes clinic from the Consortium of Government Diabetes Clinics, Inc. (based at the University of the East Ramon Magsaysay Medical Center, a private tertiary-care hospital);
- c) Two TB DOTS (directly observed therapy, short-course) Clinics where both TB and DM tests are likely to be done (DOTS clinics at the Philippine General Hospital and the Manila Doctors Hospital, which are public and private tertiary-care level hospitals, respectively).

Our records review were limited to included only private and public tertiary-care hospitals/facilities that screen and care for TB patients (Manila Doctors), DM patients (UERM) or TB-DM patients (UP PGH). In addition, no health centers or rural health units were included as study sites for records review.

3. Cross-sectional survey on knowledge, attitudes and practices (KAP) of health care providers on TB/DM screening and care

Purposive sampling of physicians taking care of TB, DM and TB/DM was done through questionnaires distributed at conventions and meetings of the following professional

medical societies: UP-PGH Society of Infectious Diseases Alumni (April 15-18, 2013), Philippine College of Physicians (May 5-8, 2013).

Sample size

The calculation of the sample size for the KAP survey was based on the following assumptions:

- Proportion of physicians recognizing the need for screening for TB among diabetic patients and for screening for diabetes mellitus among TB patients (key KAP indicators) = 50%
- Estimated target population of physicians ~ 6,000
- Acceptable margin of error = 10%
- Confidence interval around the point estimate = 95%
- Estimated design effect due to sampling by professional society = 2

Calculated sample size = 95 (sample size calculator for a proportion. Available at: <http://www.berrie.dds.nl/calcss.htm>). With an estimated design effect of 2 due to sampling by professional society, the sample size was doubled to 190. With an adjustment for an estimated response rate of 90%, the total sample size for the KAP survey was 211.

Content areas

The survey questionnaire is attached in Appendix B. This was pilot tested among 10 resident physicians and fellows in PGH to evaluate the length of the questionnaire, clarity of the questions and ease in responding to the mobile application and online version of the questionnaire. The questionnaire was developed based on clinical practice guidelines and

recommendations for bidirectional screening and management of TB/DM as well as sample questionnaires on KAP surveys for TB and DM. The main subject areas covered were:

- Socio-demographic characteristics
- Clinical practice profile, e.g., type of practice (public-private; level of care; specialty/subspecialty if any; solo/group/hospital practice), year of graduation, estimate of numbers of TB, DM and TB/DM patients seen per month
- Knowledge questions: knowledge on prevalence of TB, DM and TB/DM; clinical screening questions for TB and DM; choice of screening tests for TB and DM; treatment and care of TB, DM and TB/DM
- Attitude questions: questions reflecting possible stigmatization of TB patients; perceptions of challenges of management TB, DM and TB/DM; attitudes towards the need for bidirectional screening for TB and DM
- Practice questions: case scenarios for TB, DM and DM/TB

4. Focus group discussions (FGDs)

Two FGDs of staff from the DOH Disease Prevention and Control Bureau (DPCB) were held. One FGD of 3 participants was conducted with the OIC-program manager of the National TB Control Program (NTP) together with the technical advisor of NTP, and the medical officer of the WHO country office, while the other FGD of 3 participants was with staff of the Degenerative Diseases Office of the DPCB. An outline of the questions used in the FGDs is found in Appendix C.

5. Costing of bidirectional screening of TB in diabetic patients and vice-versa

Using data from IV.1 - IV.4, information to be collected for the costing exercise consisted of:

- Range of prevalence estimates for TB, DM and TB/DM in order to calculate estimated numbers of TB/DM patients in the Philippines. Data source: desk review and records reviews
- Estimated costs of diabetes screening tests [fasting blood sugar (FBS), two-hour oral glucose tolerance test (2hr OGTT), and glycated hemoglobin (HbA1c] and TB screening tests (sputum AFB smear 2x, and chest x-ray (CXR))

6. Data Analyses

Data from the records reviews and KAP survey were encoded into Google Docs. For the desk review, various estimates of prevalence of TB, DM and TB/DM were tabulated and sorted in terms of the quality of the evidence. Descriptive statistics (proportions for categorical variables and measures of central tendency and dispersion for continuous variables) were used to describe results from the record reviews and KAP survey. Epi Info Version 7.1.1.4 was used for the descriptive statistics.

The costing exercise was done and the prevalence estimates for TB/DM derived from the review records and moderate to high-quality studies were projected to national estimates. Costs for bidirectional screening using recommended screening tests for TB or DM and costs for associated health services were inputted. Sensitivity analyses were done, using variations of prevalence estimates of TB/DM and variations in costs of screening tests (range of estimates).

V. Ethical Considerations

This study is covered under the health policy and systems research agenda of the DOH Research Reference Hub. No clinical interventions were involved. Informed consent was obtained from the individual participants of the KAP survey and the FGDs. For the records review and the KAP survey, permission for access to clinical records or members of professional societies was obtained from the head of the hospital/clinic or professional society, respectively. Our clinical data sheets and the questionnaire forms did not contain names of patients or physicians involved. All data obtained were treated as confidential and all survey and medical records forms were stored under lock and key. Encoded data were password-protected. Informed consent forms for the FGDs and questionnaire are found in Appendix. Approval for the conduct of this study was obtained from University of the Philippines Review Ethics Board (UPMREB).

VI. Results

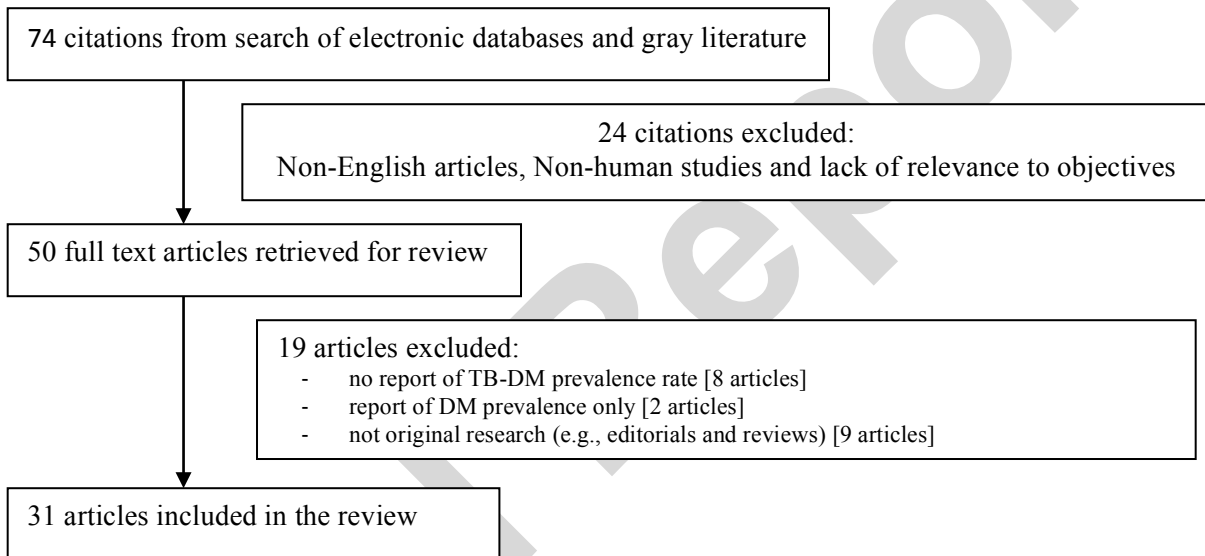
1. Desk review results

The literature search of electronic databases and gray literature yielded 74 citations for consideration. After screening of article titles and abstracts, 24 citations were excluded based on their lack of relevance to the study objectives, non-English articles and non-human studies. Fifty-one citations were retrieved and their full texts reviewed. Upon full text review, 19 articles were further excluded. Figure 1 outlines the selection process for the articles included in the review.

Thirty-one local and international studies on DM-TB co-infection were identified (Table 1). There were 10 prospective, 8 retrospective, and 5 cross-sectional studies (total of

23 studies) that looked only at DM among TB patients; 5 prospective, 1 retrospective and 1 cross-sectional studies (total of 7 studies) that looked at TB among DM patients; and 1 prospective study that looked at both DM among TB patients and TB among DM patients. The prevalence of DM among TB patients ranged from 4.0% to 44.0%, while the prevalence of TB among DM patients ranged from 10 per 100,000 to 11,900 per 100,000.

Figure 1. Selection process of reviewed studies



A few studies reported on morbidity and mortality outcomes of DM-TB co-infection. For DM among TB patients studies, morbidities reported in the study of Jimenez et al. included an increased probability of lung cavitations [Odds ratio (OR): 1.8, 95% confidence interval (95% CI): 1.25 - 2.41], delayed sputum conversion (OR 1.51, 95% CI: 1.09 - 2.10, treatment failure (OR 2.93, 95% CI 1.18 - 7.23), recurrence (OR 1.76, 95% CI 1.11 to 2.79), and relapse (OR 1.83, 95% CI 1.04 - 3.23).²⁶ However, Alisjahbana and co-workers reported that neither cavities (OR, 0.76; 95% CI, 0.39–1.48) nor mycobacterial load (OR, 1.71; 95% CI, 0.90–3.25) were significantly associated w/ DM, and diabetic patients with TB had more symptoms but had no evidence of more-severe TB.¹⁴ One study, however, pointed to a significantly lower proportion of bilateral lung cavitations among TB-DM patients (3.2% vs. 5.1%) compared to TB patients without diabetes ($p < 0.05$).³¹

Likewise, several studies reported on mortality among TB patients.^{14, 19, 24, 26, 33, 39-40, 42} One study reported higher mortality (28.97% vs 11.80%) due to causes other than TB among diabetic patients vs. non-diabetic patients,²⁶ while the other reported an increased risk [crude relative risk (RR) 2.70, 95% CI 1.53 - 4.77] of mortality within 100 days of TB treatment.¹⁹ Uchimura et al. reported higher mortality for TB cases with DM for males of younger ages (< 35) but similar mortality for older age groups with DM, compared with all smear-positive PTB cases of same age group.⁴⁰ Furthermore, Wang and colleagues reported that mortality for PTB-DM patients was 17.6%, in sharp contrast to 7.7% for PTB patients (OR 2.56, 95% CI: 1.084–6.034). PTB-related deaths were significantly more common in the PTB-DM group than the PTB group (12.2% vs 4.2%; OR 3.16, 95% CI 1.08–9.26) and Type 2 DM still remained as an independent and significant risk factor for PTB-related death (OR 7.6, 95% CI 1.98–29.08).⁴²

For TB among DM patients studies, Leung et al. in 2008 published that DM was associated with an increase in the risk of active, culture-confirmed, and pulmonary but not extra-pulmonary TB, w/ adjusted hazard ratios (aHR) of 1.77 (95%CI: 1.41-2.24), 1.91 (95% CI: 1.45-2.52), 1.89 (95%CI: 1.48-2.42), and 1.00 (95% CI: 0.54-1.86), respectively. Patients w/ poor recent glyceamic control (HbA1c \geq 7%) had significantly increased risk of TB (aHR 2.56, 95% CI: 1.95-3.35), while those with HbA1c $<$ 7% did not (aHR 0.81, 95% CI: 0.44-1.48).²⁸ These findings imply that hyperglycemia, rather than a DM diagnosis *per se*, increases the risk of developing active TB.²⁸ A study by Dobler et al. in 2012 reported that people with DM had a 1.5-fold increased risk of developing TB [adjusted relative risk (RR) 1.48, 95% CI 1.04-2.10], while the risk for TB was higher among people who using insulin for DM (adjusted RR 2.27, 95% CI 1.41-3.66).¹⁸ A study in Ethiopia in 2013 reported that DM patients who had the disease for more than 10 years were 9 times [odds ratio (OR) 8.89, 95% CI 1.88–58.12] more likely to develop PTB than those who had lived with DM for less than five years.¹⁶ In addition, a study in Pakistan in 2006 reported that the prevalence of TB increased progressively with duration of DM. The highest prevalence was seen in those who had been diagnosed with DM for more than 10 years.²⁴

In the studies identified, testing for TB among DM patients included the standard chest x-ray, and sputum specimens for smear microscopy, culture and drug susceptibility testing of *Mycobacterium tb*.^{16, 23, 27, 30, 37} However, prior to testing for TB, screening for TB patients was based on either WHO guidelines or on questions regarding the following symptoms: 1) cough for longer than 2 weeks, 2) night sweats, 3) fever, 4) weight loss, 5) hemoptysis and 6) any suspicion of active TB to account for extra-pulmonary TB.^{23, 25, 30, 37}

Screening for DM among TB patients included patients with known history of DM, received insulin and/or an oral hypoglycemic agent, diagnosed as diabetic during hospitalization, and self-reported DM status.^{36, 38, 42} In addition, testing for DM was based on blood glucose estimation (random blood glucose or fasting blood glucose),^{14-15, 22, 25, 33-36, 42} glycated hemoglobin (HbA1c) levels,^{17, 36} or plasma glucose levels 2 hours after a 75-g oral glucose load (glucose tolerance test).³⁵⁻³⁶ Patients were diagnosed diabetic if any one of the following conditions existed: 1) fasting blood glucose levels ≥ 126 mg/dL; 2) plasma glucose ≥ 200 mg/dL 2 hours after a 75-g oral glucose load (glucose tolerance test); 3) symptoms of hyperglycemia and casual plasma glucose ≥ 200 mg/dL; or 4) HbA1C $\geq 6.5\%$.^{36, 42}

Recommendations for screening and testing included bi-directional screening of TB and DM,¹⁵ bi-directional addition of TB and DM prevention and control interventions in their respective public health programs,²⁶ and improved screening through free testing and use of low-cost testing devices (e.g., adequately calibrated glucometers).^{15, 29, 33, 34} Additionally, TB screening for staff and clients in institutions caring for the elderly were recommended. One study observed that persons with DM had about a three times higher risk of developing TB and therefore recommended a more intensive TB screening strategy.⁴⁰

2. Records Review on the TB/DM Double Burden

A total of 270 clinical charts of patients from DM clinics and TB-DOTS clinics seen in 2012 were retrieved and reviewed for the study. Table 2 shows the characteristics of the patients by clinic site (DM clinic or TB-DOTS clinic). Patients from TB-DOTS clinics were older [mean age, SD (51.1, 14.5)] compared to patients from the DM clinics (mean age 39.5, SD 16.4). There were more male (56.7%) than female patients in TB-DOTS clinics while in

the DM clinics percentage of males (30.1%) were lower than female. Never smokers were higher in the DM clinics compared to the TB-DOTS clinics (67% vs. 58%, p-value =0.18) while the current and former smokers were higher in the TB-DOTS clinics compared to the DM clinics (p-values > 0.10). Patients from the DM clinics had a higher family history of DM percentage than the patients from the TB-DOTS clinics (59% vs 22%, p-value < 0.001). In addition, both the DM and TB-DOTs clinics were dominated by unemployed patients (>70%) and low close contact with a TB patient (< 25%).

Table 2. Characteristics of patients included in medical records review, by clinic site

Characteristics	TB-DOTS Clinic (n=97)		DM Clinic (n=173)		p-value
	No.	Percentage	No.	Percentage	
Age (mean, SD)	97	39.5, 16.4	173	51.1, 14.5	
Sex	97		173		
Male		56.7		30.1	<0.001
Female		43.3		69.9	<0.001
Smoking Status	84		146		
Never		58.3		67.1	0.18
Former		21.4		20.6	0.87
Current		20.3		12.3	0.11
With family history of DM	77		155		
No		77.9		40.6	<0.001
Yes		22.1		59.4	<0.001
With close contact, history of TB	74		48		
No		77.0		79.2	0.78
Yes		23.0		20.8	0.78
Occupation	65		121		
Unemployed		70.8		74.4	0.60
Blue-collar worker		20.0		14.9	0.37
Professional		4.6		6.6	0.58
Entrepreneur		0		3.3	0.14
Student		4.6		0.8	0.09

Table 3 summarizes the diagnostic characteristics of patients by clinic site. In the TB-DOTS clinics, 10/97 (10.3%) of the patients had both DM and TB, while in the DM clinics, 27/173 (15.6%) of the patients had both TB and DM.

Table 3. Clinical features related to diagnosis of TB and DM, by clinic site, based on the medical records review

Characteristics	TB-DOTS Clinic (n=97)		DM Clinic (n=173)		p-value
	No.	%	No.	%	
Disease status	97		173		
With TB		89.7		0.0	< 0.001
With DM		0.0		84.4	<0.001
With TB and DM		10.3		15.6	0.23
Year of onset of DM	9		156		
2012		33.3		32.7	0.97
2011		22.2		7.0	0.10
2010		0.0		4.5	0.52
< 2010		44.5		55.8	0.51
Age at diagnosis of DM (in years)	9		156		
> 64		0.0		7.0	0.10
55 – 64		0.0		21.2	0.12
45 – 54		66.7		19.9	0.001
35 – 44		22.2		26.9	0.76
25 – 34		11.1		16.7	0.66
< 25		0.0		8.3	0.37
Year of onset of TB	97		27		
2012		79.4		29.6	< 0.001
2011		8.2		11.1	0.65
2010		2.1		7.4	0.16
< 2010		10.3		51.9	< 0.001
Age at diagnosis of TB ^a (in years)	97		26		
> 64		7.2		15.4	0.19
55 – 64		16.5		23.1	0.44
45 – 54		20.1		15.4	0.55
35 – 44		18.6		34.6	0.08
25 – 34		19.6		7.7	0.15
< 25		32.0		3.8	0.004
TB location (%)	97		27		
Pulmonary		49.5		92.6	< 0.001
Extrapulmonary		26.8		7.4	0.03
Both		23.7		0	0.005
Extrapulmonary location ^b	49		2		
Lymph node		28.6		0	0.37
Spine		18.4		0	0.50
Gastrointestinal		12.2		0	0.60
Abdominopelvic		8.2		0	0.67
Pleura		8.2		-	0.67
Others		34.7		100.0	0.06
PTB	66		7		
Minimal		56.7		71.4	0.48

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Severe		28.4		14.3	0.46
Cavitary		14.9		14.3	0.95
PTB, AFB smear result at diagnosis	57		5		
Smear-negative		55.2		40.0	0.54
Smear-positive		44.8		60.0	0.54
Presenting symptoms for suspected/diagnosed TB ^c	97		30		
Weight loss		54.6		16.7	< 0.001
Fever		36.1		13.3	0.02
Cough		28.9		13.3	0.09
Cough for ≥ 2 weeks		23.7		16.7	0.42
Back pain		23.7		6.7	0.04
Easy fatigability		19.6		3.3	0.03
Anorexia		15.5		6.7	0.21
Hemoptysis		11.3		6.7	0.46
Abdominal pain		11.3		0	0.054
Dyspnea		10.3		6.7	0.55
Neck mass		10.3		0	0.07
Chest pain		6.2		20.0	0.02
Difficulty in breathing		5.2		3.3	0.68
No symptoms, diagnosed by screening		4.1		6.7	0.57
Others		37.1		13.3	0.01
DM category	10		173		
Type I		0		3.5	0.55
Type II		100.0		78.6	0.10
Gestational		0		17.9	0.14
DM, complications ^d	4		84		
Nephropathy		25.0		60.7	0.16
Neuropathy		75.0		47.6	0.28
Retinopathy		0		39.3	0.11
Stroke		0		19.0	0.34
Peripheral vascular disease/diabetic foot		0		10.7	0.49
CAD		0		4.8	0.65
Others		0		2.4	0.76
Measure used for level of DM control ^e	5		130		
HbA1c		40.0		56.1	0.48
FBS		60.0		35.4	0.26
Self-monitoring blood glucose (SMBG)		0		26.2	0.19
2hr OGTT		0		14.5	0.36
Others		20.0		2.3	0.02
DM controlled at most recent check-up	5		129		
No		40.0		54.3	0.53
Yes		60.0		45.7	0.53

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Presenting symptoms for diagnosed DM ^f	3	99		
No symptoms, diagnosed based on screening		33.3	39.4	0.83
Symptoms of DM complication		33.3	30.3	0.91
Polyuria		0	27.3	0.29
Weight loss		33.3	18.2	0.51
Polydipsia		0	15.2	0.47
Polyphagia		0	10.1	0.56
Nocturia		0	9.1	0.58
Others		33.3	9.1	0.16

^aMultiple ages at diagnosis of TB, total not equal to 100%; ^bMultiple extrapulmonary locations, total not equal to 100%; ^cMultiple presenting symptoms for TB, total not equal to 100%; ^dMultiple DM complications, total not equal to 100%; ^eMultiple levels of control measured, total not equal to 100%; and ^fMultiple presenting symptoms for DM, total not equal to 100%

For patients with diabetes mellitus, 51/156 (33%) were recently diagnosed; 55% had diabetes for more than 4-5 years ago; and 27% were diagnosed with DM at the age of 35 to 44 years old. Furthermore, 79% had type II diabetes with nephropathy (61%), neuropathy (48%), retinopathy (39%), stroke (19%) or other complications (18%). Thirty-nine percent of the patients had no presenting symptoms but were diagnosed by screening while 30% presented symptoms of a DM complication.

For TB patients, 77/97 (79%) were recently diagnosed; 10% had TB for more than 4-5 years ago, and 32% were diagnosed with TB at the age of < 25 years old. Moreover, 24% had both extrapulmonary and pulmonary TB location with lymph nodes (29%), spine (18%) and gastrointestinal (12%) as major extrapulmonary TB locations. The patients had the following presenting symptoms at the TB DOTS clinics: weight loss (55%), fever (36%), cough (29%), and with cough for \geq 2 weeks (24%).

Table 4 presents by clinic site the different tests used to screen/diagnose both TB and DM patients. In TB-DOTS clinics, chest x-ray (CXR) and at least two smears for acid fast bacilli (AFB) were the top two tests used to screen or diagnose TB. The top two tests used in

DM clinics to screen or diagnose TB were also CXR and at least two AFB smears. In addition, more than half of the patients at the TB-DOTS clinics had other tests done (56%) including CT scan and biopsy. For DM diagnostic/screening tests, fasting blood sugar (FBS) determination was the most frequently ordered test in both the TB-DOTS and DM clinics, followed by 2-hour oral glucose tolerance test (OGTT) and HbA1c test.

Table 4. Screening/diagnostic tests used, by clinic site, based on the medical records review

Types of diagnostic test	TB-DOTS Clinic (n=97) Percentage	DM Clinic (n=173) Percentage	P-value
TB diagnostic test^a			
Chest x-ray (CXR)	76.3	10.4	< 0.001
AFB smear (at least 2x)	70.1	8.1	< 0.001
TB culture	4.1	0	0.01
TB PCR	4.1	0	0.01
PPD test	1.0	0	0.18
No diagnostic test	0	80.1	< 0.001
Unspecified diagnostic test	1.0	6.4	0.04
Others ^a	55.7	1.2	< 0.001
DM diagnostic test^b			
FBS	23.7	43.9	< 0.001
2h OGTT	5.2	28.9	< 0.001
Hb1Ac	4.1	25.4	< 0.001
2hr PP	0	2.9	0.09
Random blood sugar	0	1.7	0.19
No diagnostic test	71.1	0	< 0.001
Unspecified diagnostic test	4.1	31.2	< 0.001

^a Other tests include biopsy, CT scan, etc.; and ^bMultiple diagnostic tests, total not equal to 100%

Table 5 shows the main treatments provided to DM and TB patients at both clinic sites. For TB patients in TB-DOTS clinics, 60/97 (62%) patients were treated with 2 HRZE + 4 HR. For DM patients in DM clinics, 84/173 (49%) patients were treated with metformin, 56/173 (56%) for insulin, and 43/173 (25%) were treated with sulfonylureas.

Table 5. Main TB or DM treatments provided by clinic site, based on the medical records review

Main TB/DM treatment	TB-DOTS Clinic (n=97) Percentage	DM Clinic (n=173) Percentage	p-value
TB treatment^a			
2 (HRZE) + 4 (HR)	61.8	2.9	< 0.001
2 (HRZE) + 6 (HR)	2.1	0	0.29
2 (HRZE) + 7 (HR)	6.2	0	< 0.001
2 (HRZE) + 10 (HR)	6.2	0	< 0.001
2 (HRZE) + 4 (HRE)	0	0.6	0.45
2 (HRZE) + 10 (HRE)	4.1	0	0.007
2 (HRZES) + 1 (HRZE) + 5(HRE)	14.4	0	< 0.001
2 (HRZE) + 2(HR) + 10(HRE)	5.2	0	0.18
Unspecified treatment regimen	0	12.1	0.06
No treatment regimen	0	84.4	< 0.001
DM treatment			
Biguanide/metformin	9.3	48.6	< 0.001
Sulfonylureas	4.1	24.8	< 0.001
Insulin	0	32.4	< 0.001
DPP-4 inhibitors	1.0	19.1	< 0.001
Diet	0	21.4	< 0.001
No treatment regimen	91.8	0	< 0.001
Others	0	6.9	0.008

^aTreatment regimen for TB in two phases: initial phase + continuation phase. The number before a phase is the duration of the phase in months, with fixed-dose combinations of drugs indicated by the letters in parenthesis; isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E), and streptomycin (S).

3. Knowledge, Attitudes, and Practices (KAP) on the TB/DM Double Burden

A total of 196 physicians participated in the survey. The characteristics of the survey participants are listed in Table 6. Sixty percent of the participants were female, and 54.7% graduated from medical school between 2000-2009. There were 88.6% from the field of Internal Medicine, and 43.9% practice in the National Capital Region.

Table 6. Sociodemographic characteristics of KAP survey participants (n=196)

Characteristic	Value
Age [years (mean, SD), n = 182]	35.5 ± 8.8
Sex (% , n=195)	
Male	40.0
Female	60.0
Graduate year from medical school (% , n=181)	
2010 – 2012	16.6
2000 – 2009	54.7
1990 – 1999	17.1
1980 – 1989	07.7
< 1980	03.9
Highest post-graduate training (% , n=194)	
Internship	04.6
Residency	54.6
Fellowship	38.2
Others	02.6
Residency specialty (% , n=185)	
Internal Medicine	88.6
Family Medicine	10.3
Others	01.1
Fellowship subspecialty (% , n=74)	
Cardiology	10.8
Endocrinology	12.2
GI	06.8
IDS	25.7
Medical Oncology	04.0
Nephrology	09.4
Pulmonary	21.6
Rheumatology	02.7
Others	06.8
Practice setting (% , n = 186) ^a	
Private practice (clinic/hospital)	57.5
Gov't health service (clinic/hospital)	48.9
Academe-affiliated (clinic/hospital)	18.8
HMO (clinic/hospital)	09.1
NGO (clinic/hospital)	01.6
Other	01.2
Location of practice (% , n=164)	
Luzon	12.2
Visayas	31.7
Mindanao	12.2
NCR	43.9

^a Total does not equal 100 because of multiple types of practice.

Table 7 shows the distribution of the number of DM cases, TB cases and cases with TB and DM that participating physicians have seen in their clinical practice. Most of the physicians (53.2%) have 5-20 DM cases. In terms of tuberculosis, 44.4% of the participants

have about 5 - 20 TB patients. Majority of the participants (53.8%) have seen only less than five cases of combined TB and DM, but 34.5% have seen 5 - 20 patients of combined TB-DM disease.

Table 7. Distribution of estimated number of patients seen by doctors per month, by clinical diagnosis

# of patients seen	Clinical diagnosis of patients		
	DM (%)	TB (%)	DM & TB (%)
< 5	17.0	05.3	53.8
5 – 10	33.0	20.1	19.4
11 – 20	20.2	24.3	15.1
21 – 40	18.6	22.8	07.5
41 – 80	05.3	14.3	02.1
81 – 160	04.3	10.6	02.1
> 160	01.6	02.6	-

The first part of the questionnaire asked about the participants' knowledge about TB and DM. Table 8A shows the distribution of how the physicians answered the different knowledge questions. Majority of the participants were able to correctly answer questions on symptoms seen and diagnostic tests used for tuberculosis and diabetes. However, less than half of the respondents were able to correctly answer questions regarding the prevalence of and the risk of acquiring TB, DM and the combination of these two diseases.

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Table 8A. KAP survey results, Part 1: General knowledge on TB and DM (n = 196)

	No.	%
1. What is the estimated prevalence of pulmonary TB in the Philippines today?		
1 per 100,000 Filipinos has pulmonary TB	10	5%
1 per 10,000 Filipinos has pulmonary TB	36	19%
1 per 1,000 Filipinos has pulmonary TB	45	23%
4 per 1,000 Filipinos have pulmonary TB⁺	103	53%
2. What percentage of Filipinos have diabetes mellitus?		
1 %	3	2%
5 %⁺	34	17%
10 %	78	40%
20%	81	41%
3. Who among the following persons is most likely to have pulmonary tuberculosis?		
A patient with cough of 2-3 weeks or more duration⁺	123	63%
A patient with hemoptysis	24	12%
A close contact to a TB patient	49	25%
4. What is the recommended initial test for an adult patient with symptoms of pulmonary TB?		
Chest X-ray	64	33%
Purified Protein Derivative (PPD) skin test	5	3%
At least 2 sputum specimens sent for sputum microscopy for acid fast bacilli⁺	127	65%
5. The clinical response of TB patients to treatment is best monitored by:		
Serial chest x-ray	10	5%
Follow-up sputum microscopy⁺	123	63%
Clinical improvement (ex. weight gain, decreased coughing)	61	31%
6. Which of the following is/are strongly associated with DM?*		
Impaired glucose tolerance⁺	162	83%
Sedentary lifestyle⁺	103	53%
Hyperlipidemia⁺	87	44%
History of gestational diabetes⁺	94	51%
7. The risk of tuberculosis among patients with diabetes mellitus is:		
Not significant	14	7%
2 times more than non-diabetic patients⁺	84	43%
5 times more than non-diabetic patients	72	37%
10 times more than non-diabetic patients	24	12%
8. The diagnostic fasting plasma glucose level in diabetes mellitus is:		
>= 110 mg/dl	35	18%
>= 126 mg/dl⁺	150	77%
>= 146 mg/dl	7	4%
>= 180 mg/dl	4	2%
9. The diagnostic post-prandial glucose level for diabetes is:		
>= 140 mg/dl	39	20%
>= 160 mg/dl	13	7%
>= 180 mg/dl	38	19%
>= 200 mg/dl⁺	105	54%
10. The optimal method/s of assessing the effectiveness of the treatment plan to glycemic control is/are:		
Oral glucose tolerance test	2	1%
Self-monitoring of blood glucose	6	3%
HbA1c⁺	72	37%
Oral glucose tolerance test AND Self-monitoring of blood glucose	7	4%
HbA1c AND Self-monitoring of blood glucose	107	55%
Oral glucose tolerance test, self-monitoring of blood glucose, and HbA1c	2	1%

*Total does ≠ 100 because of multiple answers to the question ⁺ Correct answers

The second part of the questionnaire asked about the participants' opinions regarding the NTP, DOTS, the need to screen for TB in DM patients and vice versa, and the management of TB, DM and the combination of these two diseases. Table 8B shows the distribution of the participants' perceptions on the public health management of TB and DM. Combining "agree" and "strongly agree" answers, more than 70% of participants had favorable perceptions about the NTP and the DOTS program. More than 70% of the participants also agreed that screening for diabetes should be done in patients with tuberculosis; similarly, that tuberculosis screening should be performed for patients with diabetes. Around 50% of participants agreed to the statements implying difficulties in treating patients with the combined TB and DM.

Table 8B. KAP survey results, Part 2: Perceptions and attitudes on public health aspects of TB and DM (n = 196)

	No.	%
11. The National TB Control Program (NTP) has been efficient in improving TB cure rates	7	4%
Strongly disagree		
Disagree	15	8%
Neither Disagree nor Agree	25	13%
Agree	106	54%
Strongly agree	35	18%
I don't know	7	4%
12. You are confident that your patient will be cured if you enroll him/her to a TB Directly Observed Treatment Short-course (DOTS) Clinic		
Strongly disagree	6	3%
Disagree	11	6%
Neither Disagree nor Agree	11	6%
Agree	99	51%
Strongly agree	67	34%
I don't know	1	1%
13. You are worried about getting PTB infection while examining a patient who has TB.		
Strongly disagree	8	4%
Disagree	49	25%
Neither Disagree nor Agree	26	13%
Agree	80	41%
Strongly agree	29	15%
I don't know	1	1%

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14. Patients with TB should be screened for diabetes.		
Strongly disagree	8	4%
Disagree	17	9%
Neither Disagree nor Agree	27	14%
Agree	93	48%
Strongly agree	48	25%
I don't know	1	1%
15. Patients with diabetes should be screened for TB.		
Strongly disagree	2	1%
Disagree	23	12%
Neither Disagree nor Agree	30	15%
Agree	95	49%
Strongly agree	42	22%
I don't know	2	1%
16. It is difficult to treat TB in diabetic patients.		
Strongly disagree	11	6%
Disagree	51	26%
Neither Disagree nor Agree	24	12%
Agree	89	46%
Strongly agree	17	9%
I don't know	3	2%
17. It is difficult to control the blood sugar of diabetic patients infected with TB.		
Strongly disagree	4	2%
Disagree	65	33%
Neither Disagree nor Agree	25	13%
Agree	79	41%
Strongly agree	13	7%
I don't know	9	5%
18. At a minimum, people with diabetes should be asked about the presence of cough (lasting more than 2 weeks) at the time of diabetes diagnosis.		
Strongly disagree	4	2%
Disagree	13	7%
Neither Disagree nor Agree	26	13%
Agree	116	59%
Strongly agree	35	18%
I don't know	1	1%
19. A referral system should be established so that diabetic patients with suspected TB are promptly sent to TB diagnostic and treatment centers.		
Strongly disagree	4	2%
Disagree	6	3%
Neither Disagree nor Agree	5	3%
Agree	118	60%
Strongly agree	63	32%
I don't know	0	0%
20. The same TB treatment regimen should be prescribed to people with diabetes as for people without diabetes		
Strongly disagree	3	2%
Disagree	14	7%
Neither Disagree nor Agree	7	4%
Agree	126	64%
Strongly agree	44	22%
I don't know	2	1%

The third part of the questionnaire asked about how participants manage persons with tuberculosis and/or diabetes. The distribution of the participants' on the clinical management of TB and DM is presented in Table 8C. Less than 55% of participants routinely screen for TB in DM patients or screen for DM in TB patients. The most favored next step for DM patients suspected of having TB is ordering a chest x-ray and sputum AFB (both used by >70% of participants). Given a patient with diabetes who is found to have TB, 46% would refer the patient to a DOTS clinic for management, but would continue to manage the patient's diabetes themselves. On the other hand, given a patient with TB who was found to have diabetes, 45% of participants said that they would manage the patient for both conditions themselves.

Table 8C. KAP survey results, Part 3: Professed practices on clinical management of TB and DM(n = 196)

	No.	%
21. For adult diabetic patients that I see in my clinic or at the hospital, I routinely ask them for symptoms suggestive of TB at each clinic visit		
Always	49	25%
Most of the time	54	28%
Sometimes	84	43%
Never	7	4%
Not applicable. I do not see diabetic patients in my practice.	2	1%
22. When I see a diabetic patient in my clinic or hospital for whom I suspect pulmonary TB, I do the following (check all that apply): ^a		
I prefer to refer them to a DOTS clinic or specialist for further work-up & management	29	15%
I request for a chest x-ray	152	78%
I request for sputum AFB	144	74%
I request for sputum TB culture	24	12%
I request or do a PPD skin test	22	11%
Other	3	2%
23. If my diabetic patient is confirmed to have PTB, I will:		
Manage and treat the patient myself for both TB and diabetes	35	18%
Co-manage the patient with a specialist (for example, an infectious disease specialist or pulmonologist)	34	18%
Refer to a DOTS clinic but I will continue to manage the patient for diabetes	87	46%
Refer to a DOTS clinic and ask patient to return to me after completion of TB treatment	7	4%
Not applicable. I am a pulmonary specialist.	5	3%
Other	22	12%

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24. For my adult patients who are diagnosed to have TB, I routinely screen for diabetes mellitus:		
Always	32	17%
Most of the time	53	28%
Sometimes	90	47%
Never	14	7%
Not applicable. I do not see TB patients in my practice.	1	1%
25. If a TB patient I am managing also has diabetes mellitus, I will:		
Manage and treat the patient myself for both diabetes and TB conditions	87	45%
Refer the patient to a specialist (for example, endocrinologist or diabetologist) for further work-up and treatment of both disease conditions	39	20%
I will co-manage the patient with a specialist in diabetes	50	26%
Not applicable. I am a specialist in endocrinology/diabetes management.	8	4%
Other	9	5%

^aTotal does not equal 100 because of multiple answers to the question.

4. Focus Group Discussions on the TB/DM Double Burden

FGDs were conducted with three of the Degenerative Diseases Office (DDO) staff members and on a separate venue, with three of the National TB Control Program (NTP) members. The epidemiology and screening of DM in TB and TB in DM were discussed. They were also asked about their insights on collaborative activities related to the control and management of TB and DM.

DM in TB

The DDO members considered DM in TB not much of a public health problem in the Philippines. One participant estimated that only 1 out of 10 TB patients have DM. They opined that the extent of the problem is not that much appreciated because the communicable diseases programs are separate from the non-communicable diseases program. There are separate screening and management activities for DM and TB. Also, they stated that physicians at the local health centers would tend to focus primarily on the chief complaint due to a big patient load.

Similarly, the NTP staff did not consider DM in TB as a serious problem. One of the members estimated that the prevalence of DM among TB patients would probably be similar to the prevalence of DM among the general population because TB is not a risk factor for DM. However, they agreed that DM is a risk factor for TB.

Regarding actual figures on the burden of disease for these two conditions, the DDO staff expressed that opinion that it would be difficult to get additional information on the epidemiology of DM in TB because of the separate registries for DM and TB at the Rural Health Unit (RHU) level. It would take time to match patient records in the TB and DM registries. A more personalized registry form is now available; however, they have just started using this form. The NTP staff mentioned that there is an ongoing study on TB-DM led by Dr. Camilo Roa.

The DDO staff recognized the importance of screening DM among patients with TB but they expressed the need to for a pilot study to consider the feasibility of screening at the RHU level since the caseload is heavy in these facilities. One of the suggestions they offered was to do screening if the patient has risk factors for DM. The Package of Essential Non-Communicable Diseases (PEN) form might be useful for screening. The DDO staff opined that the Mayor/Local Government Unit (LGU) should provide for these, with possible contributions from the private sector.

Moreover, the NTP staff also considered screening for DM among patients with TB as very important but may not be feasible due to substantial resource requirements. The consensus of this group was that RBS by a glucometer is a cost-effective method for screening. Although FBS would have been more appropriate, they expressed the view that

this would not be readily available. The estimated cost for RBS would be around PhP 150 to PhP 250 per person. But initially, acquiring the glucometer would cost around PhP 3,000 to 4,000. The strips would cost PhP 1,000 per 25 strips. Furthermore, one of the members feared that this might cause stigma among patients with DM when associated with TB.

TB in DM

The DDO members found it difficult to answer the question on the epidemiology of TB among DM patients. They think this is due to the vertical nature of the different programs. But according to the NTP staff, the immunocompromised state of diabetic patients make them more at risk for developing TB compared to the general population, stating an odds ratio of 2.4. Again, the ongoing TB-DM study of Dr. Roa was mentioned as a good source of information regarding the extent of this problem, once the study is completed.

The DDO members opined that screening for TB among diabetic patients is important but not routine. They were aware of the importance of having a holistic approach to patient management but they did not believe that the RHU has the ability and resources to address all of these problems in an integrated manner. Likewise, the NTP staff opined that screening for TB among diabetic patients is important considering that they are more at risk.

Two of the DDO members thought that in a scale of 1 to 10 (with 10 being the most feasible), feasibility to screen for TB among DM patients would be around 8. No opinion was given on the most cost-effective tests to use for TB screening, although CXR and sputum AFB smears were regarded as helpful. They emphasized the importance of good history and physical exam. A chest X-ray would cost around PhP 175 to 300, but did not have estimates on the cost of an AFB smear.

The NTP staff also thought that it would be feasible to screen for TB among DM patients but there would be difficulty in reaching out to the population of diabetic patients – where/how to find these patients for them to be screened. They were not sure on the awareness of the physicians/implementers as well as the patients/clients regarding DM as a risk for TB. For the screening tests, one of the members considered GeneXpert MTB/RIF, a cartridge-based automated test to identify *Mycobacterium tuberculosis* and resistance to rifampicin, as the most sensitive test. However this would cost around USD 9 (approximately PhP 400) per cartridge, good only for one person. This cost estimate does not include the fee for the technician, capital costs, training, and others. Sputum AFB smear is a lot cheaper: PhP 50 or free in public centers, and PhP 150 in private centers. However, they stated that the sensitivity of this test is low especially among diabetic patients, who are more likely to be smear-negative. A CXR (estimated cost of PhP 200 - 300 per firm) in addition to sputum AFB smears would increase the diagnostic yield. If CXR is not available, they suggested that the healthcare provider should screen for TB signs and symptoms before ordering diagnostic tests.

Collaborative TB/DM activities

The DDO members are not aware of any existing TB/DM initiatives in the Philippines. They thought that it would be difficult to mount such activities because there is still not enough evidence on the combined TB-DM prevalence, which makes budget allocation a low priority. One of the opportunities that they see is the PEN form. If TB would be included in the form, it would serve as an integrated screening checklist. Data from this

might help establish the prevalence of TB/DM and therefore make it justifiable to plan and implement TB/DM collaborative activities.

The NTP members also expressed the need for more data on the TB-DM double burden. They emphasized the collaborative TB-DM study headed by Dr. Roa, which is already on the final stage of completion. One of the opportunities that they see for them to do collaborative work with DDO is the proximity of their offices at the Department of Health.

5. Costing of Bidirectional Screening of TB in Diabetic Patients and Vice-Versa

Prevalence estimates for TB, DM, and TB & DM

The 2013 global TB report of WHO reported that the prevalence estimate for TB in the Philippines (population 97 million) in 2012 was 450,000 in numbers (uncertainty interval 390,000-500,000) or 461 per 100,000 population (uncertainty interval 405-520).⁴⁴ While the study of Sy and co-workers on the prevalence of metabolic syndrome among Filipinos reported that 5% or approximately 5 million people have diabetes in the Philippines.⁴⁵ As for the TB/DM double burden, results from the review of medical records estimated that the prevalence for TB/DM double burden ranges from 10.3% to 15.6% (Table 2).

Estimated cost for screening DM and TB

Several DM and TB screening tests were used to compute the cost of bidirectional screening of TB in diabetic patients and vice-versa. Fasting blood sugar (FBS), and two-hour oral glucose tolerance test (2hr OGTT) were included in the costing exercise since these DM tests were the top 2 favored tests for screening DM according to the results from the review of medical records (Table 4). Both FBS and 2hr OGTT were used as baseline tests for screening DM among TB patients while the follow up DM test at year 1 used only FBS.

Sputum AFB smear 2x (AFB 2x) and chest x-ray (CXR) were also used for the costing exercise. Both TB tests were the preferred tests for screening TB in DM clinics and TB DOTS clinics (Table 4). For the baseline screening cost, these two tests, AFB 2x and CXR were included in the computation. Furthermore, three follow-up programs were used in the computation for the follow-up screening cost: CXR at year 1, AFB 2x at year 1, and CXR + AFB 2x at year 1.

Table 9 summarizes the unit cost for the preferred DM and TB screening tests. The cost estimates used came from the laboratory service department price list/fees of the Lung Center of the Philippines (LCP), the reference cost center hospital of the study.

Table 9. Cost of DM and TB Screening Test

Test	Cost in PhP
DM Screening	
FBS	275.00
2hr OGTT	1,142.00
TB Screening	
CXR	396.00
Sputum AFB 2x	770.00

Figure 1 shows the costs for screening DM in persons with TB. The DM tests used in the costing exercise for the computation of the screening cost were FBS, 2hr OGTT and HbA1c. The basis for the maximum number of TB patients to be screened for DM was from the WHO report that estimated the prevalence of TB to be 450,000 in numbers (uncertainty interval 390,000-500,000).⁴⁴

Figure 1. Screening cost for DM in persons with TB

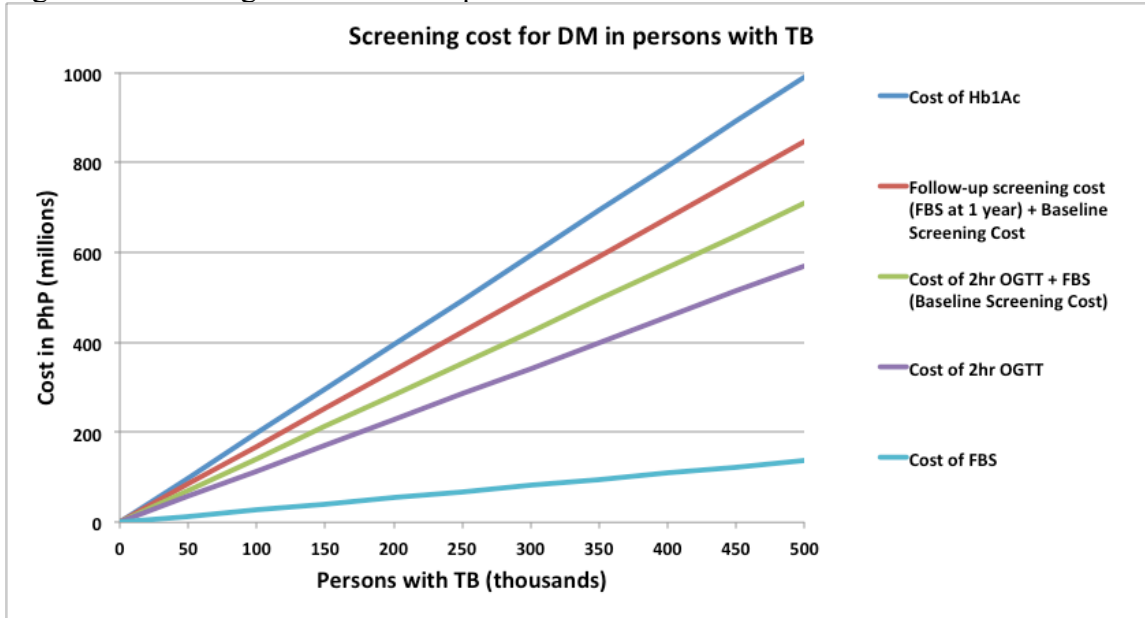


Table 10 presents by percentage of TB patients screened for DM, the estimated cost of each DM screening test (FBS, 2hr OGTT, and Hb1Ac), the baseline screening test (FBS + 2hr OGTT), and the total screening cost [baseline cost + follow-up cost (FBS at year 1)] for 500,000 TB patients. The estimated cost for screening all TB patients by FBS, 2hr OGTT, or Hb1Ac would be 137.5, 571, and 990 million pesos, respectively. Furthermore, the estimated costs of doing baseline screening (FBS + 2hr OGTT) and baseline +follow up (FBS at year 1) screening were compared to the estimated cost of doing a baseline Hb1Ac screening test. The results showed that the costs of a baseline test and baseline + follow-up test were cheaper by 28.4% and 14.5%, respectively, than the cost of a Hb1Ac test.

Table 10 Screening cost (in million PhP) for DM among TB patients

DM Screening Test	Percentage of TB patients to be screened for DM				
	10%	15%	25%	50%	100%
FBS	13.8	20.6	34.4	68.8	137.5
2hr OGTT	57.1	85.6	142.8	285.5	571.0
Hb1Ac	99.0	148.5	247.5	495.0	990.0
Baseline screening ^a	70.8	106.3	177.1	354.2	708.5
Total screening ^b	84.6	126.9	211.5	423.0	846.0

^a Baseline screening: FBS + 2hr OGTT; and ^b Total screening: Baseline screening + follow-up FBS screening at 1 year

Figure 2 presents the screening cost for TB in persons with DM. CXR and AFB 2x were the two TB tests used to compute the screening costs. Since the current prevalence of diabetes in the Philippines is 5% or approximately 5 million people,⁴⁵ the computation of the maximum screening cost was based on the assumption that all persons with DM (5 millions) will be screened for TB. The estimated cost for screening all DM patients by CXR and AFB 2x would be 1.98 and 3.85 billion pesos, respectively. In addition, the cost of a sputum AFB 2x in LCP (PhP 770.00) was 94% more than the cost of a CXR (PhP 396.00).

Figure 2. Screening cost for TB in persons with DM

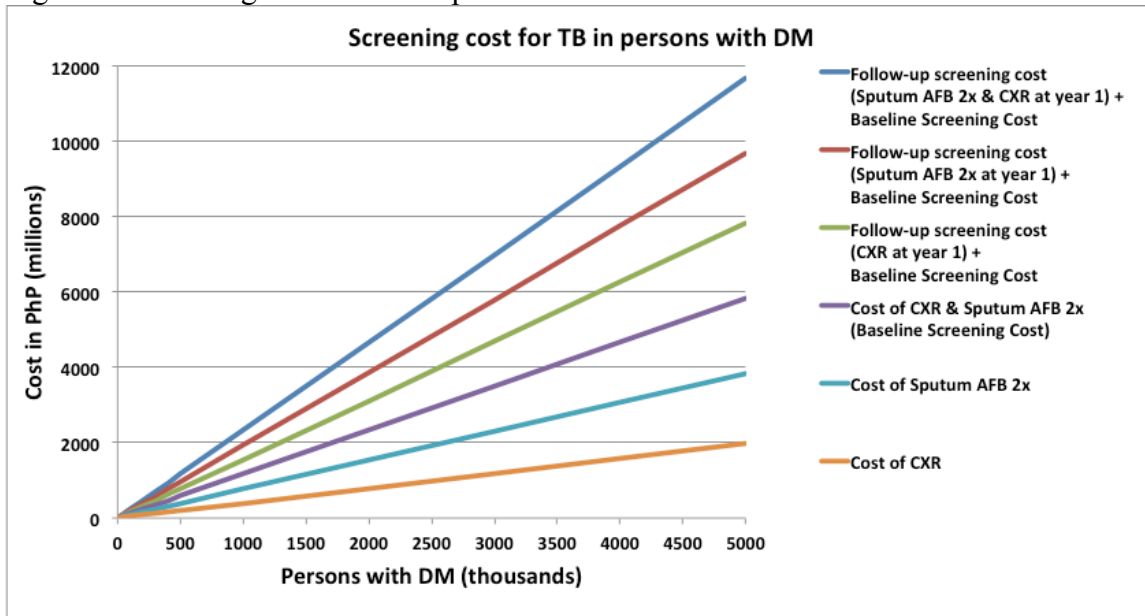


Table 11 shows by percentage of DM patients screened for TB, the estimated cost of each TB screening test (CXR, and AFB 2x), the baseline screening (CXR + AFB 2x), and three screening programs [baseline cost + follow-up cost (CXR at year 1), baseline cost + follow-up cost (AFB 2x at year 1), and baseline cost + follow-up cost (CXR + AFB 2x)] for 5 million persons with DM. Follow-up screening programs 1, 2 and 3 would require an additional 34%, 66% and 100% increase from the baseline screening cost, respectively.

Table 11 Screening cost (in million PhP) for TB among DM patients

TB Screening Test	Percentage of DM patients to be screened for TB				
	10%	15%	25%	50%	100%
CXR	198	297	495	990	1980
Sputum AFB 2x	385	578	962	1925	3850
Baseline screening ^a	583	874	1458	2915	5830
Screening program 1 ^b	781	1172	1952	3905	7810
Screening program 2 ^c	968	1452	2420	4840	9680
Screening program 3 ^d	1166	1749	2915	5830	11660

^aBaseline screening: CXR and Sputum AFB 2x; ^bScreening program 1: Baseline screening + follow-up CXR screening at 1 year; ^cScreening program 2: Baseline screening + follow-up sputum AFB 2x screening at 1 year; and ^dScreening program 3: Baseline screening + follow-up CXR and sputum AFB 2x screening at 1 year

The results of the costing exercise revealed that bidirectional screening of TB in diabetic patients and vice-versa would require a huge budget for the screening programs to be implemented especially for screening TB among persons with DM.

VII. Discussion and Recommendations

Our retrospective study suggests that 1 in 10 patients in TB clinics have concomitant DM, while almost 2 in 10 patients seen in DM clinics have concomitant TB. In addition, the 2007 National Tuberculosis Prevalence Survey (NTPS) also reported that almost 2 in 10 participants in the survey with DM have PTB, which was in agreement with our retrospective study.⁴⁶ These figures are derived from clinics where there is no systematic screening of TB or DM—i.e., 71.1% of patients in TB clinics did not have any test done to detect DM, while 80.1% of patients in DM clinics had no tests done for TB detection. Hence our estimates of 10.3% - 15.6% for combined TB-DM are likely to be grossly underestimated. Our desk review of 23 studies of concomitant DM in TB patients showed estimates of 4 – 44%, including a retrospective study in a Metro Manila hospital (~20%); estimates of ~30-40% may very well be the case in the Philippines with more systematic screening. On the other hand, our desk review of 7 studies showed a wide range of 0.01% to 11.9% prevalence of TB among DM patients. Our records review suggests that the latter (higher) estimate applies to

our setting, given that the very low estimate of 0.01% in the literature was found in a setting with low TB prevalence in the general population. Moreover, our survey of practicing physicians revealed that one-third saw around 5 – 20 patients with both TB and DM in a month, although the majority saw less than 5 in a month.

We investigated whether symptoms suggestive of TB in DM patients or DM in TB patients would be useful in filtering and reducing the number of patients who need to undergo laboratory-confirmed screening tests. Our records review suggests that clinical symptoms alone would not be sensitive or specific enough to detect concomitant TB or DM. Only 16.7% of diabetic patients presented with weight loss, 16.7% with cough of 2 or more weeks duration, while only 13.3% had fever. On the other hand, for patients in TB clinics, 54.6% presented with weight loss, but this is not specific enough to suspect DM as its cause, given that TB itself is associated with weight loss. In the TB clinics, 33.3% of patients with concomitant DM were diagnosed by doing a screening test without the benefit of accompanying signs and symptoms. In the DM clinics, an additional 6.7% of the TB cases detected were due to the performance of a screening test alone.

These findings suggest that there is added value in bidirectional screening for TB and DM, regardless of symptoms. Early detection and treatment of TB will reduce the risk of transmission from untreated patients and morbidities associated with late treatment of TB-DM.⁴² Similarly, early detection and good control of DM among TB patients are likely to improve treatment outcomes. Extrapolated to national estimates for TB and DM prevalence, if screening tests for DM and TB, respectively, were applied consistently nationwide and assuming that all the patients will be detected by the health care providers, around 150,000

more diabetic patients would be detected among the 450,000 existing patients with culture-positive TB, and some 355,000 more TB patients would be detected by chest x-ray, sputum AFB or both among the estimated 5 million cases of DM.

However, there are fundamental issues to consider and some constraints to overcome prior to programmatic bidirectional screening for these two diseases nationwide. The major issues to be considered are:

1. Costs of bidirectional screening—estimated to be around PhP 68.8 - 137.5 million for one-time FBS screening among prevalent TB cases, and around PhP 1.98 billion for one-time chest x-ray and an additional PhP 3.85 billion for two sputum AFB smears, among diabetic patients. The costs are based on user charges in a government hospital and thus include costs for human resources, use of equipment, materials and supplies. If carried out as government-initiated screening programs or if covered by a PhilHealth outpatient benefit package, there will be economies of scale that would significantly drive down costs. As an interim step, rolling out of screening programs could also consider socioeconomic factors in prioritizing screening among those with increased risk of combined diseases, such as urban poor areas, where overcrowding, poor ventilation, smoking and the marketing of cheap but unhealthy ‘fast food’.
2. Time required in busy outpatient services to carry out the screening tests—this concern was raised at the FGDs, suggesting the need for pilot studies to determine the feasibility of implementing the screening programs in both TB clinics and medical services where diabetic patients are seen. Corollary to this is the need to determine the most cost-

effective screening tests for DM and TB as well as the availability and accessibility of these tests in healthcare facilities at various levels.

3. Awareness building and acceptability of screening tests among patients—as raised in the FGDs, there is still stigma attached to the diagnosis of TB and reluctance to provide sputum (for TB screening) or blood samples (for DM screening), or to undergo a chest x-ray (for TB screening).
4. Costs of treatment for diagnosed TB or DM—there will be a significant increase in the TB case detection rate once TB screening among DM patients is rolled out; public services and private-public partnerships must be ready to meet the demand for TB-DOTS services, including quality anti-TB drugs. Similarly, with the expected rise in DM cases detected through screening programs, the government's Package for Essential Non-Communicable Disease Interventions will need to ensure an adequate supply of anti-diabetes drugs and educational materials for diet and lifestyle change.
5. Creation of an integrated information management system or incorporation with an existing integrated information management system (e.g. ITIS: Integrated TB information system) for TB-DM surveillance, control and management—this is needed to address information and research gaps on the magnitude of the TB-DM problem in the country, long-term outcomes, other associated morbidities, best screening tests to use, cost-effectiveness of interventions including bidirectional screening, and other public health issues in prevention and control.
6. Collaborative or integrated nature of interventions for TB-DM—in addition to the above information and research gaps, it is not clear at this point whether collaborative

arrangements should be made between TB clinics and medical clinics serving DM patients involving inter-clinic referrals, or whether health providers in TB clinics and DM-focused services should be trained to manage both diseases. In the survey of practicing physicians, only 50% of the respondents stated that they referred DM patients with TB to TB-DOTS clinics, preferring to manage both diseases by themselves. However, they recognized the challenges of managing combined TB-DM and the standards that need to be met for directly observed treatment for TB. In the FGDs, the DOH staff acknowledged that there are no existing collaborative activities between the National TB Program and the Degenerative Diseases Office with regard to integrated management of TB-DM, even as they recognized the importance of such, especially in terms of screening for and management of TB among diabetic patients. Some of the reasons for the absence of collaboration stem from the vertical nature of the programs, even though both communicable and non-communicable disease programs are housed under one Center in the Department of Health.

The above research issues complement the research agenda drawn by international experts on TB and DM,⁴⁷ and which remain relevant and not fully answered today. Of the ten research questions identified by the expert meeting held in November 2009, four were identified as high priority and hopefully these research questions be included in the next TB research agenda of DOH: (i) whether, when and how to screen for TB in patients with DM, and vice versa; (ii) the impact of DM and non-diabetes hyperglycemia on TB treatment outcomes and deaths; (iii) implementation and evaluation of the TB-DOTS model for DM

management; and (iv) the development and evaluation of better point-of-care diagnostic and monitoring tests for DM patients.

There are several limitations inherent to the rapid assessment techniques used in this study. The small and retrospective nature of the clinical chart review and the desk review of other studies can only provide very rough estimates of the double burden from TB and DM. The results of the ongoing prospective study supported by WHO/CIDA/DOH is much awaited to bolster burden of disease estimates, even though, the study only looked into diabetics with TB. Similarly, the physician survey and FGDs merely provide a snapshot of the knowledge and practices of healthcare providers and public health programs, but additional studies are needed, including operational research to address the issues raised in Items 1 – 6 above.

In conclusion, our rapid assessment provides additional information to support an integrated approach to the considerable double burden of tuberculosis and diabetes mellitus, however, a pilot study should be done first. Given the government's commitment to the nationwide control of TB, the under-explored frontier of TB among diabetic patients can be among the stretch goals towards increased case detection, management and prevention efforts. Likewise, the increasing prevalence of diabetes in the country and the associated risk of TB transmission in a TB-endemic population suggest the need for raising awareness on the need for TB screening. However, there is a body of programmatic and operational research questions to answer before an integrated approach to bidirectional screening can actually be implemented.

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Appendix A

Guidelines for the Critically Appraising Studies of the Prevalence of Health Problems¹⁴

1. Are the results of the study valid?

Is the study design appropriate for the research question?

- *Ideally a cross-sectional survey should be used*

Are the study subjects obtained appropriately?

- *A random sample, (stratified if appropriate) of the target population needs to be identified*

Is the sampling frame appropriate?

- *Must be the best possible (ie, census data) to minimize bias*

Is the response rate adequate?

- *The greater the number not available for measurement, the less valid the prevalence estimate*

Are objective and suitable criteria used for measurement of the issue or concern?

- *Outcomes need to be valid and reliable, definitions and details of the survey questions need to be provided*

Is the concern or outcome measured in an unbiased fashion?

- *Assessors/interviewers should be trained and blinded, if possible*

2. What are the results?

Are the estimates of prevalence or incidence given in detail?

- *95% confidence intervals should be provided*

Is the sample size adequate?

- *A large sample size will produce a smaller error rate and smaller confidence intervals*

Are the results given by subgroup, if appropriate?

3. What is the applicability of the results?

Are the study subjects and the setting described in detail and similar to those of interest to you?

- *Study sample should be described in enough detail to determine the generalizability of the results to your population*

Will the results lead directly to a health care or policy decision?

Item	Score
1. Random sample	10 points
2. Unbiased sampling frame (ie, census data)	10 points
3. Adequate sample size	10 points
4. Outcomes valid and reliable	10 points
5. Adequate response rate	10 points
6. Point prevalence estimates provided	10 points
7. Confidence intervals provided	10 points
8. Definition and duration of low back pain given	10 points
9. Study refusers described	10 points
Maximum score	90 points

Score of ≥ 70 : high quality study

Score of ≥ 45 to 69: moderate quality

Score of < 45 : low quality

Appendix B

KAP Questionnaire

Tuberculosis and Diabetes Mellitus Control and Care

Greetings. We are doing a study on “Tuberculosis and Diabetes Mellitus Control and Care” under the auspices of the Foundation for the Advancement of Clinical Epidemiology (FACE, Inc.), in collaboration with the Dept. of Clinical Epidemiology, UP Manila College of Medicine, and the Institute of Clinical Epidemiology, UP Manila National Institutes of Health. We are conducting this study to determine the extent of the association between tuberculosis and diabetes in the Philippine setting and existing efforts to address this dual burden.

We would like to learn about your knowledge, attitudes and practices regarding tuberculosis and diabetes. This will help us develop recommendations to the Department of Health on the approach to the detection and management of these two diseases and how you as physicians could be better involved. The questionnaire will take less than 30 minutes of your time. Please feel free to ask questions from any member of the research team should you have any clarifications.

A. General information on you and your practice:

Your age (in years): _____

Sex:

- Male
- Female

Year you graduated from medical school: _____

Highest post-graduate training (including ongoing training)

- Internship
- Residency
- Fellowship
- Other: _____

Residency Specialty: _____

Fellowship Subspecialty: _____

Practice setting: (check all that apply)

- Private practice (clinic or hospital)
- Government health service (clinic or hospital)
- Health maintenance organization (clinic or hospital)
- Academe-affiliated clinic or hospital
- NGO clinic or hospital
- Other: _____

Location of practice (city or town or municipality): _____

Estimated number of patients with TB that you see in a month: _____

Estimated number of patients with diabetes mellitus that you see in a month: _____

Estimated number of patients with both TB and diabetes mellitus that you see in a month: _____

B. General information questions on tuberculosis and diabetes mellitus

1. To the best of your knowledge, what is the estimated prevalence of pulmonary TB in the Philippines today? (Please choose only 1 answer)

- 1 per 100,000 Filipinos has pulmonary TB
- 1 per 10,000 Filipinos has pulmonary TB
- 1 per 1,000 Filipinos has pulmonary TB
- 4 per 1,000 Filipinos have pulmonary TB

2. To the best of your knowledge, what percentage of Filipinos have diabetes mellitus? (Please choose only 1 answer)

- 1%
- 5%
- 10%
- 20%

3. Who among the following persons is most likely to have pulmonary tuberculosis? (Please choose only 1 answer)

- A patient with cough of 2-3 weeks or more duration
- A patient with hemoptysis
- A close contact to a TB patient

4. What is the recommended initial test for an adult patient with symptoms of pulmonary TB? (Please choose only 1 answer)

- Chest X-ray
- Purified Protein Derivative (PPD) skin test
- At least 2 sputum specimens sent for sputum microscopy for acid fast bacilli (AFB)

5. The clinical response of TB patients to treatment is best monitored by: (Please choose only 1 answer)

- Serial chest x-ray
- Follow-up sputum microscopy
- Clinical improvement (ex. weight gain, decreased coughing)

6. Which of the following is/are strongly associated with diabetes mellitus? (Select all that apply)

- Impaired glucose tolerance
- Sedentary lifestyle
- Hyperlipidemia
- History of gestational diabetes

7. The risk of tuberculosis among patients with diabetes mellitus is: (Please choose only 1 answer)

- Not significant
- 2 times more than non-diabetic patients
- 5 times more than non-diabetic patients
- 10 times more than non-diabetic patients

8. The diagnostic fasting plasma glucose level in diabetes mellitus is: (Please choose only 1 answer)

- ≥ 110 mg/dl
- ≥ 126 mg/dl
- ≥ 146 mg/dl
- ≥ 180 mg/dl

9. The diagnostic post-prandial glucose level for diabetes is: (Please choose only 1 answer)

- ≥ 140 mg/dl
- ≥ 160 mg/dl
- ≥ 180 mg/dl
- ≥ 200 mg/dl

10. The optimal method/s of assessing the effectiveness of the treatment plan to glycemic control is/are:

- Oral glucose tolerance test
- Self-monitoring of blood glucose
- HbA1C
- Oral glucose tolerance test AND Self-monitoring of blood glucose
- HbA1C AND Self-monitoring of blood glucose

C. Information on your views on TB and diabetes

11. The National TB Control Program (NTP) has been efficient in improving TB cure rates.

- Strongly disagree
- Disagree
- Neither Disagree nor Agree
- Agree
- Strongly agree
- I don't know

12. You are confident that your patient will be cured if you enroll him/her to a TB Directly Observed Treatment Short-course (DOTS) Clinic.

- Strongly disagree
- Disagree
- Neither Disagree nor Agree
- Agree
- Strongly agree
- I don't know

13. You are worried about getting PTB infection while examining a patient who has TB.

- Strongly disagree
- Disagree
- Neither Disagree nor Agree
- Agree
- Strongly agree
- I don't know

14. Patients with TB should be screened for diabetes.

- Strongly disagree
- Disagree
- Neither Disagree nor Agree
- Agree
- Strongly agree
- I don't know

15. Patients with diabetes should be screened for TB.

- Strongly disagree
- Disagree
- Neither Disagree nor Agree
- Agree
- Strongly agree
- I don't know

16. It is difficult to treat TB in diabetic patients.

- Strongly disagree
- Disagree
- Neither Disagree nor Agree
- Agree
- Strongly agree
- I don't know

17. It is difficult to control the blood sugar of diabetic patients infected with tuberculosis.

- Strongly disagree
- Disagree
- Neither Disagree nor Agree
- Agree
- Strongly agree
- I don't know

18. At a minimum, people with diabetes should be asked about the presence of cough (lasting more than 2 weeks) at the time of diabetes diagnosis.

- Strongly disagree
- Disagree
- Neither Disagree nor Agree
- Agree
- Strongly agree
- I don't know

19. A referral system should be established so that diabetic patients with suspected TB are promptly sent to TB diagnostic and treatment centers.

- Strongly disagree
- Disagree
- Neither Disagree nor Agree
- Agree
- Strongly agree
- I don't know

20. The same TB treatment regimen should be prescribed to people with diabetes as for people without diabetes

- Strongly disagree
- Disagree
- Neither Disagree nor Agree
- Agree
- Strongly agree
- I don't know

D. Information on your clinical management of patients suspected/diagnosed to have TB and/or diabetes

21. For adult diabetic patients that I see in my clinic or at the hospital, I routinely ask them for symptoms suggestive of TB at each clinic visit

- Always
- Most of the time
- Sometimes
- Never
- Not applicable. I do not see diabetic patients in my practice. GO TO QUESTION NO. 24.

22. When I see a diabetic patient in my clinic or hospital for whom I suspect pulmonary TB, I do the following (check all that apply):

- I prefer to refer them to a DOTS clinic or specialist for further work-up & management.
GO TO QUESTION NO. 24.
- I request for a chest x-ray
- I request for sputum AFB
- I request for sputum TB culture
- I request or do a PPD skin test
- Other: _____

23. If my diabetic patient is confirmed to have PTB, I will:

- Manage and treat the patient myself for both TB and diabetes
- Co-manage the patient with a specialist (for example, an infectious disease specialist or pulmonologist)
- Refer to a DOTS clinic but I will continue to manage the patient for diabetes
- Refer to a DOTS clinic and ask patient to return to me after completion of TB treatment

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- Not applicable. I am a pulmonary specialist.
- Other: _____

24. For my adult patients who are diagnosed to have TB, I routinely screen for diabetes mellitus:

- Always
- Most of the time
- Sometimes
- Never
- Not applicable. I do not see TB patients in my practice. END OF SURVEY.

25. If a TB patient I am managing also has diabetes mellitus, I will:

- Manage and treat the patient myself for both diabetes and TB conditions
- Refer the patient to a specialist (for example, endocrinologist or diabetologist) for further work-up and treatment of both disease conditions
- I will co-manage the patient with a specialist in diabetes
- Not applicable. I am a specialist in endocrinology/diabetes management
- Other: _____

THANK YOU VERY MUCH FOR YOUR PARTICIPATION!

Appendix C

Topic Guide for the Focus Group Discussions

Date:

Venue:

Length of discussion:

List of attendees (including position and DOH office/program affiliation)

List of topics for discussion:

Set A Questions (to be started first for the FGD among National TB Control Program staff, followed by Set B Questions)

- As far as you know, how extensive is the problem of TB among diabetic patients? Do you have suggestions on where we might find additional sources of information on this?
- In a scale of 1 to 10, how important do you think it would be to screen for TB among diabetic patients? Why?
- In a scale of 1 to 10, how feasible would it be to screen TB among diabetic patients? Why? What are the challenges that you see in implementing such a program?
- What cost-effective methods or tests could be used for screening for TB among diabetic patients?
- What are your estimates of the cost of these tests or methods that you suggested?

MODERATOR (IF FGD STARTED WITH SET A): LET'S TURN THE TABLE AROUND AND LOOK AT PATIENTS WITH TB WHO MAY NOT KNOW THEY ARE DIABETIC.

Set B Questions (to be started first for the FGD among Non-communicable/Degenerative Disease Office staff, followed by Set A Questions)

- As far as you know, how extensive is the problem of diabetes mellitus among TB patients? Do you have suggestions on where we might find additional sources of information on this?
- In a scale of 1 to 10, how important do you think it would be to screen for diabetes mellitus among patients with TB?
- In a scale of 1 to 10, how feasible would it be to screen for diabetes mellitus among patients in DOTS clinics and MDR-TB clinics? Why? What are the challenges that you see in implementing such a program?
- What cost-effective methods or tests could be used for screening for diabetes among patients in TB-DOTS clinics and MDR-TB clinics?
- What are your estimates of the cost of these tests or methods that you suggested?

MODERATOR (IF FGD STARTED WITH SET B): LET'S TURN THE TABLE AROUND AND LOOK FROM THE LENS OF PATIENTS WITH DIABETES.

Appendix D

Informed Consent Forms for KAP Survey

Information Sheet and Informed Consent Form for Physicians Participating in a Survey on the Double Burden of Tuberculosis and Diabetes Mellitus

Greetings. We are doing a study on “Tuberculosis and Diabetes Mellitus Control and Care.” We are doing this study in collaboration with the Dept. of Clinical Epidemiology, UP Manila College of Medicine, and the Institute of Clinical Epidemiology, UP Manila National Institutes of Health.

We are conducting a study to determine the extent of the association between tuberculosis and diabetes in the Philippine setting and existing efforts to address this dual burden.

1. Why are we doing this research?

We are doing the research to determine the extent of the association between tuberculosis and diabetes in the Philippines and to make recommendations to the Department of Health (DOH) on ways to approach this dual burden of disease. This topic is one of the priorities in the 2012 Research Agenda of the DOH Research Reference Hub.

2. Why have we asked you to take part?

We have asked you to take part because of the likelihood that you see patients with TB, diabetes or both, in your clinical practice.

3. Do you have to take part?

No, you don't have to take part if you wish so. Participating in the study is entirely voluntary. After reading this information, please feel free to ask any questions from any member of our research team (indicated at the end of this information sheet) before deciding whether or not you would like to answer our questionnaire.

4. What will you have to do?

We invite you to answer a brief questionnaire on a mobile device to be provided (or online https://docs.google.com/forms/d/1C4RhFbpTflx2cNsP6q8PaoXD73KO_oF1m7iOK0erER4/vie wform?sid=466e478bd2a9e78f&token=re3NGz4BAAA.YwprJgEIM_wT3OK7n6FnLw.bQIc-NueriyI45q6XBpJdw). The questionnaire will take less than 30 minutes of your time. It will ask you about your type of clinical practice, followed by questions on your knowledge, attitudes and practice related to TB and diabetes.

5. What will happen to the information you give?

Everything that you tell us will be in confidence. This means that we will not tell anyone outside the research team what you have said. Your name is not reflected in the questionnaire, so there will be no way of linking you individually to your responses during the analysis and in the research findings.

6. What do you do now?

If you do not want to answer the questionnaire, then you do not need to do anything. If you would like to participate, please sign the informed consent form below and hand it to one of our research team members.

7. What can you do to know more about this study?

If you want to know more about this research, you may contact the following persons:

Dr Emmanuel Baja
Dr Mary Ann Lansang
Dr Marissa Alejandria
Dr Jill Itable
Dr Kathryn Roa

CONTACT DETAILS: Telephone No. 525 4098
Email one of us at: updce@post.upm.edu.ph

THANK YOU!

Informed Consent Form

I have understood the information about the study: Yes No

I have been able to ask all the questions I want to about the study: Yes No

Are you willing to participate in the questionnaire survey?: Yes No

If yes, please sign the consent form below:

Name of Respondent : _____

Signature: _____

Date signed (Month/Day/Year) _____

Appendix E

Informed Consent Forms for Focus Group Discussions

Information Sheet and Informed Consent Form for Participants in a Focus Group Discussion on the Double Burden of Tuberculosis and Diabetes Mellitus

Greetings. We are doing a study on “Tuberculosis and Diabetes Mellitus Control and Care.” We are doing this study in collaboration with the Dept. of Clinical Epidemiology, UP Manila College of Medicine, and the Institute of Clinical Epidemiology, UP Manila National Institutes of Health. We are conducting a study to determine the extent of the association between tuberculosis and diabetes in the Philippine setting and existing efforts to address this dual burden.

1. Why are we doing this research?

We are doing the research to determine the extent of the association between tuberculosis and diabetes in the Philippines and to make recommendations to the Department of Health (DOH) on ways to approach this dual burden of disease. This topic is one of the priorities in the 2012 Research Agenda of the DOH Research Reference Hub.

2. Why have we asked you to take part?

We have asked you to take part in a focus group discussion because you are involved in a public health program/s that addresses tuberculosis and/or diabetes mellitus control and care.

3. Do you have to take part?

No, you don't have to take part if you wish so. Participating in the study is entirely voluntary. After reading this information, please feel free to ask any questions from any member of our research team (indicated at the end of this information sheet) before deciding whether or not you would like to join the focus group discussion.

4. What will you have to do?

We would like to talk with you and other DOH staff for about 30 minutes to one hour. Please discuss with us freely and openly. If there are any topics or issues we bring up that you do not want to discuss, just let us know during the course of the discussion.

5. What will happen to the information you give?

Everything that you tell us will be held in confidence. This means that in the report of our study findings, we will not link statements during the FGD to anyone in particular. All data and recorded proceedings are in secure storage and available only to the research team.

6. Why do we want to record the FGD?

We would like to record what you say on a recorder. This means we will capture everything you say. The recording will not have your name on it. If you don't want to be recorded let us know and we will take notes instead.

7. What do you do now?

The FGD will be held on _____, 2013, at _____, DOH Compound, Rizal Avenue, Manila. If you do not want to join the FGD, then you do not need to do anything. If you would like to participate, please sign the informed consent form below and either hand it to one of our research team members or email to Dr. Emmanuel S. Baja (principal investigator) at:

updce@post.upm.edu.ph.

8. What can you do to know more about this study?

If you want to know more about this research, you may contact the following persons:

- Dr Emmanuel Baja
- Dr Mary Ann Lansang
- Dr Marissa Alejandria
- Dr Jill Itable
- Dr Kathryn Roa

CONTACT DETAILS: Telephone No. 525 4098

Email one of us at: updce@post.upm.edu.ph

THANK YOU!

Informed Consent Form

I have understood the information about the study: Yes No

I have been able to ask all the questions I want to about the study: Yes No

Are you willing to participate in the focus group discussion?: Yes No

If yes, please sign the consent form below:

Name: _____

Signature: _____

Date signed (Month/Day/Year) _____

Appendix F
FGDs

FGD Table No. 1. **Demographic Profile of Respondents**

Demographics	DDO Staff	NTP Staff
N	3	3
Age	27,34,49	-
Sex	2F, 1M	2F, 1M
Highest Level of educational Attainment	Post-graduate (Masters, MD)	Post-graduate (Masters, MD)

Comparative analysis of responses

Re-aligned responses according to COMMON THEMES

Epidemiology of DM in patients with TB

Question 1: As far as you know, how extensive is the problem of diabetes mellitus among TB patients?

COMMON THEME	DDO 1	DDO 2	DDO 3
Not much of a problem	<ul style="list-style-type: none"> Not much of a problem during my short practice 	<ul style="list-style-type: none"> 1 out of 10 TB patients has DM 	<ul style="list-style-type: none"> I have no direct contact with patients
Communicable diseases are separate from non-communicable diseases	<ul style="list-style-type: none"> Separate screening and management for DM and TB 	<ul style="list-style-type: none"> Focus is on the chief complaint due to a big patient load 	<ul style="list-style-type: none">
COMMON THEME	NTP 1	NTP 2	NTP 3
Not much of a problem	<ul style="list-style-type: none"> Not much of a problem 	<ul style="list-style-type: none"> Not a problem 	<ul style="list-style-type: none"> Not much of a problem because TB is not a risk factor for diabetes. The prevalence of DM among TB patients would probably be similar to that of DM among the general population.

Epidemiology of DM in patients with TB

Question 2: Do you have suggestions on where we might find additional sources of information on this?

COMMON THEME	DDO 1	DDO 2	DDO 3
No central registry. Separate registry (for TB and DM) at the RHU level	•	• Patient personalized form at the RHU and LHC still at infant stage	• It would take time to dig deeper to match the TB and DM registry
COMMON THEME	NTP 1	NTP 2	NTP 3
We are waiting for the TB DM study of Dr Camilo Roa	•	•	•

Screening for DM in patients with TB

Question 3: In a scale of 1 to 10, how important do you think it would be to screen for diabetes mellitus among patients with TB?

COMMON THEME	DDO 1	DDO 2	DDO 3
	• 6 • 10 if the patient has risk factors	• 9	• 10
	• Depends on the patient (presence of risk factors)	• Should have an integrated approach. But we have to check feasibility in the RHU	• Need to see the totality especially since DM is a complicated disease
COMMON THEME	NTP 1	NTP 2	NTP 3
	• 5	• 5	• 3 to 4

Screening for DM in patients with TB

Question 4: In a scale of 1 to 10, how feasible would it be to screen for diabetes mellitus among patients in DOTS clinics and MDR-TB clinics? What are the challenges that you see in implementing such a program?

COMMON THEME	DDO 1	DDO 2	DDO 3
	<ul style="list-style-type: none"> • 10 	<ul style="list-style-type: none"> • 7 	<ul style="list-style-type: none"> • 10
	<ul style="list-style-type: none"> • If we have PEN (Package of Essential Non-communicable disease), we can do screening 	<ul style="list-style-type: none"> • Come up with pilot test first since in most facilities, case load is heavy. • Facility enhancement program is also critical (there are several RHUs that are small, narrow and don't have enough windows). 	
COMMON THEME	NTP 1	NTP 2	NTP 3
	<ul style="list-style-type: none"> • 6 	<ul style="list-style-type: none"> • 6 	<ul style="list-style-type: none"> • 5
	<ul style="list-style-type: none"> • 	<ul style="list-style-type: none"> • A possible challenge in implementing this – might cause stigma to the people that DM is correlated with TB 	<ul style="list-style-type: none"> •

Screening for DM in patients with TB

Question 5: What cost-effective methods or tests could be used for screening for diabetes among patients in TB-DOTS clinics and MDR-TB clinics?

COMMON THEME	DDO 1	DDO 2	DDO 3
	<ul style="list-style-type: none"> • Random Blood Sugar or using a glucometer 	<ul style="list-style-type: none"> • Agree with RBS. At least we have results than nothing 	<ul style="list-style-type: none"> • FBS, but may not be available
	<ul style="list-style-type: none"> • If blood sugar is elevated by glucometer, advise lifestyle change. If still elevated, start meds. Also do risk assessment. If negative family history and no symptoms of DM, no need to do RBS. • Follow up every 3 months • If also with TB, ff up is every month. 	<ul style="list-style-type: none"> • 	<ul style="list-style-type: none"> •
COMMON THEME	NTP 1	NTP 2	NTP 3
Not sure what tests to use	<ul style="list-style-type: none"> • Not sure 	<ul style="list-style-type: none"> • Maybe Fasting blood sugar or random blood sugar 	

Screening for DM in patients with TB

Question 6: What are your estimates of the cost of these tests or methods that you suggested?

COMMON THEME	DDO 1	DDO 2	DDO 3
	<ul style="list-style-type: none"> • Glucometer ~ Php 3,000 to 4,000 • 25 strips ~ Php 1,000 	<ul style="list-style-type: none"> • Php 250 	<ul style="list-style-type: none"> • Php 150
	<ul style="list-style-type: none"> • If labs are not available, refer to the hospital 	<ul style="list-style-type: none"> • Mayor/LGU should provide for the RHU • Should also involve the private sector – transfer of technology 	<ul style="list-style-type: none"> •
COMMON THEME	NTP 1	NTP 2	NTP 3
		<ul style="list-style-type: none"> • For RBS, pen is around Php 1,000; then Php 25 per strip 	

Epidemiology of TB in Diabetic patients

Question 7: As far as you know, how extensive is the problem of TB among diabetic patients?

COMMON THEME	DDO 1	DDO 2	DDO 3
Difficult to answer. Program view is vertical.	<ul style="list-style-type: none"> • No idea 	<ul style="list-style-type: none"> • 	<ul style="list-style-type: none"> • Inquire at the other office (NTP)
There may be budget issues when there are points of integration	<ul style="list-style-type: none"> • 	<ul style="list-style-type: none"> • The view of the program is very vertical 	<ul style="list-style-type: none"> •
COMMON THEME	NTP 1	NTP 2	NTP 3
Diabetic patients are at higher risk for developing TB	<ul style="list-style-type: none"> • Odds Ratio of 2.4 	<ul style="list-style-type: none"> • agree 	<ul style="list-style-type: none"> • The immune compromised state of DM patients make them more susceptible to TB compared to General Pop'n

Epidemiology of TB in Diabetic patients

Question 8: Do you have suggestions on where we might find additional sources of information on this?

COMMON THEME	DDO 1	DDO 2	DDO 3
No answer. Maybe inquire from NTP office.	•	•	•
COMMON THEME	NTP 1	NTP 2	NTP 3
Still waiting for the TB DM study headed by Dr Camilo Roa	•	•	•

Screening for TB in diabetic patients

Question 9: In a scale of 1 to 10, how important do you think it would be to screen for TB among diabetic patients?

COMMON THEME	DDO 1	DDO 2	DDO 3
	• 6	• 7	• 8 or 9
	• It is not routine. There is limitation of resources.	• Important to have a holistic approach if the RHU has the ability to address all of these problems	• At the start, focus is on diabetes.
COMMON THEME	NTP 1	NTP 2	NTP 3
It is important because these are high risk patients	• 7	• 7	• 8

Screening for TB in diabetic patients

Question 10: In a scale of 1 to 10, how feasible would it be to screen TB among diabetic patients?

What are the challenges that you see in implementing such a program?

COMMON THEME	DDO 1	DDO 2	DDO 3
	<ul style="list-style-type: none"> • 8 	<ul style="list-style-type: none"> • I can't answer. I don't know. 	<ul style="list-style-type: none"> • 8
	<ul style="list-style-type: none"> • Screen if symptomatic 	<ul style="list-style-type: none"> • 	<ul style="list-style-type: none"> •
COMMON THEME	NTP 1	NTP 2	NTP 3
	<ul style="list-style-type: none"> • 7 	<ul style="list-style-type: none"> • 7 	<ul style="list-style-type: none"> • 7
	<ul style="list-style-type: none"> • Problem in how to reach these diabetic patients? Where/How to find them? 	<ul style="list-style-type: none"> • How knowledgeable are the implementers (physicians) and the clients re susceptibility of diabetic patients in developing TB? • Might cause stigma among diabetic patients 	<ul style="list-style-type: none"> •

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Screening for TB in diabetic patients

Question 11: What cost-effective methods or tests could be used for screening for TB among diabetic patients?

COMMON THEME	DDO 1	DDO 2	DDO 3
	<ul style="list-style-type: none"> • CXR – practical and fast • Sputum afb x 3 days 	<ul style="list-style-type: none"> • I’m not an expert with labs • Do good history and PE 	<ul style="list-style-type: none"> • Comprehensive questionnaire is ok but only for initial assessment. Validation is needed.
COMMON THEME	NTP 1	NTP 2	NTP 3
	<ul style="list-style-type: none"> • Sputum AFB smear 	<ul style="list-style-type: none"> • Sputum AFB – a lot cheaper and more available (free in a lot of centers) 	<ul style="list-style-type: none"> • Ideally gene expert would be a good screening test. • Sputum AFB smear has low sensitivity especially among diabetics who are most likely smear negative. If chest xray is added to sputum afb smear, sensitivity will increase. • If cxr is available, then may use it to screen. If not, wait for signs and symptoms.

Screening for TB in diabetic patients

Question 12: What are your estimates of the cost of these tests or methods that you suggested?

COMMON THEME	DDO 1	DDO 2	DDO 3
	<ul style="list-style-type: none"> Adult CXR ~Php 175 to 200 Pedia CXR ~Php 300 (2 plates needed) 	<ul style="list-style-type: none"> CXR Php 300 	<ul style="list-style-type: none">
Ask NTP regarding sputum AFB	<ul style="list-style-type: none"> 	<ul style="list-style-type: none"> 	<ul style="list-style-type: none">
COMMON THEME	NTP 1	NTP 2	NTP 3
	<ul style="list-style-type: none"> Sputum AFB Php50 public; Php150 private 	<ul style="list-style-type: none"> CXR Php 200-300 per view 	<ul style="list-style-type: none"> Gene xpert ~9 USD per cartridge used for 1 patient. Other fees (technician etc) not included in the cost estimate.
	<ul style="list-style-type: none"> Cost for 6 month treatment is around Php 1,000 per patient 	<ul style="list-style-type: none"> 	<ul style="list-style-type: none">

Collaborative TB/DM activities

Question 13: Do you know of any collaborative TB/DM initiatives in the Philippines?

COMMON THEME	DDO 1	DDO 2	DDO 3
No idea. None as far as they know	<ul style="list-style-type: none"> I think there are in India and China but none here 	<ul style="list-style-type: none"> The TB-DM framework by WHO is just an art. We can make policies but are these effective? 	<ul style="list-style-type: none">
COMMON THEME	NTP 1	NTP 2	NTP 3
None; only the study headed by Dr Camilo Roa			<ul style="list-style-type: none">

Collaborative TB/DM activities

Question 14: What do you think are the opportunities and barriers for mounting collaborative TB/DM activities?

COMMON THEME	DDO 1	DDO 2	DDO 3
Barrier: not enough evidence	<ul style="list-style-type: none"> Not enough information yet 	<ul style="list-style-type: none"> Allocating budget to find out the numbers (prevalence data) is an outside of the box activity. Approach is reactive. 	<ul style="list-style-type: none"> Not enough evidence on TB-DM prevalence
	<ul style="list-style-type: none"> 	<ul style="list-style-type: none"> Political problem – the MHO may not have the capability to influence the mayor especially if from a different partylist. 	<ul style="list-style-type: none">
Opportunity: might be feasible if there is an integrated screening checklist. Maybe include TB in the PEN form.	<ul style="list-style-type: none"> 	<ul style="list-style-type: none"> 	<ul style="list-style-type: none">
COMMON THEME	NTP 1	NTP 2	NTP 3
		<ul style="list-style-type: none"> Opportunity: NTP and DDO offices are just very near each other 	
	<ul style="list-style-type: none"> Barriers: not enough data yet; budget. 		

Collaborative TB/DM activities

Question 15: What information do you think is needed to guide planning and implementation of TB/DM collaborative initiatives?

COMMON THEME	DDO 1	DDO 2	DDO 3
	<ul style="list-style-type: none"> For it to be justifiable, first show evidence of TB-DM prevalence – establish the numbers. 	<ul style="list-style-type: none"> 	<ul style="list-style-type: none">
COMMON THEME	NTP 1	NTP 2	NCP 3
Prevalence to show the extent of the TB/DM problem	<ul style="list-style-type: none"> 	<ul style="list-style-type: none"> 	<ul style="list-style-type: none">

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Table 1. Prevalence Studies on TB - DM Co-infection

Author/ Year Location Sample Population	Number of participants Type of Study	Prevalence Rates		TB-DM Outcomes		Interventions Used/ Recommended	Protocols Used/ Recommendations for Screening/ Testing
		TB among DM	DM among TB	Morbidity	Mortality		
Alora et al., 1984 ¹³ Philippines Patients from the ward and outpatient service who were suspected to have pulmonary tuberculosis (June 1982 to May 1984)	118 56 confirmed TB cases Prospective descriptive study		19.69%	Among diabetics, no significant differences were found that distinguished an "AFB positive" from an AFB negative" patient.	Not reported	Triple therapy consisting of any 3 of the following drugs, i.e., H, R, S, Z or E.,	Chest x-ray, sputum AFB, culture, and bronchial biopsy.
Alisjahbana et al., 2007 ¹⁴ Indonesia Consecutive new patients with pulmonary TB who were aged >15 years and who presented at 3 outpatient TB clinics in Jakarta and Bandung in Indonesia from October 2000 to December 2005.	634 Prospective cohort study		14.8%	Neither cavities (OR, 0.76; 95% CI, 0.39–1.48) nor mycobacterial load (OR, 1.71; 95% CI, 0.90–3.25) was significantly associated w/ DM. On presentation, diabetic patients with TB had more symptoms but had no evidence of more- severe TB.	2.1%	TB treatment: standard regimen of daily HRZE for 2 months and HR for another 4 months, DM treatment: oral anti-DM drugs after 2–4 weeks of TB treatment.	For TB: clinical presentation and chest x-ray findings and was confirmed by microscopic detection of acid- fast bacilli. For DM: measurement of fasting blood glucose (FBG) concentrations
Alladin et al., 2011 ¹⁵ Guyana TB patients attending TB clinics in Georgetown, Linden, and New Amsterdam	100 Cross- sectional study		14%	Not reported	Not reported	Recommended: Isoniazid prophylaxis for diabetics with latent infection	1. Routine screening for DM among TB patients; 2. Use of adequately calibrated glucometers for RBS tests; 3. Routine screening for TB among DM patients

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Amare et. al., 2013 ¹⁶	225	Prevalence of smear positive PTB - 6.2% 6,200 per 100 000	DM patients who had the disease for more than 10 years were 9 times (OR = 8.89; 95% CI: 1.88–58.12) more likely to develop PTB than those who have lived with DM for less than five years.	Not reported	Not reported	Sputum acid-fast bacilli (AFB) 3x and X-Ray.
Ethiopia	Cross-sectional study					
TB suspected diabetic patients from February 2012 to April 2012						
Balakrishnan et al., 2012 ¹⁷	552 TB patients	44.0% (95% CI: 38.8–49.3)	Not reported	Not reported	All TB patients are treated with a rifampicin containing, fully intermittent (thrice weekly), standardized treatment regimen delivered under direct observation.	Sputum smear microscopy is performed for all TB suspects. Patients are diagnosed with PTB if at least one initial sputum sample contains AFB. Smear negative cases are diagnosed by chest radiograph subsequent to negative results for repeated sputum smear microscopy, after 2 weeks of the first results. ETB cases are diagnosed by a combination of histopathology, mycobacteriology and/or clinical features.
India	Cross-sectional study					
All patients aged >15 years diagnosed and registered with any type of TB in Kerala's 73 TB units between June and July 2011						For patients consenting to DM screening, HbA1c levels were measured from whole blood.

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Dobler <i>et al.</i> , 2012 ¹⁸	802,087 DM population	There were 271 (188 culture positive) cases of TB (33.8 per 100,000 or 0.03%) among 802,087 members of the DM cohort and 130 cases of TB among 273,023 people using insulin (47.6 per 100,000 or 0.05%).		The adjusted RRs were 1.48 (95% CI: 1.04-2.10) for people with DM and 2.27 (95% CI: 1.41-3.66), for people with DM using insulin.	Not reported	All TB treatment is provided free of charge.	Diabetes type is self-reported by the patients at the time of registration and confirmed by a health professional.
Australia	6,276 TB population			Overall, people with DM had a 1.5-fold increased risk of developing TB. The risk for TB was higher among people who were using insulin for DM. DM accounted for a small proportion of TB cases in a low TB incidence setting.			Notification of TB is compulsory in Australia. All TB cases are collected at State and Territory level (screening and testing for TB not specified).
All Australian States and Territories with a mean TB incidence of 5.8/100 000.	Prospective cohort study						
Cases of TB in people with DM were identified by record linkage using the National Diabetes Services Scheme Database and TB notification databases for the years 2001 to 2006.							
Faurholt-Jepsen <i>et al.</i> , 2013 ¹⁹	1,205	16.40%	Not reported	Time-dependant association (score process test, p = 0.02) with excess mortality risk exclusively within the initial 100 days of treatment (crude RR 2.70, 95% CI: 1.53-4.77)		Used: Nutrition interventions (not reported in paper); Recommended: Better supervision of TB treatment and more frequent routine visits during initial treatment phase	Initiate blood glucose testing immediately after TB diagnosis
Tanzania	Prospective study nested in 2 nutritional intervention studies						
TB patients recruited for nutritional intervention studies							
Gnanasan <i>et al.</i> , 2011 ²⁰	35	14.9%	Not reported	Not reported		Used: Individualized drug regimens for TB-DM patients; Recommended: 1. Pharmacists can play a major role in integrating the care for tuberculosis and diabetes mellitus by individualizing drug regimens; 2. Optimize treatment and monitoring of	None
Malaysia	Prospective descriptive study						
Newly diagnosed TB patients treated at a tertiary hospital in Northern Malaysia							

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						DM in TB patients.
Gupta et al., 2011 ²¹	192 PTB and 37 ETB	31.8% for PTB	Not reported	Not reported	Not reported	PTB: sputum smear microscopy and/or culture. ETB: smear microscopy and/or culture or polymerase chain reaction.
India	Retrospective study	5.4% for ETB				
PTB and ETB patients from Kasturba Hospital, Manipal, south India (2005-2006)		27.5% total				
India TB-Diabetes study group, 2013 ²²	8,269	13% (8% known DM and 5% newly diagnosed DM)	The proportion of patients diagnosed with DM was higher in hospitals (16%) compared with TB units (9%) (OR 1.9, 95% CI: 1.6–2.1, p < 0.001); this was predominantly due to the fact that more patients had a known diagnosis of DM in hospitals (10%) than in TB units (5%) (OR 2.1, 95% CI: 1.7–2.5, p < 0.001). Once diagnosed with DM, the proportion of patients referred to DM care was higher in hospitals (96%) than in TB units (92%) (OR 2.1, 95% CI: 1.2–3.8, p < 0.01).	Not reported	Treatment regimens and anti-TB drug formulations were in accordance with those recommended by WHO and in line with Revised National TB Control Program guidelines.	The screening for and diagnosis of DM followed national guidelines, which stipulate that a FBG is used with cut-off thresholds in line with those recommended by the WHO. In those with no known diagnosis of DM, RBG was carried out followed by FBG at the next visit.
India	Prospective observational study					
Patients from eight tertiary care hospitals and 67 peripheral health institutions in 8 TB units						
At tertiary care hospitals, patients were all persons aged 15 years and older who were consecutively diagnosed and registered for TB treatment between January and March up to 30 September 2012.						
At the tuberculosis units, patients from all ages who were consecutively diagnosed and registered for TB treatment during the period were included.						

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India DM-TB study group, 2013 ²³	7,218 1 st Quarter 2012	105 newly diagnosed TB case rates per 100,000 1 st Quarter 2012 (0.10%)	Not reported	Not reported	When active TB was diagnosed, the patient was referred for TB treatment (regimen not specified).	The screening for active TB followed the RNTCP guidelines, which are based on WHO guidelines on how to identify suspected active TB amongst persons seeking care.
India	12,237 2 nd Quarter 2012	172 newly diagnosed TB case rates per 100,000 2 nd Quarter 2012 (0.17%)				Sputum smear microscopy for acid-fast bacilli was performed followed by chest radiography in those with negative sputum smears for suspected pulmonary disease, and appropriate investigations were carried out for suspected extra-pulmonary disease.
Patients were persons aged 15 years and older who had been diagnosed with DM and who were receiving care and treatment in the six DM clinics from the first or second quarter of 2012 up to 20 September 2012.	11,691 3 rd Quarter 2012	88 newly diagnosed TB case rates per 100,000 3 rd Quarter 2012 (0.09%)				
Jabbar et al. 2006 ²⁴	1458	11,900 per 100,000 or 11.9%	Prevalence of TB increased progressively with duration of DM. The highest prevalence was seen in those who had been diagnosed with DM for more than 10 years.	The number of patients who died was 10 overall, giving a mortality rate in 93 patients with DM and TB of 11%.	80% required oral hypoglycemic agents, 9% insulin, and 11 diet-controlled.	Chest x-ray in patients with DM
Pakistan	Retrospective descriptive study					
Patients with a diagnosis of DM who were admitted to The Aga Khan University Hospital, 1992 to 1996.						

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<p>Jali et al., 2013²⁵</p> <p>India</p> <p>Patients included all persons aged 15 years and above who were consecutively diagnosed and registered with TB-DM within the single center (Diabetes Centre and Pulmonary Medicine Department) from February 2012 to September 2012.</p>	<p>307 patients diagnosed with TB and 4,118 diabetes patients</p> <p>Prospective observational study</p>	<p>2,695 per 100,000 or 2.7% (111 patients: 52 new smear positive, 29 new smear negative, 30 new extra pulmonary)</p>	<p>19.54% were known cases of diabetes, and 15.96% were newly diagnosed cases of diabetes.</p>	<p>Not reported</p>	<p>Not reported</p>	<p>Treatment regimens and anti-TB drug formulations were in accordance with those recommended by WHO and Revised National Tuberculosis Control Program (RNTP) of India.</p>	<p>The random blood glucose (RBG) of diagnosed, and registered cases of TB were done on the first visit. If RBG was more than 110 mg/dL, the patients were called next day for fasting blood sugar. Screening for TB was based on asking about cough for longer than 2 weeks, fever, weight loss, hemoptysis, and or any suspicion of active TB to account for ETB. Patients with a positive symptom screen were referred to TB services.</p>
<p>Jimenez-Corona et al., 2012²⁶</p> <p>Southern Mexico</p> <p>Patients w/ TB in the Orizaba Health Jurisdiction in Veracruz State</p>	<p>1,262</p> <p>Prospective observational study</p>	<p>29.63%</p>	<p>Patients w/ DM had higher probability of cavitations on chest x-ray (OR 1.8, 95% CI: 1.25-2.41); delayed sputum conversion (OR 1.51, 95% CI: 1.09-2.10); treatment failure (OR 2.93, 95% CI 1.18-7.23); recurrence (OR 1.76, 95% CI: 1.11-2.79); and relapse (OR 1.83, 95% CI: 1.04-3.23).</p>	<p>Mortality due to some other cause than TB was higher among patients with DM than among those without DM (28.97% vs. 11.80%)</p>	<p>Between 1995-1998: new cases - 2HRZ/4HR; retreatment cases received either E or S. After 1998: new cases -2HRZE/4HR; previously treated - 2HRZES/1HRZE/5HRE. After 2000: patients harboring isolates resistant to both H & R - second-line standardized regimen using at least 4 drugs highly likely to be effective for 18–24 months after culture</p>	<p>Add DM prevention and control strategies to TB control programs and vice versa and to evaluate their effectiveness</p>	

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					conversion.	
Kim, Hong, Lew, et al, 1995 ²⁷	790,145 (7,705 diabetics; 782,440 non-diabetics)	10 per 100,000 or 0.01% (incidence rate)	Not reported	Not reported	Not reported	For TB: first by chest x-ray, and then sputum specimens. For DM: glucose oxidase method
Korea Diabetic and non-diabetic civil servants who are members of the Korean Medical Insurance Corp.	Prospective longitudinal study					
Leung et al., 2008 ²⁸	6,444 DM	Active TB rate: 295 per 100,000 or 0.30% person-years (95% CI: 193-237) PTB rate: 190 per 100,000 or 0.19% person-years (95% CI: 170-211) ETB rate: 24 per 100,000 or 0.02% person-years (95% CI: 17-32)	DM was associated w/ an increase in the risk of active, culture-confirmed, and PTB but not ETB, w/ adjusted hazard ratios of 1.77 (95% CI: 1.41-2.24), 1.91 (95% CI: 1.45-2.52), 1.89 (95% CI: 1.48-2.42), and 1.00 (95% CI: 0.54-1.86), respectively. Patients w/ poor recent glycemic control HbA1c \geq 7% had significantly increased risk of TB aHR 2.56, 95% CI: 1.95-3.35), those with HbA1c < 7% did not (aHR 0.81, 95% CI: 0.44- 1.48).	Not reported	Not reported	DM was diagnosed, mainly by a fasting plasma glucose level of 7.0 mmol per liter or higher, together with confirmatory symptoms and/or blood/plasma glucose determinations. Patients with symptoms suspicious of active tuberculosis or radiologic abnormalities were referred to the 18 chest clinics (tests not specified).
Hong Kong, China Clients aged 65 years or more were recruited into the health maintenance program of the Elderly Health Service in 2000.	Prospective cohort study					

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Li <i>et al.</i> , 2012 ²⁹	8,886		12.4% overall; 13.8% urban vs. 10.6% rural	Not reported	Not reported	Used: 1995-98-2HRZ/4HR; after 1998- 2HRZE/4HR (for newly diagnosed) & 2HRZES/1HRZE/5HRE (previously treated); Recommended: integration of TB and DM services	1. Screen for DM in TB clinics; 2. Free blood tests
China	Prospective observational study						
Patients of 6 TB clinics/hospitals aged ≥ 15 yrs. old consecutively diagnosed and registered with TB							
Lin <i>et. al.</i> , 2012 ³⁰	15,342 patients screened in the study	Incidence 958 per 100,000		The TB case notification rate was significantly higher for quarter 1-2012 (774 per 100,000 DM screened) than for quarter 4-2011 (352 per 100,000 DM screened) – OR 2.2 (95% CI: 1.9–2.5, p < 0.001).	Not reported	Patients with TB were started on anti-TB treatment (regimen not specified).	The screening base on five questions regarding symptoms: 1) cough for longer than 2 weeks; 2) night sweats for 4 weeks or longer; 3) fever for 4 weeks or longer; 4) weight loss over the previous 4 weeks; and 5) any suspicion of active TB to account for extra-pulmonary TB. Investigations and diagnosis of TB use sputum smear microscopy for acid-fast bacilli and chest x-ray.
China	Prospective observational study	A total of 55 DM patients (established and new) were identified as having TB: 40 with new and 15 with recurrent TB, 28 with smear-positive PTB, 24 with smear-negative PTB, and 3 with extra-pulmonary TB.					
Patients aged 14 years and above who had been diagnosed with DM and who were receiving care and treatment in the 5 DM clinics from September 2011 – March 2012.							

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<p>Magee <i>et al.</i>, 2012³¹</p> <p>Peru</p> <p>Patients aged ≥ 15yo with suspected or confirmed TB with respiratory symptoms in Lima, Peru, w/ specific risk factors for drug resistance</p>	<p>1,671</p> <p>Prospective Study</p>	<p>11.10%</p>	<p>TB-DM patients had a significantly lower proportion of bilateral lung cavitations (3.2% vs. 5.1%) compared to TB patients without diabetes ($p < 0.05$). Overall, TB-DM patients were significantly less likely than those without diabetes to have MDR-TB (15.6% vs. 24.6%, $p < 0.01$).</p>	<p>Not reported</p>	<p>Recommended: Optimal diabetes control among TB-DM patients</p>	<p>1. Screening for drug resistance among TB-DM patients; 2. Active TB screening for DM patients</p>
<p>Mugusi, Swai, Alberti, & McLarty, 1990³²</p> <p>Tanzania</p> <p>Patients with AFB sputum-positive with PTB admitted to the TB wards of Muhimbili Medical Center, Dar es Salaam</p>	<p>506</p> <p>Cross-sectional survey among TB patients</p>	<p>4.00%</p>	<p>Not reported</p>	<p>Not reported</p>	<p>Not reported</p>	<p>Routine testing for urine sugar among TB patients; Diagnosis of DM should be considered in patients who do not progress as expected on anti-TB therapy, those who complain of excessive fatigue, polyuria or polydipsia, soft tissue infections, or those who have evidence of diabetic complications such as paresthesias.</p>

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<p>Nandakumar et al. 2013³³</p> <p>India</p> <p>All TB cases above the age of 14 years, registered under RNTCP in Malappuram District of Kerala state, India, from April 2010 to September 2011 excluding transfer- in cases.</p>	<p>3,116</p> <p>Retrospective study</p>	<p>24%</p>	<p>Male sex, older age, PTB, retreatment cases, sputum smear positivity and regularity of DOT in the intensive phase were significantly associated with TB treatment outcome. DM and unknown DM status were also significantly associated with TB treatment outcome, as was unknown DM control status.</p>	<p>6% (42/677) mortality for diabetics</p> <p>3% (71/2127) mortality for non-DM</p> <p>11% (34/322) mortality for unknown DM</p>	<p>Local innovation, diabetes care has been standardized.</p>	<p>In centers, blood glucose estimation using the calorimetric method / auto analyzers. In field setting, calibrated digital Glucometers and standard test strips were used. Diagnostic and follow up sputum smear examination was done.</p>
<p><u>Olayinka AO, Anthonia O, Yetunde K., 2013³⁴</u></p> <p>Nigeria</p> <p>Patients from an outpatient TB-DOTS clinic at a tertiary health care facility in Lagos (12-months).</p>	<p>351 TB patients</p> <p>Cross-sectional study</p>	<p>5.7%</p>	<p>Not reported</p>	<p>Not reported</p>	<p>Not reported</p>	<p>Fasting blood glucose was done in all patients. The sputum smear result, and the tuberculin test were reviewed from the case folders.</p>

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<p>Oluboyo & Erasmus, 1990³⁵</p> <p>Nigeria</p> <p>Newly diagnosed patients with PTB selected from the chest clinic of University of Ilorin Teaching Hospital</p>	<p>54</p> <p>Prospective study</p>	<p>5.60%</p>	<p>Not reported</p>	<p>Not reported</p>	<p>Daily HRZS for 3 months, and 3 months continuation phase with HR.</p>	<p>1. Markedly elevated fasting blood glucose together with other clinical parameters should identify co-existing diabetes; 2. In moderate degree impairment of glucose tolerance, an OGTT should be done only after objective clinical evidence of patient improvement on anti-tuberculosis medication; 3. Reassess TB patients with diabetes or impaired glucose tolerance with an OGTT once they are cured.</p>
<p>Park S. W. et al., 2012.³⁶</p> <p>South Korea</p> <p>All new culture-confirmed pulmonary TB patients who started anti-TB medication between January 2005 and December 2009 at Chung-Ang University Hospital & Yong San Hospital in South Korea</p>	<p>492</p> <p>Retrospective study</p>	<p>25.2%</p>	<p>No difference in clinical symptoms between DM & non-DM, nor was there more frequent involvement of the lower lobes. Diabetic patients had more cavitations and a higher incidence of positive smears; however, these effects were only found in diabetic patients with poor glycemic control.</p>	<p>3.0% died during the intensive phase of treatment and 0.8% died during the continuation period.</p>	<p>For TB treatment: patients received HRZE</p>	<p>For DM screening: patient had a previous history of DM & had been receiving insulin and/or oral hypoglycemic agents at the time of TB diagnosis, or were found to have any one of following: 1. FBG levels ≥ 126 mg/dL; 2. plasma glucose ≥ 200 mg/dL 2 hours after a 75-g oral glucose load (glucose tolerance test); 3. symptoms</p>

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							of hyperglycemia and casual plasma glucose ≥ 200 mg/dL; or 4. HbA1C $\geq 6.5\%$.
Rahim et al., 2012 ³⁷	17,344	213 per 100,000	Not reported	Not reported	DM patients were receiving treatment consisting of insulin injections (56%), oral medication (36%) or both (7%).	DM patients were asked about persistent cough of > 2 weeks. Sputum sample was collected from each suspect for smear microscopy (SM), culture and drug susceptibility testing (DST) of <i>M. Tb</i> .	
Bangladesh DM patients at the Bangladesh Institute for Research and Rehabilitation for Diabetes, Endocrine and Metabolic Disorders (BIRDEM) hospital located at Dhaka, Bangladesh (from 25 December 2010 to 25 January 2011).	Prospective study						
Restrepo et al. 2006 ³⁸	3,935 for Mexico	17.8% in Mexico and 27.8% in Texas.	Patients with TB and diabetes were older, more likely to have hemoptysis, pulmonary cavitations, be smear positive at diagnosis, and remain positive at the end of the first (Texas) or second (Mexico) month of treatment.	Not reported	Not reported	In Texas, TB diagnosis is based on clinical findings, supported by routine smear & culture and DM diagnosis is self-reported. In Mexico, TB diagnosis is supported in most cases by direct smear alone and self-reported DM.	
Mexico/USA All patients reported to the respective TB control programs (consortium for TB control both sides of the South Texas/northeastern Mexico border). USA data: 1996-2002 Mexico data: 1998-2003.	1,788 for USA Retrospective study						

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<p>Sulaiman et al., 2013.³⁹</p> <p>Malaysia</p> <p>Patients with TB at respiratory clinic of Hospital Pulau Pinang, Malaysia, from January 2006 to December 2007</p>	<p>1,267</p> <p>Retrospective study</p>	<p>26.7%</p>	<p>No statistically significant difference was observed in treatment outcomes of TB-DM and TB-only patients. Study revealed that TB-DM is 2 times more prevalent in PTB as compared with ETB.</p>	<p>4.8% mortality</p>	<p>Treatment protocol was defined as per WHO guidelines.</p>	<p>Sputum smear examinations were done at the end of 2, 4 and 6 months of treatment in new cases and at the end of 2, 3, 5, and 8 months in retreatment cases.</p>
<p>Uchimura et al., 2013⁴⁰</p> <p>Japan</p> <p>All new TB cases registered in the Japanese TB surveillance system between 2007 and 2010</p>	<p>96,689</p> <p>Descriptive cross-sectional study</p>	<p>13.1%</p>	<p>Not reported</p>	<p>23.7% mortality among male smear-positive pulmonary tuberculosis cases. 18.9% among female smear-positive pulmonary tuberculosis cases. 21.1% mortality among male DM smear-positive pulmonary tuberculosis cases. 21.6% for female DM smear-positive pulmonary tuberculosis cases. Higher mortality for TB cases with DM for males of younger ages (< 35) but similar mortality for older age groups with DM, compared with all smear +PTB cases of same age group.</p>	<p>No direct intervention to prevent active TB among the elderly.</p> <p>A three-month extension of treatment is also recommended for patients with a co-morbidity such as DM.</p>	<p>TB screening for staff and clients in institutions caring for the elderly are recommended.</p> <p>Persons with DM have ~ 3x higher risk of TB and therefore may require a different TB screening strategy.</p>

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Wang, Lee, & Hsueh, 2005 ⁴¹	461	21.50%	Diabetic patients more likely to present with cavitory nodules; DM independently affected the radiographic pattern and was associated with a higher probability of nodular pattern	Not reported	Non-standardized treatment protocol for PTB	PTB should be considered in diabetic patients with cavitory pulmonary nodules.
Taiwan	Retrospective study					
New culture-proven TB patients						
Wang et al., 2009. ⁴²	217	34.1%	Isolated lower lung field lesions were significantly more common in the PTB-DM group than the PTB group (OR 2.04, 95% CI: 1.03-4.04). The PTB-DM group also had significantly higher frequencies of consolidation (OR 2.23, 95% CI: 1.04-4.80) and cavity (OR 1.91, 95% CI: 1.07-3.41) in terms of lung lesions.	Mortality for PTB-DM patients was 17.6%, in sharp contrast to 7.7% for PTB patients (OR 2.56, 95% CI: 1.08-6.03). PTB-related death was significantly more common in the PTB-DM group than the PTB group (12.2% vs 4.2%; OR 3.16, 95% CI 1.08-9.26) and type 2 DM (OR 7.60, 95%CI 1.98-29.08) still remained as an independent and significant risk factor for PTB-related death.	TB treatment consisted of a standard regimen of daily HRZE for 2 months and HRE for another 4 months or daily HRE for 9 months.for 9 months.	For DM screening: known history of DM, receiving insulin and/or an oral hypoglycemic agent, or were diagnosed as having DM during the hospitalization with subsequent confirmation by two or more fasting plasma glucose levels > 126 mg/dl on a different day in outpatient setting. For TB screening: Chest x-ray and sputum smear/AFB stain
Taiwan	Retrospective study					
Patients with PTB from 1 January 2003 to 31 December 2006 at the Kaohsiung Municipal Hsiao-Kang Hospital.						
Weng, Hsu, Lirn, & Huang, 2008 ⁴³	75	20% among ETB	Prevalence of HPN and chronic liver disease higher among ETB patients; incidence of tuberculous peritonitis higher among ETB patients	Not reported	Not reported	Not reported
Taiwan	Retrospective study					
ETB patients w/ and w/out DM being treated at Taipei Medical University Hospital						

Abbreviations: AFB - acid-fast bacilli, aHR - adjusted hazards ratio, DM - diabetes mellitus, E - ethambutol, ETB - extrapulmonary TB, HbA1c - glycated hemoglobin, H - isoniazid, OR - odds ratio, PTB - pulmonary TB, R rifampicin, S streptomycin, TB tuberculosis, and Z pyrazinamide.