The validity and limitations of IGRA (QFT-GIT) and TST in screening for pulmonary tuberculosis among adults applying for residency in the Emirate of Abu Dhabi, UAE in 2013

by

Huda Saeed Al-Shemeili

A dissertation submitted to Johns Hopkins University in conformity with the requirements for the degree of Doctor of Philosophy

Baltimore, Maryland

July, 2018

Abstract

Mycobacterium tuberculosis (MTB), the agent causing tuberculosis (TB) and latent tuberculosis infection (LTBI) imposes a significant public health concern world-wide. The utility and the value for simultaneous (parallel) testing with Interferon Gamma Release Assay [IGRA (QFT-GIT)] and Tuberculin skin test (TST) in detecting MTB infection among applicants for residency in Abu Dhabi requires evaluation.

The objectives of this study are to 1) Provide demographic characteristics of the study sample by age categories, and 2) Explore the validity measures of IGRA (QFT-GIT) and TST, and 3) Further, to assess the risk of MTB among younger visa applicants compared to older applicants.

This cross-sectional study analyzes data routinely collected on all adults (18-64 years) seeking a residency visa in the Emirate of Abu Dhabi from January – December 2013. Among the 1,529,389 adults who applied for this visa in 2013, 2,596 individuals presented with an abnormal chest X-ray (and who also were HIV negative).

In our study, nearly two-thirds of males in the sample were from Pakistan and India while almost 50% of females were from the Philippines. The sensitivity of IGRA (QFT-GIT) test was 72.7%, (95% CI: 67.8-77.2) compared to TST sensitivity of 59.1%, (95% CI: 53.8-64.2), ($P<0.001$). The net sensitivity of simultaneous (parallel) testing was 88.8%. The net sensitivity of simultaneous (parallel) testing for the younger age group (18-34) years was 91.6% compared to 83.1% net sensitivity among older individuals (35-64) years. Kappa agreement between IGRA (QFT-GIT) and TST was 0.33 (95% CI: 0.29-0.36). The role of chest X-ray in our study was not adequate and older individuals (35-64) years had lower proportions of MTB infection when

compared to younger individuals (18-34) years, yielding an Odds Ratio (OR) of 0.62 (95% CI 0.48– 0.81), (*P<0.001*).

In conclusion, nearly two-thirds of males in the sample were from Pakistan and India. IGRA (QFT-GIT) was more sensitive than TST. The net sensitivity of simultaneous (parallel) testing was high. However, Kappa agreement between IGRA (QFT-GIT) and TST in the study was considered as only fair concordance.

Primary Reader: David Celentano

Secondary Readers: Lilly Engineer, Jonathan Golub, Josh Sharfstein, Amal Mohammed

Acknowledgements

- ***SEHA in Abu Dhabi:*** Dr Amal Mohammed, Dr Said Musa.
- ***DOH in Abu Dhabi:*** Dr Jala Taher, Dr Zainab Khazal, Dr Farida Al-Hosani, Dr. Shereena Khamis Al Mazrouei, Meera Albuloshi, Kaltham Hasan Al Obeidli and Aymen.
- ***Faculty:*** David Celentano, Laura Morlock, Lilly Engineer.
- ***Staff:*** Judith Holzer, Mary Sewell, Mary Wisniewsk.
- ***IT support in JHU and IT support in Abu Dhabi.***
- ***Family and best friends.***

Contents

List of tables

List of figures

Abbreviations

AFB	Acid Fast Bacilli
BCG	Bacillus Calmette-Guerin
CXR	Chest X-ray, Chest Radiography
DOH	Department of Health (previously Health Authority – Abu Dhabi, or HAAD)
ELISA	Enzyme-Linked Immunosorbent Assay
HCWs	Healthcare Workers
HIV	Human Immunodeficiency Virus
IGRA	Interferon-γ release Assay
LTBI	Latent Tuberculosis Infection
MDR TB	Multi Drug-Resistant Tuberculosis
MGIT	Mycobacteria Growth Indicator Tube
MOTT	Mycobacteria Other Than Tuberculosis
MTB	Mycobacterium tuberculosis (infection with bacteria can be active or latent)
NTM	Non-Tuberculous Mycobacteria
NNS	Number Needed to Screen (to detect one true case of active tuberculosis)
NLR	Negative Likelihood Ratio
NPV	Negative Predictive Value
PLR	Positive Likelihood Ratio
PPV	Positive Predictive Value
PTB	Pulmonary Tuberculosis

TB	Tuberculosis (mainly pulmonary tuberculosis)
TB-PCR	Tuberculosis polymerase chain reaction
TST	Tuberculin Skin Test
WHO	World Health Organization

Definitions

Active tuberculosis
Active tuberculosis (TB): A seriously infectious disease caused by a bacterium known as *Mycobacterium tuberculosis*. Mostly affects the lungs but can affect any part of the human body.[1, 2, 3]

Active tuberculosis case-finding
Active tuberculosis case-finding: is identical to systematic screening for active TB, although it usually indicates screening that is implemented outside of healthcare facilities.[6, 11, 12]

Close contacts
Close contacts: are individuals who had shared an airspace with a person with pulmonary TB for at least 15 hours per week for 71 weeks, or a total of 180 hours during a contagious phase, defined as 3 months prior to the collection of the first culture-positive sputum or the date of onset of a cough (whichever was longer) until 2 weeks after the start of appropriate anti-tuberculosis treatment.[62]

Enzyme-linked immunosorbent assay (ELISA)
Enzyme-linked immunosorbent assay (ELISA): is a widespread and potent laboratory technique utilized to detect proteins with antibodies.[63]

Incidence
Incidence: is defined as "the number of new and relapse cases of TB arising in a given time period, usually 1 year".[6]

Latent tuberculosis infection
Latent tuberculosis infection (LTBI): is defined as a status of persistent immune reaction to *Mycobacterium tuberculosis* without clinical evidence of active TB disease. Infected individuals are asymptomatic and are not contagious, yet they signify a future risk of TB disease.[4]

Mortality
Mortality: is defined as "the number of deaths caused by TB in a given time period, usually 1 year".[6]

The Number Needed to Screen
The Number Needed to Screen (or NNS): is the number of individuals that need to undergo screening to diagnose one person with active TB.[11, 12]

Negative predictive value
The negative predictive value (NPV) of a test: is the proportion of individuals with a negative test result who do not actually have the disease. (d)/(c+d) [28]

Negative Likelihood Ratio

The Negative Likelihood Ratio (NLR): is "the ratio of the probability of negative test in diseased to non-diseased". LR- = (1- sensitivity)/specificity [30]

Passive tuberculosis case-finding
Passive tuberculosis case-finding: is a pathway initiated by patient to diagnose TB involving: (1) a person recognizes his/ her symptoms of active TB as serious; (2) the person having access and seeking care spontaneously at a suitable health facility; (3) a clinician correctly identifying that the person fulfills the criteria for suspected TB; and (4) the successful use of a diagnostic algorithm with sufficient sensitivity and specificity to diagnose TB.[6, 11, 12]

Prevalence
Prevalence: is defined as the probability of having the disease also called prior probability of having the disease. (a+c)/ (a+b+c+d) [28]

Positive predictive value
The positive predictive value (PPV) of a test: is defined as the proportion of individuals with a positive test result who truly have the disease. (a)/ (a+b) [28]

Positive Likelihood Ratio
The Positive Likelihood Ratio (PLR): is "the ratio of the probability of positive test in diseased to non-diseased". LR+ = sensitivity/ (1-specificity) [30]

Risk groups
A risk group: is a group of individuals with a prevalence or incidence of TB that is extensively higher than the general population.[6, 11, 12]

Second screening
A second screening test: is an examination or other procedures which may be done to individuals whose results were positive during the initial screening.[6, 11, 12]

Sensitivity
The sensitivity: is defined as the proportion of diseased individuals with a positive test result.[30]

A screening test, examination or procedure for active tuberculosis
A screening test, examination or procedure for active tuberculosis: is "a test, examination or other procedure for active tuberculosis distinguishing people with a high likelihood of having active TB from people who are highly unlikely to have active TB.[6, 11, 12]

Specificity
The specificity: is defined as the proportion of non-diseased individuals with negative test results.[30]

Systematic screening for active TB

Systematic screening for active TB: is the systematic detection suspected active TB disease in individuals within a predetermined target group, utilizing tests, examinations or other rapid procedures.[6, 11, 12] Among those screened positive, the establishment of diagnosis needs to be via one or multiple diagnostic tests along with additional clinical assessments, which together have high accuracy.[6, 11, 12]

Tuberculosis

Tuberculosis (TB): is caused by a bacterium known as *Mycobacterium tuberculosis*. Direct person to person transmission occurs through the exposure to the airborne bacterium present in the sputum of the patient. Tuberculosis is present in two major forms, active TB disease and latent TB infection (LTBI).[2, 4]

Chapter 1

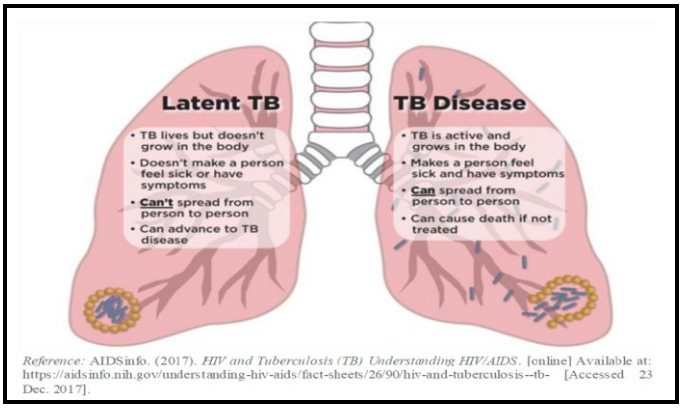
Introduction

Chapter 1 will briefly introduce the concept of *Mycobacterium tuberculosis* (MTB) infection comprised of active (TB) and latent tuberculosis infection (LTBI). This chapter will then briefly touch on the status immigrants working in the United Arab Emirates and current health challenges. Chapter 1 will then introduce the visa screening standard for residency in Abu Dhabi and the role of the Disease Prevention and Screening Centers (DPSCs) in visa screening for applicants. A brief description of the required investigations for individuals presenting with abnormal chest X-ray will be provided. Finally, the specific aim and objectives of the study will be presented.

Mycobacterium Tuberculosis (MTB) infection: Active (TB) vs. latent tuberculosis (LTBI)

Mycobacterium tuberculosis (MTB) infection is transmitted through the air from one person to another and is present in two major forms, active TB disease and latent TB infection (LTBI) (Figure 1.1).[1,2,3]

Figure 1. 1: Latent tuberculosis infection and TB

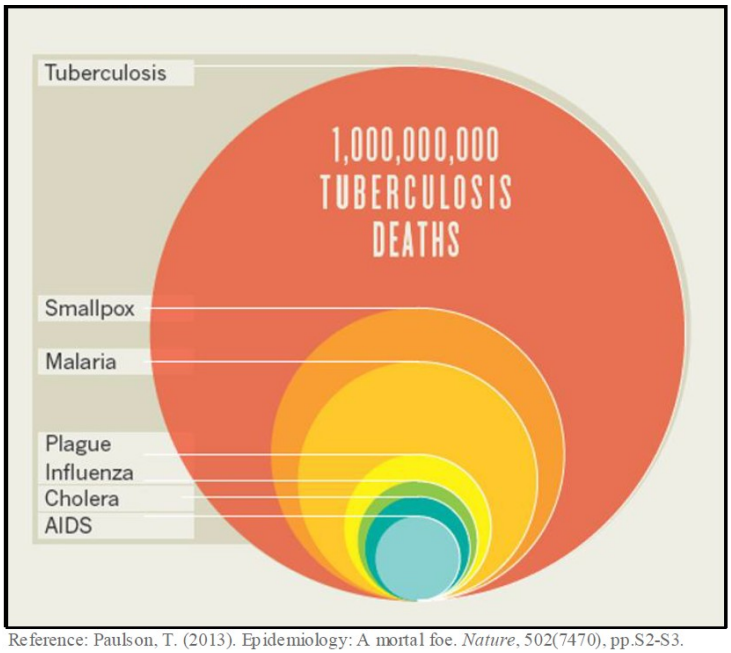


Reference: AIDSinfo. (2017). *HIV and Tuberculosis (TB) Understanding HIV/AIDS*. [online] Available at: https://aidsinfo.nih.gov/understanding-hiv-aids/fact-sheets/26/90/hiv-and-tuberculosis--tb- [Accessed 23 Dec. 2017].

Tuberculosis (TB) is a serious infectious disease that primarily affects the lungs, but can infect any part of the human body.[2] On the other hand, latent tuberculosis infection (LTBI) is a status of persistent immune reaction to *Mycobacterium tuberculosis* without clinical evidence of active TB disease.[4]

Fortunately, TB is a curable disease despite the difficult and long treatment requiring a minimum of six months of compliance with the treatment regimen.[5] Worldwide, TB is the ninth leading cause of death and had been the leading cause of a single infectious agent, ranking above HIV/AIDS for the past five years (from 2012-2016).[6] In history, TB is the leading cause of infectious disease mortality; more than a billion lives have been lost due to TB in the past two hundred years (Figure 1.2).[1]

Figure 1. 2: TB disease a global leading killer



Reference: Paulson, T. (2013). Epidemiology: A mortal foe. *Nature*, 502(7470), pp.S2-S3.

Worldwide, there were 10.4 million new TB cases which is equivalent to 140 cases per 100000 population (6.2 million were men, 3.2 million were women and 1 million were children) in the year 2016.[6] There were nearly 1.3 million TB deaths among HIV negative individuals with an additional 374000 deaths occurred among HIV-positive individuals in 2016.[6]

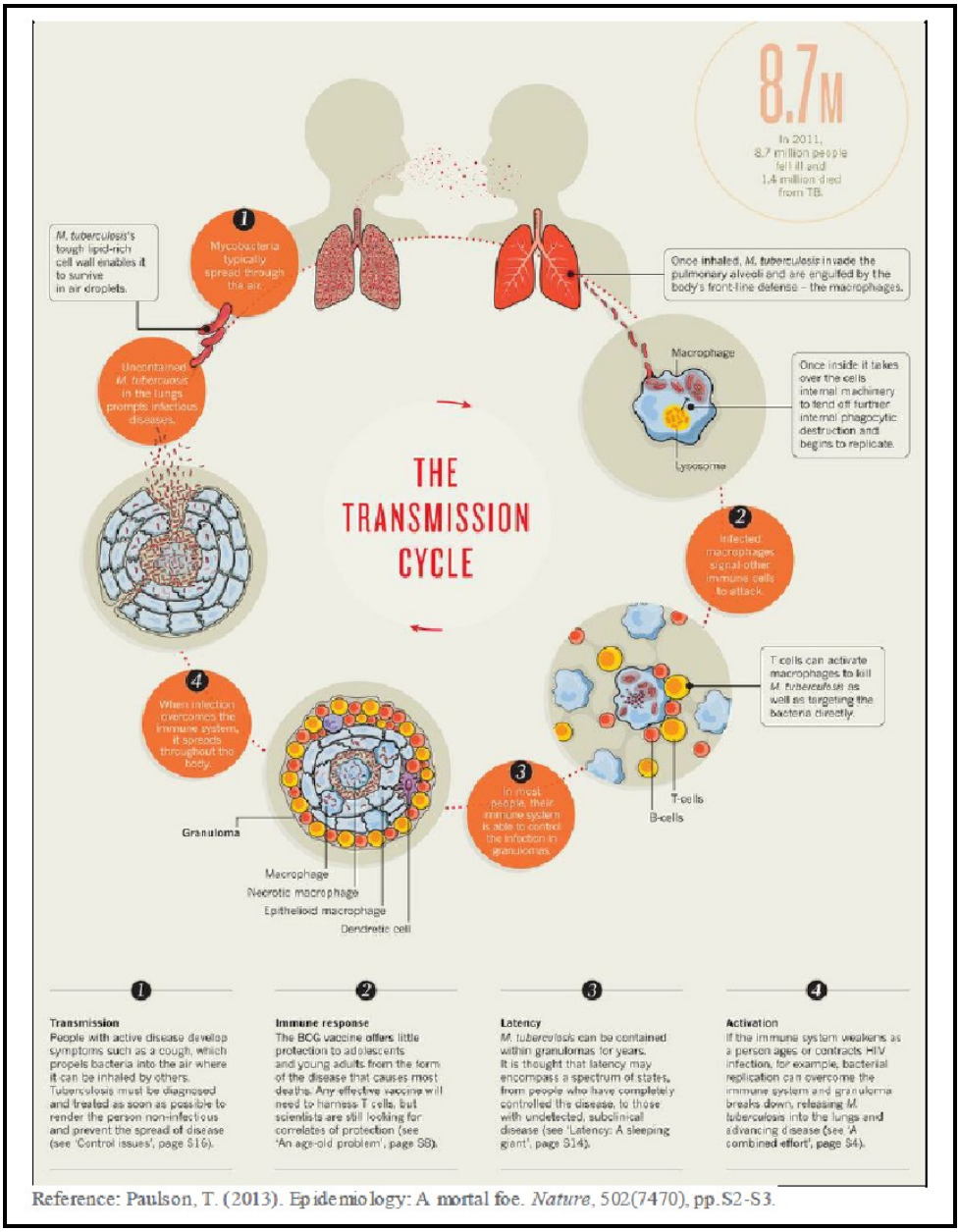
The case-fatality ratio (CFR) of an untreated case of active TB is about 50% and the patient will transmit the infection to ten to fifteen contacts yearly prior to death or recovery.[7] According to the World Health Organization, too many individuals have undetected TB for too long; late detection of TB increases the risk of having poor health outcomes besides the risk of transmission of TB to others and consequent distress and poverty that the families of sick individuals will eventually have to face.[2, 5, 6]

Recent onset of active TB can go unnoticed by healthcare providers as an individual might present with mild signs and symptoms of the disease such as a cough and fatigue.[7] Furthermore, the majority of pulmonary tuberculosis infections are not evident clinically or not apparent on radiological tests.[8] A study was done recently that showed that the reliance on symptom reporting may be inadequate for identifying active TB disease.[9] According to the World Health Organization, systematic screening has the potential to identify TB in individuals who would otherwise be missed or would be diagnosed too late.[6] If systematic screening is properly implemented targeting the right risk group, it can reduce suffering from disease and potential deaths.[6,10] However, countries implementing systematic screening need to balance potential benefits against the risks and costs of screening.[6,10,11,12]

Though tuberculosis has been declared a global emergency due to its high prevalence, most individuals do not develop the disease after infection.[13]Almost one-third of the world's population has latent TB infection (LTBI).[6, 14] Individuals with LTBI are asymptomatic and are not contagious, yet they signify a future risk of TB disease.[6,14] Since active TB infection is usually the result of endogenous reactivation in countries with a low incidence of TB, detecting and treating LTBI is therefore emphasized.[6, 15]

About one-third of the world populations (i.e. two billion individuals) have been infected with the tubercle bacillus, yet the great majorities only have latent tuberculosis infection (LTBI).[13] In general, only 5–10% of individuals having LTBI will develop active pulmonary TB disease and become infectious and the greatest risk of progression to active TB disease is during the first two years following the exposure.[7, 8] Nearly, 8–10 million new cases of tuberculosis arise every year from the infected one-third of individuals and eventually 2–3 million will die of the disease (Figure 1.3).[13]

Figure 1. 3: The transmission cycle of TB disease



Reference: Paulson, T. (2013). Epidemiology: A mortal foe. *Nature*, 502(7470), pp.S2-S3.

Unfortunately, in countries with low incidence of the disease, the majority of active TB cases are identified among migrants coming from high incidence countries.[16] There are three main mechanisms through which migrants can develop active TB after arrival into a low-incidence country: 1) active TB is already present in the migrant upon their arrival; 2) active TB can result

from the reactivation of the pre-existing LTBI within months or years after the arrival into the country in which migrant is seeking residency; and 3) active TB can be attributed to a newly acquired infection occurring in the migrants prior to their return to their home countries.[16] The progression of the disease can be triggered by several factors and HIV infection is the highest known risk.[7] In addition, individuals with compromised immune systems have a much higher risk of falling ill including those living with malnutrition or diabetes, or those who use tobacco.[6]

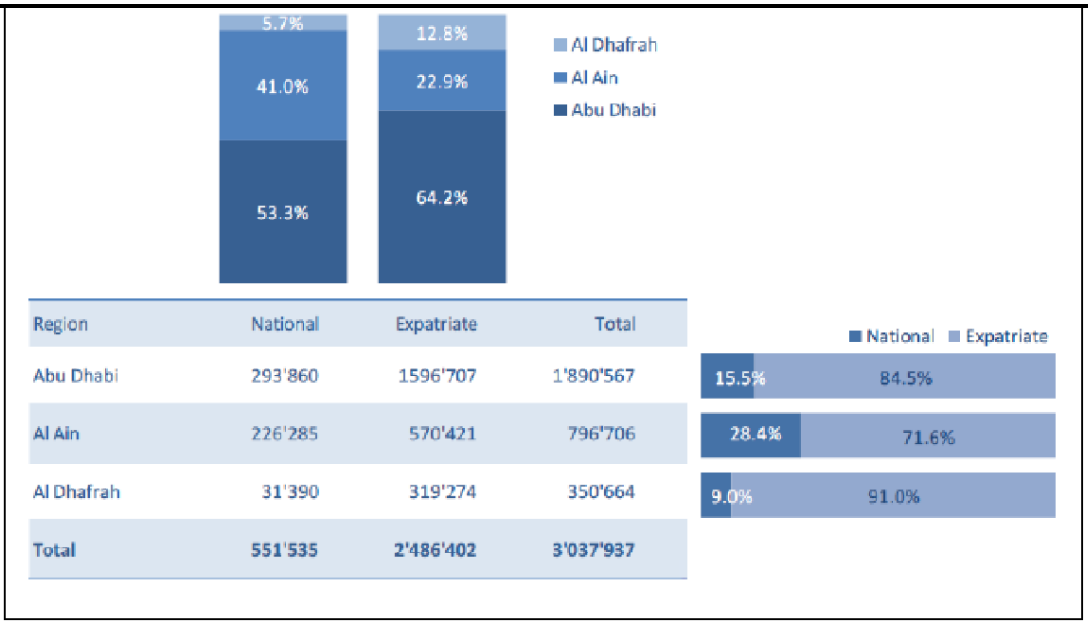
In most low TB incidence countries, TB screening programs are implemented for migrants coming from high TB incidence regions.[16] Soon after their arrival into the host country, migrants are screened by chest X-ray for active TB, while LTBI screening is not routinely implemented.[16] The primary approach to reducing the incidence of new cases is to interrupt the disease process by early identification of individuals with active TB disease and treating them immediately as well as by providing prophylactic treatment for those with latent tuberculosis infection (LTBI).[6,10,11,12] Both active TB and LTBI can be detected by the standard diagnostic and screening tests.[17]

As international travel for business and pleasure has increased dramatically in recent years, countries around the world must be increasingly cautious in detecting the presence of MTB infection (active or latent) among individuals seeking residency within their borders. This has heightened the need for efficient, affordable tests to detect MTB infection, especially among those without obvious symptoms of the disease.

Immigrant's status in the United Arab Emirates and current health challenges

The UAE is a country with a high expatriate level; this is especially true in Abu Dhabi where the national residents comprise only 18.2% of the 3.04 million residents.[18, 19, 20] The median age for nationals is 19 years and the median age for expatriates is 31 years (Figure 1.4 and Figure 1.5).[18, 19, 20]

Figure 1. 4: Population by region and nationality in

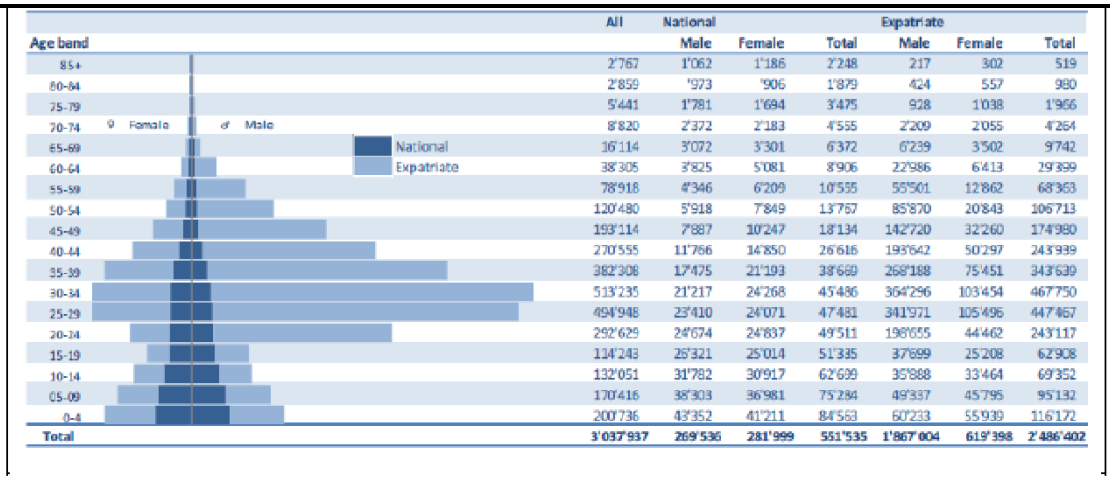


Region	National	Expatriate	Total
Abu Dhabi	293'860	1596'707	1'890'567
Al Ain	226'285	570'421	796'706
Al Dhafrah	31'390	319'274	350'664
Total	**551'535**	**2'486'402**	**3'037'937**

Reference: Department of Health. (2017). [online] Available at: https://www.haad.ae/HAAD/LinkClick.aspx?fileticket=gCldzf5KGsQ%3d&tabid=1516 [Accessed 30 Dec. 2017].

The high level of immigration into Abu Dhabi has contributed to the growing population in the Emirate and the rising demand for the screening of adults who apply for resident visas for the first time or for renewals of their visa (Figure 1.5).[18, 19]

Figure 1. 5: Population by age, gender and nationality in 2016



Age band	All	National			Expatriate		
		Male	Female	Total	Male	Female	Total
85+	2'767	1'062	1'186	2'248	217	302	519
80-84	2'859	973	906	1'879	424	557	980
75-79	5'441	1'781	1'694	3'475	928	1'038	1'966
70-74	8'820	2'372	2'183	4'555	2'209	2'055	4'264
65-69	16'114	3'072	3'301	6'372	6'239	3'502	9'742
60-64	38'305	3'825	5'081	8'906	22'986	6'413	29'399
55-59	78'918	4'346	6'209	10'555	55'501	12'862	68'363
50-54	120'480	5'918	7'849	13'767	85'870	20'843	106'713
45-49	193'114	7'887	10'247	18'134	142'720	32'260	174'980
40-44	270'555	11'766	14'850	26'616	193'642	50'297	243'939
35-39	382'308	17'475	21'193	38'669	268'188	75'451	343'639
30-34	513'235	21'217	24'268	45'486	364'296	103'454	467'750
25-29	494'948	23'410	24'071	47'481	341'971	105'496	447'467
20-24	292'629	24'674	24'837	49'511	198'655	44'462	243'117
15-19	114'243	25'321	25'014	51'335	37'699	25'208	62'908
10-14	132'051	31'782	30'917	62'699	35'888	33'464	69'352
05-09	170'416	38'303	36'981	75'284	49'337	45'795	95'132
0-4	200'736	43'352	41'211	84'563	60'233	55'939	116'172
Total	3'037'937	269'536	281'999	551'535	1'867'004	619'398	2'486'402

Reference: Department of Health. (2017). [online] Available at: https://www.haad.ae/HAAD/LinkClick.aspx?fileticket=gCldzf5KGsQ%3d&tabid=1516 [Accessed 30 Dec. 2017].

In the Emirate of Abu Dhabi, respiratory infections are rated as the second most common non-lifethreatening condition, accounting for 17.2% of inpatient or out-patient consultation with physicians across all healthcare facilities and eventually impacting the workforce productivity and the quality of life.[18, 19, 20] The population continues to grow rapidly in Abu Dhabi and the introduction of mandatory health insurance granted to all residents of the Emirate ensures access to high-quality health care.[18, 19, 20]

Although the incidence rate of TB in UAE is considered low according to the WHO tuberculosis report in 2016 (0.79 per 100000 population), the growing number of expatriate workers seeking residency in Abu Dhabi is imposing a public health challenge.[6] A significant number of expatriates aged between 20 and 40 years old are employed in construction and are provided accommodation in labor camps where the high density of residents in large dormitories can contribute to the rapid spread of disease.[18, 19] Other factors implicated in the transmission of MTB include: (1) exposure to an infected person, (2) susceptibility of the person who is

contacted (immunity status), (3) intensity/duration of exposure (e.g., being a household member or a roommate increases risk), (4) high-risk environments (crowded and poorly ventilation areas), and (5) infectiousness of the TB strain.[8]

Health system responses in Abu Dhabi to residency applicants suspected to have MTB

In Abu Dhabi, as elsewhere, the main tasks for the public health sector include a proper screening of individuals seeking residency in order to ensure early detection and initiate appropriate treatment of active TB cases. These efforts aim at reducing the risk of transmission of the disease within the community and thereby reducing future incident cases of TB. This requires continuous improvement of the comprehensive TB screening programs to ensure that they are able to effectively react in a timely manner as necessary in this evolving healthcare sector. The early diagnosis and treatment of TB require a thorough understanding of the health system in order to ensure that the developments of comprehensive TB control programs are proactive and responsive to the current demands.

A. Visa screening standard for residency in Abu Dhabi

In the UAE, three Federal Laws require the health investigation of all applicants for a residence visa (No. 27, enacted in 1981 and its Ministerial Decree amendments, No. 7 (2008) and No. 28 (2010).[20, 21] The Department of Health (DOH) previously known as the Health Authority of Abu Dhabi (HAAD), is the regulatory body of the health sector in the emirate of Abu Dhabi.[21] DOH/HAAD set the requirements for visa screening and requires that all individuals seeking residence in Abu Dhabi receive a certificate of clearance (a certificate indicating that they are free from specific communicable diseases).[21, 22] The visa screening standards in Abu Dhabi

mandate the guidelines that the healthcare providers of visa screening services are obliged to follow.[21, 22] The routine application of these processes and the procedures as specified by DOH/HAAD ensure the consistency of results.[21,22]

B. Disease Prevention and Screening Centers (DPSCs): Role in visa screening

Expatriates are screened for communicable diseases prior to acquiring their residency status.[21, 22] Visa screening centers in Abu Dhabi are connected electronically with the DOH/HAAD which emphasizes the importance of the use of highly sensitive and highly specific screening services by the DPSC's.[19]

Among all adults applying for a residency visa in Abu Dhabi, a posterior-anterior chest radiograph is used for applicants to identify chest abnormalities according to the requirement of DOH/HAAD visa screening standard implemented in 2011.[22] All Chest X-ray Images are evaluated by a DOH/HAAD licensed radiologist and documentation is following DOH/HAAD reading and reporting format: all images are evaluated either as 'Normal' or as 'Abnormal' (Not Pulmonary TB, Old Pulmonary TB, or Suspicion of Active Pulmonary TB).[22] Lesions may be seen anywhere in the lungs and may vary in size, shape, solidity, and in the presence or absence of cavitations.[2, 17] These abnormalities might suggest TB, nevertheless they cannot be used to definitively diagnose TB.[2, 17]

C. Investigations required for individuals with abnormal chest X-ray

1. AFB sputum microscopy and sputum culture for MTB: The screened individuals are required to provide a total of three sputum samples (collected within 8-24 hours interval) for microscopy and one of the three samples is used for sputum culture.[22] The first

sputum sample must be collected within three working days from receipt of the notification of abnormal chest X-ray evaluation.[22]

2. Tuberculin Skin Test: TST is performed by the expert nursing staff in DPSCs disease control section using the Mantoux method and the result is read 72 hours later.[22] Indurations of 15 mm or larger defines a positive TST in adult BCG-vaccinated or non-vaccinated subjects.[22] A positive TST result suggests active TB disease or latent TB infection.
3. IGRA: QuantiFERON-TB Gold In-tube test (QFT-GIT) is a whole-blood based enzyme-linked immunosorbent assay (ELISA) measuring the amount of IFN-γ concentration produced in response to three MTB antigens.[10, 17, 23] Results are measured in IU/ml and interpreted according to the manufacturer's recommendations as positive, negative, or indeterminate.[10, 17, 23] The test used in the central laboratory in DPSCs is the QuantiFERON-TB Gold In-tube test (QFT-GIT).[24]

Aims of the study

This study has three major aims to inform and help guide the work of the immigration screening service in Abu Dhabi. The data used in the study was collected by the Emirate of Abu Dhabi over a one-year period (2013) on all adult expatriates seeking residency visas. All adult visa applicants had a chest X-ray and several blood tests to identify the presence or absence of communicable diseases as determined by the Federal Law in the United Arab Emirates.

In our study, all adults who had a negative HIV test and presented with abnormal chest X-ray requiring further investigations to confirm or to rule out *Mycobacterium tuberculosis* (MTB)

infection were included as potential TB cases. The final diagnosis of MTB in the study is based on the sputum culture test -- "the gold standard" test. Therefore, the study individuals were divided according to the final diagnosis result into two main groups: MTB (sputum culture positive for MTB) and No MTB (sputum culture negative for MTB). The three aims of the study are to:

1. Provide demographic characteristics of the study sample by age categories.

2. Explore the sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) as well as the negative and positive likelihood ratio of IGRA (QFT-GIT) and TST. In addition, the study explores the validity of simultaneous testing (parallel) with IGRA (QFT-GIT) and TST, to measure agreement of IGRA and TST using a kappa statistic and to explore chest X-ray validity measures.

3. Explore the risk of MTB among younger age groups (18-34) vs. older (35-64) age groups.

Conclusions

Chapter 1 introduced the concept of *Mycobacterium tuberculosis* (MTB) infection which is transmitted through the respiratory route from one individual to another and is present in two major forms -- active TB disease and latent TB infection (LTBI). In this chapter, the immigration status in the UAE in relation to MTB infection revealed that the UAE as a country has a low incidence of TB and a very high expatriate level; this is especially true in Abu Dhabi. In countries with low-incidence of TB, the majority of active TB cases are identified among

immigrants coming from high-incidence countries and active TB infection is usually the result of reactivation of latent TB infection.

All visa applicants desiring to enter Abu Dhabi for residency are required to undergo visa screening. In Abu Dhabi and as per visa screening requirements for the year 2013, applicants with abnormal chest X-ray evaluation had to undergo further diagnostic investigations to confirm or to rule out TB disease. Diagnostic investigations included: sputum samples that are sent for sputum-smear microscopy (sputum smear AFB test) and sputum culture test as well as giving the blood sample for IGRA (QFT-GIT) and doing TST. This chapter then highlighted the three aims of the study including the provision of demographic characteristics of the study sample, particularly by age, exploring the validity of IGRA (QFT-GIT), TST and chest X-ray and finally, exploring the risk of MTB among younger visa applicants in comparison to older via applicants.

Chapter 2

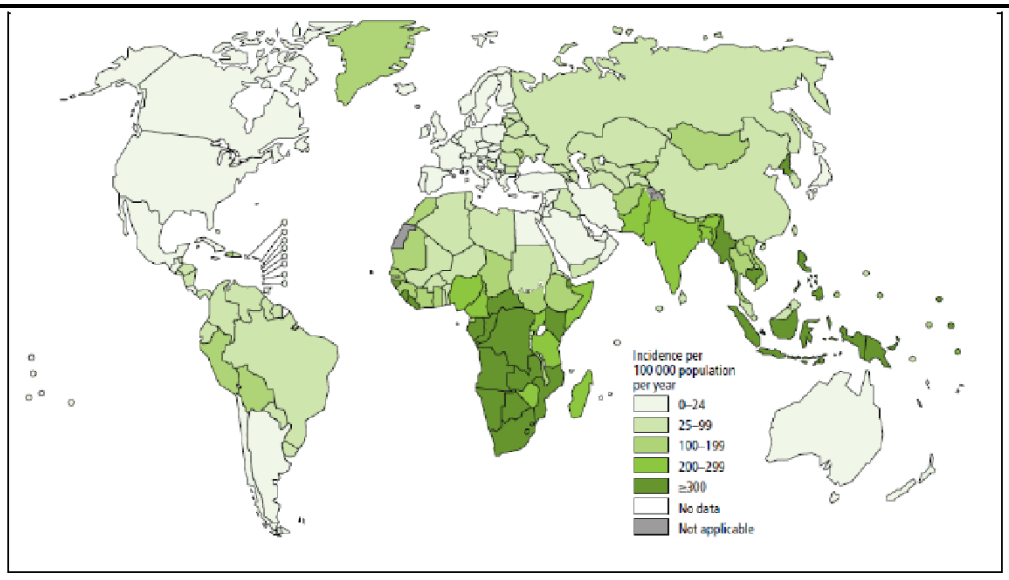
Introduction

Chapter 2 will briefly introduce the current epidemiology of tuberculosis at the global level and TB mortality in 2016. This chapter will then review the role of early diagnosis and treatment of TB in saving lives and will highlight efforts and possible interventions targeting LTBI. The chapter will then introduce the systematic screening of tuberculosis (TB); the main focus will be on the objectives and goals of screening, followed by an introduction of the number needed to screen (NNS) to detect a case of TB, screening algorithms, screening tests, and diagnostic tests. Chapter 2 will then highlight the validity of screening tests (addressing sensitivity and specificity of tests) and its limitations in clinical practice, the concept of predictive values, followed by likelihood ratios in relation to clinical practice. Finally, guidelines for IGRA and TST in immigrant screening will be addressed.

Current epidemiology of tuberculosis (TB) worldwide

The TB annual incidence rate in 2016 (that is the annual number of incident TB cases relative to population size) varied extensively among countries, from under 10 per 100000 population in the majority of high-income countries to 150–300 in most of the 30 high TB burden countries (Appendix. 3.1- 3.3).[6] In a few countries such as Democratic People's Republic of Korea, Lesotho, Mozambique, the Philippines and South Africa, the incidence rate reached above 500 in 2016 (Figure. 2.1).[6]

Figure 2. 1: Estimate TB incidence rate, 2016

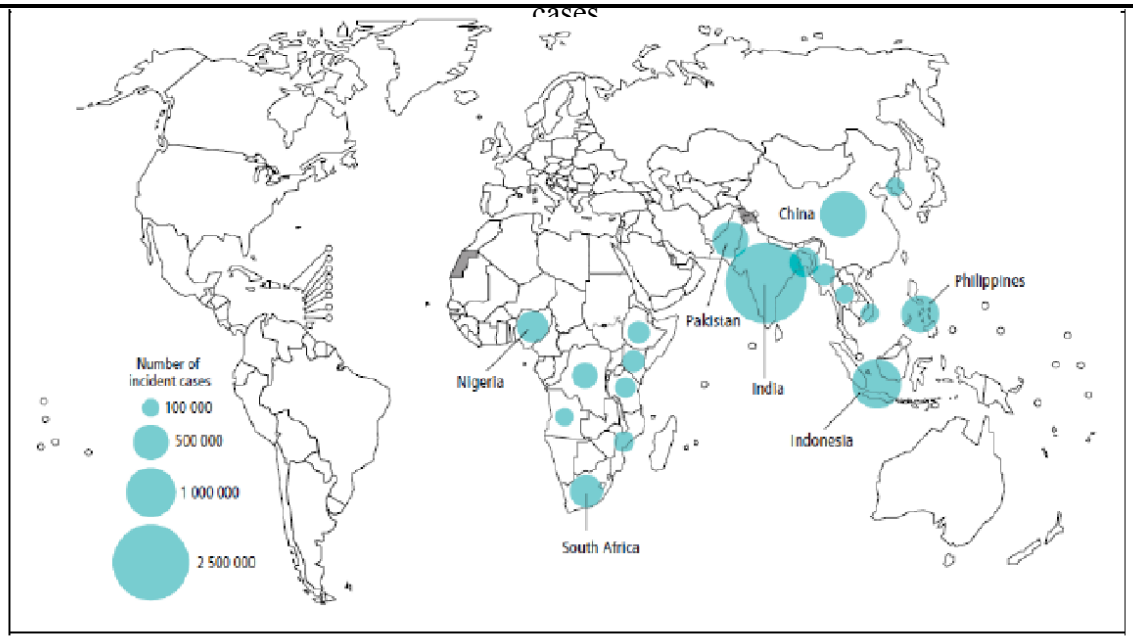


Reference: World Health Organization. (2017). *Global tuberculosis report*. [online] Available at: http://www.who.int/tb/publications/global_report/en/ [Accessed 29 Dec. 2017].

Tuberculosis cases are unevenly distributed across the world. The majority of the estimated number of tuberculosis cases in 2016 occurred in the WHO South-East Asia Region (45%), the WHO African Region (25%) and the WHO Western Pacific Region (17%); lesser numbers of cases occurred in the Eastern Mediterranean Region (7%), the European Region (3%) and the Region of the Americas (3%).[6] Of all estimated incident cases worldwide, the 30 high TB burden countries accounted for the majority (87 %) of those cases.[6]

In 2016, six counties (in descending order) -- India, Indonesia, China, Nigeria, Pakistan, and South Africa accounted for the largest number (56%) of incident cases globally.[6] And of these, China, India, and Indonesia alone accounted for 45% of global tuberculosis cases in 2016 while Nigeria and South Africa each accounted for 4% of the global total of tuberculosis cases (Figure 2.2).[6]

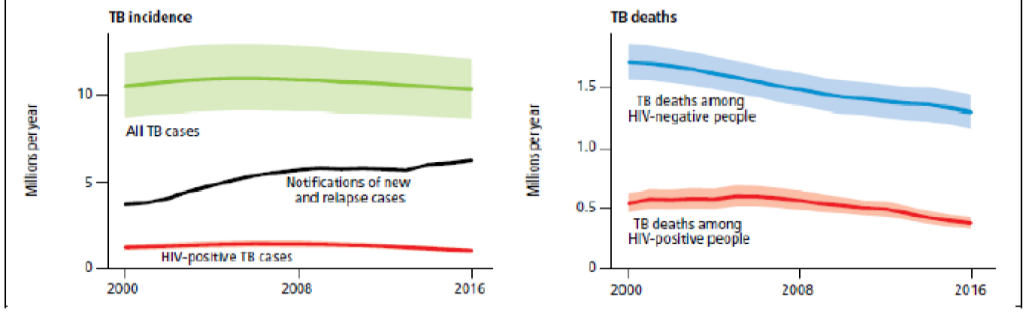
Figure 2. 2: Estimate TB incidence rate in 2016, for countries with at least 100 000 incident cases



Reference: World Health Organization. (2017). *Global tuberculosis report.* [online] Available at: http://www.who.int/tb/publications/global_report/en/ [Accessed 29 Dec. 2017].

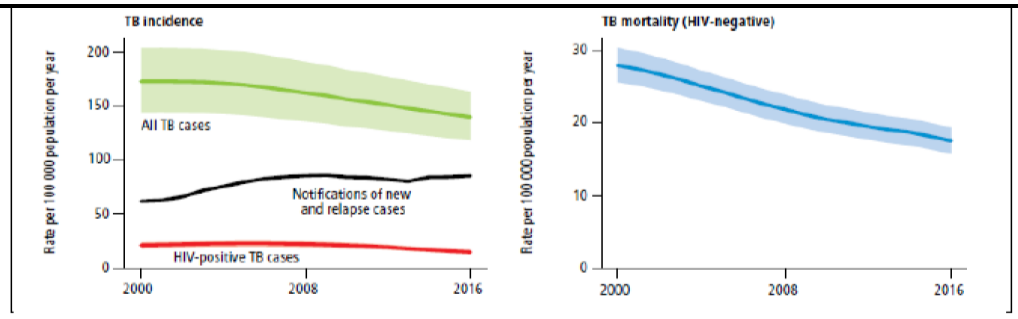
According to the estimated trends of TB incidence in 2000-2016, the number of incident cases is falling slowly as illustrated in the Figures 2.3 and 2.4.[6] Worldwide, in 2000−2016, the average rate of decline in the TB incidence rate was 1.4% per year and was even slightly larger between 2015 and 2016 as the decline rate reached 1.9%.[6] To achieve the milestones for reductions in cases and deaths as outlined in the End TB Strategy, the decline in the TB incidence rate needs to be accelerated to 4–5% per year by 2020.[6, 25, 26]

Figure 2. 3: Global trends in the estimated number of incident TB cases and the number of TB deaths (in millions), 2000-2016



Reference: World Health Organization. (2017). *Global tuberculosis report*. [online] Available at: http://www.who.int/tb/publications/global_report/en/ [Accessed 29 Dec. 2017].

Figure 2. 4: Global trends in the estimated TB incidence and mortality rates, 2000-2016. Shaded areas represent uncertainty intervals



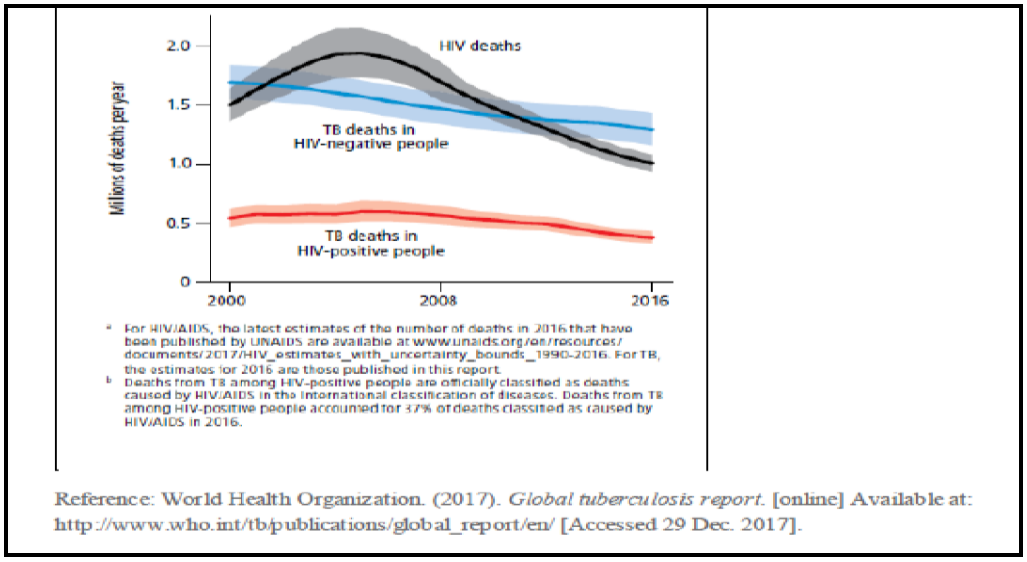
Reference: World Health Organization. (2017). *Global tuberculosis report*. [online] Available at: http://www.who.int/tb/publications/global_report/en/ [Accessed 29 Dec. 2017].

TB mortality in 2016

There were an estimated1.3 million (range, 1.2 million to 1.4 million) deaths from TB among HIV-negative individuals in 2016 and an additional 374000 deaths from TB among HIV-positive individuals.[6] At a global level, among HIV-negative individuals, the absolute number of TB deaths has been falling since 2000, from 1.7 million in 2000 to 1.3 million in 2016 (Figure 2.3, Figure 2.4).[6] Between 2000 and 2016, the TB mortality rate (per 100000 population) fell by 37%

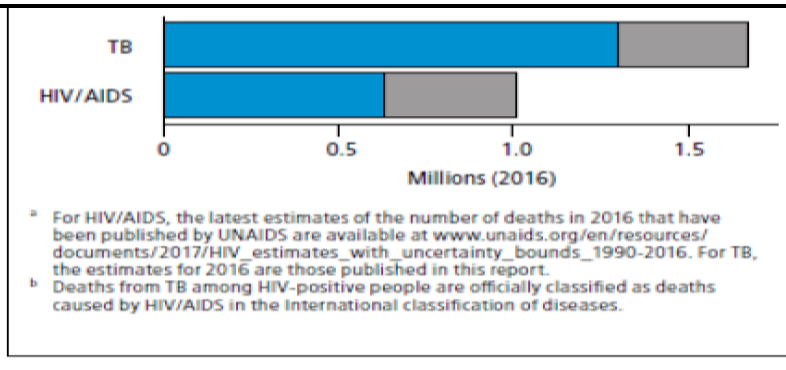
(Figure 2.4) and by 3.4% between 2015 and 2016.[6] TB caused more deaths than HIV/AIDS in 2016 (Figure 2.5 and Figure 2.6).[6]

Figure 2. 5: Global trends in the estimated number of deaths caused by TB and HIV (in millions), 2000-2016. Shaded areas represent uncertainty intervals



Reference: World Health Organization. (2017). *Global tuberculosis report*. [online] Available at: http://www.who.int/tb/publications/global_report/en/ [Accessed 29 Dec. 2017].

Figure 2. 6: Estimated numbers of deaths from HIV/AIDS and TB in 2016. Deaths from TB among HIV-positive people are shown in grey



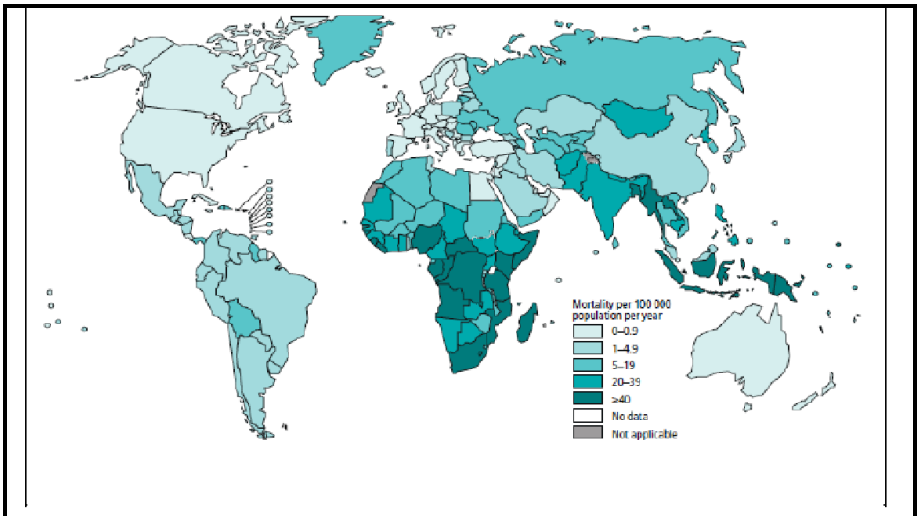
Reference: World Health Organization. (2017). *Global tuberculosis report*. [online] Available at: http://www.who.int/tb/publications/global_report/en/ [Accessed 29 Dec. 2017].

The majority of TB deaths (about 82%) occurred among HIV-negative individuals in the WHO African Region and the WHO South-East Asia Region in 2016 compared to India which accounted for 33% of global TB deaths in 2016 among HIV-negative individuals.[6]

Worldwide, the number of TB deaths among HIV-negative individuals per 100000 population was 17 in 2016, and 22 when TB deaths among HIV-positive individuals were included. A considerable variation in the number of TB death among HIV-negative individuals among countries was noted in the year 2016 (Figure 2.7).[6]

The variation in TB deaths among HIV-negative individuals ranged from less than one TB death per 100000 population in several high-income countries to more than 40 deaths per100000 population in a large number of the WHO African Region and in five high TB burden countries in Asia, namely Bangladesh, Indonesia, the Democratic People's Republic of Korea and Papua New Guinea (Figure 2.7).[6]

Figure 2. 7: Estimate TB mortality rates excluding TB deaths among HIV-positive people, 2016



Reference: World Health Organization. (2017). *Global tuberculosis report*. [online] Available at: http://www.who.int/tb/publications/global_report/en/ [Accessed 29 Dec. 2017].

At a global level, estimates of TB mortality rates (per 100000 population) for the six WHO regions and for the 30 high TB burden countries are shown in (Appendix 3.4).[11]

Early diagnosis and treatment of TB saved lives

Unfortunately, over one-third of the 9 million individuals who suffer from tuberculosis (TB) each year are not diagnosed, and hence are either not notified or fail to initiate or complete known, effective treatment.[11] For those who do initiate treatment a delayed start is attributed to a variety of challenges including: difficulties in receiving care resulting in poor health outcomes for the affected individuals, disastrous costs for their families and continuous transmission of TB to others in their communities.[11]

Furthermore, often those with the least access to healthcare and therefore treatment for the disease are the individuals and communities who are at highest risk of acquiring TB which will further complicate the harmful effects of the disease.[11] Therefore, the call to intensify efforts to ensure early identification of an urgent treatment for all individuals with TB is essential due to the current obstacles to care, which reflect the magnitude and persistence of the global TB burden.[11]

Worldwide, almost 4% of newly diagnosed TB patients and about 20% of patients receiving retreatment have multidrug-resistant tuberculosis.[11] With a standard 6-month course of 4 antimicrobial drugs that are provided with information and direct supervision, active drug-susceptible TB disease can be treated and the patient can be cured. [11] The support of the patient and the provision of treatment with supervision by a health worker or trained volunteer are

essential to assure adherence to treatment.[11] Without support and supervision, treatment adherence can be challenging and the disease can spread to other community members.[11]

An estimated 53 million lives were saved through proper TB diagnostic procedures and the provision of treatment under supervision between 2000 and 2016.[11] TB treatments averted an estimated 44 million deaths among HIV-negative individuals between 2000 and 2016.[6] An additional 9 million deaths among HIV-positive individuals were averted by TB treatment supported by ART.[6] On the other hand, the currently available treatment regimens for drug-resistant tuberculosis are insufficient in terms of duration, cost, safety, and effectiveness.[11] Therefore, improving treatment outcomes requires the development of new safer, affordable and more effective medicines allowing treatment regimens to be administered in easier and shorter duration.[11]

Efforts targeting LTBI are needed to lower TB burden worldwide

Achieving the End TB Strategy targets set for 2030 and 2035 and reducing the burden of disease and death caused by TB necessitate the prevention of new infections of *Mycobacterium tuberculosis* and the progression to TB disease (Appendix 3.5).[6, 25] Therefore, an extraordinary acceleration in the rate at which TB incidence drops after 2025 is required in order to reach the targets of an 80% reduction in TB incidence by 2030 and a 90% reduction by 2035 compared with 2016 (Appendix 3.6).[6] This can merely occur if the probability of progression from latent

TB infection (LTBI) to active TB disease among the already infected 1.7 billion individuals decreases below the current lifetime risk of 5–15%.[6]

The emphasis on the importance of lowering the progression of LTBI to active disease is evident knowing that reactivation of TB is responsible for about 80% of new cases of the disease in some low-burden countries.[6] Therefore, in low-burden countries, there is a clear call for advancing the initiation, completion, and reporting of TB preventive treatment for at-risk populations such as "patients with silicosis, patients starting anti-tumor necrosis factor (TNF) therapy and patients preparing for organ transplantation".[6]

Possible interventions targeting LTBI

Possible interventions that might result in an improved reduction in the number of cases due to reactivation of LTBI include a more effective treatment for LTBI and the development of a vaccine capable of preventing reactivation of LTBI in adults. [6] There are three main health intervention categories available currently for the prevention of TB including: first, the provision of LTBI preventive treatment such as isoniazid for 6-9 months; second, the implementation of infection control measures to limit the transmission of the causative agent of TB disease and finally, the universal provision of the bacille Calmette-Guerin (BCG) vaccine to children.[6]

A. Contact investigations

As recommended by World Health Organization, there are two main risk groups requiring definite efforts to diagnose and treat LTBI, including children aged less than 5 years (household

contacts of confirmed pulmonary TB cases) and individuals living with HIV.[6] Therefore, the coverage of contact investigation and treatment of LTBI among the previously mentioned categories is listed among the high priority indicators intended to monitor the implementation of the End TB Strategy aiming at a target of more than 90% coverage by 2025.[6, 26] In 2016, only 13% of the 1.3 million children estimated to be eligible for treatment had initiated LTBI preventive treatment.[6] In addition, in the year 2016, a total of 60 countries (compared to 57 countries in 2015) reported the initiation of LTBI preventive treatment to individuals under HIV care.[6]

B. Infection control

In the medical literature, it was reported that "healthcare workers (HCWs) are at higher than average risk for infection with *Mycobacterium tuberculosis* and of developing TB disease".[26] Therefore, TB infection control measures, including early diagnosis and prompt treatment of contagious cases, need to be a priority in healthcare facilities.[26] In addition, the assessment of infection control measures in healthcare facilities periodically is necessary to assure the proper adherence to appropriate measures.[6]

C. BCG vaccination

In countries with a high TB burden WHO recommends the provision of a single dose of the BCG vaccine to all infants shortly after birth as part of childhood immunization program.[6] On the other hand, in countries with low TB burden, the provision of BCG may be restricted to neonates and infants in recognized high-risk groups, or to older children with negative skin-test.[6]

BCG vaccination is of value in preventing the dissemination of TB disease including TB meningitis and miliary TB, which are in particular associated with high mortality among infants and young children.[6] BCG vaccination coverage in the 30 high TB burden countries varied between 58% in Angola and Nigeria and 99% in "Cambodia, China, Mozambique, the United Republic of Tanzania and Zambia".[6] The need for a new vaccine that is more effective than BCG is apparent particularly to reduce the risk of infection with *Mycobacterium tuberculosis* and the risk of progression from LTBI status to active TB disease in adults.[6]

Systematic screening of tuberculosis (TB): Objectives and goals

In general, a major objective of screening is to detect active TB as early as possible in order to contribute towards two crucial goals:

1. Lowering the risk of poor treatment outcomes, health consequence and the adverse societal and economic burdens of TB in individuals diagnosed with the disease. This will eventually reduce suffering, the prevalence of TB and ultimately death from TB;

2. Minimizing the risk of TB transmission by shortening the duration of infectiousness among those with the disease. This will eventually reduce the incidence of latent TB infection (LTBI) and, as a result, contribute to a reduced incidence of TB disease.[11, 12]

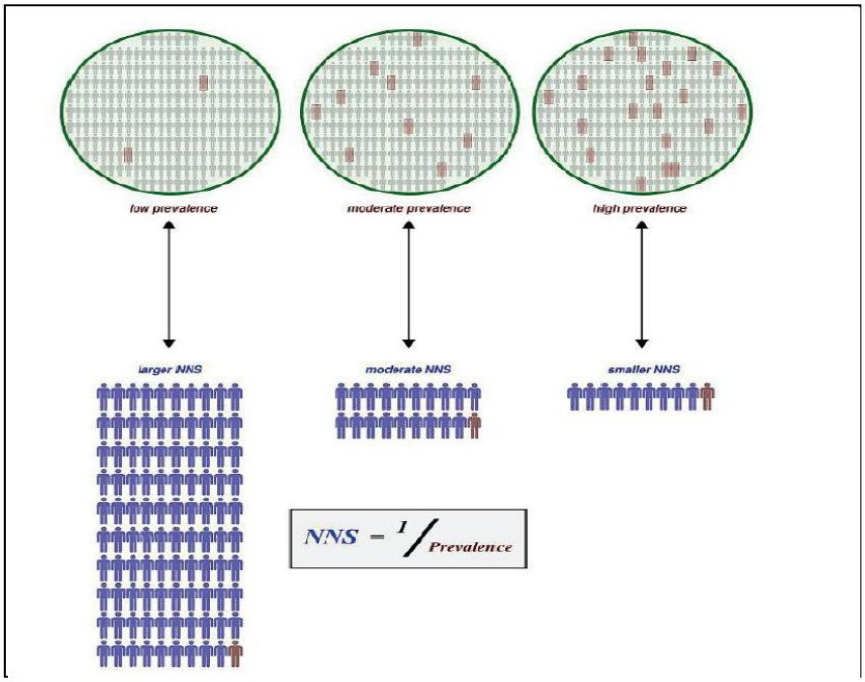
Another major objective of screening is to help identify people who are eligible for treatment of latent TB infection, such as close contacts and individuals with other clinical conditions.[11, 12]

Moreover, screening can aid in identifying individuals who are at high risk of developing active TB and thus may need periodic screening. For instance, individuals with an abnormal chest X-ray that is compatible with TB (yet not diagnosed with an active disease at the time of screening) can get the advantage from periodic screening in the future.[11] The systematic screening of those at high risk for TB is, therefore, a key element of the World Health Organization's (WHO) End TB strategy, 2016 to 2035.[11, 12, 25]

A. The number needed to screen (NNS) to detect a case of TB

In a specific risk group, the Number Needed to Screen (NNS) to identify one true case of TB is "the inverse of the prevalence of detectable TB in that risk group, assuming 100% sensitivity of the screening and diagnostic tools being used".[11] For instance, in a given risk group with a very low prevalence of detectable TB, a very large number of individuals will need to undergo screening in order to find one case of TB, and this will be interpreted as a high NNS.[11] Nevertheless, if a given risk group has a high prevalence of TB that can be detected by available screening and diagnostic tools, fewer individuals will need to be screened for each case detected, resulting in a lower NNS (Figure 2.8).[11]

Figure 2. 8: The number needed to screen (NNS) to detect a case of TB



Reference: World Health Organization. (2018). Systematic screening for active tuberculosis: an operational guide. [online] Available at: http://www.who.int/tb/publications/systematic_screening/en/ [Accessed 13 Jan. 2018].

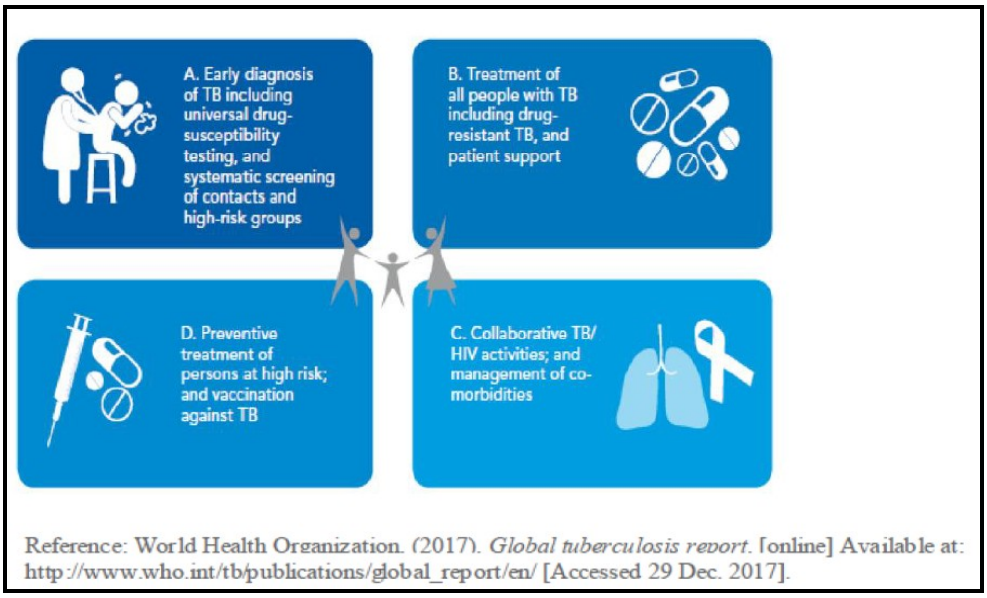
One or several screening tests and one or several diagnostic tests combined together are used to build an algorithm intended for systematic screening for TB. [11] Screening tests must differentiate between individuals with a high likelihood of having active TB and those who are unlikely to have active TB.[11]

Furthermore, a screening test is intended to identify the subgroup(s) of individuals with the highest likelihood of disease and therefore is not intended to be diagnostic.[11] Individuals with positive results on a screening test will then undergo diagnostic tests to confirm or rule out active TB based on bacteriological tests.[11]

A negative diagnostic test might have to be followed up with clinical evaluation (mostly based on chest radiography, the presence or absence of symptoms and the evaluation of an individual's medical history).[11] A positive diagnostic test result, on the other hand, might have to be re-confirmed with additional testing and a detailed clinical evaluation if the positive predictive value (PPV) of the test result is low.[11]

Until recently, the primary approach to case-finding to detect TB cases was only through individuals presenting themselves to health facilities with symptoms suggestive of the disease, a passive approach.[11] The need for a more active approach to detect TB early was brought about by the ongoing case-detection gap, predominantly in certain vulnerable populations, along with the persistent delays in diagnosis and continuous transmission of the infection in the community.[11] Therefore it is crucial to consider systematic screening for active TB, particularly in selected risk groups.[11] Given the global impact of the disease, WHO's End TB Strategy includes systematic screening for active TB in certain high-risk groups within the first component of Pillar 1, which emphasizes the necessity for early diagnosis of TB (Figure 2.9).[11, 25]

Figure 2. 9: End of TB Strategy includes systematic screening for active TB in certain high risk groups in the first component of Pillar 1



Reference: World Health Organization. (2017). *Global tuberculosis report*. [online] Available at: http://www.who.int/tb/publications/global_report/en/ [Accessed 29 Dec. 2017].

Therefore, guidelines for screening for active TB and recommendations on prioritizing certain risk groups and deciding screening approaches have been published by The World Health Organization (WHO) (Appendix 3.7).[11]

To improve the early detection of TB two complementary approaches are advised:

1. Improving the patient-initiated pathway to TB diagnosis; and

2. Employing the provider-initiated screening pathway to TB diagnosis.[11]

B. Screening algorithms

Systematic screening for active TB according to the WHO's guidelines includes 10 screening algorithm options, consisting of a combination of one or two screening tests and a diagnostic test (Appendix 3.8).[11] The development of those algorithms aimed mainly to detect pulmonary TB and culture-confirmed pulmonary TB had been established as the gold standard diagnostic tests

to assess the accuracy of the tests used in the algorithms.[11] Although the sputum culture is the gold standard for diagnostic testing for TB, in these algorithms it is not considered as an initial diagnostic test since it demands more resources and requires a much longer waiting time for results (2–8 weeks) compared to other tests such as the GeneXpert MTB/RIF test and sputum-smear microscopy, both of which results can be generally provided in less than 1 day.[11]

Each of the algorithms has different sensitivity and specificity, and, as a result, different potential yields of "true-positive and true-negative cases and false-positive and false negative" TB.[11] Moreover, yields differ with the prevalence of TB in the population being screened.[11] As the prevalence of the disease declines, the risk of a false-positive diagnosis increases and this is applicable for all algorithms.[11] For that reason, special attention must be paid to diagnostic accuracy, mainly when the prevalence of TB in the screened population is less than 1%.[11] "At a TB prevalence of 0.5% in the screened population, all of the algorithms have a PPV of less than 75% (i.e., 25% have a false positive diagnosis) when clinical diagnosis is used for all or some of those with a negative result from their initial diagnostic test".[11] The PPV is below 80% for all but one algorithm when clinical diagnosis is not considered.[11] To guarantee high quality of diagnostic procedures and clinical assessment special efforts must be taken particularly when TB prevalence in the screened population is moderate to low.[11]

It is important to consider what proportion of false positive and false negative results are unacceptable for each given screening situation.[11] The acceptable sensitivity and specificity of the algorithm should be guided by ethical considerations which will vary across risk groups

especially in groups with a high risk of severe negative effects from missed or delayed diagnosis and treatment.[11] Still, it is essential to utilize an algorithm that has very high sensitivity, even though this choice will often lead to lower specificity.[11] The predictive values of all tests and, consequently, the true-positive and false-positive cases and true-negative and false-negative cases are influenced directly by the prevalence of TB in a risk group.[11]

When the prevalence is low, it is essential to use an algorithm with a very high specificity so that a high proportion of false-positive cases will be avoided.[11] It might be helpful to evaluate the PPV for a number of algorithms which can be much simpler than evaluating accuracy.[11] That is because assessing the accuracy of an algorithm involves the evaluation of the sensitivity which requires testing a large number of individuals with the reference standard.[11] Assessing the PPV, on the other hand, necessitates only testing those diagnosed as having TB with a reference standard.[11]

The costs and requirements of algorithms vary according to the status of human resources and health systems.[11] The choice of an algorithm for screening and diagnosis depends on several factors including: the risk group, the prevalence of TB, the accessibility of resources and the feasibility of implementing the algorithm.[11]

C. Screening tests

Screening immigrants and close contacts for active tuberculosis (TB) and latent tuberculosis infection (LTBI) is essential to enhance infection control strategies, especially in low incidence countries.[11]

Some frequently used initial screening tests comprise:

- Screening for the presence of a cough lasting for longer than 2 weeks;
- Screening for any symptoms suggestive of TB, such as –
  - ✓ A cough of any duration (a cough of more than three weeks duration is more compatible with TB)
  - ✓ Hemoptysis (coughing blood)
  - ✓ Weight loss
  - ✓ Fever
  - ✓ Chills
  - ✓ Chest pain
  - ✓ Shortness of breath
  - ✓ Loss of appetite
  - ✓ Night sweats;
- Screening with chest radiography.[2, 11, 12,17]

If symptom screening is used initially, this can be followed by chest radiography as a second screening step to decrease the number of individuals who need to experience a full diagnostic assessment and to improve the pretest probability of the subsequent diagnostic test.[11] The visa screening process in Abu Dhabi follows the same screening methodology described earlier. The visa applicants in Abu Dhabi will see the healthcare clinician for history taking and physical examination followed by chest radiography as a second screening step.

D. Diagnostic tests

For individuals who screen positive, each screening algorithm also comprises one of two options for diagnostic testing such as sputum-smear microscopy; or a rapid molecular test such as the GeneXpert MTB/RIF test.[2, 11, 17] In the Abu Dhabi visa screening algorithm, the sputum-smear microscopy was the test of choice until 2013 prior to the introduction of the GeneXpert MTB/RIF test in 2014 as an additional rapid diagnostic test.

The validity of a screening test: sensitivity and specificity in the literature

The validity of a screening test is defined as the ability of the test to differentiate between those who have a disease and who do not.[27] Validity comprises two components: sensitivity and specificity.[27] The sensitivity of a screening test is defined as the ability of the test to correctly identify those who have the disease (i.e., the proportion of diseased individuals correctly identified with positive test result).[27] The specificity of a screening test, on the other hand, is defined as the ability of the test to correctly identify those who do not have the disease (i.e., the proportion of non-diseased individuals correctly identified with negative test results).[27]

When an individual has a negative result on a screening test, then using a test with a high sensitivity will be helpful for 'ruling out' a disease.[28] A highly sensitive test is most useful to the clinician when the test result is negative.[28] Similarly, a test with a high specificity is helpful for 'ruling in' a disease if an individual's test result is positive.[28] And a highly specific test is thus most useful to the clinician when the test result is positive.[28] The value of diagnostic tests is their ability to detect an individual with disease or exclude an individual without disease; this is

generally described by terms such as sensitivity, specificity, positive predictive value and negative predictive value (Table 2.1).[28]

Table 2. 1: Defining sensitivity, specificity and predictive value from 2x2 table

	Patients with disease	Patients without disease	
Test is positive	a	b	Total positive tests (a+b)
Test is negative	c	d	Total negative tests (c+d)
	Total number of patients with disease (a+c)	Total number of patients without disease (b+d)	Total number of patients (a+b+c+d)

Sensitivity: proportion of people with disease who will have a *positive* result {a/(a+c)}.
Specificity: the proportion of people without the disease who will have a *negative* result {d/(b+d)}.
Positive predictive value: the proportion of people with a positive test result who actually have the disease {a/(a+b)}.
Negative predictive value: the proportion of people with a negative test result who do not have disease {d/(c+d)}.

Reference: Akobeng, A. (2007). Understanding diagnostic tests 1: sensitivity, specificity and predictive values. *Acta Paediatrica*, 96(3), pp.338-341.

In the anticipation of occurrence of a high prevalence tuberculosis setting, it is essential that screening would recognize those participants requiring additional investigation.[29] An easy screening strategy should be implemented utilizing tool/s with have high sensitivity.[29] This generally would be followed by a diagnostic test of high specificity to recognize individuals with tuberculosis.[29] However, the performance of the diagnostic test (such as sensitivity and specificity) may be expected to vary according to disease prevalence and other characteristics of the screened population.[30]

A. Limitation of sensitivity and specificity in clinical practice

Both sensitivity and specificity have a major limitation that they are of no practical use in helping the clinician in the estimation of the probability of disease in individual patients.[28] When

a clinician sees a patient in the clinic with a positive result for a particular test, the question that needs to be answered then would be 'what is the chance (probability) of disease given the positive test?' and sadly neither sensitivity nor specificity can be used to answer such a question.[28] This is because both sensitivity and specificity are calculated based on an external source of truth, i.e., a gold standard test on the basis of individuals with or without a disease.[27, 28] Given that the patient would have presented to a clinician with a set of signs and symptoms rather than a diagnosis, a clinician would not know at the time of visit whether the patient has a disease or not and cannot, for that reason, apply these parameters directly to the patient.[28] As an alternative, clinicians need to know the predictive values of tests which are more helpful measures of diagnostic accuracy in routine clinical practice.[28]

B. Predictive values

The main purpose of a diagnostic test is to utilize its results to make a diagnosis, thus we need to know the probability that the test result will provide the correct diagnosis. Once the result of a patient is known, the positive and negative predictive values illustrate a patient's probability of having a disease.[28] The positive predictive value (PPV) of a test is defined as the proportion of individuals with a positive test result who truly have the disease.[28] The negative predictive value (NPV) of a test, on the other hand, is the proportion of individuals with a negative test result who do not actually have the disease.[28]

The test's sensitivity and specificity and the prevalence of the condition for which the test is being used determine the predictive value of a test.[28] Changing prevalence of the disease will ultimately result in the variation of both PPV and NPV.[28] Clinicians, therefore, cannot directly

apply published predictive values of a test to their own populations, knowing that the prevalence of disease in their population is different from that in the published study.[28] Looking at the relationship between the prevalence and the predictive values in (Table 2.2) we can notice that the higher prevalence of the disease, the higher the PPV and the more likely a positive result is able to predict the presence of disease.[28]

Table 2.2: Relationship between predictive values and disease prevalence (a test with a sensitivity of 80% and a specificity of 94%)

Prevalence (%)	Positive predictive value (%)	Negative predictive value (%)
5	40	99
10	62	98
20	76	95
40	89	87
50	93	82
60	96	76

Reference: Akobeng, A. (2007). Understanding diagnostic tests 1: sensitivity, specificity and predictive values. *Acta Paediatrica*, 96(3), pp.338-341.

On the other hand, and despite using a test with high sensitivity and specificity, when the prevalence of a disease is low, the PPV will be low as well.[28] In such a condition, a significant proportion of individuals who tested positive might not necessarily have the disease.[28] In clinical practice, therefore, the usefulness of a test result for an individual depends on the prevalence of the disease in the population being examined and tested.[28] The diagnostic value of a test will improve if the use of the test is limited to those patients who are likely to have the disease in question-based on the history and clinical assessment.[28]

C. Likelihood Ratio

Although the sensitivity and specificity of a test cannot be used to estimate the probability of disease in any particular individual, both parameters can be joined together as an index called the likelihood ratio (LR).[28, 30] A likelihood ratio in simple words is the percentage of sick individuals with a given test result (can be positive or negative) divided by the percentage of well individuals with the same result.[31] Therefore, "the positive LR is the ratio of the probability of positive test in diseased to non-diseased and negative LR is the ratio of the probability of negative test in diseased to non-diseased".[30] Positive LR greater than (10) indicates that a positive test is good at ruling in a diagnosis.[31] On the other hand, a negative LR lesser that is lesser than (0.1) implies that a negative test is good at ruling out a diagnosis.[31]

Recommended tests for Tuberculosis (TB) and latent tuberculosis (LTBI)

TB disease is a leading cause of infectious disease morbidity and mortality worldwide with a lot of diagnostic uncertainties.[8] Both LTBI and TB could be looked at as different moments occurring in the context of a continuous pathological process.[32] LTBI and TB are generally distinguished based on the presence (TB) or absence (LTBI) of clinical, laboratory, and chest radiography findings.[32] A comprehensive diagnostic assessment for TB infection must comprise medical history, physical examination, chest X-ray, TST, IGRA, microbiologic smears, and cultures.[32]

A. Radiographic screening

Radiographic screening can aid in the detection of individuals at high risk of TB.[33] Radiographic findings consistent with former healed pulmonary TB are predictive of subsequent reactivation of the disease over nearly 10 years of observation.[33] The best criterion (strong predictor) for identifying individuals at risk of subsequent tuberculosis include the presence of calcified nodular densities or fibrosis, and the presence of non-calcified nodular densities in mid and or upper lung zones or the presence of typical TB pulmonary infiltrates.[33] This criterion has a sensitivity of 66% and a specificity of 82% for subsequent pulmonary tuberculosis.[33]

In high-risk populations, chest X-ray screening for TB/LTBI might reveal findings consistent with prior and/or active infection.[32] Imaging, therefore, plays an essential role in risk stratification in patients with positive TST or positive IGRA by helping to differentiate between latent infection, previous inactive disease, and active disease.[34] In addition, stratifying for risk of the disease and the assessment of asymptomatic active disease can be accomplished through chest radiographs.[34]

B. Sputum for smear and culture

When individuals are suspected of having active TB, they should be placed in respiratory isolation.[34] Laboratory assessments then should be initiated with obtaining sputum for smear and culture.[34] Performing acid-fast bacilli (AFB) smear microscopy in all patients suspected of having pulmonary TB is considered a strong recommendation based on moderate-quality evidence.[8] Three consecutive sputum samples must be given by the patient at 8-to 24-hour

intervals, if possible in the early morning hours.[34] The detection of acid-fast-bacilli (AFB) on a sputum smear often indicates TB disease.[2, 17]

Though the acid-fast-bacilli microscopy is easy and quick, it cannot confirm a diagnosis of TB since some acid-fast-bacilli are not *M. tuberculosis*.[2, 17] Therefore, a culture is done on all initial samples to confirm the diagnosis.[2, 17] The gold standard for the diagnosis of TB is achieved by culturing *tuberculosis* bacteria from a specimen taken from the patient.[32] A positive culture for *Mycobacterium tuberculosis* confirms the diagnosis of TB disease.[2, 17] Unfortunately, the diagnosis usually takes a long time owing to the slow-growth of this aerobic, non-motile bacterium.[32] Culture examinations, therefore, should be completed on all specimens, despite AFB smear results.[2, 17]

Both liquid and solid mycobacterial cultures were suggested by guideline taskforces (including: the Official American Thoracic Society, Infectious Diseases Society of America and the Centers for Diseases Control and Prevention) to be performed for every specimen obtained from an individual with suspected TB disease considered as a conditional recommendation based on low-quality evidence.[8] Both liquid and solid mycobacterial cultures are used for all the specimens in the laboratories of Abu Dhabi to detect the infection among individuals suspected to have TB.[24]

C. TST and IGRA

The Tuberculin Skin Test (TST) and Interferon Gamma Release Assay (IGRA/QFT-GIT) are both indirect tests in that they indicate a cellular immune response to a recent or to a remote sensitization with mycobacterial antigens.[35] These tests cannot differentiate between individuals with active TB, LTBI (dormant infection) or even old TB.[35] Most commonly, the only indication

that infection with TB has taken place is a positive TST or IGRA result, and those asymptomatic individuals who develop a positive TST are considered to have latent tuberculosis infection (LTBI).[8]

MTB infection can stimulate a vigorous adaptive cell-mediated immune response that has been utilized to discover MTB infection, particularly LTBI.[36] Currently, two approaches exist to verify the adaptive immunity, the tuberculin skin test (TST) and the gamma interferon-γrelease assay (IGRA).[36] The TST measures delayed-type hypersensitivity reactions to a basic combination of MTB antigens which do also exist in bacillus Calmette-Guerin (BCG) and non-tuberculous mycobacteria (NTM).[36]

IGRA test, on the other hand, is based on the measurement of IFN-γ secreted from T cells previously exposed to MTB when stimulated in vitro with the MTB-specific antigens such as ESAT-6 and CFP-10.[36] Both ESAT-6 and CFP-10 antigens are encoded by RD1, a genomic region present in *Mycobacterium tuberculosis* yet lacking in all *Mycobacterium* bovis, BCG vaccine strains and most of the NTM.[36, 37]

The tuberculin skin test (TST) had been used to detect LTBI for about a century; however, the TST has known limitations.[38] TST has a non-specific reactivity in individuals vaccinated with BCG and in those with non-tuberculous mycobacteria (NTM).[38] The development of the interferon-γ released by sensitized T cells after stimulation with M. tuberculosis antigens came as a result of the advances in molecular biology.[38]

The interferon-γ tests are more specific than the TST as they use antigens that are not shared by any of the BCG vaccine strains or by the more common species of NTM (e.g., M. avium).[38]

IGRAs have higher specificity and sensitivity than the TST.[38] In addition, IGRAs is more useful in close contacts in low-incidence settings as they have a higher predictive value for LTBI progression to active TB.[38]

Guidelines for IGRA and TST in screening

Since 2005, the use of IGRAs has increased considerably in low-incidence countries.[35] Various studies, meta-analyses, and systematic reviews have been completed to evaluate the role of these tests in the diagnosis of latent and active TB.[35] In general, the use of IGRAs is increasingly recommended, however, the majority of current guidelines do not use objective, transparent techniques to grade evidence and recommendations, moreover they do not reveal conflicts of interests.[35] There is a considerable variety in the recommendations on IGRAs, and across all the guidelines, four main approaches are followed mostly:

- Two-step approach of TST initially, followed by IGRA
- IGRA only
- TST and IGRA together
- Either TST or IGRA.[35]

The high specificity of IGRAs is considered as their most obvious strength since they allow the clinician to distinguish between a sensitization caused by BCG vaccination or non-tuberculous mycobacterial exposure and contact with an active TB case.[35] Recent cohort studies suggested that IGRAs, similar to the TST, have only modest predictive ability.[35] Even in high burden

countries, only 1–3% of IGRA-positive contacts develop active TB over 2 years of follow-up.[35] This indicates that interferon-γ alone is perhaps inadequate as a biomarker for disease progression, particularly if only measured at baseline.[35] A more helpful approach may, therefore, include a combination of TST/ IGRA and risk factor information.[35]

Immigrant screening is often a key component of TB control in low-incidence countries as the majority of the TB cases occur among recent immigrants and foreign-born individuals.[35] Most of guidelines that have recommendations are from countries with low-incidence (Table 2.3) and focus on immigrants from high-incidence countries.[35]

Table 2. 3: Guidelines on IGRAs: Recommendations for screening of immigrants

Recommendation	Guideline or position statement[a]
TST followed by IGRA, if TST positive	UK (for children age 5–15 years), Italy, Switzerland, Spain, Norway, Ireland, Bulgaria, France (in children), Slovakia, the Netherlands (for children only; dependent on BCG vaccination status and result of TST, only TST might be sufficient)
Both TST and IGRA	Czech Republic, UK (for adults age 16–35 years; or IGRA alone alternatively)
Either TST or IGRA	USA (IGRA preferred in BCG-vaccinated persons), Canada, Australia
IGRA alone	France (in adults)
No recommendations/ not recommended	Germany, Japan, Saudi Arabia, Brazil, Portugal, Croatia, Denmark, South Korea, Finland, Poland, Austria

BCG, bacille Calmette–Guérin; CDC, US Centers for Disease Control and Prevention; ECDC, European Centre for Disease Prevention and Control; IGRA, interferon-gamma release assay; TST, tuberculin skin test; WHO, World Health Organization.

[a]Some countries/organizations are listed more than once because their recommendations vary across risk groups.

Reference: Denkinger, C., Dheda, K. and Pai, M. (2011). Guidelines on interferon-γ release assays for tuberculosis infection: concordance, discordance or confusion?. *Clinical Microbiology and Infection*, 17(6), pp.806-814.

However, other guidelines also include recommendations for immigrants who are expected to develop the active disease (e.g., children or individuals with underlying clinical diseases that predisposes them to a reactivation of an LTBI) irrespective of their country of origin (e.g., Canada, the Netherlands).[35]

IGRAs are incorporated in all the guidelines that make recommendations for screening of immigrants.[35] TST followed by an IGRA if positive is the most commonly used algorithm in "(UK (for children 5–15 years of age), Italy, Switzerland, Spain, the Netherlands, Norway, Ireland, France, Slovakia and Bulgaria)".[35] The goal from this algorithm is to increase specificity due to the extensive use of BCG vaccination in TB endemic countries.[35]

There several advantages of IGRAs over TSTs:

- A second visit for reading of the test is no longer required;
- Boosting due to repetitive testing is avoided;
- Have greater specificity for latent TB infection;
- Biases are less occurring compared to measuring the size of skin reactions.[39]

Conclusions

TB annual incidence rate in 2016 varied among countries, from under 10 per 100000 population to 150–300 per 100000 population. Most TB cases occurred in the WHO South-East Asia Region and countries including: India, Indonesia, China, Nigeria, Pakistan, and South Africa had accounted for the largest number of incident cases globally in 2016. Fortunately, the number of incident cases is falling slowly when looking at the trend from the year 2000 till 2016 and this decline needs to be accelerated in order to achieve End TB Strategy milestones. In 2016,

estimated 1.3 million deaths occurred from TB among HIV-negative individuals. Fortunately, an estimated 44 million deaths among HIV-negative individuals between 2000 and 2016 were averted by TB treatment.

The prevention of new infections of *Mycobacterium tuberculosis* and the progression to TB disease are essential steps in order to reduce the burden of disease and deaths caused by TB and eventually to achieve the End TB Strategy targets set for 2030 and 2035. Coverage of contact investigation and treatment of LTBI among children below 5 years old is listed among the high priority indicators intended to monitor the implementation of the End TB Strategy.

A screening test is intended to identify the subgroup of individuals with the highest likelihood of disease aiming at minimizing the risk of TB transmission and lowering the risk of poor treatment outcomes. Screening algorithm options are available as per WHO guidelines. Individuals with positive results on a screening test need to undergo diagnostic tests to confirm or rule out active TB based on bacteriological tests. Both sensitivity and specificity depend on a gold standard test and, therefore, the predictive values are more useful and informative for clinicians. However, the predictive values of tests are influenced by the prevalence of the disease. A higher prevalence of the disease will, therefore, give a higher positive predictive value and a positive diagnostic test will most likely indicate the presence of disease. A comprehensive assessment of MTB infection includes medical history, physical examination, chest X-ray, TST, IGRA, microbiologic smears, and cultures.

Chapter 3

Introduction

The presentation of the study methodology will be initiated by research questions and hypotheses of the study. A TB conceptual framework will be explained briefly followed by study design and description of the study population. This will be followed by the data collection process and the tests procedures used in visa screening followed by data management and interpretation. The chapter will then touch on the study variables and statistical analysis methods used in the study. Finally, data limitations, ethical considerations, and protection of human rights and IRB approval will be addressed.

Hypotheses of the study

The evidence in support of the use of IGRAs in screening high-risk groups, such as healthcare workers, immigrants from high-incidence countries, and close contacts is provided by the available studies on cost-effectiveness of TB screening.[38] In addition, IGRA has been widely used to diagnose MTB infection under national guidelines in several developed countries, such as the USA, UK, and Japan given its higher sensitivity and specificity for detecting MTB infection compared with TST.[35, 36] Therefore we assume that IGRA is more sensitive than TST in detecting MTB among adults during the visa screening process.

In Poland, a total of 126 adult patients with clinically active TB were enrolled in a study that assessed sensitivity, specificity, positive predicted value (PPV), negative predicted value (NPV), and analytic accuracy of TST and IGRA among those diagnosed as culture-positive and culture-negative TB patients.[40] In that study, "the sensitivity of TST and IGRA was age-dependent and

decreased significantly with the age of the patients".[40] Therefore we assumed that IGRA and TST sensitivity will reduce as the applicants are older.

To determine the pooled sensitivity and specificity values for TST and IGRA (QFT-GIT), Keyser and colleagues conducted a random effects model meta-analysis that was performed using articles in English published between January 2010 and July 2012 in which TST and IGRA were performed simultaneously in individuals with and without active tuberculosis infection.[15] In this meta-analysis, QFT-GIT appeared to be more sensitive than TST [75% (95% CI: 61-86) versus 64% (95% CI: 48-78)] but similarly specific [71% (95% CI: 62-86) versus 70% (95% CI: 57-81)].[15] According to the meta-analysis, IGRA was more accurate in detecting TB infection than TST.[15] Therefore, in our study, we assumed that simultaneous testing (parallel) with IGRA (QFT-GIT) and TST will improve the net sensitivity for detecting MTB among adults during the visa screening process.

Chest radiography has good sensitivity yet poor specificity when utilized for the diagnosis of pulmonary TB.[32] In a study done in Kenya assessing the performance of chest X-ray in all suspects of tuberculosis (using the sputum culture as the gold standard test), the sensitivity/ specificity/ PPV/ NPV of the score 'any pathology' were 92% (95% CI: 90–94), 63% (95% CI: 58–67), 76% (95% CI: 73–79) and 86 (95% CI: 82–90), respectively.[41] Therefore we assume that chest X-ray has a good sensitivity in detecting TB among adults during the screening for visa purposes.

It was noticed through our clinical practice in visa screening and TB management that the majority of confirmed TB cases occurred among younger visa applicants and therefore we

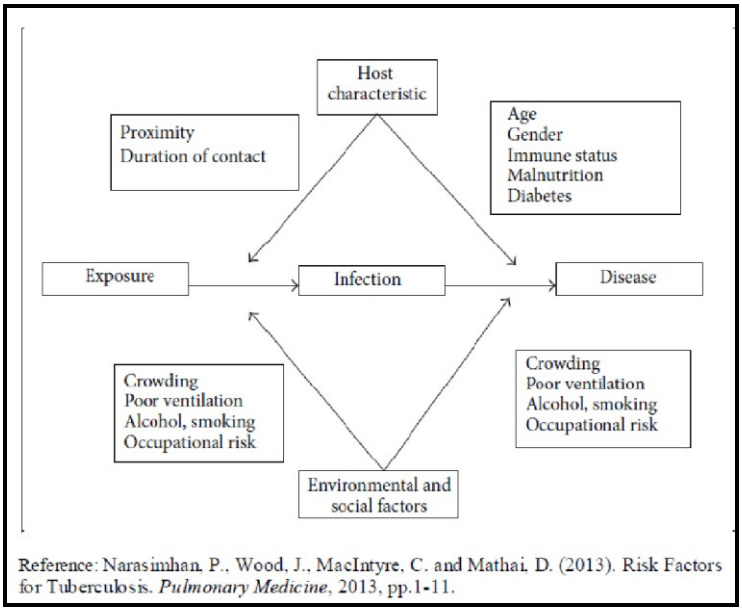
assumed that younger visa applicant carries a higher risk of TB compared to older visa applicants.

TB conceptual framework

Tuberculosis can be clinically suspected in patients with a variety of risk factors.[34] Therefore, any individual at increased risk of the disease is eligible for tuberculosis testing in order to recognize and treat those with LTBI, prevent the development of active TB, and prevent further spread of the disease.[34] Two categories are recognized as risk factors for TB including: those that result in an increased risk of exposure to TB, and those that increase the risk of developing active disease (Figure 3.1).[34, 42]

Approximately 10 individuals per year will be infected and two new cases of TB will result upon contact with an untreated sputum positive patient (Figure 3.1).[42] Close contacts such as household members and healthcare workers are at a higher risk of infection with *Mycobacterium tuberculosis* and the development of active tuberculosis (Figure 3.1).[42]

Figure 3. 1: TB conceptual framework



Reference: Narasimhan, P., Wood, J., MacIntyre, C. and Mathai, D. (2013). Risk Factors for Tuberculosis. *Pulmonary Medicine*, 2013, pp.1-11.

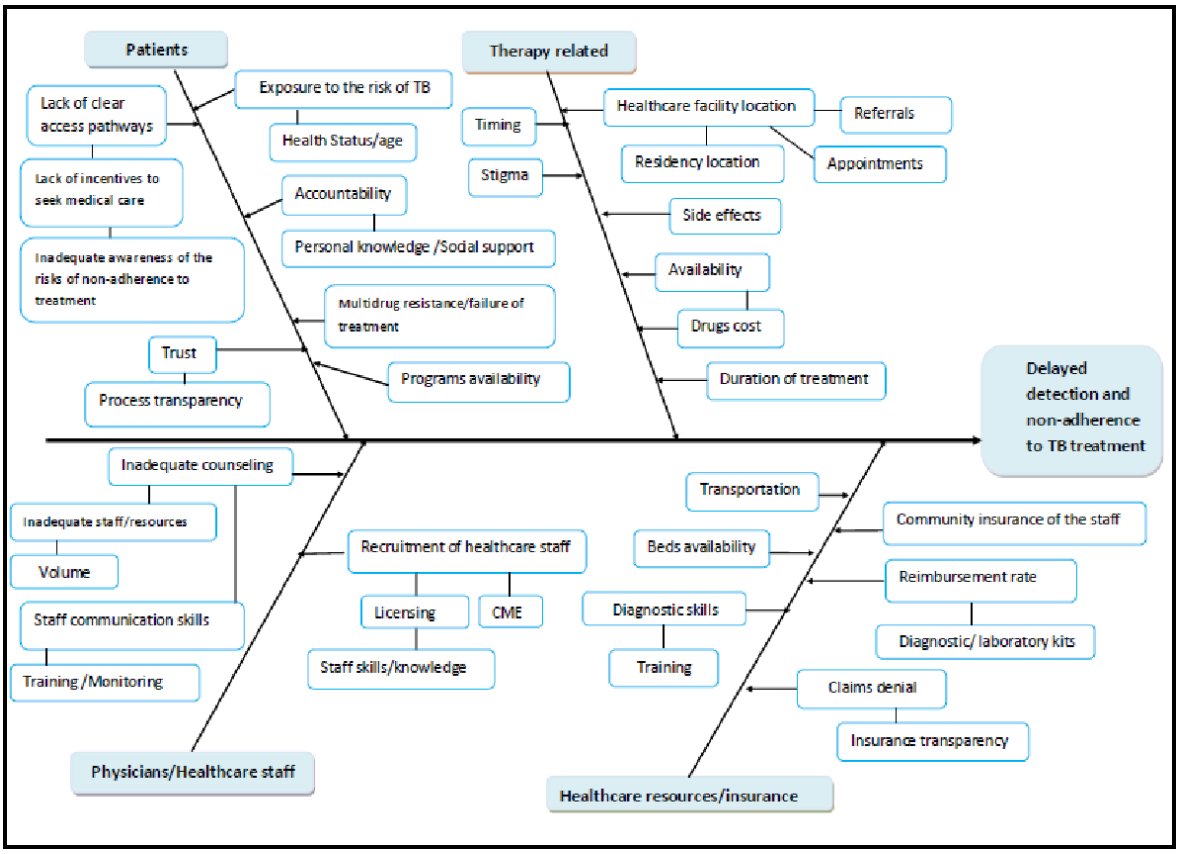
Individuals at increased risk of exposure are immigrants from endemic regions, individuals with a low-income and limited access to health care, intravenous drug users, those who live or work in high-risk residential centers such as nursing homes and correctional facilities, and healthcare workers.[34] On the other hand, risk factors associated with a higher risk of progression to active TB include: children younger than 4 years, intravenous drug users, recent tuberculosis infection, and compromised immunity due to HIV infection and organ transplantation or treatment with immunosuppressive drugs.[34]

Diabetes is considered as a factor that increases the risk of active TB disease.[42] In low- and middle-income countries almost 70% of individuals are affected by diabetes and the rates are steadily increasing in TB endemic areas such as India and sub-Saharan Africa (Figure 3.1).[37, 42] Similarly, alcohol had been shown as a strong risk factor for TB disease due to the alteration in the immune system (Figure 3.1).[42]

The situation is even worse when addressing smoking as a risk factor for TB infection and disease as it is considered an additional risk of death in individuals diagnosed with active TB (Figure 3.1).[42] Susceptibility to pulmonary tuberculosis in smokers is increased as the clearance of mucosal secretion is impaired and the phagocytic ability of alveolar macrophages is reduced due to the nicotine in the cigarettes (Figure 3.1).[42] Therefore it is crucial to consider systematic screening for active TB, particularly in selected risk groups.[11]

Figure 3.2 highlights possible causes of patient safety challenges in TB resulting in delayed diagnosis and management. Attaining desired health outcomes in patient management aspects in TB while considering multiple inputs were highlighted. Patients' geographical location, culture, and income along with scarce resources contribute to the ongoing TB challenges.[6, 11, 12]

Figure 3. 2: TB delayed detection and non-adherence to treatment factors



Study design and study population

Design:

This is a cross-sectional study that analyzed data routinely collected by DOH/HAAD on adults (18-64) years seeking a residency visa (new or renewal) in the Emirate of Abu Dhabi from January – December 2013.

Location:

Data came from eleven approved visa screening centers in Abu Dhabi, namely: Abu Dhabi Disease Prevention and Screening Center (DPSC) which is the largest screening center in the Emirate of Abu Dhabi, Mussafah (DPSC), Al Ain (DPSC), Madinat Zayed (DPSC), Gaiathy (DPSC), Silla (DPSC), Delma (DPSC), Al Mirfa (DPSC), Shahama (DPSC), Etihad Airways (DPSC) and Sweihan (DPSC).

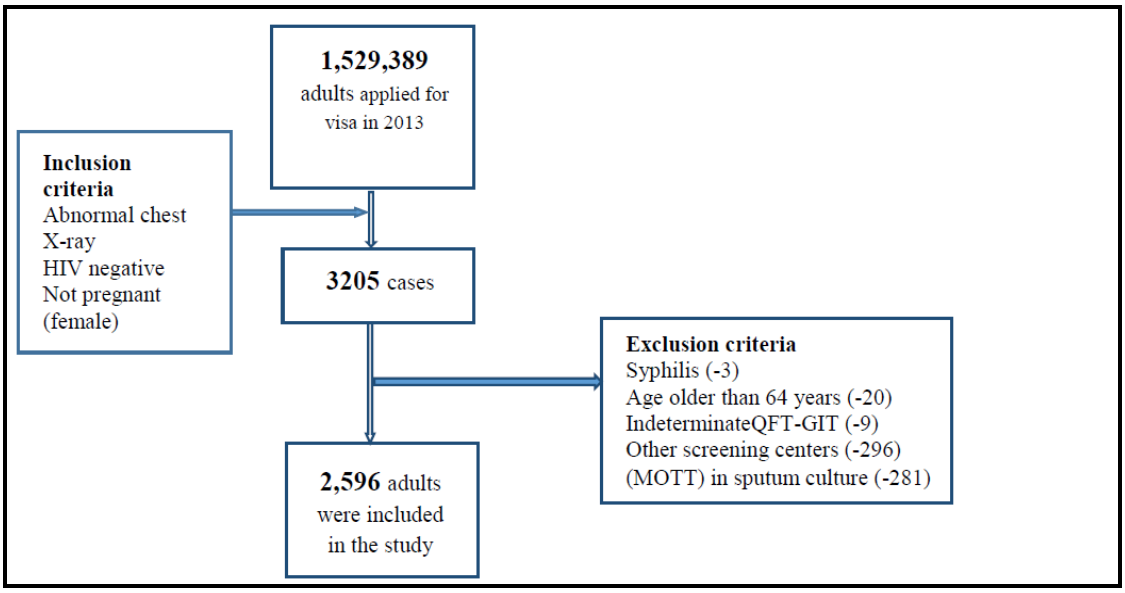
Inclusion criteria:

Inclusion criteria included: abnormal chest X-ray observation by radiologist, adults 18 to 64 years, HIV negative and negative for pregnancy (in females).

Exclusion criteria:

Exclusion criteria included: syphilis (3 adults were excluded), age older than 64 years (20 adults were excluded), indeterminate result for QFT-GIT (9 adults were excluded), cases from screening centers other than DPSCs (296 adults screened in Mubadala were excluded) and the growth of *Mycobacterium* Other than Tuberculosis (MOTT) in sputum culture (281 adults were excluded). As a result, a total of 2,596 adult individuals were included in the analysis (Figure 3.3).

Figure 3. 3: Study sample size from visa screening data



Data collection

All visa applicants desiring to enter Abu Dhabi for residency purposes (such working, residence or study) are required to undergo visa screening.[22] Applicants, therefore, should either have entry permit (for new visa applicants) or a valid residence visa (renewal; for applicants wishing to renew their residency) issued in the Emirate of Abu Dhabi and should sign the visa screening general consent.[22]

All healthcare providers of visa screening services such as Abu Dhabi Disease Prevention and Screening Center (DPSC) must comply with the DOH/HAAD visa screening standards.[22] The process of visa screening is initiated by obtaining a prior consent from applicants applying for residency including the consent for testing for HIV, TB, pregnancy, and consent for treatment and follow-up.[22] Applicants are then educated by the healthcare providers in the screening centers about the screening tests in a simple language (a language bank is available in DPSCs) while maintaining a culturally appropriate approach.[22] The healthcare provider then reports and submit electronically complete and accurate data for all individual screening observations, in

compliance with the DOH/HAAD Reporting of Health Statistics Policy to DOH/HAAD via the visa screening reporting system within a specified format and timeframe.[22] Reported data must comprise all clinical findings (including physician's history and physical examinations), radiologists' observations and reports, blood tests observations and sputum smear results and sputum culture results. [22]

As determined by the Federal Law in UAE, visa screening tests are classified into occupational categories: (A): white collar, construction, and housewives, (Bi/Bii): maids and drivers/food handlers and hygienic staff.[22] Therefore, approved screening providers must comply with the visa screening process and perform the screening tests determined for each occupational group.[22]

Test procedures

A. Tuberculin Skin Test (TST)

Trained TB-nurses in Disease Prevention and Screening Centers in Abu Dhabi performed this test as an intradermal injection at a recommended dose of 0.1 ml tuberculin solution (5 tuberculin units, describes as a clear colorless solution) was injected on the lower part of the forearm.[2, 17] If the test was done properly then, at the needle site, a distinct pale bump will rise and will disappear within minutes and no dressing is advised.[2, 17] If a drop of blood appeared following the administration of the tuberculin test then the site shall be touched lightly to remove the blood while avoiding squeezing out the test material. The individual who received the TST must return within 2 or 3 days to have a trained nurse looking for a reaction on the lower part of the arm where the solution was injected.[2, 17]

The trained TB-nurse then looks for an elevated, firm area or swelling, over the injection site and if present, measures its size using a ruler.[2, 17] Positive TST indicates that the individual's body was infected with TB bacteria and that further testing are required to determine if the individual has latent TB infection or TB disease.[2, 17] On the other hand, a negative TST means that the individual's body did not react to the test and that latent TB infection or TB disease is unlikely.[2, 17] Induration of ≥ 15 mm was considered a positive test in screening for residency.[22]

B. Interferon-γ release assay (IGRA)

The QuantiFERON-TB Gold In-Tube test (QFT-GIT) uses three special blood collection tubes to collect whole blood samples.[24, 43] Initially, whole blood (1 ml) is collected into each of the three tubes. One tube contains test antigens and the other two complementary tubes serve as negative (Nil control tube) and positive (Mitogen tube) controls.[24, 43]

The blood in the tubes shall be kept at 37C shortly after extraction and within 16 hours of collection and then should be incubated for 16-24 hours.[24, 43] After the incubation period, tubes are centrifuged and plasma separated, and the IFN-γ concentration in the plasma measured using ELISA.[24, 43] Results are then generated by The QuantiFERON-TB Gold In-Tube test IT analysis software (version 2.17 or later).[24] For the diagnosing of infection with *Mycobacterium tuberculosis*, IGRA should be used as an adjunct test to aid in the diagnosis.[43] A positive IGRA test result implies that MTB infection is likely; a negative result, on the other hand, suggests that infection is not likely. In addition, an indeterminate result signifies an uncertainty regarding the likelihood of infection with *Mycobacterium tuberculosis*.[43]

C. Sputum collection for AFB smears and cultures

Sputum is collected in a negative pressure sputum collection room under the supervision of a nurse or physician.[44,45,46] The visa applicant is educated about the process of sputum collection that he/she need to follow in order to produce the best specimen.[44, 45, 46] The applicant is advised to deeply inhale air 2 to three times and then to breathe out hard each time.[44, 45, 46] The applicant is advised to cough deeply from the chest while placing the open sputum container close to the mouth.[44, 45, 46]

A sputum specimen should have a volume of 3-5 ml in order to be considered satisfactory sample.[44, 45, 46] Disinfection of the collection room is done by UV lights for 15 minutes prior to and after the collection of the specimen from an applicant and in between patients.[44, 45, 46] A strict daily disinfection procedure emphasized and is followed by the laboratory personnel in the central laboratory to assure the proper handling of the equipment and the contagious specimens.[44, 45, 46] Three sputum samples are collected from each applicant presenting with abnormal chest X-ray evaluation by a radiologist in 8-24 hours interval for investigation under microscopy and for culture.[44, 45, 46] Upon receipt of the sample, the process is initiated shortly on the same day of collection and is stored at 2-8 C if the processing cannot be initiated immediately.[44, 45, 46] The biological safety cabinets are always utilized for smear preparation procedures while using the proper personal protective equipment.[44, 45, 46] This is followed by the Ziehl-Neelsen staining procedure to examine the acid-fast bacilli in the smear by the binocular light microscopy.[44, 45, 46]

The mycobacteria growth indicator tube (MGIT) is utilized to foster growth of the bacteria as it is made of liquid broth medium known to yield a faster growth and recovery of the mycobacteria.[44, 45, 46] The labeled MGIT tube is labeled with applicant name, lab number, screening application number and date of inoculation prior to incubation in the MGIT machine.[44, 45, 46] In addition, the processed specimen is further inoculated on LJ media and incubated as a backup of the main MGIT liquid medium.[44, 45, 46] A positive growth is detected by a signal produced by the instrument as a green light showing the exact location of the positive tube in the drawer of the machine.[44, 45, 46] The positive tube will then be removed and scanned for details outside the machine.[44, 45, 46]

Data management and interpretation

The data was received as password protected multiple excel sheets. Those sheets were eventually merged into one excel sheet after the removal of subjects with incomplete test results and the removal of subjects who had normal chest X-rays. The data sheet contained initially 68 variables and 3205 observations. Unrelated variables (of which there were 42) were eliminated and 26 variables (and 3202 observations) were selected to establish the data set for analysis.

Age was not provided in the data set and therefore dates were formatted in order to generate an age variable utilizing the date when chest X-ray was first performed during the visa screening. Four age categories were created initially: (18-34) years, (35-51) years and (52-64) years and (65-85) years. The (65-85) year category contained only 20 observations and those are not to be included in the sample as the maximum age will be 64 years and therefore those 20 observations were eliminated and the age category contained three subsets: (18-34) years, (35-51) years and

(52-64) years. The older two age categories were combined to create the final two age categories: younger adults (18-34) and older adults (35-64) years.

Other variables were labeled as appropriately and categories were created to generate, recode and label commands (for nationality, applicant category, and visa type, IGRA value category, AFB smear value and chest X-ray categories). Similar to the age categories, three TST categories were created initially: (0-9) mm, (10-14) mm and (15-40) mm. TST observation results were also reclassified into two groups: TST (0-14) mm was defined as negative and TST (15-40) mm was considered positive in the study. Nationality was initially explored per country and then due to inadequate cell numbers, it was categorized using WHO classification of countries.[6] To provide adequate cell sizes, those variables again were collapsed to three-category variable (SEAR, AFR/EMR, and WPR/EUR/AMR).

Chest X-ray evaluations by radiologists were also collapsed into two groups as the numbers in the cells were not sufficient for analysis. Therefore, chest X-ray with three levels of suspicion of active TB (low, medium and high suspicion) merged together in one group (named: Suspicion of TB) and the other two groups were merged together (named: Abnormal Not/Old TB). Similarly, the applicant employment category group was collapsed to two categories where Bi (domestic helpers) group and Bii (food handlers and hygienic staff) group were merged together due to inadequate numbers in the cells. The screening centers were eventually grouped into two main categories due to limited numbers and the reference group was changed to the combined DPSCs of Abu Dhabi and Mussafah.

Cases of MTB were extracted from the sample of those with abnormal chest X-ray and identified based on the positive result of the sputum culture "gold standard" test. Then a 'control group' was generated defined as those with a negative sputum culture test. Therefore, based on the sputum test results, two data sets were created where controls included those with sputum test negative (MTB=0) and cases were defined as sputum culture test positive (MTB=1) and the final dataset were merged together to form the final data set for the study sample analysis. Thus, the final analytic sample included both cases and controls in one data sheet for analysis.

Study variables

A. Independent variables (Predictors)

1. **Gender (sex)**: Two level categorical variable: Male/Female; M=0 F=1

2. **Applicant employment category (app_cat)**: Two level categorical variable: (A): white collar and construction, (Bi/ Bii): maids and drivers/ food handlers and hygienic staff. Also, each occupation was analyzed separately prior to being classified according to visa categories mentioned earlier.

3. **Nationality (Nat)**: categories based on WHO classification: SEAR: WHO South-East Asia Region, EMR: WHO Eastern Mediterranean Region, AFR: WHO African region, WPR: WHO Western Pacific Region, EUR: WHO European Region, AMR: WHO region of America. Also, nationality was analyzed separately prior to being classified as regional WHO classification.

4. **Visa type (visa_type_nr)**: Two level categorical variable: New/Renew

5. **Age:** continuous variable

6. **(agecate3)**: Two level categorical variable: (18-34); (35-64) years

7. **Chest X-ray final evaluation (CXR_Final_eval)**: Two level categorical variable: Abnormal Not/Old Pulmonary TB and (Suspicion of Active Pulmonary TB

8. **IGRA Result (IGRA_VAL)**: Two level categorical variable: negative/ positive
9. **TST observation (TST_observation)**: Two level categorical variable: Negative indurations (0-14) mm; and positive indurations (15-40) mm
10. **(tstobservation)**: continuous variable for TST
11. **Sputum smear AFB value (AFB_smear_val)**: Two level categorical variable: negative/positive
12. **Disease Prevention and Screening Centers (Facility_DPSCS)**: Two level categorical variable

B. Outcome variable (Dependent)

MTB= 0 when sputum culture is negative (TB culture value shows no growth of MTB)

MTB=1 when sputum culture is positive (TB culture value shows growth of MTB)

Table 3. 1: Study variables

Table 3.1 Study variables	Variable in Sata	To summarize use	Level of measurement
Gender	sex	Frequency/Proportions/Percentage	Nominal level
Nationality	Nat	Frequency/Proportions/Percentage	Nominal level
Nationality by WHO	nat_cate	Frequency/Proportions	Nominal level
Visa type (new vs renew)	Visa_type_nr	Frequency/Proportions/Percentage	Nominal level
Age	age	Mean/Median/Standard deviation	Interval/continuous
Age category	Agcate3	Frequency/Proportions	Nominal level
IGRA value	IGRA_VAL	Frequency/Proportions	Nominal level
TST	tstobservation	Mean/Median/Standard deviation	Interval/continuous
TST category	TST_observation	Frequency/Proportions	Nominal level
Chest X-ray evaluation	CXR_Final_Eval	Frequency/Proportions/Percentage	Nominal level
Chest X-ray category	CXR_Final	Frequency/Proportions	Nominal level
occupation	occupation	Frequency/Proportions/Percentage	Nominal level
Applicant category (A), (Bi) and (Bii)	app_category	Frequency/Proportions	Nominal level
Applicant category A, (Bi, Bii)	app_cat	Frequency/Proportions	Nominal level
TB culture	MTB	Frequency/Proportions/Percentage	Nominal level
AFB smear value	AFB_smear_1st_val	Frequency/Proportions/Percentage	Nominal level
AFB smear value (category)	AFB_smear_val	Frequency/Proportions	Nominal level
Screening Facility	Facility_ID	Frequency/Proportions	Nominal level
Screening Facility	Facility_DPSCs	Frequency/Proportions	Nominal level

The final data set included the following variables: sex, applicant employment category (A vs. Bi/Bii), nationality, visa type (new vs. renew), and age category, chest X-ray evaluation by radiologist, IGRA (QFT-GIT) value, TST observation, sputum smear AFB result and screening centers DPSCs in which the tests were conducted.

Statistical software and data analysis plan

Descriptive summary statistic and sample distribution characteristics

Stata 11 statistical software package was used as the main program for data management and analysis in the study. Descriptive summary of the data was produced (using Frequency and percentages for categorical variables and mean and standard deviation (SD), median, interquartile range (IQR) and variance for continuous variables).[47] Descriptive summary statistics helped in the assessment of the skewness and the kurtosis of the sample and the identification of possible outliers and/or other characteristics that may affect the outcome variable.

Exploratory data analysis of the continuous predictors in the data was then intended to further diagnose skewness and to identify outliers. As most statistical methods perform best when applied on normally distributed samples, normality tests and transformations of the continuous variables were assessed in our study sample using graphs such as histogram and boxplot. The transformation was assessed to find the best match of a normally distributed sample. The transformation choice was further supported by the generation of the histograms and normal distribution curve for each transformation and by boxplot graphs.[47] Pearson's chi-square tests and Fisher's exact tests were then performed through cross-tabulation of the predictors of interest

with age group category; younger (18-34 years and older 35-64 years), to identify the characteristics of the study sample.

Testing hypothesis by cross tabulation (the validity of IGRA, TST, and chest X-ray)

In order to test the hypothesis of IGRA being more sensitive than TST, cross-tabulation of the predictors of interest with MTB using Pearson's chi-square and Fisher's exact tests were done to calculate the sensitivity, specificity, PPV, NPV, positive and negative likelihood ratios. Similar steps were followed to generate the validity measures for chest X-ray. To test the level of agreement between IGRA (QFT-GIT) and TST a kappa statistic was calculated. Interpretation of kappa was based on a commonly cited scale in which kappa of less than zero is interpreted as poor, kappa of (0.01-0.20) is interpreted as slight agreement, kappa of (0.21-0.40) is interpreted as fair agreement, kappa of (0.41-0.60) is interpreted as moderate agreement, kappa of (0.61-0.80) is interpreted as substantial agreement and finally kappa of (0.81-0.99) is interpreted as almost perfect agreement.[48]

Simple and multiple regression analysis to identify predictors of MTB

Simple and multiple regression analysis of the two continuous variables were intended to the relationship of each the continuous variables to the predictors of interest. The two continuous variables were then grouped into two categories and bivariate cross-tabulation analyses using Pearson's chi-square tests and Fisher's exact tests tested the relationship of each independent variable to the outcome, presence/absence of MTB. The Variance Influence Factor (VIF) was used to check for multi-collinearity among the predictors and pseudo-regression and correlation analyses were performed in our study.[47]After the regression test, the predict command was used

to calculate the predicted values and the residuals. This was followed by the multiple regression model analysis and the test of correlation in the sample. A 95% confidence interval was used for the prevalence estimates.

Logistic regression analysis and MTB

Logistic regression was used to estimate the crude and adjusted relative odds in order to measure the effect of the factors included in the analysis. Logistic regression was used to produce the crude and relative odds of MTB. Similarly, the crude and relative odds of MTB per age category were measured. Factors of interest such as age category, chest X-ray evaluation by a radiologist, IGRA (QFT-GIT) value, TST observation and sputum smear AFB were finally included in the logistic model. Wald tests were then performed initially to test each model separately and this was then followed by the likelihood ratio tests for the nested logistic regression model to test the scientific hypothesis and to confirm the Wald test results.

Data limitations

Cross-sectional studies are usually considered as quick and relatively inexpensive to conduct and can give a picture of the health situation at hand.[49] Those studies are generally done to determine the prevalence of a disease and are useful in the identification of certain associations (putative risk factors) that can be studied more specifically using cohort or randomized controlled trials.[49] On the other hand, a couple of disadvantages might be encountered because of the study design itself one example could be the lack of the ability of generalizability.[49] Other examples include unequal distributions of confounders and unequal group sizes.[49] Finally, causal inference cannot

be made using cross-sectional data; the predictors/risk factors and the outcomes are both collected at the same time.

The results of the initial bivariate cross-tabulation analyses highlighted the presence of several cells in which there was an insufficient sample size to support analysis by the outcome of interest. Reclassification of TST observation, age category, applicant employment category, nationality, and sputum smear (AFB) result was needed to avoid inadequate numbers in certain cells and to allow for subsequent logistic regression analyses.

Another limitation is the specificity of the test as it was underestimated most probably due to the prevalence of latent tuberculosis and or old MTB in the sample. Moreover, it was difficult to explore the relationship of the diseases to an occupation. This was challenging given the wide range of available occupations (445 occupations) and the small and inadequate number of cells needed for analysis. Therefore, analysis was restricted to using applicant occupational categories instead.

The dataset was restricted to one-year duration although the intention initially was to assemble a dataset for three years. This was attributed to the fact that some visa applicants renew their visa on a yearly basis such as those who are 60 years and older. Including multiple years will lead to a duplication of subjects in the study sample and as per consultation with the IT personnel in DOH/HAAD it was recommended to restrict the dataset to a one-year interval to avoid this disadvantage. The use of multiple years for creating such a multi-year dataset will implicate further efforts and extra unplanned work time that can extend beyond working hours for IT personnel in DOH/HAAD.

Ethical considerations and protection of human rights

Data on demographics, visa type information and final disease status of MTB collected through the standard visa screening services are uploaded and made available in the DOH/HAAD electronic system. Each screened individual is linked to the system using a unique identifier code. The data used for this study was obtained from the existing visa screening data available in the DOH/HAAD electronic system. Data were de-identified to eliminate personal information (such as name, contact information, sponsor details and passport number etc., ...) by IT experts in the surveillance and statistics section in DOH/HAAD. The data was stored on a secure server protected by limited access and strong password systems. Data were coded when possible.

Data remained in a DOH/HAAD secured PC and was not transferred to a personal computer. Portable electronic devices did not contain identifiable information. The principal investigator (Huda Alshemeili) had access only on the decoded (de-identified) data provided by DOH/HAAD as an excel sheet secured by a password. The principal investigator was instructed to inform the Ethical Committee and submit a revised and complete application for approval of changes in the project occurred which might affect patient safety or privacy, or the purpose of the project. The principal investigator completed an ethical training course at John Hopkins University prior to initiating the request to conduct the study.

Ethical approval, IRB

The local Institutional Review Board (IRB) at Al-Ain University approved this study, giving it Exempt Status, which was accepted by the Johns Hopkins Bloomberg School of Public Health, with Al-Ain University IRB designated as the IRB of record.

Conclusions

The hypotheses of the study were established based on evidence from the literature. According to the TB conceptual framework, two main categories are recognized as risk factors for TB including: those that result in an increased risk of exposure to TB (such as immigrants coming from high endemic regions and healthcare workers), and those factors that increase the risk of developing active disease (such as age younger than 4 years and diabetes).

Our study is a cross-sectional study that analyzed data routinely collected by DOH/HAAD on adults (18-64) years seeking a residency visa (new or renewal) in the Emirate of Abu Dhabi from January – December 2013. Test procedures performed on abnormal and suspicious Chest X-ray findings included TST, IGRA and sputum collection for AFB smears and cultures. Data management using Excel and the Stata 11 statistical software package finally yielded a total of 12 independent (predictors) variables and MTB was the dependent (outcome) variable signifying the presence or the absence of *Mycobacterium tuberculosis* infection based on the gold standard test (i.e., the sputum culture). Several statistical analytical methods such as cross-tabulation, simple and multiple regression analysis, and logistic regression analysis were applied in order to generate results for chapter 4. The dataset was restricted to one-year duration and is considered as an unavoidable limitation. Unfortunately, information on known risk factors for TB such as smoking and diabetes were not available for analysis. The IRB board approval was obtained from Al Ain University in UAE.

Chapter 4

Introduction

Chapter 4 will provide the results needed to answer the hypotheses mentioned earlier in chapter 3 and the results are, therefore, divided into three sections and the conclusions of main findings will be provided at the end of the chapter.

Section (A): *Demographic characteristics by age category.* This section will highlight the results of the descriptive analysis of the main variables by age categories as presented in table (4.1.1) and related graphs.

Section (B): *IGRA and TST validity/Chest X-ray validity.* This section will present the validity of IGRA and TST results in graphs and related tables. Table (4.2) shows the sensitivity, specificity, negative predictive value (NPV), the positive predictive value (PPV), the negative likelihood ratio (NLR), the positive likelihood ratio (PLR) and then validity by age category in the table (4.3). This will be followed by the validity of parallel testing of TST and IGRA and per age category as demonstrated in Tables (4.4), (4.5) and (4.6) then kappa agreement of IGRA and TST. Finally, the validity of chest X-ray will be addressed in the table (4.7). Tables 4.8.1- 4.8.6 will present data related nationality and gender, occupation and MTB and WHO regions by MTB and gender. The tables will also provide information about the results of the analysis of the continuous variables in the study sample.

Section (C): *Predictors of MTB.* This section will explore the relationship of the predictors of interest to the outcome, the presence or absence of MTB using graphs and related tables. The

crude and adjusted relative odds of MTB will be provided in the table (4.9) and by age category in the table (4.10).

Results

A. Demographic characteristics by age category

The study sample comprises 2,596 (170/100000) individuals with abnormal chest X-rays who met all eligibility criteria, (Table 4.1.1).

Table 4.1. 1: Baseline characteristics by Age-category (2013)

Table (4.1.1) Baseline characteristics by Age-category (2013)	**Total* (n= 2, 596)**	**Younger (18-34) years (n=1,364) (52.5 %)**	**Older (35-64) years (n= 1,232) (47.5 %)**	**P Value†**
Demographics Sex – no. (%)				
Male	2,124 (81.8)	1,082 (79.3)	1,042 (84.6)	**< 0.001**
Female	472 (18.2)	282 (20.7)	190 (15.4)	
Applicant category – no. (%)				
A (White collar and Constructions)	2,065 (79.5)	1,055 (77.3)	1,010 (82.0)	**< 0.003**
Bi/Bii (Maids and Drivers)/ (Others)	531 (20.5)	309 (22.7)	222 (18.0)	
Nationality – no. (%)**				
SEAR(reference)	1,218 (46.9)	606 (44.4)	612 (49.7)	**< 0.028**
AFR/EMR	1,002 (38.6)	552 (40.5)	450 (36.5)	
WPR/EUR/AMR	376 (14.5)	206 (15.1)	170 (13.8)	
Visa type – no. (%)				
New (reference)	1,415 (54.5)	914 (67.0)	501 (40.7)	**< 0.001**
Renew	1,181 (45.5)	450 (33.0)	731 (59.3)	
Chest X-ray evaluation by radiologist-no.(%)				
Suspicion of TB	1,272 (49.0)	739 (54.2)	533 (43.3)	**< 0.001**
Abnormal Not/ Old TB	1,324 (51.0)	625 (45.8)	699 (56.7)	
IGRA value-no.(%)				
Negative (reference)	1,050 (40.5)	524 (38.4)	526 (42.7)	**< 0.027**
Positive	1,546 (59.5)	840 (61.6)	706 (57.3)	
Tuberculin Skin Test TST-no.(%)				
TST (0-14) mm	1,371 (52.8)	697 (51.1)	674 (54.7)	0.066
TST (15-40) mm	1,225 (47.2)	667 (48.9)	558 (45.3)	
Sputum Smear AFB result-no.(%)				
Negative (reference)	2,517 (97.0)	1,314 (96.3)	1,203 (97.7)	0.052
Positive	79 (3.0)	50 (3.7)	29 (2.3)	
Disease Prevention &Screening Centers (DPSCs)-no.(%)!				**< 0.001**
Abu Dhabi & Mussafah (DPSCs)	1,502 (57.9)	835 (61.2)	667 (54.1)	
Al Ain & Other (DPSCs)	1,094 (42.1)	529 (38.8)	565 (45.9)	

*Total adult population investigated for **mycobacterium tuberculosis in 2013.**

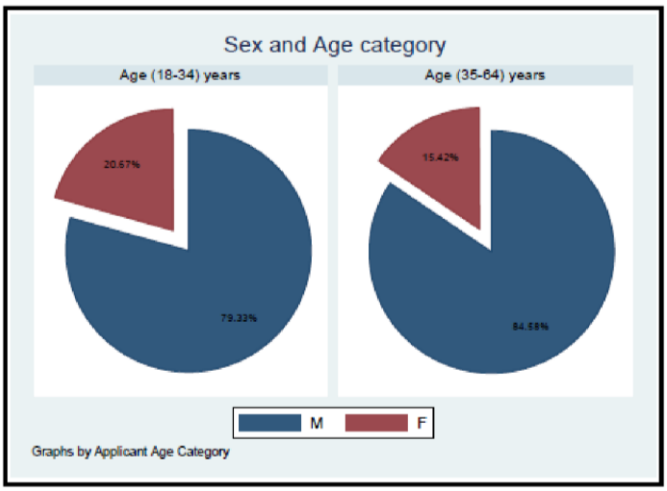
** SEAR: WHO South East Asia Region, EMR: WHO Eastern Mediterranean Region, AFR: WHO African region, WPR: WHO Western Pacific Region, EUR: WHO European Region, AMR: WHO region of America

! Abu Dhabi Disease Prevention and Screening Center (DPSC) which is the largest screening center in the Emirate of Abu Dhabi, Mussafah (DPSC), Al Ain (DPSC), Madinat Zayed (DPSC), Gaiathy (DPSC), Silla (DPSC), Delma (DPSC), Al Mirfa (DPSC), Shahama (DPSC), Etihad Airways (DPSC) and Sweihan (DPSC)

†P value (2- sided) determined from Pearson's chi- square test and Fisher's exact test

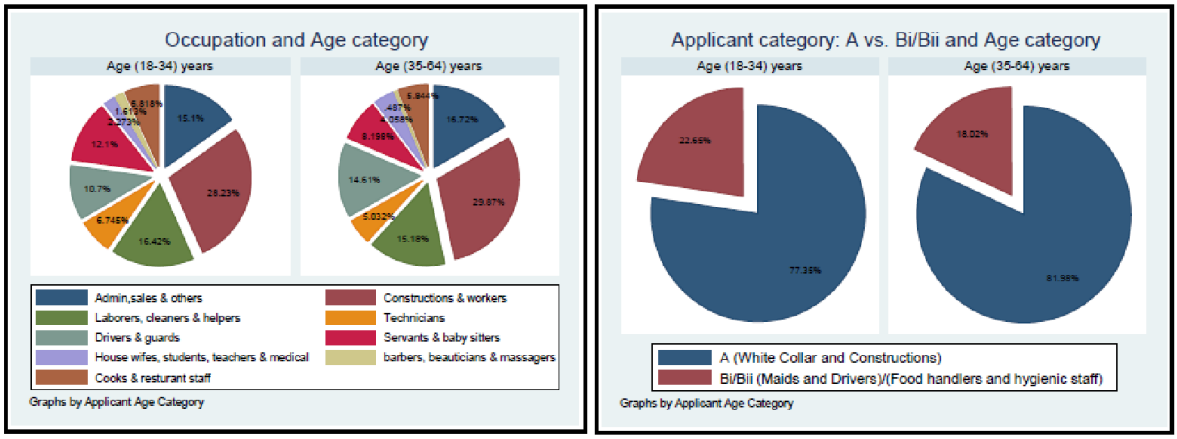
In our study, males constituted the largest percentage of visa applicants compared to females (81.8% vs 18.2%) (Table 4.1.1) (Figure 4.1.1). High gender imbalance was noticed in our study as more males were present in the older age group category and male/female ratio was 3.8 for the (18-34) age group and 5.5 for the age group (35-64) (Table 4.1.1) (Figure 4.1.1).

Figure 4.1. 1: Sex and age category



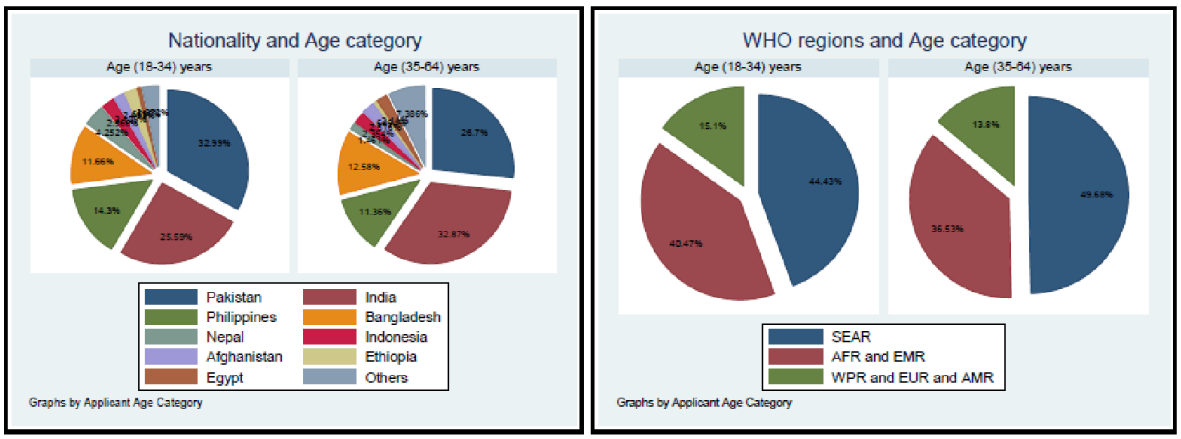
The percentage of younger vs. older applicants was almost comparable among the majority of occupations yet a higher percentage of younger individuals were working as servants and babysitters, *(P<0.001)* (Figure 4.1.2). A higher percentage of older individuals were among applicant category A: white collar and construction compared to applicant category Bi/Bii: maids and drivers/food handlers and hygienic staff, *(P<0.003)* (Figure 4.1.2).

Figure 4.1. 2: Occupation and Age category/ Applicant category A vs. Bi/Bii and Age



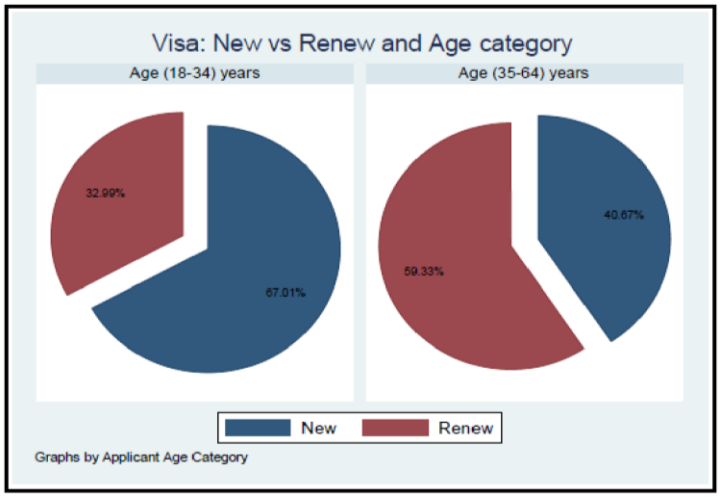
A higher percentage of older individuals came from SEAR compared to other WHO regions, *(P<0.028)* (Figure 4.1.3).

Figure 4.1. 3: Nationality and Age category/ WHO regions and Age category



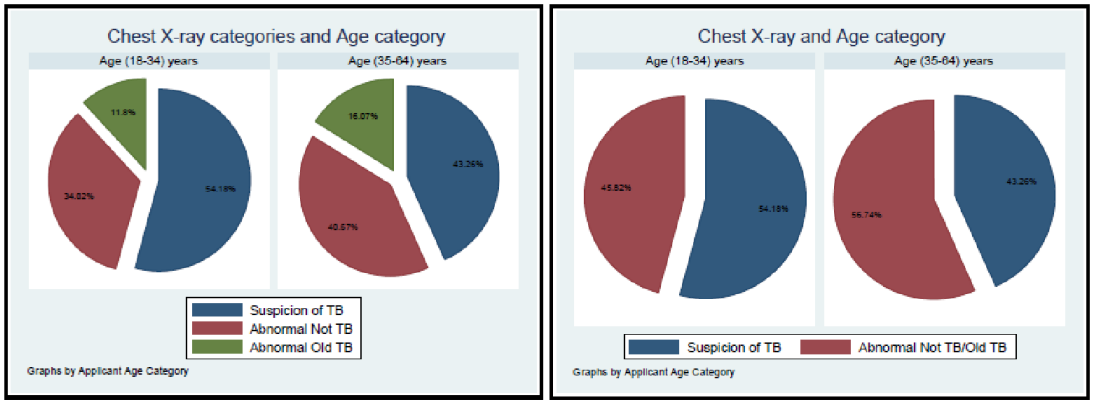
Older individuals were more commonly found in the renewal visa category compared to younger individuals, *(P<0.001)* (Figure 4.1.4). On the other hand, younger individuals were mainly found in the new visa applicant category, *(P<0.001)* (Figure 4.1.4).

Figure 4.1. 4: Visa: New vs. Renew and Age category



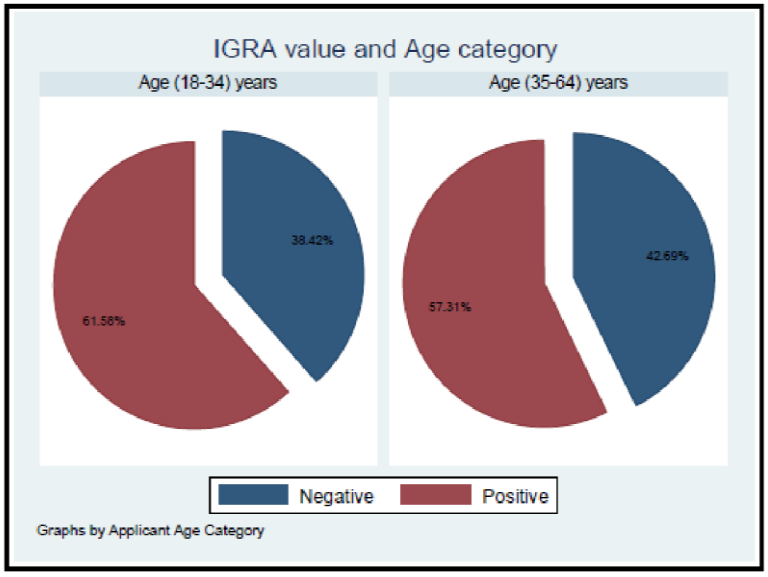
A higher percentage of younger individuals were suspected to have MTB by chest X-ray evaluation report, *(P<0.001)* (Figure 4.1.5).

Figure 4.1. 5: Chest X-ray categories and Age category/ Chest X-ray and Age



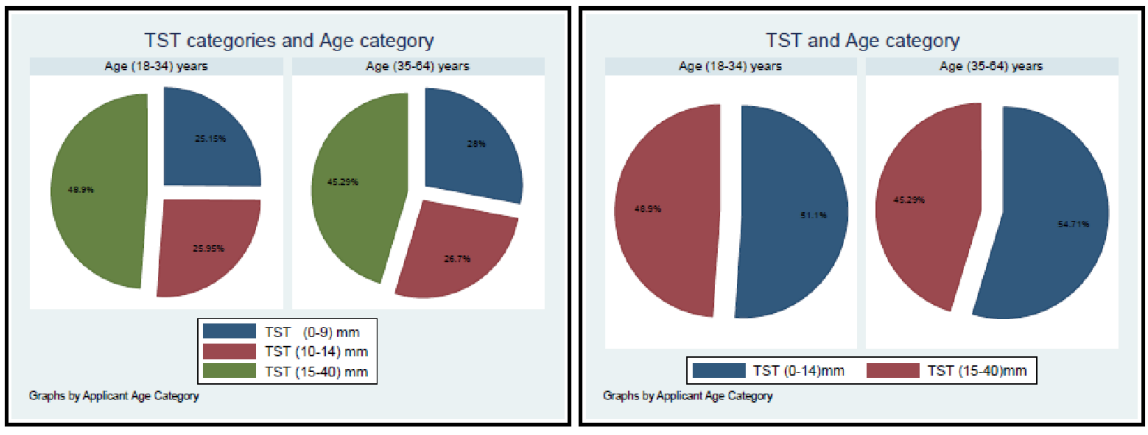
A higher percentage of younger individuals also had positive IGRA results compared to older individuals, *(P<0.027)* (Figure 4.1.6).

Figure 4.1. 6: IGRA value and Age category



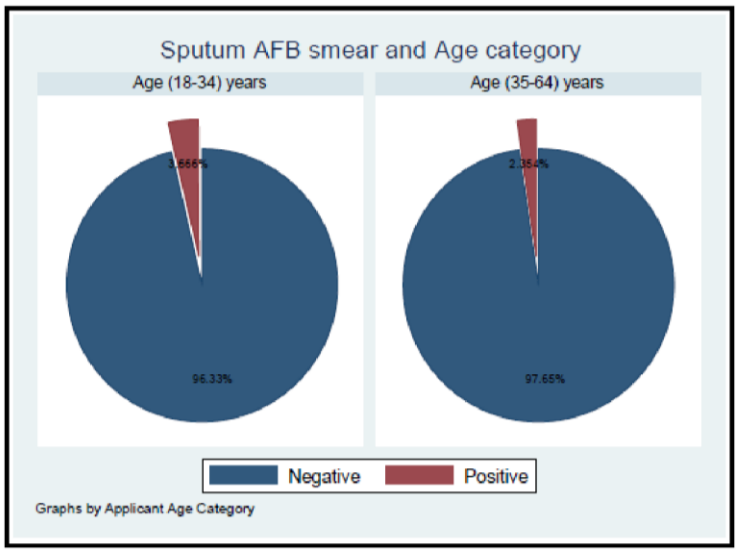
A slightly higher percentage of younger individuals had positive TST results compared to older individuals, (P=0.066, not significant) (Figure 4.1.7).

Figure 4.1. 7: TST categories and Age category/ TST and Age category



A slightly higher percentage of younger individuals had positive sputum AFB smear results compared to older individuals, (P=0.052, not significant) (Figure 4.1.8).

Figure 4.1. 8: Sputum AFB smear and Age category



B. The validity of IGRA, TST and chest X-ray

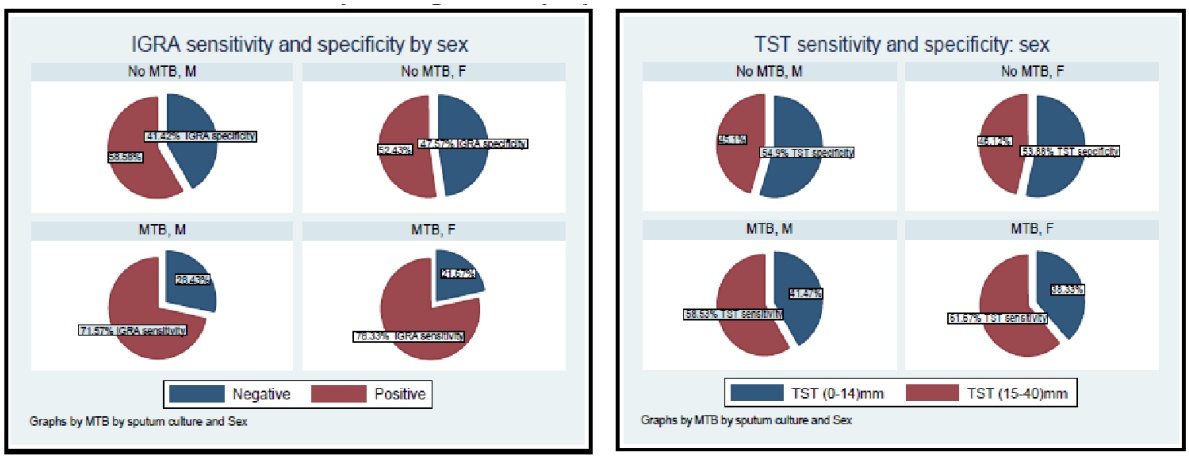
The validity of IGRA and TST by sex

In our sample, IGRA is more sensitive among females (78.3%) compared to males (71.6%) (Table 4.1.2) (Figure 4.2.1). TST, on the other hand, has less sensitivity than IGRA and TST is of a comparable sensitivity among males (58.5%) and females (61.7%) (Table 4.1.2) (Figure 4.2.1).

Table 4.1. 2: The validity of IGRA and TST by sex

Test	IGRA		TST	
Sex	Sensitivity % (95%CI)	Specificity % (95%CI)	Sensitivity % (95%CI)	Specificity % (95%CI)
Male	71.6 (66-77)	41.4 (39-44)	58.5 (53-64)	54.9 (53-57)
Female	78.3 (66-88)	47.6 (43-53)	61.7 (48-74)	53.9 (49-59)

Figure 4.2. 1: IGRA and TST sensitivity and specificity by sex



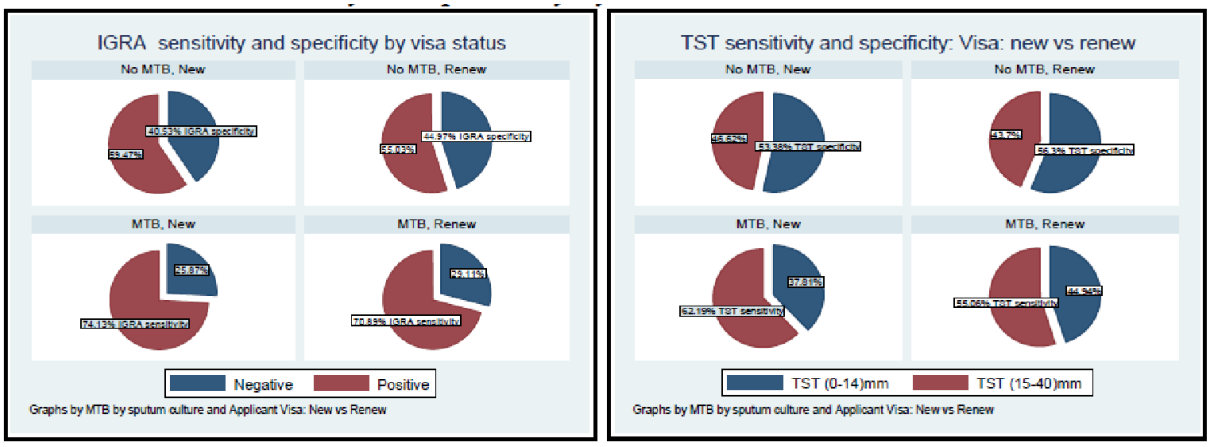
The validity of IGRA and TST by visa type

When looking at the visa type in our sample, IGRA is slightly more sensitive among new visa applicants (74.1%) compared to renewal (70.9%) (Table 4.1.3) (Figure 4.3.1). TST, on the other hand, has lower sensitivity than IGRA and TST is more sensitive among new visa applicants (62.2%) compared to renewal (55.1%) (Table 4.1.3) (Figure 4.3.1).

Table 4.1. 3: The validity of IGRA and TST by visa type

Test	IGRA		TST	
Visa type	Sensitivity % (95%CI)	Specificity % (95%CI)	Sensitivity % (95%CI)	Specificity % (95%CI)
New	74.1 (68-80)	40.53 (38-43)	62.2 (55-69)	53.4 (51-56)
Renew	70.9 (63-78)	45.0 (42-48)	55.1 (47-63)	56.3 (53-59)

Figure 4.3. 1: IGRA and TST sensitivity and specificity by visa status: new vs. renew



The validity of IGRA and TST by country

When looking at the visa applicants from Pakistan, IGRA is more sensitive (74.1%) than TST (52.6%) (Table 4.1.4). Similarly, IGRA is more sensitive (78.4%) than TST (59.5%) in visa applicants from Bangladesh (Table 4.1.4). IGRA is also more sensitive (90.9%) than TST (63.7%) among visa applicants from Indonesia (Table 4.1.4).

Table 4.1. 4: The validity of IGRA and TST by country

Test	IGRA		TST	
Country	Sensitivity % (95%CI)	Specificity % (95%CI)	Sensitivity % (95%CI)	Specificity % (95%CI)
Pakistan	**74.1 (65-81)**	36.2 (32-39)	52.6 (43-62)	54.7 (51-59)
India	65.3 (55-75)	41.0 (37-44)	**66.3 (56-75)**	51.1 (47-55)
Philippines	67.4 (51-80)	46.4 (40-52)	54.3 (39-69)	56.7 (51-63)
Bangladesh	**78.4 (62-90)**	55.2 (49-61)	**59.5 (42-75)**	59.2 (54-65)
Nepal	78.1 (56-92)	39.6 (26-54)	52.2 (31-73)	39.6 (26-54)
Indonesia	**90.9 (58-99)**	56.6 (42-70)	**63.7 (31-89)**	67.9 (54-80)
Afghanistan	100 (40-100)	20 (11-34)	75.0 (19-99)	51.8 (38-65)
Ethiopia	100 (63-100)	29 (15-47)	62.5 (24-91)	44.1 (27-62)
Egypt	50 (12-90)	42 (25-61)	100 (16-100)	58 (39-74)
Other	73 (39-94)	56 (46-64)	73 (39-94)	62 (53-70)

When looking at the visa type by country, majority of applicants for new visa were from Pakistan, the Philippines and Indonesia while applicants for visa renewal were from Bangladesh, Ethiopia and Egypt (Table 4.1.5).

Table 4.1. 5: Visa type by country

Visa type by country	New (n=1,415) (54.5%)	Renew (n=1,181) (45. 5%)
Pakistan	**486 (62.4)**	293 (37.6)
India	451 (59.8)	303 (40.2)
Philippines	**237 (70.7)**	98 (29.3)
Bangladesh	19 (6.0)	**295 (94.0)**
Nepal	51 (67.1)	25 (32.9)
Indonesia	**52 (81.3)**	12 (18.7)
Afghanistan	28 (46.7)	32 (53.3)
Ethiopia	11 (26.2)	**31 (73.8)**
Egypt	5 (14.3)	**30 (85.7)**
Other countries	75 (54.7)	62 (45.3)

The validity of IGRA and TST by WHO regions

When looking at the applicants for WHO region perspective in our sample, IGRA is slightly more sensitive among visa applicants in AFR/EMR regions (76.7%) compared to SEAR (70.4%) and other regions (Table 4.1.6). TST, on the other hand, is of a lesser sensitivity in all WHO regions and is of lesser sensitivity when compared to IGRA (Table 4.1.6).

Table 4.1. 6: The validity of IGRA and TST by WHO regions

Test	IGRA		TST	
WHO regions	Sensitivity % (95%CI)	Specificity % (95%CI)	Sensitivity % (95%CI)	Specificity % (95%CI)
SEAR	70.4 (63-77)	45.7 (43-47)	63.1 (55-70)	53.7 (51-57)
AFR/EMR	76.7 (69-84)	36.9 (34-40)	54.9 (46-64)	54.9 (52-58)
WPR/EUR/AME	70.0 (55-82)	47.6 (42-53)	56.0 (41-70)	57.4 (52-63)

The validity of IGRA and TST by Chest X-ray evaluations

When looking at the chest X-ray for applicants in our sample, IGRA is more sensitive among visa applicants with a chest X-ray evaluation of abnormal Not/Old TB (85.3%) than those with chest X-ray evaluation of Suspicion of TB (67.7%) (Table 4.1.7). TST, on the other hand, is of a lesser sensitivity than IGRA and TST is of a comparable sensitivity among those with a chest X-ray evaluation of abnormal Not/Old TB (Table 4.1.7).

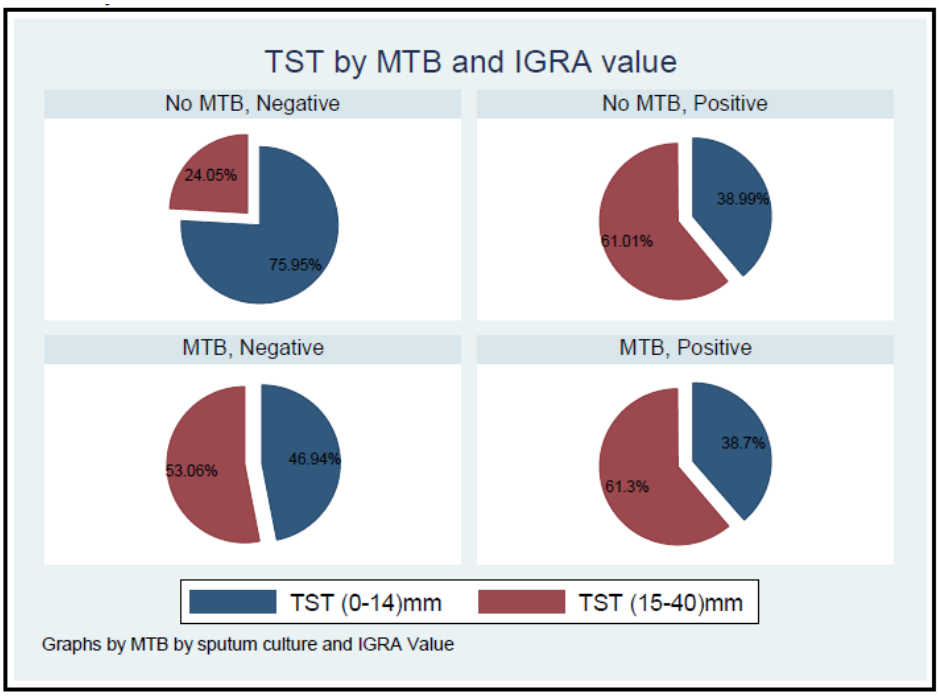
Table 4.1. 7: The validity of IGRA and TST by Chest X-ray evaluation

Test	IGRA		TST	
Chest X-ray	Sensitivity % (95%CI)	Specificity % (95%CI)	Sensitivity % (95%CI)	Specificity % (95%CI)
Suspicion of TB	67.7 (62-73)	43.0 (40-46)	59.1 (53-65)	51.8 (49-55)
Abnormal Not/Old TB	85.3 (77-92)	42.1 (39-45)	58.8 (49-68)	57.1 (54-60)

When looking at the results for the applicants after merge of the first two TST categories in our sample, we found that among those diagnose with MTB and had negative IGRA: 46.9% had

negative TST and 53.1% had positive TST result, *(P<0.001)* (Figure 4.4.1). Among those diagnosed with MTB and had positive IGRA: 38.7% had negative TST and 61.3% had positive TST result, (P=0.930, not significant) (Figure 4.4.1).

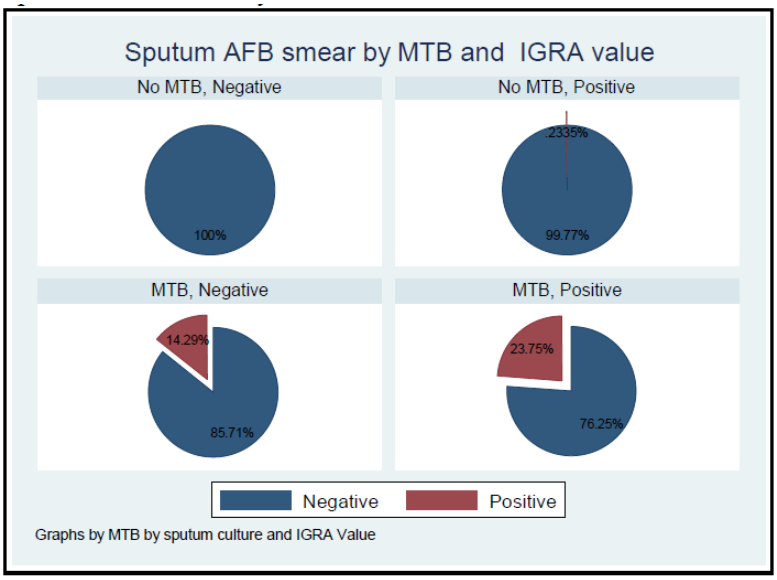
Figure 4.4. 1: TST by MTB and IGRA value



The validity of IGRA and TST by sputum AFB smear results

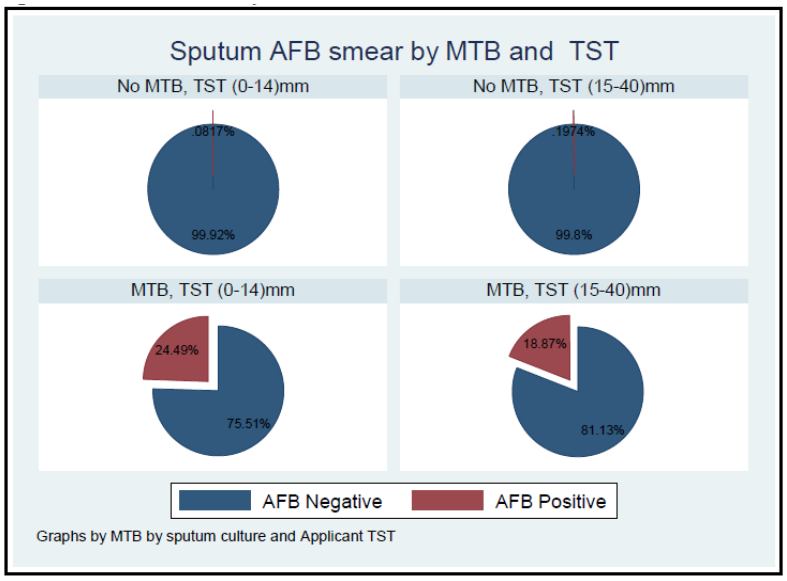
When exploring the relationship between AFB smear results and IGRA we found that among those diagnosed with MTB disease: 14.3% had positive AFB smear results among those with negative IGRA compared to 23.7% positive AFB smear results among those with positive IGRA, *(P<0.001)* (Figure 4.5.1).

Figure 4.5. 1: Sputum AFB smears by MTB and IGRA value



Among those diagnosed with MTB disease: 24.5% had positive AFB smear results in the TST (0-14) mm category and 18.9% in the (15-40) mm category, *(P<0.001)* (Figure 4.6.1).

Figure 4.6. 1: Sputum AFB smears by MTB and TST



When looking at the sputum AFB smear results in relation to TST for applicants in our sample, TST sensitivity is 60.8%, *(P<0.001)* among those with negative AFB smear results compared to 52.6% in the positive AFB smear results, (P=0.633, not significant) (Figure 4.7.1).

Figure 4.7. 1: TST by MTB and Sputum AFB smears

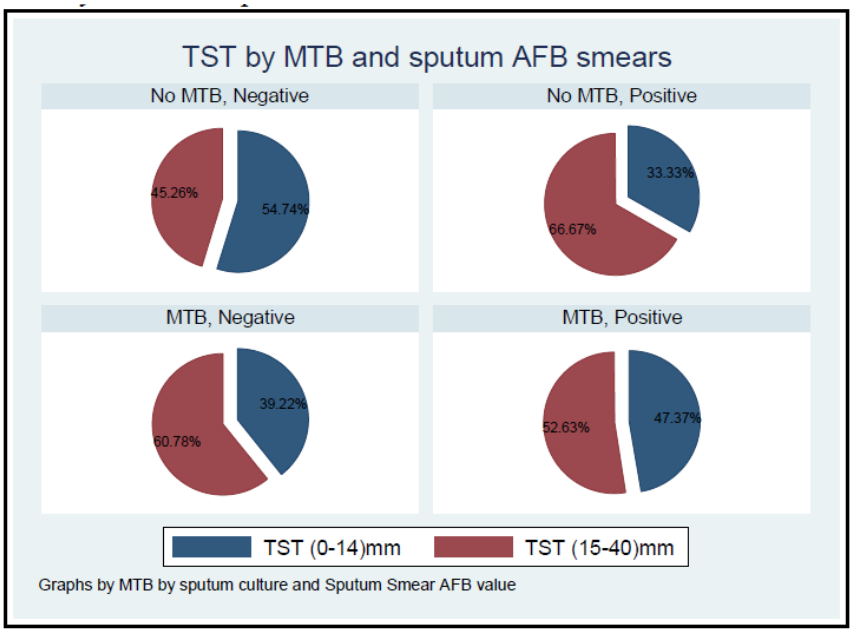


Table 4.2.1 shows the sensitivity, specificity, the negative likelihood ratio (NLR), the positive likelihood ratio (PLR), negative predictive value (NPV), the positive predictive value (PPV) of all the screening tests used in the study. IGRA (QFT-GIT) sensitivity is 72.7%, (95% CI: 68.8-77.2) compared to TST sensitivity of 59.0%, (95% CI: 53.8-64.2). ***Therefore, and as we assumed earlier, IGRA is more sensitive than TST in detecting MTB among adults during the visa screening process.***

When considering IGRA predictive values in our study, an individual's prior probability of having the disease is 0.14 and is modified to 0.169 if he/she has a positive IGRA test result. An

individual's prior probability of not having the disease is 0.86 and is modified to 0.91 if he/she has a negative IGRA test result. Similarly, when considering TST predictive values in our study, an individual's prior probability of having the disease is 0.14 and is modified to 0.17 if he/she has a positive TST test result and an individual's prior probability of not having the disease is 0.86 and is modified to 0.89 if he/she has a negative TST test result.

Table 4.2 1: Sensitivity and specificity of IGRA/TST (2013)

	Sensitivity (95% CI)	Specificity (95% CI)	NLR†	PLR‡	NPV†	PPV‡
IGRA*	72.7% (67.8-77.2)	42.6% (40.5-44.6)	0.6	1.3	90.7	16.9
TST **	59.0% (53.8-64.2)	54.72% (52.6-56.8)	0.7	1.3	89.3	17.3

*** IGRA test that was used in the is Quantiferon TB Gold test and the total study population is 2,596**
****TST Tuberculin Skin Test**
NLR† Negative Likelihood Ratio
PLR‡ Positive Likelihood Ratio
NPV† Negative Predictive Value at a prior probability of infection = 0.14
PPV‡ Positive Predictive Value at a prior probability of infection = 0.14

Table 4.3.1 shows the sensitivity, specificity, the negative likelihood ratio (NLR), the positive likelihood ratio (PLR) by age group. Among the younger age group (18-34) years IGRA (QFT-GIT) sensitivity was 78.1%, (95% CI: 72.2-83.2). IGRA (QFT-GIT) sensitivity was better than TST sensitivity and was even better than IGRA (QFT-GIT) sensitivity in the older age group in the study. ***Therefore, and as we assumed earlier, IGRA and TST sensitivity were reduced as the applicants aged.***

Table 4.3 1: Sensitivity and specificity of IGRA/TST by age groups (2013)

Age category				
Younger (18-34) years	**Sensitivity (95% CI)**	**Specificity(95% CI)**	**NLR†**	**PLR‡**
IGRA*	78.1% (72.2-83.2)	41.8% (38.9-44.8)	0.5	1.3
TST **	61.4% (54.8-67.7)	53.7% (50.7-56.6)	0.7	1.3
Older (35-64) years	**Sensitivity (95% CI)**	**Specificity(95% CI)**	**NLR†**	**PLR‡**
IGRA	62.7% (53.6-71.1)	43.3% (40.4-46.3)	0.9	1.1
TST	54.8% (45.6-63.6)	55.8% (52.8-58.7)	0.8	1.2

*** IGRA test that was used in the is Quantiferon TB Gold test and the total study population is 2,596**
****TST Tuberculin Skin Test**
NLR† Negative Likelihood Ratio
PLR‡ Positive Likelihood Ratio

Simultaneous (parallel) test: IGRA (QFT-GIT) and TST

The net sensitivity of parallel testing with both IGRA (QFT-GIT) and TST is 88.8% (Table 4.4.1). The net sensitivity of parallel testing with both IGRA (QFT-GIT) and TST for the younger age group (18-34) years was even higher, 91.5% (Table 4.5.1 and Table 4.6.1). IGRA (QFT-GIT) therefore may have a 'rule out' value for active tuberculosis when used with other investigations. ***Therefore, and as we assumed earlier, simultaneous testing (parallel) with IGRA (QFT-GIT) and TST had improved net sensitivity for detecting MTB among adults during the visa screening process.***

Table 4.4. 1: Sensitivity and specificity of IGRA/TST (parallel and serial)

Table (4.4)	IGRA	TST	Parallel	Serial
Sensitivity	72.7	59.05	88.82	42.93
Specificity	42.56	54.72	23.29	73.99

Table 4.5. 1: Sensitivity and specificity of IGRA/TST (parallel and serial) in younger age category (18-34) years

Table (4.5)

(18-34) years	IGRA	TST	Parallel	Serial
Sensitivity	78.11	61.37	91.54	47.94
Specificity	41.82	53.67	22.44	73.05

Table 4.6. 1: Sensitivity and specificity of IGRA/TST (parallel and serial) in older age category (35-64) years

Table (4.6)

(35-64) years	IGRA	TST	Parallel	Serial
Sensitivity	62.7	54.76	83.13	34.33
Specificity	43.31	55.79	24.16	74.94

Kappa agreement between IGRA (QFT-GIT) and TST is 0.33 and (95% CI: 0.29-0.36) which is considered as only fair concordance.

The validity of chest X-ray

When considering the performance of chest X-ray in this study (using the sputum culture as the gold standard test), the sensitivity and specificity of chest X-ray is 71.6% (95% CI: 66.6–76.2) and 54.6% (95% CI: 52.5–56.7), respectively (Table 4.7.1).

Table 4.7. 1: Sensitivity and specificity of Chest X-ray (2013)

	Sensitivity (95% CI)	Specificity (95% CI)	NLR†	PLR‡	NPV†	PPV‡
Chest X-ray *	71.6% (66.6-76.2)	54.6% (52.5-56.7)	0.5	1.6	92.3	20.2

***Chest X-ray evaluation by radiologists: Suspicion of MTB and Abnormal Not/Old MTB**
The total study population is 2,596
NLR† Negative Likelihood Ratio
PLR‡ Positive Likelihood Ratio
NPV† Negative Predictive Value at a prior probability of infection = 0.14
PPV‡ Positive Predictive Valueat a prior probability of infection = 0.14

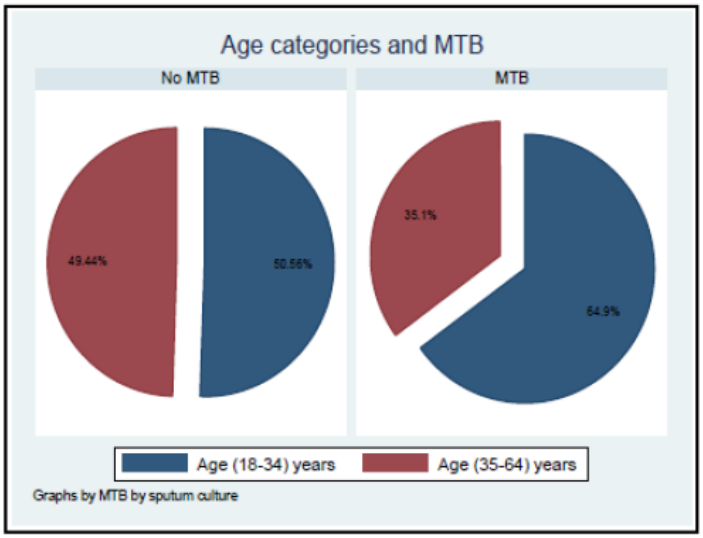
Therefore, we still consider that chest X-ray has a good sensitivity in detecting TB among adults during the screening for visa purposes as we assumed earlier yet the role of chest X-ray in our study was not adequate due to low sensitivity and modest accuracy (only 57%).

When considering chest X-ray predictive values in our study, an individual's prior probability of having the disease is 0.14 and is modified to 0.20 if he/she has abnormal chest X-ray evaluation result. An individual's prior probability of not having the disease is 0.86 and is modified to 0.92 if he/she has a negative chest X-ray evaluation. The net sensitivity of parallel testing with both IGRA (QFT-GIT) and chest x-ray is 92.2%. The accuracy of chest X-ray in our study is modest (only 57%) and the accuracy of IGRA and TST are 47% and 55% respectively.

C. Predictors of MTB

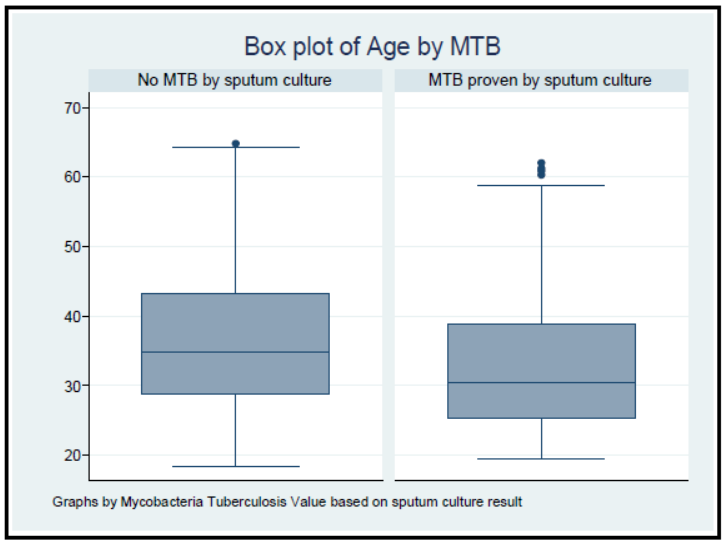
A total of 359 cases were eventually confirmed to have MTB based on positive sputum culture result in our study. Thus, 13.8% of applicants with abnormal chest X-ray were diagnosed with tuberculosis, compared to 2,237 individuals (86.2%) confirmed as MTB negative based on negative sputum culture results. When comparing the proportion of adults diagnosed to have MTB in the sample to those who do not have the disease; the prevalence of the disease was 14% (359/2,596) and the (95% CI: 0.13-0.15). Around 14% (299/2124) of males were diagnosed to have MTB compared to 13% (60/472) in females, a non-significant difference (P=0.437). Around two-thirds of MTB cases occurred among the younger age group (18-34) years, *(P<0.001)* (Figure 4.8.1).

Figure 4.8. 1: Age categories by MTB



Among MTB positive cases, the mean age is 33.2 (SD ±9.87) years and the median age is 30.4 (IQR 13.5-14.4). Those diagnosed with MTB were younger than individuals proven not having the disease (Figure 4.9.1).

Figure 4.9. 1: Boxplot of Age by MTB



Almost two-thirds of the applicants in the study came from Pakistan and India. Nearly two-thirds of males in the sample were from Pakistan and India while almost 50% of females were from the Philippines (Table 4.8.1).

Table 4.8. 1: Nationality and sex

Nationality	Males n=2,124 (81.8) %	Females n=472 (18.2) %
Pakistan	746 (35.1)	33 (7)
India	704 (33.1)	50 (10.6)
Philippines	96 (4.5)	239 (50.6)
Bangladesh	305 (14.4)	9 (1.9)
Nepal	68 (3.2)	8 (1.7)
Indonesia	8 (0.4)	56 (11.9)
Afghanistan	55 (2.6)	5 (1.1)
Ethiopia	1 (0.1)	41 (8.7)
Egypt	32 (1.5)	3 (0.6)
Other	109 (5.1)	28 (5.9)

In our study sample, the majority of applicants who applied for residency in Abu Dhabi to work in construction and were employed as workers, laborers or cleaners and helpers came mainly from Pakistan, India, Bangladesh, and Nepal. Drivers were mainly from Pakistan and Afghanistan while servants and babysitters were from Ethiopia, Indonesia and, Philippines.

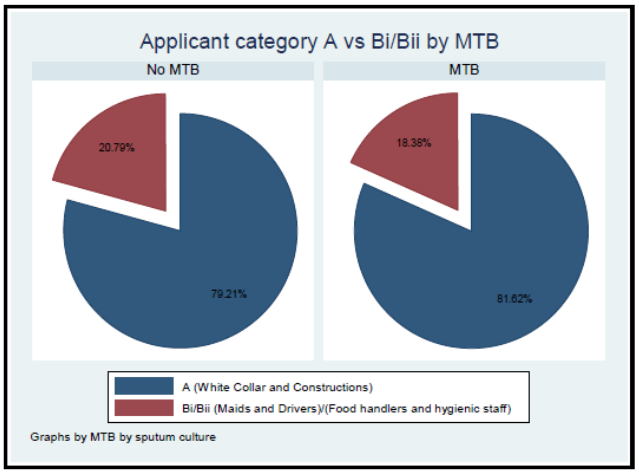
Almost 48% of MTB cases occurred among applicants working in construction and were employed as workers, laborers or cleaners and helpers, (P=0.315, not significant) (Table 4.8.2).

Table 4.8. 2: Occupation and MTB

Occupations	MTB n=359 (13.8) %	No MTB n=2,237 (86.2) %
Administration, sales and others	57 (15.9)	355 (15.9)
Constructions and workers	108 (30.1)	645 (28.8)
Laborers, clears and helpers	63 (17.6)	348 (15.6)
Technicians	26 (7.2)	128 (5.7)
Drivers and guards	42 (11.7)	284 (12.7)
Servants and babysitters	28 (7.8)	238 (10.6)
Housewives, students, teachers and medical	5 (1.4)	76 (3.4)
Barbers, beautician and massagers	4 (1.1)	24 (1.1)
Cooks and restaurant staff	26 (7.2)	139 (6.2)

For the sake of convenience, the applicant category grouping of A and Bi Bii (as in DOH/HAAD visa standard) was used instead of occupation in the analysis due to limited numbers in cells of occupation variable. Among the two applicant employment categories, almost 80% came from group A (white collar and construction) and the majority of MTB cases belongs to this group as well, (P=0.32, not significant) (Figure 4.10.1).

Figure 4.10. 1: Applicant category A vs. Bi/Bii by MTB



Considering the nationality and MTB diagnosis in the sample, approximately 60% of MTB cases came from Pakistan and India. A smaller percentage (12.8%) of MTB cases were diagnosed among individuals coming from the Philippines and 10.3% of cases were from Bangladesh, *(P<0.001)* (Table 4.8.3).

Table 4.8. 3: Nationality and MTB

Nationality	MTB n=359 (13.8) %	No MTB n=2,237 (86.2) %
Pakistan	116 (32.3)	663 (29.6)
India	101 (28.1)	653 (29.2)
Philippines	46 (12.8)	289 (12.9)
Bangladesh	37 (10.3)	277 (12.4)
Nepal	23 (6.4)	53 (2.4)
Indonesia	11 (3.1)	53 (2.4)
Afghanistan	4 (1.1)	56 (2.5)
Ethiopia	8 (2.2)	34 (1.5)
Egypt	2 (0.6)	33 (1.5)
Other	11 (3.1)	126 (5.6)

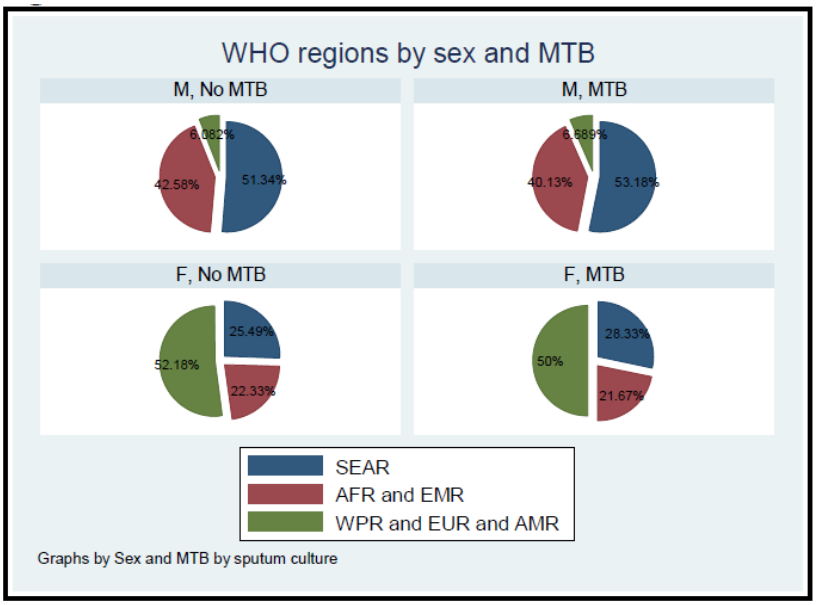
When considering the WHO regional classification of nationality and MTB diagnosis in the sample, approximately 47% of MTB cases came from countries of the South East Asia Region (SEAR) followed by the African and Eastern Mediterranean Regions (39%). However, there were no differences in MTB by WHO region of origin, (P=0.703, not significant). Similarly, there were no differences in MTB by sex and WHO region of origin, (P=0.895, not significant) (Fig. 4.11.1) (Table 4.8.4).

Table 4.8. 4: WHO regions by MTB and sex

*WHO regions	Total** (n= 2, 596)	MTB n=359 (13.8) %	No MTB n=2,237 (86.2) %
SEAR-n. (%) Males Females	 1,096 (51.6) 122 (25.8)	 159 (53.2) 17 (28.3)	 937 (51.3) 105 (25.5)
AFR and EMR- n. (%) Males Females	 897 (42.2) 105 (22.3)	 120 (40.1) 13 (21.7)	 777 (42.6) 92 (22.3)
WPR and EUR and AMR- n. (%) Males Females	 131 (6.2) 245 (51.9)	 20 (6.7) 30 (50.0)	 111 (6.1) 215 (52.2)

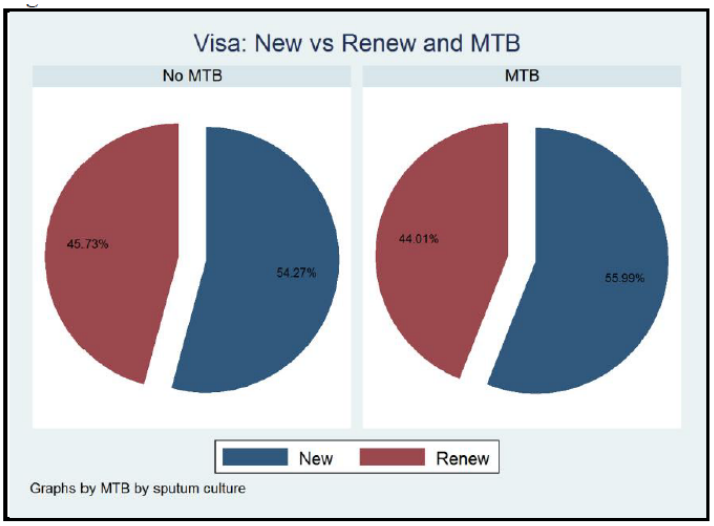
*SEAR: WHO South East Asia Region, EMR: WHO Eastern Mediterranean Region, AFR: WHO African region, WPR: WHO Western Pacific Region, EUR: WHO European Region, AMR: WHO region of America.
**Total adult population screened for mycobacterium tuberculosis in 2013.

Figure 4.11. 1: WHO regions by sex and MTB



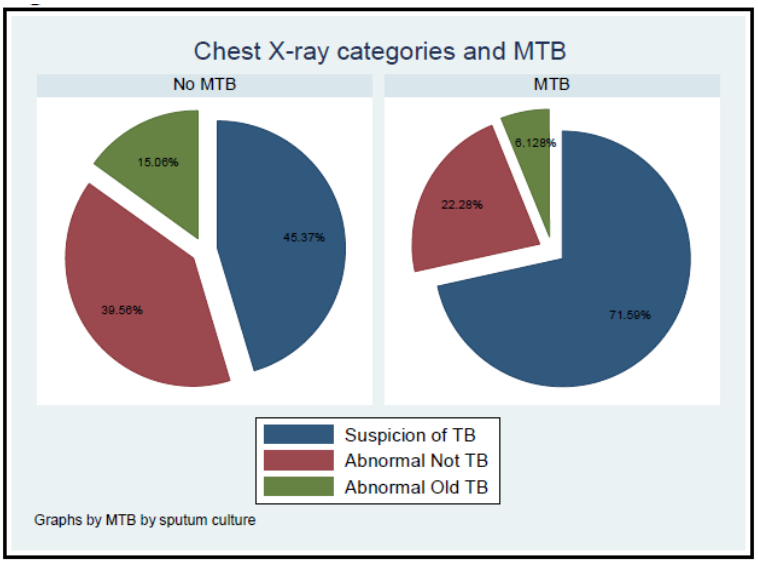
When comparing between the visa type applicants, more cases were detected among the new visa applicants. Around 56% of MTB cases occurred among the new visa applicants compared to 44% positive cases in the renewal visa applicants, (P=0.54, not significant) (Figure 4.12.1).

Figure 4.12. 1: Visa: New vs. Renew and MTB



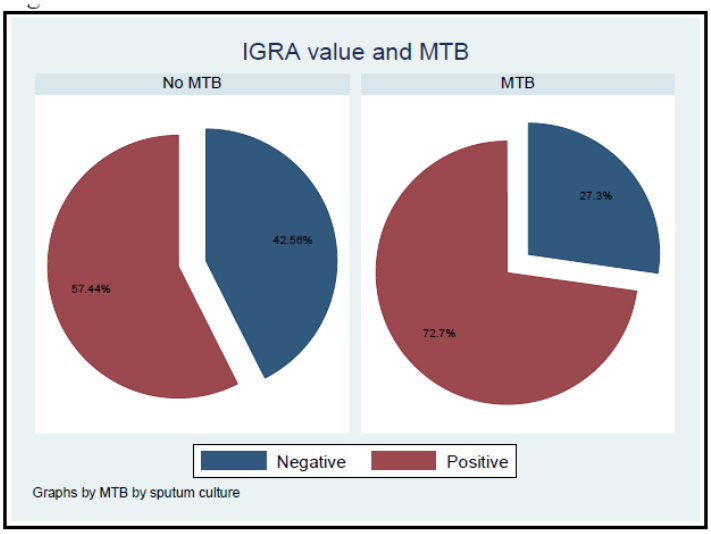
More than two-thirds of confirmed MTB cases occurred among those with a chest X-ray evaluation of Suspicion of TB, *(P<0.001)* (Figure 4.13.1).

Figure 4.13. 1: Chest X-ray categories and MTB



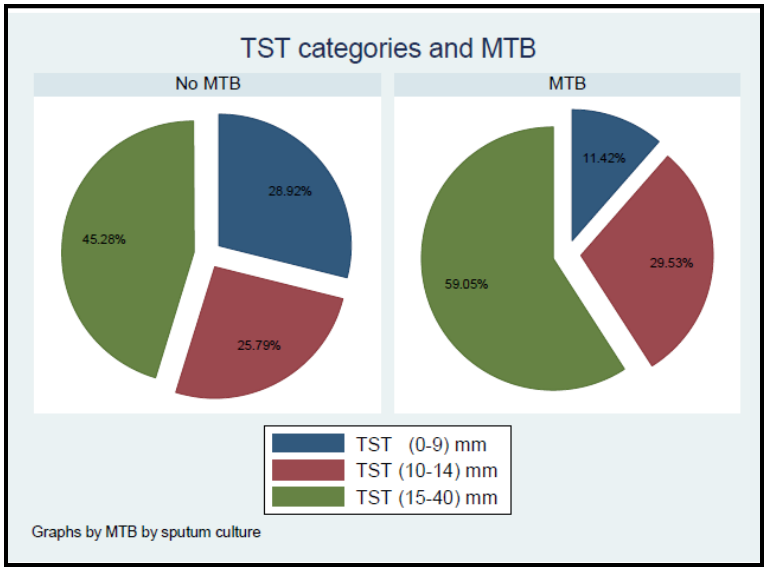
Similarly, more than two-thirds of confirmed MTB cases occurred among applicants with IGRA positive test, *(P<0.001)* (Figure 4.14.1).

Figure 4.14. 1: IGRA value and MTB



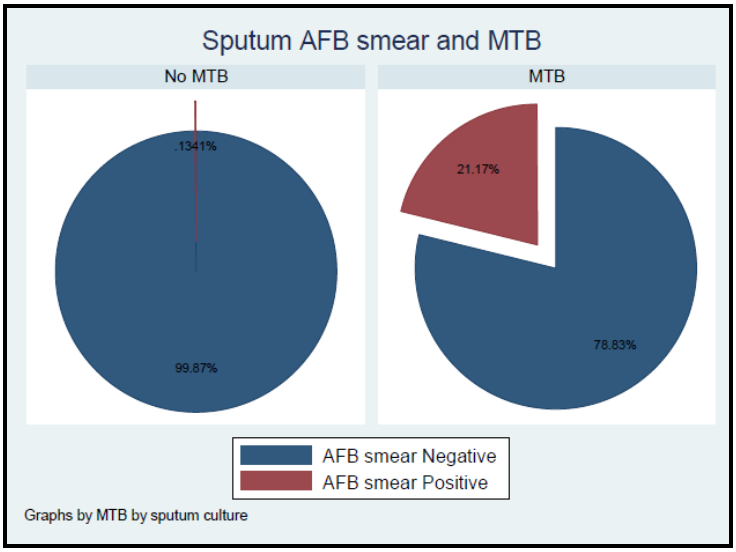
Almost two-thirds of confirmed MTB cases had TST positive test (59%) compared to 45% of positive TST test in individuals with the non-MTB diagnosis, ***(P<0.001)*** (Figure 4.15.1).

Figure 4.15. 1: TST categories and MTB



Positive AFB smear test was found mainly in confirmed MTB cases compared to those without the disease, *(P<0.001)* (Figure 4.16.1).

Figure 4.16. 1: Sputum AFB smear and MTB



The Two-sample t-test used to assess the difference in mean for the continuous variable TST(tstobservation) in the sample showed a non-significant association for gender, applicant employment category (A vs. Bi/Bii), age category and visa type (new vs. renew) (Table 4.8.5). However, individuals with IGRA positive had a significantly higher TST mean compared to those with IGRA negative result, *(P<0.001)* (Table 4.8.5). Similarly, individuals with a diagnosis of the MTB disease had a significantly higher TST mean compared to those diagnosed with non-MTB disease, *(P<0.001)* (Table 4.8.5). On the other hand, those with chest X-ray evaluation of Abnormal Not/Old TB had a significantly lower TST mean compared to those with chest evaluation of Suspicion of TB, *(P<0.001)* (Table 4.8.5). The results were further supported and the conclusion was checked using non-parametric tests; the Mann-Whitney U test and the Kruskal-Wallis test.

Table 4.8. 5: Two-sample tests of the continuous variable: tstobservation

Table (4.8.5) Two-sample tests of the continuous variable tstobservation	**Total* (n= 2, 596)**	**Mean**	**SD**	**(95% CI)**	**P Value†**
Demographics Sex – no. (%) Male Female	 2,124 (81.8) 472 (18.2)	 12.1 12.5	 6.9 7.1	 (11.8-12.4) (11.8-13.1)	0.315
Applicant category – no. (%) A (White collar and Constructions) Bi/Bii (Maids and Drivers)/(Others)	 2,065 (79.6) 531 (20.5)	 12.1 12.4	 6.9 7.1	 (11.8-12.4) (11.8-13.0)	0.439
****Age category– no. (%)** Younger (reference) Older	 1364 (52.5) 1232 (47.5)	 12.4 11.9	 6.9 7.1	 (12.0-12.7) (11.5-12.3)	0.080
Visa type – no. (%) New (reference) Renew	 1,415 (54.5) 1,181 (45.5)	 12.4 11.9	 6.9 7.0	 (12.0-12.7) (11.5-12.3)	0.104
Chest X-ray evaluation by radiologist-no.(%) Suspicion of TB Abnormal Not/Old TB	 1,272 (49.0) 1,324 (51.0)	 12.6 11.7	 6.5 7.4	 (12.3-13.0) (11.3-12.1)	**< 0.001**
IGRA value-no.(%) Negative (reference) Positive	 1,050 (40.5) 1,546 (59.6)	 8.6 14.6	 6.9 5.9	 (8.2-9.0) (14.3-14.9)	**< 0.001**
Sputum culture results-no.(%) No MTB MTB	 2,237 (86.2) 359 (13.8)	 11.8 14.3	 7.2 5.0	 (11.5-12.1) (13.8-14.9)	**< 0.001**
Sputum Smear AFB result-no.(%) Negative (reference) Positive	 2,517 (97.0) 79 (3.0)	 12.1 14.0	 7.0 4.8	 (11.8-12.4) (12.9-15.1)	**< 0.001**

*Total adult population screened for **mycobacterium tuberculosis in 2013.**
** Age category: younger (18-34) years, older (35-64) years.
†P value (2- sided) determined from Pearson's chi- square test and Fisher's exact test

Similarly, the Two-sample t-test used to assess the difference in mean for age, a continuous variable in the sample, showed that females were significantly younger than males and that applicants for a renewal visa were older than those applying for new visa, *(P<0.001)* (Table 4.8.6). Similarly, individuals with IGRA positive were younger than those with IGRA negative result, *(P<0.012)* (Table 4.8.6). Also, individuals with a diagnosis of MTB disease were younger than those diagnosed with non-MTB disease, *(P<0.001)* (Table 4.8.6). On the other hand, those with chest X-ray evaluation of Abnormal Not/Old TB were older than those with chest evaluation of Suspicion of TB, *(P<0.001)* (Table 4.8.6).

Table 4.8. 6: Two-sample tests of the continuous variable: Age

Table (4.8.6) Two-sample tests of the continuous variable age	**Total* (n= 2, 596)**	**Mean**	**SD**	**(95% CI)**	**P Value†**
Demographics Sex – no. (%) Male Female	 2,124 (81.8) 472 (18.2)	 36.6 34.0	 10.3 8.1	 (36.2-37.1) (33.3-34.8)	**< 0.001**
Applicant category – no. (%) A (White collar and Constructions) Bi/Bii (Maids and Drivers)/(Others)	 2,065 (79.6) 531 (20.5)	 36.6 34.4	 10.3 8.6	 (36.1-37.0) (33.7-35.2)	0.439
Tuberculin Skin Test TST-no.(%) TST (0-14) mm (reference) TST (15-40) mm	 1,371 (52.81) 1,225 (47.19)	 36.6 35.7	 10.1 9.9	 (36.0-37.1) (35.1-36.2)	**<0.021**
Visa type – no. (%) New (reference) Renew	 1,415 (54.5) 1,181 (45.5)	 33.0 39.9	 8.6 10.3	 (33.5-40.5) (39.3-40.5)	**< 0.001**
Chest X-ray evaluation by radiologist-no.(%) Suspicion of TB Abnormal Not/ Old TB	 1,272 (49.0) 1,324 (51.0)	 35.1 37.1	 9.8 10.2	 (34.6-35.7) (36.6-37.7)	**< 0.001**
IGRA value-no.(%) Negative (reference) Positive	 1,050 (40.5) 1,546 (59.6)	 36.7 35.7	 10.1 9.9	 (36.1-37.4) (35.2-36.2)	**< 0.012**
Sputum culture results-no.(%) No MTB MTB	 2,237 (86.2) 359 (13.8)	 36.7 33.2	 10.0 9.9	 (36.2-37.0) (32.2-34.2)	**< 0.001**
Sputum Smear AFB result-no.(%) Negative (reference) Positive	 2,517 (97.0) 79 (3.0)	 36.2 34.5	 10.0 10.5	 (35.8-36.6) (35.1-36.2)	0.158

*Total adult population screened for **mycobacterium tuberculosis in 2013.**
†P value (2- sided) determined from Pearson's chi- square test and Fisher's exact test

The ANOVA test showed a non-significant difference in the mean of age for gender, visa type (new vs. renew) and applicant employment category A vs. Bi/Bii. On the other hand, ANOVA test showed a significant difference in the mean of age for IGRA, the diagnosis of MTB and chest X-ray evaluation of Suspicion of TB. While holding age constant, multiple linear regression showed a non-significant association between TST and other variables including gender, visa type (new vs. renew) and applicant employment category A vs. Bi/Bii. In the study sample, factors including gender, applicant employment category, nationality, visa type and DPSCs did not show significant association in cross tabulation and did not show significant

results running the logistic regression and therefore were not included in the final analysis. The regression equation for the final analysis is:

$$\boxed{MTB = \hat{\beta}_0 + \hat{\beta}_1 agecate3 + \hat{\beta}_2 CXR\_Final + \hat{\beta}_3 IGRA\_VAL + \hat{\beta}_4 TST\_Observation + \hat{\beta}_5 AFB\_Smear\_val}$$

where the dependent variable (Y) is MTB= Mycobacterium tuberculosis categorized into two groups: (MTB= 0 when sputum culture is negative) and (MTB=1 when sputum culture is positive) and the independent variables (Xs) as follows:

agecate3= age categorized into two groups: (18-34) and (35-64) years;

CXR_Final= chest X-ray evaluation categorized into two groups: (Suspicion of TB) and (Abnormal Not/Old TB);

IGRA_VAL= IGRA results reported as: (negative) and (positive);

TST_Observation= TST results categorized into two groups: negative indurations (0-14) mm and positive indurations (15-40) mm; and

AFB_Smear_val= AFB sputum smear results reported as: (negative) and (positive).

Consistent with the previously mentioned results, older individuals (35-64) years had a lower probability of having MTB when compared to younger individuals (18-34) years (OR = 0.62; 95% CI: 0.48 - 0.81, *(P<0.001*), after adjustment for other demographic characteristics (Table

4.8). ***Therefore, as we assumed earlier, younger visa applicant carried a higher risk of TB compared to older visa applicants.***

Table 4.9 1: Crude and adjusted relative odds of MTB (2013)

Table (4.9) Crude and adjusted relative odds of MTB (2013)	**Crude**			**Adjusted***		
	RO	**95% CI**	**P value**	**RO**	**95% CI**	**P Value†**
Age category	1.00			1.00		
(18-34) years						
(35-64) years	0.55	(0.44- 0. 70)	**<0.001**	0.62	(0.48- 0.81)	**<0.001**
Chest x-ray evaluation by radiologists						
Suspicion of TB	1.00			1.00		
Abnormal Not/ Old TB	0.33	(0. 26- 0. 42)	**<0.001**	0.35	(0. 27- 0. 47)	**<0.001**
IGRA value-no						
Negative (reference)	1.00			1.00		
Positive	1.97	(1.54- 2.53)	**<0.001**	1.51	(1.14- 2.01)	**<0.004**
Tuberculin Skin Test (TST)						
TST (0-14) mm	1.00			1.00		
TST (15-40) mm	1.53	(1.39- 2.19)	**<0.001**	1.42	(1.17- 2.01)	**<0.002**
Sputum Smear AFB result-no.(%)						
Negative (reference)	1.00			1.00		
Positive	**199.98**	**(62.67- 638.13)**	**<0.001**	**190.22**	**(58.79- 615.46)**	**<0.001**

*Adjusted multiple logistic model includes age category, chest x-ray evaluation by radiologists, IGRA value, Tuberculin Skin Test and sputum smear AFB result
† P value determined from likelihood ratio tests

As expected, individuals with chest X-ray evaluation of Abnormal Not/Old TB had a lower probability of MTB when compared to individuals with a chest X-ray evaluation of Suspicion of TB group (OR= 0.35; 95% CI: 0.27 – 0.47, ***P<0.001***). (Table 4.9)

More than two-thirds of MTB cases had a positive IGRA test, ***(P<0.001***). As expected, IGRA (QFT-GIT) was significantly higher among those diagnosed with MTB compared to those without MTB which infers a possible association between positive IGRA (QFT-GIT) result and

being diagnosed with MTB (OR= 1.5; 95% CI: 1.14 - 2.01, *(P<0.004*). A similar relationship was shown for a positive TST value (15-40 mm) among those confirmed to have MTB compared to those without MTB (OR= 1.4; 95% CI: 1.17- 2.0, *(P<0.002*) (Table 4.9).

Table 4.10 shows the relationship of age groups to MTB diagnosis, IGRA and TST results.

Table 4.10: Relative odds of MTB by age category (2013)

Table (4.10) Relative odds of MTB* by age category (2013)	**Younger (18-34) years**			**Older (35-64) years**		
	RO	**95% CI**	**P value**	**RO**	**95% CI**	**P Value†**
****IGRA value**						
Negative (reference)	1.00			1.0		
Positive	**2.6**	(1.8- 3.6)	**<0.001**	1.3	(0. 9- 1.9)	0.197
Tuberculin Skin Test (TST)						
TST (0-14) mm	1.00			1.00		
TST (15-40) mm	**1.8**	(1.4- 2.6)	**<0.001**	1.5	(1.1- 2.2)	**< 0.025**

*__MTB__ mycobacterium Tuberculosis as confirmed by sputum test result "gold standard" test
*Total adult population screened for **mycobacterium tuberculosis in 2013. MTB Prevalence /Proportion is 0.14 (95% CI 0.13-0.15)**
** Interferon Gamma Release Assay (IGRA/QFT-GIT)
† P value determined from likelihood ratio tests

More than two-thirds of younger individuals (18-34) years diagnosed with MTB had a positive IGRA (QFT-GIT), ***(P<0.001)***. The odds of positive IGRA (QFT-GIT) result among MTB positive cases in the younger age group (18-34) years is 2.6, ***(P<0.001)*** which infers a possible association between positive IGRA (QFT-GIT) result and being diagnosed with MTB in younger individuals. (Table 4.10) A similar relationship is noticed for a positive TST value (15-40 mm) among younger individuals (18-34) diagnosed with MTB, *(P<0.001)* (Table 4.10). In contrast, the IGRA was not significantly associated with being an MTB case for those in the older age group and only positive TST result was significant in this age group (Table 4.10).

Conclusions

In our study, males constituted a larger percentage of visa applicants compared to females. Older individuals were more commonly found in the renewal visa category compared to younger individuals. Majority of applicants for new visa were from Pakistan, the Philippines and Indonesia while applicants for visa renewal were from Bangladesh, Ethiopia and Egypt. A higher percentage of younger individuals were working as servants and babysitters. When compared to older visa applicants, a higher percentage of younger individuals were suspected to have MTB by chest X-ray evaluation report and had positive IGRA (QFT-GIT) result.

IGRA was shown to be more sensitive than TST, but the sensitivity is reduced in the older age group. Simultaneous testing (parallel) with IGRA (QFT-GIT) and TST had a high net sensitivity (88.8%) for detecting MTB among adults. The net sensitivity of simultaneous (parallel) testing with both IGRA (QFT-GIT) and TST for the younger age group was even higher (91.6%). However, Kappa agreement between IGRA (QFT-GIT) and TST in the study is considered as only fair concordance. Chest X-ray had a good yet lower sensitivity in detecting TB among adults compared to findings in other studies. Older individuals (35-64) years had a lower probability of having MTB when compared to younger individuals (18-34) years.

Chapter 5

Introduction

Chapter 5 will provide a summary of the key findings and will provide a discussion of this study's findings in the context of the currently available literature. This chapter will initially address the implications of economic growth in the United Arab Emirates and the subsequent growth of population due to immigration. This will be followed by a reflection of the key findings of the study sample in three sections:

Section (A): *Discussion of demographic characteristics by age category*. This section will discuss the main demographic findings in the study in comparison to the reported findings internationally.

Section (B): *Discussion of the validity measures*. This section will present and discuss the validity of IGRA and TST, the predictive values and likelihood ratio. The discussion of the simultaneous testing results of our study in comparison to other studies will be addressed. Similarly, the validity measures of chest X-ray will be discussed.

Section (C): *MTB screening in relation to other investigations*. This section will discuss the main findings regarding MTB results in the study in relation to other investigations and other studies in the context of current literature.

Finally, study limitations and conclusions of main findings will be provided.

Discussion

Economic growth and immigration in the UAE

The blessing of wise leadership in the United Arab Emirates (UAE) supported by the wealth of oil contributed significantly to the rapid growth of the population and its related services in multiple sectors.[50] The UAE, therefore, captured the attention of the world as a rapidly growing country with high potential towards excellence and innovation.[50] For the past 40 years, a significant economic growth in the United Arab Emirates in several sectors including the petroleum, construction and healthcare industries.[50] Rapid industrialization was therefore brought by and supported by the recruitment of foreign expertise and manpower from all over the globe to satisfy the rapid demand of the economic and industrial development.[50] To satisfy the manpower demands of numerous projects, e.g., in the construction and service industries, low skilled or unskilled laborers were often recruited from less developed countries.[50]

The United Arab Emirates' culture is based on the family as the core element in the community. The extended family had constantly been the source of security and vitality of the Arabian tribes in the country. In the past, the members of an extended family used to share the same house. In recent years and due to the growth in of the local population, and subsequently a growth in the demand for servants and drivers, each family would have its own house. However, individuals of the same family would be neighbors in order to protect the intimacy of family relationships.

Section (A): Discussion of demographic characteristics by age category

As a result of the rapid economic growth and the urbanization of the local families in the country, the UAE population had increased considerably expanding from 4.1 million in 2005, to an estimated 8.3 million in 2010, mostly owing to the high net inward migration of expatriate

workers.[50] In 2014, UAE nationals in the emirate of Abu Dhabi were only 18% of the 2.76 million residents.[18]

The United Arab Emirates is recognized for its highly diverse population where only 10% are UAE nationals and the rest is made up of expatriates.[51, 52] Globally, the UAE was ranked as a country with the highest gender imbalance with a male/female ratio of 2.2, or 2.75 for the 15-65 age group.[52] In our study, males constituted the largest percentage of visa applicants compared to females 81.8% vs 18.2% and male/female ratio of 3.8 for the (18-34) age group and 5.5 for the age group (35-64) which exceeds the reported ratios reported above. In our study, a higher percentage of younger individuals were found among those applying for a new residency visa while older individuals were more predominantly in the renewal category.

A cross-sectional study that recruited immigrant females 18 years and older in Al- Ain to study the prevalence of diabetes among immigrant females according to their residency duration reported that females from South Asia and the Philippines comprised a significant proportion of immigrants that were typically employed as housemaids (female servants responsible for common household work).[53] In our study, the percentage of younger vs. older applicants was almost comparable among the majority of occupations yet a higher percentage of younger individuals were employed as servants and babysitters mainly from Ethiopia, Indonesia, and the Philippines.

UAE ranked as having the 7th highest net migration rate in the world where the majority was from South Asian countries (58%) followed by other Asians (17%) and expatriates from western countries (8.5%).[52] The findings in our study were consistent with the data from the WHO as

almost half of the visa applicants were from the South East Asian Region. In our study, nearly two-thirds of males in the sample were from Pakistan and India while almost 50% of females were from the Philippines.

In a study conducted among immigrant applicants in Vietnam bound for the United States, there were considerably fewer adult applicants who had evidence of TB on chest X-ray (22%) than those who had a positive TST result (58%) or a positive QFT- GIT (28%).[54] Accordingly, the previous study reported that their screening algorithm had lost a considerable number of LTBI undetected, untreated, and at increased risk of subsequent active TB.[54]

Similarly, a higher percentage of younger individuals in our study were suspected to have MTB by chest X-ray evaluation reports and a higher percentage of positive IGRA/TST test results occurred among them compared to older individuals. Moreover, in the younger age category with the diagnosis of MTB, (54.2%) had evidence on chest X-ray compared those who had a positive IGRA (QFT-GIT) (59.6%), a smaller difference compared to the findings of the study done among the immigrant applicants in Vietnam bound for the United States.

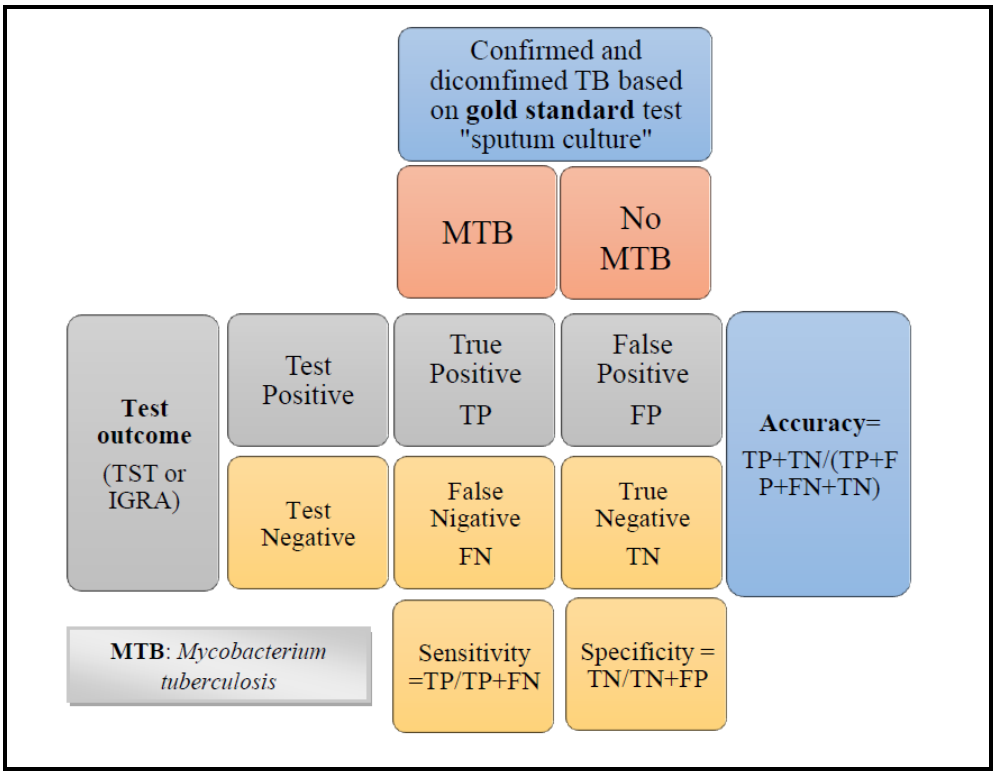
Section (B): Discussion of the validity measures

A. The Validity of IGRA (QFT-GIT) and TST

Sensitivity of a test in the study was defined as the proportion of individuals with a positive test (IGRA/TST) result among those with positive sputum culture test for tuberculosis, and specificity was defined as the proportion of individuals with a negative test (IGRA/TST) result

among those who had active tuberculosis disease ruled out (i.e., a negative sputum culture test for tuberculosis) (Figure 5.1).

Figure 5. 1: Validity measures



In a systematic review focusing on individuals living in low- and middle-income countries, the highest-quality evidence from individuals with suspected tuberculosis demonstrated a sensitivity of 69%–83% and specificity of 52%–61% for IGRAs in the diagnosis of active tuberculosis. [37]

De Keyser, De Keyser, and De Baets explored a meta-analysis based on data derived from a systematic literature review to examine the value of TST versus two types of IGRAs in the diagnosis of TB infection.[15] They included 11 studies that compared the sensitivity and specificity of TST and QFT-GIT.[15] Azghay et al. used retrospective data obtained from patients admitted with pulmonary or extra-pulmonary TB in a high TB prevalence region in France to

analyze the performance of the QuantiFERON-TB Gold In-Tube assay (QFT-GIT) in the diagnosis of tuberculosis disease.[23]

The sensitivity of IGRA (QFT-GIT) obtained in our study 72.7% (95% CI: 68.8-77.2) was similar to (yet slightly lower) the sensitivity reported by the previously mentioned studies: De Keyser, De Keyser, and De Baets found a pooled sensitivity of 75% while Azghay et al. found a sensitivity of 85% (Figure 5.2 and Figure 5.3).[15, 23]

De Keyser, De Keyser and, De Baets reported a higher pooled sensitivity of IGRA (QFT-GIT) [75% (95% CI: 61–86)] compared to the pooled sensitivity of TST [64% (48–78)].[15] Similarly, in our study, IGRA (QFT-GIT) sensitivity is higher than TST (Table 5.1) and (Figure 5.2 and Figure 5.3).

Figure 5. 2: IGRA validity measures

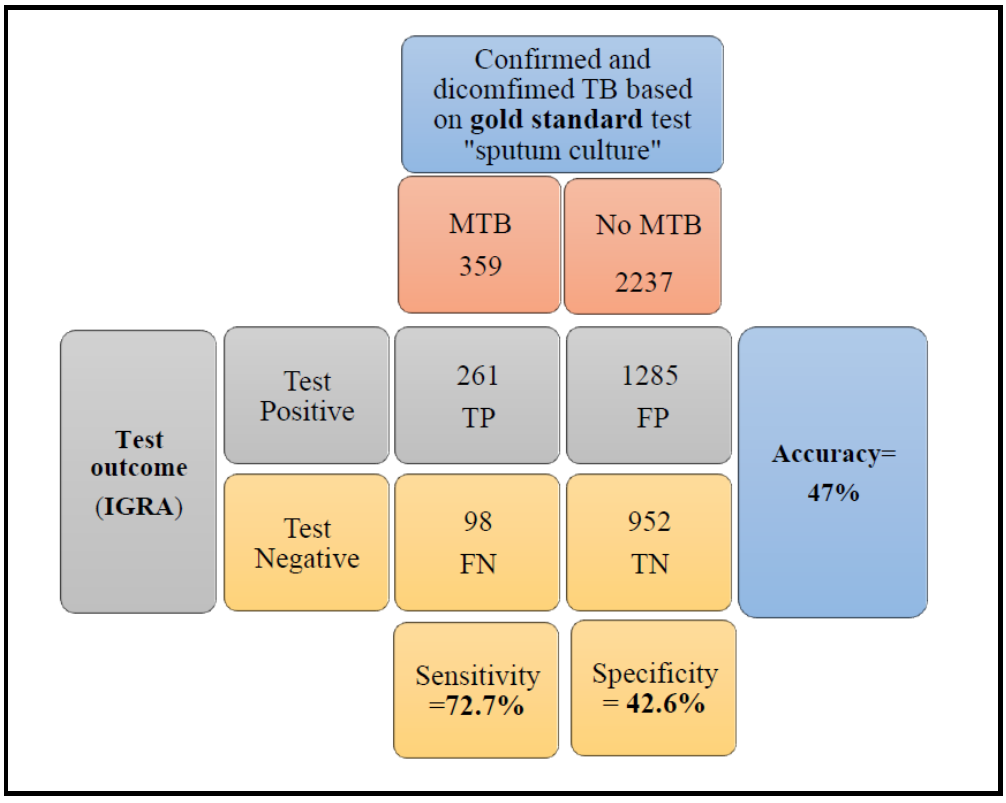


Figure 5. 3: TST validity measures

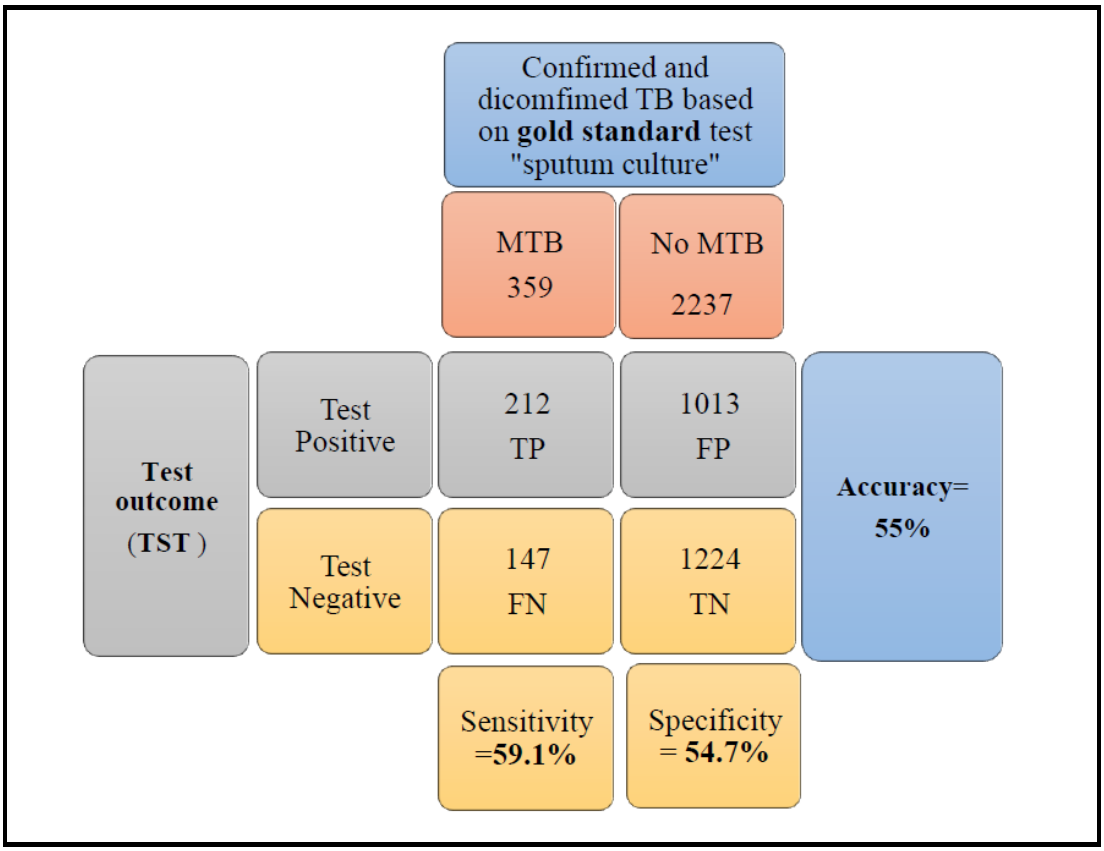


Table 5. 1: IGRA and TST sensitivity in selected independent variables

Table (5.1) IGRA and TST sensitivity in selected independent variables	***IGRA sensitivity** % (95%CI)	**Tuberculin Skin Test (TST) sensitivity** % (95%CI)
Demographics Sex		
Male	71.6% (66-77)	58.5% (53-64)
Female	**78.3%** (66-88)	61.7% (48-74)
Applicant age category		
Younger (18-34)	**78.1%** (72-83)	61.4% (55-68)
Older (45-64)	62.7% (54-71)	54.8% (46-64)
Applicant category		
A (White collar and Constructions)	69.6% (64-75)	60.1% (54-66)
Bi/Bii (Maids and Drivers)/(Others)	**86.4%** (76-94)	54.6% (42-67)
Nationality**		
SEAR(reference)	70.5% (63-77)	63.1% (55-70)
AFR / EMR	**76.7%** (69-84)	54.9% (46-64)
WPR/ EUR/ AMR	70.0% (55-82)	56.0% (41-70)
Visa type		
New (reference)	**74.1%** (68-80)	62.2% (55-69)
Renew	70.9% (63-78)	55.1% (47-63)
Chest X-ray evaluation by radiologist		
Suspicion of TB	67.7% (62-73)	59.1% (53-65)
Abnormal Not/Old TB	**85.3%** (77-92)	58.8% (49-68)
Sputum Smear AFB result		
Negative (reference)	**70.3%** (65-74)	60.8% (55-67)
Positive	81.6% (71-90)	52.6% (41-64)

* Interferon Gamma Release Assay (IGRA/GFT-GIT)
** SEAR: WHO South East Asia Region, EMR: WHO Eastern Mediterranean Region, AFR: WHO African region, WPR: WHO Western Pacific Region, EUR: WHO European Region, AMR: WHO region of America

In our sample, IGRA is more sensitive among females compared to males yet TST is of a comparable sensitivity (Table 5.1). Similarly, IGRA is more sensitive among younger visa applicants compared to older visa applicants and IGRA is more sensitive than TST among the visa applicants for administration and sales, construction and workers, technicians, drivers and guards, servants and babysitters.

In our sample, IGRA is more sensitive among visa applicants from Pakistan, Bangladesh, and Indonesia. In addition, IGRA is slightly more sensitive among visa applicants in AFR/EMR regions compared to SEAR and other regions. TST, on the other hand, is of a lesser sensitivity in all WHO regions and is of lesser sensitivity when compared to IGRA. When looking at the visa status for applicants in our sample, IGRA is slightly more sensitive among new visa applicants compared to renewal applicants. TST, on the other hand, is of lesser sensitivity than IGRA and TST is more sensitive among new visa applicants compared to renewals (Table 5.1). A retrospective study comparing two screening strategies for TB contact tracing was conducted at the TB Unit in Barcelona (Spain) between January 2006 and December 2010 added proof on the advantage of implementing QFT-GIT to target BCG-vaccinated contacts for preventive therapy.[55] The approach mentioned by Muñoz et al. reduced the exposure to unnecessary prophylactic treatment without increasing the risk of consequent active TB.[55] With a higher sensitivity of IGRA (QFT-GIT), fewer false-negative results are expected. Consequently, including IGRA (QFT-GIT) in screening algorithms should lead to fewer missed cases of LTBI and therefore, a lower risk of developing active TB infection. [23]

Although IGRA (QFT-GIT) sensitivity is higher than that of TST, the IGRA test cannot be used alone to 'rule out' active tuberculosis due to inadequate sensitivity.[23] It was concluded by two systematic reviews that in adults IGRAs must not be used in the diagnostic investigations of active TB since a positive IGRA result might not indicate active TB and similarly, a negative IGRA result might not rule out active disease. [35]

IGRA tests cannot distinguish between active TB and LTBI and therefore the specificity tends to be low in a high prevalence of LTBI.[33, 37] IGRA (QFT-GIT) specificity in our study (42.6%, (95% CI: 40.5-44.6)) (Figure 5.2) was lower than what was reported by De Keyser, De Keyser, and De Baets (71%) and Azghay et al. (73%) and therefore cannot be used to 'rule in' active disease.[15, 23]

De Keyser et al. reported that the pooled specificities were similar for IGRA (QFT-GIT) and TST [71% (62–80) versus 70% (95% CI: 57–81)].[15] However, the specificity of IGRA (QFT-GIT) was lower than TST in our study (Table 5.2 and Figure 5.2 and Figure 5.3). This may be attributed to the current latent TB (LTBI) and or old TB in the study since among individuals have not been proven not to have MTB, 55% of individuals with a chest X-ray evaluation of abnormal Not/Old TB had positive IGRA (QFT-GIT) (i.e., indicating either latent or old disease).

Table 5. 2: IGRA and TST specificity in selected independent variables

Table (5.2) IGRA and TST specificity in selected independent variables	***IGRA specificity** % (95%CI)	**Tuberculin Skin Test (TST) specificity** % (95%CI)
Demographics Sex		
Male	41.4% (39-44)	54.9% (53-57)
Female	**47.6%** (43-53)	53.9% (49-59)
Applicant age category		
Younger (18-34)	**41.8%** (39-45)	53.7% (51-57)
Older (45-64)	43.3% (40-46)	55.8% (53-59)
Applicant category		
A (White collar and Constructions)	42.4% (40-45)	56.0% (53-57)
Bi/Bii (Maids and Drivers)/(Others)	**43.0%** (38-48)	53.8% (49-58)
Nationality**		
SEAR(reference)	45.7% (43-47)	53.7% (51-57)
AFR/EMR	36.9% (34-40)	54.9% (52-58)
WPR/ EUR/AMR	47.6% (42-53)	57.4% (52-63)
Visa type		
New (reference)	40.5% (38-43)	53.4%(51-56)
Renew	45.0% (42-48)	56.3%(53-59)
Chest X-ray evaluation by radiologist		
Suspicion of TB	43.1% (40-46)	51.8% (49-55)
Abnormal Not/Old TB	42.1% (39-45)	57.1% (54-60)
Sputum Smear AFB result		
Negative (reference)	42.6% (41-45)	54.7% (53-57)
Positive	**0%** (0.0-70)	33.3% (1.0-91)

* Interferon Gamma Release Assay (IGRA/GFT-GIT)
** SEAR: WHO South East Asia Region, EMR: WHO Eastern Mediterranean Region, AFR: WHO African region, WPR: WHO Western Pacific Region, EUR: WHO European Region, AMR: WHO region of America

In addition, in our study TST was lower when age was increasing, *(P<0.004)*. This was further supported by the Spearman's correlation coefficient test that confirmed that reduction in TST as age was increasing, *(P<0.01)*. In our study TST was more sensitive among younger visa applicants (62.4%), *(P<0.001)* compared to older visa applicants (54.8%), *(P<0.024)*.

B. Discussion of the predictive values of IGRA and TST

In our study, we assessed the positive predictive value (PPV) and the negative predictive value (NPV) of TB disease for IGRA (QFT-GIT) and TST in individuals who applied for the residency

visa in the emirate of Abu Dhabi in 2013.When considering the predictive values of IGRA (QFT-GIT) in our study, among individuals who tested positive only 16.9% actually had the disease and for those who tested negative, 90.7% did not have the disease. Similarly, when considering TST predictive values in our study, among individuals who tested positive only 17.3% actually had the disease and for those who tested negative, 89.3% did not have the disease.

Though the NPV of IGRA in our study was high, this is not sufficient to 'rule out' the disease as one in 10 non-MTB cases will be missed for MTB. The PPV of IGRA was low in a study conducted in Poland to assess the validity IGRA and TST among culture negative and culture positive TB patients.[40] According to Wlodarczyk et al., the low PPV of IGRA signifies the need of using it in combination with other diagnostic methods for the diagnosis of active TB.[40] Similarly, the PPV of IGRA (QFT-GIT) and TST are relatively low in our study.

C. Discussion of the Likelihood ratio of IGRA and TST

The Positive likelihood ratio (PLR) for IGRA (QFT-GIT) and TST were similar (1.3). Thus, positive IGRA (QFT-GIT) and positive TST results are 1.3 times more likely in individuals with MTB as compared to those without MTB. Negative likelihood ratio (NLR) for IGRA (QFT-GIT) and for TST are (0.6 and 0.7) respectively. Therefore, negative IGRA (QFT-GIT) results are 0.6 times as likely in individuals with MTB as compared to those without the disease and negative TST results are 0.7 times as likely in individuals with MTB as compared to those without the disease. The positive and negative likelihood ratios of both tests are quite small and did not add

to the usefulness value for the diagnosis of active TB (Table 4.3). Both IGRA (QFT-GIT) and TST, therefore, have a limited utility in 'ruling out' or 'ruling in' active TB.

In this study, the positive likelihood ratio (PLR) for IGRA (QFT-GIT) is 1.3, quite lower than the PLR reported by Azghay et al. (PLR was 3.2).[23] While the negative likelihood ratio (NLR) in the study 0.64 is slightly higher than the finding of Azghay M. (PLR was 0.2).[23] Therefore, IGRA (QFT-GIT) test must not be requested routinely for the diagnosis of active TB as the positive and negative likelihood ratios, 1.3 and 0.64 respectively, are small and cannot add to the usefulness value for the diagnosis of active MTB. A similar rule is applicable for TST test as well. These findings are similar to what was reported in the literature in the small number of predictive studies where authors concluded that both IGRA and TST are not highly accurate at predicting active TB infection. [15] In our study as well, the accuracy of IGRA (QFT-GIT) and TST in predicting active TB disease is low (47% and 55%, respectively) (Figure 5.2 and Figure 5.3).

D. Discussion of simultaneous (parallel) test: IGRA (QFT-GIT) and TST

In the present study, the sensitivity of simultaneous (parallel) test of IGRA (QFT-GIT) and TST is 88.8%. The sensitivity increased to 91.5% when the parallel test was applied to the younger individuals (18-34) years. The result is similar to the finding reported by Azghay et al. who found a sensitivity of 92.6% (95% CI: 74–99) when using the combined QFT-GIT and TST tests.[23]

E. Discussion of Kappa agreement between IGRA (QFT-GIT) and TST

The use of Pearson's r (correlation coefficient) may result in a poor reflection of the agreements between raters (tests) resulting in extreme over or underestimations of the true level of agreement between raters (tests).[56] The Kappa statistic, in contrast, is an index used widely for assessing agreement between raters/tests when the outcomes are categorical measures as it increases the precision of estimates of the association between tests by controlling for random agreement.[56, 57]

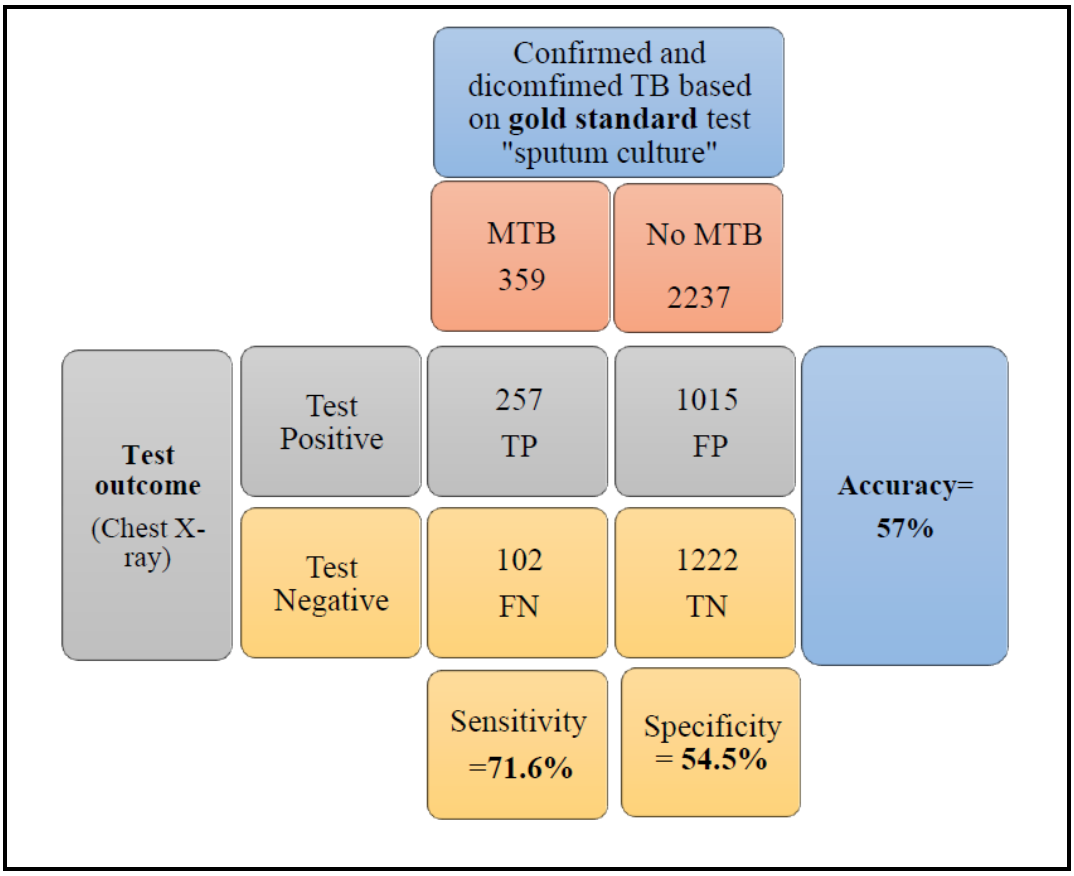
In a study among immigrant applicants in Vietnam bound for the United States, the prevalence of MTB infection (both TB and LTBI) based on TST or the QuantiFERON-TB Gold test reported Kappa of 0.24 (0.19–0.28), poor agreement.[55] In our study, Kappa agreement between IGRA (QFT-GIT) and TST was 0.33 (95% CI: 0.29-0.36) which is considered as only fair concordance and even better than what was reported by Chuke et al.[55] Positive TST and IGRA negative discordance had been attributed to false-positive TST results as a result of BCG vaccination or non-tuberculous mycobacteria (NTM) exposure.[54] On the other hand, in immune suppression, a lower TST sensitivity is noticed and negative TST yet positive IGRA discordance had been reported.[54] Among low-risk healthcare workers, false-positive IGRA results were described.[54]

F. Discussion of the validity of chest X-ray

A case-control study conducted on a cohort of migrants in Australia showed that chest X-ray at migration had limited sensitivity for the prediction of subsequent TB.[33] According to Linh and Marks, almost one-third of all consequent cases of TB and one-quarter of consequent cases of pulmonary TB occurred in individuals whose initial chest X-rays were reported as normal or near normal.[33]

Chest radiography has good sensitivity yet poor specificity when utilized for the diagnosis of pulmonary TB.[32] In a study done in Kenya assessing the performance of chest X-ray in all suspects of tuberculosis (using the sputum culture as the gold standard test), the sensitivity/ specificity/ PPV/ NPV of the score 'any pathology' were 92% (95% CI: 90–94), 63% (95% CI: 58–67), 76% (95% CI: 73–79) and 86% (95% CI: 82–90), respectively.[41] In our study, the sensitivity and specificity of chest X-ray are 71.6% (95% CI: 66.6–76.2) and 54.6% (95% CI: 52.5–56.7), respectively are lower than what was reported in the literature (Figure 5.4). *Therefore, we still consider that chest X-ray has good sensitivity in detecting TB among adults during the screening for visa purposes as we assumed earlier* yet the role of chest X-ray in our study was not adequate due to low sensitivity and modest accuracy (Figure 5.4).

Figure 5. 4: Chest X-ray validity measures



Despite the presence of a radiological form provided by DOH/HAAD for the radiologist to follow, the final chest X-ray evaluation by the radiologist is largely subjective (Appendix 3.12). Identification of radiological features that are most sensitive and specific for predicting consequent TB would aid in the effective and efficient implementation of a radiographic screening program for detecting individuals at higher risk of subsequent reactivation of TB.[33] Radiologists working in screening centers need to receive unified, common training. The establishment of a concise chest X-ray scoring system related to tuberculosis is needed to increase the sensitivity of the current radiological evaluations. A high negative predictive value had been reported for Chest X-ray indicating the presence of active TB.[32] In our study, when

considering chest X-ray predictive values, among individuals who tested positive only 20.2% actually had the disease and for those who tested negative, 92.3% did not have the disease.

Section (C): MTB screening in relation to other investigations

As mentioned earlier, a significant number of immigrants to Abu Dhabi fall in the age range of 20-40 years old are employed in the construction fields. Our study, however, did not show significant association with the diagnosis of MTB in relation to factors such as gender or nationality and application categories (group A: (white collars and construction), group Bi: (maids and drivers) and group Bii: (food handlers and hygienic staff)). Similarly, our study found that visa type of residency application (whether applying for a new visa or a renewal) did not show a significant association with the diagnosis of MTB.

The findings in our study were consistent with the data from the WHO where two-thirds of MTB cases were among males and the majority of cases came from countries of the South East Asia region. In addition, almost half of MTB cases occurred among applicants working in construction and were employed as workers, laborers or cleaners and helpers. When the applicant category grouping was used instead of occupation we noticed that more than 80% of MTB cases occurred in group A: (white collar and construction).

A nested case-control study conducted on a cohort of migrants with an increased risk of tuberculosis in Australia between 1984 and 2003 reported a higher percentage of TB cases (57%) among younger migrants (<25-44) years-old compared to (37%) TB cases identified among older migrants (45-64) years-old.[33] Similarly, in our study, more than 50% of immigrants fall into the younger age group (18-34) years and around two-thirds of MTB cases occurred among them and

the mean age among MTB cases is 33.2 (SD ±9.9) years. Therefore, more attention shall be directed towards finding the best screening algorithm to accelerate case detection and possible dormant infection among residency applicants eligible for chemoprophylactic therapy in the younger visa applicants.

A study In Japan enrolled bacteriologically confirmed active TB patients and healthy volunteers assumed to be uninfected with *Mycobacterium tuberculosis* as controls. The study evaluated the diagnostic performance of QFT-Plus in comparison to that of QuantiFERON-TB Gold In-Tube (QFT-GIT) and the sensitivity in the TB patients and specificity in the healthy volunteers were obtained.[58] The study found that IFN-γ values were significantly reduced with age in QFT-GIT (P = 0.035).[58] Similarly, in Poland, a study was conducted to assess the validity of IGRA and TST among culture negative and culture positive TB patients; they reported that "IGRA sensitivity was age-dependent and a higher sensitivity of the test was observed among younger patients than those aged older than 60 years".[40] In our study, among the younger age group IGRA (QFT-GIT) sensitivity was 78.1%, (95% CI: 72.3- 83.3). IGRA (QFT-GIT) sensitivity was better than TST sensitivity and was even better than IGRA (QFT-GIT) sensitivity in the older age group in the study.

The debate as to which indirect tests for TB are optimal in screening programs continues, in part due to inconsistent results of sensitivity tests for IGRA and TST across tests and populations.[35] In low-incidence TB settings, the use of IGRAs is increasingly recommended yet there is no consistency in the recommendations on how to use it.[35] Conversely, TST is still favored in high

incidence and low-resource countries since there is no strong evidence that IGRAs are superior to the TST in such settings, particularly when taking into consideration the significantly higher costs associated with the IGRA.[35]

In addition, there was no reliable evidence that IGRA was more sensitive than the TST for the diagnosis of active tuberculosis.[37] In a meta-analysis of studies in low-income and middle-income countries assessing the use of IGRAs for active TB, the pooled sensitivity in HIV-infected patients was 60% for the QFT-GIT compared with 69% for QFT-GIT in non-HIV-infected patients.[37] The specificity of IGRA was low for non-HIV-infected individuals (QFT-GIT 52%) as well as for HIV-infected individuals (QFT-GIT 50%).[35, 37]

Those results were further confirmed by another meta-analysis assessing studies from both high-incidence and low-incidence countries, including children and HIV-infected individuals especially the low specificity in individuals with suspected TB.[59] In brief, both systematic reviews concluded that IGRAs should not be used in the diagnostic investigations of active TB in adults since "a positive IGRA result may not indicate active TB and similarly, a negative IGRA result may not rule out active disease".[59] A good number of guidelines reveal these limitations of IGRAs in respect to the diagnosis of active TB (Table 5.3).[35] When IGRAs are recommended for the diagnosis of active TB, they are obviously considered only as an adjunct test in addition to, yet not replacing, the standard radiographic and microbiological tests.[35]

Table 5. 3: Guidelines on IGRAs: recommendations for active tuberculosis

Recommendation	Subgroup	Guideline or position statement[a]
For the use of IGRAs but only as an adjunct (some guidelines specify the use only when other diagnostic tests have been unrevealing)	In adults	ECDC, USA-CDC, UK, France (only for extrapulmonary TB), Australia, Slovakia, Japan, the Netherlands, Norway, Bulgaria, Portugal, Denmark, Austria
	In children	ECDC, Canada, USA (CDC and AAP), UK, Switzerland, Australia, Slovakia, Japan (children >12 years of age), Saudi Arabia, the Netherlands, Norway, Bulgaria, Portugal, Croatia, Denmark, Austria
Against the use of IGRAs	In adults	WHO, Canada, Switzerland, Saudi Arabia, Croatia, Ireland, South Korea, Brazil
	In children	WHO, France, Ireland, South Korea, Brazil
No recommendations		Germany, Italy, Spain, Finland, Poland, Czech Republic

AAP, American Academy of Pediatrics; CDC, US Centers for Disease Control and Prevention; ECDC, European Centre for Disease Prevention and Control; IGRA, interferon-gamma release assay; TST, tuberculin skin test; WHO, World Health Organization.
[a]Some countries/organizations are listed more than once because their recommendations vary across risk groups.

Reference: Denkinger, C., Dheda, K. and Pai, M. (2011). Guidelines on interferon-γ release assays for tuberculosis infection: concordance, discordance or confusion?. *Clinical Microbiology and Infection*, 17(6), pp.806-814.

Sester et al. compared TST and IGRA in individuals using active TB infection as a substitute for LTBI.[15, 59] They concluded that IGRAs are more sensitive than TST and that IGRAs have limited accuracy in diagnosing active TB.[59] It is important therefore to present such evidence in guidance documents to ascertain that the assays are only applied in diagnostic algorithms where they are of established accuracy.[59] According to the Sester et al. systematic review, the sensitivity of IGRAs performed on blood is superior to that of TST in patients with active TB, yet the low specificity may indicate a limited value of IGRAs to differentiate between individuals with LTBI from individuals with active disease.[59]

Imaging has a significant role in the diagnosis and treatment options of active tuberculosis.[34] Radiographic screening serves a primary purpose for tuberculosis as it guides the detection of possible cases of the active pulmonary disease in need for further evaluation and management.[34]

The presence of cavitations in imaging, for example, will influence treatment decisions such as the length of a course of therapy required to cure an individual of the active disease.[34]

In addition, imaging has a crucial role in risk stratification as it provides a guide to distinguish between latent infection, previous inactive disease, and active disease.[34] The presence of unique fibro-nodular lesions in upper zones of the lung and the presence of parenchymal infiltrates are both associated with subsequent active TB.[33] A significant predictor for TB in imaging is linked to the size of the lesion area.[33] Larger lesion areas in imaging are associated with an increased risk of TB compared with individuals with a normal chest X-ray or those with small lesions.[33] In the literature, minor findings consistent with past primary infection do not indicate an increased risk of consequent tuberculosis and shall not be used for further surveillance.[33] This was demonstrated in our study results as more than two-thirds of confirmed MTB cases occurred among those with a chest X-ray evaluation of Suspicion of TB. In addition, our study found that applicants with a chest X-ray evaluation of abnormal Not/Old TB group had a lower probability of MTB compared to those with a chest X-ray evaluation of Suspicion of TB. A new radiological scoring system for the visa screening standards in Abu Dhabi is needed to enhance the sensitivity of chest X-ray evaluation of tuberculosis by radiologists. The provision of unique training workshops to help establish the basis of a solid and unified reporting system among radiologists is also required.

Study limitations

In our study, several limitations need to be addressed. First, the limited budget influenced the choice of study to be conducted (cross-sectional study with a statistical control group). There is a

threat to the external validity of the study given that the participants are self-selected, the results cannot be generalized to those who decided not to participate (e.g., by not applying for a residency visa in Abu Dhabi) or to other similar geographical areas. Sample size and the absence of a true control group were other threats to the external validity of the study. Second, information about smoking history, co-morbidities such as diabetes and cancer, alcohol intake and IGRA (QFT-GIT) quantitative measurements were not available. Analysis including the previously mentioned risk factors would add to the richness of the study and would provide more information to be utilized in TB/LTBI screening and to be better management plans. Third, the merging between individuals with Abnormal Not TB chest X-ray evaluation and abnormal old TB chest X-ray evaluation in one group due to limited numbers is another limitation in the study. Future studies to explore each category separately are therefore needed. Finally, secondary analysis of the 281 cases with MOTT was not feasible and the inclusion of those cases is, therefore, advised in future studies for comparison purposes.

Conclusions

The United Arab Emirates is recognized for its highly varied population and a very high gender imbalance. Moreover, it was ranked as the 7th highest net migration rate in the world, mostly originating from South Asian countries. A higher percentage of younger individuals were applying for a new residency visa while older individuals were more predominantly seen in the renewal category. Similarly, a higher percentage of younger individuals were employed as servants and babysitters mainly from Ethiopia, Indonesia, and the Philippines.

The sensitivity of IGRA (QFT-GIT) obtained in our study 72.7%, (95% CI: 67.8-77.2) is similar to (yet slightly lower) the sensitivity reported by other studies and IGRA (QFT-GIT) is more

sensitive than TST. Though the NPV of IGRA (QFT-GIT) in our study is high, it is insufficient to 'rule out' the disease as one in 10 non-MTB cases will be missed for MTB. The positive and negative likelihood ratios of both tests are small and did not add to the usefulness value for the diagnosis of active TB. Both IGRA (QFT-GIT) and TST, therefore, have a limited utility in 'ruling out' or 'ruling in' active TB.

In our study, the sensitivity of simultaneous (parallel) tests using IGRA (QFT-GIT) and TST is 88.8%. The sensitivity had even increased to 91.5% when the parallel test was applied to the younger individuals (18-34 years). However, Kappa agreement between IGRA (QFT-GIT) and TST was 0.33 and (95% CI: 0.29-0.36) which is considered as only fair concordance. False-positive TST results due to BCG vaccination or non-tuberculous mycobacteria (NTM) exposure can explain the discordance of results (positive TST and negative IGRA (QFT-GIT)). In our study, the sensitivity and specificity of chest X-ray are 71% (95% CI: 67–76) and 55% (95% CI: 53–57) respectively, lower than what was reported in the literature. Though the NPV of chest X-ray in our study was high yet this is not enough to 'rule out' the disease. Therefore, the establishment of a concise chest X-ray scoring system related to tuberculosis is needed to increase the sensitivity of the current radiological evaluations.

In our study, two-thirds of MTB cases are males and the majority of cases are from countries of the South East Asia region. In addition, almost half of MTB cases occurred among applicants working in construction and were employed as workers, laborers or cleaners and helpers. Our study is a cross-sectional study with a statistical control group that explored several possible associations between MTB and age categories yet future studies are required to explore the

association of MTB with other risk factors such as smoking and diabetes in the same population. The significant association between younger age and MTB among the screened individuals, therefore, might be further explored by further future studies. This can be followed by cost-effectiveness analysis of treating latent tuberculosis infection among screened individuals as a future step towards MTB control.

Chapter 6

Introduction

Chapter 6 will provide a highlight of possible policy implications and recommendations in 4 sections:

Section (A): Awareness of Mycobacterium tuberculosis infection. This section will provide recommendations 1 and 2 to raise the awareness of the Mycobacterium tuberculosis infection among different target groups such as clinicians, visa applicants, sponsors and owners of companies in Abu Dhabi.

Section (B): Smoking cessation clinics. This section will provide recommendation 3 to establish smoking cessation clinics.

Section (C): Upgrading the current visa screening services. This section will provide recommendation 4, 5, and 6 to highlight the role of IGRA and TST simultaneous testing in LTBI screening among visa applicants. The screening for diabetes among adults applying for renewal residency visa will be addressed too. Finally, the importance of the healthy working environment for laborers, helpers and, workers will be emphasized.

Section (D): Children at higher risk of MTB**.** This section provides recommendation 7, and 8 to highlight BCG vaccination among children under 5 years of age and early detection of LTBI among university students.

Policy implications and recommendations

Section (A): Awareness of Mycobacterium tuberculosis infection

Recommendation 1: Enhance the current awareness of Mycobacterium tuberculosis infection early diagnosis and management among clinicians and healthcare providers in public and private sectors and correctional residential institutes in Abu Dhabi

Raising the awareness, among clinicians and healthcare providers in Abu Dhabi, regarding *Mycobacterium tuberculosis* infection risk can occur through focus groups and training workshops. The training should initially focus on the perceived severity of *Mycobacterium*

tuberculosis infection at global and local levels. The correct perception of disease burden is intended to motivate clinicians during their practice to collaborate with the efforts of the WHO to reach the End of TB strategy goals. In addition, the training should highlight the benefits of early detection and management of the disease. The information provided through the training workshops such as the proper duration of treatment regimens or how to choose the proper screening test for LTBI will establish the self-confidence and the required abilities among clinicians to practice efficiently. This will eventually help clinicians to achieve and maintain the ultimate goal of preventing the development of new TB disease among high-risk groups. In addition, clinicians will be actively involved in the prevention of the development of multidrug resistance (MDR) due to non-compliance among those receiving the treatment for TB. Moreover, barriers to care provision can be overcome through continuous and transparent feedback, reassurance and support from the DOH/HAAD and the senior management in healthcare centers.

Recommendation 2: Enhance the current awareness of Mycobacterium tuberculosis infection early management and the importance of embracing a healthy lifestyle in the community

The involvement of the visa applicants, the sponsors and the owners of companies is crucial at the initial stage to establish the understanding and the consensus on the importance of efforts aiming at minimizing the risk of *Mycobacterium tuberculosis* in the community. Therefore, the awareness of TB/LTBI needs to be emphasized initially among those stakeholders so that they can actively collaborate in passive tuberculosis case-finding and the initiation of early interventions. This can be achieved by specific messages addressing TB/LTBI risk and raising

the passion towards embracing healthy lifestyles among members of the community. Short video and internet messages, posters, illustrated awareness pamphlets and roll up banners in different languages (Arabic, English, and Hindi, Urdu, Bengali and Indonesian, Nepali and Amharic) can all be utilized for this purpose. Media would play a vital role in the modification of some of the predisposing behavioral factors in the community to support and motivate embracing healthy lifestyle changes among specific groups (such as young adults, those with diabetes, smokers, and alcohol consumers).

Section (B): Smoking cessation clinics

Recommendation 3: Establishment of smoking cessation clinic targeting clients in the Disease Control section and occupational clinics

The number of TB cases is expected to inflate in the future as a result of the growing population particularly in countries like India and China.[42] Moreover, the risk of progression to TB disease in these endemic countries will also increase as a result of high smoking rates along with rising rates of diabetes.[42] Therefore, it is advocated to consider interventions such as smoking cessation and early screening for TB in such situations.[42]

In Abu Dhabi, collaborative efforts are needed to in order to face the challenge of smoking among different community members. Policy makers and the DOH/HAAD can support the establishment of smoking cessation clinics in the government sector under mandated insurance programs. The provision of smoking cessation services linked to the visa screening process and to occupational clinics need to be integrated with efforts targeting early detection of TB/LTBI infection. An intense mass media campaign along with as a well-organized community-based

preventive program is needed to boost the effectiveness of the smoking cessation services and TB/LTBI management efforts in the community. The current anti-smoking media messages need to be revised to assess for defects and the future messages need to be designed cautiously for the intended audience. The material about smoking dangers in the current visa screening centers, occupational clinics, and private sector shall be assessed as well. Regular measurement and assessment of major outcomes in the smoking cessation clinic along with TB/LTBI successful treatment completion rates are also needed to monitor the progress of the proposed interventions.

Section (C): Upgrading the current visa screening in Abu Dhabi

Recommendation 4: Upgrading the current visa screening process to detect LTBI among high-risk groups

In high-incidence settings, TB is frequently the result of a new acquisition of *Mycobacterium tuberculosis* while in low-incidence countries a large proportion of TB disease is the result of reactivation of latent TB.[35] Therefore, in low-incidence countries, the detection and management of LTBI is a key component of TB control.[35] The attention should be directed towards treating latent infection in those individuals who present in the migration setting if not provided earlier in their home countries. Detecting and treating LTBI among individuals applying for residency is a priority in low-incidence countries such UAE. The integration of LTBI screening with the current active TB screening is therefore required. The visa screening program in the Emirate of Abu Dhabi will be most productive and efficient by the integration of LTBI screening mainly among the high-risk population, namely those who are young immigrants applying for residency.

Although it is costly to add the IGRA (QFT-GIT) to a screening program, it has an added value and can be requested for young immigrants applying for residency.[15] The integration of IGRA (QFT-GIT) test along with chest X-ray and sputum culture test for the screening of young individuals applying for residency might be a suggested step towards minimizing the risk of missed LTBI cases. The implementation of IGRA (QFT-GIT) test can aid in the detection of cases eligible for LTBI chemoprophylactic treatment. Moreover, immigrants coming from high-incidence countries may be the contact of active TB cases prior to arriving into low-incidence counties. The available studies on cost-effectiveness are supportive of the use of IGRAs in screening high-risk groups, such as healthcare workers, immigrants from high-incidence countries, and close contacts.[38] Therefore; adding IGRA (QFT-GIT) test will help in reduction of the number of unnecessary prophylactic treatment. This was evident from a recent study reported that the addition of IGRA (QFT-GIT) in BCG-vaccinated TB contacts had safely reduced TB diagnosis and treatment rates without increasing the risk of subsequent active TB.[55] The prophylactic treatment of LTBI can be offered then to younger individuals with positive IGRA (QFT-GIT) test after the exclusion of active disease (by negative sputum culture test) and or old TB infection in the Disease Control section in DPSCs as a step towards minimizing the risk of developing active TB among individuals applying for residency in the Emirate of Abu Dhabi.

Recommendation 5: Upgrading the current visa screening process to detect diabetes among residents applying for renewal visas

Shah et al. reported a high level of overweight and obesity among migrant women after 10 years of residency in the UAE.[53] In addition, the previous study reported that those women had three

times the prevalence of type 2 diabetes mellitus compared to the more recent arrivals.[53] The association between diabetes and TB was examined in a systematic review comparing 13 studies and it was concluded that patients with diabetes had a threefold higher risk of developing TB when compared to those without the disease.[42] Adding diabetes screening test for adults applying for renewal residency will be a new step that will empower the strategic efforts of the public health sector in Abu Dhabi. Individuals diagnosed with diabetes during the visa renewal screening can befit from the IGRA (QFT-GIT) test for LTBI diagnosis as well prior to referral to either chronic disease clinics in the primary care sectors or occupational health clinics for further management.

Recommendation 6: Encourage healthy working environments for immigrants in Abu Dhabi

Al-Maskari et al. reported that the majority of South Asian immigrants who are unskilled males with low educational levels, employed in low salary jobs, and living in large labor camps, suffer from stress, anxiety, and depression.[60, 61] In addition, Shah et al. found a relatively high prevalence of hypertension in a representative sample of young male South Asian immigrants living in the UAE.[61] Sadly, within this population, the awareness of hypertension, treatment, and control of disease was very low.[61]

Awareness among important stakeholders in large companies and governmental institutes in Abu Dhabi should be raised to improve the current working environments for those laborers. The implantation of the recognition strategies directed towards this category such as best performance of the month and the publication of those events and the photos of the special

performers in the magazine of the organization is advised. Recognition of laborers and helpers for good work by simple certificates and simple awards from time to time in a social gathering towards the end of a working day or during an evening outside work hours if feasible would recover the spirit of hard workers and would be a good initial step towards alleviating the hardship they are facing. Employers in this category should be encouraged and supported to seek proper medical attention especially if diagnosed with chronic diseases such as hypertension and diabetes.

The DPSCs provide a good example of a friendly working environment as the cleaners and helpers are well recognized, respected and supported by the higher management and the rest of employees. The passion of those workers towards the organization and the staff was the product of being treated and valued as important members of the community. Therefore, the current scattered and successful efforts noticed in some governmental entities in Abu Dhabi need to be merged into a policy that supports and guide the efforts of providing a healthy working environment.

Section (D): Children at higher risk of MTB

Recommendation 7: Mandate the provision of BCG vaccination records for the dependents' children below 5 years old

The highest risk for TB-related mortality occurred as a result of primary TB infection during infancy period.[42] The risk of TB-related mortality declined to 1% between 1 and 4 years of age, and then it escalates to more than 2% from 15 to 25 years of age.[42] To start, the provisions of

evidence of BCG vaccination need to be mandated as part of visa application process for individuals accompanied by their dependents below 18 years of age. If not possible, then an urgent appointment with pediatrician needs to be arranged soon after arrival in Abu Dhabi for assessment and opinion regarding BCG vaccination. The status of TB/LTBI in children, below 18 years-old, coming from high-incidence regions is not known. Furthermore, the possible exposure of Emirati children to infected maids, babysitters and drivers during their childhood cannot be ignored. Thus, the establishment of a well-organized and integrated pediatric contact tracing program in Abu Dhabi is advocated mainly among high-risk groups such as infants exposed recently to highly contagious TB cases.

Recommendation 8: Consider LTBI screening and prophylactic treatment among students applying for university

Screening for LTBI and the provision of prophylactic treatment might be considered as part of university requirements for admission for students, especially those who are going to stay in a university dormitory. In Abu Dhabi, visa screening starts at age of 18 years and the status of TB/LTBI among those young adults coming from high-incidence regions is not known. In addition, the LTBI status among local students in the UAE and in Abu Dhabi, in particular, need to be assessed given that IGRA test was positive in 8% Emirati medical students (preclinical and clinical) in a prospective cohort study between July 2011 and May 2012.[64] The earlier study recommended the inclusion of IGRA test in admission screening, particularly in areas where BCG vaccination is universal.[64] Therefore, the current public health efforts in Abu Dhabi need to consider this category among its future plans.

Conclusions

Mycobacterium tuberculosis infection continues to be a global public health challenge requiring multiple levels of consistent efforts from local and international healthcare systems. In Abu Dhabi, efforts to raise the awareness of *Mycobacterium tuberculosis* infection are needed among different community members including clinicians, visa applicants and owners of companies. The establishment and the incorporation of smoking cessation services in visa screening and occupational health clinics is a promising step requiring the support from policy-makers in Abu Dhabi. Upgrading the current visa screening services in Abu Dhabi to include the screening for LTBI among high-risk categories and the screening for diabetes among those applying for renewal residency are advocated. Additional collaboration to help guide the scattered efforts intended to create steady and healthy working environments for workers, helper, and labors serving in UAE and in Abu Dhabi, in particular, is highly emphasized. For children below 5 years-old accompanying their parents, the provision of BCG vaccination records need to be mandated as part of residency requirements. The arrangement for pediatric assessment soon after arrival into Abu Dhabi for those lacking the records for BCG counseling is advocated. In addition, the establishment of a well-organized and integrated pediatric contact tracing program in Abu Dhabi needs the attention of the policymakers. Finally, screening for LTBI and the provision of prophylactic treatment might be incorporated as part of university requirements for students planning to stay in university dormitories.

Appendices

Appendix (3.1)

Estimated epidemiological burden of TB in 2016 for 30 high TB burden countries, WHO regions and globally. Rates per 100 000 population except where indicated.

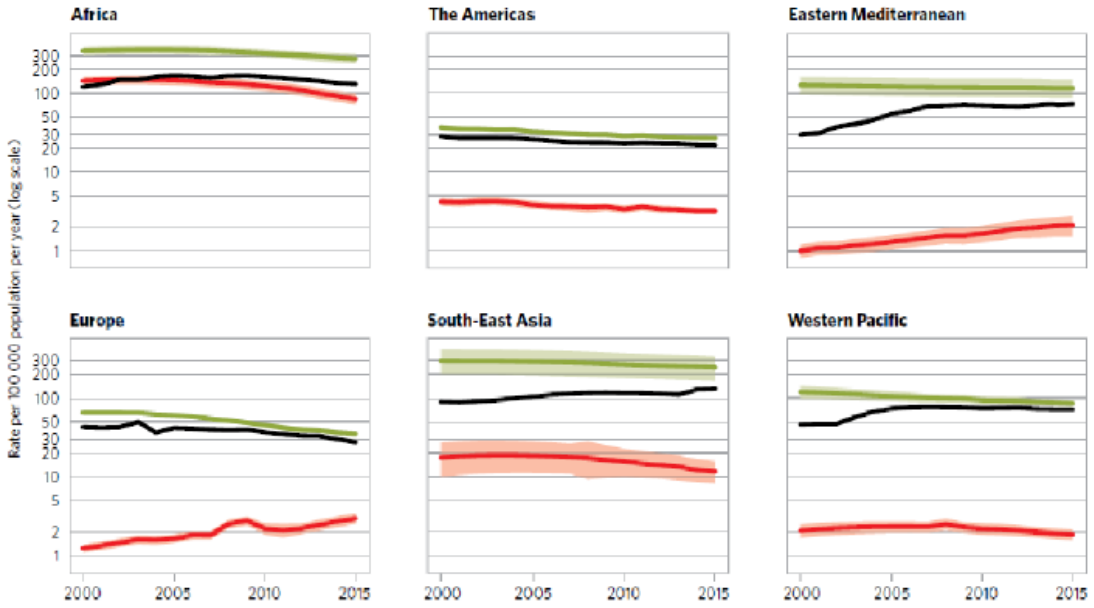
	HIV-NEGATIVE TB MORTALITY		HIV-POSITIVE TB MORTALITY[a]		TOTAL TB INCIDENCE		HIV PREVALENCE IN INCIDENT TB (%)	
	BEST ESTIMATE	UNCERTAINTY INTERVAL	BEST ESTIMATE	UNCERTAINTY INTERVAL	BEST ESTIMATE	UNCERTAINTY INTERVAL	BEST ESTIMATE	UNCERTAINTY INTERVAL
Angola	64	36–99	24	12–41	370	230–543	16	10–24
Bangladesh	40	26–58	0.11	0.05–0.18	221	161–291	0.14	0.08–0.22
Brazil	2.6	2.3–2.9	0.90	0.66–1.2	42	36–48	13	12–14
Cambodia	20	14–28	2.9	1.8–4.2	345	223–493	2.5	2.2–2.7
Central African Republic	59	33 92	54	29 87	407	263 581	33	22 45
China	3.6	2.4–5.0	0.13	0.05–0.24	64	55–74	1.2	0.50–2.1
Congo	60	34–93	41	21–66	378	240–547	26	17–37
DPR Korea	43	27–63	0.20	0.09–0.35	513	446–584	0.21	0.11–0.35
DR Congo	67	39–101	11	5.1–19	323	209–461	8.0	4.6–12
Ethiopia	25	16–36	3.9	2.6–5.3	177	125–239	7.6	7.0–8.3
India[b]	32	24–40	0.92	0.50–1.5	211	109–345	3.1	2.8–3.5
Indonesia	42	29–58	5.1	2.4–8.7	391	253–558	4.4	2.5–6.8
Kenya	60	33–93	50	30–75	348	213–516	31	29–33
Lesotho	49	26–80	238	148–350	724	468–1 030	72	64–80
Liberia	60	35 91	21	13 30	308	199 440	16	14 18
Mozambique	75	44–115	114	70–167	551	356–787	45	40–50
Myanmar	47	30–66	9.3	6.7–12	361	266–471	9.5	8.7–10
Namibia	30	20–44	35	25–48	446	347–565	38	37–40
Nigeria	62	36–95	21	12–31	219	143–311	16	13–18
Pakistan	23	18–29	1.1	0.51–1.9	268	174–383	1.3	0.74–2.1
Papua New Guinea	44	29–62	10	5.5–16	432	352–521	10	6.0–15
Philippines	21	21–22	0.29	<0.01–2.5	554	311–866	1.1	0.60–1.6
Russian Federation	8.2	7.8–8.6	1.2	0.59–1.9	66	42–94	19	18–21
Sierra Leone	47	28–70	14	9.0–20	304	195–435	14	13–15
South Africa	41	31 52	181	120 254	781	543 1 060	59	53 65
Thailand	13	10–15	5.7	3.4–8.6	172	102–261	8.8	7.9–9.6
UR Tanzania	51	23–90	48	22–83	287	136–495	34	30–38
Viet Nam	14	8.9–19	0.90	0.66–1.2	133	109–159	3.3	3.1–3.6
Zambia	29	17–44	74	48–107	376	244–535	58	53–63
Zimbabwe	7.2	4.4–11	27	19–38	208	152–273	67	65–69
High TB burden countries	24	21–27	6.7	5.7–7.8	192	158–230	9.7	7.5–12
Africa	41	34–48	31	27–36	254	227–284	30	24–35
The Americas	1.7	1.6–1.8	0.63	0.56–0.70	27	26–29	11	9.8–12
Eastern Mediterranean	12	10–14	0.45	0.27–0.68	114	85–147	1.3	0.71–2.1
Europe	2.8	2.8–2.9	0.55	0.43–0.69	32	27–36	12	8.6–15
South-East Asia	33	28–40	1.8	1.3–2.4	240	164–331	3.6	2.1–5.4
Western Pacific	5.4	4.5–6.5	0.26	0.16–0.39	95	79–113	1.6	1.2–2.1
GLOBAL	17	16–19	5.0	4.4–5.7	140	118–164	10	8.1–12

[a] Deaths among HIV-positive TB cases are classified as HIV deaths according to ICD-10.
[b] Estimates of TB incidence and mortality for India are interim in nature, pending results from the national TB prevalence survey planned for 2018/2019.

Reference: World Health Organization. (2017). *Global tuberculosis report*. [online] Available at: http://www.who.int/tb/publications/global_report/en/ [Accessed 29 Dec. 2017].

Appendix (3.2)

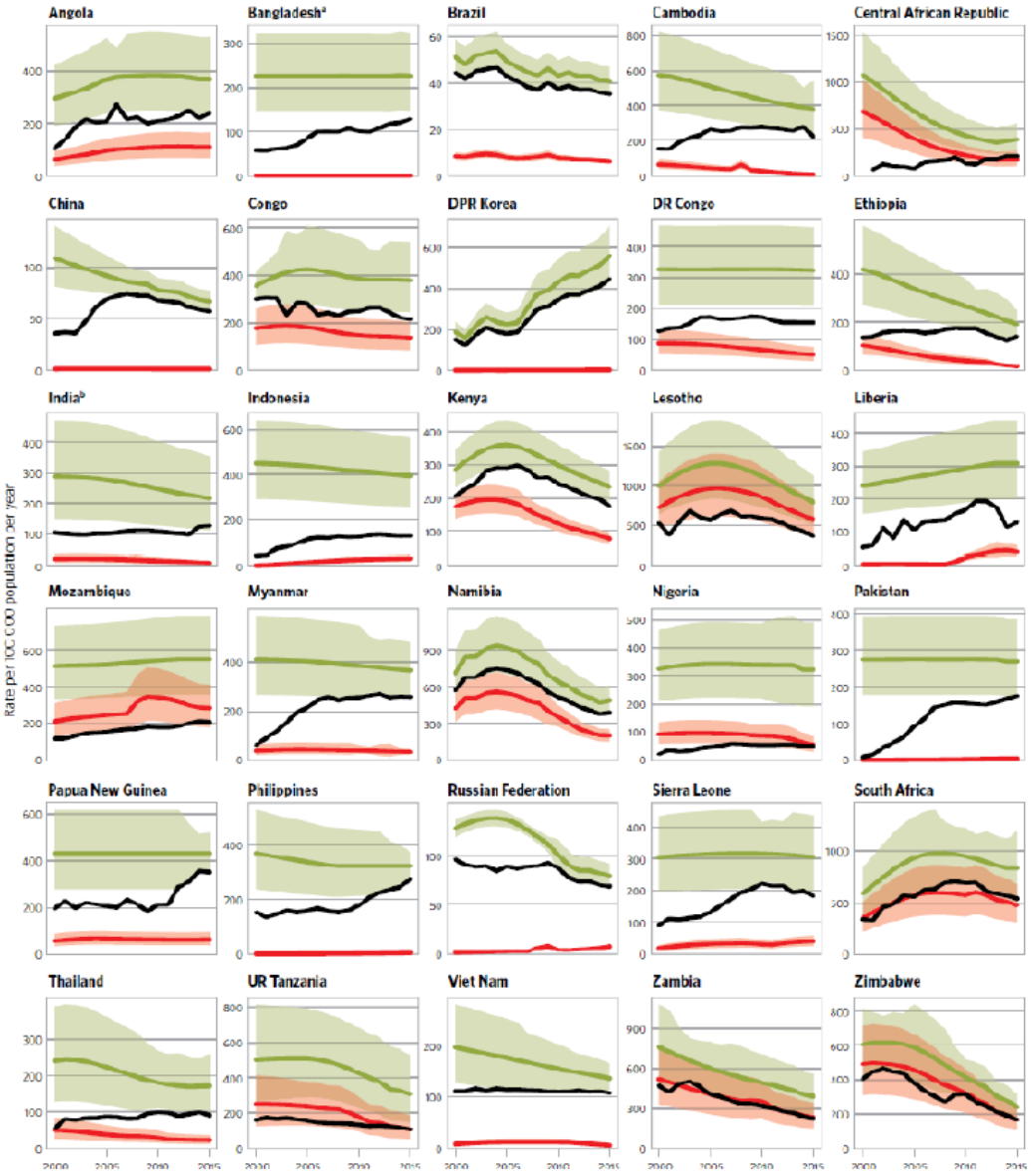
Regional trends in estimated TB incidence rates (log scale) by WHO region, 2000–2015. Total TB incidence rates are shown in green and incidence rates of HIV-positive TB are shown in **red**. Shaded areas represent uncertainty intervals. The **black** lines show notifications of new and relapse cases for comparison with estimates of the total incidence rate.



Reference: World Health Organization. (2017). *Global tuberculosis report*. [online] Available at: http://www.who.int/tb/publications/global_report/en/ [Accessed 29 Dec. 2017].

Appendix (3.3)

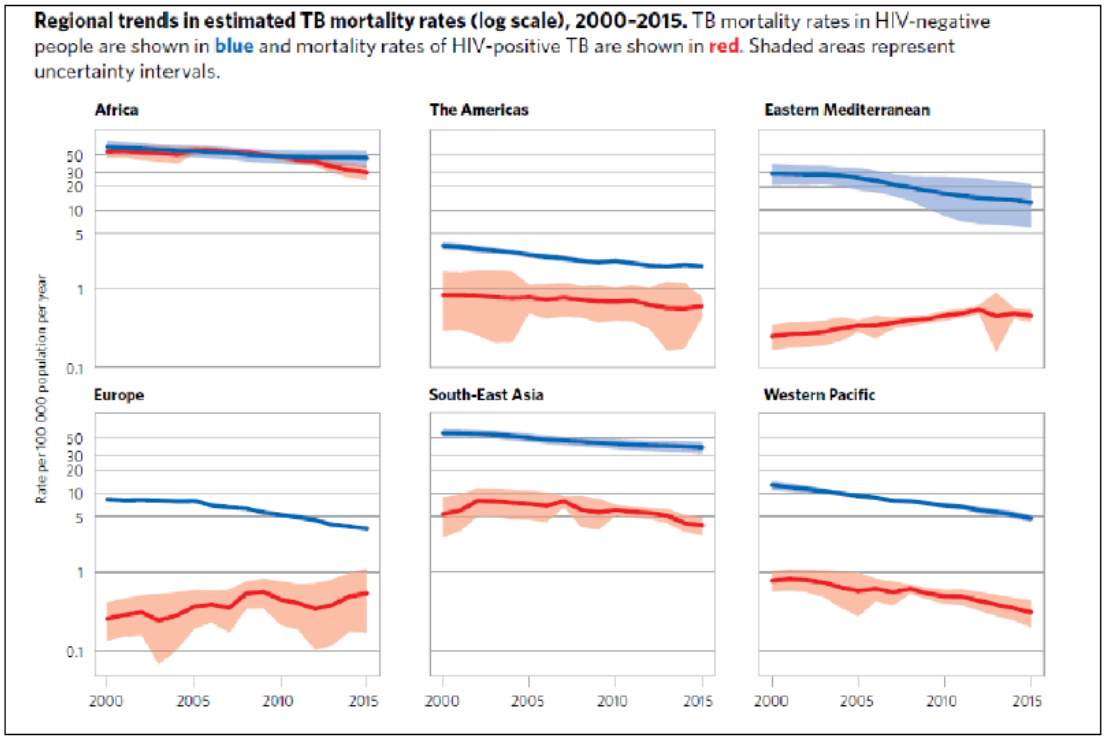
Trends in estimated TB incidence in the 30 high TB burden countries, 2000–2015. TB incidence rates are shown in **green** and incidence rates of HIV-positive TB are shown in **red**. Shaded areas represent uncertainty intervals. The **black** lines show notifications of new and relapse cases for comparison with estimates of the total incidence rate.



[a] Estimates of TB incidence for Bangladesh will be reviewed once final results from the 2015/2016 national TB prevalence survey are available.
[b] Estimates of TB incidence for India are interim in nature, pending results from the national TB prevalence survey planned for 2017/2018.

Reference: World Health Organization. (2017). *Global tuberculosis report*. [online] Available at: http://www.who.int/tb/publications/global_report/en/ [Accessed 29 Dec. 2017].

Appendix (3.4)



Reference: World Health Organization. (2017). *Global tuberculosis report*. [online] Available at: http://www.who.int/tb/publications/global_report/en/ [Accessed 29 Dec. 2017].

Appendix (3.5)

The Sustainable Development Goals

Goal 1. End poverty in all its forms everywhere

Goal 2. End hunger, achieve food security and improved nutrition and promote sustainable agriculture

Goal 3. Ensure healthy lives and promote well-being for all at all ages

Goal 4. Ensure inclusive and equitable quality education and promote lifelong learning opportunities for all

Goal 5. Achieve gender equality and empower all women and girls

Goal 6. Ensure availability and sustainable management of water and sanitation for all

Goal 7. Ensure access to affordable, reliable, sustainable and modern energy for all

Goal 8. Promote sustained, inclusive and sustainable economic growth, full and productive employment and decent work for all

Goal 9. Build resilient infrastructure, promote inclusive and sustainable industrialization and foster innovation

Goal 10. Reduce inequality within and among countries

Goal 11. Make cities and human settlements inclusive, safe, resilient and sustainable

Goal 12. Ensure sustainable consumption and production patterns

Goal 13. Take urgent action to combat climate change and its impacts[a]

Goal 14. Conserve and sustainably use the oceans, seas and marine resources for sustainable development

Goal 15. Protect, restore and promote sustainable use of terrestrial ecosystems, sustainably manage forests, combat desertification, and halt and reverse land degradation and halt biodiversity loss

Goal 16. Promote peaceful and inclusive societies for sustainable development, provide access to justice for all and build effective, accountable and inclusive institutions at all levels

Goal 17. Strengthen the means of implementation and revitalize the Global Partnership for Sustainable Development

Reference: World Health Organization. (2017). *Global tuberculosis report*. [online] Available at: http://www.who.int/tb/publications/global_report/en/ [Accessed 29 Dec. 2017].

Appendix (3.5) continued

Sustainable Development Goal 3 and its 13 targets

SDG3: Ensure healthy lives and promote well-being for all at all ages

Targets

3.1 By 2030, reduce the global maternal mortality ratio to less than 70 per 100 000 live births

3.2 By 2030, end preventable deaths of newborns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1000 live births and under-5 mortality to at least as low as 25 per 1000 live births

3.3 By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases

3.4 By 2030, reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promote mental health and well-being

3.5 Strengthen the prevention and treatment of substance abuse, including narcotic drug abuse and harmful use of alcohol

3.6 By 2020, halve the number of global deaths and injuries from road traffic accidents

3.7 By 2030, ensure universal access to sexual and reproductive health-care services, including for family planning, information and education, and the integration of reproductive health into national strategies and programmes

3.8 Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all

3.9 By 2030, substantially reduce the number of deaths and illnesses from hazardous chemicals and air, water and soil pollution and contamination

3.a Strengthen the implementation of the World Health Organization Framework Convention on Tobacco Control in all countries, as appropriate

3.b Support the research and development of vaccines and medicines for the communicable and non-communicable diseases that primarily affect developing countries, provide access to affordable essential medicines and vaccines, in accordance with the Doha Declaration on the TRIPS Agreement and Public Health, which affirms the right of developing countries to use to the full the provisions in the Agreement on Trade-Related Aspects of Intellectual Property Rights regarding flexibilities to protect public health, and, in particular, provide access to medicines for all

3.c Substantially increase health financing and the recruitment, development, training and retention of the health workforce in developing countries, especially in least developed countries and small island developing States

3.d Strengthen the capacity of all countries, in particular developing countries, for early warning, risk reduction and management of national and global health risks

TRIPS, Trade-Related Aspects of Intellectual Property Rights

Reference: World Health Organization. (2017). *Global tuberculosis report*. [online] Available at: http://www.who.int/tb/publications/global_report/en/ [Accessed 29 Dec. 2017].

Appendix (3.6)

The End TB Strategy at a glance

VISION	A WORLD FREE OF TB — zero deaths, disease and suffering due to TB			
GOAL	END THE GLOBAL TB EPIDEMIC			
INDICATORS	MILESTONES		TARGETS	
	2020	2025	SDG 2030[a]	END TB 2035
Percentage reduction in the absolute number of TB deaths (compared with 2015 baseline)	35%	75%	90%	95%
Percentage reduction in the TB incidence rate (compared with 2015 baseline)	20%	50%	80%	90%
Percentage of TB-affected households experiencing catastrophic costs due to TB (level in 2015 unknown)	0%	0%	0%	0%

PRINCIPLES

1. Government stewardship and accountability, with monitoring and evaluation
2. Strong coalition with civil society organizations and communities
3. Protection and promotion of human rights, ethics and equity
4. Adaptation of the strategy and targets at country level, with global collaboration

PILLARS AND COMPONENTS

1. **INTEGRATED, PATIENT-CENTRED CARE AND PREVENTION**
   - A. Early diagnosis of TB including universal drug-susceptibility testing, and systematic screening of contacts and high-risk groups
   - B. Treatment of all people with TB including drug-resistant TB, and patient support
   - C. Collaborative TB/HIV activities, and management of comorbidities
   - D. Preventive treatment of persons at high risk, and vaccination against TB
2. **BOLD POLICIES AND SUPPORTIVE SYSTEMS**
   - A. Political commitment with adequate resources for TB care and prevention
   - B. Engagement of communities, civil society organizations, and public and private care providers
   - C. Universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control
   - D. Social protection, poverty alleviation and actions on other determinants of TB
3. **INTENSIFIED RESEARCH AND INNOVATION**
   - A. Discovery, development and rapid uptake of new tools, interventions and strategies
   - B. Research to optimize implementation and impact, and promote innovations

[a] Targets linked to the Sustainable Development Goals (SDGs).

Reference: World Health Organization. (2017). *Global tuberculosis report*. [online] Available at: http://www.who.int/tb/publications/global_report/en/ [Accessed 29 Dec. 2017].

Appendix (3.7)

Key principles of systematic screening for active TB

The following key principles should be considered when planning a TB-screening strategy.

1. Before screening is initiated, high-quality TB diagnosis, treatment, care, management and support for patients should be in place, and there should be the capacity to scale these up further to match the anticipated rise in case detection that may occur as a result of screening. In addition, a baseline analysis should be completed in order to demonstrate that the potential benefits of screening clearly outweigh the risks of doing harm, and that the required investments in screening are reasonable in relation to the expected benefits.
2. Indiscriminate mass screening should be avoided. The prioritization of risk groups for screening should be based on assessments made for each risk group of the potential benefits and harms, the feasibility of the initiative, the acceptability of the approach, the number needed to screen, and the cost effectiveness of screening.
3. The choice of algorithm for screening and diagnosis should be based on an assessment of the accuracy of the algorithm for each risk group considered, as well as the availability, feasibility and cost of the tests.
4. TB screening should follow established ethical principles for screening for infectious diseases, observe human rights, and be designed to minimize the risk of discomfort, pain, stigma and discrimination.
5. The TB screening approach should be developed and implemented in a way that optimizes synergies with the delivery of other health services and social services.
6. A screening strategy should be monitored and reassessed continually to inform re prioritization of risk groups, re-adaptation of screening approaches when necessary and discontinuation of screening at an appropriate time.

Recommendations on risk groups to screen

Seven recommendations on prioritizing risk groups for screening have been developed. The recommendations are divided into strong recommendations and conditional recommendations.

A ***strong recommendation*** is one for which the desirable effects of adhering to the recommendation are judged to clearly outweigh the undesirable effects, and for which screening is judged to be feasible, acceptable and affordable in all settings.

A ***conditional recommendation*** is one for which the desirable effects of adhering to the recommendation probably outweigh the undesirable effects but the trade-offs, cost effectiveness, feasibility or affordability, or some combination of these, are uncertain. Reasons for uncertainty may include:

- a lack of high-quality evidence to support the recommendation;
- high costs or low feasibility or acceptability, or a combination of these.

Reference: World Health Organization. (2018). *Systematic screening for active tuberculosis: an operational guide*. [online] Available at: http://www.who.int/tb/publications/systematic_screening/en/ [Accessed 13 Jan. 2018]

Appendix (3.7) continued

Strong recommendations

Recommendation 1: Household contacts and other close contacts should be systematically screened for active TB.

Recommendation 2: People living with the human immunodeficiency virus (HIV should be systematically screened for active TB at each visit to a health facility.

Recommendation 3: Current and former workers in workplaces with silica exposure should be systematically screened for active TB.

Conditional recommendations

Recommendation 4: Systematic screening for active TB should be considered in prisons and other penitentiary institutions.

Recommendation 5: Systematic screening for active TB should be considered in people with an untreated fibrotic chest X-ray lesion.

Recommendation 6: In settings where the TB prevalence in the general population is 100/100 000 population or higher, systematic screening for active TB should be considered among people who are seeking health care or who are in health care and who belong to selected risk groups.

Recommendation 7: (a) Systematic screening for active TB may be considered for geographically defined subpopulations with extremely high levels of undetected TB (1% prevalence or higher). (b) Systematic screening for active TB may be considered also for other subpopulations that have very poor access to health care, such as people living in urban slums, homeless people, people living in remote areas with poor access to health care, and other vulnerable or marginalized groups, including some indigenous populations, migrants and refugees.

Reference: World Health Organization. (2018). *Systematic screening for active tuberculosis: an operational guide*. [online] Available at: http://www.who.int/tb/publications/systematic_screening/en/ [Accessed 13 Jan. 2018]

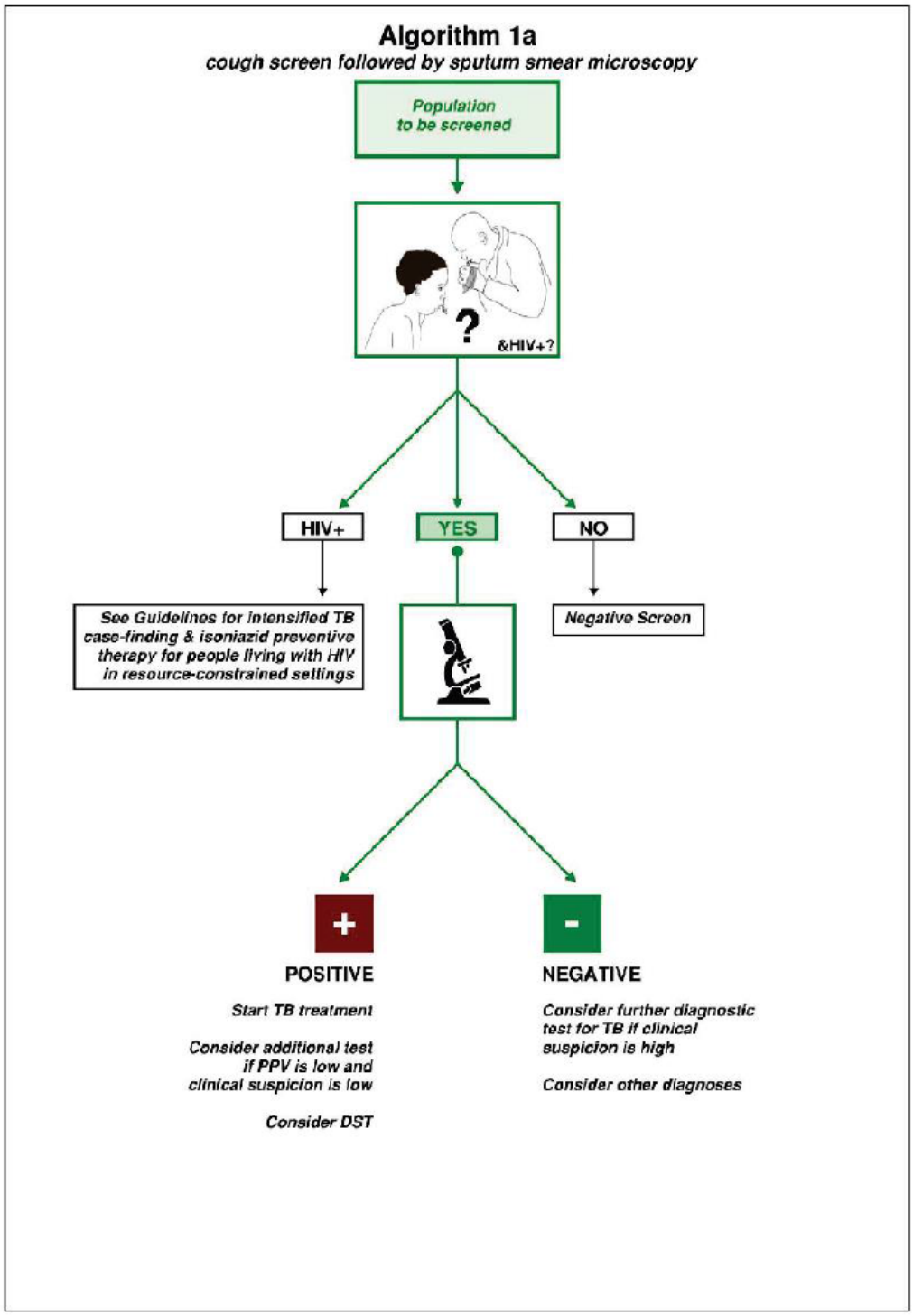
Appendix (3.7) continued

Potential site of screening	Risk group
Community	Geographical areas with a high prevalence of TB
	Subpopulations with poor access to health care and with other associated risk factors (such as living in a poor or a remote area; being a member of an indigenous or tribal population; being a migrant, refugee, homeless, or nomadic)
Hospital outpatient and inpatient departments, and primary health-care centres	People previously treated for TB
	People with an untreated fibrotic chest radiography lesion
	People living with HIV / People attending for HIV testing
	People with diabetes mellitus
	People who smoke / People with chronic respiratory disease
	Undernourished people
	People who have had a gastrectomy or jejunoileal bypass
	People with an alcohol-use disorder / Injection drug users
	People with chronic renal failure
	People on treatments that compromise their immune system
	Elderly people
	People in mental health clinics or institutions
	General outpatients/inpatients
Residential institutions	Prisoners and prison staff
	People residing in shelters
	Other congregate institutions (such as the military)
Immigration and refugee services	Immigrants from settings with a high prevalence of TB
	People in refugee camps
Workplaces	Health-care workers
	Miners or others who are exposed to silica
	Other workplaces with a high prevalence of TB

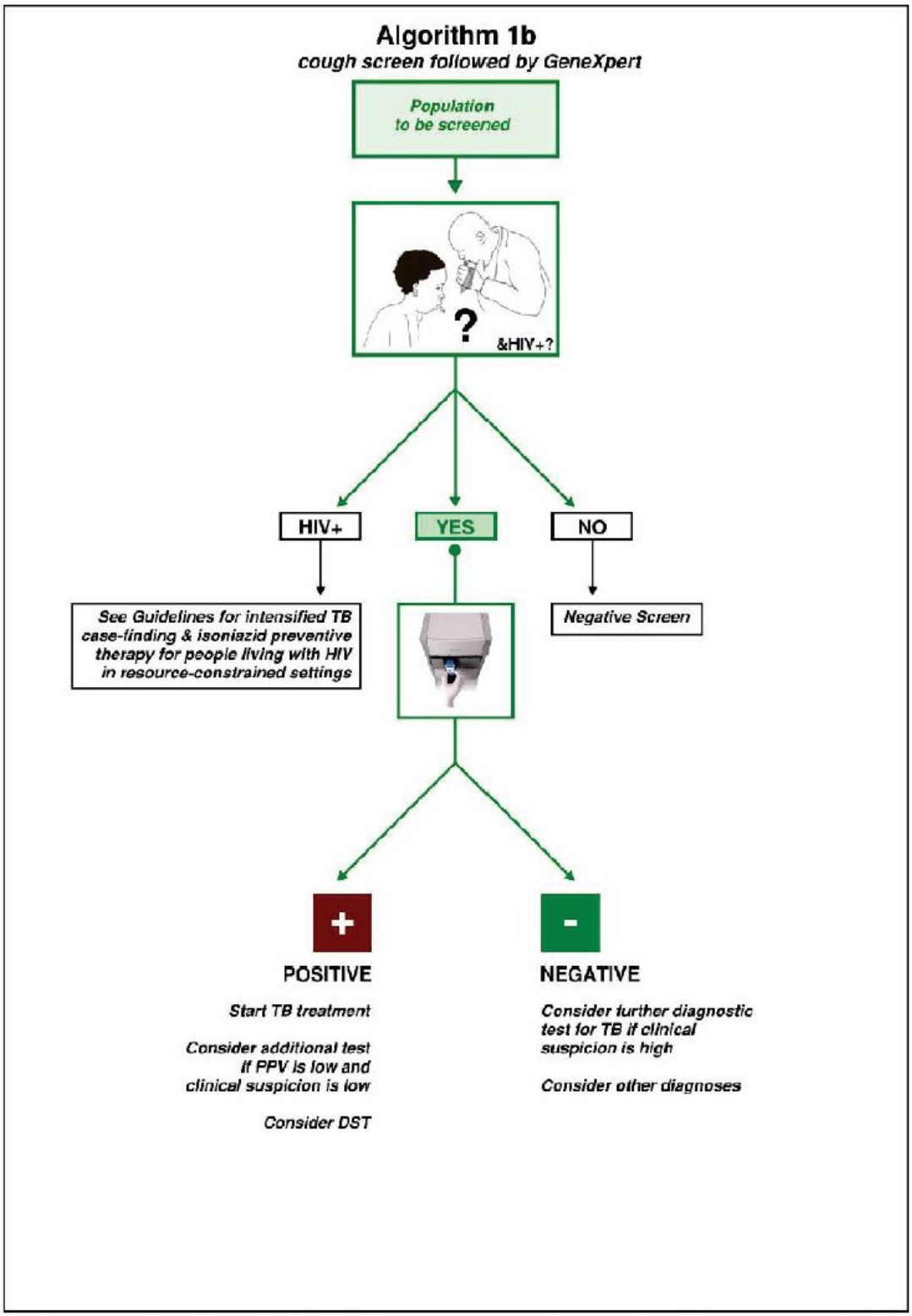
Reference: World Health Organization. (2018). *Systematic screening for active tuberculosis: an operational guide*. [online] Available at: http://www.who.int/tb/publications/systematic_screening/en/ [Accessed 13 Jan. 2018]

Appendix (3.8)

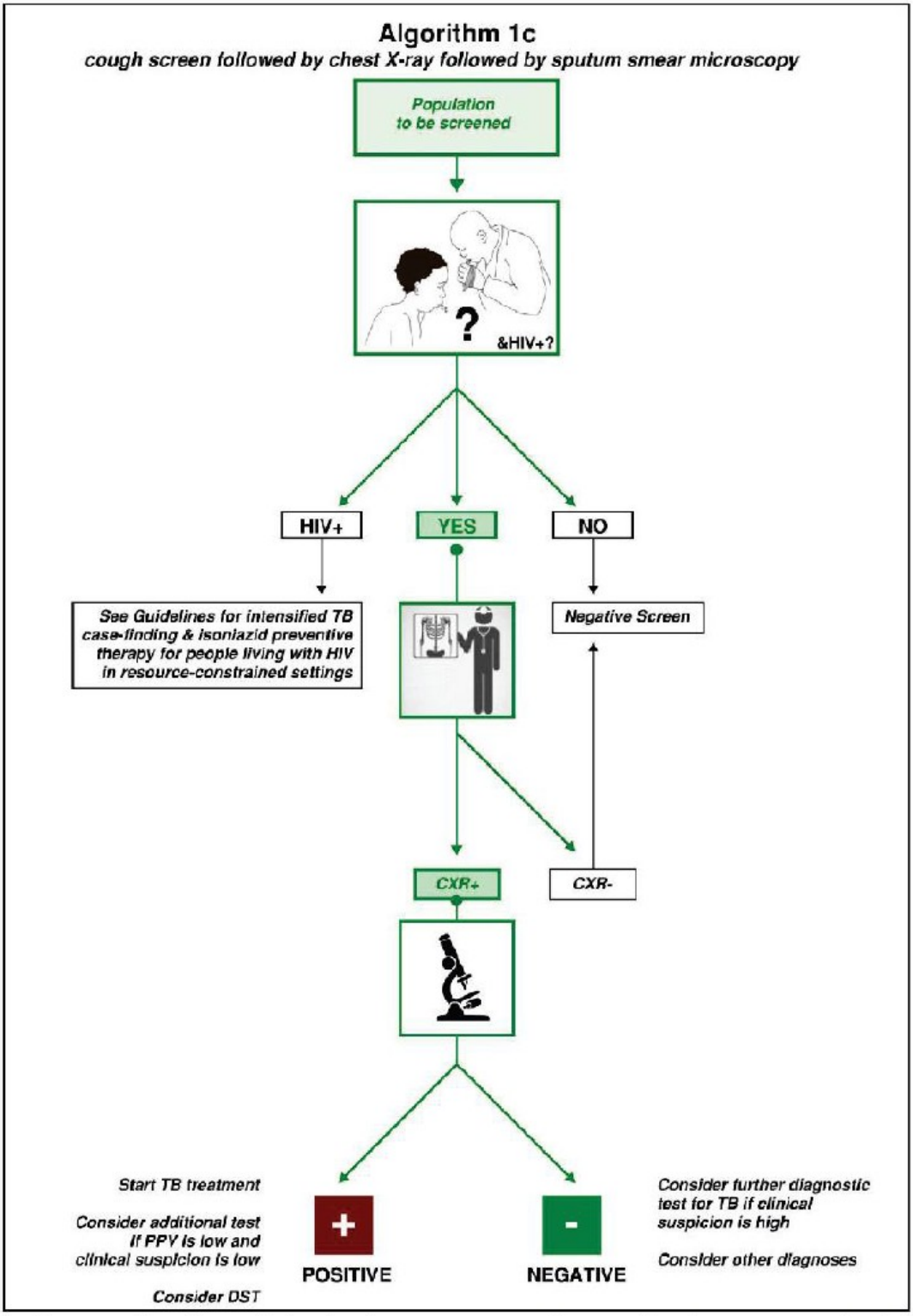
Ten potential screening algorithms



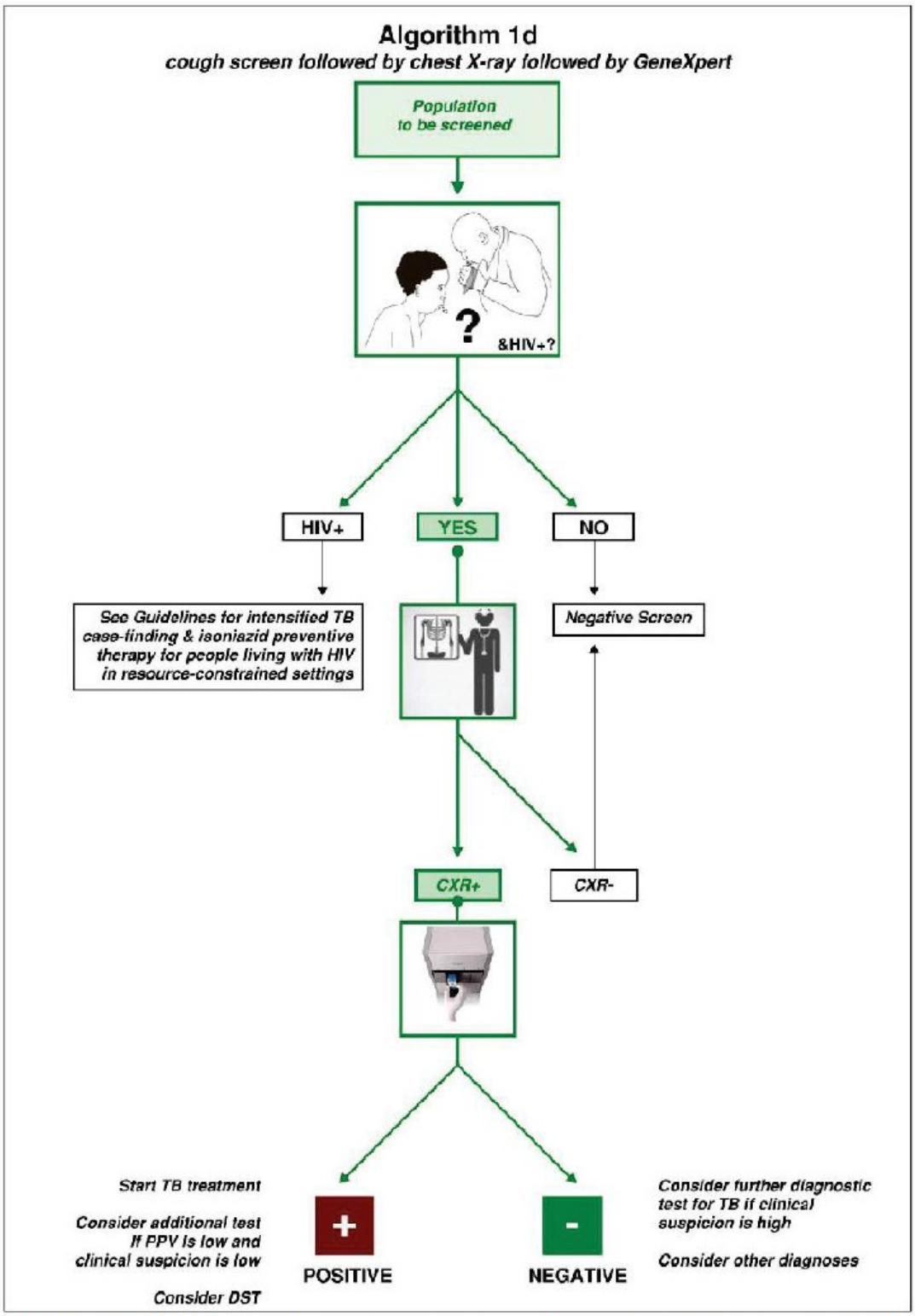
Reference: World Health Organization. (2018). *Systematic screening for active tuberculosis: an operational guide*. [online] Available at: http://www.who.int/tb/publications/systematic_screening/en/ [Accessed 13 Jan. 2018]



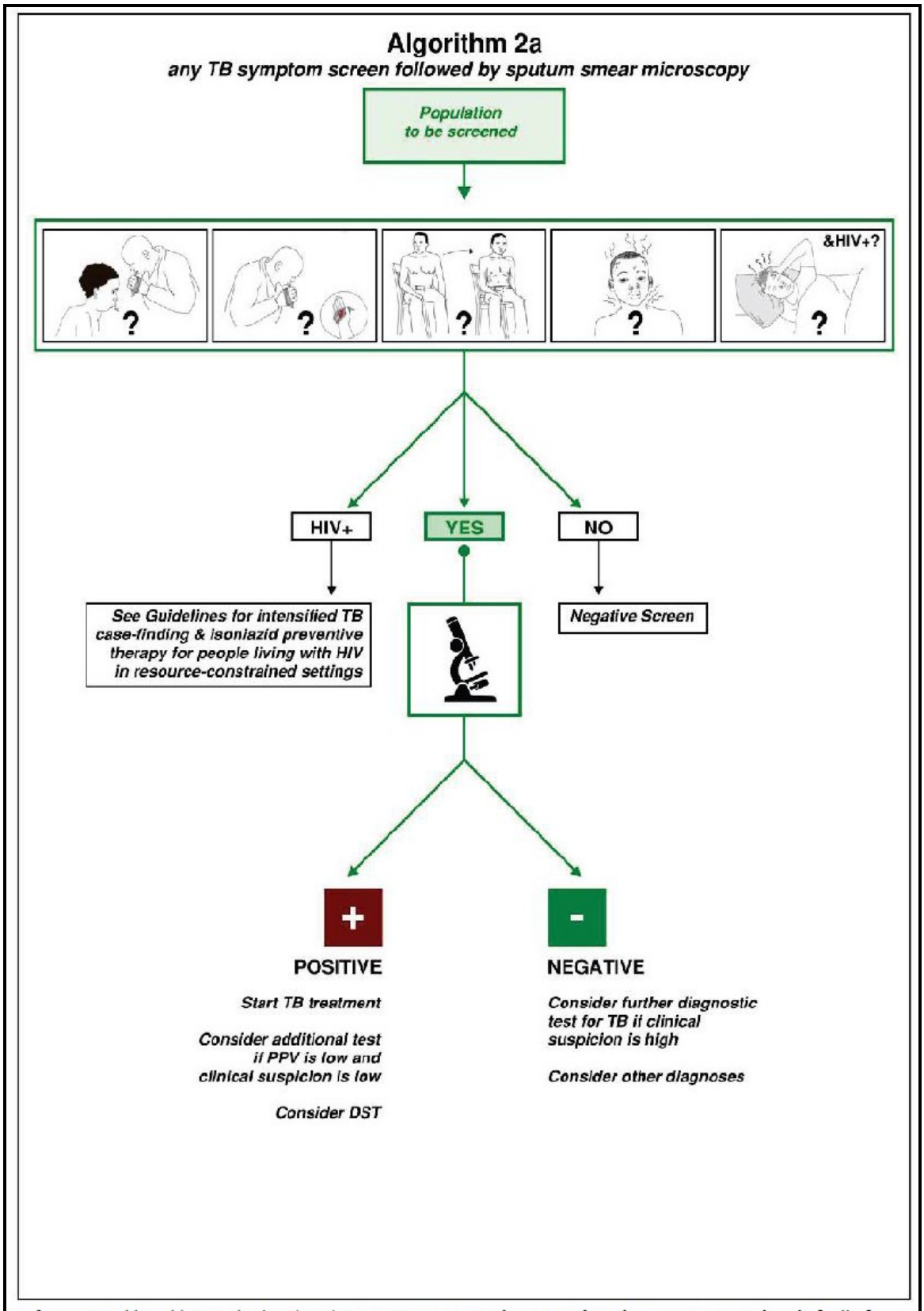
Reference: World Health Organization. (2018). *Systematic screening for active tuberculosis: an operational guide*. [online] Available at: http://www.who.int/tb/publications/systematic_screening/en/ [Accessed 13 Jan. 2018]



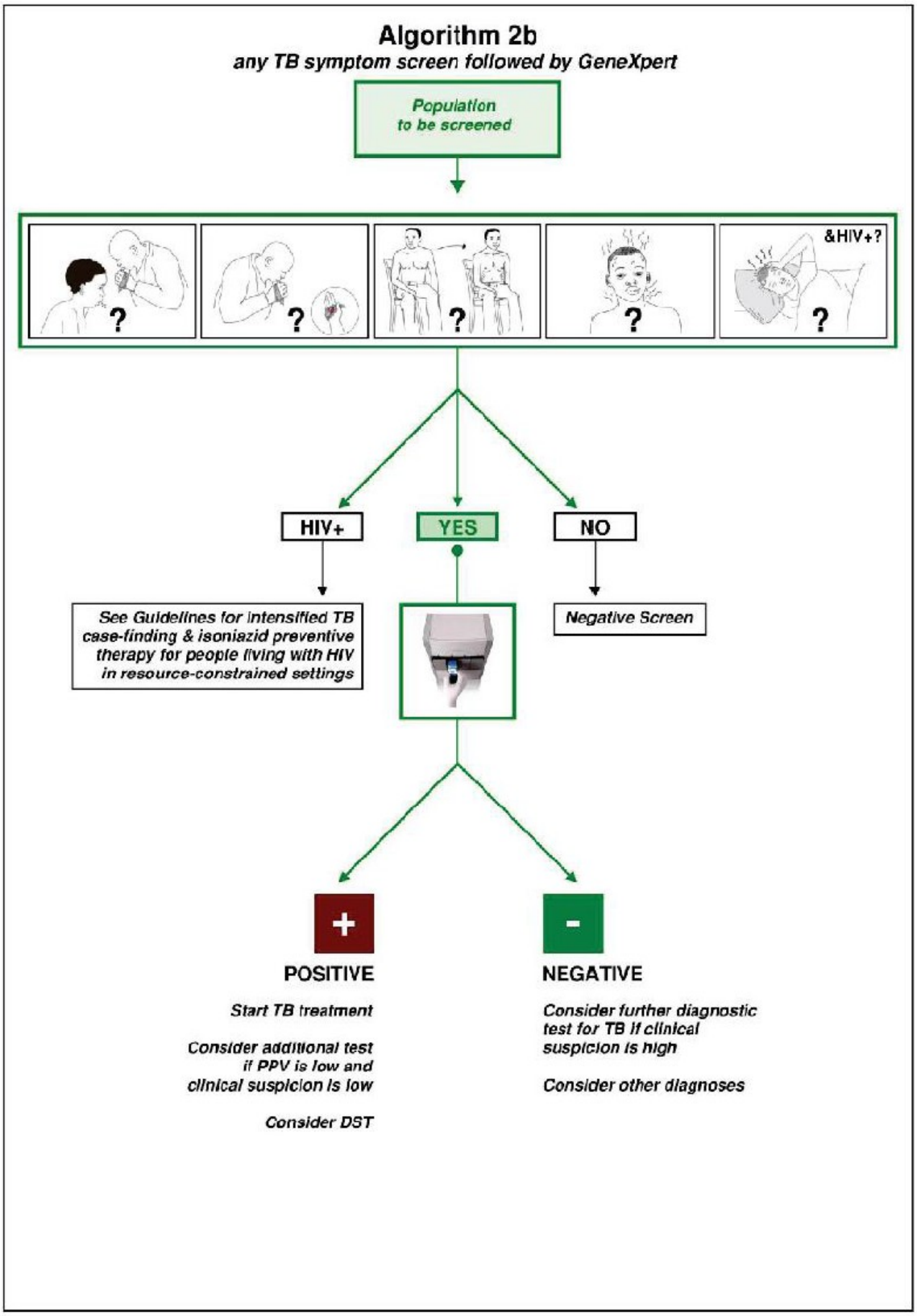
Reference: World Health Organization. (2018). *Systematic screening for active tuberculosis: an operational guide*. [online] Available at: http://www.who.int/tb/publications/systematic_screening/en/ [Accessed 13 Jan. 2018]



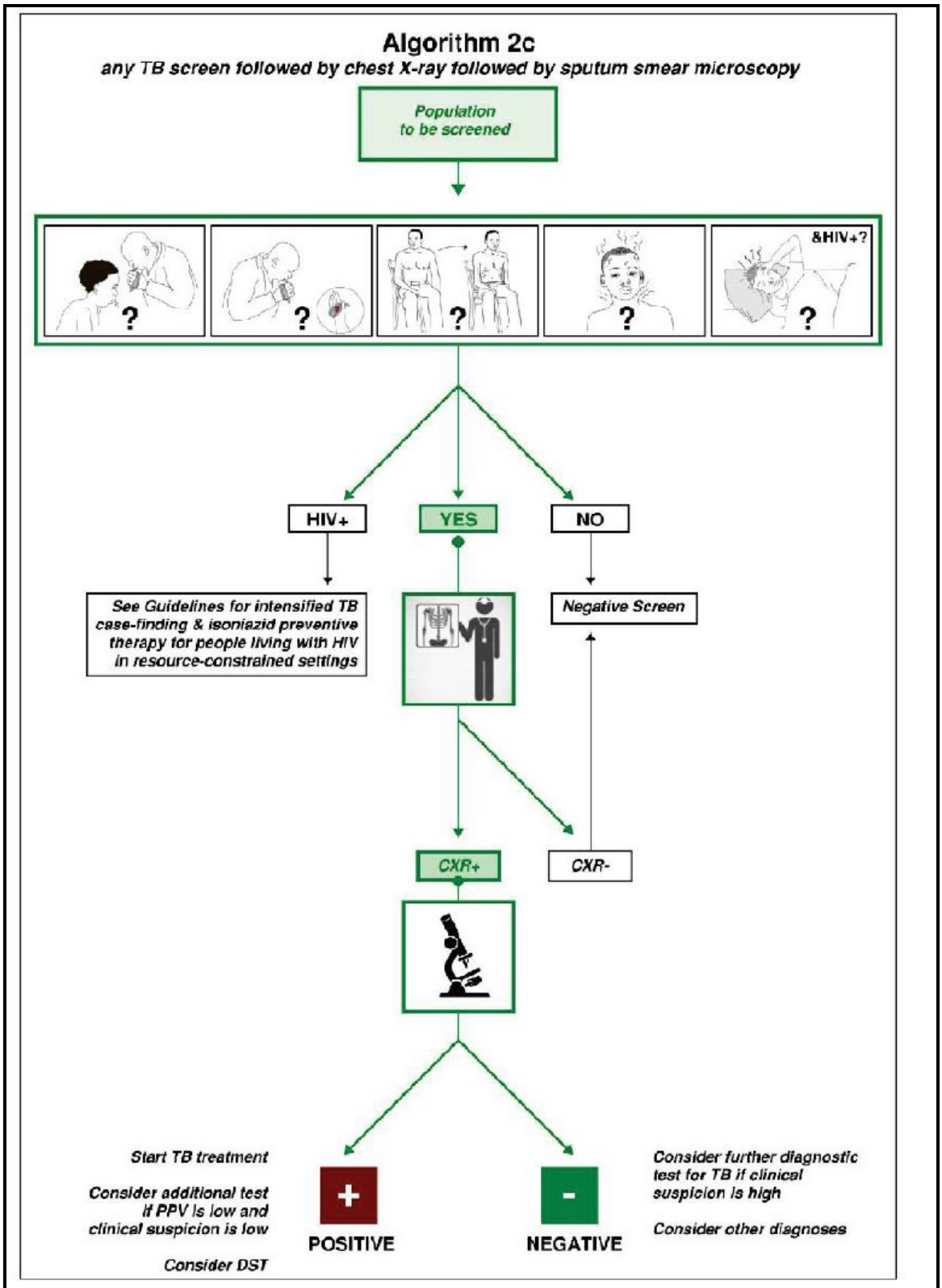
Reference: World Health Organization. (2018). *Systematic screening for active tuberculosis: an operational guide*. [online] Available at: http://www.who.int/tb/publications/systematic_screening/en/ [Accessed 13 Jan. 2018]



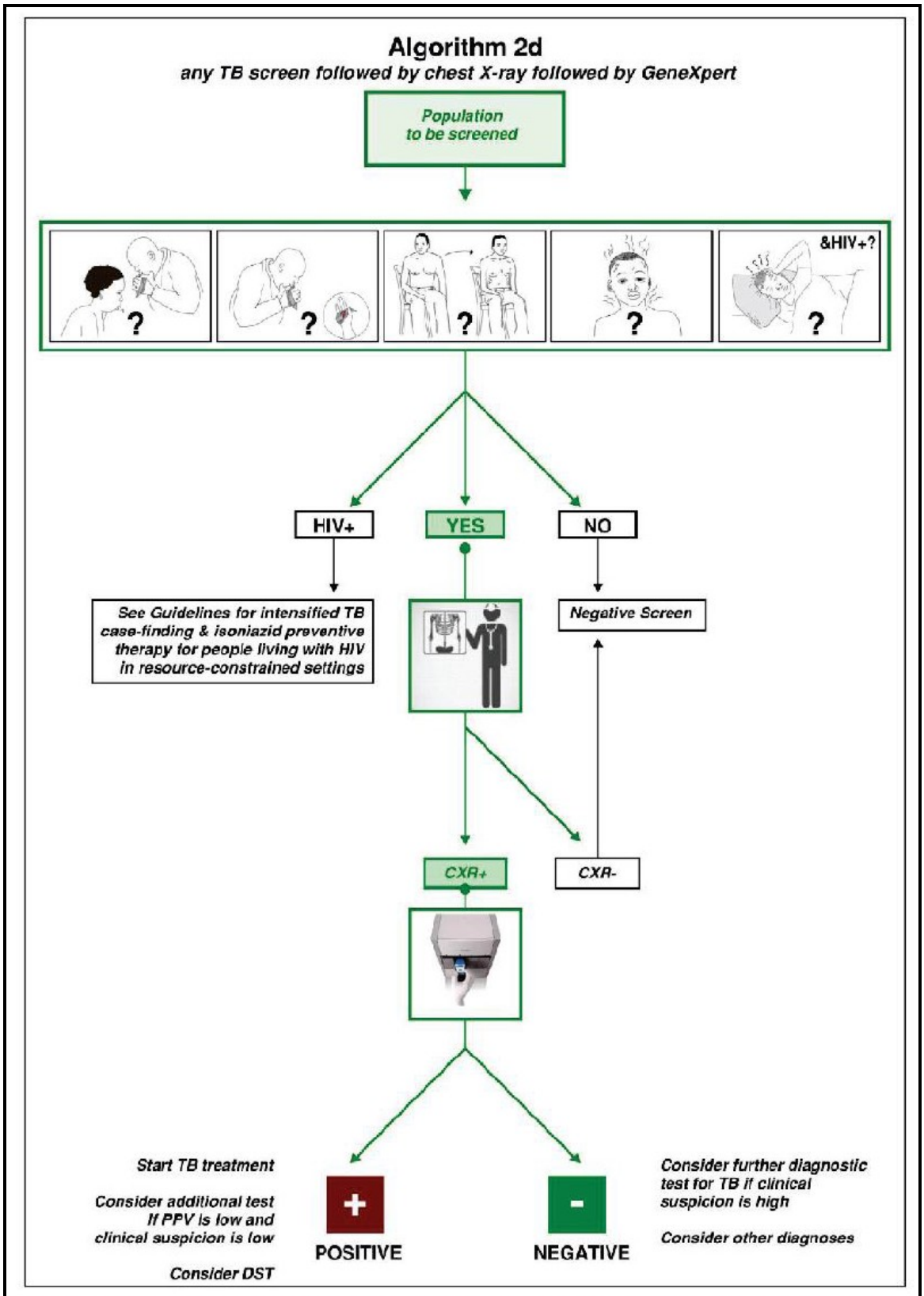
Reference: World Health Organization. (2018). *Systematic screening for active tuberculosis: an operational guide*. [online] Available at: http://www.who.int/tb/publications/systematic_screening/en/ [Accessed 13 Jan. 2018]



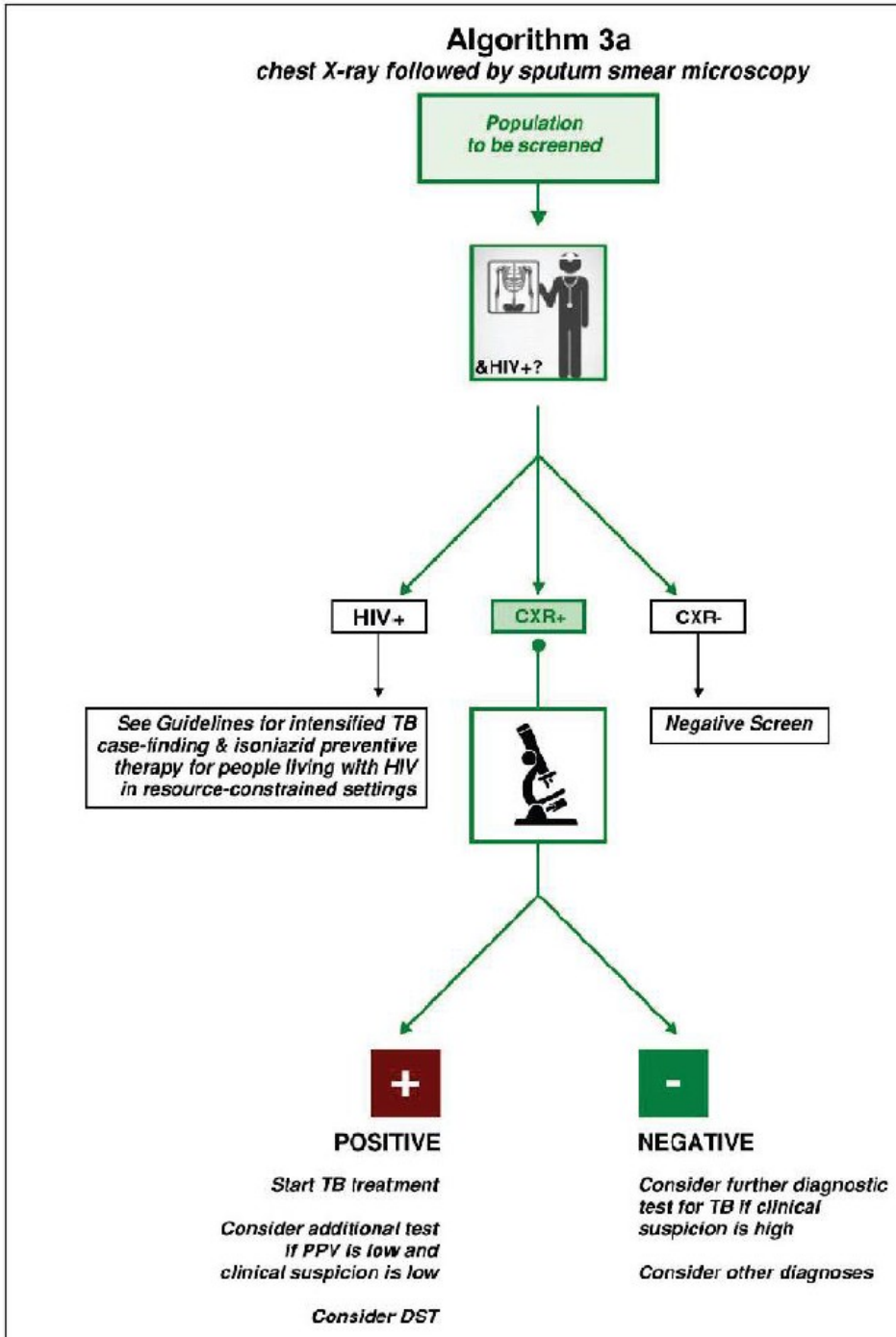
Reference: World Health Organization. (2018). *Systematic screening for active tuberculosis: an operational guide*. [online] Available at: http://www.who.int/tb/publications/systematic_screening/en/ [Accessed 13 Jan. 2018]



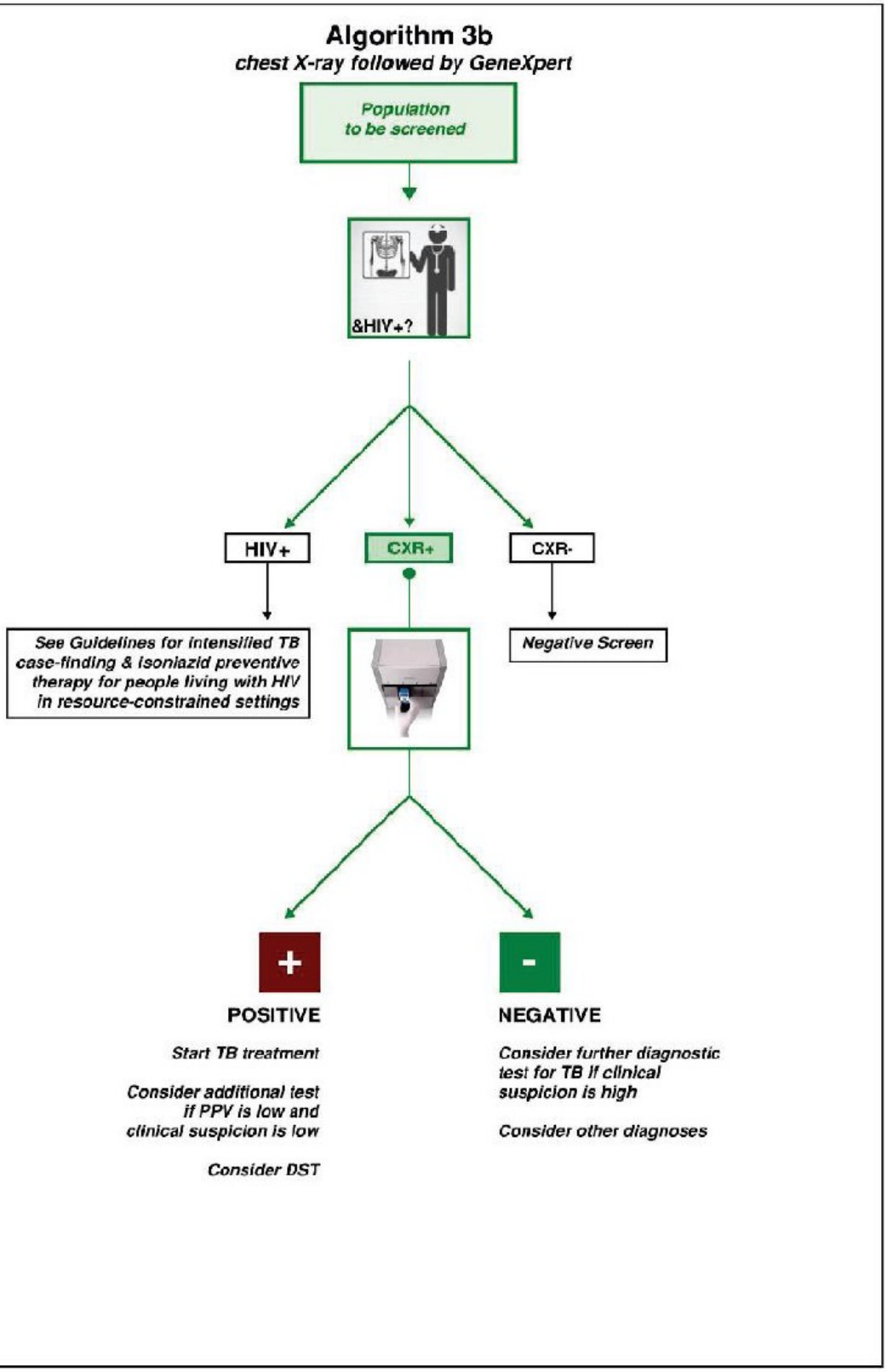
Reference: World Health Organization. (2018). *Systematic screening for active tuberculosis: an operational guide*. [online] Available at: http://www.who.int/tb/publications/systematic_screening/en/ [Accessed 13 Jan. 2018]



Reference: World Health Organization. (2018). *Systematic screening for active tuberculosis: an operational guide*. [online] Available at: http://www.who.int/tb/publications/systematic_screening/en/ [Accessed 13 Jan. 2018]



Reference: World Health Organization. (2018). *Systematic screening for active tuberculosis: an operational guide*. [online] Available at: http://www.who.int/tb/publications/systematic_screening/en/ [Accessed 13 Jan. 2018]



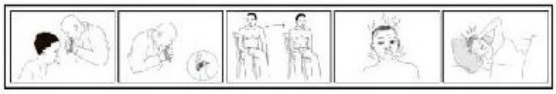
Reference: World Health Organization. (2018). *Systematic screening for active tuberculosis: an operational guide*. [online] Available at: http://www.who.int/tb/publications/systematic_screening/en/ [Accessed 13 Jan. 2018]

Algorithm Key

TB	Tuberculosis
HIV	Human Immunodeficiency Virus
PPV	Positive Predictive Value
DST	Drug Susceptibility Testing
CXR	Chest X-Ray

Algorithm Legend

Cough Screen



Any TB Symptoms Screen

Chest X-Ray

Sputum Smear Microscopy

GeneXpert MTB/RIF

Reference: World Health Organization. (2018). *Systematic screening for active tuberculosis: an operational guide*. [online] Available at: http://www.who.int/tb/publications/systematic_screening/en/ [Accessed 13 Jan. 2018]

Appendix (3.9)

Pooled sensitivity and specificity of different screening tools for pulmonary tuberculosis (TB) using culture-confirmed pulmonary TB as the gold standard

Screening tool	Pooled sensitivity[a]	Pooled specificity[a]
Chest radiography		
Any abnormality compatible with TB (active or inactive)	98 (95–100)	75 (72–79)
Abnormalities suggestive of active TB	87 (79–95)	89 (87–92)
After positive screening for symptoms (any abnormality)[b]	90 (81–96)	56 (54–58)
Symptom screening		
Prolonged cough (lasting >2–3 weeks)	35 (24–46)	95 (93–97)
Any cough	57 (40–74)	80 (69–90)
Any TB symptom (in settings with a low prevalence of HIV)	70 (58–82)	74 (53-95)
Any TB symptom (in settings with a high prevalence of HIV)	84 (76–93)	61 (35-87)
Any TB symptom (in settings with a low prevalence or high prevalence of HIV)	77 (68–86)	68 (50–85)

[a] Values are % (95% confidence interval).

[b] Results from only one study; data are for any abnormality seen on chest radiography.

Reference: World Health Organization. (2018). *Systematic screening for active tuberculosis: an operational guide*. [online]

Available at: http://www.who.int/tb/publications/systematic_screening/en/ [Accessed 13 Jan. 2018]

Appendix (3.10)

Pooled sensitivity and specificity of different screening tools for pulmonary tuberculosis (TB) using culture-confirmed pulmonary TB as the gold standard

Diagnostic test	Pooled sensitivity[a]	Pooled specificity[a]
Liquid culture (gold standard)	100	100
Conventional sputum-smear microscopy[b]	61 (31–89)	98 (93–100)
Xpert MTB/RIF assay	92 (70–100)	99 (91–100)
Clinical diagnosis	24 (10–51)	94 (79–97)

[a] Values are % (95% confidence interval).

b This refers to conventional light microscopy used to examine direct smears stained with Ziehl–Neelsen. Fluorescence microscopy, including microscopy with light-emitting diodes generally has higher sensitivity than conventional light microscopy.

Reference: World Health Organization. (2018). *Systematic screening for active tuberculosis: an operational guide*. [online]

Available at: http://www.who.int/tb/publications/systematic_screening/en/ [Accessed 13 Jan. 2018]

Appendix (3.11)

Screening test	Final diagnostic test	Outcome of screening[a]				Outcome of diagnosis in persons with positive screening[a]						
		TN	FN	NPV[b] (%)	Screened positive[c]	TP	Detected of true cases (%)	FP	PPV[d] (%)	TN[e] (n)	FN[f]	NPV[g] (%)
Cough lasting >2 weeks	SSM	93 753	649	99.3	5 598	214	21	105	67.1	5 142	137	97.4
	Xpert	93 753	649	99.3	5 598	324	32	52	86.0	5 195	27	99.5
1st screen: cough >2 weeks 2nd screen (if 1st screen positive): chest radiography	SSM	96 691	684	99.3	2 625	193	19	46	80.7	2 263	123	94.8
	Xpert	96 691	684	99.3	2 625	291	29	23	92.7	2 286	25	98.9
Any TB symptom	SSM	67 023	230	99.7	32 747	470	47	640	42.3	31 337	300	99.1
	Xpert	67 023	230	99.7	32 747	710	71	320	68.9	31 657	60	99.8
1st screen: any TB symptom 2nd screen (if 1st screen positive): chest radiography	SSM	84 930	307	99.6	14 763	423	42	281	60.0	13 788	270	98.1
	Xpert	84 930	307	99.6	14 763	639	64	141	82.0	13 929	54	99.6
Chest radiography: abnormality suggestive of active TB	SSM	88 506	132	99.9	11 362	529	53	210	71.6	10 284	339	96.8
	Xpert	88 506	132	99.9	11 362	800	80	105	88.4	10 389	68	99.4
Chest radiography: any abnormality compatible with TB	SSM	74 646	22	100.0	25 332	597	60	487	55.1	23 867	381	98.4
	Xpert	74 646	22	100.0	25 332	902	90	244	78.7	24 110	76	99.7

TN, true negative; FN, false negative; NPV, negative predictive value; TP, true positive; FP, false positive; PPV, positive predictive value; SSM, sputum-smear microscopy; Xpert, Xpert MTB/RIF test.

[a] Values are numbers unless otherwise indicated.

[b] The negative predictive value for screening is the likelihood that someone whose screening test is negative does not have TB.

[c] This is the number of people whose screening test would be positive, which equals the number of people who should have the diagnostic test

[d] The positive predictive value is the likelihood that a person with a final diagnosis of TB has true culture-positive TB. It summarizes the specificity and sensitivity of the entire algorithm, not just the diagnostic part.

[e] The number of true negatives among people whose screening test is positive is the number of people correctly diagnosed as not having TB among those whose screening test is positive and who have a diagnostic test.

[f] The number of false negatives among people whose screening test is positive is the number of people falsely diagnosed as not having TB among those whose screening tests are positive and who have a diagnostic test.

[g] The negative predictive value for diagnosis among people whose screening test is positive is the likelihood that a person whose screening test is positive and who is not diagnosed with TB does not have culture-positive TB.

Reference: World Health Organization. (2018). *Systematic screening for active tuberculosis: an operational guide*. [online] Available at: http://www.who.int/tb/publications/systematic_screening/en/ [Accessed 13 Jan. 2018]

Appendix (3.12)

DOH/ HAAD Chest X-ray Report of Tuberculosis for Visa Screening

Date (*dd/mm/yyyy*)			
FacilityID		Radiologist Name	
Unique Identifier		1st Radiologist	
Nationality		2nd Radiologist	
Passport Number		Third Opinion	

A. Record of **General findings** noted on the applicant's Chest X-ray Image.

Review the list below and check all appropriate boxes.

1. Skeletal and/or soft tissue abnormalities?	No	Yes
2. Abnormal great vessels or heart shadows?	No	Yes
3. Abnormal hilar shadow and/or lymphatic glands?	No	Yes
4. Abnormal hemidiaphragms?	No	Yes
5. Abnormal lung fields?	No	Yes
6. Evidence of ANY fibrosis / fibrocalcification involving the upper lobes or superior segments of the lower lobes?	No	Yes
7. Any other *abnormalities?*	No	Yes

Reference; Department of Health (2011). *Visa Screening Standards: version 1.4*. Abu Dhabi: Health Policy and Regulation, pp.6-11.

Appendix (3.12) continued

B. Record of **Special findings** noted on the applicant's Chest X-ray Image.

Minor findings

- ☐ Single fibrous streak / band / scar
- ☐ Bony islets
- ☐ Apical pleural capping with a smooth inferior border (less than 1 cm thick at all points)
- ☐ Unilateral or bilateral costophrenic angle blunting (below the horizontal)
- ☐ Calcified nodule(s) in the hilum / mediastinum with no pulmonary granulomas

Minor findings (occasionally associated with TB infection)

- ☐ Solitary granuloma (less than 1cm and of any lobe) with unremarkable hilum
- ☐ Solitary granuloma (less than 1cm and of any lobe) with calcified / enlarged hilar lymph nodes
- ☐ Single / multiple calcified pulmonary nodules / micronodules with distinct borders
- ☐ Calcified pleural lesions
- ☐ Costophrenic angle blunting (either side above the horizontal)

Findings sometimes seen in active TB or other conditions

- ☐ Notable apical pleural capping (rough or ragged inferior border and or > 1cm thick at any point)
- ☐ Apical fibronodular / fibrocalcific lesions or apical microcalcifications
- ☐ Multiple / single pulmonary nodules / micronodules (noncalcified or poorly defined)
- ☐ Isloated hilar or mediastinal mass / lymphoadenopathy (noncalcified)
- ☐ Single / multiple pulmonary nodules / masses more than 1cm
- ☐ Non-calcified pleural fibrosis and / or effusion
- ☐ Interstitial fibrosis / parenchymal lung disease / acute pulmonary disease
- ☐ ANY cavitating lesion OR "Fluffy" or "Soft" lesions felt likely to represent active TB

☐ **None of the above is present**

Reference; Department of Health (2011). *Visa Screening Standards: version 1.4*. Abu Dhabi: Health Policy and Regulation, pp.6-11.

Appendix (3.12) continued

C. **Final Evaluation** with regards to pulmonary tuberculosis (PTB) based on General and Special findings.

1. Normal chest X-ray		Yes		No
2. Abnormal	NOT PTB	Yes		No
3. Old inactive PTB		Yes		No
4. High suspicion of active PTB		Yes		No
5. Medium suspicion of active PTB		Yes		No
6. Low suspicion of active PTB		Yes		No
7. Excluded due to pregnancy. CXR postponed to *dd/mm/yyyy:*				

Signature of reporting doctor:

Reference; Department of Health (2011). *Visa Screening Standards: version 1.4*. Abu Dhabi: Health Policy and Regulation, pp.6-11.

Bibliography

1. Paulson T. Epidemiology: A mortal foe. *Nature*. 2013; 502(7470):S2-S3. Doi:10.1038/502s2a.

2. CDC | TB | Testing & Diagnosis | Diagnosing latent TB infection and TB disease. *Cdcgov*. 2018. Available at: https://www.cdc.gov/tb/topic/testing/diagnosingltbi.htm. Accessed December 30, 2017.

3. HIV and Tuberculosis (TB) Understanding HIV/AIDS. *AIDSinfo*. 2018. Available at: https://aidsinfo.nih.gov/understanding-hiv-aids/fact-sheets/26/90/hiv-and-tuberculosis--tb- Accessed December 27, 2017.

4. Latent tuberculosis infection (LTBI). *World Health Organization*. 2018. Available at: http://www.who.int/tb/areas-of-work/preventive-care/ltbi_faqs/en/. Accessed December 27, 2017.

5. Guidelines for treatment of drug-susceptible tuberculosis and patient care (2017 update). *World Health Organization*. 2018. Available at: http://www.who.int/tb/publications/2017/dstb_guidance_2017/en/. Accessed January 6, 2018.

6. Global tuberculosis report. *World Health Organization*. 2017. Available at: http://www.who.int/tb/publications/global_report/en/. Accessed December 29, 2017.

7. Kimbrough W, Saliba V, Dahab M, Haskew C, Checchi F. The burden of tuberculosis in crisis-affected populations: a systematic review. *The Lancet Infectious Diseases*. 2012;12(12):950-965. doi:10.1016/s1473-3099(12)70225-6.

8. Lewinsohn D, Leonard M, LoBue P et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. *Clinical Infectious Diseases*. 2017;64(2):111-115. doi:10.1093/cid/ciw778.

9. Nuzzo J, Golub J, Chaulk P, Shah M. Postarrival Tuberculosis Screening of High-Risk Immigrants at a Local Health Department. *Am J Public Health*. 2015;105(7):1432-1438. doi:10.2105/ajph.2014.302287.

10. Early TB detection. *World Health Organization*. 2018. Available at: http://www.who.int/tb/areas-of-work/laboratory/early-detection/en/. Accessed December 30, 2017.

11. Systematic screening for active tuberculosis: an operational guide. *World Health Organization*. 2018. Available at: http://www.who.int/tb/publications/systematic_screening/en/. Accessed January 13, 2018.

12. WHO | Systematic screening for active tuberculosis: principles and recommendations. *Whoint*. 2018. Available at: http://www.who.int/tb/tbscreening/en/. Accessed January 13, 2018.

13. Davies P, Grange J. Factors affecting susceptibility and resistance to tuberculosis. *Thorax*. 2018. Available at: http://thorax.bmj.com/content/56/suppl_2/ii23. Accessed December 29, 2017.

14. Tuberculosis (TB). *World Health Organization*. 2018. Available at: http://www.who.int/mediacentre/factsheets/fs104/en/. Accessed December 30, 2017.

15. De Keyser E, De Keyser F, De Baets F. Tuberculin skin test versus interferon-gamma release assays for the diagnosis of tuberculosis infection. *Acta Clin Belg*. 2014;69(5):358-366. doi:10.1179/2295333714y.0000000043.

16. Zammarchi L, Casadei G, Strohmeyer M et al. A scoping review of cost-effectiveness of screening and treatment for latent tuberculosis infection in migrants from high-incidence countries. *BMC Health Serv Res*. 2015;15(1). doi:10.1186/s12913-015-1045-3.

17. Fact Sheets | Testing and Diagnosis | TB | CDC. *Cdcgov*. 2018. Available at: https://www.cdc.gov/tb/publications/factsheets/testing.htm. Accessed February 2, 2018.

18. Department of Health. *Health Statistics*. Abu Dhabi: Health Authority of Abu Dhabi; 2014:2-9.

19. Department of Health. *Health Statistics*. Abu Dhabi: Health Authority of Abu Dhabi; 2016:2-14.

20. Department of Health. *Communicable Disease Bulletin*. Abu Dhabi: Health Authority of Abu Dhabi; 2010:7.

21. Department of Health. *Visa Screening Standard: Version 1.2*. Abu Dhabi: Health policy and regulation; 2009:7-15.

22. Department of Health. *Visa Screening Standard: Version 1.4*. Abu Dhabi: Health policy and regulation; 2011:6-11.

23. Azghay M, Bouchaud O, Mechaï F, Nicaise P, Fain O, Stirnemann J. Utility of QuantiFERON-TB Gold In-Tube assay in adult, pulmonary and extrapulmonary, active tuberculosis diagnosis. *International Journal of Infectious Diseases*. 2016;44:25-30. doi:10.1016/j.ijid.2016.01.004.

24. AHS Central Laboratory. *Quantiferon-TB GOLD (In-Tube Method)*. Abu Dhabi: Ambulatory Health Services/ SEHA; 2009:1-6.

25. The End TB Strategy. *World Health Organization*. 2018. Available at: http://www.who.int/tb/strategy/en/. Accessed January 13, 2018.

26. Baussano I, Nunn P, Williams B, Pivetta E, Bugiani M, Scano F. Tuberculosis among Health Care Workers. *Emerging Infect Dis*. 2011;17(3):488-494. doi:10.3201/eid1703.100947.

27. Gordis L. *Epidemiology*. Philadelphia (PA): Saunders Elsevier; 2009.

28. Akobeng A. Understanding diagnostic tests 1: sensitivity, specificity and predictive values. *Acta Paediatr*. 2007;96(3):338-341. doi:10.1111/j.1651-2227.2006.00180.x.

29. Telisinghe L, Fielding K, Malden J et al. High Tuberculosis Prevalence in a South African Prison: The Need for Routine Tuberculosis Screening. *PLoS ONE*. 2014;9(1):e87262. doi:10.1371/journal.pone.0087262.

30. Kramer M. *Clinical Epidemiology And Biostatistics*. Berlin, Heidelberg: Springer Berlin Heidelberg; 1988.

31. Grimes D, Schulz K. Refining clinical diagnosis with likelihood ratios. *The Lancet*. 2005;365(9469):1500-1505. doi:10.1016/s0140-6736(05)66422-7.

32. Piccazzo R, Paparo F, Garlaschi G. Diagnostic Accuracy of Chest Radiography for the Diagnosis of Tuberculosis (TB) and Its Role in the Detection of Latent TB Infection: a Systematic Review. *The Journal of Rheumatology Supplement*. 2014;91(0):32-40. doi:10.3899/jrheum.140100.

33. Linh NN e. Radiographic predictors of subsequent reactivation of tuberculosis. - PubMed - NCBI. *Ncbinlmnihgov*. 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17945072. Accessed January 13, 2018.

34. Nachiappan A, Rahbar K, Shi X et al. Pulmonary Tuberculosis: Role of Radiology in Diagnosis and Management. *RadioGraphics*. 2017;37(1):52-72. doi:10.1148/rg.2017160032.

35. Denkinger C, Dheda K, Pai M. Guidelines on interferon-γ release assays for tuberculosis infection: concordance, discordance or confusion?. *Clinical Microbiology and Infection*. 2011;17(6):806-814. doi:10.1111/j.1469-0691.2011.03555.x.

36. Liu Y, Ou M, He S et al. Evaluation of a domestic interferon-gamma release assay for detecting Mycobacterium tuberculosis infection in China. *Tuberculosis*. 2015;95(4):523-526. doi:10.1016/j.tube.2015.05.007.

37. Metcalfe J, Everett C, Steingart K et al. Interferon-γ Release Assays for Active Pulmonary Tuberculosis Diagnosis in Adults in Low- and Middle-Income Countries: Systematic Review and Meta-analysis. *J Infect Dis*. 2011;204(suppl_4):S1120-S1129. doi:10.1093/infdis/jir410.

38. Nienhaus A, Schablon A, Costa J, Diel R. Systematic review of cost and cost-effectiveness of different TB-screening strategies. *BMC Health Serv Res*. 2011;11(1). doi:10.1186/1472-6963-11-247.

39. Pai M, Zwerling A, Menzies D. Systematic Review: T-Cell–based Assays for the Diagnosis of Latent Tuberculosis Infection: An Update. *Ann Intern Med*. 2008;149(3):177. doi:10.7326/0003-4819-149-3-200808050-00241.

40. Wlodarczyk M, Rudnicka W, Janiszewska-Drobinska B et al. Interferon-Gamma Assay in Combination with Tuberculin Skin Test Are Insufficient for the Diagnosis of Culture-Negative Pulmonary Tuberculosis. *PLoS ONE*. 2014;9(9):e107208. doi:10.1371/journal.pone.0107208.

41. van Cleeff M, Kivihya-Ndugga L, Meme H, Odhiambo J, Klatser P. The role and performance of chest X-ray for the diagnosis of tuberculosis: A cost-effectiveness analysis in Nairobi, Kenya. *BMC Infect Dis*. 2005;5(1). doi:10.1186/1471-2334-5-111.

42. Narasimhan P, Wood J, MacIntyre C, Mathai D. Risk Factors for Tuberculosis. *Pulm Med*. 2013;2013:1-11. doi:10.1155/2013/828939.

43. Updated Guidelines for Using Interferon Gamma Release Assays to Detect Mycobacterium tuberculosis Infection --- United States, 2010. *Cdcgov*. 2018. Available at: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5905a1.htm?s_cid=rr5905a1_e. Accessed February 2, 2018.

44. AHS Central Laboratory. *AFB Smear Preparation And Staining*. Abu Dhabi: Ambulatory Health Services/ SEHA; 2012:1-6.

45. AHS Central Laboratory. *Sputum Collection*. Abu Dhabi: Ambulatory Health Services/ SEHA; 2012:1-6.

46. AHS Central Laboratory. *TB Culture*. Abu Dhabi: Ambulatory Health Services/SEHA; 2012:1-8.

47. Hamilton L. *Statistics With Stata*. 10th ed. Belmont: Brooks/ Cole; 2009:135-215.

48. Viera A, Garrett J. Understanding interobserver agreement: the kappa statistic. *Fam Med*. 2005;37(5):360-3.

49. Study Designs - CEBM. *CEBM*. 2018. Available at: http://www.cebm.net/index.aspx?o=1039. Accessed January 26, 2018.

50. Loney T, Cooling R, Aw T. Lost in Translation? Challenges and Opportunities for Raising Health and Safety Awareness among a Multinational Workforce in the United Arab Emirates. *Saf Health Work*. 2012;3(4):298-304. doi:10.5491/shaw.2012.3.4.298.

51. World Population Prospects - Population Division - United Nations. *Esaunorg*. 2018. Available at: https://esa.un.org/unpd/wpp/. Accessed March 13, 2018.

52. *Worldpopulationreviewcom*. 2018. Available at: http://worldpopulationreview.com/countries/united-arab-emirates-population/. Accessed January 26, 2018.

53. Shah S, Ali R, Loney T et al. Prevalence of Diabetes among Migrant Women and Duration of Residence in the United Arab Emirates: A Cross Sectional Study. *PLoS ONE*. 2017;12(1):e0169949. doi:10.1371/journal.pone.0169949.

54. Chuke S, Yen N, Laserson K et al. Tuberculin Skin Tests versus Interferon-Gamma Release Assays in Tuberculosis Screening among Immigrant Visa Applicants. *Tuberc Res Treat*. 2014;2014:1-11. doi:10.1155/2014/217969.

55. Muñoz L, Gonzalez L, Soldevila L, Dorca J, Alcaide F, Santin M. QuantiFERON®-TB Gold In-Tube for contact screening in BCG-vaccinated adults: A longitudinal cohort study. *PLoS ONE*. 2017;12(8):e0183258. doi:10.1371/journal.pone.0183258.

56. McHugh M. Interrater reliability: the kappa statistic. *Biochem Med (Zagreb)*. 2012:276-282. doi:10.11613/bm.2012.031.

57. Tang W, Hu J, Zhang H, Wu P, He H. Kappa coefficient: a popular measure of rater agreement. *Shanghai Arch Psychiatry*. 2015;27(1):62-67.

58. Yi L, Sasaki Y, Nagai H et al. Evaluation of QuantiFERON-TB Gold Plus for Detection of Mycobacterium tuberculosis infection in Japan. *Sci Rep*. 2016;6(1). doi:10.1038/srep30617.

59. Sester M, Sotgiu G, Lange C et al. Interferon- release assays for the diagnosis of active tuberculosis: a systematic review and meta-analysis. *European Respiratory Journal*. 2010;37(1):100-111. doi:10.1183/09031936.00114810.

60. Al-Maskari F, Shah S, Al-Sharhan R et al. Prevalence of Depression and Suicidal Behaviors Among Male Migrant Workers in United Arab Emirates. *J Immigr Minor Health*. 2011;13(6):1027-1032. doi:10.1007/s10903-011-9470-9.

61. Shah S, Loney T, Sheek-Hussein M et al. Hypertension prevalence, awareness, treatment, and control, in male South Asian immigrants in the United Arab Emirates: a cross-sectional study. *BMC Cardiovasc Disord*. 2015;15(1). doi:10.1186/s12872-015-0024-2.

62. Fiske C, Yan F, Hirsch-Moverman Y, Sterling T, Reichler M. Risk factors for treatment default in close contacts with latent tuberculous infection. *The International Journal of Tuberculosis and Lung Disease*. 2014;18(4):421-427. doi:10.5588/ijtld.13.0688.

63. Xiao Y, Isaacs S. Enzyme-linked immunosorbent assay (ELISA) and blocking with bovine serum albumin (BSA)—not all BSAs are alike. *J Immunol Methods*. 2012;384(1-2):148-151. doi:10.1016/j.jim.2012.06.009.

64. Seroprevalence of measles, mumps, rubella, varicella–zoster and hepatitis A–C in Emirati medical students. BMC Public Health. 2012;12(1). doi:10.1186/1471-2458-12-1047.

Curriculum Vitae

Huda Saeed Obaid Mohamed Subait Al Shemeili
United Arab Emirates
Mobile (050) 8181280
subait_h@hotmail.com
hbnaishemali@seha.ae
subait_h@hotmail.com

Personal details:	Date of birth: Dec 06, 1978 Born in Ras Al Khaimah, UAE Present Residence: Abu Dhabi
Education:	DrPH: from Johns Hopkins Bloomberg School of Public Health, USA, 2018 HMS-GCSRT: Harvard Medical School Global Clinical Scholars Research Training (GCSRT) program, USA, 2014 MPH, Master of Public Health: Johns Hopkins Bloomberg School of Public Health, USA, 2011 MBBS: Faculty of Medicine and Health Sciences, United Arab Emirates University, Collage of Medicine and Health Sciences, Al-Ain, 2003 General Secondary Education (Science Section): July 1996
Current post:	Specialist Physician, SEHA, AHS, DPSC AD Joined SEHA, AHS since 2008 Acting clinic Lead: Disease Control (DC) Section

Experience:

Promoted to a specialist physician, DC section, AHS, SEHA, (2014). Acted as the clinic lead since then and held responsibilities including supervision and annual appraisals of public health technicians working in DC.

Received SEHA sponsorship for Harvard Medical School Global Clinical Scholars Research Training (GCSRT) program, (2013). This is a one year training program in clinical research.

Had successfully passed the Johns Hopkins Bloomberg School of Public Health (JHSPH) qualifying exam with “honor Pass”, (2013)

Nominated and acted as a member of the Primary care committee, AHS, SEHA, (2012-2014).

Nominated and acted as a member of the Privileging committee, AHS, SEHA, (2012-2014)

Nominated and acted as a member of the AHS's Medical Executive Committee, AHS, SEHA, (2012-2014).

Nominated and acted as DPSC AD lead Physician (2012-2014) where I was responsible for the supervision and annual appraisals of physicians working in DPCS AD (13 physician) and one on-charge nurse.

Participated as a member in TB Task Force/ DOTS initiative meetings since August 2011-2014 and contributed a proposal raised to the higher management in SEHA for DOTS program implementation in Abu Dhabi.

Joined Disease Control Section in DPSC AD, AHS, SEHA, (2011). Dealing with contagious diseases under investigation such as suspected tuberculosis cases, malaria eradication and contact management.

Attended workshops training in outbreak response and management. Participated in field visits to provide vaccinations such as hepatitis A vaccines to contacts and investigated TB contacts during outreach visits as part of outbreak management initiatives in Abu Dhabi.

Graduated as an MPH holder (2011) and started DrPH program, (2011)

Accepted in the Johns Hopkins Bloomberg School of Public Health's Master of Public Health and Doctor of Public Health Program for the Emirate of Abu Dhabi (MPH-DrPH Program for the Emirate of Abu Dhabi), (2008)

Participated in the National Gender Mainstreaming Initiative Course arranged by the UNDP and the Women Union Institute, (2008)

Participated in the meetings of the National breast cancer awareness committee, 2008

Joined SEHA, AHS in 2008 and worked as an Medical doctor in visa screening section

Worked as an officer/ MD in ZMH, initially in accident and emergency department and pediatric department from 2004 till 2006

Successfully completed Internship Training (2003- 2004)

Elective course in Sant Joseph's Hospital, University of Western Ontario, London, Ontario, Canada, (2002).