Prevalence and clinical characteristics of Diabetes in Tuberculosis patients in Newham

Jalal Miah

A thesis submitted in partial fulfilment of the requirements of Sheffield Hallam University for the degree of Professional Doctorate

July 2020

Candidate Declaration

I hereby declare that:

1. I have not been enrolled for another award of the University, or other academic or professional organisation, whilst undertaking my research degree.

2. None of the material contained in the thesis has been used in any other submission for an academic award.

3. I am aware of and understand the University's policy on plagiarism and certify that this thesis is my own work. The use of all published or other sources of material consulted have been properly and fully acknowledged.

4. The work undertaken towards the thesis has been conducted in accordance with the SHU Principles of Integrity in Research and the SHU Research Ethics Policy.

5. The word count of the thesis is 70496.

Name	Jalal Miah
Date	July 2020
Award	DProf
Faculty	Faculty of Health and Wellbeing
Director(s) of Studies	Professor Nicola Woodroofe

Abstract

Background. There is substantial evidence of the increasing burden of diabetes mellitus (DM) posing a threat to tuberculosis (TB) control globally. The global estimate of DM is expected to reach 592 million by 2030. In Europe, the estimated prevalence of DM is 8.5% and the rate of TB is 40 cases per 100,000 persons, with 74, 000 new cases per year (Badawi *et al.,* 2014). It is estimated that DM triples the risk of developing TB when exposed an actively infected TB case, as well as modify the presenting features of TB, with more atypical radiological presentation, adverse TB treatment outcome, increased rates of relapse rates and death. The UK has the highest number of cases of TB in Western Europe. The London Borough of Newham has the highest number of cases in the UK, and this poses a public health risk. Thus, this research is aimed at analysing the prevalence of DM in TB patients in Newham and to describe the clinical presentation of Tuberculosis-Diabetes Mellitus (TB-DM) patients. ***Aim and objectives***. The major objectives: 1. To determine the prevalence of DM in TB patients in Newham, with close attention paid to differences between UK-born and non-UK born patients; 2. To analyse the demographic, clinical characteristics and microbiological features associated with TB-DM compared with TB only patients. ***Methodology.*** The study was a retrospective cross-sectional survey on the prevalence of DM among diagnosed adult TB patients in Newham between the period of 2012-2015 with a follow-up period of 24 months from the London Borough of Newham, participants recruited from Barts Health NHS Trust. ***Results.*** Among the 489 TB patients used for this study, the prevalence of DM was 25.8 (range 24.3 – 33.0), greater than the UK average of 6.0%, and from the general population of Newham (3.9%) at the time of the study. The average patient age ranged from 27.5-49.9 years, with 85.3% of TB cases reported in the non-UK born population (P-value 0.087). Non-UK born individuals are more likely to be infected with TB, likely as a result of recent travel to high TB incidence areas or reactivation of latent TB, DM is not exclusively associated with the non-UK born population. DM was found to be significantly associated with age (P-value <0.005), comorbidities (P-value

0.007), worsening symptoms (night sweats (P-value 0.01), fever (P-value 0.02) and weight loss (P-value <0.001), social factors (heavy drinking (P-value 0.054) and person who injects drugs (P-value 0.04)). Microbiologically, the TB-DM cohort was likely to remain infectious for a longer period due to a higher bacterial load (P-value <0.001). ***Conclusion.*** In conclusion, DM poses a major challenge to controlling TB in Newham. A bi-directional screening of DM and TB cases, including screening of latent TB with DM, and tackling social determinants, i.e. the rise in the homeless population, use of illicit drugs and alcohol abuse, should be further evaluated to control the impact of TB cases.

Contents

List of Appendices

List of Tables

List of Figures

Abbreviations

AFB Acid-fast bacilli,

BMI Body mass index

CD4+ Cluster of differentiation 4 positive

CD8+ Cluster of differentiation 8 positive

CDC Centre for disease control and prevention

CI Confidence intervals

EPTB Extra-pulmonary tuberculosis

FBG Fasting blood glucose

HIV Human Immunodeficiency Virus

ICD International Classification of Diseases

IDF International Diabetes Federation,

IFN-γ Interferon gamma

IGT Impaired glucose tolerance

IL Interleukin

IRR Incidence rate ratios

Mtb *Mycobacterium tuberculosis*

NICE National Institute for Clinical Excellence

OR Odds ratio

PTB Pulmonary tuberculosis

RR Relative risk

T2DM Type 2 diabetes mellitus

TB Tuberculosis

Th1 T helper 1

TNF-α Tumour necrosis factor alpha

WHO World Health Organization

AIDS Acquired immunodeficiency syndrome

ART Antiretroviral treatment

BG Blood glucose

DM Diabetes mellitus

DOT Directly observed therapy

HbA1c Glycosylated haemoglobin

IFG Impaired fasting glucose

IGT **Impaired glucose tolerance**

LTBI **Latent tuberculosis infection**

MDR-TB **Multidrug-resistant TB**

OGTT **Oral glucose tolerance test**

Pre-DM **Pre-diabetes**

RBG **Random blood glucose**

CXR **Chest X-ray**

ZN **Ziehl Nielsen**

Acknowledgements

I would firstly like to show both my gratitude and say thank you to my study supervisor, Professor Nicola Woodroofe, who went above and beyond the role of a supervisor to help me complete my thesis. I thank Professor Woodroofe for sharing her experience through her scientific guidance, providing constructive feedback of my work, and having immense patience to allow me to complete this piece of work during all these years.

I would like to thank my colleagues at Barts Health NHS Trust within the IPCT/ ID/ Microbiology/ Respiratory team for their continued support.

I would like to give a special thanks to Dr Simon Tiberi, who helped guide, develop and made this research possible. Dr Simon Tiberi provided both clinical and academic expertise, as well as guided me to participate in producing peer-review publications. This would not have been possible without the help of Dr Tiberi and the way he has developed me in my clinical practice.

I also thank the TB Net collaboration for exposure to the TB expertise made available across so many other countries, enabling work on research projects aimed at TB-DM.

I would like to say a big thanks to my friends and my family for their support and help over these last six years. Finally, I would like to show my heartfelt gratitude to my wife Ratna and my baby boy Dawud. Both had to endure hard times, especially when I had to dedicate time to the thesis and give up valuable time with my young family. I am ever so grateful to them both as we all eagerly wait for the new addition of our baby daughter in October-20. Without their love, patience, support and encouragement, it would not have been possible to complete this thesis and I am truly grateful to have them in my life.

Chapter 1 - Introduction

Chapter 1 - Introduction

1.1 Background

Globally, Tuberculosis (TB) remains a major public health concern and in 2016, it was estimated that 10.4 million people have developed active TB (new cases and relapses), and a further 1.3 million HIV- negative and 374,000 who were HIV-positive have died from the disease (Noubiap *et al.,* 2019). TB disease historically has been associated with risk factors including HIV, substance misuse, chronic renal disease, malnutrition, and treatment with immunosuppressants or immunosuppressive conditions (Narasimhan *et al.,* 2013). It is only now that there is a focus on diabetes mellitus (DM) as a risk factor for TB. Diabetes triples the risk of developing TB, and poor glycaemic control affects treatment outcomes, including treatment failure, relapse and death. It is estimated that diabetes accounted for 10.6% of the global TB deaths among HIV-negative individuals in 2015 (Harris *et al.,* (2016). In 2017, globally, 425 million individuals are estimated to have been affected by diabetes and a 48% increase to 629 million individuals who will have diabetes by 2045 has been predicted (www.idf.org). The current trend would suggest this increase in the prevalence of diabetes will contribute to an increase in TB cases. In England, the rates of TB have declined since 2014, with a total reduction of 28% in incidence from 2014 to 2018 (PHE, 2019, Tuberculosis in England). However, London had the highest rate of TB cases reported and the Borough of Newham had the highest in England. Regions which experience a high incidence of TB are also likely to experience a large increase in the diabetes prevalence (Noubiap *et al.,* 2019). In England, and especially in the highest risk cities, further work is required to improve the outcome of those most at risk of TB. Current TB work is focused on a 5-year TB Action Plan (2020 to 2025) to move England towards TB elimination. Therefore, it is crucial that the diabetes epidemic is curbed as part of this strategy, to tackle the burden of TB in England and, more predominantly, in high-incidence areas.

However, there is limited recent study in England to present a clear estimate of a regional burden of diabetes among patients with TB. This is the first study on the prevalence of TB and DM studying the London Borough of Newham, which has the highest incidence of TB compared to any western city. The findings from this study will hopefully help curb the burden of diabetes among active TB cases through a systematic screening for DM in TB patients.

1.2 Introduction

The increasing burden due to the co-occurrence of TB and DM is an emerging global health concern. The relationship between TB and DM was first discussed by Richard Morton in 1698 in his Phthislogia: Or a Treatise of Consumptions, in which he described DM symptoms as a consuming disease associated with TB (Olayika, Anthonia & Yetunde 2013). Prior to the development of effective treatment for either disease, TB was the leading cause of death among DM patients. In recent times, with the global increase of DM and the struggle to eradicate or reduce TB, the incidence has resulted in an increased number of individuals experiencing concurrent TB and DM conditions. This co-occurrence of TB-DM pandemic exemplifies a new epidemiological transition where chronic conditions commonly occur with an infectious disease, not only in the same population but the same individual.

1.3 *Mycobacterium tuberculosis* overview

Tuberculosis disease in humans is caused by the bacterium *Mycobacterium tuberculosis* (Mtb), that is a non-motile, slow-growing, rod-shaped bacillus (Figure 1.1) (Grosset & Chaisson, 2017; Brennan, 2003). Mtb spreads via respiratory droplets that contain the *tubercle bacillus*. Bacilli are expelled from an infective person and is inhaled by close contacts and infected with Mtb. The outcome of the disease is determined by the protective ability of the host immune system and the pathogenicity of these bacteria. In the vast majority of cases, the host can control the infection and contain it inside a granuloma, which is an aggregate of immune cells which walls off the mycobacteria, but

does not eradicate them, such that they are contained and do not spread the disease (Grosset & Chaisson, 2017; Brennan, 2003).

1.4 Host-pathogen interactions

Mycobacteria are a set of micro-organisms which can cause disease in humans and they consist of *Mycobacterium tuberculosis, Mycobacterium africanum, Mycobacterium bovis, Mycobacterium microti* and *Mycobacterium canetti*. Mtb is an intracellular pathogen that can infects human and animals. It is an acid-fast, non-motile, non-encapsulated, non-spore-forming bacillus. It multiplies successfully in tissue with high oxygen content, i.e. the lungs. The cell wall of a mycobacterium is rich and can be impermeable to dyes unless blended with phenol. Mtb is neither a gram positive or negative bacterium and it resists decolourisation with acidified organic compounds (Grosset & Chaisson, 2017; Brennan, 2003). Mtb tuberculosis multiples every 15-20 hours, which makes it a slow-replicating pathogen compared to other organisms, such as *Escherichia coli* which divides every 20 minutes. However, the slow replication of the bacterium allows the Mtb to persist in a latent state, resulting in the need for a longer treatment duration and preventive therapy. Infection with Mtb results from the exposure of the lungs mucous membranes to the infected aerosol droplets from an infected individual. These aerosol droplets are 2-4 µm in diameter in individuals with active pulmonary TB (Patterson *et al.,* (2018); a single cough can generate 3,000 infective droplets, with as few as 10 bacilli required to initiate an infection. Once the bacilli are inhaled into a host, the tubercle bacilli are deposited within the terminal air-space of the lung (Grosset & Chaisson, 2017; Brennan, 2003). The organism usually multiplies in 2-12 weeks until it reaches between 1000–10,000 in number, which is sufficient to stimulate a cellular immune response that can be detected by a response to the tuberculin skin test. The proportion of Mtb infected individuals going on to developing active clinical tuberculosis infection is low, with a lifetime risk of about 10% due to activation of latent TB. Latent TB is a clinical disorder in persons infected with Mtb whereby the host retains control over replication of the bacterium to prevent development into an active infection (Amin *et al.,* 2018). The risk of

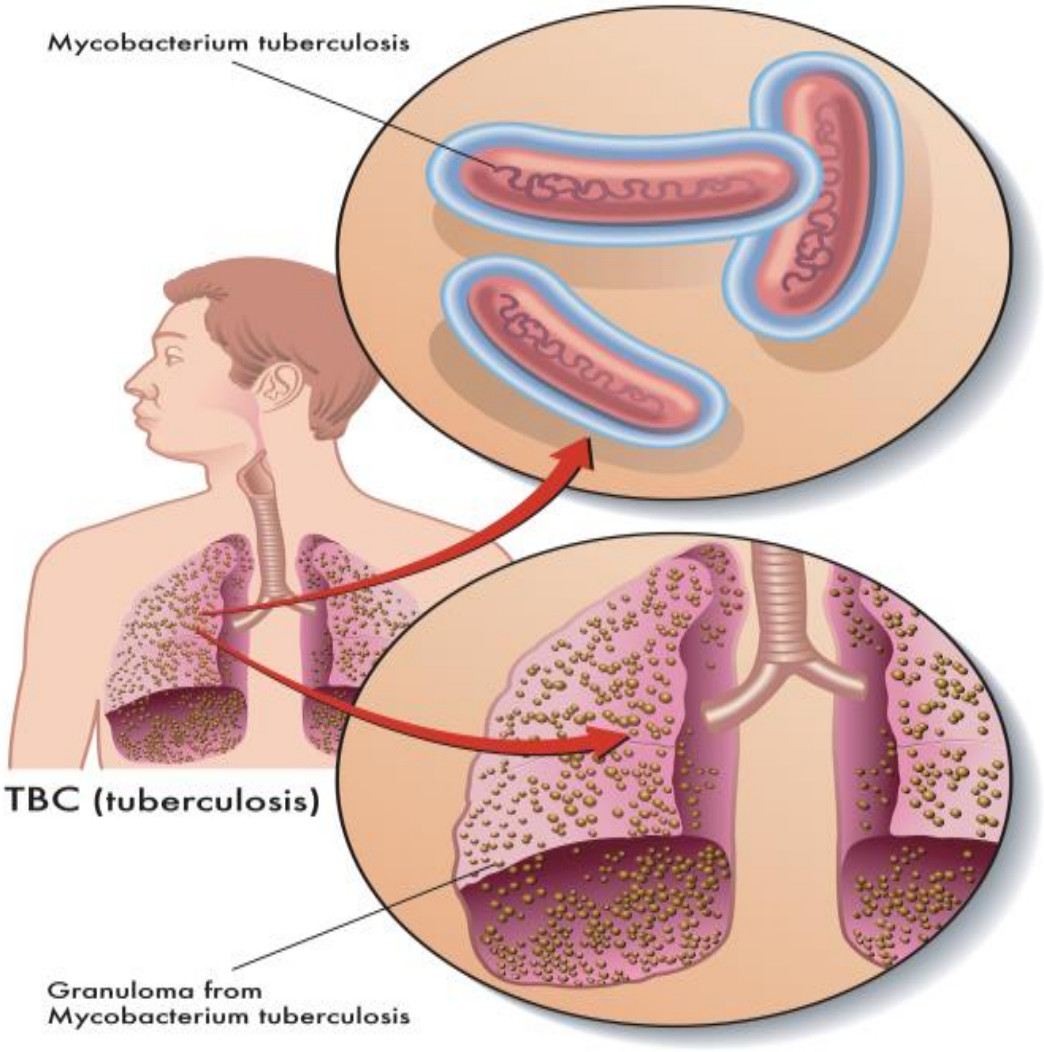
infection is highest within the first few years after inhalation of Mtb but decreases substantially thereafter. An immunocompetent person will likely eliminate the inhaled Mtb or retain it in a latent state. TB also reactivates from latent infection and risk is associated with age, with many aging populations have the highest TB incidence rates per capita in older age groups (Ku and Dodd, 2019).

Mtb promotes a host immune reaction that is nonspecific and expressively antigenic. This antigenicity is owed to the cell wall including phospholipids and glycoproteins, which triggers Langerhans cells, including lymphocytes and polymorphonuclear leukocytes. In most cases the infection is cleared by the host immune system or suppressed into an inactive latent form (Grosset & Chaisson, 2017).

1.5 Innate immune defence against Mtb

For Mtb bacteria to cause an infection, they must pass through the physical defence mechanisms of the upper respiratory tract (URT), which are the nose, nasal cavity, turbinates and the pharynx, and hence avoid the infringement and expulsion by mucociliary action or through cough and sneeze reflexes. The URT also contains antimicrobial substances which aid in bacteria elimination, including cathelicidin and defensin proteins, which play a major role in the active lysing of Mtb bacilli (Grosset & Chaisson, 2017). If Mtb bacilli can penetrate through the URT defences they then need to overcome the lower respiratory tract (LRT) defence mechanisms (Lerner, Borel & Gutierrez, 2015). Any organism of a size of 10 µm or less can pass through the initial physical barrier into the LRT, which includes the larynx, trachea, bronchi and the lungs. Once in the LRT, mucociliary and antimicrobial action takes place to encourage the elimination of Mtb. The bronchioles and alveoli are covered with a fluid layer which contains antimicrobial substances, immunoglobulins and molecules of both forms of the alternative and the classical complement pathway (Grosset & Chaisson, 2017).

Figure 1.1. *Mycobacterium tuberculosis* and Progression of Disease



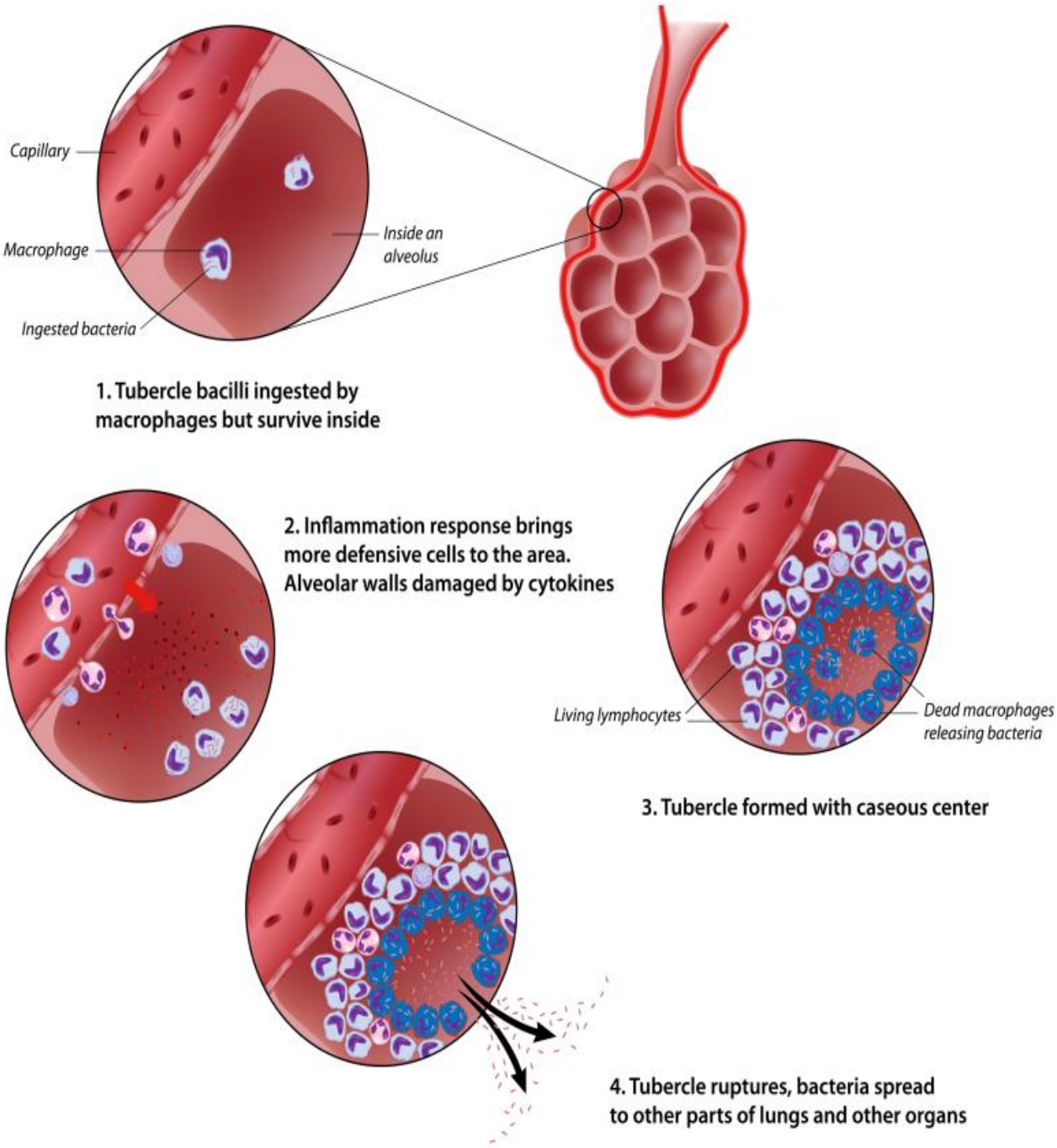
Tuberculosis in the lung and formation of granuloma (Copyright made available from Fotosearch.com to reproduce image).

1.6 Cellular immune response against Mtb

Once Mtb has penetrated the LRT, several different host immune cells, which can all mediate different immune responses after the initial contact with Mtb bacterium, are then encountered. Mtb can be phagocytosed by these cells, such as macrophages, dendritic cells and/or pneumonocytes (Cooper, 2009; Grosset & Chaisson, 2017). This process occurs via many routes: the multiple components of the bacterial cell wall act as a ligand for host cell receptors to facilitate bacterial uptake. Once Mtb is engulfed by the immune cells, the phagosomes are fused with lysosomes, resulting in the formation of a phagolysosome. Within the phagolysosome, the bacteria encounter a hostile environment. This acid-rich environment creates toxic reactive oxygen and nitrogen species, lysosomal enzymes and toxic peptides; such exposure is detrimental for Mtb. However, some Mtb bacilli can survive in the phagocytic cells by blocking the phagolysosomal fusion process. Macrophages, which are unable to destroy the Mtb, become a perfect environment for the bacteria to “hide” within and replicate. Dendritic cells, which phagocytose Mtb but are also unable to kill the bacilli, migrate to the draining lymph nodes, where they present bacterial antigens to naive effector T-cells (Kumar *et al.,* 2016). Presentation of the bacterial antigen to naive effector T-cells causes T-cell activation. The activated T-cells can then migrate into the circulatory system, where they remain until they reach a site of TB infection, such as the lung (Cooper, 2009).

Once activated at the site of TB infection, the CD8+ T cells and CD4+ T cells can control TB infection, although the mechanism through which this occurs is not fully understood. The CD4+ T cells can produce cytokines, such as tumour necrosis factor alpha and interferon gamma (IFNγ), which activate macrophages, enabling the killing of Mtb bacteria. CD8+T cytotoxic cells can destroy infected macrophages and Mtb bacilli by releasing cytotoxic mediators such as granulysin, perforins and granzymes (Grosset & Chaisson, 2017). Furthermore, certain Mtb can persist, subverting the dendritic immune response which brings about T-cell activation (Grosset & Chaisson, 2017).

Figure 1.2. Mtb Pathogenesis



A minimal dose of Mtb aerosolised into a host into the lower airways and the alveolar tissue can cause an infection. Once inhaled into the lungs the bacteria do not propagate until nine days' post-infection, when they can be found in the draining lymph nodes from the lung. This dissemination and the initial activation of naive T cells coincide. The response requires 18--20 days to achieve an effective amount and consequently prevent bacterial growth (Copyright made available from Fotosearch.com to reproduce image).

1.7 Classic clinical presentation of TB

Tuberculosis disease is a multi-system disease with a myriad presentation. The classic features of active pulmonary TB are as follows:

- Cough
- Weight loss/ anorexia
- Fever
- Night sweats
- Haemoptysis
- Chest pain (can be a cause of tuberculosis pericarditis)
- Fatigue

Other sites of infection include TB meningitis, which is associated with headaches, which can be intermittent or persistent for a period of 2-3 weeks. With TB meningitis, a subtle permanent mental status changes, which may progress over a period of days to weeks, and low-grade or absent fever is common.

In skeletal TB, symptoms can range from back pain and stiffness to lower-extremity paralysis and TB arthritis, which usually involves one joint being implicated (Heemskerk *et al.,* 2015).

In gastrointestinal TB, non-healing ulcers of the mouth or anus are common. Difficulty in swallowing (with oesophageal disease), abdominal pain, which can mimic peptic ulcer (with gastric or duodenal infection), malabsorption, pain, diarrhoea and haematochezia (with infection of the colon) are also common (Crus & Starke, 2007).

1.8 Immunology and TB-DM

DM increases the risk of TB infection including patients presenting with more severe symptoms and worse overall clinical outcome (Gil-Santana *et al.,* 2016). The dual presentation of TB-DM requires further investigation especially in the management of TB-DM patients. Raposp-Garcia et al.

(2017) analysed blood transcriptome for immunological events in the lung, and the gene expression profile specific to active TB, comparing non-diabetic TB patients to TB-DM patients, and found a difference in the blood of gene expression suggestive of a changed immune response. The TB-DM cohort had a distinct difference in their plasma cytokine and growth factor levels, which was associated with increased neutrophilic inflammation (Prada-Medina *et al.,* 2017).

The mechanism responsible for TB susceptibility and severity caused by DM is not well understood. However, *in-vitro* testing in diabetic mice has shown a delayed response by alveolar macrophages after infection by inhaling Mtb and subsequent expression in the lungs, the T cell medicated immunity showing a greater burden of inflammatory pathology due to the higher bacterial burden along with possible defects in counter-regulation (Raposo-Garcia *et al.,* 2017). The elevated level of plasma cytokines and growth factors are distinguishable in the TB-DM mice from the non-diabetic TB mice group. When comparing neutrophil inflammation with TB severity, DM amplifies this response, which is likely to reflect the high bacterial load, or a specific perturbation of the immune function.

In published work on the human blood transcriptomic signature of active TB, a role for type 1 IFN signalling in neutrophils has been highlighted (Berry *et al.,* 2012). A high molecular degree of perturbation was positively related to radiographic severity of TB, a high neutrophil count and a low BMI. Previous data has demonstrated that BMI is a protective mechanism in TB, but this association is lost in diabetic obesity. Low high-density lipoprotein (HDL) with high molecular degree of perturbation is unique in the TB-DM subgroup. HDL cholesterol modulates innate and adaptive immunity via connections with lipids on lymphoid and myeloid cells. The very low HDL cholesterol is associated with pre-diabetes and T2DM, which may act as an independent factor for increasing susceptibility to Mtb. These findings suggest the significance of an increase in cytokines, growth factors and other biomarkers associated with diabetic complications (Berry *et al.,* 2012).

The possible factors which may impact the host response from patients with DM are short-chain fatty acids (SCFAs), which are a key metabolic product of fermentation of non-digestible dietary fibres by the gut microbiota (Knudsen *et al.,* 2014). It is believed that DM also alters the make-up of the gut microbiota affecting metabolic process and immune response. SCFAs, control immune and inflammatory responses, including prompting a response to Mtb. Out of all the SCFAs, butyrate (C4) is the most prominent of all SCFAs, as it directly affects the immune response via at least two mechanisms: activation of G-protein coupled receptors (GPCRs) and inhibition of histone deacetylase (HDAC) (Knudsen *et al.,* 2014). In the presence of DM both these mechanisms are altered causing a dysfunctional immune response. Several studies have reported that a drop in C4-producing bacteria in T2DM, which all exhibit anti-inflammatory properties, and reduced quantities of C4 reduces the Mtb-induced pro-inflammatory cytokine feedback on either the transcriptional and/or the translational levels, altering the immune response in TB-DM patients (Lachmandas *et al*., 2016).

The anti-inflammatory result is independent of HDAC activity and Toll-like receptor (TLR) signalling, both the eicosanoid pathway and cellular metabolism. The inhibitory effect of SCFAs on the production of TNFα and IL-1B and C2, C3, and C4 has a much stronger inhibitory effect on T-cell-derived cytokine IL-17 than on T-cell-derived cytokines IFN-y and IL-22. C4 is also strongly correlated with decreased Th17 proliferation; the stimulatory impact of C3 and C4 on anti-inflammatory IL-10 release with Mtb, and IL-10 delineated is an important mediator in Mtb disease as it depresses pro-inflammatory response to Mtb (Knudsen *et al.,* 2018). The suppression of cytokine production and the multinucleated giant cell formation, which is a significant element for preventing infection in macrophages and inhibits the progression of protective immunity.

1.9 TB diagnosis

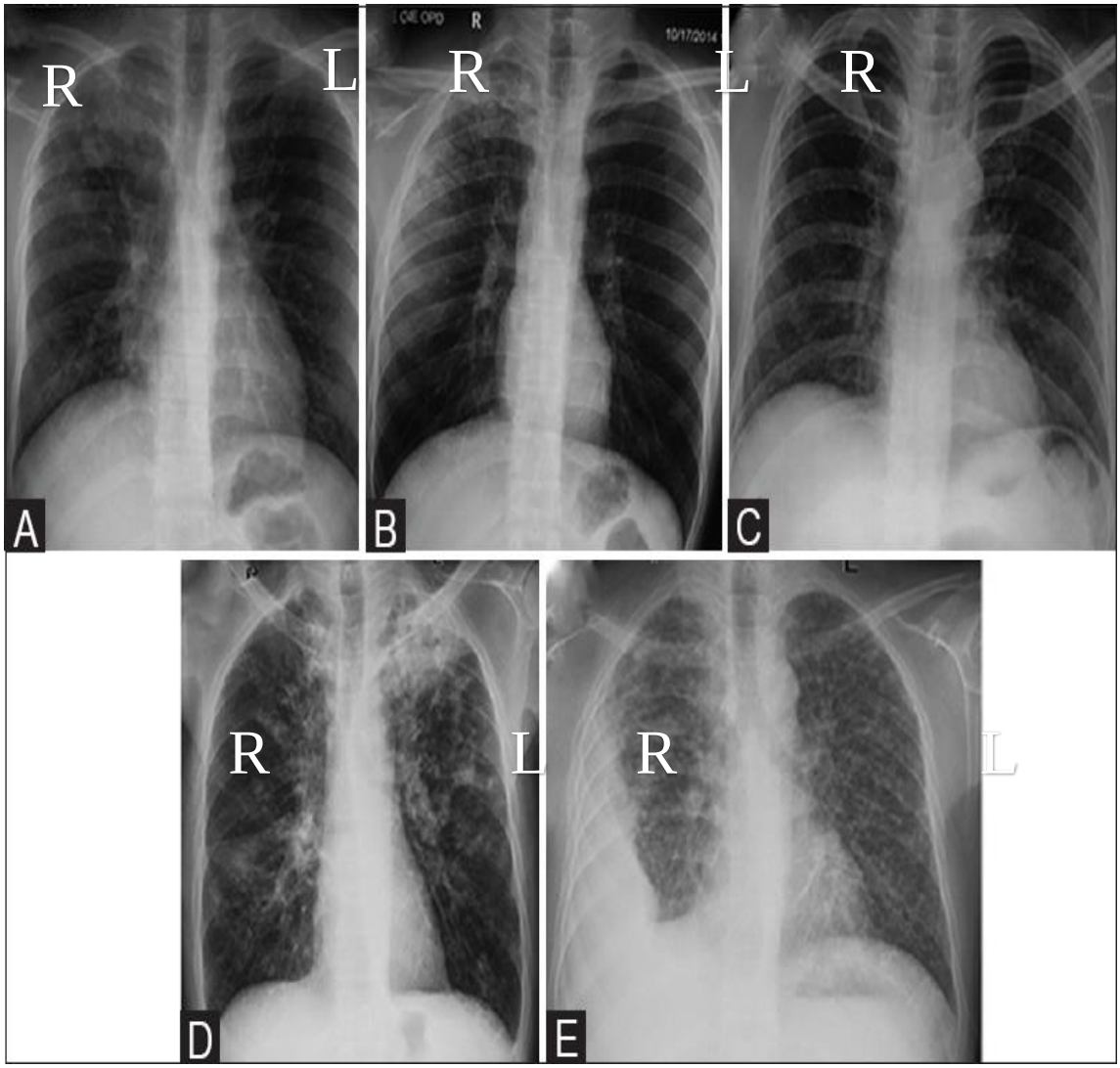
Early diagnosis is key to effective treatment of TB disease. However, there is no global consensus on the finite definition of a TB diagnosis and thus no

standardised diagnostic guidelines are available. Diagnosis of TB can be made clinically and/or microbiologically. Testing methods for TB include a Mantoux tuberculin skin test with a purified protein derivative (PPD) for diagnosis of active or latent TB infection or a blood test based on interferon-gamma release assay (IGRA) utilizing antigens, which are unique to Mtb, to diagnose latent infection. For laboratory microbiology testing, acid-fast bacilli (AFB) smear and culture, using sputum or other samples are obtained from a patient (Takasaki *et al.,* 2018). AFB culture has come to be the gold standard test for the diagnosis of TB. Not having a positive AFB smear result does not exclude TB disease. Drug susceptibility testing usually follows a smear then a culture test. Symptoms and radiographic film findings do not differentiate multi-drug-resistant TB (MDR-TB) from fully-susceptible TB; therefore, further testing using automated molecular testing and rapid test (i.e. TB-RIF assay) are used - a polymerase chain reaction (PCR) technique which identifies Rifampicin-resistant TB.

A chest radiograph is taken, mainly in pulmonary TB, this is to investigate for possible pulmonary tuberculosis, which may show the following (see figure 1.3):

- A cavity formation: which indicates advanced infection, associated with a high bacterial load.
- Non-calcified round infiltrates: this may mimic lung carcinoma.
- A tuberculoma; calcified nodule (usually 2-20mm) representing an old infection.
- Primary TB: infiltrates in a middle or lower lung region: this may present as a pneumonia-like feature.
- Reactivation of TB: pulmonary lesions in the posterior segment of the right upper lobe, apicoposterior segment of the left lobe and apical segments of the lower lobes.

Figure 1.3. Radiological Presentation of Mtb



A-E: Chest radiographs in active TB. (A) Chest x-ray (CXR) depicts right (RT) upper zone consolidation with prominent RT hilum. (B) CXR in another individual show multiple coalescent air-space nodules at RT upper zone. (C) CXR at another individual show multiple ill-defined reticulo-nodular lesions in both lungs with basal predominance, suggestive of miliary TB. (D) CXR in another patient shows active post-primary TB. Cavity with encircling consolidation is seen in left (LT) upper zone. Scattered air-space nodules can be seen in both lungs using hilar adenopathy. (E) There is a RT-sided lobulated pleural effusion with numerous air-space nodules in both lungs (Bhalla *et al.,* 2015).

1.10 Epidemiology of TB

1.11 Global Epidemiology of TB

Tuberculosis is thought to be a leading cause of death by an infectious agent, with multiple people dying every minute from a curable disease (Dodd *et al*., 2018). Based on notification reports on the incidence of TB infection, 10 million new TB cases were reported globally by the end of 2017 (WHO, Global Tuberculosis Report, 2017; MMWR, 2019), with 1.3 million deaths in non-HIV infected individuals, and an additional 300,000 deaths from TB amongst HIV-positive individuals. Of these cases, 5.8 million of those with active TB infection were men, 3.2 million women and 1 million children. Globally, over 90% of the cases occurred in the age group over the age of 15 years, 9% of the cases occurred in those living with HIV (72% of these are in Africa) and two-thirds of the cases were reported in the following eight countries: India (27%), China (9%), Indonesia (8%), the Philippines (6%), Pakistan (5%), Nigeria (4%), Bangladesh (4%) and South Africa (3%) (figure 1.4) (WHO, 2017). In addition to these, a further 22 countries in the WHO list of 30 high incidences for TB rates accounted for 87% of worldwide cases.

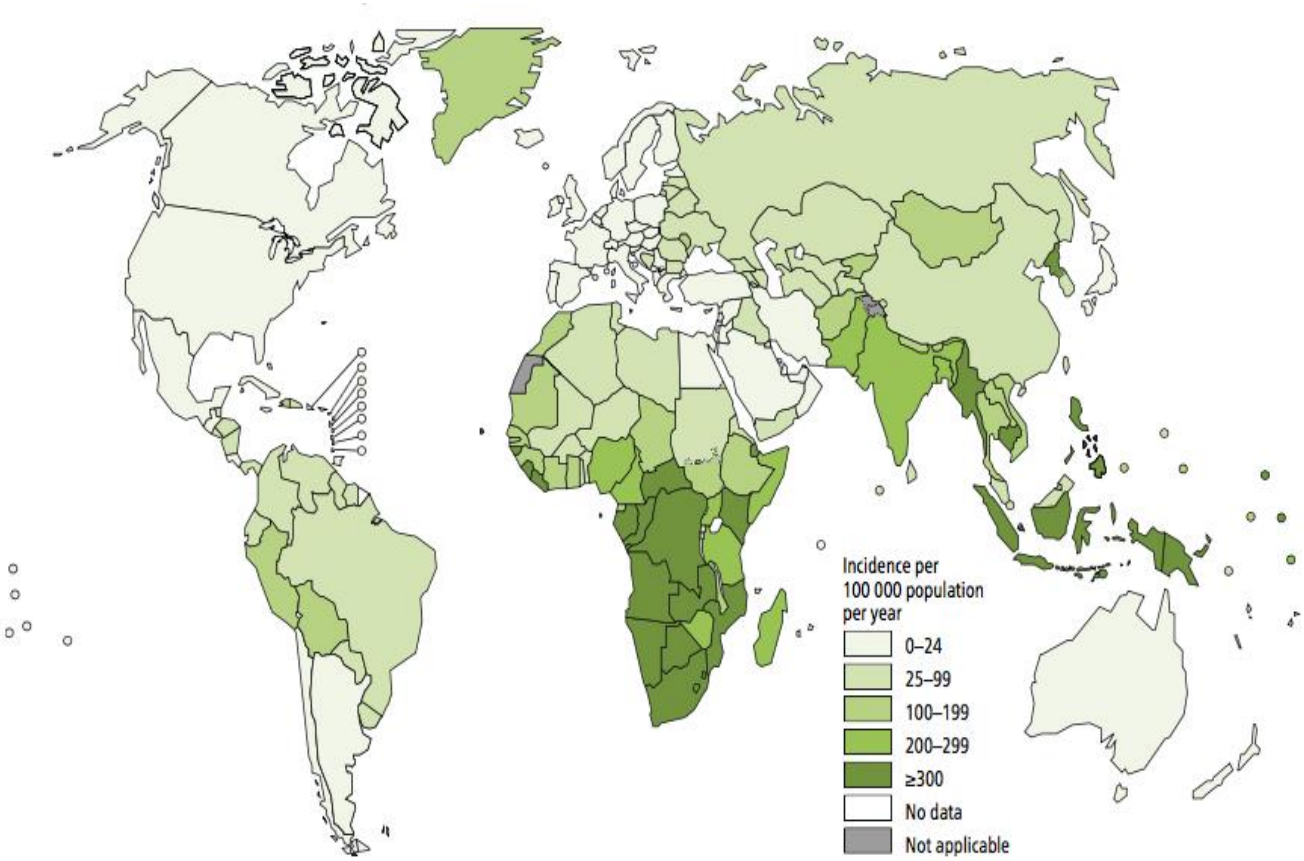
In general, developed countries, including the UK, have low TB incidence rates among UK-born nationals, but a rising number of TB cases are reported amongst non-UK born residents (Glaziou, Floyd & Raviglione, 2018). Death registrations have seen an increasing number of TB cases in the former Soviet countries since the 1980s, but falling numbers in Central Europe, Latin America and in the industrialised world (Alimuddin, Zumla and Schaaf, 2009). It is not possible to assess the precise global trend of TB deaths because many countries, including most in Africa and Asia, have no system of death registration.

1.12 Risk Factors

The common risk factors associated with TB are human immunodeficiency virus and acquired immunodeficiency syndrome (HIV/AIDS), social and economic decline, immigration and ageing. It is estimated that up to 11% of all

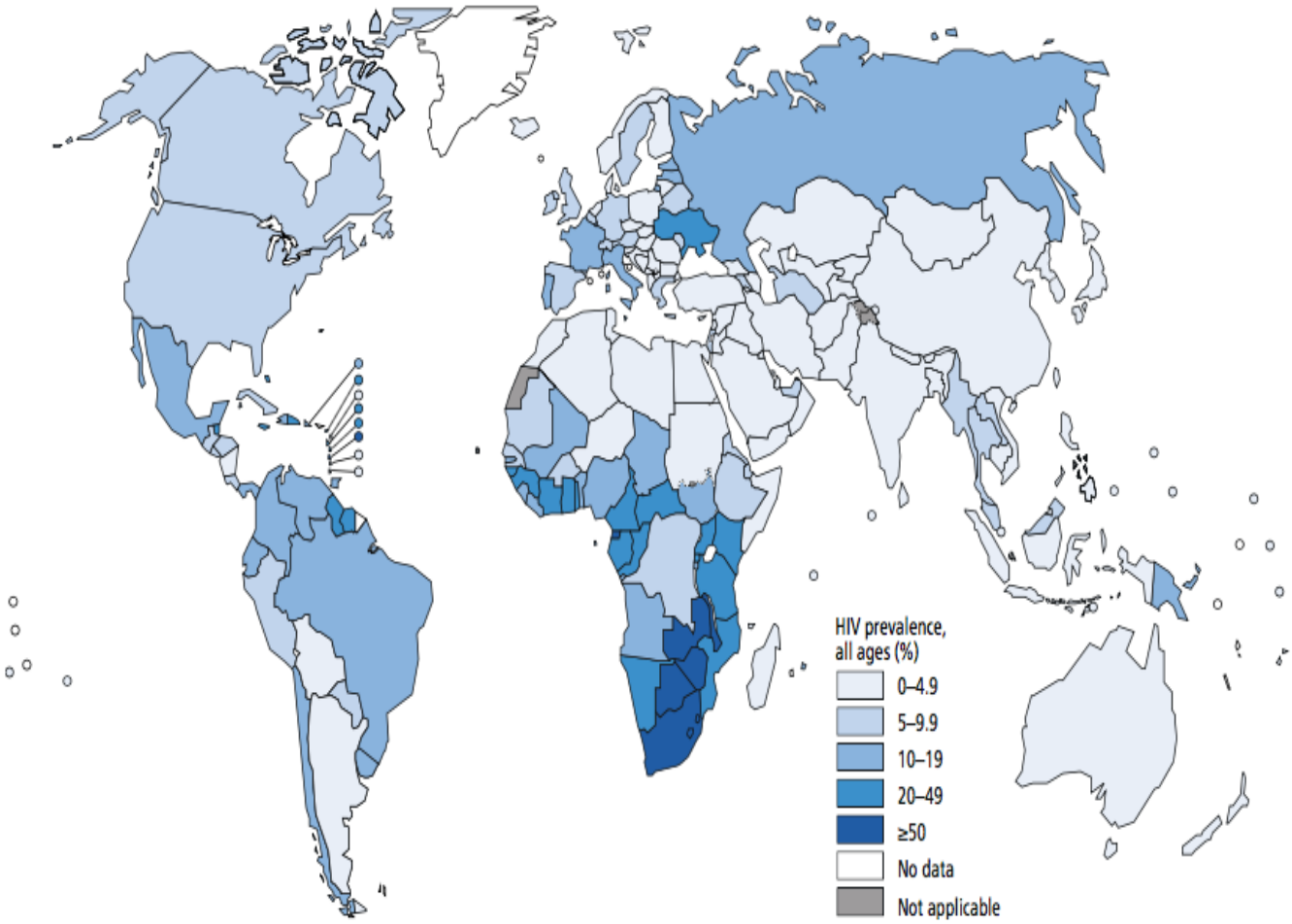
new adult TB patients were co-infected with HIV in 2017 (figure 1.5), although a marked variation is seen amongst regions (WHO, 2017). The extent to which HIV is fuelling TB transmission remains poorly understood; one analysis suggested that 1-2% of all global transmission events were from HIV infected, smear-positive TB cases (Kato-Meda *et al.,* 2013). Immigration from high-incidence countries is part of the reason why an increase in TB cases has been seen in Western Europe, North America and the Gulf States, which had either stopped observing a decline in cases or seen a reversal, with an increased number of cases (WHO, 2017). The TB incidence stopped falling in some east Asian countries, notably Hong Kong, Japan and Singapore; one explanation for this is the rise in cases is a result of reactivation from an ageing human population (Yang *et al.,* 2017). In low-incidence country, migration is a key driver for TB, with cases mostly related to the reactivation of LTBI which has been acquired from country of origin (Dale *et al.,* 2018).

Figure 1.4. Global estimated TB incidence rates, 2017



South Africa region, Asia and Oceania regions have TB rates of 300 per 100,000 population. Eastern Europe, Russia, China, South American region have a TB incidence rate of 200-299 per 100,000. The dark green shades indicate higher rates of TB (WHO, 2017).

Figure 1.5. Global estimated HIV prevalence in new and relapse TB cases including all age groups, 2017



In 2016, it is estimated 10% of all TB cases were co-infected with HIV. The large proportion of TB cases co-infected with HIV was highest in the African Region (WHO, 2017).

1.13 TB rates in England

TB has been a notifiable disease in England and Wales since 1913, and data for England has been available since 1971. The data is used to monitor TB trends in England and to understand the changing epidemiology of TB. In 2000, Enhanced Surveillance was introduced, which involved collecting data on detailed demographics, clinical information and other risk factors for TB at the point of notification. More recently, the WHO introduced the WHO End TB

Strategy in 2015, with the aim of eliminating global TB by reducing the number of TB deaths by 96% and reducing new TB notifications by 90% by 2035.

The incidence of TB in England is greater than in any other European country and four times greater than the US (Andorra, 2 per 100,000, Austria 7 per 100,000, Denmark 5 per 100,000, France 8 per 100,000, Germany 8 per 100,000, Sweden 6 per 100,000, UK 9 per 100,000) (PHE, 2017). The TB incidence in England is in a small cluster of high-incidence populations, but the risk of multi-drug-resistant TB can occur in any location in England (Kendall, Fofana & Dowdy, 2017).

In 2018, 4,655 cases of TB were notified to PHE in England; the number of cases had fallen from a peak of 8,280 in 2011, a reduction of 44% (PHE, 2018). The incidence in 2018 was 8.3 per 100,000 population, the lowest ever recorded in England, and a reduction of 8.2% compared to 5,070 in 2017. However, if we are to reach the World Health Organisations (WHO)'s End TB Strategy Target of a 90% reduction on new notifications by 2035, further efforts are required. Non-UK born patients accounted for 72% (3,283/4,580) of notifications in 2018, with an incidence rate of 39.0 per 100,000 population. The rate is 14 times greater than those born in the UK (2.8 per 100,000).

1.14 TB-HIV co-infection

In 2018, in England, 120 of 4,504 people with TB were co-infected with HIV, which was the lowest proportion of co-infection since 2011, with the median age of individuals with TB-HIV co-infection being 46 years old (PHE, 2018).

1.15 Latent TB infection

In 2018, in England, 15,883 latent TB tests were positive, an increase of 3.5% from 2017. Similarly, the Latent TB treatment completion increased from 65.1% (358/550) in 2016 to 76.5% (349/456) in 2018 (PHE, 2018).

TB is largely concentrated in large urban cities with high numbers observed in non-UK born nationals, including London, Leicester, Birmingham, Luton, Manchester and Coventry, which have more than three times the national average number of cases. Up to 75% of all TB cases in the UK occur in those born abroad, mainly from high TB-burden countries and regions, with 85% of the cases occurring in those settled non-UK born individuals who have been in England for more than two years, as opposed to new entrants. Socio-economic factors are a risk factor, with 70% of cases among individuals who live in two of the most deprived populations in England, and a further 9% of these cases have at least one social risk factor (a history of alcohol or drug abuse, are or have been homeless or been in prison) (PHE, 2016).

1.16 Epidemiology and clinical characteristics of TB in London

In 2017, 1,919 cases of TB were notified to PHE: a rate of 21.7 per 100,000 of the population. This represented a 12% decline in cases reported from 2016 and a 45% decrease from the peak in 2011, but the rate remains twice the rate of England's average (9.2 per 100,000) and accounts for 37% of the 5,102 cases reported in 2017. The incidence in London is higher than national average, this includes Newham (47 per 100,000), Brent (45 per 100,000) and Hounslow and Redbridge (PHE, 2017).

Many of the cases in London are in men, with small differences by age group (PHE, 2017). A total of 79% of the cases occurred in individuals born outside the UK, with India remaining the most common country of birth, with the median time between entry into the UK and the time of diagnosis having increased to 10 years. Other common countries of birth include Pakistan, Somalia and Bangladesh (PHE, 2017). In London, during 2017, 58% (1,105) of all the cases were male (25 per 100,000) and 42% were females (18 per 100,000). The rates were highest for males aged over 80 (42 per 100,000) and for females 70-79 years old (28 per 100,000). This was a change from 2016, where the highest rate in males was observed in those aged 40-49, and in women aged 20-29 years old (Figure 1.6) (PHE, 2017). All TB cases in England are reportable to PHE and are termed as notifications. In 2017, 79%

of the TB cases reported in London were from individuals born outside of the UK, which is higher than the same population living in England, with an average of 74%. The TB incidence in non-UK born in 2017 was 44 per 100,000, a decline of 15.5% from 2016 (52 per 100,000). However, non-UK born are 7 times more likely to have TB than the UK born population (PHE, 2017). The incidence of TB in UK-born is 6.9 per 100,000 (378 cases) compared to 2016 (7.4 per 100,000, 397). The incidence of TB in individuals born in the UK in London remains double the England rate (3.2 per 100,000). In 2017, the country of birth was known for 97% (1,465/1,518) of individuals not born in the UK. The most common country of birth outside the UK was India (26%, 379/ 1,456), and the median time since entry was nine years (IQR 9-17 years), which was an increase from a median of eight in 2016.

In 2017, almost half of the people with TB had pulmonary disease. Sixty-one percent of the TB cases were culture confirmed, 77% of those had pulmonary TB (PHE, 2017). In 2017, the enhanced surveillance was implemented which included collecting data of key co-morbidities (diabetes, hepatitis B, hepatitis C, chronic renal disease, chronic liver disease and immunosuppression); more than 1 in 5 cases had a key co-morbidity (22%). With 90% of data available on co-morbidity (1,728/1,919) in 2017, the most common co-morbidity was diabetes: 12% (214/ 1,844) (PHE, 2017). When comparing the prevalence of PTB between UK-born and non-UK born individuals, UK-born cases had reported more PTB (63%, 238/378) than non-UK born cases (47%, 717/1,518). Pulmonary TB was more common in the white ethnic group (78%, 232/296) and less common in Bangladeshi patients (36%, 37/104) (PHE, 2017). In 2017, 5.7% (108/889) of UK PTB cases were also known to have had a previous TB diagnosis, with the median time between diagnoses being 6.5 years (IQR 3-20) (PHE, 2017).

Although the TB rates have continued to decline since 2011, this decline is mostly seen in the non-UK born population, with only a small decrease being seen in the UK-born population of London, where the rate has remained more than twice the rate as for England.

More than 1 in 4 had at least one of either of the key social risk factors or co-

morbidities. Diabetes was the most common co-morbid factor affecting more than 10% of all people with TB in London in 2017.

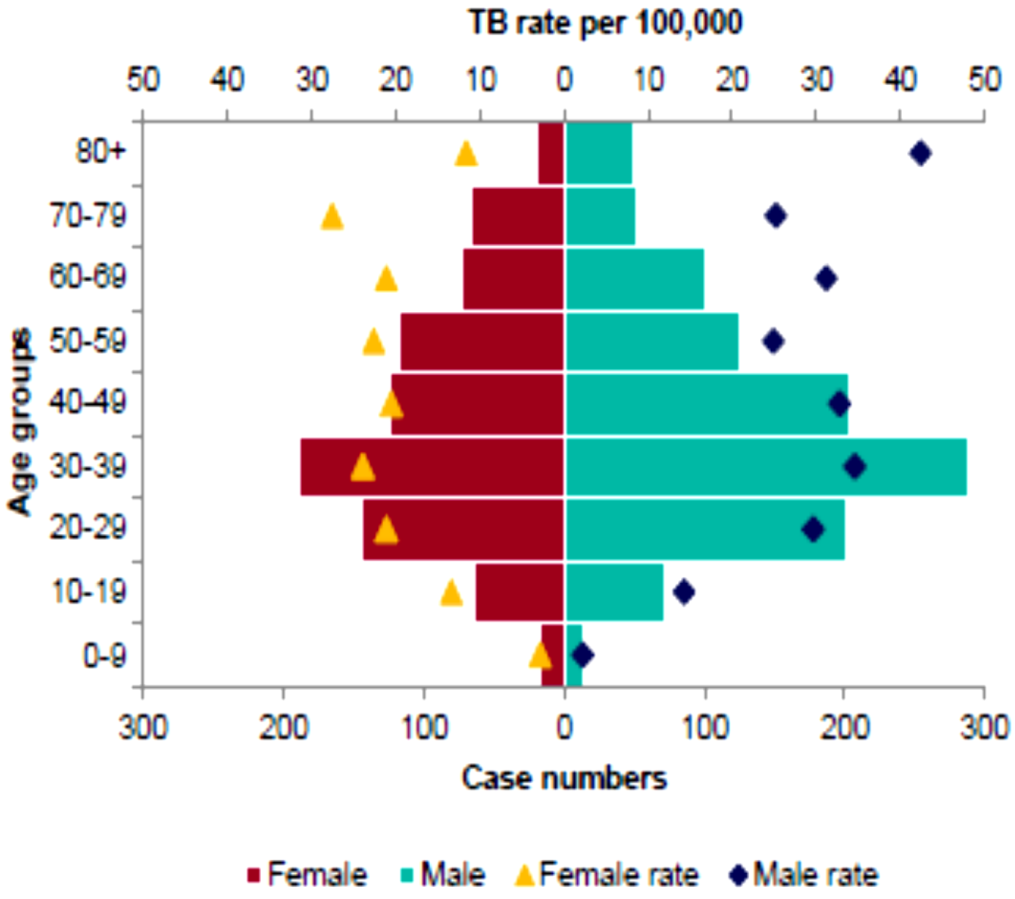
When comparing social risk factors, 10% of all cases had a social risk factor, which was more common in the UK-born cases, particularly in the white or in the black Caribbean ethnic groups. This remains the same when compared to 2015, and patients with social risk factors are more likely to pose an infection risk and be hospitalized, as well as being less likely to complete TB treatment (PHE, 2017).

All TB patients are offered HIV testing on TB diagnosis, with 97% test compliant, and 2.7% of all cases in London are known to be co-infected with HIV (PHE, 2017).

In relation to UK-born cases, which includes all ethnicities, the rates have fallen but remain twice the England average, with the white ethnic group being the most common group to be affected, accounting for 37% of patients born in the UK with TB (PHE, 2017).

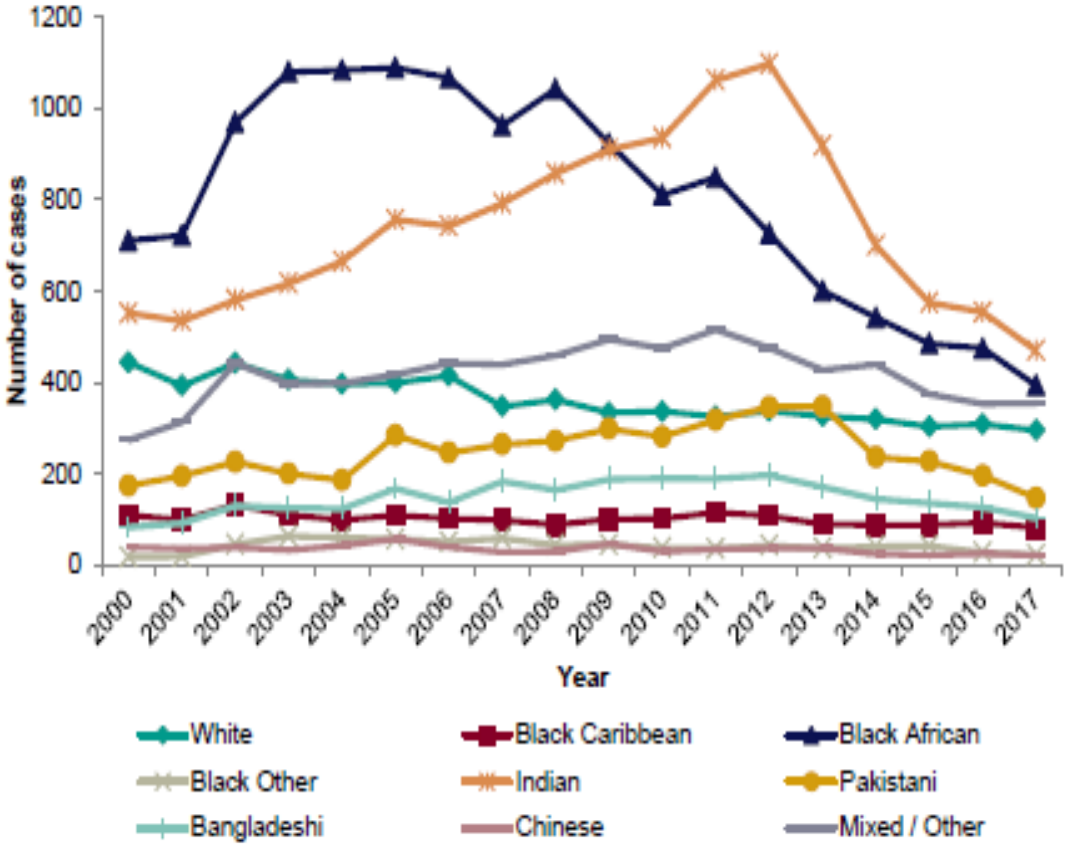
In 2016, there were 2,210 TB cases reported in London at a rate of 25 per 100,000 of the population; however, since 2011, a 41% reduction in cases has been observed, except for four London Boroughs, including Newham, with rates above 40 per 100,000 people (figure 1.9) (PHE, 2017).

Figure 1.6. TB case reports and rates by age and sex, London, 2017



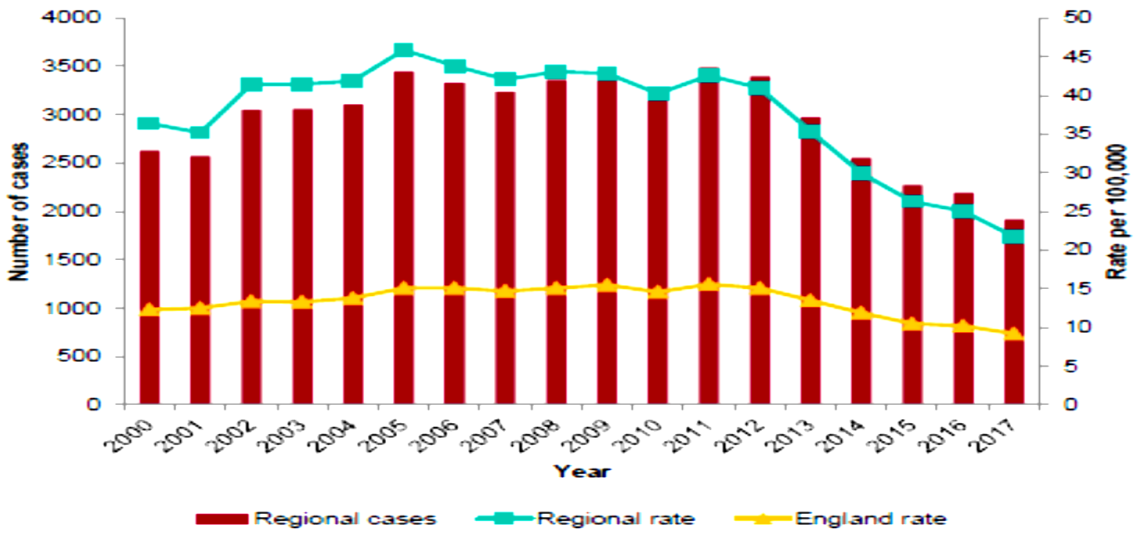
The graph illustrates the number of TB cases, the rate by per 100,000, and age groups of TB cases being reported. The largest number of cases and highest rate is in men between the ages of 30-39. (PHE, 2017).

Figure 1.7. Active TB case rates by ethnic group in London from 2001 – 2017



(PHE, 2017)

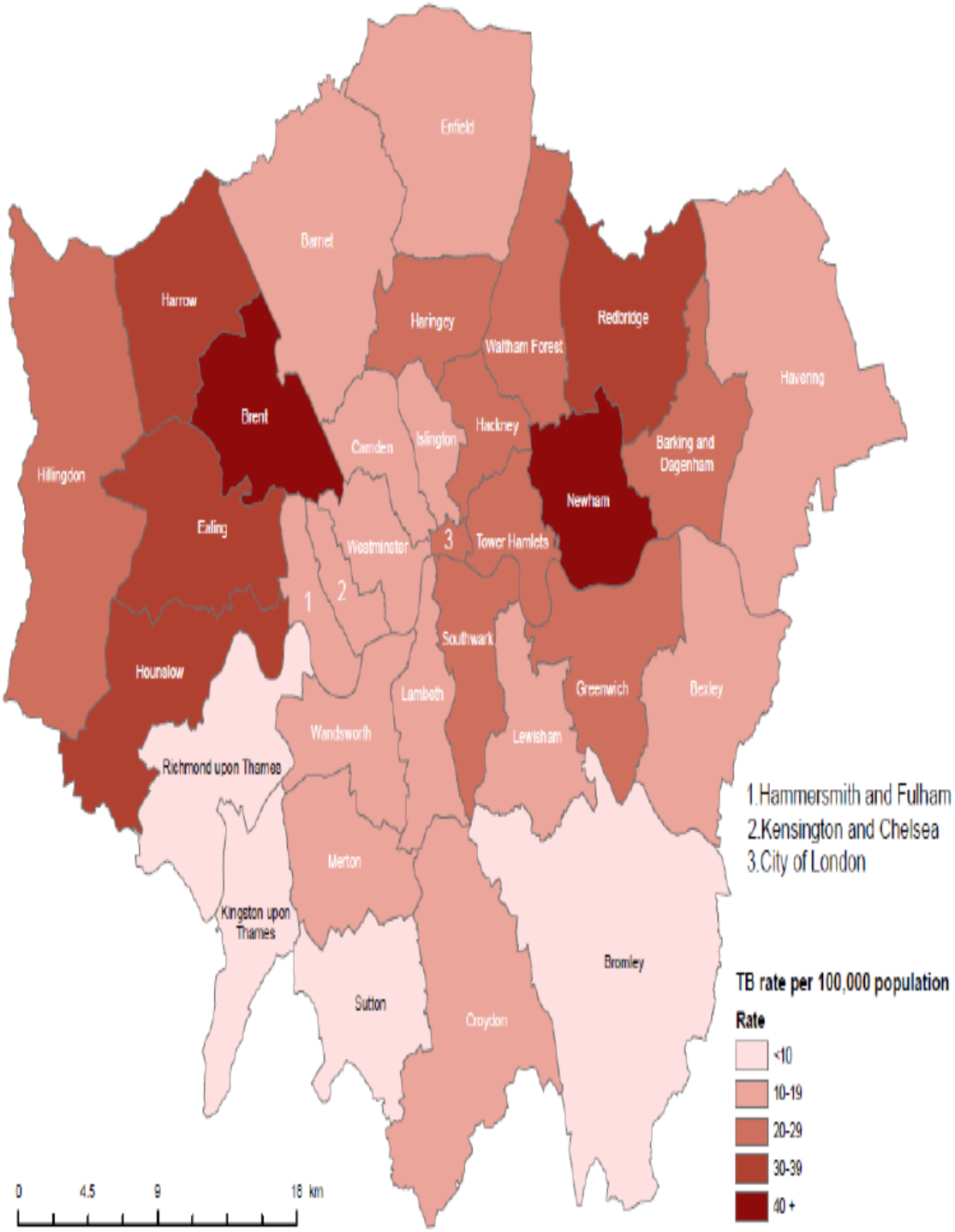
Figure 1.8 Active TB case reports and rates, London 2000 – 2017



A general trend of decrease of TB notification in London since 2011 is seen

(PHE, 2017)

Figure 1.9. Active TB rate per 100,000 of population and local authority of residence, London, 2017



Dark red shades indicate active TB rate per 100,00 population. Newham and Brent continue to have the highest incidence of TB, with a rate greater than 40-49 per 100,000 population (PHE, 2017).

1.17 Social determinants - increasing the risk of developing active TB infection

Social factors are important in the prevalence of TB; determinants such as poverty and low-socio-economic factors directly increase the risk of developing the condition. Globally, the distribution of TB prevalence is unequal, and TB has an inverse relationship with wealth. Colombani *et al.,* (2015) identified the social determinants as a risk for TB using National TB surveillance data from the WHO European Region (Colombi *et al.,* 2015). The study implemented a semi-structured questionnaire sent to 53 national TB surveillance programmes, of which a total of 47 countries completed the survey. This included reporting on occupation, homelessness, diabetes mellitus, alcohol and drug abuse, history of imprisonment, nationality, birth country and citizenship status, employment abroad and ethnic group, with a further 12 risk factors explored: age, sex, housing status, smoking, silicosis, use of alcohol, HIV infection, drug use, chemotherapy, pregnancy, other immunodeficiency's and malnutrition. The data on social determinants found more than half of the TB incidents occurred in non-UK born nationals, the homeless and those with a history of imprisonment.

A study by Colombani *et al.* (2015) suggested that employment and being homeless are important social determinants of TB infection, having a tuberculosis and diabetes mellitus combination, and the use of alcohol are important risk factors for the development of TB. The strength of the survey was the high participation of countries in the WHO European Region and the high levels of accuracy retrieved from the network of national TB surveillance programs. A limitation of the study was that the only languages used in the survey were English and Russian, which may have caused some misunderstanding or mistranslation of the questions. Similarly, the case definitions were not universal, which may have resulted in assigning certain

conditions or social determinants to the wrong category. Hargreaves *et al.* (2011) further supported the social determinants theory and that risk factors were important considerations. Social stratification increased the unequal distribution of the social determinants of health, including living conditions and psychosocial circumstances, as well as behavioural and biological risk factors. The key determinants of TB included the global socioeconomic inequalities, increase in population mobility, rapid urbanisation and population growth. Social determinants also include the lack of food or adequate nutritional intake, financial insecurity, malnutrition, poor housing and cultural barriers affecting access to health. For instance, poor ventilation and overcrowding in homes, workplaces and communities increase the risk of TB transmission from an infected host to uninfected individuals. Poverty and malnutrition increase the susceptibility to infection and clinical outcome. Those with delayed access to healthcare have a delayed diagnosis, which increases the severity of the disease and the outcome, and increases the population burden of TB, making comparisons with the social determinants in HIV/AIDS, where the infections had been controlled, mostly through a better emphasis on social factors and treatment access.

Research into gender and socioeconomic inequalities in HIVS have helped to reduce HIV infection and the development of effective treatments (Hajizadeh *et al.,* 2014; ECDC, 2018). TB is predominantly concentrated in Asia and regions of Africa, with smaller proportions of cases reported in the Eastern Mediterranean region, Europe and America. It is estimated up to 12% of global TB cases are co-infected with HIV, with most being reported in Sub-Saharan Africa and Southeast Asia (ECDC, 2018). HIV is a risk factor known to increase the risk of developing TB infection by 3 to 5 times (Leanardo, Jurado & Palacios, 2017).

The current efforts to control TB include increased access to health systems in communities and treatment support, surveillance to identify active cases through contact tracing and outreach to high-risk populations, an increase in TB health promotion to inform at-risk populations of the condition and its risk factors. Further measures to optimise contact tracing including of household

contacts require improvement, with more than 3 million people with TB remain undiagnosed each year, therefore, case detection must be optimised (Fox, Dodd and Marais, 2019). These efforts have the aim of changing behaviour, including smoking and alcohol consumption, to help reduce the TB burden (Jurado & Palacios, 2017; Hayward *et al.,* 2018).

1.18 TB rates in the London Borough of Newham

In 2016, 366 cases of TB were diagnosed in Newham, at a rate of 117 per 100,000 population. The completion of anti-TB treatment was below the London average, with 1 in 10 cases being lost to follow-up; drug resistance was also higher than London's average (Aston Mansfield, 2017). The London Borough of Newham's TB rate is 8 times the national average and 3 times greater than the London average. The London Borough of Newham is one of the most affected of any of the Western European Countries, with a rate greater than high burden developing countries.

The total population of Newham in 2017 was 308,000, with a population density of 85.1 per hectare compared to 31 per hectare in Central London (UK Census, 2017). This reflects that the fact that Central London is a populated district and Newham has an even higher density of population. The population of Newham is one of the most diverse in the country, with 61% of people coming from a non-white ethnic group, including an increasing number of ethnic minorities due to refugees and asylum seekers setting in London (Contini *et al.,* 2017).

The deprivation level in Newham is the third highest in London, with large numbers of people living in dwellings such as high tower blocks and overcrowded accommodation with poor ventilation, all of which aids the spread of TB. Evidence from the literature supports housing and poverty being a driver for TB spread (Vassall, 2009; Anderson *et al.,* 2001). The distribution of cases of TB in Newham is also concentrated in certain locations, with 70% of the cases focused around Manor Park, Green Street and East Ham, with TB incidence increasing there since 2006. When

comparing the incidence of TB in Newham to other neighbouring boroughs, the rate is significant, and it is essential for intervention to be identified and implemented to help reduce these rates.

1.19 DM as a risk factor for TB

DM is a chronic life-long condition in which the glucose content in the blood is above normal. There are two types of DM, type 1 DM (T1DM) and type 2 DM (T2DM). In T1DM, also referred as insulin dependent DM, this is an autoimmune disorder whereby the insulin producing beta cells of the pancreas are destroyed by the body's own immune system, as a result no insulin is produced to regulate blood glucose levels. In T2DM cases, which are related to a lack of insulin production or a resistance to insulin, blood glucose is not regulated (Diabetes UK, 2019). T2DM is usually diagnosed later in life compared to T1DM, which is more common in younger children and adults but can manifest at any age. T2DM is associated more with age (over 40 years), differs with ethnicity as some ethnic groups are at a higher of developing DM. However, with increasing obesity globally T2DM is becoming more common in younger age groups. DM can also manifest as gestational DM, this occurs during pregnancy and usually diagnosed in the 2nd and 3rd trimester of pregnancy. In any form of DM, if not treated and glucose levels are poorly maintained this leads to serious health problems. DM causes microvascular damages to small blood vessels in the kidney (nephropathy), the eyes (retinopathy), peripheral nervous system (neuropathy) or cause macrovascular damages, in which the large blood vessels are affected and cause cardiovascular disease and peripheral vascular disease. DM also increases risk to pathogenic infectious (e.g. bacterial infection causing foot ulcers) (Diabetes UK, 2019).

In relation to DM as a risk factor, a gap remains in our understanding of the extent to which socioeconomic determinants drive the current TB burden in London, and in the proposed study population of Newham Borough. The association between TB and DM as a socio-determinant is significant from a healthy diet and lifestyle aspect. Recognition of this will aid understanding and provide a framework to develop local structural interventions to tackle TB

(Duarte *et al.,* 2018). The key to the success of this study will be the sharing of findings with multidisciplinary teams managing patients with TB and DM, using an approach with a common conceptual framework, with the evaluations of the financial impact for the NHS and the development of local programmes for TB control. The findings will be shared formally using Barts Health NHS Trust Quality Improvement Framework and actions agreed with the clinical supervisor. Furthermore, the study findings will be discussed at the yearly TB summit is held annually in March and at internal journal study days for peers to comment and discuss findings. The recommend actions based on the study outcomes will be included and reflected in the TB Policy for management of TB patients at for review in April 2021.

1.20 Historical association of Tuberculosis and Diabetes

Tuberculosis (TB) has been around for thousands of years. It was highly prevalent during the 19th century, accounting for 25% of all deaths in Europe during this period (Glaziou *et al.,* 2015). During the 20th century, the death rate caused by TB fell as living standards (housing, nutrition and income) improved alongside the advancement in TB treatment (Glaziou *et al.,* 2015).

Although the first drugs for the treatment of TB were discovered over 60 years ago, TB has caused approximately 1.7 million deaths annually worldwide (Glaziou *et al.,* 2015). The diagnosis of TB has improved with the advances in diagnostic testing and treatment, but this progress has been slowed down by the HIV epidemic, and the emergence of drug-resistant strains of the condition (Glaziou *et al.,* 2015).

The association between TB and DM has been documented throughout time, but only recently has the magnitude of the DM incidence been considered a major risk factor. The impact of this association and its potential implications has been highlighted (Lee *et al.,* 2017; Girardi *et al.,* 2018). The current knowledge of the association of TB and DM as a co-morbidity in the UK and globally is limited. This association requires further investigation as the rate of DM is increasing globally year on year, the global DM prevalence in 2019 is

estimated to be 9.3% (463 million cases), rising to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045 (Saeedi *et al., 2019*). The global TB prevalence in 2018 was estimated to be 10.0 million, the burden of TB varies by country and region. The death rate associated with TB is estimated amongst HIV-negative individuals to be 1.2 million, with estimated 251,000 people living with HIV are estimated to have dies from TB, the true prevalence of TB-DM is unknown. Therefore, WHO's End TB Strategy targets (a 90% reduction in the number of TB deaths and an 80% reduction in TB incidence rates by 2030), are unlikely to be met in the UK, based on current estimates (WHO, 2019, Global Tuberculosis report 2019). The current literature on TB-DM association consists of secondary research and lacks any clinical recommendations on the management of TB-DM cases as a dual presentation, with limited recommendation on the use of bi-directional screening in TB and DM cases, and no alternative treatment regimens recommended for patients with TB-DM comorbidity, as is the case in TB-HIV patients.

A meta-analysis study based on TB-DM conducted by Lee *et al.* (2017) found that DM increases the risk of developing active TB by statistically pooling data from three pre-existing cohort studies which assessed the association (relative risk (RR) 3.11, 95% confidence interval (CI) 2.27-4,26). However, the validity of this study was questionable as two of the three cohort studies used within the analysis involved individuals suffering from renal failure, which itself is a risk factor for TB, and likely to have skewed the data in favour of DM as a risk factor without controlling the confounding effects.

Future studies on TB-DM association should provide a risk estimate of the likelihood of developing TB infection in the presence of DM, which can be used to inform policies and change practices to improve disease outcomes (Pealing *et al.,* 2015). Current ideology indicates that DM increases the risk of TB with a more severe clinical outcome; however, there is a lack in our knowledge of the bi-directional effect of TB leading to the development of DM. Further insight into screening for diabetes in TB patients and screening for TB

in diabetic cases to identify a risk factor should be beneficial for patient clinical outcomes (Pealing *et al.,* 2015).

1.21 Association between Tuberculosis and Diabetes

In England, which has experienced an increase in the prevalence of DM, in 2013, an estimated 2.7 million (6%) of the adult population have been diagnosed with DM and this is expected to increase to 9.5% by 2030 (Diabetes UK). In England, in 2018, 4,655 TB cases have been reported at a rate of 8.3 per 100,000. The rate of TB is higher in the most deprived areas by 6-fold compared to the least deprived areas (PHE, 2019, Tuberculosis in England 2018). Therefore, the investigation of DM as a potential significant risk factor in developing TB is required to particularly inform policies which can target areas of high TB incidence. It is critical to evaluate current health policy in regards to managing DM patients with TB, as well as assessing the role of ethnicity, age and social factors which may increase the risk of TB-DM. Gonzalez *et al.* (2009) estimated, using general practice (GP) data in the UK, that between 1996 and 2005, the prevalence of DM increased from 2.8% to 4.3% for the general population. It has been further predicted that the true rate of DM is unknown, with many cases remaining undiagnosed. In 2010, the estimated figure of both diagnosed and undiagnosed DM was estimated at 3.1 million, and this is expected to rise to 4.6 million by 2030. In comparison, TB remains a public health concern, with a UK prevalence increasing from 11.4 to 13.6 per 100,000 population from 2000 – 2016 (Nnadi *et al.,* 2016). As DM is a chronic condition and TB can present in a latent form, and presentation of each condition is not a sudden on-set, they are likely to have some association with each other, which may help either or both conditions to manifest further, increasing the rate of mortality and morbidity. Insight into both these co-morbidities is necessary to understand any links, disease progression and aid knowledge in managing these cases, singly or in tandem, to help prevent and manage cases better.

Males are more likely to have TB-DM since male adults acquire the disease in earlier years and it persists throughout their life, being related to environmental exposure. The use of tobacco is a risk factor for TB and is an environmental cause for TB; however, findings remain inconclusive (Barron *et al.,* 2018). The relative risk for developing TB caused by smoking is increased 2.5-fold as smoke activates alveolar macrophages to produce local inflammatory responses, and nicotine suppresses the antigen presentation function of macrophages, leading to a reduced immune response to Mtb.

Empirical evidence suggests environmental factors, such as sharing of needles by intravenous (IV) drug users, homelessness and poor nutrition, contribute to a high prevalence of TB. However, being diabetic has not been clearly associated with increased prevalence of TB (Barron *et al.,* 2018).

Poor glycaemic control and repeated chest infections are a pre-disposing factor for the development of TB. Both reflect a state of decreased immunity: hyperglycaemia results in protein glycation and formation of advanced glycation end-products (AGEs), which affects the host cell function (Skowronski *et al.,* 2014). Such impairments are likely to cause functional issues in complement activation, bacterial uptake and phagocytic action, and change the binding of host surface receptors to Mtb pathogens (Skowronski *et al.,* 2014).

Diabetic patients with TB are widely associated with atypical radiological appearance and a higher rate of treatment failure and resultant death (Martinez and Kornfeld, 2014). Diabetes alters the innate immune cells; the macrophages and monocytes are less expressed in TB-DM and results in a decreased hydrogen peroxide production, affecting phagocytosis function via the complement or Fc-γ pathway. Martinez and Kornfeld (2014) assessed the role of BMI and found a high BMI increases the risk of TB infection; in TB-DM cases, a prolonged state of hyperglycaemia was observed.

A quarter of the global population is thought to have latent TB, of which, only 10% of those infected progress onto develop an active TB infection (Houben

& Dodd, 2016). Individuals with diabetes in an area of low TB incidence have a 2-fold risk of developing active TB, compared to 15% of all TB cases which are attributed to diabetes (Restrepo, 2016). The global co-incidence of TB and DM is increasing, and the negative impact of this co-morbidity is significant to individual health, as well as public health. It is estimated that by 2040, the prevalence of diabetes globally will have reached 642 million, and the prevalence of latent TB will be twice as high in those with DM than those without (Restrepo, 2016).

Disease associations or disassociation may occur due to either:

a) A direct causal relationship, when the presence of a certain disease causes another disease to be likely to develop;
b) An indirect causal relationship, when the presence of a certain disease affects a third variable (e.g. an environmental factor) which causes another disease to be likely to occur or, in other words, is likely to increase or decrease the risk of both diseases through two separate mechanisms.
c) Or a third factor may be causally linked to outcome s (a) and (b)

Identifying any associations or disassociations can aid knowledge about disease sequences, aetiology and outcome. Such knowledge allows prevention of disease and control of the development of the disease (Eybpoosh *et al.,* 2017). For instance, co-infection with HIV increases the risk of developing active TB. Such knowledge allows the implementation of prevention strategies, which includes routinely testing any patient confirmed with TB for HIV. This allows earlier diagnosis of the disease, prompt appropriate treatment and a reduction in the disease burden and control (Eybpoosh *et al.,* 2017).

DM is thought to worsen the clinical presentation and exacerbate the symptoms of TB in those with TB-DM co-morbidity (Astane-Poku, 2019). This is further aggravated by poor glycaemic control. TB-DM patients more frequently present with cough, night sweats, haemoptysis and malaise than

those without DM. Leung *et al*. (2017) and Gil-Santana *et al. (*2016) reported an independent association of DM with chest symptoms at TB presentation.

Radiologically, it is more common for DM to impact upon the radiological features of PTB, with greater infiltrates, cavity lesions and hilar or parabrachial lymphadenopathy, compared to non-DM patients. Greater extensive lesions with increased involvement of the parietal pleura and a multilobular involvement are common in TB-DM cases (Huang *et al.,* 2017). Huang *et al.* (2017) evaluated the impact of glycaemic status on radiological findings in PTB cases using a study sample of 214 TB-DM patients with culture-positive PTB, of which 123 had computed tomography (CT) scans, compared to an equal number of non-DM patients. Glycaemic status was assessed using an HbA1c of 8% as a cut-off point. A higher involvement of the lower lobe is associated with TB-DM cases, and TB patients with uncontrolled DM often present with cavity and nodular lesions (Huang *et al.,* 2017). Banureka *et al.* (2017) showed sputum conversion in 90% of patients with TB-DM; DM is a major risk factor for increased time of sputum conversion in TB patients.

Poorer treatment outcome, with increased rates of failure, relapse and death, is associated with TB-DM co-morbidity. Mukhtar and Butt (2018) reported an increased risk of adverse TB treatment outcome result (adjusted OR 3.38, 95% CL 2.19-5.22, p= <0.001) and one-year mortality (adjusted OR 2.80, 95% 1.89-4.16) in people with TB-DM. The risk of treatment failure and death was 7 times higher in TB-DM group compared to TB only. This negative outcome is likely related to drug resistance that is greater in TB-DM groups, because of weakened cellular immune response, higher drug resistance and a lower concentration of TB drug in plasma serum and blood levels of anti-TB medication, and the delay in sputum conversion. This was a prospective cohort study in the high-incidence country of Pakistan which recruited new PTB patients from the age of 15 years and above and commenced treatment on anti-TB drugs. The PTB patients were screened for DM using random and fasting glucose tests and followed up at the second, fifth and sixth month of treatment after completing the course of anti-TB drugs. A total of 614 PTB

were recruited, of which 113 had DM and 501 non-DM. Their study found poor outcome of treatment in DM-PTB patients.

There is a positive correlation between active TB and the level of HbA1c (hazard ratio 1.39, CI 1.18-1.63 per unit increase). It is thought an HbA1c >9% (75mmol/mol) increases the severity of TB symptoms, including cough, haemoptysis, malaise and weight loss. Using a hospital-based prospective study with newly diagnosed smear-positive PTB with DM, a total of 630 patients were recruited for the study, of which 423 had poor glycaemic control (HbA1c >7%). These individuals also had the highest odds (OR 3.55) of being smear-positive following two months of treatment and had more extensive lung disease, cavitation and a positive sputum smear at baseline (Mahishale *et al.,* 2017). Furthermore, uncontrolled diabetes is associated with increased cavity lesions on chest x-rays and a higher frequency of positive-smear and more severe symptoms and being likely to show a positive culture after two months (P= 0.009), treatment failure (P- 0.015) and death (P= 0.027) (Siddiqui *et al.,* 2018).

The co-morbidity of TB-DM is likely to lead to MDR-TB because of sub-optimal treatment drug concentration being a key factor for resistance. A lowered serum concentration of rifampicin and isoniazid is likely to happen in patients with TB-DM compared to TB only. Anti-TB drugs are thought to interact with DM medication and cause suboptimal blood glucose control, or the DM medication can also interact with anti-TB drugs, especially newer agents and lower their efficacy. Rifampicin is a hepatic enzyme-inducer, known to lower the plasma concentration of numerous oral agents, especially sulphonylureas and biguanides, by accelerating their metabolism (Niazi & Kaira, 2012). Isoniazid impairs the release and action of insulin, which leads to hyperglycaemia (Niazi and Kaira, 2012). Therefore, insulin dosage should be adjusted when prescribing for patients with co-morbidity with TB, and their dosage of oral anti-diabetic medications should be adjusted according to their plasma glucose concentration. In contrast, DM is thought to lower the plasma concentration of anti-TB medication, which is likely to reduce the expected therapeutic efficacy of the drugs in TB-DM patients. Kumar *et al.* (2017)

studied the concentration of rifampicin in TB-DM cases to find the median and interquartile range (IQR) concentrations of isoniazid [6.6 (3.9-10.0) vs 7.8 (4.6-11.3)] and pyrazinamide [31.0 (22.3-38.0) vs 34.1 (24.6-42.7)], in µg/mL, finding significantly lower levels in individuals with TB-DM compared to TB only (P = <0.001 for both drugs). Kumar *et al.* (2017) also reported a negative correlation between blood glucose and plasma isoniazid (r = -0.09, P = < 0.001) and pyrazinamide (r = -0.092, P= <0.001) concentrations. DM reduced both isoniazid and pyrazinamide concentrations by 0.8 and 3.0 µg/mL respectively and, therefore, a strategy to optimise the dose of these drugs is necessary for better therapeutic outcomes in patients with TB-DM.

The current issue surrounding TB-DM is the lack of clinical awareness in the diagnosis, prevention, screening, management and reduction of the burden caused by both TB and DM. There are currently no clinical pathways to optimally manage patients with concurrent TB-DM conditions. Those with TB-DM should also be managed by specialist endocrinologists for guidance on the management of DM alongside the TB specialist. Increasing anti-TB medication in TB-DM cohorts has not been reported as no randomised controlled trials have assessed the efficacy of extending treatment beyond the standard six months for susceptible TB (Baghaei *et al.,* 2013; Workneh *et al.,* 2017).

1.22 Diabetes Mellitus Epidemiology in the UK

Diabetes is a condition where the amount of glucose in the blood is above the normal range. Diabetes can be categorized into two types: type 1 and type 2. Type 1 diabetes develops when an individual's body is unable to produce any insulin due to autoimmune attack against the islet cells in the pancreas. It is usually acquired genetically. Type 2 diabetes occurs when the body is unable to produce enough insulin or categorised by insulin resistance (Sanchez-Jimenez *et al.,* 2018, Magliano, 2019). The prevalence of type 2 diabetes is around 90% in the UK (Magliano, 2019). Currently, in the UK, diabetes is diagnosed by measuring the glycated haemoglobin (HbA1c) levels of >48mmol/mol, as recommended by the WHO (American Diabetes

Association, 2009). The risk factors for developing type 2 diabetes include advancing age, ethnicity, a familial history of diabetes, increased body mass index (BMI) and/ or waist circumference, high blood pressure and heart attack or stroke. Men from a deprived socio-economic status are at more risk of being diagnosed with T2DM. Deprivation is a key independent risk factor for diabetes, and the PHE diabetes prevalence model predicts the significance after adjustment for age, sex and ethnicity (P= <0.0001) (Wu *et al.,* 2014).

The PHE figure for 2016 estimates 3.8 million individuals in the UK over the age of 16 have diagnoses (diagnosed or undiagnosed) for T2DM. Men are more likely to be diagnosed than women, 9.6% compared to 7.6%. The prevalence of diabetes is more common in individuals from South Asia and black ethnic groups compared to white and other ethnic groups: 15.2% compared to 8.0% (PHE, 2016).

The figures published in 2016 by PHE estimates that 3.8 million people in England over the age of 16 have diabetes and that this will increase to 4.9 million by 2035, approximately 9.7% of the adult population, of which 90% of the cases are T2DM, which is largely preventable or managed through lifestyle changes. This is equivalent to 1 in 4 people having diabetes. An estimated 940,000 people are unaware of their condition and are undiagnosed (PHE, 2016). Diabetes is known to lead to serious complications, including foot amputation, kidney disease, increased risk of stroke and heart disease.

1.23 Diabetes in Newham

Newham diabetes prevalence is more than the national average due to the high levels of deprivation and the varied ethnic groups who are at risk of the condition. Currently, there are over 20,800 people in Newham living with diabetes, with 1,800 more diagnosed every year (Diabetes UK, 2019). The current population in Newham is 332,583, with 30% of the population being under 20 years old, making it the youngest population in any of borough in London or England. 90% of the school population are from an ethnic minority group, with 42% of these children living in poverty (Newham CCG, 2018).

1.24 Radiological presentation in TB-DM patients

Studies which focus on the radiological appearance of TB in the presence of DM have suggested atypical presentation is common among the TB-DM cohort, and they are more commonly misdiagnosed for longer periods of time than those presenting with TB alone. Pulmonary TB is normally found in the lung apices, but in patients with DM, this does not occur. It is suggested that multi-lobular cavity TB is more common in individuals with DM, with increased levels of lower lobe involvement and effusion. However, other studies have contradicted this, demonstrating no difference in radiological findings between PTB suffers with and without DM. Sum *et al.* (2017) undertook one of the largest studies to observe radiological appearance, with the highest statistical power, to detect differences in radiological presentation between a TB-only cohort compared to a TB-DM cohort. The study concluded that there were no differences in the localisation of TB lesions between the groups. Many of these studies assessing the radiological presentation of TB in DM patients were carried out in low- to middle-income countries, where the incidence rates of other co-morbidities are likely to affect the presentation of TB (e.g. HIV).

Radiographically, patients with TB-DM are thought to present with a confluent cavity, a wedge-shaped lesion spreading from the hilum towards the periphery, predominantly seen in the lower zones. The prevalence of the involvement of the lower zone in TB-DM has been seen in up to 29% of patients with DM compared to 4.5% in non-diabetic patients (Skowronski *et al.*, 2013). Furthermore, CT scans from patients with TB-DM have also demonstrated a higher prevalence of non-segmental distribution (30%) and multiple small cavities (44%).

Appleton *et al*. (2017) assessed 154 patients who attended emergency departments six months prior to TB diagnosis, of which 24% (37/154) did not have a radiological examination in ED. In PTB cases, 86% (55/64) of patients who had a chest x-ray showed abnormality, compared with those with extra-pulmonary TB. The findings of the x-ray showed those with abnormal chest

images also had multiple abnormalities. The three most common abnormalities were: consolidation in 55% (42/76), effusions in 26% (20/76) and a decreased volume or a collapse in 22% (17/76). Of the patients, 35 presented with abnormal radiological appearance when TB had not been suspected. In relation to gender, 63% (22/35) were men, with an average age of 45, with 71% (25/35) of these patients being foreign and born outside of the UK. Furthermore, 69% (107/154) of the patients with an abnormal chest image had reported symptoms of cough, fever or weight loss. There is no validated scoring system in acute TB diagnosis to correlate the radiological appearance to the severity of the symptoms.

Appleton *et al.* (2017) assessed 397 TB cases, and 39% (154/397) had presented to the emergency department within the past six months before TB diagnosis. Chest radiography was carried out in 76% (117/154) of those patients; in newly suspected TB cases, 73% (41/56) had abnormal radiographic demonstration in contrast to 36 percent (35/98) of patients who had not. Abnormal x-ray was present in 73% (55/75) of PTB cases and at 40% (21/52) of EPTB cases. The research highlighted how almost half the EPTB cases did not present with classical TB symptoms, and the other three-quarters presented with other symptoms, with gastrointestinal symptoms being the most common. The low level of classic symptoms in EPTB makes the diagnosis based on symptoms alone unreliable. Using multivariable analysis, suggested abnormal chest x-ray was an independent risk factor, along with night sweats, in PTB cases. The study by Appleton *et al.* (2017) suggested standard chest imaging is valuable in diagnosis for both PTB and EPTB. The strength of this study is that it is one of the first studies in the UK to systematically assess radiological images and symptoms as a risk factor. The data collected was based on a large study population across two sites in moderately high-incidence populations based in two urban ED department in England. The limitation of the approach was the design of the study was a retrospective study, which relied on the availability of scanned or electronic records, and the study could not confirm if all patients had had active TB six months before their diagnosis or if a diagnosis had been made on their ED visit. The study included two EDs in the UK, departments which only

diagnosed 39% of TB at admission on first visits, with a large proportion not being diagnosed with TB.

1.25 TB drug management in TB-DM patients

The initial empirical treatment of TB consists of drug regimens using isoniazid, rifampicin, pyrazinamide, streptomycin and ethambutol. Special consideration is given to pregnant women, including those not using streptomycin as they are at increased risk for isoniazid-induced hepatoxicity (Bothamley, 2001). Special considerations are also made for HIV patients with TB, where dose adjustments are required, and rifampicin is avoided in those receiving protease inhibitors. An early start of anti-TB medication reduces the risk of AIDS and death. Patients with a high CD4+ T-cell count may be able to defer anti-retroviral therapy until the continuation phase of TB treatment. If MDR-TB is suspected, commencing empirical treatment before the culture results become available is recommended, and the regimen is modified, as necessary. Antibiotics are prescribed in combination and over a prolonged period to prevent the development of drug resistance (Prasad, Gupta & Banka, 2018)

Diabetes impacts TB drug therapy, particularly for individuals who have poor glycaemic control, that is probably because of altered TB medication pharmacokinetics at DM (Alfarisi *et al.,* 2018). DM influences drug pharmacokinetics, in addition to carbohydrate, lipid and protein metabolism. DM affects the enzymes/transporters involved with drug biotransformation, in addition to the decrease in plasma protein binding and displacement of drugs out of their own protein binding sites (because of high amounts of fatty acids at DM) which affect drug pharmacokinetics. Drug toxicity is also likely to increase from excessive accumulation in the body, leading to diabetic nephropathy (Alfarisi *et al.,* 2018; Shewade *et al.,* 2017).

Rifampicin is a hepatic enzyme-inducer; it accelerates the metabolism of oral hypoglycaemic agents, particularly sulphonyureas and biguanides, this lowers their plasma serum levels, inducing hyperglycaemia in diabetic patients on these drugs (Niazi & Kaira, 2012). Non-diabetics also likely to experience symptoms of hyperglycaemia and stimulate a pre-diabetes state. Isoniazid, however, inhibits the metabolism of oral hypoglycaemic agents and influence a rise in the plasma levels of these medications. As a result, both these anti-TB drugs interact with DM medication, in particularly with sulfonylureas, subsequently affecting glucose levels in the blood. It further interrupts the release and activity of insulin, leading to hyperglycaemia including in non-diabetic patients. The dose of insulin should be corrected while removing or adding these medications when treating TB patients (Niazi & Kaira, 2012).

1.26 Use of Vitamin D in TB Treatment

Human monocytes have receptors including 1,25-dihyrdroxivitamin D, which initiates an anti-mycobacterial reaction in human monocytes and macrophages from the mechanism of phagocytosis and granuloma formation (Yang *et al.,* 2016). The host response to infection is initiated by reactive oxygen and nitrogen intermediates; the suppression of matrix metalloproteinase enzymes inhibits the pathogenesis of both peptide and cathelicidin. Human vitamin D receptors (VDRs) are polymorphic, they are carried on the t allele of taq 1 VDR gene, which is associated with increased calcitriol-initiated phagocytosis of Mtb *in vitro* and more frequent conversion of sputum positive in patients with pulmonary tuberculosis. A low vitamin D level is associated with an increased risk of developing PTB (Kedzierska *et al.,* 2003).

Chesdachai *et al.* (2016) explored the role of vitamin D as a supplementary treatment when added to the first-line anti-tuberculosis drugs in treating active pulmonary tuberculosis. Using a randomised case-controlled study, involving patients above the age of 18 with active PTB diagnosed by sputum examination, it was found that vitamin D accelerates the resolution of the host inflammatory response in those treated with supplementary vitamin D. Clinical

trials have reported a significant increase in the serum vitamin D levels from the start of anti-TB treatment and at the end of the 2nd month after the initiation of anti-TB treatment ($p < 0.001$). This signifies the good response of patients with active PTB to vitamin D supplementation, regardless of the vitamin D status in serum before the start of vitamin D therapy.

Sita-Lumsden *et al.* (2007) reported a lower level of serum vitamin D levels in those patients with active PTB compared too controls, including those from a similar ethnic and social group. Systematic reviews suggest vitamin D deficiency is common in those with TB (Huang *et al.,* 2017) but severe deficiency is rare. When assessing the sputum conversion, reports from studies show there is a significant negative correlation of vitamin D levels with the duration until the sputum conversion (Afzal *et al.,* 2018). This suggests a low serum vitamin D increases the risk of TB and potentially affects the outcome of treatment (Zhao *et al.,* 2017). Essam *et al.* (2016) studied vitamin D deficiency and its association with impaired immune function and the increased risk of active PTB. The study evaluated the use of vitamin D as a supplement treatment with first-line anti-TB medication for active PTB. Using a case-control approach, based in the El Maamora Chest Hospital, Egypt, 60 adult cases were identified with active PTB. One group (n=30) received vitamin D (200,00 IU) as an intramuscular injection with TB treatment and the other group (n=30) received TB treatment only. Vitamin D was detected in 54 (90%) of the cases and, when the two groups where compared, there was a rapid decline in sputum conversion time and severity in TB infection in group 1 with vitamin D supplement compared to the TB treatment only group (P-value <0.001 and P-value 0.02, respectively). Therefore, vitamin D supplement helps to improve TB outcome and therapy, but further studies on the effect on immunological interactions and cut-off levels are required (Raposo-Garcia *et al.,* 2017). Kota *et al.* (2011) studied the effect of vitamin D supplementation in DM type 2 with PTB and found in those receiving 60,000 IU of cholecalciferol per week in combination with anti-TB medication that the duration of sputum conversion to 100% negative for AFB was six weeks, compared to eight weeks in subjects not receiving cholecalciferol.

1.27 Treatment outcomes in TB-DM patients

Nijland *et al.* (2006) noted that rifampicin is not absorbed as effectively in people with TB-DM and the plasma concentration of rifampicin was 53% lower in Indonesian patients with TB-DM compared to TB-only cases. This was due to the differences in metabolism, excretion and body weight between the two cohorts.

The WHO considers DM to be a global epidemic which mostly affects low and middle-income countries. Globally, 1.7 billion adults are classed as overweight and 312 million obese, with 18 million death associated with cardiovascular disease in which DM is a predisposing factor (Majumder, Chaudri & Sanyal, 2019). TB continues to increase mortality, with recent work by the WHO and the International Union Against TB and Lung Disease acknowledging the need for guidelines on the joint management and control of TB and DM. Jimenez-Corona *et al*. (2012) conducted a population-based prospective study of pulmonary TB patients in Southern Mexico, where almost one-third of the global TB cases with DM have been diagnosed. The study aimed to describe the clinical manifestation and treatment outcome of those with confirmed TB and DM compared to TB-only cases. The study included health facilities in Veracruz State from 1995 to 2010. Participants included those over the age of 15 with positive acid-fast bacilli cultures. All cultures were performed on smears (both smear-positive and smear-negative). DM was either diagnosed by a physician or confirmed by participants being on either oral hypoglycaemic medication or insulin treatment; all radiological images were assessed by an independent radiologist.

Jimenez-Corona *et al.* (2013) reported individuals with TB-DM to have more severe clinical manifestations, delayed sputum conversions and a higher probability of treatment failure, reoccurrence and relapse. The study included the use of molecular testing to differentiate the subsequent episodes of infections within patients with DM as either bacteria with the same genotype or reinfection caused by a different strain. They observed a higher frequency of TB (29.6%) and treatment failure outcome in DM patients, although there

are limited studies published to support these findings. The clinical and radiological presentations are more severe in the TB-DM cohort, with the study demonstrating a delayed sputum conversion at 60 days, which is reflected in other similar studies, although the timing of the delay conversion has varied amongst these studies. The independent risk of treatment failure associated with DM was at 2.93 (95% CI 1.18- 7.23), which is higher than reported in previous studies, and the combined outcome of failure and death was set at 1.69 (95% CI 1.36 to 2.12). One limitation of the study included the inability to analyse failure as a sole outcome due to the small sample size. The rate of reoccurrence and relapse among TB patients with DM were higher and this was an independent factor.

Jimenez-Corona *et al*. (2013) used molecular fingerprinting of Mtb, which allowed the determination of whether DM cases experienced subsequent episodes of TB caused by reinfection with a different strain or a relapse with the same strain. The occurrence of reinfection is seen in one-fifth of all TB cases. TB reinfection in patients with DM is likely due to hospital-acquired TB transmission occurring because of patients attending clinics in which there is a large prevalence of both undiagnosed and diagnosed TB, for instance attending TB outpatient clinics (Dunachie & Chamnan, 2018).

Khalil and Ramadan (2016) studied the risk factors for PTB among DM patients in a study size of 160 patients, grouped into 80 TB-DM patients and 80 patients with DM and with chest infections other than TB. The mean age of the TB-DM cohort was 52.90 +/- 11.12 and the mean for the TB cohort was 54.57 +/- 9.84, which were not significantly different. The TB-DM cohort comprised men (n=56) vs women (n=24), while in the DM group with no TB, the split was 55 male vs 25 females, with no statistically significant difference. Men were more commonly infected in the TB-DM cohort in agreement with other literature reports, including a Malaysian study with 69.3% males amongst the TB-DM the patients and in a study in Saudi Arabia using 187 TB-DM patients, where men represented 75.9% of the population. BMI was statistically significantly different between the TB-DM cohort with a mean BMI of 21.33 +/- 4.14 kg/m^2 compared to 26.62 +/- 5.34 kg/m^2 in the DM-only

group, with a p value of <0.01. The lower BMI can be most likely attributed to anorexia and consumption caused by the TB infection.

Khalil and Ramadan (2016) further examined risk factors for TB and found platelets to be statistically increased in TB-DM patients, with a mean platelet count of 351.91 x 10^9/L compared to the control group of 270.88 x 10^9/L (p=<0.001). A lower total protein in blood and lower serum albumin were also associated with a statistically higher risk for TB. The mean serum total protein in the TB-DM group was 6.62 g/dl compared to 7.03 g/dl in the DM-only group (p= <0.01), serum albumin in the TB-DM cohort was 3.35 g/dl (p= 0.02). These results reflect the state of malnutrition common amongst TB-DM patients. This is further supported by Karyadi *et al*. (2000), who found that individuals with TB are likely to have a lower serum albumin concentration than controls by 10% (p= <0.05) (a case-control study on 82 patients), which demonstrates that a poor nutritional state is common among adults with PTB. Malnutrition is associated with TB as the patient's metabolic state varies causing immune dysfunction.

1.28 Drug Resistance in TB-DM patients

Multi-drug-resistant TB (MDR-TB) is caused by the Mtb strain which fails to respond to a combination of two of the four main antibiotics (first-line anti-TB medication), rifampicin and isoniazid, and Extensively drug-resistant TB (XDR TB) is caused by an Mtb strain that is resistant to at least four of the main anti-TB drugs (rifampicin, isoniazid, fluoroquinolones and second-line injectable agents) (NHS England, 2019). Furthermore, it is estimated that 3 in every 1000 people globally are infected with latent MDR-TB, and the prevalence of latent MDR-TB is more than double that in those younger than 15 years of age. If this is not halted, the trend of MDR-TB in LTBI patients will continue to increase (Knight *et al.,* 2019).

In 2015, 10.4 million people were reported to have TB, of whom, 580,000 had MDR-TB. The risk factors of drug resistance are related to genetic factors, failure of adherence to previous TB treatment and comorbidities including DM.

The strongest predictor for the presence of MDR-TB is a history of TB treatment, partly due to initiation of an inadequate regimen using first line anti-TB drugs, the addition of a single drug to a failing regimen or failure to identify pre-existing drug resistance. Poor compliance with treatment is also seen as an important factor in the development of acquired drug resistance. More recently, the increased incidence of T2DM has been associated with the development of MDR-TB, as studies have reported a higher treatment failure rate in those patients with TB-DM (Rumende, 2018). In 2016, it was estimated that 4.1% of all new cases and 19% of all previously treated cases have MDR-TB. Surveillance data indicated that 600,000 people had developed MDR-TB in 2016 and 240,000 had died as a result. In 2016, 8,000 people had been diagnosed with XDR-TB globally and it is estimated that 6.2% of those with MDR-TB also have XDR-TB (WHO, Global TB Report, 2018).

Directly Observed Therapy (DOT) is an initiative launched to aid with the management of drug-susceptible TB. Nonetheless, it is not enough to control recognized MDR-TB. A patient with MDR-TB would receive a regimen containing five of the second-line medications for the first months of therapy, followed by three to four drugs thereafter in the continuing phase of treatment (Davies, 2001). The treatment regimen indicated by WHO for TB-DM includes ethambutol, ethionamide/prothionamide, ofloxacin/ciprofloxacin.

Pyrazinamide and aminoglycoside for the first 6 months, with the first three or four drugs being administrated for at least a further 18 months. In a large-scale study in Peru, 55 percent of patients were given an identical regimen to WHO recommendation utilizing kanamycin, ciprofloxacin, pyrazinamide, ethambutol and ethionamide, following treatment failure with susceptible TB therapy, entered retreatment using a short-course routine of streptomycin, rifampicin, isoniazid, ethambutol and pyrazinamide for a treatment alternative (Davies, 2001), which resulted in reduced relapse of cases. However, it remains unclear of the best treatment regimen available as currently MDR-TB is treated based on individual cases. This is partly owed to lack of randomised controlled trials on validation of specific recommendation.

Ofloxacin results in significant cure rates of about 80% in MDR-TB cases. The WHO, recommends a period of at least 18 months' treatment including HIV-negative patients the optimum duration of treatment for patients using MDR-TB is unclear (Seung, Keshavjee, & Rich, 2015). There is some primary evidence which demonstrates that at the very least a percentage of immunocompetent patients that managed to achieve a sustained sputum culture conversion early in their treatment course, may be treated for 12 months employing fluoroquinolone-containing regimens (Yew, Lange & Leung, 2010). However, in patients who are immunocompromised (including people who have DM) or have extensive radiographic signs of illness (particularly with fascia), extensive drug resistance *in-vitro*, postponed sputum culture conversion (i.e. following over three weeks of chemotherapy) or extra-pulmonary involvement, should get longer than 12 weeks of therapy (Yew, Lange & Leung, 2010).

In 2006, the WHO declared the emergence of XDR-TB, which is thought to be a virulent strain of drug-resistant TB. This follows previous research showing the extent of XDR-TB, a newly identified TB threat which is difficult to treat. This was based on a survey conducted by WHO and CDC from 2000-2004 which found XDR-TB had been identified globally but most frequent in Asia and former Soviet Union. In South Africa, an outbreak of XDR-TB in HIV-positive population in Kwazulu-Natal was associated with high mortality rate, of 544 patient studies, 221 had MDR-TB. of the 221 MDR-TB, 53 had met the definition of XDR-TB. XDR-TB has been identified in all regions of the globe, with potentially devastating consequences (Seung, Keshavjee & Rich, 2015). Epidemiological studies have shown the DM to be a risk factor for TB by increasing the risk from 2- to 4- fold depending on population. Within the last decade, a increase in MDR-TB and XDR-TB have been reported globally with increasing association with DM. The rate of DM in Mexico where both MDR-TB and XDR-TB have been reported alongside a rise on DM from 5.8% in 2000 to 9.2% in 2012. Munoz-Torrico *et al.* (2017) studied the outcome of TB treatment and the impact of DM, as well as the prevalence of adverse events (AEs), in a cohort of patient with MDR/XDR pulmonary TB from a national Mexican reference centre. The study findings suggested TB resistance is

more common in the DM cohort (54.4%): the treatment outcome in the DM cohort compared to non-DM cohort remained the same, and the DM cohort had higher and more severe AEs to TB treatments. DM, therefore, has negative outcome amongst TB patients and is likely to be associated with increased risk of primary treatment failure using first-line TB drugs in susceptible TB cases. To improve treatment adherence compliance a fixed drug combination is a pragmatic approach which is likely to provide better treatment outcome. However, the implementation of a fixed combination of drugs would be difficult to implement, due to the different pharmacokinetics of anti-TB drugs and their interactions (Lima *et al.,* 2017).

As DM is reported as an independent risk factor for a slow response to treatment and low serum anti-TB drug concentrations, Heysell *et al.,* (2013) undertook a Virginia state-wide study on the initiative of early therapeutic drug monitoring therapeutic dose of isoniazid and rifampicin for the first 2 weeks after TB treatment was commenced in patient newly diagnosed with TB with DM. Over a one year period, 21 DM patients had C_{2hr} concentrations performed, of which 16 DM patients (76%) had a value below the therapeutic range for isoniazid, rifampicin, or both. Fifteen patients of these patients had dose adjusted, with 12 patients (80%) showed an increase to within the expected range. Early therapeutic drug monitoring in patients with DM is likely to increase the response to TB treatment by ensuring appropriate dose is met as DM itself and DM medications are known to alter TB medication absorption.

Munoz-Torrico *et al.* (2017) reported the severity of AEs varied from gastritis to fatal syndrome with nephrotoxicity and hypothyroidism and ototoxicity most likely in TB-DM patients. This was correlated with high levels of HbA1c, which is a predisposing factor to the development of systemic chronic complications.

1.29 TB Treatment in HIV infected patients

Treatment of active or latent TB patients with HIV infection is managed as with HIV-negative patients, but dose adjustment is to be considered. The most

significant differences involve avoiding prescribing rifampicin to patients who are on medication which are protease inhibitors. An alternative is rifabutin for these patients. Patients with HIV and TB are likely to develop a paradoxical response immune reconstitution inflammatory syndrome (IRIS) when commencing antiretroviral therapy. This response has been linked more strongly with the immune response to Mtb, with increasing clinical severity of symptoms, including fever, greater pulmonary infiltrates and lymphadenopathy occurring (Cohen & Meintjes, 2011).

A randomised controlled trial has proven that survival was improved by the initiation of antiretroviral treatment during TB treatment. The analysis found that the mortality rate together using the initiation of antiretroviral treatment and TB treatment has been 5.4 deaths per 100,000 individual years (25 deaths in 429 patients). In comparison to 12.1 deaths per 100,000 individual years (27 deaths in 213 patients) with antiretroviral treatment beginning after the conclusion of TB treatment, a comparative decrease of 56 percent (Karim *et al., 2011*).

Ku *et al.* (2013) compared CD4+ T cell counts in patients with co-infection with HIV and TB, which included patients with high CD4+ T cells. They found when starting antiretroviral therapy early (within four weeks after the start of TB treatment) patients had reduced progression of TB infection and death. There is the possibility of deferring initiation of antiretroviral therapy until the continuation phase of TB treatment.

When comparing the duration of treatment of those with a coinfection of HIV and TB, studies have shown the TB reoccurrence is slower when a 9-month treatment is prescribed compared to a 6-month course of treatment (Bruchfeld, Correia-Neves & Kallenius, 2015). The association of TB-DM with HIV patients is of great interest. TB is known to induce secondary hyperglycaemia and insulin resistance without the presence of DM (Kwan & Ernst, 2011). Moreira *et al.* (2017) evaluated the prevalence of hyperglycaemia amongst a co-infected HIV and TB cohort who had commenced on anti-TB treatment in Rio de Janeiro, Brazil. The retrospective

cohort analysis included adults who had been diagnosed with TB and HIV between 2010-2015. They excluded the known DM population at baseline but included newly-onset DM after TB treatment and TB outcome had been evaluated as successful or adverse. The study found 414 individuals were euglycemic (87.5%), 49 hyperglycaemic (10.3%) and 10 had been diagnosed with new onset of DM (2.1%).

The risk factors for DM included age, as is observed when comparing euglycemic and hyperglycaemic levels in patients (47.9 vs 39.7 years, p = < 0.0001). The DM patients presented with more cavitation on chest radiological imaging compared to the hyperglycaemic and euglycemic patients (50% vs 23.4% vs 15.3%, P value 0.0007). The hyperglycaemic patients were more likely to have new onset of DM at follow-up, compared to the euglycemic (22 vs 1, P value <0.0001). The hyperglycaemic patients were associated with greater adverse outcomes (71.4% vs 24.6%, P value <0.0001) compared to the euglycemic patients. Using a 1-year crude mortality rate, this was higher in individuals with hyperglycaemia compared with those with euglycemia (48.9% vs 7.9%). Moreira *et al.,* (2018) found that transient hyperglycaemia is common in HIV infected patients who have commenced anti-TB medication and have an increased risk of adverse outcome. A limitation of their study included not having HbA1c testing available, which may have led to misclassification of hyperglycaemia in cases that had undiagnosed DM. The findings are consistent with a study conducted by Said (2017) in Tanzania, where there was a reported negative impact of hyperglycaemia during TB treatment. They had a median follow-up rate of five months after TB treatment had commenced, and the proportion of TB/ HIV co-infection was 32%.

1.30 Summary on the clinical presentation of TB-DM

If DM increased the risk of acquiring TB infection, the manifestation of TB in individuals with DM may also likely result in a different clinical presentation compared to classic TB presentation. Although the severity of TB in DM patients has not been truly investigated, a difference in TB disease severity and symptoms in patients with co-occurrence has important clinical

implications. For instance, a baseline TB characteristic can predict which patients might not respond to anti-TB drugs or have a higher rate of relapse. Smear-positive TB patients produce more bacteria in expectorated sputum, which is an indication of higher bacterial load and a greater infection risk compared to those who are smear-negative. For instance, a recent study in Taiwan found 88% of TB patients with DM had AFB smear-positive TB, with only 59% of TB patients without DM being AFB smear-positive (P value <0.01) (Workneh, Bjune and Yimer, 2017). However, most studies on the microbiological aspects of TB show DM is associated with smear-positive TB; whereas others do not and thus studies are inconclusive. Therefore, whether DM causes more TB bacterial burden, and consequently more positive smear results, remains under-investigated. Radiographs of the chest are used to diagnose TB and measure the extent and severity of the disease. Studies on TB-DM and radiographic findings suggest CXR of those with TB-DM is likely to be more atypical in appearance, with lower-lung involvement with greater cavities. If this is true, from these early studies, clinically this has implications for the diagnosis. However, these studies have shown no association and are inconclusive. The emergence of TB drug resistance poses a threat to global TB control due to a greatly increased risk of poor TB treatment outcomes by patients failing to complete TB treatment, not adhering to treatment regimens, or suffering from an insufficient absorption mechanism. A meta-analysis of MDR-TB on treatment outcome estimated an overall success rate of TB treatment at less than 62% of patients, while an estimated 8% fail and 11% die (Kibret *et al*., 2017).

XDR-TB is defined as mycobacteria resistant to at least four of the main anti-TB drugs (rifampicin, isoniazid, fluoroquinolones and second-line injectable agents) (NHS England, 2019). Individuals with XDR-TB have a poor treatment outcome, and 20% of XDR-TB patients die because of unsuccessful treatment (Eshetie *et al.,* 2018). Similarly, regarding AFB smear and CXR results, most studies have shown no association between TB-DM and drug resistance to TB, with some exceptions. Absorption of anti-TB medication is important, and this may be altered by DM, which could lead to increased development of drug resistance. Only two previous studies have examined the difference in

the absorption of rifampicin in TB with and without DM; they both reported conflicting results. If a TB patient with DM increases the resistance at the time of TB diagnosis or develops drug resistance during therapy, the clinical success is important. Sputum culture conversion from positive to negative after two months of anti-TB treatment is used as a measure of treatment efficacy and is associated with TB treatment success. From evaluating the literature from the systematic review on the association between DM and TB 2-month culture conversion found a delayed response to treatment among the TB-DM cohort. Furthermore, the SR review of nine studies that determined the proportion of TB-DM patients who converted sputum cultures by two-month TB treatment, when comparing two-month data, only six of the nine reported having found an increased risk of no culture-positive in TB.

Alisjahbana *et al.* (2007) reported that 71% (67/94) of the TB-DM cohort compared to 8.3% of the TB-only (466/540) cohort were AFB sputum negative after the initial intensive phase of TB treatment. Although many studies have been reported on TB-DM patients being examined for 2-month culture conversion, few have used adequate measures of DM or had sufficient sample sizes. Relapse among TB patients is defined as a patient who previously completed TB retreatment successfully and, subsequently, is diagnosed with sputum smear or culture-positive TB. Whether DM increases the risk of TB relapse has been examined in few publications. A retrospective cohort study in China reported 20% of 203 treatments completed in a TB-DM cohort returned to TB clinic within two years of their first completion (Mishkin, 2018). Baker *et al.* (2011) developed a pooled risk ratio from five studies to help estimate TB relapse. Comparing patients with and without DM, the risk of relapse in TB-DM was 3.89 (95% CI 2.43 - 6.23) times the risk of TB patient without DM. The mortality rate has been examined as it is thought DM is the risk of death in TB-DM patients. A 2011 systematic review by Baker *et al.* (2011) showed that 95.5% (21 of 23) of studies found an increased unadjusted risk of death among a TB-DM cohort when compared to TB patients without DM. However, there were many limitations to this study, including follow-up times and mortality measurements being inconsistent.

1.31 Bi-directional screening

A bidirectional screening for DM in all patients with TB should be considered; this would help identifying TB patients with a risk of DM. Screening for DM in the initiation of TB drugs should improve the management of DM, with better TB treatment outcomes. Further to this, active TB infection should also include assessing DM symptoms, including polydipsia, polyuria, polyphagia, weight loss, blurred vision and poor wound healing. Bidirectional screening would depend on the availability of staff and technology, and would include those with known risk factors, e.g. old age, male, smoking, previous history of TB (Siddique *et al.,* 2018).

Screening for DM in TB patients also requires further caution as Mtb infection elevates blood glucose levels of HbA1c over a shorter duration of time (Siddique *et al.,* 2018). Therefore, any screening for DM should be done at the earliest stage of TB confirmation (Zheng, Hu & Gao, 2017). In relation to testing methods for DM, as a routine practice, they pose problems, with either fasting 2-hour post-prandial or HbA1c as the choice of test. A random or fasting blood glucose test will aid to diagnose DM but this has low sensitivity of fasting blood glucose (FBG). HbA1c offers a better method for screening. In the UK, there is a lack of a multidisciplinary integrated program and quality evidence on the feasibly of good DM management. A quality study is required to understand the association between TB and DM, which would be useful in targeting and reducing TB incidence and improving the TB treatment outcome.

1.32 Identification of gap in knowledge and current clinical practice for management of TB-DM patients in the UK

1.33 Objective

A systematic review of recent literature was undertaken to evaluate current knowledge of any association of DM in patients with TB.

1.34 Inclusion criteria

Studies included in the review were cross-sectional, case-control and cohort studies from adult patients diagnosed with both TB and DM. In addition, latest National Institute of Clinical Excellence (NICE), Public Health England (PHE), and World Health Organisation (WHO) studies were included. The diagnoses included pulmonary TB and extra-pulmonary TB, either diagnosed clinically (including commencement of anti-TB medication) or through using laboratory diagnosis, i.e. culturing of *M. tuberculosis*. The diagnosis of DM was defined by measurement of fasting plasma glucose, oral tolerance test, self-reported, glycated haemoglobin or diagnosis by a physician.

1.35 Exclusion of studies

- All duplicate publications of studies were removed.
- Studies where data was not fully accessible.
- All studies prior to 2010
- Language other than English

Table 1.1. Search Strategy

Search	Category	Search Strategy
1	Therapy	Tuberculosis AND trial OR TB* OR meta-analysis OR TB* OR systematic reviews OR TB* OR therapeutic use OR TB* OR Literature Review OR Diabetes AND trial OR diabet* OR meta-analysis OR diabet* OR systematic reviews OR diabet* OR therapeutic use OR diabet* OR Literature Review
2	Diagnosis	Sensitive*TB OR diagnosis OR diagnose TB OR diagnosed TB OR diagnoses TB OR diagnosing TB OR diagnosis TB OR diagnostic TB OR diagnosis OR diagnosis. Differential
3		# 1 AND 2
4	Aetiology	risk*TB OR risk*[TB:noexp]
5	Prognosis	Incidence [TB:noexp] OR mortality TB OR follow up studies [TB:noexp] OR prognos*TB OR predict*TB OR course*TB
6		# 4 AND 5
7	Clinical outcomes guide	Outcomes*TB OR predictive value of tests
8		# 3 AND 6 AND 7
9		Studies published in English

1.36 Databases used

The search of databases included Science Direct, PubMed, Excerpta Medica Database (Embase) to identify relevant abstracts on the prevalence and

association of TB and DM from 1st of January 2010 to 31st of December 2019, using the above key terms (Table 1.1).

The search strategy used included using medical subject heading (MeSH) terms and text word terms to identify all relevant studies, whether catalogued under the relevant terms or not. Special characters, search functions and Boolean Operators were used to produce a strict search strategy. The use of “exp” and the back slash within search strings 1 to 5 indicate that these strings used the explode command; an exploded search string selected articles indexed with that search term, plus articles indexed with the related narrower terms. The search was restricted to English language papers only. All duplicate references were removed after citations were downloaded into Mendeley using the duplicate function in the programme. All relevant abstracts were reviewed, and where relevant the full articles were reviewed.

1.37 Selection of studies for full review

All relevant studies were assessed using an assessment guide/grid to ensure that the selection criteria were reliably applied to all the articles. These full texts were screened using a standardised form for final inclusion in the review.

1.38 Data extraction and management

Data extracted included authors, country, region, year of publication, study design, study period, country of study, DM diagnosis, TB diagnosis, data collection method, number of DM cases, age, % of resistant TB and total population size.

1.39 Search results

All publications which cited analytical estimates of the association between DM and TB were included. After abstract review of 103 citations, 42 publications were deemed relevant for full data extraction (Table 1.2).

Table 1.2 Articles from Systematic Review													
Author	**Year of publication**	**Study Design**	**Period**	**Country**	**DM diagnosis confirmation***	**Site**	**Diagnosis of Diabetes Mellitus**	**Diagnosis of Tuberculosis**	**% with resistance TB**	**Mean/median Age, years**	**Population**	**% with HIV infection**	**Sample Size**
Alisjahbana et al.	2014	Cohort	2000-05	Indonesia	Yes	Hospital based	Fasting plasma glucose	Clinically based, Laboratory-based, X-ray- based	12.6		Adults	0	634
Alladin et al.	2011	Cross sectional	2006	Guyana	No	Hospital based	Random Plasma Glucose	Clinically based, Laboratory-based, X-ray- based			Adults and Children		100
Baker et al.	2012	Cohort	2001-04	Taiwan	Yes	Population based					Adult		17715
Leegaard et al.	2011	case-control		Denmark	Prescription Database and Danish NHIS Registry			First time TB diagnosis in hospital records based on ICD 8 (-1993), or ICD 10 (-2008)					

Table 1.2 Articles from Systematic Review													
Author	**Year of publication**	**Study Design**	**Period**	**Country**	**DM diagnosis confirmation***	**Site**	**Diagnosis of Diabetes Mellitus**	**Diagnosis of Tuberculosis**	**% with resistance TB**	**Mean/median Age, years**	**Population**	**% with HIV infection**	**Sample Size**
Davis et al.	2016	case-control	2012-2014	Kazakstan	Self reported			Identified by national TB program new PTB by positive TB culture or on clinical and radiographic grounds and respond to anti-TB treatment					
Dobler et al.	2012	cohort	2001-2006	Australia	Self-reported	National Diabetes Service	self-reported DM confirmed by health professional	Laboratory based			Adults		
Pealing et al.	2015	Cohort	1990-2013	UK	Patients identified within the CPRD with incident diabetes (types 1 and 2 included), ≥5-years old,	A matched cohort study using the UK Clinical Practice Research					Adults		

Table 1.2 Articles from Systematic Review													
Author	**Year of publication**	**Study Design**	**Period**	**Country**	**DM diagnosis confirmation***	**Site**	**Diagnosis of Diabetes Mellitus**	**Diagnosis of Tuberculosis**	**% with resistance TB**	**Mean/median Age, years**	**Population**	**% with HIV infection**	**Sample Size**
					who had their first recorded diagnosis for diabetes using NHS Read codes.	Datalink (CPRD) in which 7 million patients registered.							
Barss *et al*.	2016	Cross sectional	2007-12	Canada	No		Fasting plasma glucose, 2h-Plasma Glucose-OGTT, Taking antidiabetics	Clinically based, Laboratory-based			Adults	5.2	788
Benoit *et al*.	2017	Case control	2009-14	USA	No	Population based		Clinically based, Laboratory-based			Adults		2262
Boillat-	2016	Case	2013	Tanzania	Yes	Hospital	Fasting	Clinically		33.7	Adults	30.7	167

Table 1.2 Articles from Systematic Review													
Author	**Year of publication**	**Study Design**	**Period**	**Country**	**DM diagnosis confirmation***	**Site**	**Diagnosis of Diabetes Mellitus**	**Diagnosis of Tuberculosis**	**% with resistance TB**	**Mean/median Age, years**	**Population**	**% with HIV infection**	**Sample Size**
Blanco		control				based	plasma glucose, 2h- Plasma Glucose-OGTT	based, Laboratory-based, X-ray-based					
Bridson *et al.*	2015	Cross sectional	1995-14	Australia	No	Hospital based	Fasting plasma glucose, HbA1c	Laboratory-based			Adults		69
Cai *et al.*	2017	Cross sectional	2010-13	China	No	Population based	Fasting plasma glucose	Laboratory-based, X-ray- based		31.8	Adults		3505
Caraffa *et al.*	2016	Cross sectional	2007-12	Italy	Yes	Hospital based	Fasting plasma glucose, 2h- Plasma Glucose-OGTT	Clinically based, Laboratory-based, X-ray-based		40.8	Adults	14.4	971
Chen *et al.*	2014	Cross	2010-	China	Yes	Hospital	Fasting	Clinically		54	Adults		1126

Table 1.2 Articles from Systematic Review													
Author	**Year of publication**	**Study Design**	**Period**	**Country**	**DM diagnosis confirmation***	**Site**	**Diagnosis of Diabetes Mellitus**	**Diagnosis of Tuberculosis**	**% with resistance TB**	**Mean/median Age, years**	**Population**	**% with HIV infection**	**Sample Size**
		sectional	11			based	plasma glucose, Taking antidiabetics	based, Laboratory-based, X-ray- based					
Chiang *et al.*	2015	Cohort	2005-10	Taiwan		Hospital based	Fasting plasma glucose, 2h- Plasma Glucose-OGTT, Taking antidiabetics, Random Plasma Glucose, HbA1c	Clinically based, Laboratory-based, X-ray- based	11.8		Adults	0.3	1594
Dave *et al.*	2013	Cohort	2012	India	No	Hospital based	Fasting plasma glucose	Laboratory-based			Adults	4.32	556
De la Garza Ramos *et al.*	2016	Cross sectional	2002-11	USA	No	Hospital based				51	Adults	4	2789

Table 1.2 Articles from Systematic Review													
Author	**Year of publication**	**Study Design**	**Period**	**Country**	**DM diagnosis confirmation***	**Site**	**Diagnosis of Diabetes Mellitus**	**Diagnosis of Tuberculosis**	**% with resistance TB**	**Mean/median Age, years**	**Population**	**% with HIV infection**	**Sample Size**
Delgado-Sanchez *et al.*	2015	Cross sectional	2000-12	Mexico	No	Hospital based	Fasting plasma glucose, 2h- Plasma Glucose-OGTT	Laboratory-based, X-ray- based	8.44	46	Adults		181378
Ekeke *et al.*	2017	Cross sectional	2015	Nigeria	Yes	Hospital based	Fasting plasma glucose, Random Plasma Glucose	Clinically based, Laboratory-based, X-ray- based			Adults	19.5	2094
Faurholt-Jepsen *et al.*	2011	Case control	2006-09	Tanzania	No	Hospital based	Fasting plasma glucose, 2h- Plasma Glucose-OGTT	Clinically based, Laboratory-based		34.8	Adults	43.2	803
Gadallah *et al.*	2016	Cohort	2006-10	Egypt	No	Hospital based		Clinically based, Laboratory-based, X-ray- based	100	37	Adults and Children		228

Table 1.2 Articles from Systematic Review													
Author	**Year of publication**	**Study Design**	**Period**	**Country**	**DM diagnosis confirmation***	**Site**	**Diagnosis of Diabetes Mellitus**	**Diagnosis of Tuberculosis**	**% with resistance TB**	**Mean/median Age, years**	**Population**	**% with HIV infection**	**Sample Size**
Haraldsdottir *et al.*	2015	Case control	2010-11	Guinea-Bissau	Yes	Hospital and Population based	Fasting plasma glucose				Adults		110
Hermosilla *et al.*	2017	Cross sectional	2012-14 2014	Kazakhstan	No	Hospital based		Clinically based, Laboratory-based, X-ray- based		35	Adults	1.48	562
Jerene *et al.*	2017	Cross sectional	2015	Ethiopia	No	Hospital based	Fasting plasma glucose, 2h- Plasma Glucose-OGTT	Laboratory-based, X-ray- based		30	Adults	12.5	435
Kayhan *et al*.	2012	Cross sectional	2003-10	Turkey	No	Hospital based		Clinically based, Laboratory-based, X-ray- based	3.9	42.6	Adults		2404
Khandkar *et al.*	2015	Case control	2000-12	Australia	No	Hospital based	Fasting plasma glucose,	Laboratory-based			Adults and Children	3.64	577

Table 1.2 Articles from Systematic Review													
Author	**Year of publication**	**Study Design**	**Period**	**Country**	**DM diagnosis confirmation***	**Site**	**Diagnosis of Diabetes Mellitus**	**Diagnosis of Tuberculosis**	**% with resistance TB**	**Mean/median Age, years**	**Population**	**% with HIV infection**	**Sample Size**
							Taking antidiabetics						
Kornfeld *et al.*	2016	Cross sectional		India	No	Hospital based	Fasting plasma glucose, 2h- Plasma Glucose-OGTT, Taking antidiabetics	Laboratory-based			Adults	0	209
Lee *et al.*	2017	Cross sectional	2010-12	South Korea	No	Hospital based	Fasting plasma glucose, 2h- Plasma Glucose-OGTT	Laboratory-based, X-ray- based, Histology	3.8	56	Adults		1044
Perez-Guzman *et al.*	2014	Cross sectional	2008	Mexico	No	Hospital based		Clinically based, Laboratory-based, X-ray-based		53.5	Adults	9.3	86
Pealing *et al*.	2015	Cohort	1990-2013	UK	Yes	Population based	Physician						

Table 1.2 Articles from Systematic Review													
Author	**Year of publication**	**Study Design**	**Period**	**Country**	**DM diagnosis confirmation***	**Site**	**Diagnosis of Diabetes Mellitus**	**Diagnosis of Tuberculosis**	**% with resistance TB**	**Mean/median Age, years**	**Population**	**% with HIV infection**	**Sample Size**
Pearson *et al.*	2019	Cross sectional	2019	UK	Yes	Population Based		Clinically based, Laboratory-based, X-ray- based		60	Adults		224 508
Perez-Navarro *et al.*	2017	Cohort	2006-14	Mexico	No	Hospital based	Fasting plasma glucose	Clinically based, Laboratory-based, X-ray-based	11	43	Adults		507
Rajapakshe *et al.*	2015	Cross sectional	2013-14	Sri Lanka	No	Hospital based	Fasting plasma glucose			51	Adults		112
Ruslami *et al.*	2010			Global	Yes	Population based		Clinically based, Laboratory-based, X-ray-based			Adults		
Restrepo *et al.*	2011	Cross sectional	2006 - 08	USA; Mexico	NA	Hospital based	Fasting plasma glucose, HbA1c	Clinically based, Laboratory-based		49.9	Adults	3.9	233

Table 1.2 Articles from Systematic Review													
Author	**Year of publication**	**Study Design**	**Period**	**Country**	**DM diagnosis confirmation***	**Site**	**Diagnosis of Diabetes Mellitus**	**Diagnosis of Tuberculosis**	**% with resistance TB**	**Mean/median Age, years**	**Population**	**% with HIV infection**	**Sample Size**
Tahir *et al.*	2016	Cross sectional	2014 – 15	Pakistan	Yes	Hospital based	Fasting plasma glucose, HbA1c	Clinically based, Laboratory-based, X-ray-based		38	Adults		500
Uwanpimolkul *et al*.	2014	Cross sectional	2005 - 12	USA	No	Hospital based	Taking antidiabetics	Clinically based, Laboratory-based, X-ray-based	1		Adults	7.7	791
Wang *et al*.	2016	Cross sectional	2011-13	China	Yes	Hospital based	Fasting plasma glucose, Taking antidiabetics	Clinically based, Laboratory-based, X-ray-based			Adults	0	2280
Walker *et al.*	2010	Cross sectional	2005	UK	Yes	Population based		Laboratory-based			Adults		3461
Workneh *et al.*	2016	Cross sectional	2013-15	Ethiopia	Yes	Hospital based	Fasting plasma glucose, Taking antidiabetics, Random	Laboratory-based		35.7	Adults	20	1314

Table 1.2 Articles from Systematic Review													
Author	**Year of publication**	**Study Design**	**Period**	**Country**	**DM diagnosis confirmation***	**Site**	**Diagnosis of Diabetes Mellitus**	**Diagnosis of Tuberculosis**	**% with resistance TB**	**Mean/median Age, years**	**Population**	**% with HIV infection**	**Sample Size**
							Plasma Glucose						
Wu *et al.*	2016	Cross sectional	2007-08	China	Yes	Population based		Clinically based, Laboratory-based, X-ray-based	13.9	48	Adults		201
Zhao *et al.*	2016	Cross sectional	2013-14	China	No	Population based	Fasting plasma glucose, HbA1c	Laboratory-based, X-ray- based		50	Adults		1363

1.40 Evidence of an association between DM and TB from published studies

Nine studies (two cohort and seven case-control studies) estimated DM to increase the risk of TB infection in individuals by 1.5 to 7.8-fold. Fourteen studies found DM was associated with an overall RR of 3.11 for contracting TB, although a limitation of this was the studies by Benoit *et al.* (2017), Caraffa *et al*. (2016), and Rajapakshe *et al.* (2015), which were heavily weighted, as pooled results consisted largely of patients with renal failure (renal failure was identified as a risk factor for TB), which limited the applicability of the findings more widely. Furthermore, the impact of age on the estimation of the association between DM and TB, found increasing age to increase the risk of TB and this was confirmed in reports by Barss *et al.* (2016) and De La Garza *et al*. (2016) but not in the study by Ekere *et al.* (2017); Boillat-Blanco *et al.* (2016); and Davis *et al.* (2016).

Evidence suggests a potential link between DM and TB, from a UK based study by Pealing *et al.* (2015) using a cohort study approach. They used data from the Clinical Practice Research Datalink (CPRD), which contains rich data primarily from primary care databases. However, the limitation of this study includes the variable completeness of the database, misclassification and disease definitions. Patients were identified within the CPRD with incident diabetes (types 1 and 2 included), ≥5-years old, who had their first recorded diagnosis for diabetes using NHS codes. This study reported an overall 1.3-fold increased risk of TB in those with DM. There was no evidence for higher relative increase in TB rates among DM patients of different age groups or ethnicities, longer duration of disease, those using insulin or with worse glycaemic control. There was strong evidence for differences among DM patients with different health care utilization patterns (adjusted RR 1.30, 95 % CI 1.01 to 1.67, $P = 0.04$). No evidence of effects of age, time since diagnosis and severity of DM on the association between DM and TB was reported.

Further research into DM and TB association is needed, especially in high TB incidence populations. Furthermore, patient follow-up is required to ensure

DM did not contribute to worsening of TB condition i.e. DM increased TB treatment failure, relapse, or development of MDR-TB. Similarly, whether TB impacted upon the risk of developing DM post treatment (Zhao *et al.,* 2016); (Delgado-Sanchez *et al.,* (2015). Although a risk estimation was made, no UK study has been done on the prevalence of TB-DM in a regional or local setting using primary data. Therefore, a gap in knowledge of the true estimation of DM prevalence in the TB population is unmet and should be investigated.

1.41 Risk of DM amongst individuals with TB

Most studies have reported on the risk of DM developing amongst individuals with TB. The estimation of the risk of TB developing in DM patients ranged from a 1 to 7-fold increase (Bridson *et al*., 2015; Hermosillia *et al*., 2017). The potential of a bi-directional association between DM and TB is not evident as yet. Patients with DM are at increased risk of TB infection and risk factors need to be identified for clinical pathways to be created to manage the patient with TB including an appropriate testing and treatment regimen. Therefore, a gap in knowledge of the true prevalence of DM in the TB population is currently unknown. Pearson *et al. (*2019), reported a UK based study, which recognised an increased risk of PTB among those with DM. However, the evidence on whether the association was bidirectional remained sparse, and Pearson *et al.* (2019) investigated the DM rates among those with and without TB disease as a reverse. Using data from the UK general practice population between 2003 to 2009, from the Health Improvement Network database, the study reported DM risk was substantially raised amongst individuals with a history of TB disease (IRR 5.65 (95% CI 5.19 to 6.16)), PTB) IRR 5.74 (95% CI 5.08 to 6.50)) and EPTB (IRR 4.66 (95% CI 3.94 to 5.51)) compared to those without. These findings indicated the need for screening of patients with TB for DM, who are at a higher risk of DM and related complications.

1.42 Risk of TB amongst individuals with DM in the UK

From the systematic reviews, only two UK based studies were conducted with others being in high TB incidence countries. The data for the UK, which is

generally a low incidence country, with selected areas of high incidence, therefore is lacking and provides a gap in our understanding of the prevalence of TB-DM and its characteristics in UK hot-spot areas, such as Newham.

1.43 Measures of association between sub-types of TB and DM

Of the systematic reviews, 10 did not specify if the studies were assessing the association between specific sub-types of DM or TB and were to be assumed to be assessing the association between all types of DM and TB.

- One study specified they were assessing the association between PTB and DM (Faurhoult-Jepsen *et al.,* 2011).
- One study assessed the association between post-transplant TB and DM (Zhao *et al.*, 2016).
- Two studies assessed the sub-types of T1DM, T2DM and TB (Dobler *et al.,* 2012 and Leegaard *et al.,* 2011).
- a single study measured the association between DM and both PTB and EPTB (Pearson *et al.,* 2019).

Papers which included a measure of TB risk amongst individuals with T1DM identified an increase in risk, although only one estimate showed significance RR 2.27 (95% CI 1.19-3.66) and (Odds Ratio (OR) 2.59 (95% CI 0.44-15.20) (Cai *et al.,* 2017). Subtype studies reported an increased risk estimate for TB amongst those with T1DM compared to those without T1DM, a reason for this is T1DM is associated with hyperglycaemia due to poor glycaemic control (Workneh *et al.,* 2016).

Only one study measured PTB and EPTB risk amongst individuals with T1DM compared to those without and found that the risk of PTB was significantly increased in individuals with DM, whereas there was no significant increased risk of EPTB, although the study had a small number of participants (n=69) (RR 1.42 (95% CI 1.12-1.80) and (OR 1.05 (95% CI 0.49-2.31)) (Bridson *et al.,* 2016). The study was underpowered to explore the potential association with EPTB, as it accounts for less than 20% of global TB and only 10% of DM is T1DM; therefore, it is difficult to confirm cases with diagnosis of both in

many low-income and middle-income countries (LMIC), where TB burden is the highest. The most significant finding was the association between T2DM and PTB as approximately 90% of individuals with DM have T2DM and PTB is the most prevalent infectious form of TB. However, further investigation is required. Due to the lack of studies on DM subtypes (T1DM and T2DM) and TB subtypes (PTB or EPTB) which are managed differently, a UK based study is required to understand the characteristics of PTB and EPTB in terms of presentation and diagnosis in patients with diabetes, which is likely to affect treatment course.

1.44 Co-morbid DM and TB

The systematic review identified two studies which highlighted the estimation of the association between DM and TB on TB incidence (Ruslami *et al.,* 2010 and Walker *et al.,* 2010). Both studies calculated the population attributable fraction (PAF) of TB due to DM considering best estimates of the association size, DM prevalence and TB incidence for specific regions. Walker *et al*. (2010) calculated the PAF for the UK showing that the effects of an association between DM and TB would not be negligible in this setting, especially amongst those already at an increased risk of TB, due to their ethnicity. The risk estimated for all ages varied showing that from 6.9% of incident TB (amongst white British) to 19.6% of incident TB (amongst those of Asian ethnicity) attributed to concomitant DM.

Ruslami *et al.* (2010) outlined the estimated proportion of TB incidence attributable to concomitant DM in the population in the ten countries with the highest incidence of TB: India (12.9%), China (7.8%), Indonesia (9.5%), Nigeria (7.6%), South Africa (8.7%) Bangladesh (11.2%) Ethiopia (4%), Pakistan (14.4%), the Philippines (12.9%) and the Democratic Republic of Congo (5.2%), noting that these estimates would be expected to rise as DM prevalence increases. The paper identified the context of the association between DM and TB, and highlighted the possible impact of the association, given the numbers expected to present with co-occurrence of TB and DM.

Only one UK study demonstrated the TB risk in the non-UK born population to be higher, this did not consider other co-morbid factors i.e. renal disease and DM (which is linked more to Asian and black ethnic individuals) (Walker *et al.* (2010). Therefore, a further investigation into comorbid links is required in a UK TB-DM cohort.

1.45 Radiological appearance

There are several studies which have assessed the radiological presentation of TB amongst individuals with DM. Radiological evidence is used to aid TB diagnosis and at times may be solely used to diagnose active TB disease. If radiographic presentation is atypical, as is the case in DM patients with TB, it is likely that they will go undiagnosed for a longer period than those with TB alone and clinically have worse outcomes (Moreno-Martinez *et al.,* 2015).

PTB is predominantly found in the lung apices, however, in individuals with TB-DM this is thought not to be the case. Lower lung field TB may occur, but is often misdiagnosed as pneumonia, bronchial carcinoma or lung abscess, as these patients are often smear test negative (Perez-Navarro *et al.,* 2017). Studies from this systematic review show individuals with TB-DM are more likely to present with lower lobe involvement, with increased numbers of multi-lobular cavities and increased prevalence of pleural effusion. Kayhan *et al.* (2012) found that multi-lobular cavity TB is more common in individuals with DM. Perez-Guzman *et al.* (2014) conducted one of the largest radiological study (TB-DM, n=202 vs control, n= 226; p= 0.02)) with high statistical power to detect differences in presentation between patient subgroups, found no difference in the localisation of TB lesions in those with and without DM.

Most of the identified studies looking at the differences in the radiographic presentation of TB amongst individuals with DM were completed within low to middle income countries, where incidence rates of other co-morbidities, which may affect presentation of TB are high (such as HIV). Walker *et al.* (2010) reported only 8% of individuals with TB had abnormal radiographic presentation. The UK study by Walker *et al.* (2010) was limited to using

national database data which does not report in-depth radiographic presentation. As a result, current published data on the lung pathology in TB-DM individuals is contradictory and evidence should be considered with caution. Therefore, further studies are required as this remains inconclusive. A closer investigation into TB-DM radiographic images is required and to assess whether in areas where there is high TB incidence, there is a difference in radiographic appearances in individuals, furthermore, those with EPTB (or suspected) i.e. abdominal TB should also have radiographic assessment to rule out possible PTB with EPTB. This would allow for a clinical pathway to be created for testing TB-DM patients appropriately for sending for more routine tests, if set criteria are met. For example, a DM patient presenting with a persistent cough for more than 2-weeks would be referred for a chest x-ray.

The radiographical presentation of TB is likely to depend on many factors, including the duration of illness and the host immune system. Perez-Navarro *et al.* (2017) reported that a large proportion of DM patients with TB had lower-lung involvement compared to non-DM TB patients, who presented with upper-lobe involvement. Their findings suggested PTB in TB-DM patients had an atypical radiographic presentation, with lower-lobe involvement. Clinically this is significant, as this may be misdiagnosed as community acquired pneumonia. Furthermore, those PTB patients that do not present with upper lobe involvement are less likely to have positive sputum smears and culture.

Furthermore, lower-lobe lung involvement is observed in older individuals and this change is likely to be related to changes in lower-lobe alveolar oxygen tension related to age or DM. Perez-Navarro *et al.* (2017) have reported multi-lobar disease or the presence of multiple cavities more commonly in TB-DM patients, but lower-lung disease was rare in TB-DM patients compared to the control group. Results vary vastly between studies and findings are possibly overstated.

1.46 Signs and symptoms

As with radiographic presentation, atypical presentation of signs and symptoms amongst TB-DM individuals could increase the likelihood of TB being undiagnosed for longer periods of time, than those with TB alone, leading to poorer clinical outcomes (Tahir *et al.,* 2016). A late TB diagnosis also poses a risk to public health and increases the risk of TB transmission to others. As TB remains undiagnosed, the index case will have significant contact with core groups of people increasing the spread of TB. Study participants also presented with weight loss and weakness, a feature in TB-DM. Therefore, TB should be considered in patients with DM, who have unintentional weight loss and night sweats that cannot be explained by poor control of diabetes. Furthermore, TB-DM patients presented with further complications including lung abscess, pleural effusion and hydro-pneumothorax (Gadaliah *et al.* (2015) and Jerene *et al.* (2017)).

Evidence from this systematic review suggests that the sociodemographic and clinical characteristics of those presenting with TB-DM differ from those with TB alone. Individuals with TB-DM are thought to present with TB at an older age, predominantly male, have a higher BMI before and after treatment and are less likely to present with EPTB, and more likely to present with more severe symptoms and differences in radiological features.

Wang *et al.* (2016) undertook a retrospective study and found that patients with TB and DM showed higher frequencies of fever and haemoptysis, although symptoms were self-reported. Alladin *et al.* (2011) found no difference in symptoms between patients with PTB in those with or without DM, except for polyuria in TB-DM cases. There are few studies which assess the role of symptoms of the co-affected DM and TB patients, and with sparse data and contradictory findings, further research is required for TB-DM cohorts and to determine whether symptoms and diagnostic testing should be more tailored to TB-DM cohorts.

1.47 Management of TB-DM co-morbidity

Studies have shown a decreased effectiveness of TB treatment amongst individuals with DM. DM patients are thought to have impaired gastrointestinal drug absorption, due to gastroparesis, which may affect the uptake and absorption of medication. The uptake of rifampicin was 53% lower in Indonesian patients with TB and DM compared to patients with TB only (Khandkar *et al.,* 2015). This could be due to poor gastrointestinal uptake, or due to differences in metabolism, excretion and body weight amongst those with DM. Furthermore, individuals with TB-DM are less likely to adhere to medication schedules (Khandkar *et al.,* 2015). These findings are inconsistent with some studies which demonstrate a lower proportion of co-morbid individuals defaulting on their TB treatment compared to those with TB alone (Haraldsdottir *et al.,* 2015). The findings of these studies are debatable in terms of clinical significance, and further assessment of efficacy of treatment regimen amongst TB-DM is required.

It is known that TB medication leads to transient hyperglycaemia, and it is likely that amongst those being treated for TB, hyperglycaemia is occurring as a side effect of treatment with rifampicin and isoniazid, or that the hyperglycaemia is observed as a stress hyperglycaemia rather than a real indication of metabolic dysfunction (Restrepo *et al.,* 2011). Therefore, it remains to be seen whether TB increases the risk of DM or undiagnosed DM leads to poor clinical outcome for TB. A bi-directional screening is likely to be of benefit in this instance.

The systematic review identified studies assessing TB outcomes amongst those with and without DM. No study proposed treatment regime alteration or methods for checking for adherence to medication, which is likely to affect patient outcome. Therefore, there is an unmet need to assess whether TB medication is in the therapeutic range comparing both TB only and TB-DM groups to ensure an appropriate plasma concentration is achieved, and where necessary the drug dosage could be altered.

As DM and TB have an increased reciprocal risk, there could be a bi-directional screening opportunity for TB in DM patients and DM in TB patients. Screening for active TB in DM clinics would allow earlier detection of TB and reduce the risk of TB transmission in DM clinics and within the community (Kornfeld *et al.,* 2016). Especially if a patient presents with a cough for more than 2 weeks alongside weight loss, night sweats, fever and a history of TB contact. TB is also likely to increase the risk of DM, anti-TB medication, predominantly rifampicin can cause hyperglycaemia. Therefore, screening for DM should be investigated in all patients over the age 18 years with TB. The preferred method for screening for DM and time should also be further investigated. Screening for DM in TB patients has been conducted in India and the Pacific Islands, which can be mirrored in other countries with a high prevalence of TB, although more evidence for this is required (Pealing *et al.,* 2015).

In the UK, in high TB incidence localities, screening for DM should be investigated and understanding of the prevalence of TB-DM would provide evidence for this. Furthermore, individuals with DM who have TB are likely to respond less well to treatment than those without DM. Baker *et al.* (2012) found that the risk ratio of treatment failure or death in TB cases was 1.69 (95% CL 1.36-2.12) after adjusting for confounders such as age, the risk of death was 4.95 (2.69-9.10) among individuals with DM compared to those without. There was an increased risk of relapse (RR 3.89; 2.423-6.23). Individuals with DM have lower plasma concentrations of rifampicin than expected. In an Indonesian study, rifampicin levels were 50% lower in TB patients with DM compared with those without. It is thought a larger dose maybe required for overweight individuals (Delgado-Sanchez *et al*., 2015).

Furthermore, if DM is thought to alter immunity to TB in affected individuals, this is likely to lead to higher mycobacterial burden and increase in time to culture conversion with treatment, and a higher rate of relapse may result. Three retrospective studies (Dave *et al.,* 2013; Chian *et al.,* 2015 and Chen *et al.,* 2014) suggested that mycobacterial burden is higher in DM patients than in controls. The results assessing sputum-culture conversion report mixed

findings. In studies which assessed sputum-culture conversion at 2-months of treatment (intensive phase), the conversion proportions were similar in DM patients and controls. For instance, in the Indonesian study by Alisiahbana *et al.* (2014) found DM was not a risk factor for sputum smear or sputum culture positivity at 2-months of treatment. In a Turkish study Kayhan *et al.* (2012), patients with DM who received TB treatment had longer sputum-culture conversion times, TB-DM patients took longer to achieve culture negativity than non-DM patients (67 vs 55 days, p=0.02). The use of a survival analysis to measure time to culture conversion, median time to culture negativity was significantly longer in DM patients than in controls (42 vs 37 days, p=0.03). These data suggest the bacillary load to be higher at presentation in TB-DM patients, this leads to a longer time to sputum-culture conversion. Whether this increased time to culture conversion in TB-DM patient leads to higher risk of relapse requires further study.

1.48 Treatment failure and death

Whether DM increases the treatment failure of TB or increase death remains unanswered. Study by Lee *et al.* (2017), compared 119 patients with treatment failure to 1119 controls, DM increased the risk of treatment failure by 3.9-fold. In an Indonesian study (Alisiahbana *et al.* (2014), patients with higher treatment adherence found at 6-months 22.2% of the patients with DM and 6.9% of the controls were positive, with drug resistance was lower in DM, therefore treatment failure was not due to drug resistance or non-adherence to treatment.

Two retrospective cohort studies, Restrepo *et al.* (2011) and Uwanipimolkul *et al.* (2014) on patients with PTB in the USA showed a 6.5-6.7 times increased risk of death in DM patients compared to non-DM controls. In Wang *et al.* (2016) the 1-year mortality rate was 17.6% in DM patients compared to 7.7% in non-DM controls, and death related to PTB was more common in DM patients (12.2% vs 4.2%). Among the 416 TB deaths, DM was a common co-morbid factor.

Studies on treatment failure and mortality rate suggest this to be more likely to occur in TB-DM patients. However, there is no suggestive management of TB-DM patients, as this could improve treatment response, which remains to be investigated, furthermore, deaths reported does not explain if the increased severity of symptoms is presented in TB-DM patients or by the existence of comorbidities attributable to DM compounded by advanced age.

Furthermore, TB drugs may affect DM treatment, DM is also likely to alter the pharmacokinetics of TB drugs. In a study by Wu *et al. (*2016), DM patients with TB had rifampicin serum concentrations that were 53% lower than in non-DM patients with TB. This low concentration of TB drug may be linked to treatment failure or resistance. DM can cause changes in oral absorption, decreased protein binding of drugs, and renal insufficiency or fatty liver with impaired drug clearance. The effect of DM on TB drug concentration is yet to be fully understood.

1.49 National Clinical Evidence for TB-DM screening and management

NICE (TB Clinical Guidelines, 2016) reported patients with DM have both an increased risk of developing TB and significant morbidity and mortality. This is due to an impaired immune response to TB infection in patients with DM. Furthermore, NICE acknowledges treatment course is more difficult with poorer treatment outcomes in TB-DM patients compared to those without DM.

NICE reviewed the use of standard treatment regimens to be adapted to accommodate DM and the effect of these regimens for treatment of active PTB or EPTB. This was based on evidence reviewed from Medline, Embase, Medline in Process, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment database. The review included randomised, quasi-randomised and non-randomised controlled trials, prospective studies, comparing treatment regimens of TB in patients with active drug-susceptible TB and DM. The review included 3838 abstracts, 218 full-text, with 7 studies reporting on comorbidities or co-existing

conditions of interest, no papers relating to the treatment of TB in patients with coexisting DM met the inclusion or exclusion criteria (NICE, 2016).

No evidence comparing the effectiveness of different anti-TB regimens in patients with DM was identified. However, it was noted that TB treatment in DM patients was more difficult due to diabetic complications, such as renal failure or due to adverse effect profiles of anti-TB drugs and DM, for example neuropathy, or because of drug interactions between treatments used for both conditions. As a result, DM patients can be at risk of poorer treatment outcomes including treatment failure, relapse or the development of drug resistance, in comparison to those without DM (NICE, 2016).

NICE (2016) identified individuals with co-morbidity including diabetes as a significant risk factor for TB. NICE (2016) stipulates that coexisting conditions should be managed by a specialist multidisciplinary team with experience in managing TB and the coexisting condition. However, no further advice was given in relation to dual management i.e. screening options, treatment management and follow-ups. For instance, as is the case for individuals with HIV and active TB, where advice on treatment course, including avoiding drug interactions when co-prescribing antiviral and anti-TB medication due to interaction is given. In the case of TB-DM, rifampicin is known to accelerate the metabolism of oral hypoglycaemic agents, mostly sulphonylureas and biguanides, which lowers their plasma concentration and potentially therapeutic efficacy. However, such guidance is not available from NICE, PHE, Royal College of Nursing, or the British Thoracic Society.

The British National Formulary (BNF) (2020) recognises isoniazid is associated with an increased risk of not controlling DM, increasing risk of peripheral neuropathy due to overlapping toxicity profiles with isoniazid and those with DM should receive pyridoxine when taking isoniazid, evidence of a need for advice on drug treatment protocols for those with TB-DM.

UK guidelines (PHE, 2020; NICE, 2016) do not provide guidance on screening for DM in TB patients, nor for guidance on treatment duration for

those with TB-DM, and on follow-up of DM patients with TB. There is no current data on prevalence of TB-DM in the UK. Although PHE (2020) and NICE (2016) guidance acknowledges DM as a risk factor for TB, there is no guidance on the management of TB-DM patients in the UK and this is an unmet need.

NICE (2016) and PHE (2020) encourage an active case finding (ACF) strategy to identify and treat individuals with TB. ACF targets high-risk groups, which includes professionals at risk of TB (e.g. healthcare workers) close contacts of patients with TB (or an active TB case is suspected), individuals with social risk factors (homeless people, people with drug or alcohol problems, prisoners) and non-UK born individuals from within high TB incident regions. However, currently there is no mention of DM screening in TB patients.

In the absence of national guidelines on the joint management and control of TB and diabetes, the World Health Organisation (WHO) (2014) had developed a framework aimed at a guidance programme for clinicians and others engaged in the care of patients and prevention and control of DM and TB. The framework is based on evidence collated from systematic reviews of TB-DM and therefore is a provisional. The framework includes the following provisional recommendations:

1. A joint coordination of TB and DM programmes to be established at regional and local levels.
2. Surveillance of TB should be initiated among TB patients in all countries.
3. Surveillance of diabetes should be initiated among TB patients in all countries.
4. At a minimum, individuals with DM should be screened for chronic cough (a cough lasting more than 2 weeks) at the time of their diagnosis with DM.

5. Screening for TB infection on broader indication should be explored as part of a research agenda to improve the diagnosis of TB among people with diabetes.
6. A referral system should be established so DM individuals suspected to have TB are appropriately referred to TB diagnostic and treatment facilities.

In the latest 2019 WHO report, globally most WHO regions and high TB burden countries are not on track to reach the 2020/3 milestone of the End TB Strategy. Globally there was a decline of 1.6% per annum from 2000-2018, and a 20% decline between 2017 and 2018. A cumulative reduction of 6.3% from 2015 to 2018, which is short of the End TB Strategy target (WHO, 2019. GLOBAL TUBERCULOSIS REPORT 2019: EXECUTIVE SUMMARY).

PHE (in partnership with NHS England) TB prevention strategy is working with commissioners to ensure TB prevention and control programmes target all ages. Their strategy programme includes:

- active case finding (contact investigations and identifying latent TB in high-risk groups)
- awareness-raising activities
- standard and enhanced case management (including providing directly observed therapy and free treatment)
- finding people lost to follow-up and encouraging them back into treatment
- incident and outbreak control
- monitoring, evaluating and gathering surveillance and outcome data

The TB prevention programmes target specific high-risk groups, such as asylum seekers and refugees, under-served children, the homeless, offenders and people who misuse substances. They also considered integrating TB and HIV services, joint clinics. There was no mention on the management of TB-DM cases and no joint clinical pathway between TB clinical and DM clinics.

Currently there is no monitoring, evaluation or surveillance of TB-DM cases nationally or locally. This research will aim to help to establish the prevalence of TB-DM in a high TB incidence area. Identify the key characteristics (clinical symptoms, microbiological assessment and radiological presentation) to develop criteria for screening for DM (including best test method and time) in TB patients, assessing treatment efficacy in DM patients with TB to establish a clinical pathway between TB physicians and endocrinologists to better manage TB-DM patients.

1.50 Conclusion

Although there is substantial evidence to suggest DM is a risk factor for the development of TB, it is not yet clear whether DM significantly affects the presentation of TB, i.e. increased fever, cough haemoptysis and atypical radiological images. There are ambiguous results from limited studies based on the UK population. Diabetes is known to alter the pharmacokinetics of several anti-TB drugs and the efficacy of TB treatment depends on drug plasma concentrations and, therefore, DM is likely to have a negative effect on the treatment of TB. Currently, there are no guidelines on the optimal treatment duration of TB or screening for DM in TB patients. The overall management of DM in TB has no clear guidance available within the UK healthcare services. The literature suggests DM treatment in TB disease should be aggressive. By having an optimal glycaemic level, patients are likely to have better outcomes; therefore, aims to achieve this are paramount.

The latest guidance from NICE 2019 mentions DM on two occasions within the guidance. This refers to people with comorbidities or coexisting conditions and DM is seen as an immunocompromised condition. There is currently no case management of TB-DM, as there is with TB and HIV, in the British HIV Association guidelines for the management of TB. This includes diagnosis of active TB, where recommendation of performing microscopy on respiratory samples followed by molecular testing, e.g. Xpert MTB/RIF. They also recommend molecular testing on pulmonary smear-negative samples. In relation to treatment, the guidelines recommend the daily administration of

standard TB treatment with ART and the use of PI/r rifampicin is substituted with rifabutin. In HIV patients with TB meningitis they should receive corticosteroids. Furthermore, the guidelines recommend using fixed-dose combination therapy, where possible, to enhance treatment adherence. In relation to ART treatment, the recommendation with TB patients is to commence ART as soon as practically possible, within 8-12 of diagnosis of TB and ART to commence within two weeks if the patient CD4 cell count is less than <50 cells/ mm^2.

In TB-DM this approach to case management is missing and requires investigation of the association to guide clinical management of these patients.

The clinical case management guide produced and endorsed by the Royal College of Nursing, PHE, National TB Programme, does not reference DM as a risk factor in its management. The Tuberculosis Coalition for Technical Assistance (TBCTA), which collaborates with WHO, has developed International Standards for TB Care (ISTC) stating the basic principles of care for individuals suspected or having active TB globally (TBCTA, 2006).

The diagnosis of unexplained productive cough in DM patients should be tested for TB and any chest findings of TB should have sputum samples sent for microbiological testing. However, both HIV and DM patients with TB are likely to have atypical presentations. In relation to treatment, it recommends adherence to be monitored using DOT and furthermore therapy response to be monitored using sputum microscopy at the completion of the intensive treatment phase, and at 5 months and end of treatment. A positive smear at the 5^{th} month is deemed as failure. In TB and HIV coexisting condition, the international standard recommends counselling and testing as a routine, managing all patients with TB and HIV infection, cotrimoxazole prophylaxis is given and to evaluate when to start antiretroviral therapy (ARV) (BHIVA guidelines for the management of TB/ HIV co-infection in adults, 2017).

However, for TB-DM patients there is currently no screening for DM, in TB cases. There is no pathway to provide the management of the co-existing conditions. No recommendations if DM is diagnosed in TB cases as to when to commence DM treatment. Lastly, no treatment monitoring of TB medication to assess if it if altered by DM or by DM medication.

1.51 Rationale for studying TB-DM association

There is a strong epidemiological association between DM and TB, as reviews suggest DM triples the risk of developing active TB infection (Jeon *et al.*, 2008).

DM modifies the presenting features of PTB and is associated with atypical radiological presentation with more severe TB treatment, including increased risk of treatment failure, relapse and death during TB treatment. The current estimation by the International Diabetes Federation (IDF) is the prevalence of DM will continue to increase globally to 592 million by 2030. In Europe, the prevalence of DM was estimated at 8.5% in 2013, with the WHO estimating a TB incidence rate of 40 per 100,000 population (74,000 new cases per annum) to 592 million by 2035 (WHO, 2016).

The epidemiological association and the effect on the clinical presentation and treatment outcome resulting from the interaction between DM and TB are like those observed in co-infection with HIV and TB (Harries *et al.,* 2011). Although the risk of developing TB because of DM is lower than with HIV, with a DM pandemic, the association between TB-DM may come to resemble HIV-TB association (Lonnoth *et al.,* 2010). As with HIV, DM should be considered as an immunosuppressive condition which affects immune function and as a result affected patients are less likely to eradicate Mtb when infected, and are more likely to have re-activation of Mtb in its latent state.

DM is influenced by the immigration of different ethnic groups, as with TB. A study in Italy amongst 974 TB cases, of which 725 patients were non-UK born, 62 (6.4%) had DM, of which 40 (64.5%) cases were non-UK born, with

common countries of birth being Romania, Bangladesh, Philippines and India. In comparison to TB-only cases, TB-DM cases are usually of an older age group (median 58.6 years compared to 39.5) and men are more commonly affected (77.4% compared to 64.4%) (Odeone *et al.,* 2011). Chest radiograph presentation demonstrated greater cavity pattern in TB-DM cases compared to TB-only (45% compared to 31.7%) (P= <0.05) (Ebrahimzadeh, Mohammadifard and Naseh, 2014). Bacteriological positive sputum smears and culture were more frequently reported in the TB-DM cohort (sputum smear: 75% compared to 56%, P = <0.05); sputum culture: 83% compared to 67%).

Research on a high-risk population, such as in the London Borough of Newham, would help to assess the attributable risk factors for TB. The Dual Epidemic of TB and Diabetes (NICE, Tuberculosis Guidelines NG33, 2019) suggest that DM is an important risk factor in England. However, current knowledge is limited; only a handful of studies have assessed this phenomenon in Europe and fewer in England, and a comprehensive description of the epidemiology of TB-DM at a national level is still missing.

To contextualize this review of association between DM and TB, this current study will explain the disease as a co-existing condition and assess if any significant association is affecting patient clinical outcome. If so, the work will be used to implement change in current TB management of those with DM in Barts Health NHS Trust. It will be presented in terms of aetiology, diagnostic criteria, treatments and the association of these two conditions. The predominant focus, which is in London, will provide further insight into the importance of analysis and research of the association of DM and TB within the UK.

1.52 Aim and Objectives

The main aim of this research project is to:

Analyse the prevalence of DM among TB patients in Newham and to describe the clinical characteristics of the TB-DM population.

1.53 Primary Objectives:

1. To determine the prevalence of DM in TB (TB-DM) patients in Newham, with close attention paid towards differences between UK born and non-UK born patients.
2. To analyse the demographic, epidemiological characteristics and microbiological features associated with TB-DM compared with TB only patients.
3. To describe the clinical manifestation and TB post-treatment outcomes in patients with TB-DM compared with TB-only cases.

1.54 Secondary Objectives

1. To analyse any differences in the chest radiological presentation between TB only to TB-DM in PTB patients.
2. To compare the vitamin D levels between TB only and TB-DM patients
3. To determine the time for TB culture conversion to negative between TB-only and TB-DM patients
4. To analyse the HbA1c levels between TB-only and TB-DM patients and its relationship with microbiological and treatment outcome.

Chapter 2 – Methodology

2.1 Research design

We employed a retrospective cross-sectional study design, including patients diagnosed with TB and those with TB-DM, between 2012 – 2015 in the Borough of Newham, East London. DM is thought to be a risk factor for the reactivation of TB disease and has been investigated as an independent variable in this study. This study assessed the association between TB and DM by comparing cases of TB (control group) to TB-DM (case group) cases in adults, using secondary data over five years, and each case which was then followed up for two years after completion of TB treatment to capture relapse or development of MDR-TB. Data was sourced from adults on the London TB Register and Enhanced Tuberculosis Surveillance System (ETS) in England and patient medical records held at Barts Health NHS Trust. The Cerner Millennium System, which contains all patient records (clinic notes, GP notes, medications, pathology and diagnostic results) was used to identify those with DM. Barts Health NHS Trust, which serves 2.5 million people over three London Boroughs, including Newham, was selected as the study population due to its ongoing high incidence of TB (PHE, 2017). The data were anonymised for ethical reasons, and the datasheet was received in a Microsoft Excel format and exported to SPSS for analysis. The doctoral research student secured all data by taking out all patient identifiers and used unique codes to identify data sets. Quality improvement approval was received from the Clinical Effectiveness Group at Barts Health NHS Trust to undertake the quality improvement project as a doctoral degree project (see appendix 1 and 2).

Analyse the prevalence of DM among TB patients in Newham and to describe the clinical characteristics of the TB-DM cohort.

2.2 Primary Objectives:

1. To determine the prevalence of TB among DM (TB-DM) patients in Newham, with close attention paid towards differences between UK born and non-UK born patients.
2. To analyse the demographic, epidemiological characteristics and microbiological features associated with TB-DM compared with TB patients.
3. To describe the clinical manifestation and TB post-treatment outcomes in patients with TB-DM compared with TB-only cases.

The primary aim of the study was to understand the prevalence of DM in TB patients in the London Borough of Newham. The study is to aid our understanding whether a true significant association exists between DM and TB, and the overall clinical outcome. The study considers the clinical features associated with TB-DM and this is to help inform policy change to manage TB-DM patients as an entity.

The findings are also likely to highlight future gaps in knowledge, which need to be investigated prior to establishing a bi-directional screening programme for TB and DM. The study population is racially diverse in the London Borough of Newham. Patients who are diagnosed with TB are recorded on the London TB Register and ETS in England. The notification records have been kept from 2000 onwards, and the register is annually updated to consider denotifications, late notifications and other updates. DM is a risk factor for TB and was cited in recent NICE (2016) TB guidelines. However, this is not readily acknowledged in widespread clinical practice, nor is there guidance on the management of TB-DM cases. This five year (three years of active case findings with an additional two years of follow-up of all cases) period allows time for any TB relapse or reactivation or development of MDR-TB to be investigated, post completion of the initial TB treatment. However, the DM diagnosis is not registered on any national surveillance system, and all the data extracted was from the local hospital and GP databases, using the International Classification of Diseases (ICDs) coding.

The data collected from the Cerner Millennium System on each case included:

1. Sociodemographic information: country of origin, time in the host country, age, gender, education and employment. The use of alcohol was defined as a heavy drinker (>10 drinks per week or >14 units per week), smoking (>10 cigarettes per week), IV drug use and usage of illicit drugs (marijuana, cocaine, heroin, methamphetamines, hallucinogens, inhalants and other drugs) was recorded.

2. TB risk factors: previous TB diagnosis, contact with a TB case, alcohol intake, tobacco use, drug abuse, past or current imprisonment, anthropometric measurements (BMI), HIV status and other co-morbidities, long-term steroid use (inhalation corticosteroids or peri-oral corticosteroids), cytotoxic treatment, immunosuppressive medications, severe diseases (chronic renal failure, chronic liver disease, malignancies, chronic lung diseases), pregnant or lactating women.

3. Clinical symptoms: pulmonary and extra pulmonary symptoms: the presence of cough, fever, weight loss, anorexia, haemoptysis, chest pain, fatigue and night sweats.

4. Clinical data: pulmonary and extrapulmonary symptoms; TB localisation (pulmonary/ extrapulmonary), radiological findings (lung lesions and location and the presence of cavity lesions). Radiological findings collected from CXR performed at the time of diagnosis using the PACS system. CXR results were categorised by the involved field and pattern (i.e. upper lung field lesion defined as the presence of any lesion above an imaginary line across the diaphragm).

The radiographic presentation was categorised as normal, consolidation, cavity, military or pleural effusion.

- ‘Normal' pattern is defined as the absence of any abnormal lesion on CXR or TC.
- ‘Consolidation' pattern is defined as a mostly homogeneous opacity in the lungs characterised by little or no loss of volume, effacement of blood vessel shadows and sometimes the presence of an air bronchogram.
- ‘Cavity' pattern is defined as a clear area within the lung that may or may not contain a fluid level, and that is surrounded by a wall, usually of varied thickness.
- ‘Miliary' pattern is defined as multiple nodular infiltrates, with approximately 3 mm wide distribution and generalised.
- ‘Pleural effusion' is defined as a normal opacity extending upwards from the costophrenic angle in an erect film.

Mtb microbiological examinations (direct microscopy, culture and PCR results), Mtb drug sensitivity, previous history of TB, treatment regimes, TB drug resistance (any drug resistance, multi-drug resistance; extensively drug-resistant tuberculosis). DM diagnosis, plasma glucose and glycated haemoglobin results, DM treatment history and serum protein levels.

Death during treatment was recorded as death due to any cause during treatment. Death due to TB was attributed to being caused by TB based on two of the following criteria: death certificate with TB as the leading cause of death; or clinician who identified TB as a probable cause of death; or positive AFB smear or culture at the time of death.

2.3 Ethical considerations

The principal concern of this research was maintaining the confidentiality of patient data. No personal identifiers were recorded to capture patient-level data as personal identifiers were encrypted at data collection level. The study relied entirely on secondary data. Therefore, no social or psychological effects were experienced by the study subjects. All data were obtained from the Barts

Health NHS Trust and London TB Register and ETS System in England, patient identifiers were anonymised during data collection. The doctoral student did this by removing all identifiers when the datasheet was completed; only relevant data were extracted. The Clinical Effectiveness Group Department, Barts Health NHS Trust granted permission to use the information because of the potential to inform the future TB program (Quality Improvement Registration (QIP) reference number 7489, approved 23.08.2016, provided by the Clinical Effectiveness Group Department. This study involved the collection of data from routine information systems and was analysed to address the study objectives. All the information was kept no longer than required for the doctoral thesis, and all data are kept secure on an individual server with password protection, which can only be accessed by authorised researchers. No hard copies have been kept. As this is a quality improvement project it did not need to be submitted for Research Ethics Committee (REC) approval. However, the project is conducted within an ethical framework, at a practical level this means ensuring the project follows legislation and guidelines of; Caldicott Principles (1997); Data Protection Act (2018); NHS Confidentiality Code of Practice (2003); HQIP guide to managing ethical issues (2017). All QI projects are registered centrally with an allocated supervisor and in a Directorate to ensure Directorate priorities are met and components required for the project are available. A regular QI governance meeting is used to track projects and provide feedback and implement learning into practice.

2.4 Study population

The study population was obtained from the London TB Register and (ETS) in England and electronic medical records, using the TB and DM (type 1 and type 2) ICD classification, and all positive cases were included.

Table 2.1 ICD code for TB and DM classification

Diabetes Mellitus	Tuberculosis
ICD10 & E10-E14	ICD10

The codes are the agreed global codes for these conditions. This was used to pull data for each patient from the local systems. These codes were given by qualified clinical coders (WHO, 2010).

2.5 Dependent variables included

TB infection was the dependent/response variable of interest.

2.6 Independent variables including DM

The independent variable of interest was DM. The test used to diagnose DM was the level of DM control by measuring blood HbA1c levels. This test reflects the plasma glucose level for the previous 120 days, and the results are reported as a percentage (Sherwani *et al.,* 2016). The clinical diagnostic criteria for DM is HbA1c of 6.5% or higher, 5.7%-6.4% indicates pre-DM, and less than 5.7% is normal. This pre-diabetic group was excluded from the study, as this group does not meet the inclusion criteria (NICE, 2017).

2.7 Covariates

The covariates in this study were chosen based on their potential significant confounding effects. The covariates reported in this study included gender, age, country of birth (UK or elsewhere), ethnicity, previous BCG vaccination history, previous TB diagnosis, prior contact with TB patients, HIV status, other immunosuppressive conditions (including drugs), smoking status, alcohol use, history of imprisonment, social risk factors, and type of participant (contact or new entrant), this information being reported and recorded by a healthcare professional during hospital visits.

2.8 Statistical analysis

SPSS version 25 was used for the analysis of study data. All datasets were quality checked for any duplicate records, and any duplicates found were removed. The dataset collected included demographics, social risk factors, examination and laboratory results. All variables in SPSS were renamed, coded and appropriately categorised for analysis, and irrelevant data were omitted (see appendix 3).

The frequencies of each variables as calculated using univariate analysis to characterise the distribution of TB and TB-DM and any potential risk factors in the study population. The chi-squared test was used to assess the association of DM with all variables, including covariates (ethnicity, gender, age etc.) to TB, comparison of clinical and radiological findings between TB and TB-DM, and the rate of TB-DM association in UK and non-UK cohorts.

The relationship between the predictors and the response variables was further assessed using a binary logistic regression to produce unadjusted odds ratios and confidence intervals. Adjusted odds ratios and confidence intervals were used to determine the association between DM and TB, accounting for significant covariates and confounders and effect modifiers, which were obtained using multivariate logistics regression. SPSS performed an automatic stepwise selection process (utilising a P-value <0.05 as significant) to observe the effect of each covariate on the relationship between DM with TB in multiple logistic regression. The acceptable level of error was 0.05 and a P-value of <0.05 was significant when a two-tailed T-test was applied for continuous variables. As two significant groups were analysed, the TB-DM and TB only group, a chi-square test was performed for the categorical variables. The odds were used over the risk ratio to report the odds ratio in this study as they reflected the study objectives. Where records have been incomplete or values missing for any one of the stratification variables (age, gender, place of residence, and year of admission), subjects were excluded from the analysis.

2.9 Calculating the prevalence of TB-DM

The prevalence of health outcome is derived from the proportion of individuals with health outcomes in a population (Setia *et al.,* 2016). This was determined for TB-DM in a sample of the population which was divided by the total number of the TB population and expressed as a percentage.

$$\frac{\text{Number of people with TB-DM}}{\text{Number of people with TB}} \times 100 = \text{Prevalence (as\%)}$$

2.10 Chi-square Test

Statistical analysis included the use of Pearson's chi-square test which examines the independence variables. The test is used to determine if there is a statistically significant difference between the expected frequencies and the observed frequencies to illustrate a relationship between two categorical variables (McHugh *et al.,* 2013). Fisher's exact test is used when the sample size is modest, and the evaluation is not appropriate. This test calculates the probabilities of all possible tables together with all the observed row and column totals (Howell, 2014, McHugh *et al.,* 2013).

2.11 Fisher's Exact Test

Fisher's exact test is used to test the association between two binary variables in the 2 x 2 chi-square test and is usually used for smaller sample sizes (McDonald *et al.,* 2015). Fisher's exact test determines the association between two categorical variables. The chi-square test is asymptotic (i.e. it depends on a large-scale approximation) and so the more significant the sample size, the better it will perform; it is not valid for small sample sizes. A small sample size is defined as several less than 40. Fisher's exact test was chosen as it is designed for nominal level data. However, the test will be underpowered if the associations are ordinal. Fisher's exact test, as with the

chi-square, is based on significance and provides no further quantification of the size of the effect: for example, the degree/strength of association.

2.12 Inclusion criteria

Adult patients (age >18 years) with a diagnosis of TB during the period 2012-2015.
TB case: a patient with Mtb isolated from a clinical specimen by culture, or through methods such as molecular gene probes (confirmed case), or a patient for whom a physician has diagnosed TB and decided to start a full course of anti-tuberculosis therapy.

2.13 Exclusion criteria

- < 18 years of age,
- No data on glycaemic control: patients without a previous diagnosis of DM will be excluded from the analysis if: a) no blood glucose tests are available, or b) they had only one fasting blood glucose level result ≥126 mg/dL (7.0 mmol/L).

2.14 Study procedures

TB cases were identified from the London TB Register and the ETS system in England.
Patients were classified into the TB-DM group if:

- They had a previous diagnosis of DM type 1 or type 2 DM with an earlier physician diagnosis of DM before TB diagnosis and currently receiving treatment for DM, i.e. insulin or oral hypoglycaemic agents)

OR

- They were diagnosed with DM type 1 or type 2 at the time of TB (a physician diagnosis based on WHO 1999 (30), 2006 (31) and 2011 criteria (32), partly modified: – two instead of one fasting blood glucose test and one

HbA1c result ≥ 6.5% or FBG of ≥126 mg/dL (7.0 mmol/L) during TB treatments.

To consider the risk of TB stress-induced hyperglycaemia:

a. FBG of ≥126 mg/dL (7.0 mmol/L) (fasting is defined as no caloric intake for at least the previous eight hours),

OR

b. One oral glucose tolerance test (OGTT) ≥200 mg/dl (11.1 mmol/l) (two hours post-glucose load of 75g oral dose in all adults; the dose should be drunk within five minutes),

OR

c. In a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, a random plasma glucose (RPG) ≥200 mg/dl (11.1 mmol/l),

AND

d. One HbA1c result ≥ 6.5% FBG of ≥126 mg/dL (7.0 mmol/L) during TB treatment.

Stress-induced hyperglycaemia, corticosteroid-induced hyperglycaemia and other reasons for impaired glucose metabolism abstracted from the medical or laboratory records were evaluated in conjunction with clinician/clinical supervisors.

2.15 Sample size

The sample size for this cross-sectional cohort study was 168 TB-DM cases and 321 TB-only cases. The minimum total sample size required was 384. This was calculated using Cubenmax Systems Calculator (latest release 2020).

It is not practical or feasible to study the whole population in any study including this study, which is based in the London Borough of Newham with a population size of 325,005. Therefore, a set of participants were selected over a period from the population, which is less in number compared to the whole population, but adequately represents the population from which it has been

drawn from. Therefore, a true inference can be made about the population (Olayinka, Anthonia, and Yetunde, 2013).

In this study, the population of interest is the London Borough of Newham, the target population is those diagnosed with TB, in whom the incidence of DM is to be investigated. The sample subset group is TB-DM of the target population which is included in the study. The calculation of an adequate sample size is important as the calculation for optimal number of participants is required to be able to arrive at a scientifically valid result (Olayinka, Anthonia, and Yetunde, 2013).

Cubenmax System Calculator utilises the Yamaro Yamane formula, nf= n/(1+n/N) where nf is the desired sample size as the study population is less than 10,000 and the desired sample size of the` population is greater than 10,000 and N is the estimate of population size. N in this study is the number of patients with TB only and TB-DM at commencement which was 489, n = Z^2pq/d^2 where z is the standard estimate and = 1.96, P is prevalence given as 0.5 is this study, q = 1-p and d is precision at 0.05. the calculated nf adjusted for 90% response rates was 384, which is the minimum sample size. Therefore, the 489, patient cohort recruited for this study is statically representative of the Newham population.

Table 2.2 Sample size for +/-3%, +/-5%, +/-7%, and +/-10%. Precision levels, where confidence level is 95% and P=.5.

Size of Population	Sample Size (n) for Precision (e) of:			
	±3%	±5%	±7%	±10%
500	a	222	145	83
600	a	240	152	86
700	a	255	158	88
800	a	267	163	89
900	a	277	166	90
1,000	a	286	169	91
2,000	714	333	185	95
3,000	811	353	191	97
4,000	870	364	194	98
5,000	909	370	196	98
6,000	938	375	197	98
7,000	959	378	198	99
8,000	976	381	199	99
9,000	989	383	200	99
10,000	1,000	385	200	99
15,000	1,034	390	201	99
20,000	1,053	392	204	100
25,000	1,064	394	204	100
50,000	1,087	397	204	100
100,000	1,099	398	204	100
>100,000	1,111	400	204	100

a = Assumption of normal population is poor (Yamane, 1967). The entire population should be sampled.

The table is a guide for determining the sample size required with different precision levels where confidence level is 95% and) P=0.05, using Yamaro Yamane sample size calculation. (Olayinka, Anthonia, and Yetunde, 2013).

2.16 Internal validity of the study

This refers to ensuring the findings of the study are correct for the population studied. This includes considering selection bias and confounding limits, appropriate study design, study setting and methods, which is crucial for the validity of a study (Kadam & Bhalerao, 2010). The cross-sectional design used in this study has the limitation that it only provides associations between factors and outcomes, which are described, as opposed to making a causal relationship.

2.17 Selection bias in the study

The selection bias refers to when a study population is not fully representative of the population. The population for this study in Newham had the highest rate of TB in England, but the DM rate remained within the national average, which is comparable, although a possible bias is selecting an at risk group for TB, which is the non-UK born patients. To mitigate this, random sampling of TB cases were selected over the study period, increasing diversity of the study group. The diversity of the population would reflect London's diversity, allowing comparison to be made with a broader region. Persons at-risk (drug abusers, poor social housing, poor access to health, and economic bias) may be more common in the Borough of Newham compared to more affluent boroughs, which may lead to bias. Furthermore, inpatient TB cases likely to receive more thorough examinations leading to TB and DM diagnosis quicker than outpatients. This likely to affect time of diagnosis, treatment commencement, a better dual management of TB-DM which likely to affect overall outcome.

Any missing values in the data collection phase are likely to introduce bias; therefore, an adjustment was made to the statistical analysis to omit samples with missing numbers and tested to ensure no significant differences resulted between individuals with missing values and those with values. In variables with less than 10% of the sample, these were analysed using Fisher's Exact test, or if data was missing more than 40% and was an important variable, this factor was used for hypothesis generation (Madley-Gowd *et al.,* 2019).

The loss to follow-up is also likely to have caused a selection bias. As this was a longitudinal study, loss of participants to follow-up is expected to have occurred. To minimise this, data from the London TB Register and ETS System in England was used, which recorded loss of monitoring: this rate was low at 2%. Most those that were lost to follow-up either died or they transferred out to other boroughs or abroad.

2.18 Information bias

Information bias occurs when data obtained in the study is inaccurate (Althubaiti, 2016), e.g. information about symptoms and exposure factors. This inaccuracy could be either intentional or unintentional; however, as this data was captured before the research was undertaken, as both national TB surveillance and London Enhance Surveillance System collect data on key variables by case workers. As a result, the information is prospectively collected at time of diagnosis, reducing the information bias in this study. However, it is to be mindful the questions require patients to provide honest and accurate response which always poses a potential bias.

2.19 Study population

An underpowered study increases the risk of type 2 errors (false-negatives). The sample size of TSPOT, IGRA and TST analyses was too small to explore potential risk factors associated with positive samples (TSPOT, IGRA, TST). There were also too few TB/HIV co-infection cases to compare TB-DM and TB-DM-HIV cases adequately. To have an optimal sample size of TB-HIV-DM cases, more participants should have been recruited from neighbouring boroughs.

2.20 Test procedures and interpretation of results

All routine tests were conducted by biomedical scientist (BMS) staff at the Royal London Hospital Pathology, Microbiology & Virology and Biochemistry Departments. All results were entered onto Winpath, a pathology software used by pathologists to view results in detail and the Cerner Millennium for staff to view across the Trust. T.SPOT.TB. tests were done by Oxford Diagnostic Laboratories, Oxford.

2.21 Confounding Variables

A confounder also referred as confounding bias occurs when an investigator tries to determine the effect of an exposure on the occurrence of a disease (or outcome), however, in fact is measuring the effect of another factor, a confounding variable. In medical research investigating disease aetiology and casual relationship, a confounder is an undesirable, as it obscures the real effect of an exposure. As a result, confounding is managed through adjustment of the confounding variables. A confounding factor arises when a factor is associated with both the exposure (treatment) and the outcome.

For a confounder to be considered as a confounding variable to be a potential confounder, it requires having the following characteristic; 1) the variable must have an association with the disease, that is, it should be a risk factor for the disease; 2) it must be associated with the exposure, that is, it must be unequally distributed between the exposed and unexposed groups; and 3) it must not be an effect of the exposure.

As a confounding variable can obscure the real effect, it is required to be removed from investigations as much as possible to obtain real effect as much as possible. Like other types of bias found in research, in most cases bias can be controlled in study designs phase which can be managed through randomisation, restriction and matching. In randomised studies, patients are assigned randomly to exposure categories. In studies which investigates the effects of an intervention, it is possible to reduce the confounding by randomisation, this is by assigning patients to an experimental group or to a control group. Randomisation helps to prevent selection bias by the investigator. Randomisation process ensures that any differences between two groups are due to chances and not due to the choice of an investigator. Thus, any differences in the potential confounders between two groups may still exit after randomisation, they are likely to be reduced as much as possible. Furthermore, subjects in randomisation are assigned to a stratum, i.e. treated and untreated individuals who roughly share the same characteristic. A treatment effect is calculated within each stratum, and the

overall effect is weighted average across the strata. A disadvantage is the lack of efficiently to remove any differences between treatment groups and a low number of strata may cause residual confounding.

Restriction refers to when subjects with certain value/ characteristics for a potential confounder are selected (e.g. gender, age), whilst matching involves the selection of the groups to be compared to a comparable group (e.g. exposed vs not exposed). Another method of controlling confounding variables, post data collection in analysis phase is by adjusting the variable using stratification or multivariate analysis.

Another method of control of confounders at the study design phase is through matching. For instance, in a cohort study, the participants in the exposed and unexposed groups could be matched in pairs for potential confounders. For example, a study on the relationship between diabetes and ischemic heart disease, for each 'exposed participant with diabetes mellitus the investigator may select an 'unexposed', that is, nondiabetic patent of the same age. In this way, the potential confounding effect of age on outcome will be reduced. In case-control design, matching is frequently used. The advantage of this approach is it is more efficient in providing comparable treatment group. The disadvantage is the treated individuals may not have much match with the untreated individual, leading to a biased result.

An approach for controlling confounding after the completion of a study data analysis is stratification. In this method, the study population are divided into stratum subgroups, for example age can be divided into subgroup levels and relative risk of each stratum calculated. To calculate a summary statistic that describes the effect of variable and adjusting for confounder (i.e. age), one could use either polling Mentel-Haenszel procedure or standardisation. Both methods aggregate information over all strata by taking weighted averages of stratum-specific relative risks to calculate an overall 'adjusted' effect size. It may also be one potential confounder is indeed confounding a relationship of interest. This adjustment for confounding by a variable does not always remove all confounding. Stratification is an effective means for adjusting for

confounding when the number of confounding factors is limited. increasing the number of these factors will rapidly increase the number of strata, as the number of categories is multiplied.

2.22 Multivariate analysis

A multivariate analysis is used to control for confounding, this avoids the limitation of stratification, as it obtains the possibility to adjust for many confounding variables in just one model. Multivariate analysis estimates the ORs or hazard ratio (HRs). The control for confounding by multivariate analysis uses the same principles as stratification, i.e. factors of interest are investigates whilst the potential confounders are held constant.

In this study univariate and multivariate logistic regression analysis was performed to examine each factor for its association with the outcome (DM) using Pearson's chi-square test. Secondary to univariate analysis, multivariate analysis was undertaking controlling confounders (age and gender) with the statistical significance was set at p value <0.05. for north models, the risk was calculated and summarized as odds ratio and 95% CI was set. The two variables considered to be confounding variables as they both were known to be risk factors for the outcome of interest. DM especially T2DM is related to older age due to lifestyle change and later manifestation. Furthermore, male is more common to be diagnosed with TB.

2.23 T-SPOT. TB Procedure

General Principle

T-SPOT (Oxford Immunotec, Abingdon, UK) works using an enzyme-linked immune-spot (ELISPOT) technique based on enumeration of activated T-cells responding to stimulation by specific antigens (ESAT-6 and CFP10) and resulting in IFNγ secretion. The stimulation by ESAT-6 and CFP10 antigens takes place in separate microtiter plate wells.

During the procedure, the peripheral blood mononuclear cells (PBMCs) are separated from the whole blood sample and incubated with antigens to allow stimulation of any sensitised T-cells. The secreted IFNγ is captured by specific antibodies on the well membrane.

A second antibody, conjugated to alkaline phosphatase and directed to a different epitope on the (cytokine) IFNγ molecule, is then added and binds to the cytokine captured on the spot of insoluble precipitate at the site of the reaction. Each spot represents an individual's cytokine-secreting T-cell and the number of spots obtained provides a measurement of the abundance of Mtb effector T-cells in the peripheral blood.

Blood is collected in one 8ml or two 4ml CPT tubes. The white cloudy band of PBMCs was collected using a pipette and transferred to a 15-ml conical centrifuge tube, Blood was stored at room temperature and assayed within eight hours. The 8ml of CPT tubes was centrifuged at 1600xg for 28 minutes. The T-STOP. TB assay requires 2.5 x 10^5 viable PBMCs per well. A total of four wells were used for each patient. A manual count was done using a Neubauer haemocytometer. The plates were removed from the incubator and to each well was added 200 µl PBS solution, which is washed a further three times. A 50 µl of conjugate was added to each well and incubated for one hour. A substrate solution of 50 µl was added to each well for seven minutes. The plates were washed with distilled or deionised water to stop the detection reaction, allowing at least four hours drying time. A test result is positive if wells show > 6 spots.

2.24 Mtb microbiological examinations

General Principle

Microscopy of stained sputum smears is a technique based on the Mycobacterium's cell wall components being rich in lipid complexes preventing access to aniline dyes, but when stained with carbol-fuchsin or fluorochromes, they are not easily decolourised, even with alcohol-acid solutions. All *Mycobacterium* species retain this characteristic, and it is not exclusive to Mtb; this is referred to as acid-fast bacilli (Wanger *et al.,* 2017).

Royal London Hospital Microbiology Services protocol used 100 fields with a light microscope, using 1000x magnification. If there was an AFB count of less than 10 in 100 fields, then the number of AFB were counted within the actual slide. For a high positive, the examination of only 20 to 30 fields was sufficient. By examining specimens using a microscope the objective of staining is to discover acid-fast bacilli. The discoloration stains both living and dead (viable and non-viable) bacilli. This semi-quantitative evaluation reports the number of acid-fast bacilli found out of specimens in stained smears.

Table 2.3 Result interpretation using Bright field (1000x magnification: 1 length = 2 cm = 100 High Power Fields (HPF)):

IUATLD/WHO scale (1000x field = HPF) **Result**	**Microscopy system used**		
	Bright field (1000x magnification: 1 length = 2 cm = 100 HPF)	**Fluorescence** (200–250x magnification: 1 length = 30 fields = 300 HPF)	**Fluorescence** (400x magnification: 1 length = 40 fields = 200 HPF)
Negative	Zero AFB / 1 length	Zero AFB / 1 length	Zero AFB / 1 length
Scanty	1–9 AFB / 1 length or 100 HPF	1–29 AFB / 1 length	1–19 AFB / 1 length
1+	10–99 AFB / 1 length or 100 HPF	30–299 AFB / 1 length	20–199 AFB / 1 length
2+	1–10 AFB / 1 HPF on average	10–100 AFB / 1 field on average	5–50 AFB / 1 field on average
3+	>10 AFB / 1 HPF on average	>100 AFB / 1 field on average	>50 AFB / 1 field on average

2.25 Smear microscopy procedure

The property of acid-fastness is due to the presence of mycolic acids in the cell walls of mycobacteria. The primary staining is conducted using fuscin, which binds to the mycolic acids in the cell wall (Wanger *et al.,* 2017). Thereafter, decolourisation occurs using acid alcohol, which does not affect the primary stain from the cell wall mycolic acids while allowing the mycobacteria to retain the purple/blue stain colour, which is known as acid-fastness. A counterstain is added to obtain a better contrast for visualisation.

Using the Ziehl-Neelsen (ZN) technique for Mtb, slides were prepared in a class 1 biological safety cabinet. For each sample, a new, clean, grease-free slide was used, with each specimen and laboratory number recorded. A smear was prepared directly from a fresh sample (without any prior centrifugation) using an applicator stick and by selecting the purulent particles of sputum. The smear was an approximate size of 2-3 cm in length with 1-2 cm width, which allowed 100-150 fields to be counted in one smear. A thorough spreading was done before staining to allow air-drying at room temperature. The prepared slide was passed over a flame 2-3 times for approximately 2-3 seconds to heat-fix. The heat-fixed slide was covered with carbol-fuchsin using a Bunsen burner; the slides were heated until a vapour rose. The stain remained on the slide for ten minutes for the carbol-fuchsin to penetrate and stain the cell wall. The dye was gently washed from each slide with a stream of cold water until all unbound stain was washed away. Each slide was covered with acid alcohol for three minutes. The slides were rinsed again with water and the excess water was removed. The slide was then covered with methylene blue counterstain for one minute. The slides were rinsed with water and air-dried (RHL Microbiology BMS Protocol). One length of smear (2cm) was examined, or 100 fields, with a light microscope, using 1000x magnification.

2.26 Culture test for *Mycobacterium tuberculosis*

General Principle

Bacteriological culture provides a definitive diagnosis of TB and possesses higher sensitivity than sputum microscopy. This allows detection of a very low number of bacilli (approximately ten bacilli/ml of sputum compared to at least 5000 bacilli/ml of sputum for microscopy). Culture is also used to test for extrapulmonary TB. Specimen processing for Mtb was carried out in a biological safety cabinet, biosafety level 3 (BSL3), with the growth procedure performed in a class 2 biological safety cabinet using a *Mycobacterium* Growth Indicator Tube (MGIT). All cultures were incubated at 35-37^{o}C and incubation was continued until growth was observed or discarded as negative

after 8 to 12 weeks of growth. The MGIT tubes contain a fluorescent compound embedded in the tube which is sensitive to the presence of oxygen dissolved in the liquid culture during the continuous incubation at 35-37^{o}C. BD BACTEC monitors the tubes every hour for increasing fluorescence. The presence of fluorescence above a significant threshold identifies a positive tube.

2.27 PCR detection of mycobacterium complex

The Xpert MTB/RIF assay (Cepheid) does not require isolation of Mycobacterium and provides rapid diagnosis and predicts resistance to rifampicin using a cartridge-based system on clinical specimen either processed or unprocessed. The Xpert MTB/RIF assay test for the presence or absence of Mtb complex DNA using a semi-quantitative method. This estimates the bacillary load as well as provides results of RIF (rifampicin) resistance is present or absent. PCR can be carried out on all respiratory samples and other specimens where rifampicin resistance in Mtb continues to be investigated. The Xpert MTB/RIF assay is a nucleic acid amplification (NAA) which can identify possible multi-drug resistant TB (MDR-TB) that is resistant to both isoniazid (INH) and RIF, two of the most effective TB drugs (CDC, 2013). The Xpert MTB/ RIF assists in the identification of possible drug resistant TB (MDR-TB). The RIF resistance is a predictor of MDR-TB because of the resistance to RIF, in most cases, co-exists with resistance to INH.

2.28 GeneXpert MTB/RIF for Mtb

This test is used to detect Mtb and for the detection of rifampicin resistance. Using the GeneXpert cartridge, the sample is drawn i.e. (process or unprocess sputum, fluids) using a sterile transfer pipette, into the open port of the XpertMTB/RIF cartridge. The cartridge lid was closed and the test starts. A trace call should be considered as a real positive result, in line with clinical decisions. A second trace call is sufficient to make a diagnosis of PTB unless there is a recent history of TB alongside other clinical information. A Rif (rifampicin) resistance NOT DETECTED result can rule out any resistance. A

Rif DETECTED result, with a high suspicion of MDR-TB, indicates MDR-TB treatment should be considered. An Rif INTERMEDIATE result indicates the MTBC concentration was very low; as a result; resistance could not be determined (Cepheid, 2019 https://www.cepheid.com/uk/cepheid-solutions/clinical-ivd-tests/critical-infectious-diseases/xpert-mtb-rif). The test is based on real-time PCR for detecting Mtb DNA complex in samples and if rifampicin (RIF) resistance is present identified through the mutations of the rpoB gene in samples from at risk individuals of RIF resistance (Lawn and Nicol, 2011).

2.29 Vitamin D

25 (OH) and 1,25 $(OH)_2$ D were analysed by the Biochemistry Department at RLH using an Abbot Architect i2000SR with a Chemiluminescent microparticle immunoassay (CMIA). A 7.5 ml of clotted blood sample was collected for analysis. The defined reference guide from the RLH laboratory is:

1. Vitamin D levels <25 nmol/L indicates vitamin D deficiency.
2. Vitamin D levels 25-50 nmol/L suggests vitamin D insufficiency.
3. Vitamin D levels > 50 nmol/L indicates adequate vitamin D levels.

2.30 Radiology findings of TB patients

A qualified radiologist interpreted chest x-rays and CT scans, along with chest physicians and infectious diseases doctors and the findings were recorded on the London TB Register and ETS in England and in their medical notes. Any atypical images and reports identified during the data gathering were discussed with the clinical supervisor for clarification. All were reported on the Cerner system. Each case was further evaluated into appropriate categories by the researcher and cross-examined with clinical notes for the severity of symptoms and confirmed by a clinical supervisor or lead clinical physician for the patient.

Chapter 3 - Results

3.0 Chapter 3 - Results

During the 5-year study period, 489 patients with PTB and EPTB were included in this research. Of these, 84 (17%) cases had been previously diagnosed with DM before TB diagnosis, and only 5% had been previously diagnosed with TB. All data were analysed using statistical tests chi-square and Fisher's exact test for differences in sociodemographic and clinical characteristics between the TB-only and TB-DM patients.

Drug sensitivity and patterns of Mtb isolated from patients with TB-only and TB-DM were compared, using microscopy, culture and drug sensitivity testing. In patients with PTB, the association with DM and the severity of the disease (indicated by chest x-rays), delayed sputum conversions (after 30 and 60 days) after treatment commencement and symptoms were reported. The study also estimated the median sputum conversion by days using the Kaplan Meier survival plot to assess the association of sputum conversion between TB-only and TB-DM cohorts.

Clinical outcomes at the end of treatment were deemed as either failure or cured by measuring the AFB microscopy or culture-positive at six months or during treatment, or resolution of signs and symptoms of TB.

3.1 The prevalence of TB-DM in Newham

The TB-DM patients' ages ranged from 27 to 49 years, with a median of 36, with 85.3% of the cases being non-UK born with 63% being male and 37% being female. The HIV prevalence in the study population was 2.5%. From a total study population of 489, 168 patients were diagnosed with DM, with an overall prevalence of 28.5% (CI 95% 24.3-33.0) (Table 3.1). Amongst the 168 TB-DM cases, 3.88% were newly diagnosed DM cases at the time of TB diagnosis. Newly diagnosed DM patients were more frequently diagnosed at the time of TB diagnosis in non-UK born than UK born patients. However, TB-DM was not statistically significantly associated with non-UK born patients

(p=0.08) (Table 3.2). Information on DM treatment was available for all 168 TB-DM cases, of which 94% were in treatment, with only four cases treated with insulin and the remainder/majority with oral hypoglycaemic drugs. The DM prevalence in the general UK population is estimated at 3.9%, whereas in this study, the London Borough of Newham had a DM prevalence rate of 28.5%, seven times that of the general population.

Table 3.1 The prevalence of Diabetes Mellitus Among Patients with TB Diagnosed in Newham, 2012-2017.

	Years	TB, No.	Male Gender, (%)	Age Median, years for TB-DM	Foreign-Born, (%)	HIV+, (%)	DM, No.	New DM diagnosis (%)	TB-DM/ TB (%), 95% CI	DM General Population Prevalence, (%) [a]
London Borough of Newham	2012-2015	489	63	36 (range, 27.5-49.9)	85.3	2.5	168	3.88	28.5, 24.3-33.0	3.9

[a] International Diabetes Atlas, 2014. Active study period was from 2012 to 2015, with 2-years additional follow-up period. No. = number of patients.

Table 3.2 Patient demographics and clinical characteristics associated with TB only and TB-DM

Variables Total (n)	TB Only n (%)	TB-DM n (%)	Crude OR univariate analysis (95% CI)	P Value	**Adjusted OR multivariate analysis (95% CI)	P Value
Age Class **<55** **>55** **Mean (yrs)**	297(92) 24(8) 38	119(70.9) 49(29.1) 45	0.256 (0.162 – 0.407)	<0.001	0.9 (0.5-1.9)	<0.005
Gender **Male** **Female**	207 (65) 113 (35)	106 (62) 63 (38)	0.949 (0.643 – 1.400)	0.866	1.0 (0.5-1.8)	0.920
Previous TB **Yes** **No**	16 (6) 303 (94)	20 (11) 150 (89)	0.566 (0.269-1.190)	0.089	0.7 (0.3-1.6)	0.234
Migration status **UK-born** Non-UK born	55 (17) 266 (83)	19 (11) 149 (89)	1.621 (0.927-2.835)	0.087	1.2 (0.6-2.2)	0.167
Comorbidities **No** **Yes**	158 (66) 79 (34)	103 (40) 149(60)	1.6 (1.0-2.6)	0.007	1.1 (0.7-1.9)	0.009
Cough **Yes** **No**	152 (55) 120(45)	89 (41) 128 (59)	1.386 (0.858-2.239)	0.182	1.3 (0.8-2.3)	0.203
Fever **Yes** **No**	89 (33) 177 (67)	93 (41) 130 (59)	1.697 (1.080-2.667)	0.02	1.7 (1.1-2.7)	0.028

Weight Loss **Yes** **No**	121 (43) 157 (57)	56 (26) 155 (74)	1.1 (0.6-1.8)	0.795	0.4 (0.1 – 1.6)	0.117
Haemoptysis **Yes** **No**	26 (10) 221 (90)	13 (5) 229(95)	1.736 (0.852-3.540)	0.126	2.6 (1.1-5.9)	0.069
Night sweats **Yes** **No**	102 (37) 172 (63)	51 (23) 164 (77)	1.798 (1.144-2.285)	0.01	1.3 (0.8-2.2)	0.019
Smoking **Yes** **No**	36 (16) 182 (84)	43 (4) 228 (96)	2.394 (1.081-5.303)	0.309	3.53 (1.38-8.60)	0.319
Heavy Drinking **Yes** **No**	23 (10) 200(90)	11 (4) 255 (96)	2.394 (1.081-5.303)	0.054	4.0 (1.5-10.5)	0.071
HIV **Yes** **No**	6 (2) 268 (98)	8 (3) 207 (97)	0.479 (0.162-1.419)	0.176	0.5 (0.2-1.6)	0.193
IV Drug User **Yes** **No**	12 (3) 294 (97)	12 (7) 159 (93)	6.490 (0.836-50.36)	*0.04	6.1 (0.7-48.1)	0.03
Homeless **Yes** **No**	4 (2) 161 (98)	7 (2) 317 (98)	0.912 (0.263-3.163)	0.983	0.9 (0.2-3.1)	0.885
Prison **Yes** **No**	2 (1) 313 (99)	0 (0) 174 (100)	1.006 (0.998-1.015)	*0.204	0.92 (0.3-1.02)	*0.295

Known TB contact **Yes** **No**	41 (13) 267 (87)	111 (61) 70 (39)	0.852 (0.424-1.711)	0.652	0.5 (0.2-1.1)	0.446
BCG **Yes** **No**	237 (91) 23 (9)	232 (16.8) 23 (24)	1.035 (0.651-1.646)	0.885	1.2 (0.7-2.1)	0.801
Relapse **Yes** **No**	13 (1) 308 (99)	10 (5) 158(95)	0.663 (0.284-1.545)	0.242	0.8 (0.2-2.2)	0.275

* Fisher Exact Test was used to test the association between the two categorical variables when the sample size was less than 5; **adjusted for gender, age and HIV status. OR, Odds ratios, a measurement of association between exposure and an outcome. The OR represents the odds that an outcome will occur given an exposure, compared to the odds of the outcome occurring in the absence of that exposure; TB, tuberculosis; DM, diabetes mellitus; CI, confidence interval.

The odds ratio (OR) is used to measure the association between an exposure and an outcome, in this study between variables and TB-DM. To analyse the association between TB-DM and demographic and clinical characterise, the study compares TB-DM cases and TB-only control. The OR were used to compare the relative odds of the occurrence of the outcome of interest (TB-DM) given exposure to each of the variable (age, gender, alcohol intake). The OR is determined by whether an exposure is a risk factor for TB-DM outcome, and the magnitude of risk factors for outcome is measured as: OR=1 Exposure does not affect odds of outcome; OR>1 Exposure associated with higher odds of outcome; OR<1 Exposure associated with lower odds of outcome.

3.2 Age

The age cohort was stratified into those <55 years and those >55 years, this was done to assess whether older age is identified as a risk factor for TB-DM comorbidity and in agreement with recent systematic reviews (Moreno-Martínez *et al.,* (2015); Cordeiro da Costa *et al.,* (2016) Caraffa *et al.,* (2016). In the TB-only cohort, 297 (92%) who were diagnosed with TB were aged under 55 compared to 119 (70.9%) in the TB-DM group. The age stratified by either greater than or less than 55 years, in the TB-only cohort, 8% had TB and were less than 55 years. In comparison to TB-DM, where 29.1% of the cases were over the age of 55 years, and a significant factor to TB-DM (P= <0.05). Older age has been documented as a risk factor for TB-DM comorbidity, and with agreement with recent systematic review this association may reflect the current distribution of DM among the general population of Newham. Furthermore, older age > 55 years in the non-UK born DM population is approximately three times greater than UK born population in this group (Ref).

3.3 Gender

In the TB-only cohort, 207 (65%) were male compared to 113 (35%) female, compared to the TB-DM cohort, where 106 (62%) were male and 63 (38%) female. Statistically (P-value 0.920), no association was found between either group. However, the odds ratio suggests an increased risk of developing TB in men (OR 1.0; CI 0.5-1.8).

3.4 Previous TB diagnosis

A total of 17% of the total study population were known to have been diagnosed previously with TB. Statistically, there was no significance between the TB-only and TB-DM cohorts that had previously been diagnosed with TB.

3.5 Co-morbidities

In the TB-only cohort, 79 (34%) reported having at least one co-morbid risk factor compared to 149 (89%) in the TB-DM cohort. Statistically, there was a

significant association (P-value 0.009) observed between the two groups in the presence of co-morbid risk factors. Within the TB-DM cohort, 149 individuals had reported co-morbidities, which included individuals who were on long-term systemic steroids, suffered from chronic renal failure, chronic liver disease, chronic lung disease, malignancy, or were on anti-TNF treatment for rheumatoid arthritis and ulcerative colitis.

3.6 Fever

In the TB-only cohort, 189 (33%) presented with fever at the time of TB diagnosis compared with the TB-DM cohort, where 93 (41%) presented with the symptom. Statistically (P-value 0.02), this was significant, where fever presented more commonly in the TB only group.

3.7 Cough

A total of 241 patients from the study population presented with cough as a symptom of TB. Of these, in the TB-only cohort, 152 (55%) had cough compared to 89 (41%) in the TB-DM cohort. Statistically (P-value 0.203), cough is not a significant factor in either group.

3.8 Weight loss

56 (26%) of the individuals in the TB-DM cohort presented with weight loss as a symptom on presentation compared to 121 (43%) in the TB only cohort. Weight loss was not a significant factor associated in this study.

3.9 Haemoptysis

Only 13 (5%) in the TB-DM cohort compared to 26 (10%) in the TB-only cohort presented with haemoptysis as a symptom on presentation. Statistically (P-value 0.069), there is no significant association of haemoptysis being a significant variable.

3.10 Night sweats

51 (23%) in the TB-DM cohort presented with night sweats as a symptom on presentation compared to 102 (37%) in the TB-only cohort. A statistically (P-value <0.05) significant result was observed between the TB and TB-DM cohorts. The TB-DM cohort was more likely to present with night sweats.

3.11 Smoking

When comparing smoking between the two groups, in the TB-only group, 36 (16%) patients were considered heavy smokers and met the smoking criteria compared to 43 (4%) in the TB-DM group. Statistically (P-value 0.319), no significant difference was observed between the two groups.

3.12 Heavy drinking

34 of the 489 individuals included in the study were classed as heavy drinkers, of which 11 were from the TB-DM cohort and 23 from the TB-only cohort. When comparing to see whether drinking increased TB risk (P-value 0.07), no significance was observed in this study population.

3.13 HIV

Only a total of 14 cases from the total study sample population were known to be HIV positive. In the TB-only cohort, six were known to be HIV positive compared to eight in the TB-DM cohort. Statistically, no significant (P-value 0.193) risk was associated with HIV, and HIV in the presence of DM did not increase the risk of TB. Similarly, the OR value of 0.479 does not indicate an increased risk between the HIV-positive patients and the TB-DM cohort.

3.14 Persons who inject drugs (PWID)

In the TB-DM group, 24 patients were known to be an IV drug-taker, with 12 in the TB only cohort. Due to the small sample size, Fisher's exact test was

used, which resulted in a significant result with a P-value of 0.03. The result suggests IV drug use is an independent risk factor in the presence of DM to increase the risk of TB. However, the OR value of 6.1 (0.7-48.1), with such a wide range, indicates the lack of precision in the interpretation of the result and it should be taken with caution.

3.15 Homelessness

A total of 11 (4%) individuals from the total population were known to be homeless. Of those, four patients reported to be homeless within the TB-only group compared to 7 in the TB-DM cohort. Statistically (P-value 0.885) no significant difference was observed between the two groups. This may be the result of small numbers in the study population.

3.16 Prison

Only two individuals from the TB-only cohort had a history of imprisonment. Statistical analysis could not be performed.

3.17 Known contact with TB

A total of 152 cases reported having direct TB exposure, of which, 111 (61%) were in the TB-DM cohort and 41 in the TB-only cohort. Statistically, no significance was observed (P-value 0.446).

3.18 BCG

A total of 328 of the 489 cases were known to have been vaccinated against TB, of which 111 (61%) were from the TB-only cohort and 217 (76%) were from the TB-DM cohort, either in the UK or home country. Statistically, no significant difference was observed between the groups with or without BCG vaccination. Thus, vaccination does not provide additional protection against the risk of acquiring TB in the presence of DM.

3.19 Relapse

A total of 23 relapses was reported in the total study population, of which 13 were in the TB-only cohort and 10 in the TB-DM cohort. Statistically (P-value 0.275), there was no increased risk of relapse of TB in patients with DM.

3.20 Microbiology and radiological characteristics

In the TB-DM cohort, a total of 68 (41%) PTB cases were identified and 100 (54%) EPTB cases. In the TB-only cohort, 151 (47%) PTB cases were identified and 170 (53%) EPTB cases. Statistically, there was a significant difference observed between the two groups (P-value 0.03). The association between DM and radiological characteristics showing the presence of cavities was significantly associated with DM comorbidity (OR 1, 95% CI 0.9-1.6; P-value <0.05) (Table 3.3). No difference in drug resistance was observed between both cohorts.

Table 3.3 Analysis of Radiological and Microbiological Characteristics of TB and TB-DM cohorts

			Univariate		Multivariate*	
	TB-Only n No. (%)	**TB-DM n No. (%)**	**OR**	**P**	**OR**	**P**
PTB **EPTB**	151 (47) 170 (53)	68 (41) 100 (59)	1 0.7 (0.5-1.6)	0.046	1.7 (1.0-2.50 0.8 (0.6-1.5)	0.03
CXR cavities **No** **Yes**	42 (14) 242 (86)	47 (22) 159 (78)	1 1.4 (1.1 – 1.8)	0.003	1 0.9 (0.4-1.6)	0.05
Drug resistance mechanism present **Yes** **No**	9 (2) 312 (98)	5 (2) 163 (%)	1.6 (1.0-2.5) 0.4 (0.2-1.8)	0.23	1.1 (0.7-1.5) 0.4 (0.1-1.6)	0.144

* Adjusted for age and gender. TB: Tuberculosis infection; DM: Diabetes mellitus; OR: Odds Ratio; CI: Confidence interval. CXR: chest X-ray.

3.21 Comparison of culture conversion time in intensive phase of treatment

This study consisted of 489 patients who had begun anti-TB therapy, with a total of 219 PTB confirmed cases with positive culture for TB. Prior to anti-tuberculosis treatment (ATT), 151 patients were identified in the TB-only cohort compared to 68 patients in the TB-DM cohort. In the 1-month of TB treatment, 35%, in the TB-only cohort, had a negative smear after completion of the1st month ATT compared to 32% in the TB-DM cohort. After 2-months of ATT, in the TB-only cohort, 89% were smear-negative compared to 85% in the TB-DM cohort (P-value <0.05). Within the two-month intensive treatment phase, TB-DM had a slightly slower conversion rate when compared to the TB-only cohort (table 3.4).

Table 3.4 Analysis of positive sputum culture pre-anti tuberculosis treatment (ATT), and after 2-months ATT initiation.

	TB Only conversion rate (n/%)	Median day to culture conversion	TB-DM conversation rate (n/%)	Median day to culture conversion	P value
Pre-treatment culture positive	**151**		**68**		
1-month culture positive	**53 (35%)**	**10**	**46 (32%)**	**16**	**<0.05**
2-month culture positive	**135 (89%)**	**30**	**58 (85%)**	**40**	

ATT, anti-tuberculosis treatment; OR, Odds Ratio; CI, Confidence Interval.

3.22 Sputum Culture Conversion – within the intensive treatment phase (after 2 months of treatment initiation)

A Kaplan Meier curve was used to show the culture positive cases which convert to negative culture by end of day 60, post commencing treatment. The plot illustrates the time after initiation of treatment in the initial intensive treatment phase.

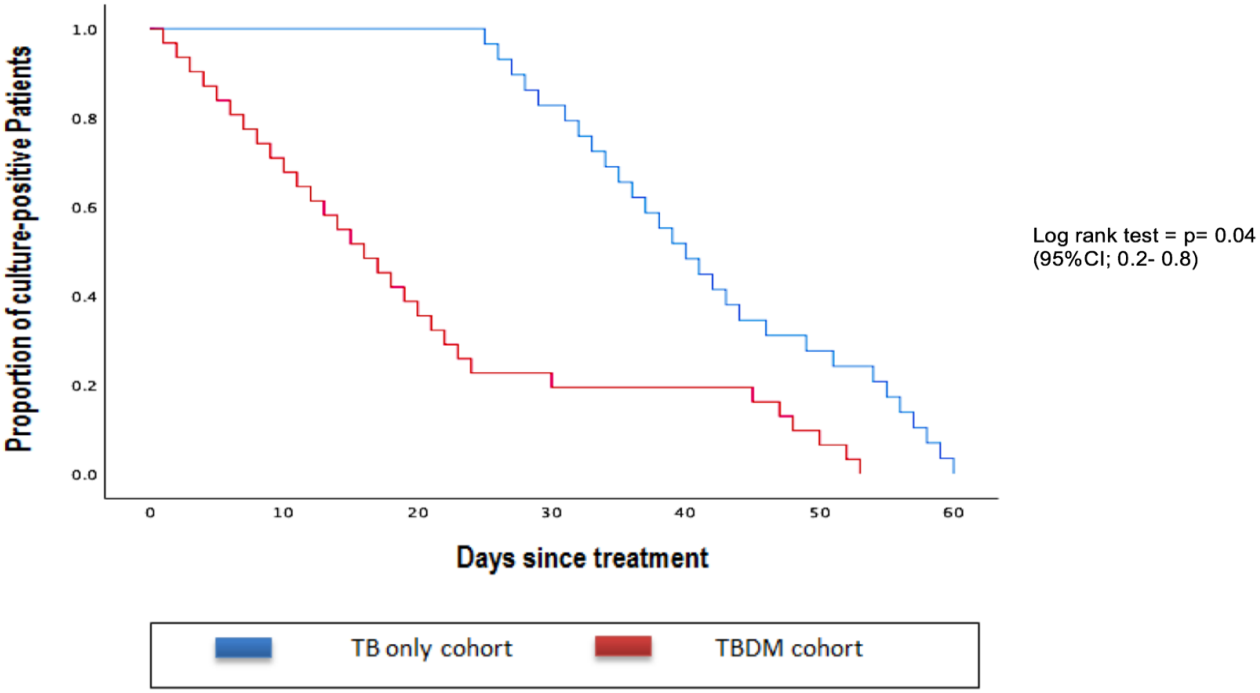
The Kaplan-Meier survival curve was used to illustrate the difference in time for sputum culture conversion from positive to negative and being clear of Mtb in the sputum. Using the Kaplan Meier curve for culture conversion by 60 days after commencement of treatment shows the TB-DM to have a slower rate of smear-positive conversion rate compared to the TB-only cohort log rank test P=<0.05, (figure 3.1). The presence of DM decreases the conversion rate as the TB-DM cohort has a lower rate of conversion, reflecting higher bacillary load. Comparison of time to culture conversion among TB-only patients and TB-DM patients by 30 days. The TB-only cohort median conversion was 10 days compared to 16 days in the TB-DM cohort.

These results illustrate how the TB-DM cohort are less likely to have a clearance result (negative sample) for TB and a reduced estimate of survival compared to the TB-only cohort. By day 60, the TB-DM cohort still had a higher bacillus load and were more infectious with TB, posing a risk to others, as well as being less likely to be able to clear Mtb. Therefore, by the end of the two-month's intensive phase of treatment, the potential levels of bacilli load in the culture were greater in the TB-DM cohort. The result would imply an aggressive initial phase of treatment in TB-DM patients with anti-TB medication and ensuring optimal control of DM is essential for a better outcome.

However, it is important to note that sputum culture conversion is a clinical tool used to predict the therapeutic efficacy in TB patients. A non-conversion of sputum smear to negative culture at the end of the intensive phased of treatment is associated with a more unfavourable outcome for the patients,

with increased treatment failure associated with death. The results from the study suggest sputum culture conversion after the first two months of treatment may be a predictor for treatment success in the TB-DM cohort. Lung cavitation and sputum culture conversion is also available to be used to monitor TB-DM patients' outcome. As this was a retrospective study, to limit selection bias, all cases were followed-up to ensure accurate TB diagnosis and treatment completion as well as relapses and drug resistance recorded. Non-differential misclassification of information can lead to information bias by clinical practitioners when entering data into the clinical system, including confounding variables such as smoking and drinking during treatment, which are likely to result in misclassification due to lack of information. Factors commonly associated with delayed sputum conversion include male gender, older age and AFB density (Gunda *et al.,* 2017). A smear non-conversion is more likely to occur with those aged 40 and over and who have poor compliance with treatment adherence. This study also assessed the chest X-ray as the presence of cavities is more common in TB-DM cohort relating this to the culture conversion rate, TB-DM patients are likely to be infected for a longer period. This likely increase the risk of treatment failure and mortality rate. Further limitations in this study include the fact that this is a single centre study; therefore, the results from are unlikely to be generalizable. Furthermore, being a retrospective study increases the likelihood of data being omitted.

Figure 3.1 Kaplan-Meier - AFB Sputum Culture Conversion – within 2-months' TB treatment initiation

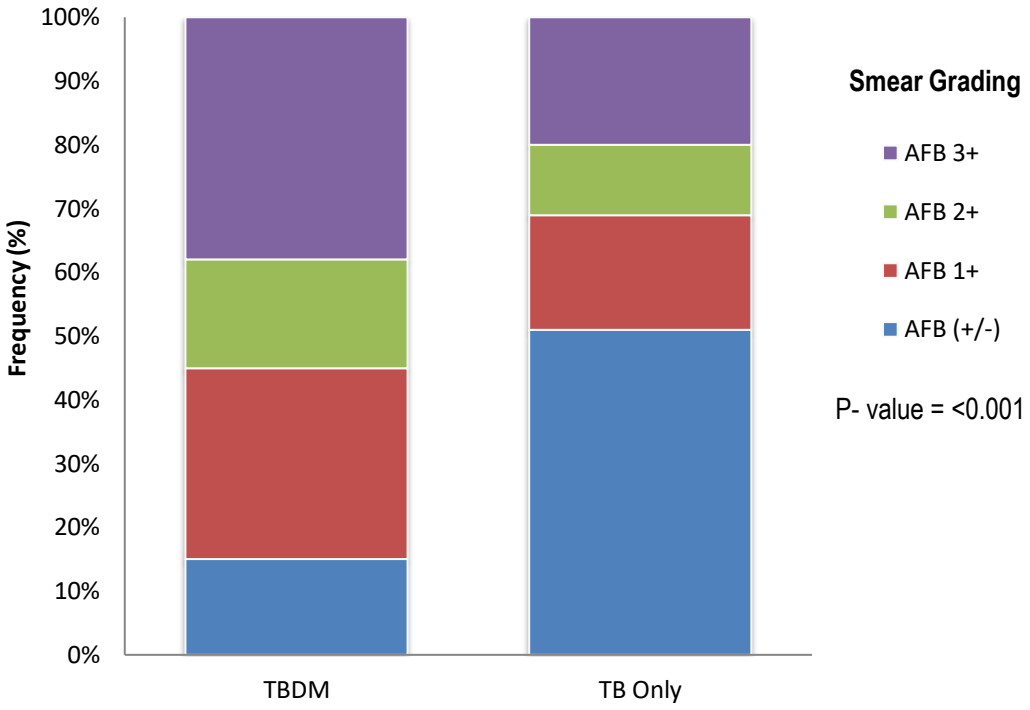


Comparison of time to culture conversion among TB-only patients and TB-DM patients at 60 days after commencement of anti-TB treatment.

3.23 Acid-Fast Bacilli (AFB) distribution profile

When comparing the AFB smears in sputum between the cohorts, in the TB-DM cohort 15% had a scanty positive result, 30% was positive for AFB 1+, 17% was positive for AFB 2+ and 38% positive for AFB 3+. In comparison, the TB-only cohort had 51% as scanty positive, 18% as AFB 1+, 11% AFB 2+ and 20% AFB 3+, with a chi-square P-value of 0.019, being significant (figure 3.2). The result demonstrates how TB-DM patients is more likely to be infected with greater severity, along with increased time for culture conversion. This reflects a higher bacterial burden and, theoretically, would imply the intensive treatment phase likely needs to be increased or better glycaemic control required to have a better clinical outcome.

Figure 3.2 AFB distribution profile between the TB-only cohort and TB-DM cohort



Sputum AFB smears were graded following CDC guidelines: those with a 3+ were defined as high AFB smear grade. By examining the baseline smear results among patients with TB-DM and the TB-only cohort, it was found that a greater proportion of AFB-positives were among TB-DM, which is statistically significant using the chi-square test (P-value <0.001).

3.24 A comparison of drug sensitivity between TB-only and TB-DM patients

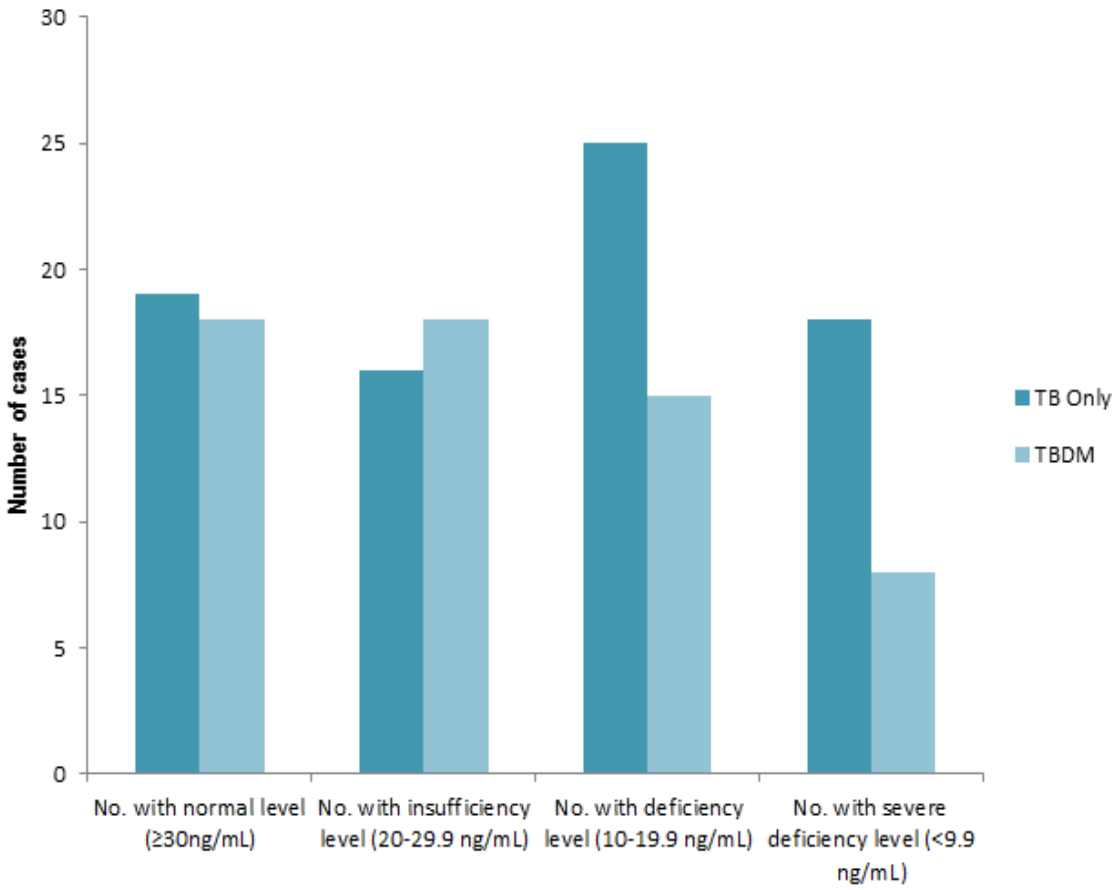
In the TB-DM cohort, out of 168 isolates, 163 (98%) were fully sensitive to first-line therapy and five reported as MDR-TB. In contrast, in the TB-only cohort, a total of 321 (98%) isolates were sent for culture testing: 312 (98%) were fully sensitive with 9 (2%) MDR-TB reported. There was no significant observed difference between the two groups in culture sensitivity patterns (P-value 0.144) (Table 3.3).

3.25 Vitamin D Levels in TB-DM vs TB only cohort

The mean vitamin D level in the TB-DM cohort was 26.90 ng/mL and in the TB-only cohort, it was 25.61 ng/mL. The vitamin D level was measured using a 25-hydroxy vitamin D concentration in blood samples. A level of 30 ng/mL to 50 ng/mL is in the normal range for healthy individuals. A level of less than 20 ng/mL indicates a vitamin deficiency (http://www.bartsendocrinology.co.uk/resources/CEG+Vitamin+D+guidance.pdf).

A total of 137 patient samples reported Vit D levels during initial diagnosis or treatment phase. In the TB-DM cohort, a mean Vit D level of 26.90 ng/mL (SD 3.6, range 1-70) was reported. In contrast, the TB-only cohort reported a mean vitamin D level of 25.61 ng/mL (SD 3.684; range 1-100). Statistically, there was no significant difference in vitamin levels between the TB-DM and TB-only cohorts. The TB-DM cohort had a mean serum vitamin D level of 26.90 ng/ml (95% CI, 19.28-34.51).

Figure 3.3 Vitamin D Levels in TB-DM vs TB-only Group



The graph compares the number of cases of Vit D levels falling into the normal level category, insufficient category, deficient category, and severely deficient category (http://www.bartsendocrinology.co.uk/resources/CEG+Vitamin+D+guidance.pdf). A level of less than 9.9ng/mL is considered severely deficient. A level between 10-19.9ng/mL is considered deficient. A level between 20-29.9ng/mL is considered insufficient. A level of 30 to 39 ng/mL is considered adequate. A level between 40 to 59 ng/mL is considered optimal. A level between 60 to 100 ng/mL is considered therapeutic. A level greater than 100 is considered excessive. Statistically, no significance (P-value 0.58) was observed between the cohorts in relation to vitamin D levels (table 3.5).

Table 3.5 Comparing vitamin D levels between TB-only cohort TB-DM cohort

	TB-Only n = 78	TB-DM n = 59	Chi-square P-Value
Medial level (ng/mL)	25.61 (95% CI, 15.90-35.33)	26.9 (95% CI, 19.28-34.51)	**0.58**
N (%) with normal level (≥30ng/mL)	19 (24%)	18 (31%)	
N (%) with insufficiency level (20-29.9ng/mL)	16 (20%)	18 (31%)	
N (%) with deficiency level (10-19.9ng/mL)	25 (32%)	15 (24%)	
N (%) with severe deficiency level (<9.9ng/mL)	18 (24%)	8 (13%)	

Vitamin D status determined by measurements of 25-(OH)D_3. N = number of patients

3.26 HbA1c Levels in TB-DM vs TB cohorts

The HbA1c levels is higher in the TB-DM cohort compared to the TB-only cohort and is statistically significant (P-value <0.05). A level of 7 mmol/L (6.5%) of more is considered to have diabetes. A total of 168 HbA1c results was available at the time of diagnosis of TB, excluding stress-induced glycaemia. The HbA1c level was taken at the same time as when the AFB samples were collected, reflecting true infectivity. HbA1c levels provide the average blood glucose levels for the three months prior to diagnosis or while individuals were symptomatic at initial diagnosis. In the TB-DM cohort, 115 cases had reported HbA1c levels with an average mean reading of 7.63% (SD +/- 5.6; range 4-13). In the TB-only cohort, 54 reported HbA1c levels on presentation or during the infectious phase. The average HbA1c level reported was 5.53% (SD +/- 5.02, range 5-8), the P-value (<0.05) (figure 3.4) (table 3.6) suggested this is a significant independent factor for developing TB.

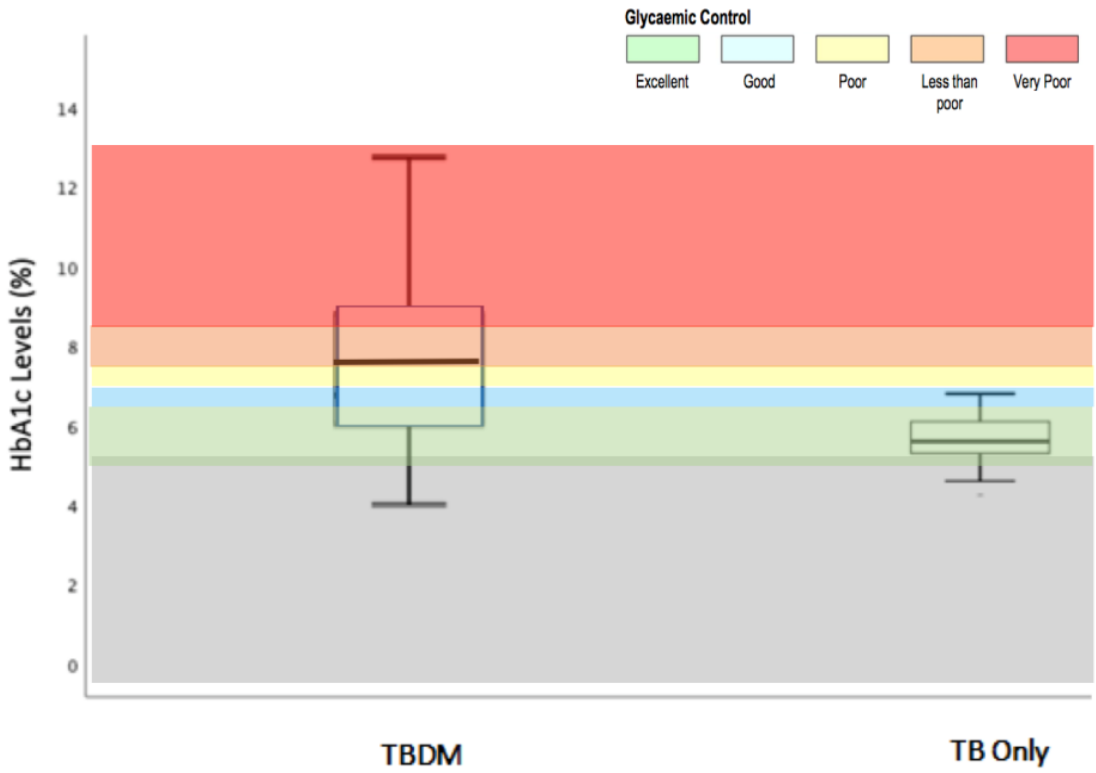
By applying chi-square statistical analysis, hyperglycaemia levels were found to be significant (P-value <0.05) between the TB-DM and TB-only cohorts. Transient hyperglycaemia frequently occurs in TB patients who have commenced anti-TB medication. However, the results excluded transient hyperglycaemia post-TB treatment completion. When comparing the HbA1c levels between the two cohorts, the TB-DM cohort had a far more uncontrolled level (mean HbA1c of 7.63%, range, 4-13%). This was in comparison to the TB-only cohort level (mean HbA1c level 5.53, range 5-8%) and suggests that a controlled glycaemia level is likely to contribute to the clinical outcome, as well as the severity of symptoms. The normal range is 5-7%, HbA1c (Diabetes UK, 2019).

Previous studies have shown that TB induces stress hyperglycaemia (due to general inflammatory factors triggered by active TB), commonly occurring in the first few months of commencing anti-TB medication. This is followed by a return to an euglycemic state (Kumpatla *et al.,* 2013; Menon *et al.,* 2016). In this study, euglycemic cases were excluded and completed a 2-year follow-up, which presented with 27 cases of post-completion of TB treatment to have been diagnosed with DM and commenced on DM medication. This, therefore, rules out any transient hyperglycaemia caused by anti-TB medication, especially in the early phases of hyperglycaemia induced by rifampicin administration or using steroids. This further reinforces the need to have a glucose measurement done at the time of TB diagnosis and the commencement of anti-TB medication to confirm DM diagnosis. Therefore, hyperglycaemia is an early marker for abnormal metabolic state and probable the insulin resistance that is associated with TB.

Table 3.6 HbA1c Levels between TB-only and TB-DM cohort

	Median HbA1c Level	Standard Deviation (SD)	P- value
TB-Only (n=321)	5.53%	3-13, SD +/- 1.32	< 0.05
TB-DM (n=168)	7.63%	5-8, SD +/- 5.61	

Figure 3.4 HbA1c Levels in TB-DM vs TB-only cohorts



TB-DM cohort mean HbA1c level recorded was 7.63% (range, 3-13, SD 5.61) compared to TB without DM mean HbA1c of 5.53% (range, 5-8, SD 1.32), chi-square P-value <0.05. A level less than/equal to 5.8% (40 mmol/mol) – requires ruling of hypoglycaemia. HbA1c levels between 5.9 - 6.6% is considered excellent; 6.7 – 7.2% is considered good; 7.3 – 7.6% is

considered poor; 7.7 – 8.6% is considered less than poor, and a level between 8.7 – 13.0% is very poor.

3.27 Clinical outcome post-completion of TB treatment

Comparing the clinical outcome post-treatment, no statistical significance was observed between the two cohorts. In the TB-DM cohort, 158 out of the 168 successfully completed their treatment. In comparison, in the TB-only cohort, 303 out of 321 successfully completed their treatment. By the end of the 6th month of the anti-TB period, of all 489 enrolled in the study, 461 had successfully completed their treatment. In the TB-DM cohort, 7 (4%) patients died during their course of treatment, the same number as in the TB-only cohort 7 (2%) (table 3.7). The proportion of deaths observed in the TB-DM patient group was higher compared to the TB-only cohort. The lost to follow-up and transferred out of study numbers were relatively similar in both cohorts.

Table 3.7 Clinical outcome post-completion of TB treatment

	Completed n (%)	Died n (%)	Lost to follow-up n (%)	Transferred out n (%)	P-value
TB-DM	158 (94%)	7 (4%)	2 (1%)	1 (1%)	0.475
TB only	303 (94%)	7 (2%)	7 (2%)	4 (1%)	

Within both groups, 94% completed treatment successfully within six months of anti-TB treatment. No significance was observed in relation to mortality or treatment failure rate.

3.28 Comparing time of TB diagnosis between TB only and TB-DM

This study observed that TB diagnosis was much later in the TB-DM cohort (17.28 years, P-value <0.001 (table 3.8). Although no previous studies have

evaluated the effect of duration of a diabetes diagnosis on the risk of TB disease, this result suggests:

1. DM alters the presentation of TB, leading to a miss-diagnosis
2. DM increases the risk of reactivation of latent TB, as T2DM predominantly presents in older age, therefore those with latent TB and who develop DM, lowering their immunity leading to activation of latent TB.

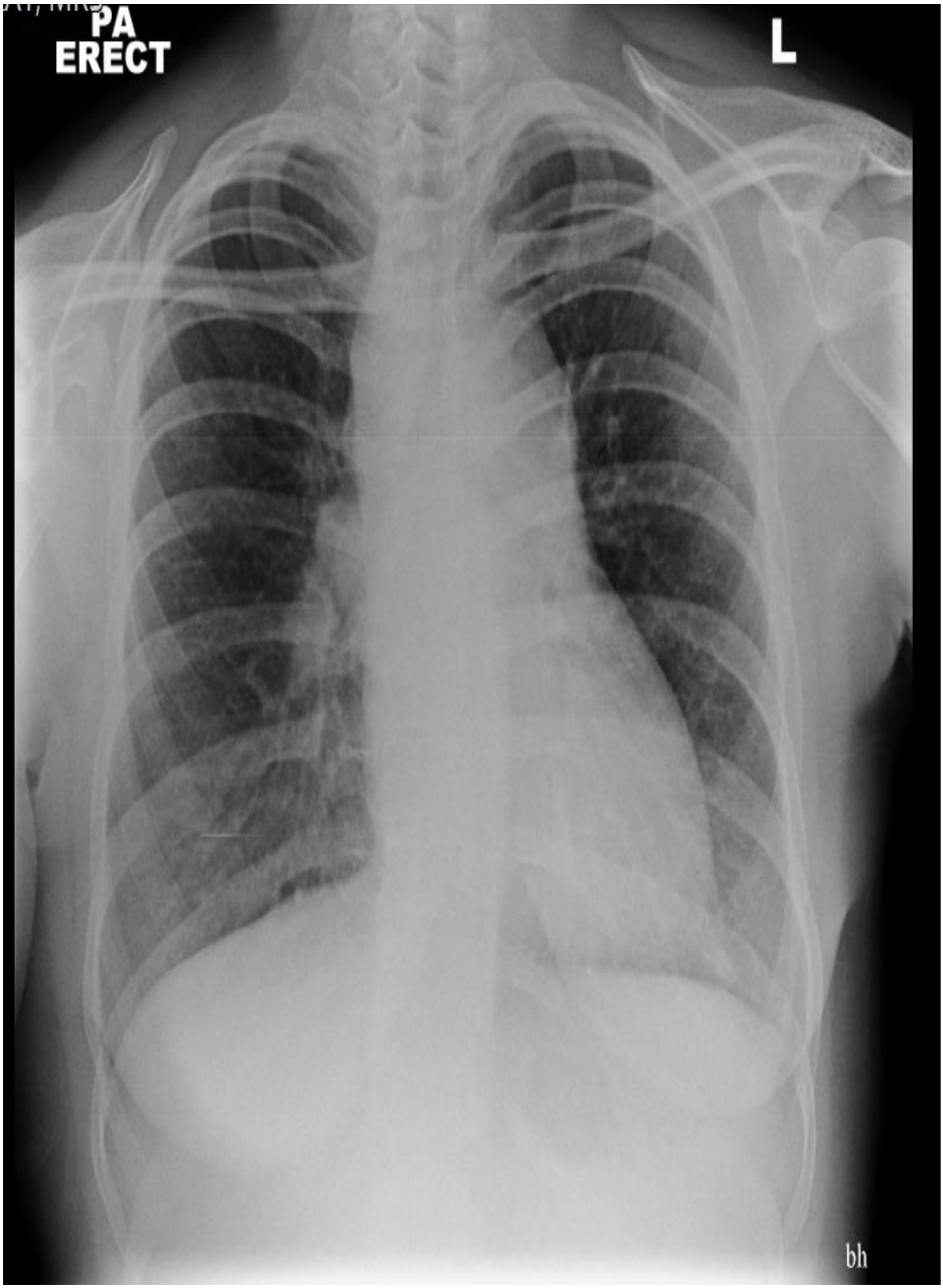
It is unclear whether the predisposition to Mtb infection and severity of illness is increased in the presence of DM, as a result of defective immunity in individuals with DM. This would imply TB disease can be impacted by this chronic condition. In addition, this is very likely to be further influenced in non-UK born individuals living in the UK, as they are more likely to become obese, suffer with DM and have high blood pressure, rather than the native UK population (Murphy, Robertson, and Oyebode, 2017). The result may reflect a late diagnosis of DM in the home country and in the host country (due to access to healthcare). The result also showed the diagnosis of DM in the younger population is observed in natives rather than in non-UK born individuals, this may reflect a population trend of DM onset because of changes in lifestyle in non-UK born or natives.

Table 3.8 Year before TB diagnosis is made in TB-only and TB-DM cohort

	Years in the UK (median, years)	P-value
TB-DM TB Only	17.28 9.38	< 0.001

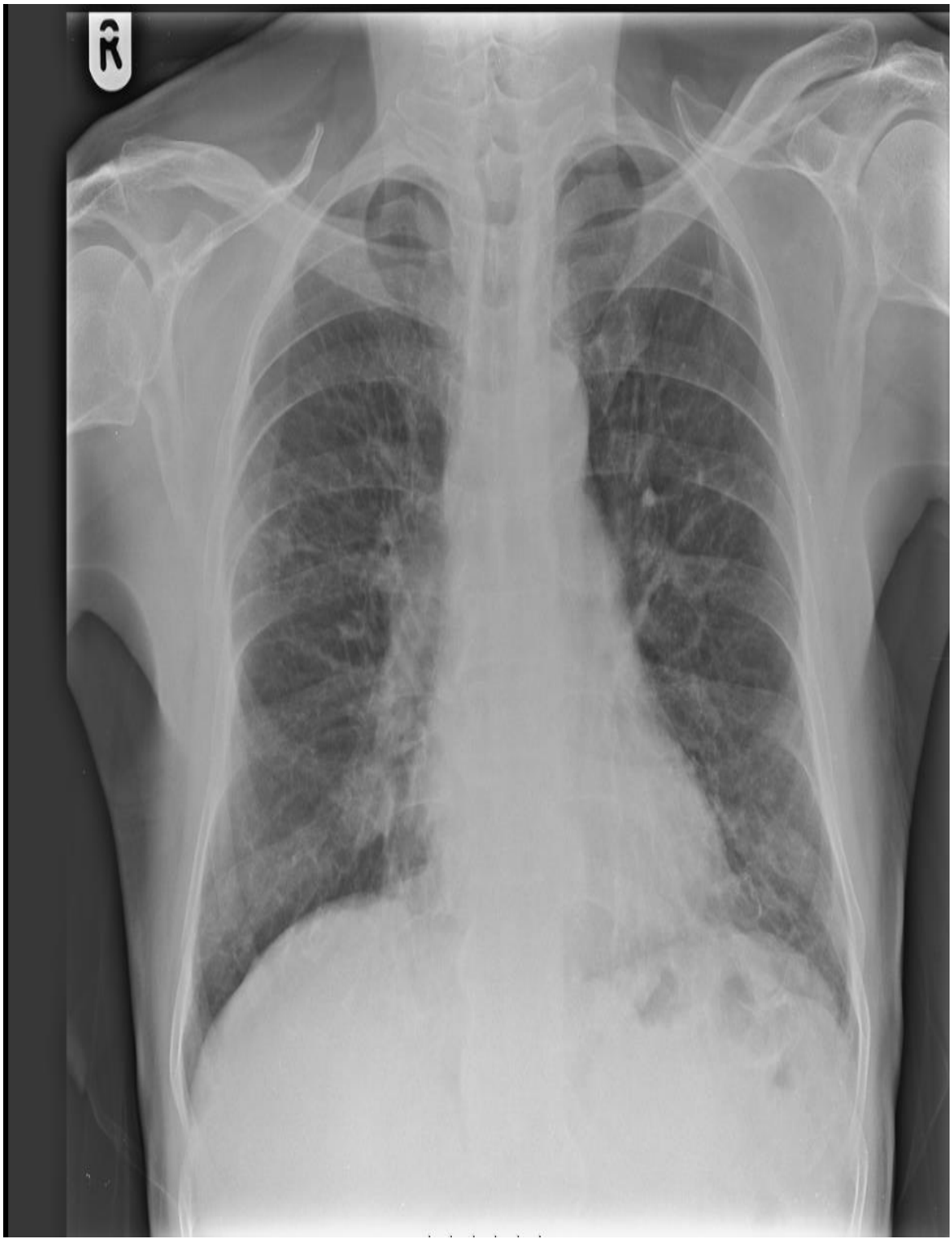
The median time (in years) for diagnosis of TB with those with DM is 17.28 years after entry into the UK. In comparison with the TB-only cohort, who do not have DM diagnosed until 9.38 years after entering the host country.

Figure 3.5 TB-DM Case 1



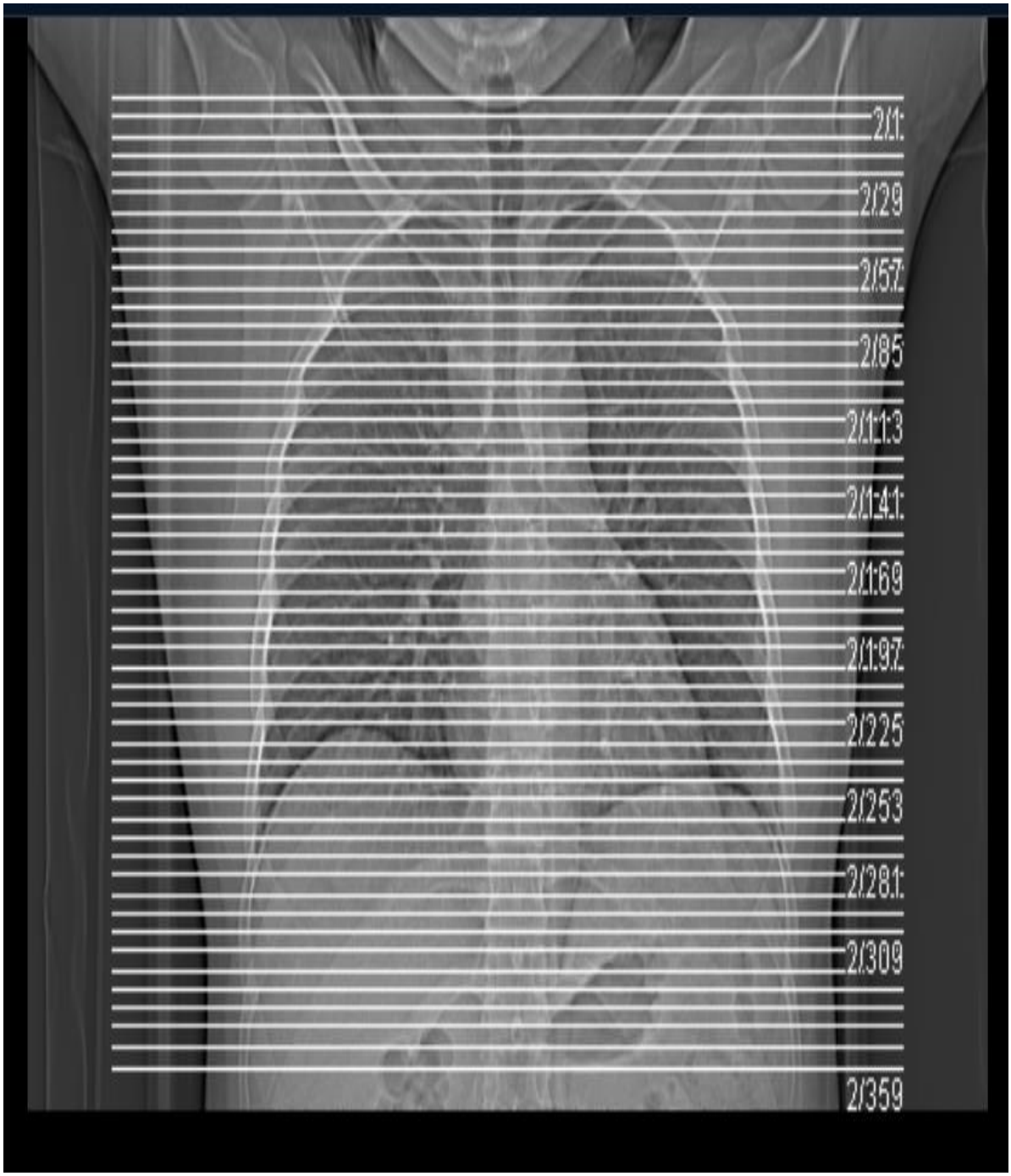
There is a widened superior mediastinum. The lungs and pleura appear normal. Appearance suggestive of TB adenopathy in the superior mediastinum.

Figure 3.6 TB-DM Case 2



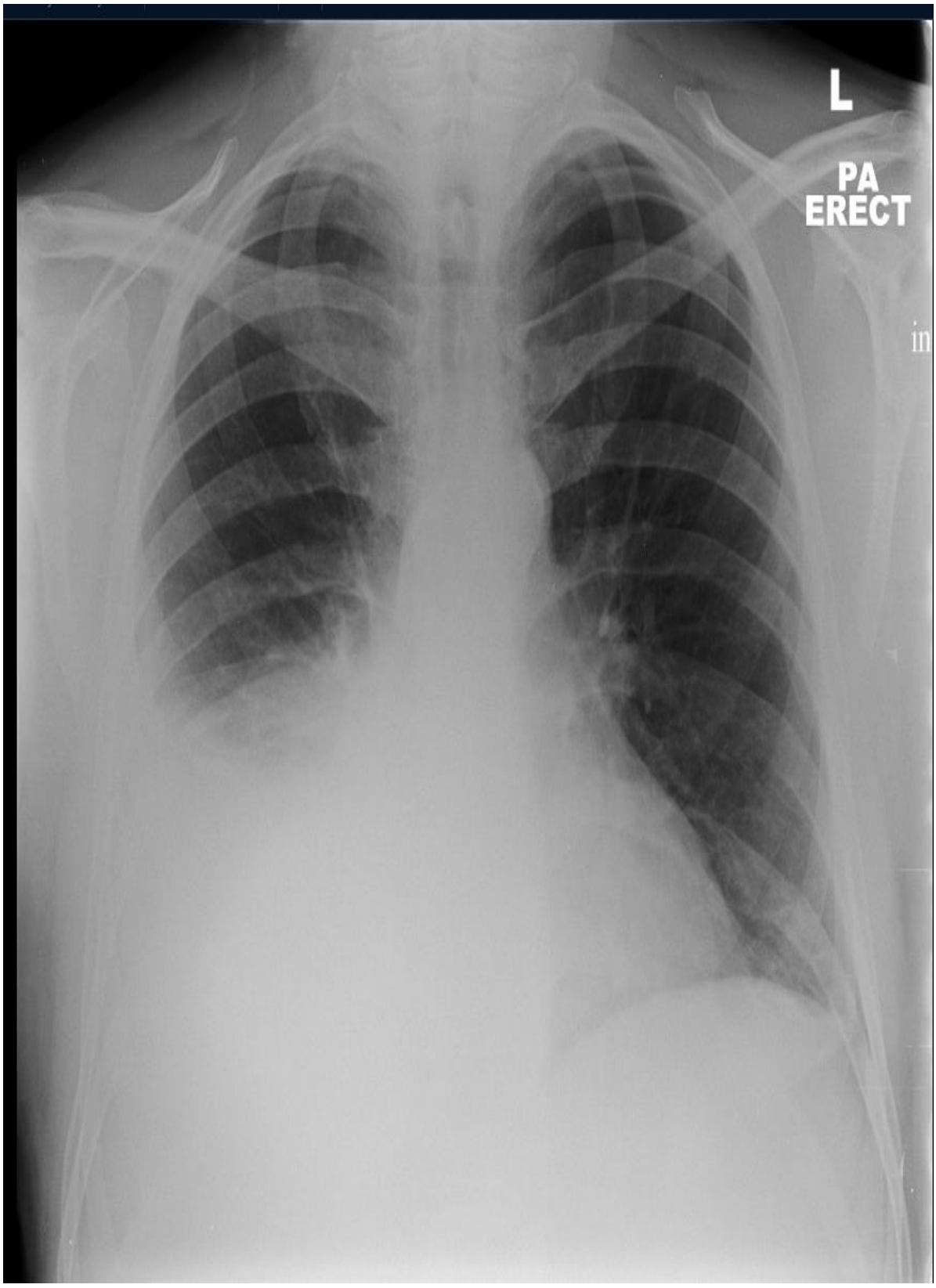
Lung fields are emphysematous. Old calcific granuloma seen in the left upper lobe. The present x-ray shows a soft tissue density on the right side between the anterior ends of the third and fourth ribs. There is some prominence of the right hilum as before and there could be underlying hilar lymphadenopathy on the right side.

Figure 3.7 TB-DM Case 3



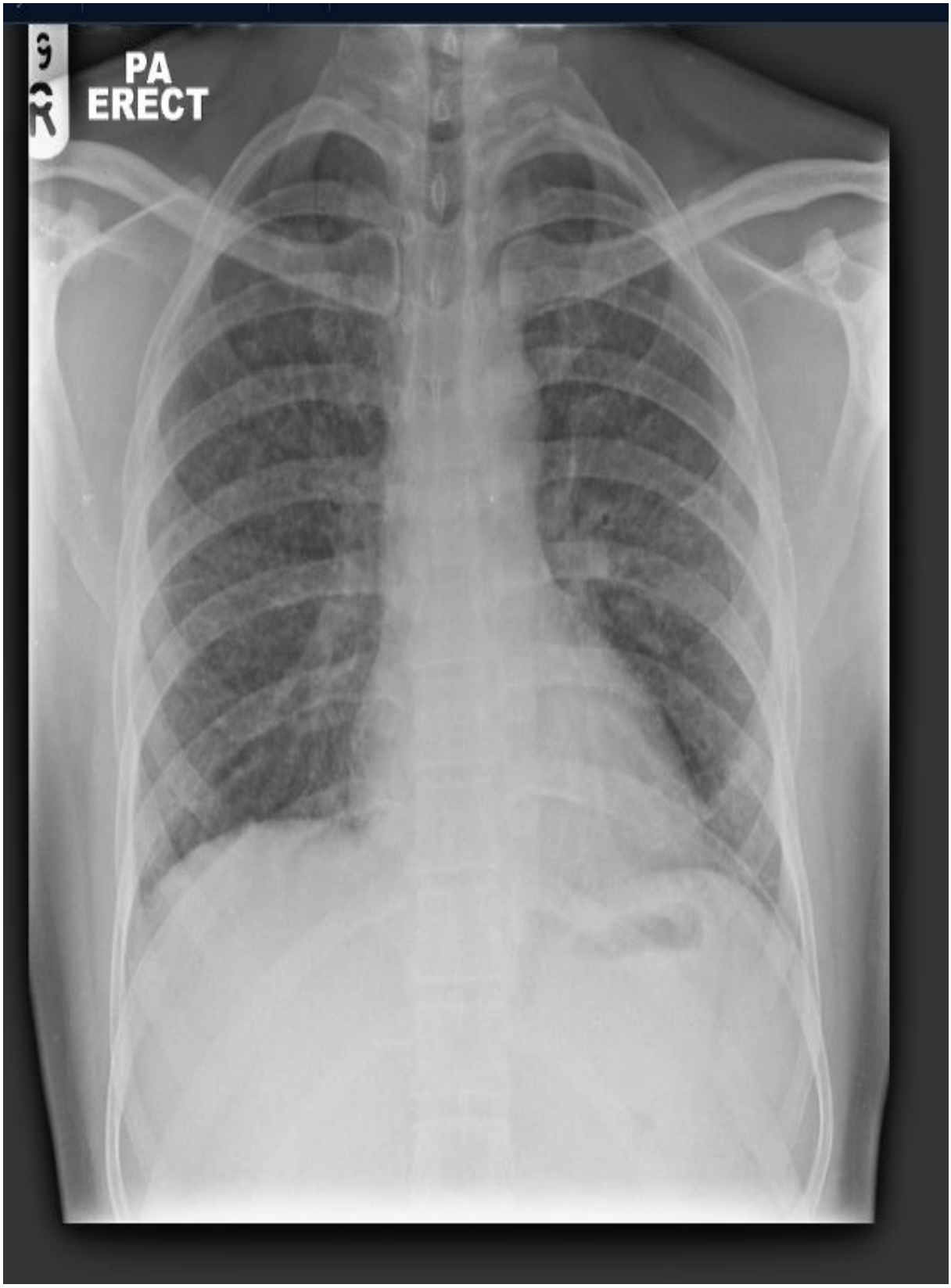
A minute (sub-centimetre) subpleural granulomatous process is seen within the lateral aspect of the upper lobe of the right lung. Otherwise, the scanned lung fields appear clear. Multiple pathologically enlarged mediastinal lymph nodes readily noticed, particularly in the paratracheal and tracheo-caval regions. The nodes in the aortopulmonary window and subcarinal regions are also seen enlarged. The enlarged nodes appear to be matted with no cystic degeneration or calcification seen within. No pleural or pericardial collections seen. Few sections passing through upper abdomen showed no focal hepatic or splenic lesions within the scanned segment.

Figure 3.8 TB-DM Case 4



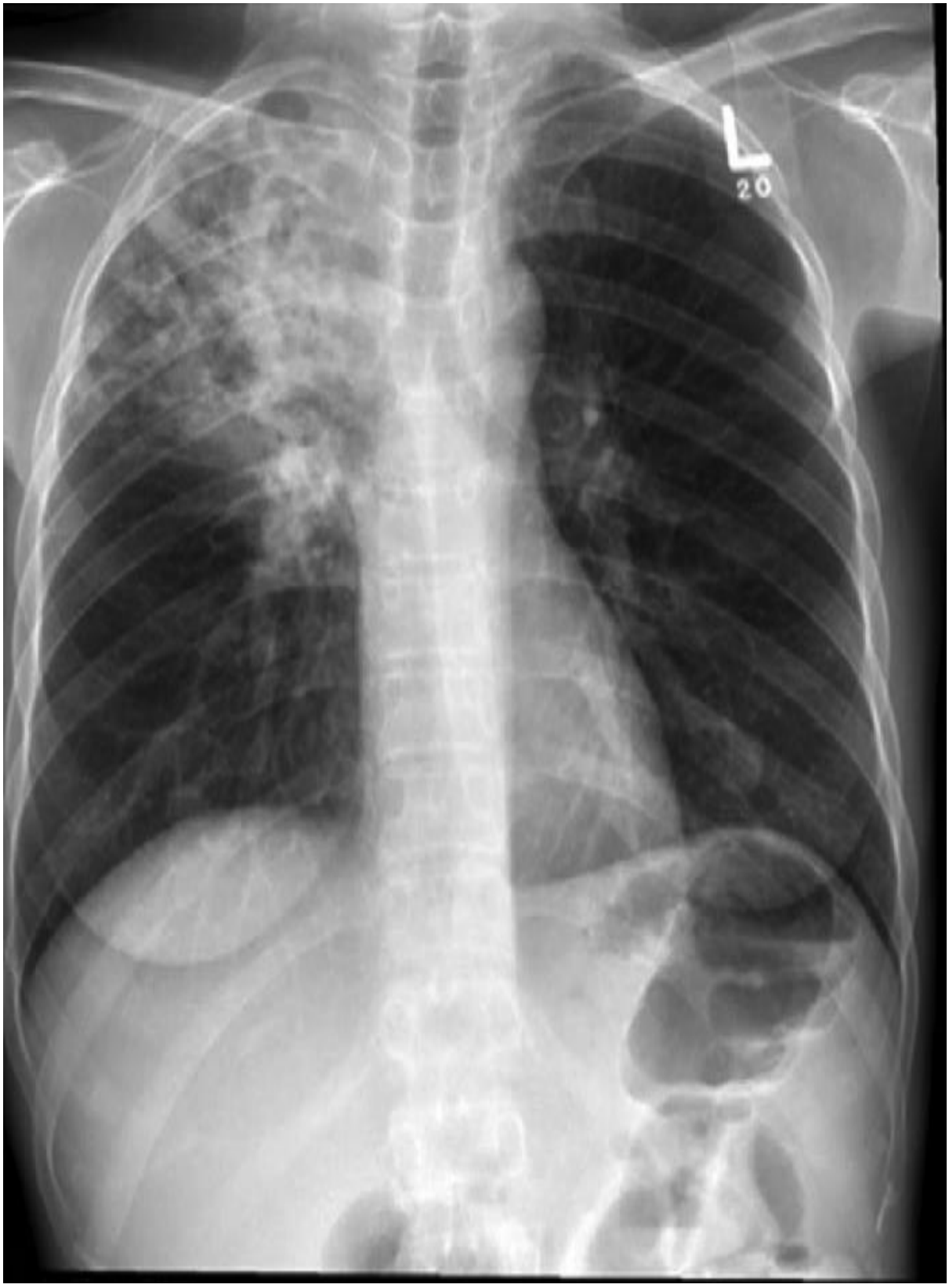
There is a large right pleural effusion. There is consolidation and atelectasis in the right lower lobe. No lesion is identified in the left lung. No mediastinal lesion.

Figure 3.9 TB-DM Case 5



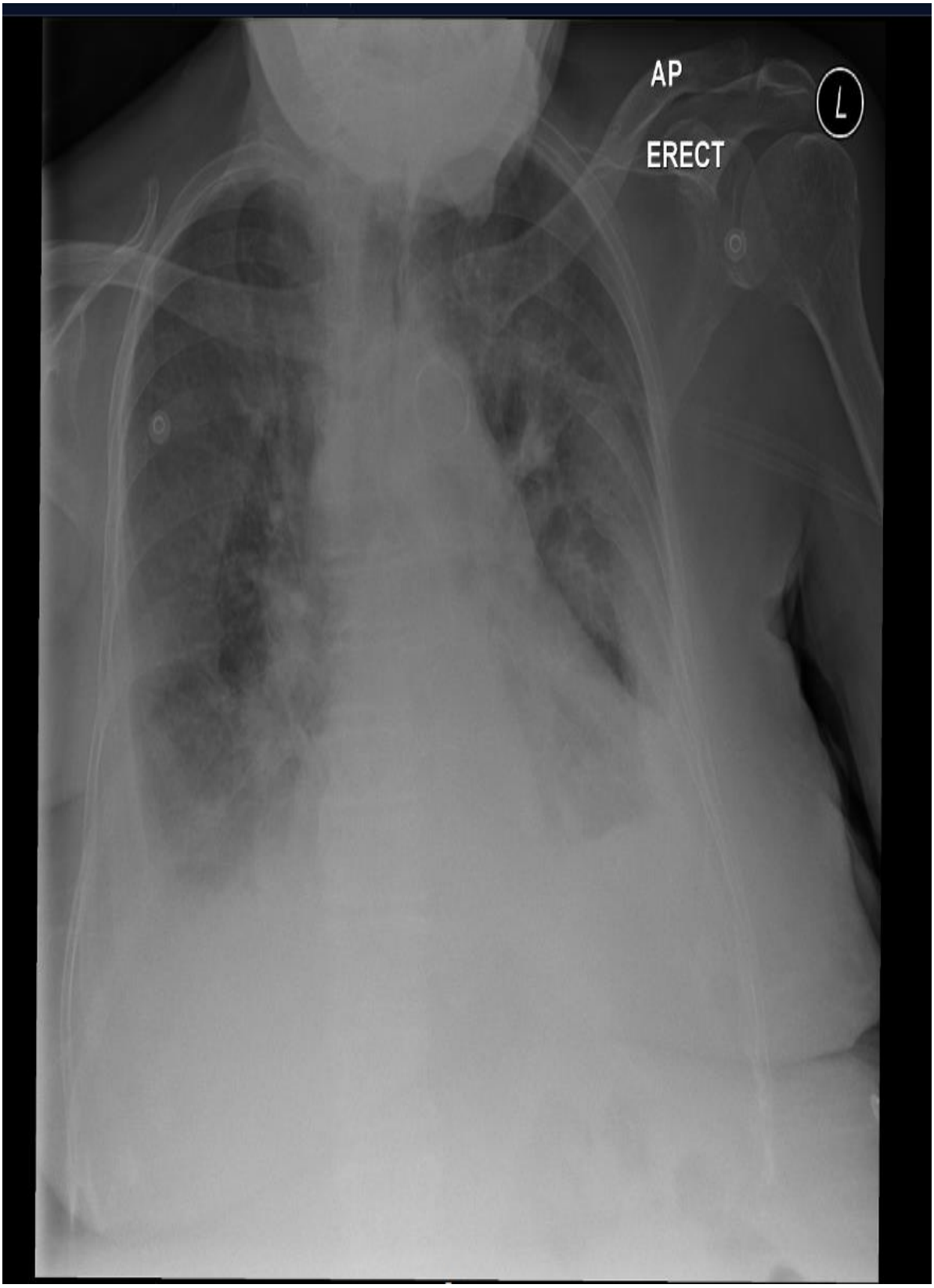
There are nodular opacities seen in both lung fields and the possibility of underlying TB should be considered.

Figure 3.10 TB-DM Case 6



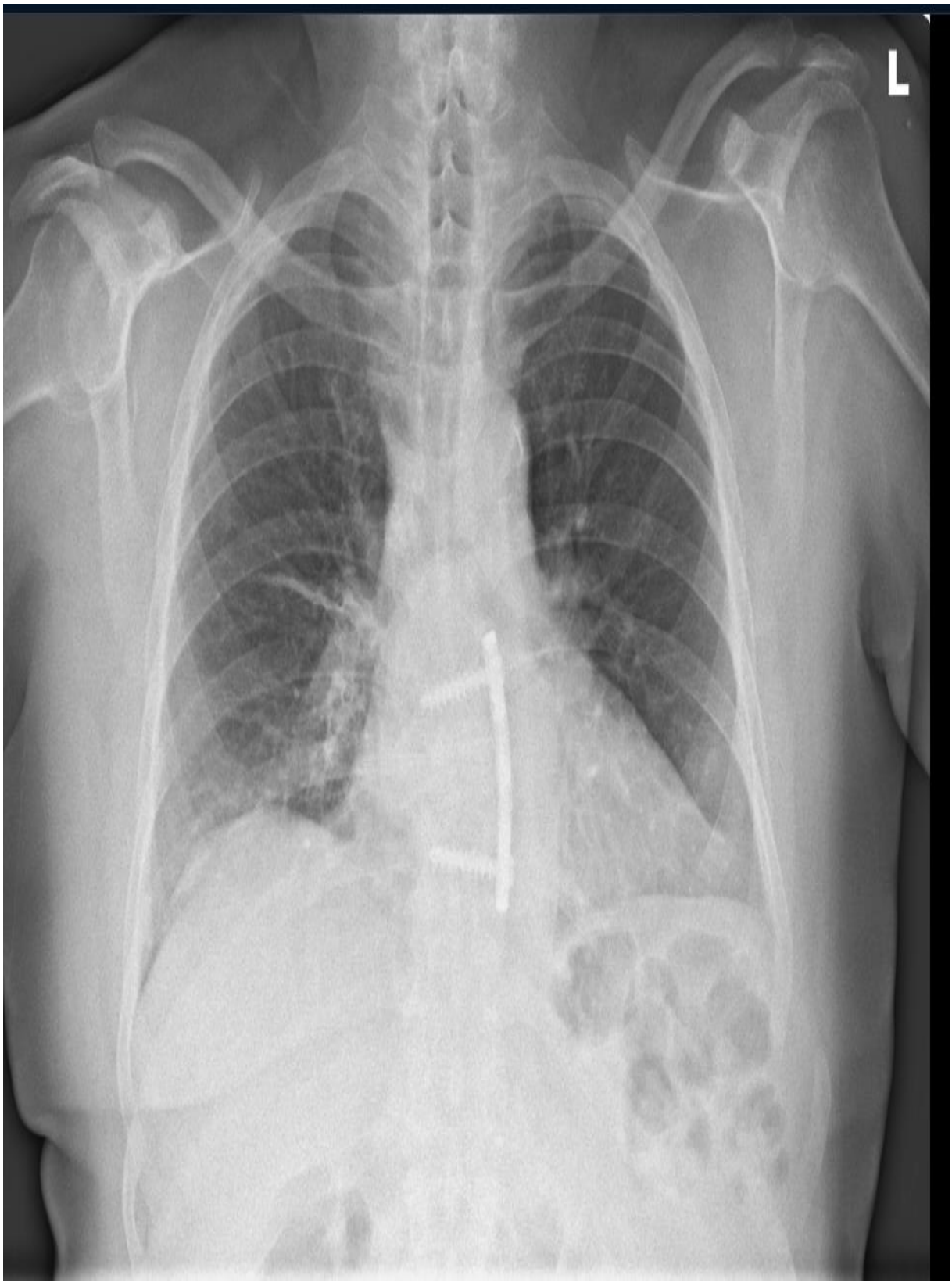
Left upper lobe consolidation and cavitation.

Figure 3.11 TB-DM Case 7



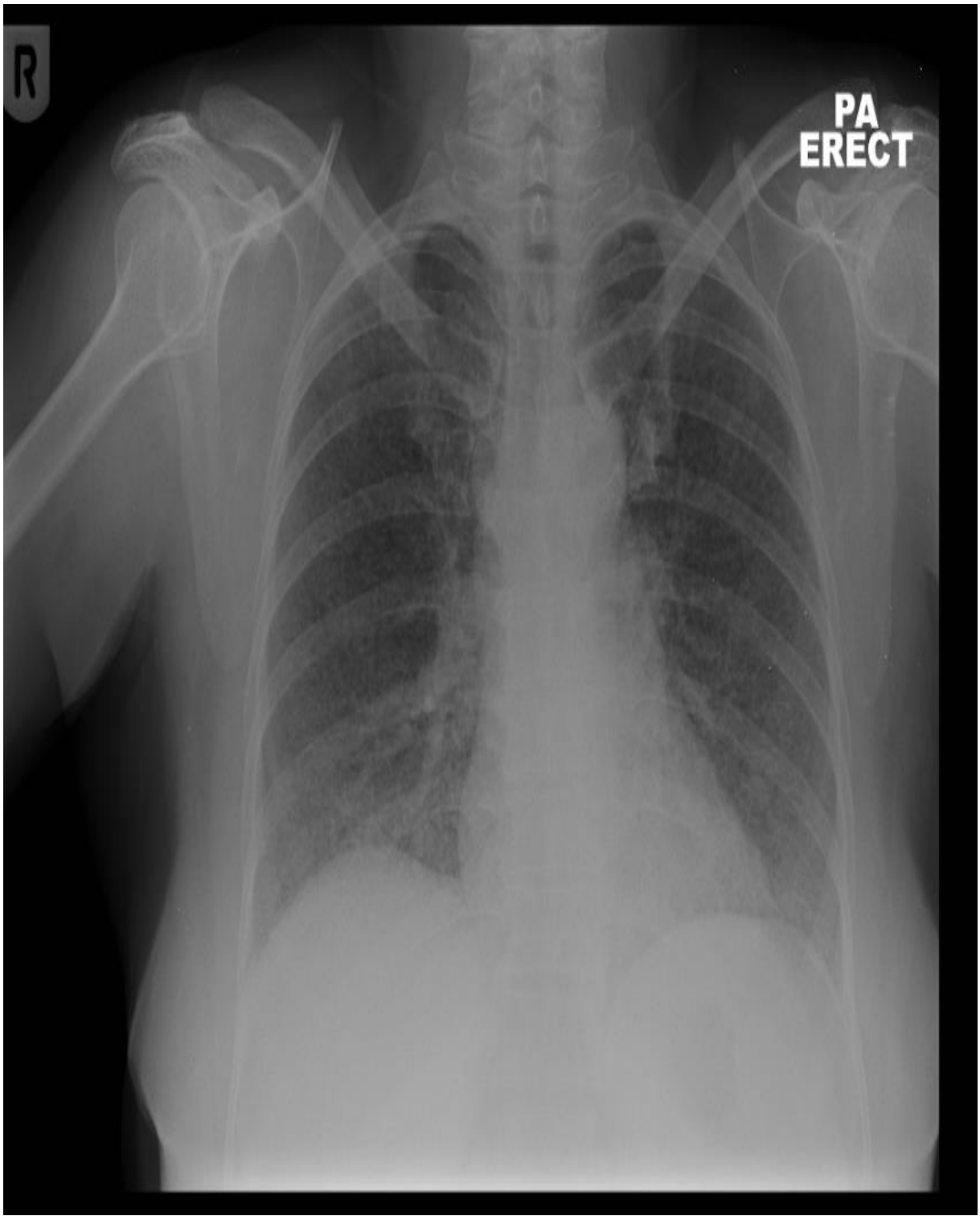
There is bilateral small moderate pleural effusions some patchy parenchymal opacification and interstitial shadowing.

Figure 3.12 TB Only Case 1



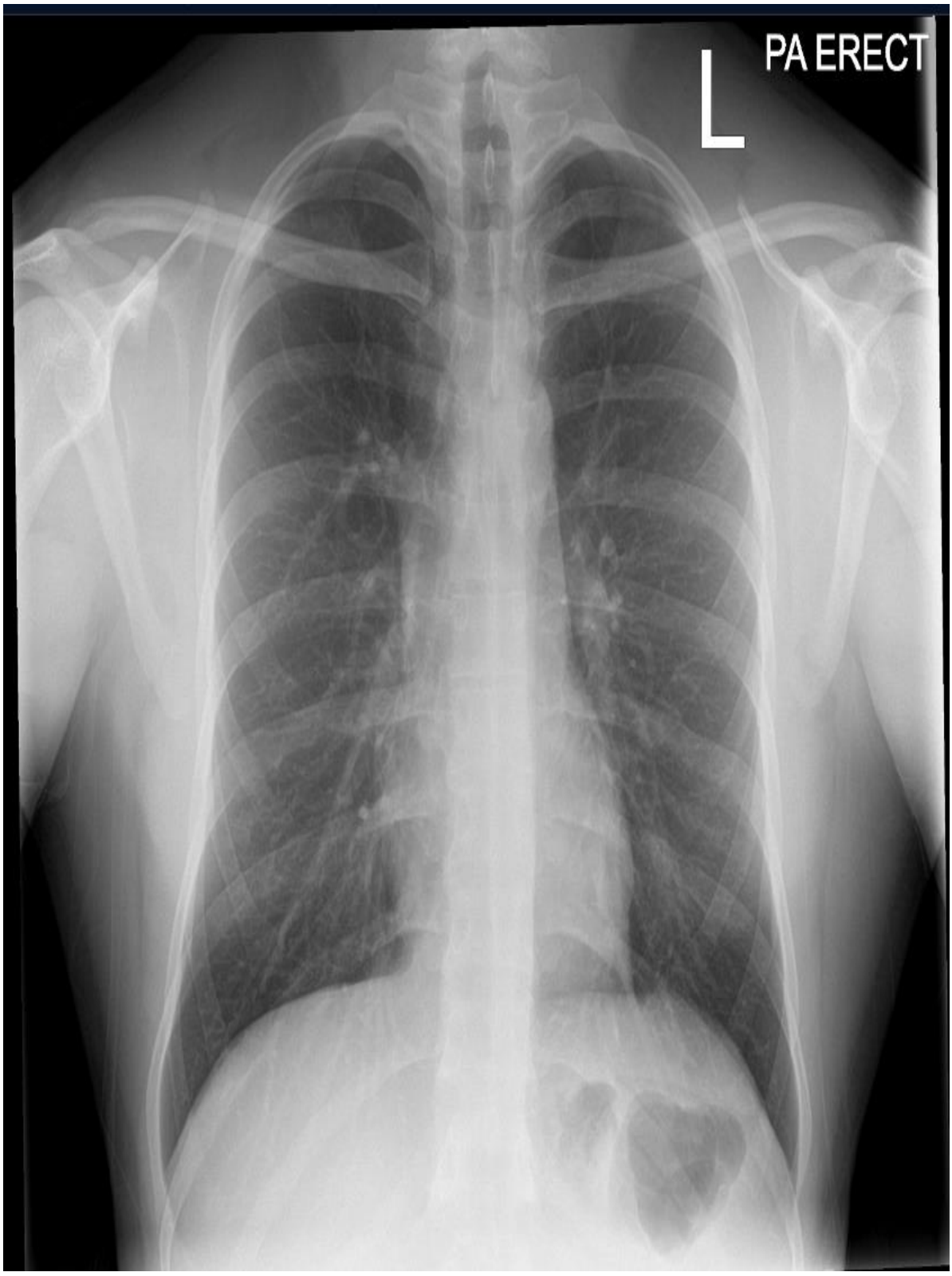
Lower thoracic spine fixation noted. No lung parenchymal abnormality of note. The mediastinal contours are normal. The pleural spaces are clear.

Figure 3.13 TB Only Case 2



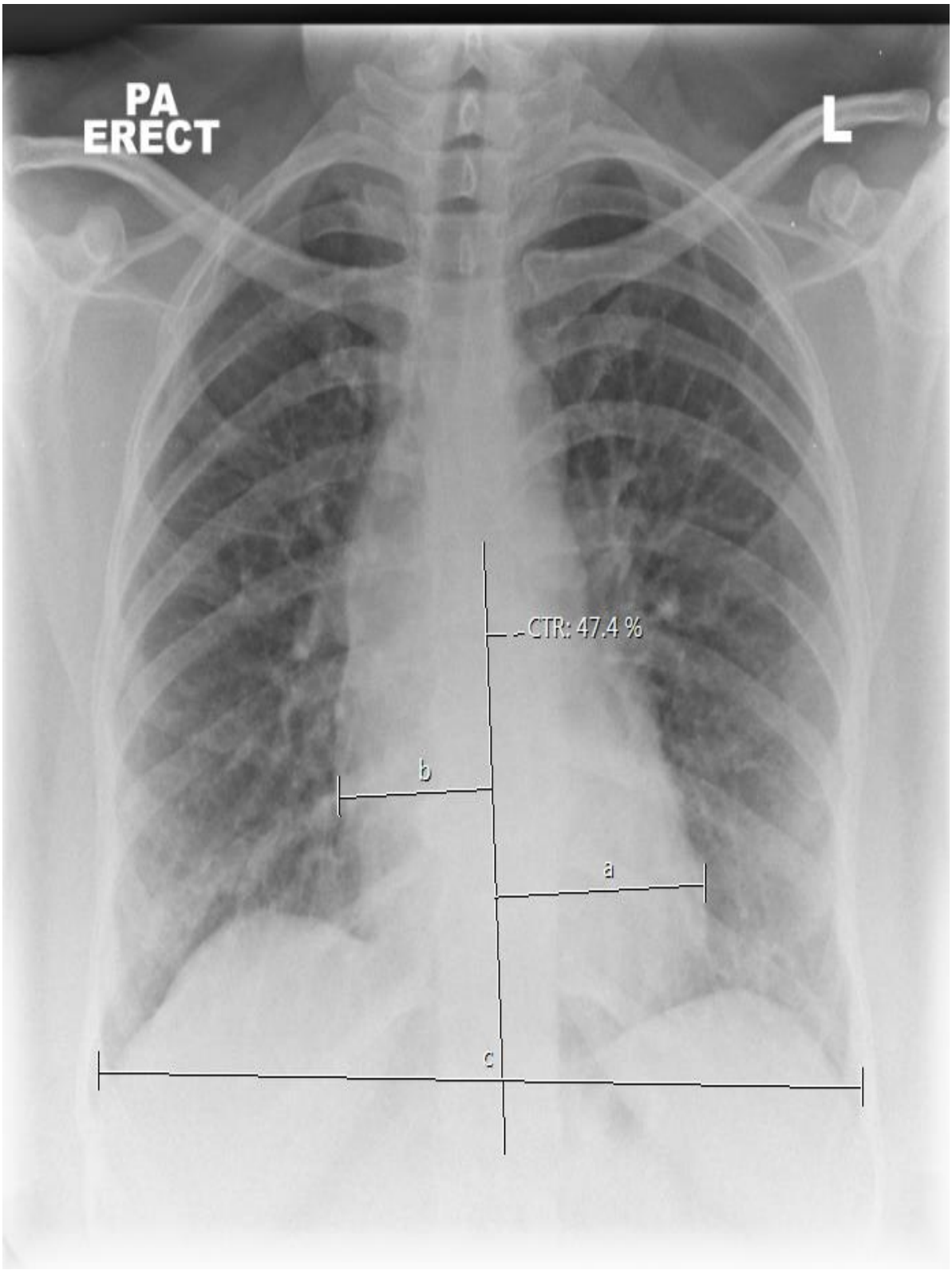
There is a miliary nodular shadowing in both lungs suspicious of miliary TB. No pleural effusions. No cavitating lesions or consolidation. No mediastinal or hilar adenopathy.

Figure 3.14 TB Only Case 3



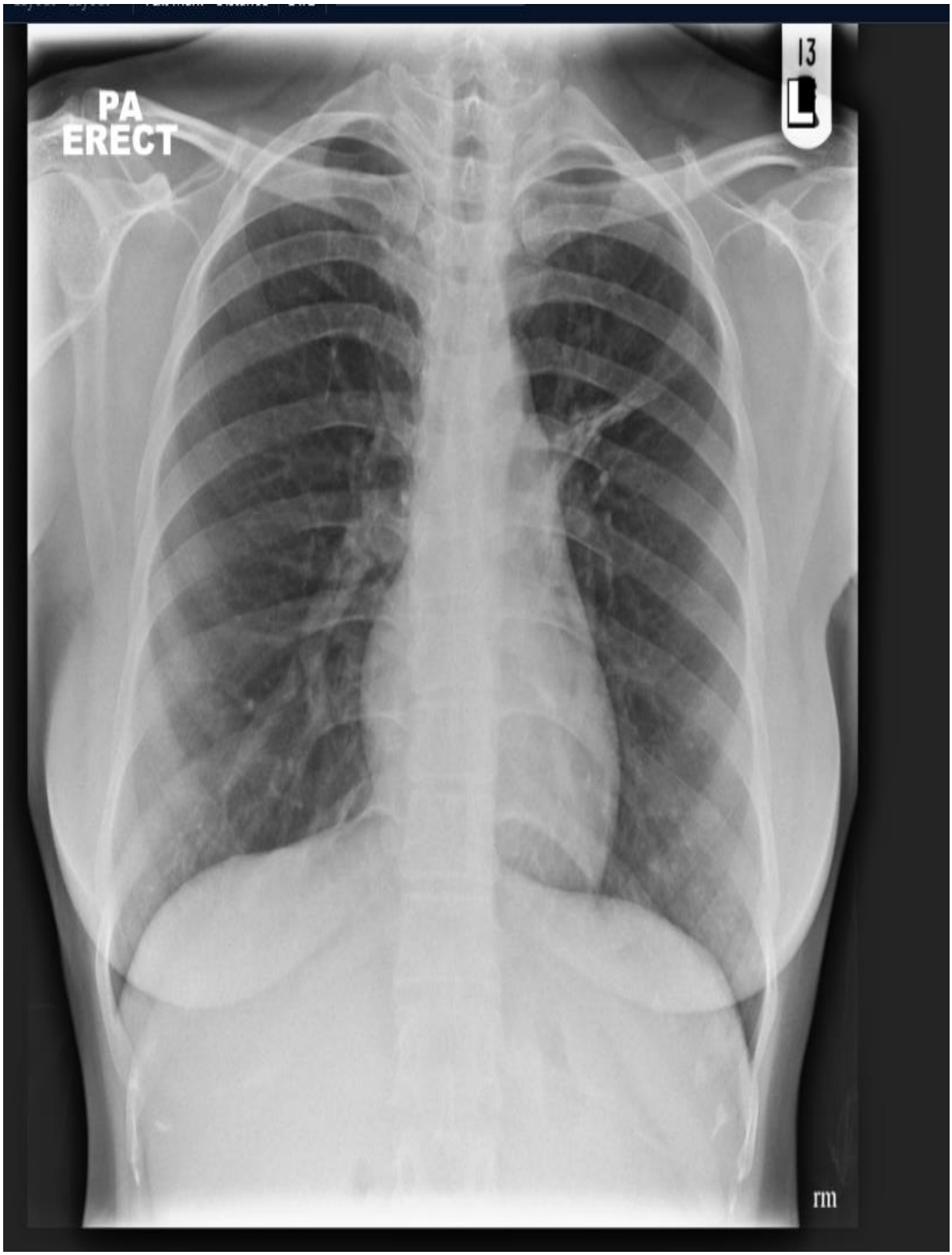
No parenchymal nodules, consolidations or evidence of collapse is seen. Cardiac, mediastinal and hilar contours appear unremarkable. No pleural effusion or pneumothorax is seen.

Figure 3.15 TB Only Case 4



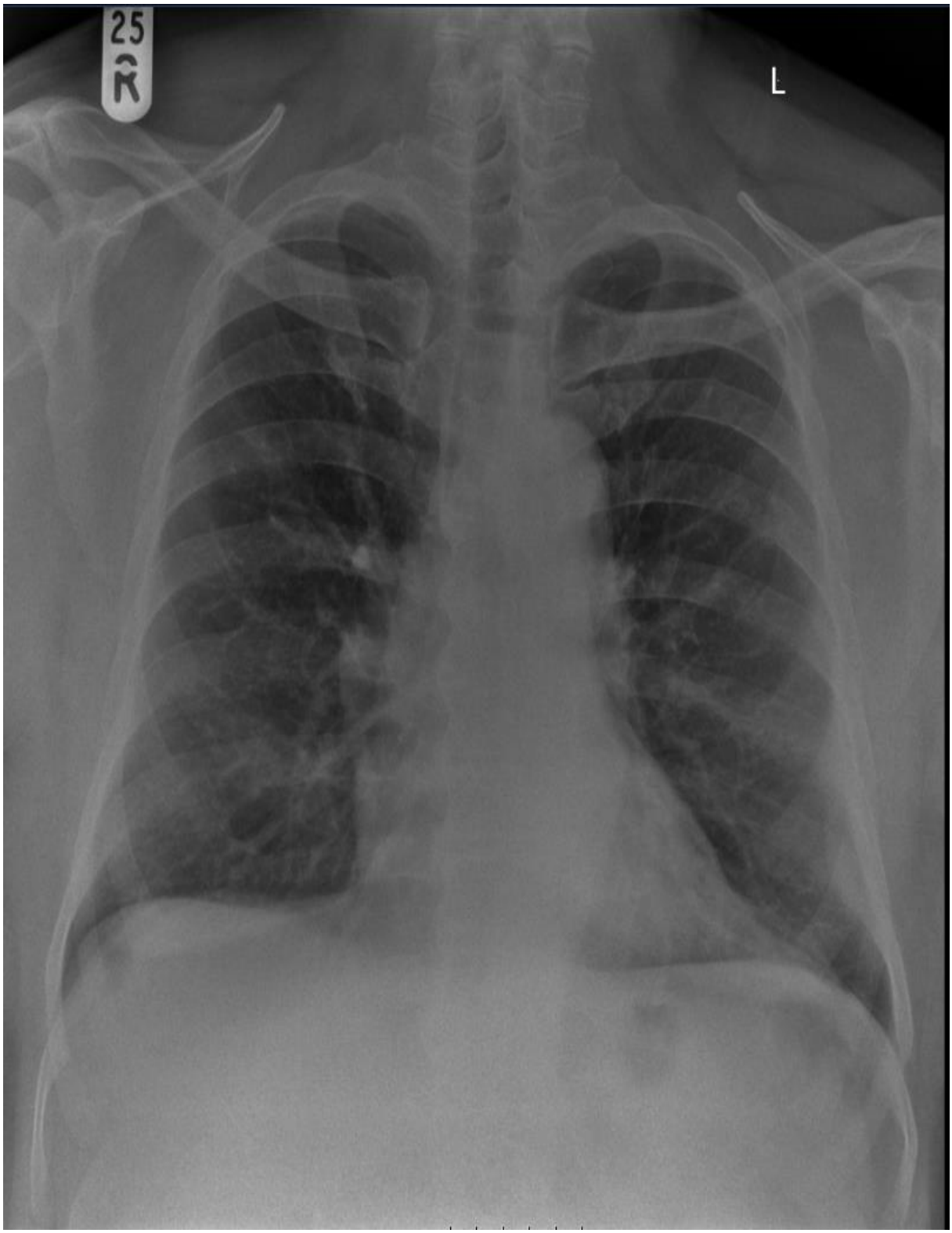
No lung mass or consolidation. No pleural effusions. There are mild pulmonary congestive changes. The heart size is at the upper limit of normal.

Figure 3.16 TB Only Case 5



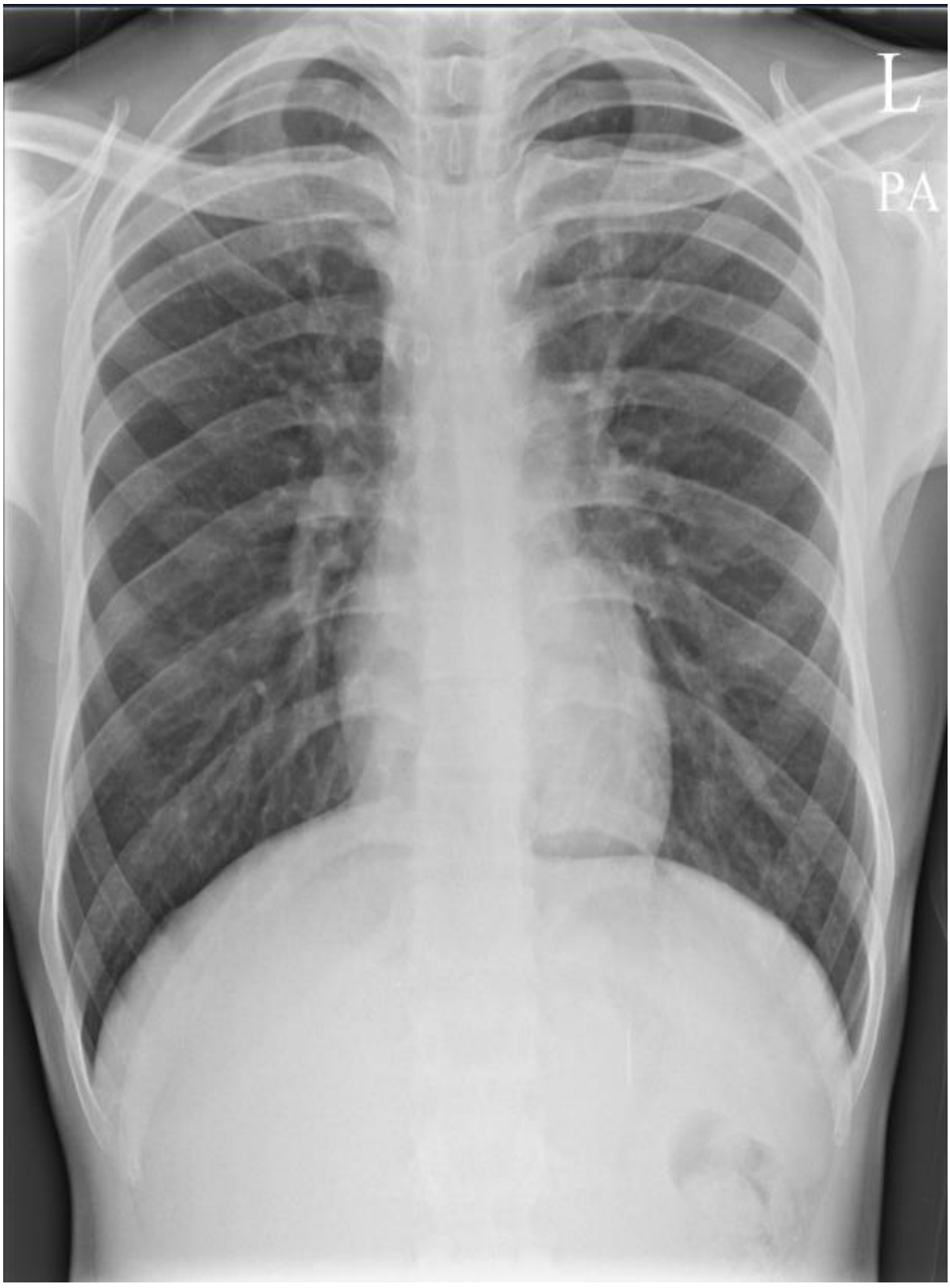
There is segmental collapse seen in the left upper lobe. Rest of the lung fields are clear. No mediastinal lymphadenopathy could be seen in the plain x ray.

Figure 3.17 TB Only Case 6



Mild diffuse accentuation of bronco-vascular markings with basal peri-bronchial thickening. No pneumonitic patches or cavitary lesions. Clear costophrenic recesses. Heart does not appear to be enlarged. Unfolded aorta with a prominent knob. Prominent hilar vascular shadows bilaterally.

Figure 3.18 TB Only Case 7



Patchy nodules noted in bilateral upper zones -? Consolidation.

Chapter 4 - Discussion

Primary Objective: 1

4.1 Determining the prevalence of DM among TB (TB-DM) patients in Newham, with a focus on differences between UK-born and non-UK born patients.

The global estimated number of TB cases was 10 million in 2018 and 1.2 million deaths are directly attributed annually to TB (WHO, 2019). The global prevalence of DM is estimated to be 415 million, with 7 million new cases diagnosed each year and 5 million deaths associated with DM (IDF, 2015). The converging epidemics of TB and DM suggest DM could increase the risk of active TB by 3-fold because of uncontrolled DM leading to increasing reactivation of latent TB, increasing immune-susceptibility and development of MDR-TB as insufficient initial treatment.

At the national level, the information on TB-DM co-epidemic is unknown, although the rate of TB has not been declining according to previous targets set by the WHO. The WHO strategy aims for the elimination of TB (defined as incidence of <1 per 100,000 people) in low-incidence countries. The incidence of TB, in England, has fallen from a peak of 8,280 in 2011to 4,655 in 2018, to reach the WHO End TB Strategy target of a 90% reduction in new notifications by 2035 (PHE, 2018) further approaches and changes in practice is required. In 2015, PHE and NHS England launched the Collaborative Tuberculosis Strategy for England 2015 to 2020, which aimed at decreasing TB on a year by year basis until its elimination. To achieve this, the following actions were given priority: improving access to health services and earlier diagnosis of TB, an increase in the quality of diagnostic equipment, carry out thorough contact tracing of known cases, improve BCG vaccination uptake, reduce MDR TB, implement new entrant latent (LTBI) testing and treatment and increase surveillance and monitoring of cases.

This is the first study in the UK to report the TB-DM rate as a tandem condition in a high TB burden population with increasing public health problems, using real-world data and follow-up of cases. The study includes the use of patient-level data from routinely recorded data on demographics, clinical course and outcome. The study assessed each patient's diagnosis alongside standard definitions, the treatment course of each patient using real-time clinical records, hospital visits, DM diagnoses, laboratory test interpretations, radiological assessments, and treatment efficacy and outcomes, with a 2-year follow-up. Recent data indicates that TB infection in Newham is above 40 per 100,000 compared to the rest of London (2017), which is a rate of 21.7 per 100,000. The latest DM incidence in the UK is estimated to be 3.9 million (6% of the UK population are classed as diabetic) (IDA, 2015) and the incidence of DM in the Borough of Newham is 22,904 for adults over the age of 18 years, which represents 6.7% of Newham's population. Therefore, the DM rate in the borough of Newham is comparable to the national average, thereby not posing a threat of being selected or biased.

The result from this study shows the prevalence of TB-DM in Newham is 28.8%, the average time to TB diagnosis post entry to the UK was 17.28 years in the TB-DM cohort compared to 9 years in the TB-only cohort (p-<0.001), with 89% of TB-DM cases being non-UK born patients. This significant finding suggests TB-DM groups are diagnosed with DM much later in adult life, and those non-UK born individuals also present with TB symptoms much later after entry into the UK, compared to the TB-only group (P-value <0.001). This may be a result of DM impacting upon the increased reactivation of latent TB in those already infected from a high-risk country. Furthermore, in the UK-born cases it is likely DM increases the risk of acquiring TB, as a result of immune deficiency and this is seen later in life, most likely as T2DM is an age related condition, therefore further studies are needed to target this group. This result would suggest a significant proportion of TB cases may have been prevented if they had been screened for TB on entry, or screened and treated for LTBI, and, furthermore, had DM screening.

The study also identified over 80% of all TB cases were diagnosed in non-UK born patients, with male patients (over 60%) being more commonly diagnosed in both UK and non-UK born populations. When analysing the prevalence of DM in TB cases, 168 cases had been diagnosed with TB-DM, with 3.8% of these being diagnosed as new DM cases, post-TB treatment. The result strengthens our knowledge that DM is an independent risk factor for an increase in TB cases in the London Borough of Newham. When comparing the age at which TB was diagnosed in the study population, the mean age was 36 years. The study found the mean age of TB only cases to be diagnosed at a younger age (mean: 38 years), compared to TB-DM cases (mean age: 45 years) which was more frequently diagnosed in those over the age of 55, and older age was a risk factor in the TB-DM cohort. This reflects T2DM which is mostly also age related.

A screening for DM as part of LTBI screening should be considered. It is plausible that the presence of DM, coupled with latent TB, increases the risk of active TB, a likely reason for the continuously high TB incidence in the London Borough of Newham and requires further investigation. It is possible that non-UK born individuals from a large TB incidence country to have active TB upon arrival in the UK or have LTBI, which reactivates post-arrival because of socio-economic risks including poor housing centres and overcrowding, or they could obtain TB through local transmission from individuals in the host nation.

Systematic reviews suggest DM increases the risk of TB, caused by immune dysfunction in diabetics, this current study strengthens our knowledge that the association between DM and TB exists, with certain characteristics: age, fever, weight loss being more common in TB-DM cases. Higher mycobacterial load, due to an increased clearance time in patients, all likely associated with poor glycaemic control, and immune deficiency, which in turn is related to DM diagnosis and medication adherence, which then affects clinical outcome. The results from this study highlight the need to investigate the management of these co-existing conditions, this includes investigating the need for bi-

directional screening, monitoring TB drug adherence and therapeutic effects, especially drug-drug interactions with hypoglycaemia agents.

It is likely, as can be seen in results reported here, that non-UK born citizens are at higher risk of TB due to increased exposure in their home country or due to the other reasons mentioned. This places individuals at risk of LTBI to progress to active TB; hence, the late diagnosis of TB after entry into the host country. Migration has been shown to be a driver of TB in low incidence countries, with most TB cases attributed to reactivation of latent TB acquired in the country of birth (Dale *et al.,* 2018). The results also suggest higher infectious risk, in the TB-DM cohort, through increased cavitation and late sputum conversion, which are significant factors. Furthermore, 5% of all those treated in the TB-DM cohort had relapsed compared to 1% in the TB-only cohort, which likely implies treatment failure is higher in the TB-DM cohort leading to an increased mortality rate as reported here.

Loutet *et al*., (2018) undertook a pilot study in Newham, which was undertaken to evaluate a national roll-out of an LTBI treatment and screening service in a high TB incidence population. Within the study period (2012-2014) the authors discovered over the 3-year period that the TB incidence was 100 per 100,000 population, which was greater than the London average of 35.4 per 100,000 population. The pilot study revealed over 80% of TB cases in Newham (including TB-DM cases) were in people from the non-UK born population. They reported the treatment of LTBI was a significant mechanism to suppress the incidence of TB in Newham. A total of 5,591 patients in Newham were screened for LTBI screening. The age ranged from 16-35 (71%) and 54% male. Of those offered LTBI, 1,254 (22.4%) declined to be screened. The result showed individuals from Sub-Saharan Africa were most reluctant to undertake LTBI testing, when compared with individuals from the Indian sub-continent (adjusted OR 0.6 (95 percent CI, 0.4-0.9) and adjusted OR 0.7 (95% CI, 0.6-0.8) (Loutet *et al.,* 2018). Their results showed an immediate impact of the LTBI screening programme on managing TB incidence, by actively identifying active cases and reducing transmission of further cases, but they came across barriers to fully embed the programme.

This current study found 85.3% of all cases occurred in non-UK born men with a mean age of 36 years (range 27.5-49.9). This study is comparable to that of Loutet *et al.* (2018), and highlights that there is an opportunity to actively find cases and treat, in addition to managing DM cases (known and new cases) to provide a better treatment outcome for patients and effectively contribute to TB elimination.

Although there is no UK-based comparable studies, a study by Restrepo *et al.* (2014) in Texas, USA to estimate the contribution of confirmed DM cases to TB rates, where both conditions were prevalent, was undertaken. This was a prospective study using TB clinics in the Texas-Mexico border area with a total of 333 TB cases enrolled in the study, 233 of whom met the study criteria: 61 in South Texas and 172 in north-eastern Mexico. All cases had pulmonary TB. The result estimated the prevalence of DM among the TB patients to be 39% in Texas and 36% in Mexico. DM contributed to 25% of the TB cases, whereas HIV contributed to 5% or fewer, with a median time until DM diagnosis of seven years. This study is suggestive of a missed opportunity for TB prevention (Restrepo *et al.,* 2014). In comparison to the Restrepo study, TB-DM patients in this study had a time of 17.28 years (see table 3.8) until DM diagnosis, a decade difference in active TB presentation in the TB-DM cohort compared to the TB only patients. This might be related to TB exposure and other environmental and societal factors. However, the TB-DM prevalence in this study was 28.5%, which is comparable to the findings by Restrepo *et al.* (2014) who cited in their study a direct association between TB and DM is likely.

The findings from this current study and previous studies have found DM to be associated with older age, which is a well-known risk factor for DM but not for TB. A likely explanation of why TB-DM is common in non-UK born nationals is that those individuals from high TB burden countries are at risk of having latent TB upon entry into the UK and poor glycaemic control has a negative impact on immunity: hence, an increased risk of latent TB becoming active TB (Burman, 2016). A study by Khalil and Ramadan (2016) addressed

risk factors for PTB among DM patients. Their study included 160 patients organised into two groups: the first group of 80 patients with TB-DM and the second of 80 patients with DM and chest disease other than TB. They reported the mean age of the TB-DM group to be 52.90 years, with the DM-only group having a mean age of 54.57 years with a p-value of 0.32. They showed no significant difference between the two cohorts in relation to mortality rate, cure rates, relapse and resistances. Ponce-de-Leon *et al.,* (2004) studied TB and DM in Mexico using a study size of 581 patients. They reported that the mean age of TB-DM was 51.5 years compared to 44 years in non-DM-TB patients. Nissapatorn *et al.* (2005), who looked at TB and DM in the South Asian population in Malaysia, found a TB-DM group age of 51.5 years compared to 37.5 years in the non-DM-TB group, using a sample size of 1651 patients.

In this study, when comparing age, the TB-DM cases are likely to be older by 10-20 years than those with only TB. This indicates an association with DM, especially T2DM, which is more prevalent globally and amongst those at an older age. It is also likely to be associated with social risk factors including lifestyle habits i.e. diet and inactivity. The male dominance in both TB-only (65%) and the TB-DM cohort (62%) has also been reported by Nissapatorn *et al.* (2005), who found 69.3% of their study population with TB-DM to be men. TB is more likely to be observed in men due to occupational exposure, although further investigations into occupational exposure in men and the impact of comorbidity of TB-DM in relation to occupational exposure is required (Davidson *et al.,* 2016).

In relation to DM diagnosis in TB patients, the result from this study reflected a high percentage of non-UK born to have TB at a much later age than those with only TB in the Newham population. This late diagnosis of DM could be due to two causes:

1. These individuals already have prediabetes, whereby the blood sugar level is high, but lower than the threshold for diagnosing DM, and this progresses to DM, mostly T2DM.

2. The risk factors for DM include age (40 and above), body mass index (25 and above), Asian ethnicity and having high blood pressure. Age and ethnicity are implicated in this study with DM being more commonly diagnosed in non-UK individuals, who have a major shift in lifestyle once resident in the UK compared with in their country of birth (Mainous *et al.,* (2014). This increases the risk of prediabetes and DM.

One explanation for this is a likely late diagnosis of diabetes in the home country, or that it reflects a population trend of earlier onset of DM, especially type 2 DM, due to the rapid changes in lifestyle experienced by non-UK born in the host country.

Furthermore, local transmission in the Borough of Newham within communities, may have also contributed to the higher incidence of TB cases observed in such a diverse migrant population with a range of ethnic groups. These ethnic groups are more likely to live in densely populated areas with a higher concentration of their own ethnic communities, which increases the spread of TB. In addition, having multi-generations living together as opposed to a nuclear family setting increased TB transmission (Hayward *et al.,* 2018).

Furthermore, the results of TB-DM prevalence in Newham is the first study to be done in the UK and in any London Borough. It is likely the social and clinical observations seen in patients with TB-DM in Newham could be representative of other London Boroughs or cities in the UK, which have similar demographic characteristics including a densely populated non-UK born population. It is documented that more non-UK born individuals are entering the country due to globalisation, conflict and for financial reasons, this has led to non-UK born individuals seeking permanent residence in the UK, and a significant proportion of these non-UK born residents are from high TB burden areas, including Sub-Saharan Africa and the Indian Subcontinent (ISC) (Restrepo and Schlesinger, 2014; Pande *et al.,* 2018). As a result, TB incidence is higher in non-UK born individuals than those in the UK-born population.

The results from this study show the average age at diagnosis of TB in the TB-DM cohort is 17 years compared to 9 years in the TB only group (p=<0.001), with poor glycaemia control (average HbA1c levels of 7.63%), age over 55 years could be because DM is playing a role in late TB diagnosis. It has been reported in previous literature that DM can decrease the immune response, which facilitates either the primary infection with *Mycobacterium tuberculosis* or reactivation of latent TB, by altering the components of the immune system, including altered levels of specific cytokines and chemokines (Nathella and Babu, 2017). Activation of latent TB in affected individuals, is more common in non-UK born patients, especially those from a high TB burden country. Furthermore, non-UK born cases with active TB, which had not been diagnosed, are likely to reflect the increased numbers. However, since 2012, the UK Home Office has introduced pre-arrival screening for active PTB for all long-term visa applications from endemic countries; those with active TB are denied entrance. Therefore, the arrival of non-UK born individuals with active TB alone is not likely to be significant to the overall TB burden seen in the UK and reported here in Newham. It is likely that poor glycaemic control leading to immune suppression is allowing the activation of latent TB, which is common in non-UK born individuals travelling from high-incidence countries.

As non-UK born cases are observed as a key risk factor for developing TB, it is advisable to investigate the mechanism leading to this susceptibility including urbanisation, modernization, changes in nutrition and lifestyle including lack of physical activity, stress and behavioural changes which are commonly experienced by non-UK born who likely have come from a poverty-ridden rural area to urban obesogenic environment. All these factors further the risk of obesity and diabetes which is commonly seen in inter and intra-country non-UK born in developed and developing countries (Tomas *et al.,* 2013). Research by Hanif and Susaria (2018) on the association between migration and diabetes, in Asian Indians living in the UK have shown a common non-UK born likely to be obese, have higher blood pressure, increased cholesterol and blood sugar levels. Furthermore, non-UK born who develop DM are more likely to become insulin-resistant than their non-

immigrant siblings living in India (Ebrahim *et al.,* 2010). The result from this study found men are at higher risk of TB-DM, which is likely to coincide with the exposure to TB through lifestyle change, living in poor housing and overcrowding, increasing obesity because of a change in lifestyle and barrier to access healthcare facilities either in birth country or host country.

The incidence of TB in 2018 was 4,655 (8.3 per 100,000 population), to meet WHO End TB Strategy target of 90% reduction of new notification by 2035, further effort is required, including understanding the variation of TB prevalence and patient profiles across the country, focusing on people with social risk factors. This study focuses on DM as a risk factor with the aim to implement policy change to manage co-existing conditions better and to subsequently reduce TB burden. The prevalence data from this study shows 85.3% of all TB cases are reported in non-UK born patients, although we found no statistical association, DM is a significant variable between UK born and non-UK born populations. But as mentioned, reactivation of LTBI maybe a cause, but this requires further investigation. The results show TB-DM cohort are diagnosed later than the TB only cohort, from a health policy perspective it would be beneficial to highlight both DM and TB in high risk groups within the population which is those over the age of 55 years, non-UK born and male are being at higher risk of TB and DM. Health providers, both primary care and secondary care, should consider this at risk group and look at implementation of TB or DM screening, if either condition is present. Further consideration of dual management of TB-DM, with referral to specialist care as early as possible and education on lifestyle behaviours.

Actively screening for TB in DM patients is not routinely conducted in the UK or globally, partly related to resource available to enable for universal screening and cost implications. This is likely to be difficult to implement in low-burden countries as a routine but likely to be beneficial in clusters of high incidences in the UK. This is unlikely to be implemented in non-UK born individuals from host countries, prior to entrance into the UK, mostly due to cost and further investigation is required especially from a endocrine perspective, i.e. sending all patients with DM for chest x-ray is not feasible,

logistically or financially, as DM clinics are not set up with an x-ray facility and sending patients for x-ray without clinical reason is not evidence based. Therefore, a screening programme targeted at non-UK born individuals with DM from ethnic groups disproportionately affected by TB and DM would prove useful, based on this research reported here.

Currently, screening for and treatment of LTBI in DM patients is not clinically recommended in any guidance. Screening for TB disease is recommended for persons migrating from countries with a high TB incidence. It would be beneficial to investigate the screening and treatment of LTBI and active TB, in addition to, testing for DM in positive TB cases. Current practice is those tested positive for TB to be screened for HIV, the same practice should be applied to DM.

The findings from these results imply TB is being diagnosed sometime after non-UK born individuals' arrival in the UK, suggesting that differential exposure among non-UK born individuals is a vital risk factor for TB. Approximately 13% of the UK foreign non-UK born population are from a country where TB prevalence is >250 cases per 100,000. Following the Second World War, a significant number of non-UK born cases came from the Commonwealth and British Empire; likely due to Britain's labour deficit for post-war reconstruction and political turbulence after decolonisation (i.e. the creation of Pakistan). Many Commonwealth nations have a high prevalence of TB: in Africa, 275 per 100,000 inhabitants in 2015; at South East Asia, 246 per 100,000 (WHO, 2018). Non-UK born individuals from high TB incidence countries are more likely to have been exposed to Mtb and have an increased risk of acquiring LTBI.

In 2016, 17.2% of all TB cases reported in England had travelled outside the UK (excluding Western Europe, USA, Canada, New Zealand and Australia) within the last two years prior to TB diagnosis. In addition, 7.3% of all TB cases in England had received an overseas visitor from high incidence countries; and with 23.3% of non-UK born cases having travelled to a high-incidence country compared to 4.7% of the UK born population (PHE, 2018).

Epidemiological evidence indicates that travels to countries with high TB prevalence increases the probability of acquiring LTBI, with a threat associated with a greater TB burden along with more travel in the destination country. The second and third generation of non-UK born individuals (born in the UK but with parents born overseas) are at a lower risk of TB compared to first-generation non-UK born individuals, however, remain at greater risk when compared with the general population. This would imply that vulnerability to Mtb from the nation of origin and the higher incidence of TB among ethnic minority groups in comparison to the overall population are most likely to be related to transmission over the migrant populations especially when travel to family back in home country (Hayward *et al.,* 2018).

Laboratory studies also provide support for the biological plausibly of TB-DM and DM-LTBI association. After the inhalation of Mtb bacilli, alveolar macrophages in the lung are the very first line of defence from mycobacterial invasion. A failure to clear Mtb from the alveolar macrophages can result in bacterial replication and increase spreading (Gomex *et al.,* 2015). In animal studies, DM mice have demonstrated that a delayed and diminished innate immune reaction to the invasion of Mtb; evidence for diminished innate response was also found in human DM patients (Vallerskog, Martens and Kornfeld, 2010). DM patients show deficiencies in serum complement factors, allowing Mtb to interrupts the mononuclear phagocytes and attain intracellular survival. However, further laboratory investigation is required to characterise the immunological responses in DM patients with Mtb (Gomex *et al.,* 2015). Non-biological plausibility exists, including DM patients being more likely to access healthcare services, therefore being at increased risk of contact with Mtb exposed patients. DM patients are more likely to be exposed to Mtb in healthcare settings, but this requires further investigation (Pan *et al.,* 2016).

This study identifies over a quarter of TB diagnosed in patients in Newham to have DM as a co-existing condition, therefore, this is the first London-based prevalence study to measure the association of TB-DM using primary data. The findings strengthen and builds on previous studies and knowledge on the association between TB-DM including acknowledging *in-vitro* and *in-vivo*

studies on DM impact on lowering the immune response. The results have shown some symptoms are more prominent or severe in TB-DM patients, because of altered immunity. Radiographic presentation was shown to differ in TB-DM cases in their presentation, with greater cavity involvement and presentation more common in the older age group compared to the TB only group. Likewise, with HIV infection, theoretically it can be assumed DM is linked to increase the risk of developing to active TB from LTBI, due to immune suppression, although more investigation is required. Therefore, future studies should focus on the impact of a targeted screening for TB in DM cases, DM in TB cases, and LTBI screening among the DM population or DM screening in LTBI and TB cases in those high risk individuals (older age, non-UK born males).

This prevalence study consisted of 85.3% of all TB diagnoses to be in non-UK born individuals within the study population. This reflects the Newham 2011 Census data (Aston-Mansfield, 2017), whereby 83.3% were from a non-White British ethnic group. This would identify BAME groups to be at risk group of TB-DM, furthermore, non-UK born individuals who have come and settled and are an at risk group of LTBI, are probably more likely to progress to active TB disease in the presence of DM and may explain the late TB diagnosis or presentation in the TB-DM cohort, this requires further investigation. In addition, health policies should highlight at risk groups of TB, including DM as a risk factor. New arrivals to the UK and healthcare workers from high TB incidence countries should have screens for TB and DM to help tackle the TB burden in the UK. However, migration alone should not be considered as a sole target for prevention as other factors affect the progression to active TB, including genetically acquired susceptibility, co-morbid factors including DM, vitamin D deficiency, HIV, societal factors (homelessness, prison history, alcohol and drug misuse), which are all documented to be key risk factors (Hayward *et al.,* 2018).

Therefore, biological and anthropological factors influence the risk of TB and its progression. TB incident in Newham maybe due to local transmission within the high immigrant population as they live in densely populated

conditions, which likely to encouraged transition, or reactivation of LTBI (Ho, 2004).

The results from this study are consistent with others in which DM (especially uncontrolled DM) increases the TB risk and progression, affecting clinical presentation and microbiological outcome. The general population of Newham has a DM prevalence of 8.57% (Diabetes UK, 2019). This study highlights the potential association between DM and active TB due to dysfunctional immunity. When comparing crude data on TB and DM rates in London, the three top London Boroughs with the highest TB incidence also have the highest level of DM rates, Newham (DM, 8.57%) (TB, 46.9 per 100,000); Harrow (DM, 9.58%) (TB, 24.8 per 100,000); Brent (DM, 8.91%) (TB, 33 per 100,000). The lowest rates of TB and DM in London, Richmond upon Thames (DM, 3.7%) (TB, 7.1 per 100,000); Camden (DM, 4.01%) (TB, 9.2 per 100,000) (Diabetes UK, 2019; PHE 2018).

The findings from this study is suggestive of non-UK born individuals having a higher incidence of TB, which is explained by the differential exposure to TB both pre-migration and familial links with their country of birth, this is in line with literature reviews on TB-DM. But this alone does not drive the incidence of TB in hot spots as seen in Newham. Non-UK born individuals face many disadvantages, including risk of exposure to TB, vulnerability to infection (local transmission or link to home country i.e. travelling back, or living in an overcrowded housing) development of disease related to poor nutrition and barriers to accessing healthcare) (Fogel, 2015). The results suggest DM is a significant co-morbid factor in non-UK born individuals, which future policy should target.

Primary Objective 2

4.2 Social, clinical characteristics and microbiological features associated with TB-DM compared with TB only patients

4.3 Social risk factors

Social determinants and clinical risk factors are important in the epidemiology of TB and are considered as part of global initiatives, such as the End TB Strategy, the global strategy and targets for TB prevention (Barron *et al.,* 2018). These determinants link poverty and low socio-economic status to the factors which directly increase the risk of being infected (exposure to an infectious source) or developing TB (impaired immunity). There is substantial evidence to link TB disease and socio-economic factors. Further to these issues, it is vital to understand the local, regional and global risk factors of social determinants in anti-TB drug resistance, and to measure the health status and performance of local healthcare systems which deal with the TB burden and associated risk factors (Barron *et al.,* 2018; Taneu *et al.,* 2017).

From this study, social risk factors, including smoking, heavy drinking, homelessness, imprisonment and known contact with TB cases, did not show any additional risk of developing active TB in either the TB-only group or the TB-DM group, as previous studies have reported. This study does report those who inject drugs to be at significant risk (p-0.04, OR, 0.836-50.36) in the TB-only group and TB-DM group. However, the number of PWID is too small to make any significant conclusions. Therefore, social risk factors do not increase the risk in the TB-DM cohort compared to the TB-only group in our study population of Newham. Social risk factors for acquisition of TB are likely the same in the DM group as in the general population.

It is well documented that there is an association between deprivation and TB disease, as those in economically disadvantaged groups are at the highest risk, with poor living standards and nutrition being the main risk factors (Hargreaves *et al.,* 2011). Therefore, public health efforts in regulating the

urban environment poverty, homelessness and overcrowding is important in controlling the spread of Mtb. In London, the TB notifications rates increased by 12% for every 1% rise in the number of people living in overcrowded conditions. Furthermore, social determinants are entwined with ethnicity; socio-economic disparities lead to inequalities in health. Referring to the findings in studies of non-UK born patients combined with the economic issues of unemployment, low income and poor housing conditions, non-UK born individuals are more likely to face homelessness and overcrowding. Cigarette smoking plays a role in the pathogenesis of TB infection and is related to ciliary dysfunction, a weakened immune response and to defects in the immune response of macrophages, this is without or with a decrease in the CD4 count in smokers, increasing susceptibility to TB infection (Silva *et al.,* 2018). The alveolar macrophages bind into the bacillus through the match receptors 1,3 and 4. Lymphocytes release cytokines that are activated whilst recruitment other alpha lymphocytes. A cytokine is macrophages TNFα, which can be released by macrophages following exposure to Mtb antigens. The TNFα activates macrophages and dendritic cells. In smokers, smoking, acting through the α7 cigarette receptor reduces the production of TNFα by the macrophages, thus preventing its protective action and being susceptible to TB (Silva *et al.,* 2018).

Globally, it is estimated that 10% of all TB cases are related to alcohol misuse. In this study only 34 patients met the drinking criteria, with 10% in TB only group and 4% in TB-DM group (P-value 0.054). Statistically no significance was observed between both the groups. In a cohort study, which assessed the TB treatment outcome in Tomsk, Serbia, found that 60.2% of their TB patients had a lifetime alcohol use disorder (AUD) and 72% of AUD cases were male increasing the risk of TB treatment failure and relapse (Shin *et al.,* 2011). In a prospective study in New York City by Silva *et al.* (2018), AUD patients reportedly had an incidence of 464 cases/100,000 person-years, which is nine times the incidence found for the age-matched general population. Alcohol and TB have been long linked, despite the fact that it is still not known if there is a higher risk of TB as a result of alcohol misuse per se or because of the sequelae of AUD, such as liver damage and nutrient

deficiency, or societal aspects, such as overcrowding or homelessness. Although, *in vivo* and *in-vitro* studies have demonstrated that alcohol use is significantly linked to the disturbance of the immune response and increased susceptibility to respiratory disorders, including TB. It is possible this study in Newham cohort may have under reported AUD incidence for various reasons including participant's honesty, how the data was captured, and if interview bias was a factor during data capture phase.

In 2015, it was estimated a quarter of a billion-people aged between 15 and 64 years of age use at least one illicit drug (Peacock *et al.,* 2018). The impact of drug use on health continues to be devastating, with an estimated figure of 207,400 drug-related deaths in 2014 (European Drug Report, 2015). The link of drugs with TB is through the presence of illicit drug users infected with Mtb in families and communities; this is a crucial risk factor in the transmission of TB. Individuals who inject drugs, infection with TB and the progress to active TB are encouraged by several variables: insecure lifestyles, crowded housing situations, isolation and accumulation of individuals inside for the usage of medication, smoking, malnutrition and acute cough. In this study we found individuals who inject drugs to be slightly higher in TB-DM group (7%) compared to TB-only (3%) (P-value 0.04, CI; 6.490 (0.836-50.36)).

A London-based case-control analysis of patients with PTB reported 19 (86%) of 22 crack cocaine users were smear-positive, in comparison to 302 (36%) of 833 non-drug-using patients. The smear positive at the time of diagnosis of PTB was 2.4 times greater in people who had been on crack cocaine (Story *et al.,* 2008). In-*vitro* studies show cocaine decreases immune reactions, including chemokine and IFY-y responses, that are required against TB infection. Overall, cocaine usage attenuated the potential for monocytes and alveolar macrophage mechanisms, resulting in failure to respond to a challenge that was mycobacterial (Kiboi, Nebere and Karanja, 2016).

In 2015, foreign nationals accounted for 13% of the UK population; 47.9% of ethnic minority groups lived in overcrowded housing (Hayward *et al.,* 2018). In UK-born TB cases, notified between 2010-2016, 33.1% of those were in the

black Caribbean ethnic group, who had at least one social risk factor - homelessness, imprisonment, drug or alcohol misuse - higher than in any other ethnic group. Evidence suggests that being socio-economically disadvantaged is likely to be an important factor in explaining the high incidence of TB in Newham.

In relation to gender, the result of this study agrees with others, with a preponderance of males in both the TB-DM (65%) and TB-only group (62%). This potentially reflects the results of smoking and alcohol consumption. Koh *et al.,* (2017) reported the synergistic effect of smoking and alcohol misuse to TB infection. The metabolism of ethanol produces acealhydehyde and or reactive oxygen species. The oxidative stress and a suppressed immune response is the suggested mechanism for the increase risk developing TB. Although this study could not find any significant difference between the two genders, it detected an increased risk of TB-DM in the case of women (P-value 0.866; CL, 0643-1.400).

Studies have shown smoking to cause increased TB disease due to the chronic exposure to cigarette smoke, which reduces the expression of surface proteins related to antigen presentation by pulmonary macrophages, a method of defence against Mtb invasion (Hayward *et al.,* 2018). This study did not find smoking to be a significant factor in TB-DM development.

Primary Objective 3

4.4 Clinical symptoms

Clinically, this study found additional co-morbid risk factors (arterial hypertension, chronic renal disorder, peripheral vascular diseases and chest) alongside DM to be significant comparing the TB-DM group and the TB-only group (p-0.007; OR, 1.0-2.6). The result also found TB-DM patients were more likely to present with fever, night sweats and weight loss than the patients in TB wrongly. Symptoms of cough and haemoptysis did not differ between patients with or without DM, a result which varies amongst previous

studies. The results of this current study can be compared to Paralija and Mujakovic' (2018), which studied the impact of DM on PTB clinical presentation. In their study, they found cough to be the most common symptom in both groups, but more so in participants with DM (P-value <0.001). 29.9% of the DM cohort had haemoptysis compared to 13.4% in the non-DM cohort (P-value <0.001), with 41.2% of DM patients having an extensive form of PTB compared to 24.8% in those without DM (P-value <0.01). This study reported comparable findings: the DM group is likely to present with more extensive clinical symptoms compared to the non-DM group. Dousa *et al.,* (2019) retrospective unmatched case-control study in a Qatar national hospital found the common presenting symptoms in TB-DM patients were cough, fever and weight loss. There are still disparities in clinical symptoms between studies regarding the exact presentation DM is likely to influence. The results from this and previous studies indicate the level of severity of symptoms overall are greater in patients with DM, and no specific symptom is more common than any other. In theory those with DM would benefit from better management of their DM during TB treatment to reduce these associated symptoms.

4.5 Glycaemia levels in TB and TB-DM cohort

DM is thought to be a risk factor for the development of active TB, especially where there is a high burden of TB. Glycaemia control is, therefore, a potential variable for modifying the risk of TB. In this study, of the 489 participants, 168 (34.35%) were DM positive, of which 3.88% were diagnosed with DM (new DM) after TB treatment. At baseline, the median HbA1c levels for the TB group without DM was 5.53% (SD +/- 1.32, range, 5-8%) compared to the TB-DM group with 7.63% (SD +/- 5.61, range, 3-13%). The 489 study participants had a follow-up after two years of completion of TB treatment, with overall incidence of DM in TB positive cases of 28.5 (95% CI; 24.3-33.0). The study reports DM to be present in 1 in 3 cases of TB, increasing the risk of active TB with poor glycaemic control. The TB-DM cohort, overall, had poor glycaemic control, ranging from hypoglycaemia to hyperglycaemia (SD +/- 5.61, range, 3-13%) (HbA1c normal with a level below 42 mmol/mol) with the

median at poorly controlled levels. In contrast, the TB without DM cohort presented more controlled glycaemic levels (SD +/- 1.32, range, 5-8%) (HbA1c diabetes with a level of > 48mmol/mol or over).

Previous observational studies have shown the risk of developing TB to be greater in patients with diabetes, to some varying degree. Lee *et al.* (2016) studied glycaemia and the risk of TB using a cohort of 123,546 participants in a community health screening service in northern Taiwan, from 2005-2008. The glycaemia amount was quantified with FPG at the time of screening. Follow-ups were obtained by the cohort until 2012 to get re-occurrence of TB. They noted that DM patients with poor glycaemic control (FPG 130 mg/dl) had a substantially higher danger of contracting TB in contrast to people without diabetes. The risk of TB in DM patients with good glycaemic control (FPG < 130 mg/dl) did not differ significantly in the non-DM patients. They estimated 7.5percent (95% CL, 4.1-11.5%) of the prevalence of TB from the analysis population could result from poor glycaemic control.

Studies on the association between TB and glycaemia control have resulted in inconclusive findings, a likely reason could be explained by the different levels of glycaemic identification, reporting and management in different study populations. Lee *et al.* (2016), used a cohort study approach to assess the association in older population in Hong Kong. They reported patients with a haemoglobin (A1c) (HbA1c) >7% units more likely to develop active TB than individuals without DM (adjusted hazard ratio (aHR) 2.56), compared to those with a controlled glycaemia level (HbA1c <7%). Baker *et al.* (2012) studied the association between TB and DM using DM-related complications as a proxy measurement for DM severity. They reported TB increased the DM severity. In a UK population-based study, a study by Pealing *et al.* (2015) investigated the association between DM and the risk of TB in a UK GP cohort to identify high-risk groups for latent TB screening (Pealing *et al.,* 2015). Using the data from the UK Clinical Practice Research Datalink, 222,731 patients with diagnosed DM between 1990-2013 and 1,218,616 control patients without DM were matched for age and gender. They found the level of HbA1c was not an associated risk of TB in the UK general practice cohort, although there are

several factors that were not adjusted for, including BMI, smoking status and alcohol use. The overall glycaemic control was good in the diabetic patients, with two-thirds of the patients having an HbA1c of < 7.5%. However, both Pealing *et al.* (2015) and this current study did not find social variables as significant risk factors.

In this study of the Newham cohort, the results evidenced a poor control of blood glucose levels to be a significant factor for TB (TB-DM). Therefore, the findings from this present study, together with previous research, suggest that a poor glycaemic control could potentially modify and increase the risk of TB among DM patients or progress the TB disease with more severe clinical outcomes. Furthermore, the current study findings concluded that glycaemia control is associated with an increase in the risk of active TB, and these findings are unlikely to be biased. This is because the distribution of all major risk factors for TB was similar in both cohorts (TB-only and TB-DM group) (good glycaemic control versus poor glycaemic control), although the possibility of confounding by other covariates not studied cannot be ruled out. Second, TB patients were likely to develop transient hyperglycaemia before receiving anti-TB treatment, which could have affected their glycaemia levels. However, all the known DM patients had their glycaemia levels measured prior to TB treatment, and the long follow-up period (two years) minimised the chance of reverse causality caused by transient hyperglycaemia. Similarly, most of the DM patients in this study had been previously known to have had DM; people with long-term DM are more likely to have poor glycaemic control than those with new onset. Therefore, the results from this study likely reflect the long-term DM condition and poor glycaemic control. Overall, the evidence from this study supports a probable causal effect of glycaemic control on the development of active TB.

Currently no one mechanism on the association between TB and DM has been documented. Laboratory studies imply that both innate and adaptive immunity are elevated in the Mtb infection as a first line defence but those with DM have an impaired function of both the innate and adaptive immune response increasing risk and progression of Mtb infection (Martinez &

Kornfeld, 2014). An improved glycaemic control is likely to restore the immune function and reverse the risk of TB. The phagocytic function is affected in DM patients with poor glycaemic control, which is significantly elevated when glycaemia control is improved. In another study granulocyte adherence was noted in patients with DM. After 1-2 weeks of being on the lowering of fasting blood sugar and diabetic treatment, with granulocyte adherence improved (Chaudhury *et al.,* 2017). Yamashiro *et al.* (2005) discovered that diabetic mice had a reduced reflection of Th-1-related cytokines in response and insulin treatment significantly enhanced the synthesis of these cytokines. Gomez *et al.* (2013) found the attachment and ingestion of Mtb in human monocytes were reduced in DM that in non-DM cases. Poorly controlled DM was a significant predictor of lower interaction between monocytes and Mtb.

This study highlights how poor glycaemic control is a major risk factor for TB, and that poorly maintained levels are likely to drive TB cases. In a modelling study by *Pan et al. (*2015) it was reported that prevention of DM could save millions of active cases of TB and TB deaths in high burden countries over the next two decades. This study supports this view; in addition to the prevention of DM, improving glycaemic control in DM patients may be beneficial in TB control in practice. The management of TB-DM should include prevention of DM through better lifestyle changes, bi-directional screening of TB and DM and early screening of DM, followed by close monitoring of glycaemic control in active TB and LTBI cases.

Furthermore, most TB-DM patients in this study were on oral metformin, which is known to provide a protective cover to the host's immune system and reduce Mtb growth and mortality rates, with a lower occurrence of cavitation in the lungs (Ayelign *et al.,* 2019). However, this study was not designed to explore the effects of metformin on survival rate, but evidence suggests those on oral DM medication with good glycaemic control had a better TB treatment outcome (Riza *et al.,* 2014). The control and management of DM would provide a better outcome of TB disease in TB-DM patients.

Secondary Objective 1

4.6 Radiological features

The findings from this study are consistent with many others, demonstrating that abnormal CXRs are more frequent in DM patients compared to non-DM patients. CXRs in the TB-DM group tended to be more abnormal than seen with classic TB features, including greater lower lobe involvement and cavitation as opposed to the common findings of segmental or lobar airspace consolidation, pulmonary infiltrates, cavitary lesions, ipsilateral hilar and mediastinal lymphadenopathy and pleural effusion (Huang *et al.,* 2017).

The result from this study indicates DM has the potential to manipulate the radiological features of PTB. This current study found a significant difference in CXR presentation between TB-DM and TB-only group. The radiological manifestations in TB-DM in those with poor glycaemic control (HbA1c >6.5%) were more likely to display cavitation.

The mechanisms underlying the atypical findings in PTB remain unclear. *In-vitro* studies utilizing hyperglycaemic mice discovered immune disorder, which is likely to impact upon TB susceptibility (Nathella *et al.,* 2017). Perez-Guzman *et al.* (2001) reported a lesser number of non-lymphocyte leukocytes were reported in DM-PTB patients, but statistically, this did not give rise to the irregular radiological findings. Furthermore, no differences in the counts in peripheral blood were seen between TB non-DM patients and the TB-DM patients. They did report an increased frequency of lung lesions in patients that were older compared to younger aged patients. They suggested a physiological dysfunction with an elevated ventilation/perfusion (V/Q) ratio and a consequent increased alveolar oxygen stress (PAO_2) which might inhibit the development of Mtb in the lower lung fields of DM patients, however the correlation between pulmonary physiological dysfunction and lower lung involvement in TB-DM patients requires further investigation.

This finding is consistent with Chiang *et al.* (2006), who studied the association between glycaemic control and radiological manifestation using CT scans of the thoracic region. They reported, statistically, a higher prevalence of abnormal findings and lesions involving all lobes of the lung in DM patients. Their study cohort included 41 PTB-DM cases with an HbA1c value >8% with an abnormal CXR. Eleven of the participants received CT scans. The scans were expected to provide a more detailed and thorough diagnostic report. However, a straightforward diagnosis of PTB by the reading physician was only made in four of the eleven patients. This suggests the limited role of thoracic CT scans in aiding the diagnosis in TB in poorly controlled DM patients. Furthermore, the findings from this study presented a greater number of EPTB to be frequent in TB-DM patients. This more probably explained as DM likely to affect the immune response to Mtb as a result more EPTB reported.

The findings from this study strengthens the argument that those with uncontrolled DM (HbA1c >6.5%) are more likely to present with cavity lesions and nodular lesions, results which are significant. In relation to pulmonary TB cases in the TB only group, they represented approximately half of the study population (47%), with 3% EPTB. This contrasts with the TB-DM cohort, where PTB contributed to 41% of the cases, with 54% EPTB. DM, therefore, is likely to influence TB dissemination, whereas in TB cases without DM, patients are likely to localize TB within the lungs. Furthermore, clinically it would be appropriate to consider TB-DM cases who present with PTB to be at risk of EPTB and vice versa, TB-DM patients who present with EPTB should be tested to exclude PTB. As part of the differential diagnosis of other lower respiratory infections, a CXR should be done even in potential patients at low or no risk of TB. A CXR should be thoroughly examined by a reading physician, considering the DM history in the diagnosis for TB. These findings, along with previous studies, suggest Mtb strains might affect the radiological presentation of PTB and may have clinical relevance.

Secondary Objective 2

4.7 Vitamin D 25(OH)D and TB

Calcitriol is an inactive form of vitamin D 25(OH)D which can induce antimicrobial activity as seen in *in-vitro* testing, and evidence suggests individuals with TB have a lower level of vitamin D 25(OH)D compared to non-TB individuals (Kota *et al.,* 2011). Similarly, the literature suggests an altered vitamin D homeostasis is likely to be vital in the development of TB, with a deficiency in vitamin D in TB-DM also likely to have adverse effects compared to TB cases without DM (Hassanein *et al.,* 2016).

In this study, the aim was to provide novel evidence for the association of 25(OH)D between TB patients with DM and those without. In the TB-only group, the median level of 25(OH)D was 25.61 ng/mL (95% CI, 15.90-35.33). In contrast, the 25(OH)D level was slightly higher in the TB-DM group (median level (26.9 ng/mL (95% CI, 19.28-34.51). This study found no statistical difference in the 25(OH)D levels between these two groups, but both were lower than the normal range.

The association between TB and DM has been demonstrated in many studies. Zhao *et al.* (2018) reported patients with TB-DM had significantly lower serum vit D levels compared to those without DM, and DM is an important independent risk factor for vit D deficiency. The data collected from 178 TB-DM patients reported 149 (84%) to have vit D deficiency (91 (51%) with vit D levels of 10-19.9 ng/ml and 58 (33%) with severe deficiency (<10 ng/ml) suggesting vitamin D is a potential mediator in the association between DM and TB; however, this is inconsistent according with these results. However, both cohorts had levels of vitamin D that are lower than normal, with only 24% in the TB-only group having levels within the normal range compared to the TB-DM group, with 31% having levels within the normal range. This is consistent with other studies. Choudhary *et al.* (2013) studied vitamin D status in patients with T2DM and PTB. The study involved 155 participants: 46 patients had T2DM, 39 were non-DM patients, 30

patients had PTB and 40 patients both PTB and T2DM. Vitamin D levels were taken from all four groups. The mean difference in vitamin D levels were not statistically significant between the groups with TB, DM, and TB-DM, but the prevalence of severe vitamin D deficiency was higher in the group with both TB-DM (45%) as compared to TB-only (26.66%) and DM (17.39%) and healthy controls (7.69%). The prevalence of severe vitamin D deficiencies with T2DM was thought to be a predisposition risk for PTB.

The findings reported by Koa *et al*. (2011) reported normal levels of vitamin D were related to better clinical outcomes for TB patients, with quicker sputum culture conversions from positive to negative, which implies vitamin D potentially plays a significant role in Mtb clearance and immune function. Severe cases of hypo-vitaminosis D have been reported to be more prevalent in diabetic patients with PTB (Wang *et al.,* 2018). Herrera *et al.* (2017) compared vitamin D and its relationship with phagocytosis of Mtb. They showed that 54% of the study population with T2DM had inadequate serum levels of vitamin D, and these results agreed with this research. Boillat-Blanco *et al.* (2016) found vitamin D was inversely associated with TB and DM, using a case-controlled approach in Dar es Salaam, Tanzania. Glycaemia and complete vitamin D 25(OH)D were quantified at enrolment. The prevalence of low 25(OH)D was similar in TB patients and controls (25.8% versus 31.0%, p=0.22). At the subgroup of patients with persistent hyperglycaemia, the percentage of individuals with low 25(OH)D tended to be greater in TB patients (50% versus 29.7%, p = 0.20). A low 25(OH)D might increase TB risk in patients with DM. Further research should investigate the association between TB-DM and vitamin D levels, its association between treatment outcome.

Future trials should inquire whether the association between TB and vitamin D levels including hyperglycaemic patients and outcome. In addition to whether therapy with vitamin D can be more beneficial in TB-DM cohorts.

Therefore, a vitamin D supplementation as adjuvant therapy in TB in selective DM patients with vitamin D deficiency is recommended: likewise, in the TB-

only group. This is to counter the inflammation-influenced hyperglycaemia (stress-induced hyperglycaemia) and is also likely to affect 25(OH)D levels (i.e. through induction of 25(OH)D metabolism or transient changes in the blood levels of proteins (vitamin D-binding protein (VDBP) bound to 25(OH)D) (Boillat-Blanco *et al.,* 2016).

4.8 HIV and TB-DM

TB is one of the leading causes of illness in HIV infected individuals living in developed countries (Restrepo and Schlesinger, 2014). The management of individuals co-infected with HIV–TB-DM is complicated regarding the underlying immune suppression, drug-drug interactions and side effects (Moneira *et al.,* 2018).

In this study, a total of 14 patients from the total study population had a co-infection with HIV, representing 2.5% of the total study population. In the TB-only cohort, eight reported co-infection with HIV, in comparison to the TB-DM cohort, where six co-infected with HIV. These were not statistically significantly different (P-value 0.479).

In a similar study by Schepis *et al.* (2017), they found both HIV and DM increased the risk of developing TB. Using a retrospective study of 2,395 patients diagnosed with TB in seven European countries, 292 (12%) were infected with HIV. The HIV-TB co-infected cohort compared to the TB-only patients were younger, more likely to be male, UK-born and to have other co-morbidities. The overall prevalence of DM among the 2,395 TB patients was 7.7%, with DM prevalence amongst TB-only patients and TB-HIV co-infected being 7.8% (164/2103) and 7.2% (21/292). No evidence of significant association was found between HIV infection and DM. In the 292 TB-HIV co-infected patients, DM was associated with cavities and night sweating, persistent cough, weight loss, haemoptysis and fever. In comparison to this study, we found TB-DM and HIV co-incidence in the study population to be 2.5%, where Schepis *et al.* (2017) reported 12.2%. However, in this study the 14 TB-HIV with DM were younger male with a median age of 41 years. No

significant association was found with HIV and DM. However, the increasing prevalence of diabetes among HIV individuals was linked to an ageing population likely to foster a recrudescence of TB-DM associated HIV.

It is known that drug-drug interactions of HIV and TB medication can be more toxic and the side-effects increased (Gengiah *et al.,* 2011). These occur because of induction or inhibition of metabolic enzymes in the liver or the intestine (Siberry *et al.,* 2013). The most prominent family of enzymes is cytochrome P450 (CYP). For example, CYP is involved in the metabolism of drugs, action includes protease inhibitors and non-nucleotide reverse transcriptase inhibitors (NNRTIs), which make up the core of most highly active antiretroviral therapy (HAART). Rifamycin is also the medication transporter P-glycoprotein from the intestinal cell wall and liver and is a powerful inducer of CYP3A4. Rifampicin is the most potent inducer of this isoform of CYP3A4 and has several interactions with anti-HIV, including, leading to a decrease in the serum concentration of drugs (Tiberi *et al.,* 2017). Rifampicin induces a broad change to gene expression and induces CYP1A2, CYP2C8, CYP2C9, CYP2E1, 2Ca9, P-glycoprotein activity and transferase enzymes. Rifabutin is a less potent inducer of CYP3A4; consequently, any CYP3A4 inhibitors increase the concentration of rifabutin, but may have no impact on rifampicin metabolism (Tiberi *et al.,* 2017). Thus, when rifabutin is administered its concentration and of its metabolism can improve its toxicity.

Although this study did not find a clear association between TB-DM and HIV probably due to low numbers of HIV cases, previous studies have shown a trilateral overlap of these three conditions. Oni *et al.* (2017) undertook a cross-sectional study in Cape Town, South Africa. They enrolled participants who were screened for DM and, using fasting plasma glucose, measured oral glucose tolerance and glycated haemoglobin (HbA1c). The study population included 414 TB and 438 non-TB patients and found DM was associated with TB (OR 2.4, 95% CI 1.3-4.3; p=0.005), and that there was an association with HIV-1 infected individuals (OR 2.4, 95% CI 1.1-5.2; p=0.030). Significant affiliation with TB (OR 2.3, 95% CI 1.6-3.3; de:<0.001) was found. The results from Oni *et al*. (2017) showed a high prevalence of impaired glucose

regulation (65.2% among TB cases) and a significant association with TB (OR 2.3, 95% CI 1.6-3.3; P-value <0.001) was found. DM was present in TB cases, and more commonly so in HIV infected patients, which further strengthens the need for screening for DM. Moriera *et al.* (2018) studied the effect of hyperglycaemia in TB-HIV patients in Brazil between 2010-2015. They used a retrospective cohort of adult patients who had TB and HIV co-infection and commenced TB treatment. with 414 euglycemic patients (87.5%), 49 with hyperglycaemia (10.3%) and 10 patients with known DM (2.1%). The DM patients were older compared to the euglycemic and hyperglycaemic patients (47.9 vs 37 vs 39.7 years, respectively, P-value 0.001). The DM patients were more likely to have cavitation in their chest x-rays compared to the hyperglycaemic and euglycemic patients (50% vs 23.4% vs. 15.2%, P-value 0.007), respectively). The hyperglycaemic patients had more new-onset of DM following the completion of TB treatment compared to the euglycemic (22 vs. 1; P-value <0.0001). Hyperglycaemia occurs more frequently in HIV infected patients who have commenced TB treatment and increases the risk of adverse TB events. In this study, due to small numbers in the HIV cohort HbA1c levels could not be compared to TB-DM cohort or TB-only cohort to investigate the association between hyperglycaemia and adverse TB events. This can be implemented in future studies.

The interplay between TB and DM in HIV infected individuals is unclear. Further research into TB-DM-HIV is required including screening for DM in patients with HIV and TB, treatment course (duration of treatment), and clinical outcome. In summary, hyperglycaemia is likely to be common and TB results are expected in HIV/TB outbreak areas.

4.9 Comparing treatment outcome between TB only and TB-DM patients

Furthermore, this study did not find DM to be negatively associated with poor TB treatment outcome, other studies reported DM to adversely affect treatment outcome (Nathella & Babu, 2017). A common reason is patient with

DM have a higher bacterial load and a dysfunctional immune system (Alisjahbana *et al.,* 2007). In this study, we found a higher bacterial load in TB-DM cohort with a longer time for sputum culture to convert from a positive to a negative, thus implying longer treatment is required in the initial intensive phase of treatment or aggressive treatment with higher dose of anti-TB therapy. Studies have shown DM to be linked to treatment failure and increase relapse including a meta-analysis which indicated a 1.7 times greater treatment failure in TB-DM patient compared to those without DM (Baker *et al.,* 2011). If the TB treatment failure is related to DM it is important to understand the mechanism for this to initiate action against the treatment failure. The common treatment of susceptible TB cases includes the use of rifampicin, isoniazid, pyrazinamide and ethambutol for first 2 months (intensive phase) then in the continuation phase using only rifampicin and isoniazid for 4 months (Alfarisi *et al.,* 2018) (see appendix 7). If it is thought that the drug concentration is lower in DM with a high HbA1c, then a treatment consisting of higher dosage is required. Furthermore, if the treatment is related to combination of variables including weight, age, glucose control then increasing the duration of treatment is likely to improve treatment outcome.

In this current study, the effect of DM on the pharmacokinetics (PK) and pharmacodynamics (PD) of anti-TB medication were not reported. Studies based on the PK and PD show inconsistent results including reporting of low serum concentration of anti-TB medication in TB-DM cohort and others show no difference (Salindri *et al.,* (2016); Viswanathan *et al.,* (2014)).

Alfarisi *et al.* (2018) used a large prospective cohort study to assess the effects of DM (HbA1c value) on first-line TB drugs PK and PD, and comparing drug dosage with clinical outcome including microbiological outcomes. Using newly diagnosed patients with TB (n=142) and TB-DM (n-101) patients on standard fixed-dose three times a week, the PK was assessed during the intensive and continuing phase. The result found a significant reduction on the maximum concentration (C_{max}) value of isoniazid and pyrazinamide but not rifampicin. After adjusting age, weight and gender DM was found to be

associated with a reduction of pyrazinamide concentration (P-value 0.03) (Alfarisi *et al.,* 2018). A higher dose of rifampicin and isoniazid was associated with a quicker culture negative time in TB-DM cohort. They found DM and a high HbA1c levels increased the risk of not achieving therapeutic target for pyrazinamide whilst DM appears to be affected the PK- PD relationship for isoniazid and rifampicin.

Although in this study the PK-PD relationship was not studied it is important to note the role of DM in reducing or slowing the absorption of anti-TB drugs. Whether the lower drug concentration is a result of confounding effect of prescribing fixed drugs opposed to adjusting for weight. DM is known to affects P-glycoprotein transporter expression and activity, likely to affect TB drug absorption. If patients with TB-DM are to receive a higher dosage of anti-TB drugs the outcome remains unknown and further investigation is required. However, ensuring an adequate therapeutic dosage is important including in DM cases. As a result, therapeutic dose monitoring is essential in patients with DM as well as HIV and any co-morbid factors which may influence absorption or any medication likely to interact with TB medication (see appendix 5). Further to this quality improvement study, a further study has been approved to assess the therapeutic dosing of TB medication for patients with DM and ensuring it remains within the therapeutic range.

Secondary Objective 3

4.10 Microbiology

Sputum conversion is a method which acts as an indicator of pulmonary TB treatment efficacy (Restrepo & Schlesinger, 2014). An early conversion is important to help prevent the transmission of infectious TB bacilli, reduce hospitalisation and the cost related to infection prevention and control. A delayed sputum conversion is also suggestive of drug resistance (Takasaki *et al.,* 2018; Shariff a& Safian, 2015).

In this study, the findings revealed a significant difference in conversion time of sputum and AFB density (P-value <0.001). TB-DM conversion was slower in the intensive phase of the treatment compared to TB without DM. DM was associated with a delayed sputum conversion, which likely affects treatment outcome. The results found a higher initial sputum AFB smear grading among patients with TB and DM alongside the delayed sputum culture conversion within the intensive phase of anti-TB treatment. These findings reflect those of Dousa *et al.* (2018), who compared the impact of DM on the clinical and radiographic presentation of PTB and bacteriologic response during anti-TB treatment between 2008 to 2011, in a retrospective case-control study from a large national hospital from a total study population of 134 adults with TB and DM. They found patients with DM had a higher initial sputum AFB smear grade and were less likely to have cavity lesions on initial chest radiographs compared to patients without DM. They found 71 (53%) cases from the study population remained sputum culture-positive after two months of anti-TB treatment compared to 36 (27%) patients without DM. Ratnawati *et al.* (2019) studied the association between HbA1c levels and TB to determine the impact of HbA1c levels on sputum conversion time in Indonesian patients with PTB. They included only adults (>15 years) with no previous DM diagnosis. This was a prospective cohort study of new PTB cases, with a study population of 123 new PTB patients, which found 12 patients had HbA1c levels >47.5 mmol/mol. More than half (56.1%) of the patients had smear-positive AFB and 11 patients (8.9%) remained AFB smear-positive after two months of being on anti-TB treatment. Statistically, there was a significant association between HbA1c levels >47.5 mmol/mol and sputum conversion for more than two months, with a relative risk of 6.3 (1.9-396), P-value 0.01).

The findings from the current study agree with previous studies showing that an increase in HbA1c levels is likely to affect the risk of sputum smear conversion failure. In relation to bacterial load, this study reported a significant difference in bacterial load through AFB density between the TB-DM and the TB without DM groups. The TB-DM group had a higher grade of AFB 1, 2 and 3 compared to the TB without DM, who were AFB (+/-), and scanty growth was more likely to be observed.

Bouti *et al.* (2013) studied the factors influencing sputum conversion time in a Moroccan population. Findings reported AFB 1+ sputum smear on eight patients (6.7%), AFB 2+ sputum smear in 19 patients (16%), AFB 3+ sputum smear in 37 patients (31.1%) and AFB 4+ sputum smear in 55 patients (46.2%), with approximately 96.6% conversion within eight weeks. This study found that TB patients with an HbA1c level of 6.5% had a higher risk of sputum conversion time of > 2 months compared to those with HbA1c levels less than 6.5%. The results of this study are consistent with the previous studies, including that by Kulsum *et al.* (2017), which found high HbA1c levels among T2DM patients increased (by two or three times) the risk of sputum smear conversion failure. Despite all this evidence, the possible association of DM to prolonged sputum conversion remains conflicting. The effect of controlling HbA1c levels using medical intervention in the improvement of sputum conversion times is still not fully understood.

The Kaplan Meier curve for culture conversion indicates TB-DM patients have a higher TB bacillary count and are more infectious within two months of the intensive treatment phase, as culture conversion is slower. The findings demonstrate a higher bacillary load in the presence of DM, rendering the TB-DM cohort more infectious. Viswanathan et al. (2014) assessed the effect of DM on TB treatment outcome and sputum conversion using a population sample of 245. They found the overall treatment success to be 93.5%; at the end of the intensive phase of treatment, 14.7% remained sputum-positive in the TB-DM group (64.2 +/- 10.5) compared to 3.5% in the TB only group (61.5 +/- 7.5) (P-value <0.001).

Sputum smear conversion after two months of anti-TB intensive treatment is an important determinant of treatment success: a predictor for relapse and the infectivity of the disease. A total of 89% (30 time to culture conversion 95% CI; 8.211-23.789) had culture conversion in the TB-only group compared to 85% (40 time to culture conversion 95% CI; 8.54-51.45) in the TB-DM cohort by the end of two months TB treatment. Findings from this study show that

DM was statistically significant (P-value <0.001) and impacts on the patient's sputum smear conversion after two months of anti-TB treatment.

Future studies should compare the benefits of longer treatment courses for the TB-DM cohort. Holtz *et al.* (2006) found that treatment outcomes were statistically significantly worse for patients who did not convert their sputum positivity within two months of treatment. The cure rate was higher among patients who were smear-negative at the second month of follow-up.

In addition, TB-DM patients with poor adherence are at more risk of sputum non-conversion compared to those adhering to medication and those without DM. This is supported by Burman *et al.* (2018). In their study, they found patients who took treatment irregularly were 9.9 times more likely to have a relapse than those who were adhering to treatment.

Sputum culture conversion is also used routinely as an indicator of the progress of treatment of TB (Akalu, Muchie & Gelaye, 2018). The results confirmed that sputum culture conversion is a useful interim indicator of treatment outcome for individuals with TB and that it is an appropriate first goal of therapy. The results support the literature which states that those individuals who achieved early sputum culture conversion were more likely to have a successful treatment outcome. The results demonstrate how a better control of glycaemia levels is more likely to increase sputum conversion to negative within the intensive phase, which, in turn, increases better treatment outcome (end of intensive treatment phase, time to culture conversion, median, days, TB non-DM 30 (95% CL, 3.9-36.01) vs TB-DM 40 (95% CI, 8.54-51.45).

4.11 Confounding variables

Confounding influences occur when a risk factor is associated with both the comparison variable and the outcome of interest. In this study, age and gender was considered as a key confounder as active TB is evidently higher in the male population and DM is related to older age. The risk of developing active TB is related to exogenous and endogenous risk factors. Exogenous

risk factors imply the progression from exposure to infection, where those with high bacillary load in the sputum and the proximity of individuals are key risk factors for development of infection (McDonald, 2014). Endogenous factors lead to the progression from infection to active TB and well-established risk factors include HIV, malnutrition, age, and gender.

Confounding refers to a situation when one finds a spurious association or missed a true association between an exposure variable and an outcome variable, because of a third factor (McDonald, 2014). A confounding variable is a factor associated with both the exposure variable and the outcome variables. In observational research, confounding is an intrinsic limitation. To identify a confounder, the usual method is to check for a potential confounding factor is, first, to find out if the assumed confounding factor is associated with both the outcome variable and exposure variable, and secondly, to compare the associations before and after adjusting for the confounding factor. In this study, the confounding variables were considered at the analysis stage and this could have been tackled using either a stratification method or a multivariate approach (McNamara & Martin, 2018).

Multivariate analysis was considered over stratification, as the stratification method is effective when dealing with dichotomous confounding variables as the data can be separated into 2 or more distinct strata sets. Stratification is more difficult to achieve in continuous datasets, such as age, therefore, the adjustment for confounding factors would not reliably remove the confounding effect of that variable (McNamara & Martin, 2018). Furthermore, there may be residual confounding when there are relatively few strata of continuous variables (i.e. in this study age was stratified into 2 strata: <55 yr and > 50 yr). Using a stratification method, this could be improved by increasing the number of age strata; however, this then would have required to inflate the number of observations in each stratum. The major disadvantage of this approach of stratification is the inability to deal with multiple confounding factors simultaneously.

The multivariate analysis estimates the association between several independent variables (potential risk factors) and 1 dependent variables (outcome; TB-DM). This method was implemented as it utilises all study data and examines multiple variables, both continuous and dichotomous. It allows the estimation of the effect of an exposure variable on a given outcome variable, after controlling for the confounding effect of other included variables (e.g. age and gender) (McNamara & Martin, 2018).

4.12 Clinical recommendations

To manage TB and DM in tandem, the detection of both is necessary. As this study has reported, the prevalence of DM among TB patients is over 25%, with those who are older more likely to be susceptible to a TB-DM coexisting condition. Therefore, screening for DM in TB patients is necessary, although not straightforward as different measurements are used. This study used HbA1c but HbA1c requires further evaluation in different settings and patient populations. In general, point of care HbA1c in combination with age and high-risk groups (non-UK born) is an approach which is sensible.

Using 2018 national data on TB and DM rates, the yield of TB screening among patients with DM is low. The prevalence in England for DM is < 25 per 100,000 (PHE, 2018), which would mean at least 1000 people with DM would need to be required to be screened to detect a single case of TB. By using a risk stratification approach (history of TB, smoking, socio-economic variables, severity of symptoms, ethnic background) could help to prioritise a subgroup of DM patients for TB screening.

Screening and treatment of LTBI have been recommended, aimed at high-risk groups of developing active TB disease, like HIV infected individuals including those between the age of 16 to 35 years old who have recently arrived in England from high incidence countries, where TB incidence is 150 per 100,000 population or over (PHE, 2015. Latent TB testing and treatment for non-UK born. A practical guide for commissioners and practitioners). Applying this approach to TB-DM theoretically is likely to help drive the elimination of

TB, especially if it is targeted where a high proportion of TB cases arise from reactivation among non-UK born individuals with DM and an increasing age for screening. As observed in this study, this group is likely to be an appropriate population as a focus for LTBI screening. Currently, there is no evidence that LTBI screening is effective in reducing TB burden among DM patients, as no studies have been conducted.

Furthermore, in this current study, the TB-DM patients were found to have higher initial cavities and residual lesions of the lung, which are all risk factors for prolonged time-to-smear conversion. The results from this current study will help to improve the planning and implementation of TB treatment courses and their length and overcome the delay in sputum conversion or in prolonging a treatment course. Therefore, early recognition and diagnosis of TB-DM can provide clinicians with the opportunity to identify patients who may benefit from a more thorough investigation, aggressive therapy and management of both TB and DM, including accelerated testing procedures, and timely utilization of behavioural therapies for treatment compliance. Frequent observation of sputum cultures in patients with risk of late sputum conversion will help to manage treatments in TB-DM cases and reduce the risk of infection to others. Reducing the time to sputum culture conversion is an important infection control measure, because individuals with TB and positive sputum cultures are infectious and likely to transmit the disease to other individuals (Restrepo & Schlesinger, 2014).

All TB patients should be screened for DM routinely as is currently undertaken with HIV patients. Such screening would likely yield new undiagnosed individuals with DM, which will allow them to be referred to specialists for care to manage their DM, leading to increased TB treatment success.

The timing of screening is essential; it is predicted that blood glucose can be affected by TB (stress-related hyperglycaemia). However, glycosylated haemoglobin is less affected than fasting blood glucose. Screening for DM at the time of diagnosis of TB is likely to be positive for stress-related hyperglycaemia, which creates unnecessary referrals and anxiety for patients.

Screening later, after initial TB treatment, is a possibility, but this would miss early intervention, which is critical considering the evidence in literature review that DM increases the risk of early TB and the mortality rate. However, transient hyperglycaemia may require treatment to increase better TB outcomes. Screening at the time of diagnosis is preferable as patients are still available at the healthcare setting and early diagnosis of DM and initial care can result in better outcomes.

DM can also be screened during the TB intensive treatment phase (2-8 weeks), by which time the stress-related hyperglycaemia would have receded and a more accurate DM diagnosis can be made, which reduces the likelihood of false-positive results.

Screening for DM can be offered at the end of the TB continuation treatment phase. This would provide an accurate result and reduce false-positive results to almost zero. But a late DM diagnosis would negatively affect the improving TB treatment outcome.

Those TB cases with transient hyperglycaemia should be re-tested at the end of TB treatment. This would ensure a more accurate diagnosis of DM. It is also likely those TB patients with transient hyperglycaemia to revert to normal levels after TB treatment, but there is a risk of developing future DM, and this should be emphasised to encourage a healthier lifestyle to reduce the future risk of DM through dietary changes, increased physical activity, smoking cessation and reduced alcohol intake.

If a patient is diagnosed with DM at the time of TB diagnosis, they should be managed by the TB clinic (with specialist advice, if required) for at least the first two weeks of TB treatment and until the end of the initial intensive treatment phase. This will ensure the patient is no longer infectious by the time the patient returns to the endocrinology clinic. If the patient has severe hyperglycaemia symptoms with an HbA1c >10%, urgent specialist care will be required.

During TB treatment in DM patient regular dosing to ensure therapeutic levels are achieved as DM directly affects absorption of TB drugs or indirectly through drug-drug interaction causing suboptimal therapeutic levels increasing risk of treatment failure, developing drug resistance and relapse. Target level to be achieved between 9-24 mg/L. A sub therapeutic level is <4 mg/L, where a change of dosage is necessary. Dose levels should be checked 6 hours' post dose in DM patients (see appendix 5).

4.13 The current TB clinical policy and change in practice

The current TB clinical policy supports the implementation of the Collaborative Tuberculosis Strategy for England: 2015 to 2020 to achieve year-on-year reductions in TB incidence and eventual elimination of TB and incorporated NICE Guidelines, NG33, Tuberculosis, 2016.

This study reported risk factors such as symptoms based on clinical notes, which were reported at the time of diagnosis, without a formal template of diagnostic criteria. There could be methodological challenges including the practitioner not accurately documenting symptoms, and a prospective study using a strict criterion for TB and DM assessment would avoid this issue and provide assurance. Furthermore, this study used a single HbA1c reading around the time of diagnosis, a measurement which might mis-classify individuals as either DM or non-DM patients. Future studies should include a DM diagnosis which is confirmed with a repeat HbA1c test unless clinical symptoms and plasma glucose levels >11.1 mmol/1 (22 mg/dl) are present during treatment course. In addition, adjustment for potential confounders is also a limitation. In this study, gender and age were adjusted for estimates. Further adjustments including smoking, drinking, imprisonment is likely to provide a stringer estimate than those controlled for age and gender alone McNamara & Martin, 2018). Furthermore, biased estimates were likely to be associated with those with renal impairment and all co-morbidities should be separately calculated or use Charlson Comorbidity Index (CCI). Current scoping work being conducted with Endocrinologists at Barts Health NHS Trust to identify a prospective study for a bi-directional screening study is

underway. In addition, a current change in practice to routinely send for HbA1c testing prior to commencing of TB treatment should be instigated.

DM can affect TB clinical and treatment outcomes, but it can also interact with TB transmission, TB acquisition, TB reactivation in those latently infected (Awad *et al,* 2019). In addition. The type of DM may have different outcomes, in this study DM included T1DM and T2DM, thereby limiting our ability to assess the association of DM types.

Furthermore, the optimum treatment strategy for concurrent TB and DM remains unknown. In general, patients with TB and DM are not treated differently to those with TB only, in practice. However, evidence from the literature shows an increase in rate of TB treatment failure in patients with DM due to excessive TB (Pizzol *et al.,* 2016), although not reported in this study. There are still uncertainties in the optimal DM treatment in TB-DM cases, including avoiding sulphonylurea derivatives and treating DM with diet, lifestyle changes, metformins and insulin. A successful treatment can only be achieved by ensuring good compliance to treatment for both TB and DM.

Currently, there is insufficient evidence to support changing the recommended TB standard treatment to one specific for clinical management of TB-DM cases. According to WHO (2011), the TB treatment regimen to be prescribed is the same as for patients without DM, whilst it is vital to provide clinical management of DM in TB patients for individuals with poor glucose control. There are no randomised trials which evaluate an adequate TB-DM treatment regimen, neither is there enough evidence on drug-drug and drug-disease interactions in TB-DM patients to provide specific guidance.

An optimal TB-DM management and integration of services could lead to the earlier commencing of treatment for DM, and improved health outcomes for those with co-existing conditions (Zheng *et al.,* 2017). Prospective studies specifically designed to address the differences between DM and non–DM TB patients and the interactions of drug-disease and drug-drug in TB and DM would be vital.

Further studies assessing TB treatment compliance and DM diagnosis in TB patients are required. A prospective cohort study design would be beneficial and enable a reduction in bias by implementing randomisation sampling techniques to manage cofounding variables. Utilisation of pre-questionnaires to be used by clinicians to record patient responses to treatment, assessment of clinical signs and symptoms, body weight to improve data reporting and regular follow-up sputum smears during the treatment course introduced. As a clinical change to practice, therapeutic dose monitoring in high risk groups have been recommended including DM as routine practice (see appendix 4).

Future studies should focus on measuring the effects of DM in patients with TB and investigate the association with treatment outcome, through potential effects on treatment compliance. Drug-drug interactions, drug side effects, glycaemic control, weight gains during treatment and patient cell-mediated immune responses need to be assessed. This should be a prospective cohort study using a multi-centre approach. Participants should include all new cases commencing a TB treatment regime and should be followed-up each month until treatment completion. At the end of TB treatment, follow-up for a further two years at six-monthly intervals for assessments of lung function and recurrent TB should be included. Participants should also provide regular blood samples for HbA1c measurement, as a marker for glucose dysregulation and probable DM. At baseline, participants should provide a venous blood sample, to assess immune responses to TB. At the end of the treatment, participants should be assessed for lung function using spirometry at 6-month intervals. This will allow measurement of adverse treatment outcomes including relapse and recurrent active TB.

For development of policy/clinical guidelines, glycaemia levels require further assessment, as it is likely that DM could present at any time during treatment for TB. Thus, HbA1c testing at more time points or following recognised treatment for DM should be undertaken (Sherwani *et al.,* 2016). An exploratory analysis will need to be performed to assess the effect of degree of hyperglycaemia during treatment on TB patient outcomes. From this

current study, improvements in clinical management have been suggested and have been implemented locally, including routine testing for HbA1c on TB diagnosis and a new Trust TB policy recognising DM as a formal risk factor with greater emphasis on management of DM in TB patients. A further quality improvement project on monitoring TB treatment dosage in high risk groups has been implemented to provide a better outcome in at risk groups, this includes DM. Future work for bi-directional screening have been suggested, with endocrinologists to contribute to further study of the association between TB and DM (table 4.1).

Table 4.1 Current practice, change in practice, and future studies in treatment of TB-DM patients			
	Current Practice	**Change in practice & policy**	**Future studies**
Risk factors	Main risk factor for active TB in the UK: Place and date of birth Caucasian population; increasing prevalence with age Afro-Caribbean, non-UK born; highest prevalence in the young, Indian subcontinent; highest prevalence in middle age HIV/AIDS Heavy alcohol consumption and smoking Medical factors – DM, end-stage renal failure, malignant disease, systemic chemotherapy, steroids and TNF-α antagonists, e.g. infliximab, vitamin D deficiency	DM in TB patients is a major risk factor, as is HIV. This is now in the Trust reviewed TB policy, which was introduced post this work.	Routine bi-directional screening. HbA1c testing for all TB patients, especially in high prevalence populations (appendix 6).

Diagnosis	The diagnosis is usually made in one of three ways: smear or culture of sputum or histology with identification of caseation granulomas. Individuals suspected to have active TB should be referred for a medical assessment this includes: Medical history Physical examination Chest x-ray Appropriate laboratory tests Diagnostics of TB includes sputum smear and culture microbiology and chest x-rays to aid TB diagnosis where high clinical suspicion. If a person does not have signs of active TB, a Mantoux test or an IGRA test can be used to diagnose latent TB. Although in patients with HIV or	HbA1c to be included into the battery of samples taken undertaken at time of TB diagnosis or commencement of TB medication. Logistically screening for DM in TB patients should be done at time of diagnosis or commencing of TB medication. Evaluation of dose monitoring of TB medication in DM patients.	A bi-directional screening programme to be investigated. This is to assess specific subset of DM patients for possible TB.

	immune-suppressive condition specialist advice should be sought i.e. HIV specialist. Nucleic acid amplification techniques using Xpert MTV/RIF assay to detect MTB and identify rifampicin resistance and WHO recommends the use of this in areas with high rates of HIV. Furthermore, blood tests include FBC, liver function tests, urea, electrolytes and creatinine, HIV and HCV and vitamin D. In HIV patient tuberculin skin test, maybe falsely negative and radiological changes may be atypical. WHO guidelines recommend isoniazid chemoprophylaxis for HIV-infected patients, with positive or unknown skin tests in the absence of active TB disease. Other tests include bronchoscopy, biopsy from extra pulmonary sites, gastric washings, urine, CT scans, bloods, and HIV test for all patients.		

Microbiology testing	Microscopy for AFB Mycobacterial culture on solid or liquid media Antimicrobial susceptibility testing of TB complex Direct molecular testing of clinical samples by PCR for TB complex and resistance to rifampicin such as Cepheid's GeneXpert. Genotypic identification of isolates from culture Whole genome sequencing for speciation	TB-DM to be tested for MTB/ Rif for resistant TB. Evaluating use of WGS in testing sensitivity for TB.	
Referral	Local referral can be made to TB services from primary and secondary care, All patients with suspected TB should be referred to TB services and must be seen within two weeks of referral being made. In urgent PTB patient should be seen within two working days of referral.		All TB cases with a DM diagnosis should be referred to a specialist secondary cases. If DM is identified in TB patients, referral

			to endocrinology specialist.

4.14 External validity

This refers to the generalisability of the study findings to the general population (Kukull & Ganguli, 2012). Although some limitations were found, the internal validity is adequate, which is a prerequisite for external validity. Results from the laboratory were quality-assured and all clinical details, including treatment, were approved by trained physicians. The conclusions of the study can be generalised to both the London population and England, more widely.

4.15 Limitations of the study

This was a retrospective cross-sectional study approach so the non-availability of data in some instances is a limitation; currently, there is no mandatory surveillance database for reporting DM in TB cases. A prospective cohort study would improve this but would fall to similar limitation including patients not attending appointments.

Although each culture-positive sample was tested for Mtb, this study did not determine the cluster outbreaks which would have provided further insight into the transmission of TB or a reoccurrence in individuals. Future studies should incorporate strain-typing results to identify clusters.

There is the potential for misclassification of DM within the study, as routinely collected clinical data without validation; this includes hospital and primary care correspondence. It is likely that misclassification was minimal as DM is an indicator condition within UK primary and tertiary care; therefore, practices have incentives to maintain accurate diabetes patient registers.

The retrospective nature of the study cannot control exposure and relies on accurate recordings; therefore, some cases of primary care may have been omitted, especially around DM care or any pre-diabetes risk factor which can be managed by a primary care physician. The data on social risk factors,

including alcohol intake and cigarette smoking, was based on data entries entered by the TB nurses into the London TB Register and, potentially, some may have been omitted or patients not declaring certain data. To overcome this, it would require working with other professionals i.e. for alcoholic abuse likely to receive input from alcohol liaison team, to gain accurate information.

4.16 Future research recommendations

Future investigations should focus on clinical trials to examine the benefit of prolonged or intensified TB treatment for TB-DM patients, and clinically relevant interventions with respect to the management of cardiovascular risk, optimal timing and dosages.

An investigation into mathematical and economic models to estimate the costs and potential impact of different interventions, i.e. screening TB patients for DM and vice versa, intensified treatment and treating of LTBI, should be undertaken.

Future studies should consider reviewing the treatment guidelines by incorporating bidirectional screening and the cost-effectiveness of treating patients with TB and DM. Future research should examine TB cases nationally; in this research, there was no difference in outcomes on death, relapse or reinfection, which was expected as the patients were recruited from one main centre. Future investigations should focus on clinical management and clinical trials to examine the benefit of prolonged or intensified TB treatment for TB-DM patients, and clinically relevant interventions with respect to the management of cardiovascular risk, optimal timing and methods of screening for DM across different ethnic groups.

4.17 Conclusion

Currently, there are no national figures for the prevalence of TB-DM, and this is the first study to make an estimate of the number of TB-DM patients in a high TB burden area and to focus on risk factors and clinical characteristics.

In 2018, the population of Newham was 352,005, with a large proportion of the adult population from the Black and Asian minority ethnic community (BAME) (70%), followed by White British (15%) and White Other (14%). Eight percent of the population over the age of 18 years are recorded to have DM compared to England's average of 6.4% (Newham Adult JSNA 2019). It is estimated that 78% of the diabetic population has been diagnosed by primary care and about 7,000 individuals are living with undiagnosed DM in the Borough of Newham. 33,000 individuals are expected to live with non-diabetic hyperglycaemia, and this is likely to influence the DM prevalence rising to 12,000 from 8,000 over the next 10-15 years. The rate of TB in Newham remains around 47 per 100,000 population (PHE, 2018) compared to England's average of 9.2 per 100,000 (PHE, 2018). The prevalence of TB-DM in Newham is 28.5 per 100,000. Therefore, introducing DM screening in TB patients, monitoring of TB drug levels in DM patients, screening of HbA1c prior to Tb treatment, these measures to increase better TB treatment response and clinical outcome, especially in a high incidence population of Newham.

References

A, Soh., C, Chee., Y, Wang., J, Yuan., & Koh. (2017). Dietary Intake of Antioxidant Vitamins and Carotenoids and Risk of Developing Active Tuberculosis in a Prospective Population-Based Cohort Study, *American Journal of Epidemiology*, 186(4), 491–500. https://doi.org/10.1093/aje/kwx132.

Abakay, O., Abakay, A., Sen, HS., & Tanrikulu, AC. (2015). The relationship between inflammatory marker levels and pulmonary tuberculosis severity. *Inflammation,* 8:691–696. doi: 10.1007/s10753-014-9978-y.

Abarca, B., Pell, C., Bueno, C., A., Guillén J., Pool, R., & Roura, M. (2013). Tuberculosis in migrant populations. A systematic review of the qualitative literature. *PloS one*, *8*(12), e82440. doi:10.1371/journal.pone.0082440.

Afzal, A., Rathore, R., Butt, N. F., & Randhawa, F. A. (2018). Efficacy of Vitamin D supplementation in achieving an early Sputum Conversion in Smear positive Pulmonary Tuberculosis. *Pakistan Journal of Medical Sciences*, *34*(4), 849–854. doi:10.12669/pjms.344.14397.

Akalu, Y., Muchie, T., & Gelaye, AK. (2018). Time to sputum culture conversion and its determinants among Multi-drug resistant Tuberculosis patients at public hospitals of the Amhara Regional State: A multicenter retrospective follow up study. *PLoS One*, 2018;13(6): e0199320. doi: 10.1371/journal.pone.0199320.

Alfarisi, O., Mave, V., Gaikwad, S., Sahasrabudhe, T., Ramachandran, G., Kumar, H., & Dooley, K. (2018). Effect of Diabetes Mellitus on the Pharmacokinetics and Pharmacodynamics of Tuberculosis Treatment. *Antimicrobial Agents and Chemotherapy*. 62 (11). e01383-18; DOI: 10.1128/AAC.01383-18.

Alisjahbana B, Sahiratmadja E, & Nelwan EJ. (2007). The effect of type 2 diabetes mellitus on the presentation and treatment response of pulmonary tuberculosis. *Clin Infect Dis*. 2007;45(4):428-435. doi:10.1086/51984.

Alisjahbana, B., Riza, A.L., Pearson, F., Ugarte-Gil, C., , Vijver, S. van de, Panduru, N.M., Hill, P.C., Ruslami, R., Moore, D., Aarnoutse, R., Critchley, J.A., Crevel,. & R. van. (2014). Clinical management of concurrent diabetes and tuberculosis and the implications for patient services. *Lancet Diabetes & Endocrinology*. 2, 740 - 753. doi.org/10.1016/s2213-8587(14)70110-x.

Alisjahbana, B., Sahiratmadja, E., Nelwan, EJ., Purwa, AM., Ahmad, Y., Ottenhoff, TH., Nelwan, RH., Parwati, I., van der Meer, JW., & van Crevel, R. (2007). The effect of type 2 diabetes mellitus on the presentation and treatment response of pulmonary tuberculosis. *Clin Infect Dis.* 45(4):428-35. doi: 10.1086/519841.

Althubaiti A. (2016). Information bias in health research: definition, pitfalls, and adjustment methods. *Journal of multidisciplinary healthcare*, *9*, 211–217. doi:10.2147/JMDH.S104807.

American Diabetes Association. (2009). Diabetes. Retrieved from https://www.diabetes.org/diabetes.

Amin, AG., De, P., Spencer, JS., Brennan, PJ., Daum, J., Andre, BG., & Chatterjee, D. (2018). Detection of lipoarabinomannan in urine and serum of HIV-positive and HIV-negative TB suspects using an improved capture-enzyme linked immuno absorbent assay and gas chromatography/mass spectrometry. *Tuberculosis (Edinb).* 11, 178-187. doi: 10.1016/j.tube.2018.06.004. Epub 2018 Jun 6.

Anderson, SR., Maguire, H., & Carless, J. (2007). Tuberculosis in London: a decade and a half of no decline. *Thorax.* 62:162-167.

Appleton, SC., Connell, DW., Singanayagam, A., Bradley, P., Pan, D., Sanderson, F., & Kon, O. (2017). Evaluation of prediagnosis emergency department presentations in patients with active tuberculosis: the role of chest radiography, risk factors and symptoms. *BMJ open respiratory research*, *4*(1), e000154. doi:10.1136/bmjresp-2016-000154.

Asante-Poku, A., Asare, P., Baddoo, NA., Forson, A., Klevor, P., Otchere, ID., & Yeboah-Manu, D. (2019). TB-diabetes co-morbidity in Ghana: The importance of Mycobacterium africanum infection. *PLoS One*, 14(2). e0211822. doi: 10.1371/journal.pone.0211822.

Aston-Mansfeild. (2017). Newham Key Statistics: 2017. Retrieved from https://www.aston-mansfield.org.uk/wp-content/themes/aston_mansfield/uploads/Newham_Statistics_2017.pdf.

Awad, S. F., Huangfu, P., Ayoub, H. H., Pearson, F., Dargham, S. R., Critchley, J. A., & Abu-Raddad, L. J. (2019). Forecasting the impact of diabetes mellitus on tuberculosis disease incidence and mortality in India. *Journal of global health*, *9*(2), 020415. https://doi.org/10.7189/jogh.09.020415.

Ayelign, B., Negash, M., Genetu, M., Wondmagegn, T., & Shibabaw, T. (2019). Immunological Impacts of Diabetes on the Susceptibility of Mycobacterium tuberculosis. *J Immunol Res*. doi: 10.1155/2019/6196532.

Back, SH & Kaufman, RJ. (2012). Endoplasmic reticulum stress and type 2 diabetes. *Annu. Rev. Biochem*, 81:767–793. doi: 10.1146/annurev-biochem-072909-095555.

Badawi, A., Sayegh, S., Sallam, M., Sadoun, E., Al-Thani, M., Alam, M. W., & Arora, P. (2014). The global relationship between the prevalence of diabetes mellitus and incidence of tuberculosis: 2000-2012. *Global journal of health science*, *7*(2), 183–191. doi:10.5539/gjhs.v7n2p183.

Baghaei, P., Marjani, M., Javanmard, P., Tabarsi, P., & Masjedi, MR. (2013) Diabetes mellitus and tuberculosis facts and controversies. *J Diabetes Metab Disord*. 12(1):58. doi: 10.1186/2251-6581-12-58. PubMed PMID: 24360398; PubMed Central PMCID: PMC3922915.

Baker, M. A., Harries, A. D., Jeon, C. Y., Hart, J. E., Kapur, A., Lönnroth, K., Ottmani, S. E., Goonesekera, S. D., & Murray, M. B. (2011). The impact of diabetes on tuberculosis treatment outcomes: a systematic review. *BMC medicine*, *9*, 81. https://doi.org/10.1186/1741-7015-9-81.

Baker, MA., Lin, HH., Chang, HY., & Murray, MB. (2012). The risk of tuberculosis disease among persons with diabetes mellitus: a prospective cohort study. *Clin Infect Dis*. 54(6):818-825. doi:10.1093/cid/cir939.

Banurekha, V., Bhatnagar, T., Savithri, S., Kumar, N. D., Kangusamy, B., & Mehendale, S. (2017). Sputum Conversion and Treatment Success among Tuberculosis Patients with Diabetes Treated under the Tuberculosis Control Programme in an Urban Setting in South India. *Indian journal of community medicine: official publication of Indian Association of Preventive & Social Medicine*, *42*(3), 180–182. doi:10.4103/ijcm.IJCM_179_16.

Barron, S., Swift, E., & Chantrey, J. (2018). A study of tuberculosis in road traffic-killed badgers on the edge of the British bovine TB epidemic area. *Sci Rep* 8, 17206. doi:10.1038/s41598-018-35652-5.

Barss, L., Orlikoe, E., Phang, S., Ainslie, M., & Fisher, D. (2014). Clinical implications of diabetes mellitus in adults with TB: risk for poor outcomes and mortality. Chest Infections Tuberculosis. 150 (4).

Benoit, SR., Gregg, EW., Jonnalagadda, S., Phares, CR., Zhou, W., & Painter, JA. (2017). Association of Diabetes and Tuberculosis Disease among US-Bound Adult Refugees, 2009-2014. *Emerg Infect Dis*. 23(3):543-545. doi:10.3201/eid2303.161053.

Berry, MP., Graham, CM., McNab, FW., Xu, Z., Bloch, SA., Oni, T., & O'Garra, A. (2010). An interferon-inducible neutrophil-driven blood transcriptional signature in human tuberculosis. *Nature*, *466*(7309), 973–977. doi:10.1038/nature09247.

Bhalla, AS., Goyal, A., Guleria, R., & Gupta, A. K. (2015). Chest tuberculosis: Radiological review and imaging recommendations. *The Indian journal of radiology & imaging*, *25*(3), 213–225. doi:10.4103/0971-3026.161431.

Bhatti ,N., Law, MR., Morris, JK., Halliday, R., & Moore-Gillon, J. (1995). Increasing incidence of tuberculosis in England and Wales: a study of likely causes. *BMJ.* 310: 967-969.

Boillat-Blanco, N., Ramaiya, KL., Mganga, M., Minja, LT., Bovet, P., Schindler, C., V., & Probst-Hensch, N. (2015) Transient Hyperglycemia in Patients With Tuberculosis in Tanzania: Implications for Diabetes Screening Algorithms. *J Infect Dis.* 213(7):1163-72. doi: 10.1093/infdis/jiv568.

Bothamley G. (2001). Drug treatment for tuberculosis during pregnancy: safety considerations. 24(7):553-65. doi: 10.2165/00002018-200124070-00006.

Bouti, K., Aharmim, M., & Marc, K. (2013). Factors Influencing Sputum Conversion among Smear-Positive Pulmonary Tuberculosis Patients in Morocco. *ISRN Pulmonology.* https://doi.org/10.1155/2013/486507.

Breathnach, AS., de Ruiter, A., & Holdsworth GMC. (1998). An outbreak of multi-drug resistant tuberculosis in a London teaching hospital. *Journal of Hospital Infection*, 39: 111-117.

Brennan, PJ. (2003) Structure, function, and biogenesis of the cell wall of Mycobacterium tuberculosis. *Tuberculosis (Edinb*). 83(1-3), pp. 91-7.

Brewer,TF., & Corditz, GA. (1995). Bacille-Calmette-Guerin vaccination for the prevention of tuberculosis in healthcare workers. *Clinical Infectious Diseases*. 20: 136-142.

Bridson, T., Matthiesson, A., Owens, L., Govan, B., Norton, R., & Ketheesan, N. (2015). Diabetes: A Contributor to Tuberculosis in Tropical Australia. *Am J Trop Med Hyg*. 93(3):547-548. doi:10.4269/ajtmh.15-0264.

Bruchfeld, J., Correia-Neves, M., & Källenius, G. (2015). Tuberculosis and HIV Coinfection. *Cold Spring Harbor perspectives in medicine*, *5*(7), a017871. doi:10.1101/cshperspect.a017871.

Burman, M., Loutet, M., Trathan, D., Dart, S., Jayasekera, N., Tiberi, S., Kunst, H., & Zenner, D. (2016). Cohort analysis of a large community-based latent tuberculosis screening and treatment programme in a high incidence setting in East London. *European Respiratory Journal,* 48 (suppl 60). DOI: 10.1183/13993003.congress-2016.PA2108.

Burman, M., Nikolayevskyy, V., Kontsevaya, I., Molina-Moya, B., Rzhepishevska, O., & Guglielmetti, L. (2018). Tackling the MDR-TB epidemic in Ukraine: every little helps … and much more needed, *Journal of Public Health*, 40(1). pp 210–211. https://doi.org/10.1093/pubmed/fdx014.

Cai, C., Huo, FM., & Liao, S. (2017). Trends in drug-resistant tuberculosis in China: data from a clinical tuberculosis centre. *Int J Tuberc Lung Dis*.21(9):990-995. doi:10.5588/ijtld.17.0086.

Caraffa, A., Conti, C., Ovidio, CD., Gallenga, CE., Tettamanti, L., & Mastrangelo, M. (2018). New concepts in neuroinflammation: mast cells pro-inflammatory and anti-inflammatory cytokine mediators. *J. Biol. Regul.* 32 (3) (2018), pp. 449-454.

Caraffa, E., Schepisi, MS., & Gualano, G. (2016). The diabetes-tuberculosis co-epidemic: the role of international migration. *Int J Tuberc Lung Dis*. 20(6):771-777. doi:10.5588/ijtld.15.0295.

Centers for Disease Control and Prevention. (1996). The role of BCG vaccine in the prevention and control of tuberculosis in the United States. A joint statement by the Advisory Council for the Elimination of Tuberculosis and the Advisory Committee on Immunisation Practices. *MMWR*;45(RR-4):1-18.

Centers for Disease Control and Prevention. (2013). Tuberculosis. Retrieved from https://search.cdc.gov/search/index.html?query=tuberculosis&sitelimit=&utf8=✓&affiliate=cdc-main.

Centers for Disease Control and Prevention. (2017). Morbidity and Mortality Weekly Report. https://www.cdc.gov/mmwr/index.html.

Chaudhary, S., Thukral, A., Tiwari, S., Pratyush, DD., & Singh SK. (2013). Vitamin D status of patients with type 2 diabetes and sputum positive pulmonary tuberculosis. *Indian J Endocr Metab*. http://www.ijem.in/text.asp?2013/17/9/670/123564.

Chaudhury, A., Duvoor, C., Reddy Dendi, V. S., Kraleti, S., Chada, A., Ravilla, R., & Mirza, W. (2017). Clinical Review of Antidiabetic Drugs: Implications for Type 2 Diabetes Mellitus Management. *Frontiers in endocrinology*, *8*, 6. doi:10.3389/fendo.2017.00006.

Chen, CH., Chen, YM., Lee, CW., Chang, YJ., Cheng, CY., & Hung, JK. (2016). Early diagnosis of spinal tuberculosis. *J Formos Med Assoc*. 115(10):825-836. doi:10.1016/j.jfma.2016.07.001.

Chesdachai, S., Zughaier, S. M., Hao, L., Kempker, R. R., Blumberg, H. M., Ziegler, T. R., & Tangpricha, V. (2016). The Effects of First-Line Anti-

Tuberculosis Drugs on the Actions of Vitamin D in Human Macrophages. *Journal of clinical & translational endocrinology*, *6*, 23–29. doi:10.1016/j.jcte.2016.08.005.

Chiang, C., Enarson, D., Yu, MC., Bai, RM., Huang., CJ. Hsu, J., & Lin, S. (2006). *European Respiratory Journal.* 28 (5) 980-985; DOI: 10.1183/09031936.06.00125705.

Chiang, SS., Roche, S., & Contreras, C. (2015). Barriers to the diagnosis of childhood tuberculosis: a qualitative study. *Int J Tuberc Lung Dis*. 19(10):1144-1152. doi:10.5588/ijtld.15.0178.

Citron, KM. (1993). BCG vaccination against tuberculosis: *International perspective.* BMJ 306:222-223.

Cohen, K., & Meintjes, G. (2011). Management of individuals requiring antiretroviral therapy and TB treatment. *Current opinion in HIV and AIDS*, *5*(1), 61–69. doi:10.1097/COH.0b013e3283339309.

Colombani, P., Hovhannesyan, A., & Wolfheze, A. (2015). Working Group on Social Determinants of TB and Drug Resistant TB. Social determinants and risk factors for tuberculosis in national surveillance systems in Europe. *Public health action*, *5*(3), 194–201. doi:10.5588/pha.15.0026.

Connolly, M. (1999). A survey of workload, resources and work practices among TB nurses in London. On behalf of The London TB Nurse Network.

Cooper, AM. (2009) Cell-mediated immune responses in tuberculosis*. Annu Rev Immunol.* 27, pp. 393-422. doi: 10.1146/annurev.immunol.021908.132703.

Cotini, C., Maritati, M., Di Nuzzo, M., Massoli, L., Lomenzo, S & Grilli, A. (2017). The impact of tuberculosis among in non-UK born: epidemiology and strategies of control in high-income countries – current data and literature review. *IntechOpen.* DOI:10.5772/66823.

Cruz, AT., & Starke, JR. (2007). Clinical manifestations of tuberculosis in children. *Paediatr Respir Rev.* 8(2), pp. 107-17.

Dale, KD., Trauer, JM., Dodd, PJ., Houben, RMGJ., & Denholm, JT. (2018) Estimating the prevalence of latent tuberculosis in a low-incidence setting: Australia. *European Respiratory Journal*, 52(6). 1801218; **DOI:** 10.1183/13993003.01218-2018.

Dave, P., Shah, A., Chauhan, M., Kumar, A. M., Harries, A. D., Malhotra, S., Pujara, K., Patel, P., Mane, M., Thakkar, A., Bharaswadkar, S., Sharath, B. N., & Achanta, S. (2013). Screening patients with tuberculosis for diabetes mellitus in Gujarat, India. *Public health action*, *3*(1), 29–S33. https://doi.org/10.5588/pha.13.0027.

Davidson, JA., Lalor, MK., Anderson, LF., Tamne, S., Abubakar, I., & Thomas, HL. (2016). TB in healthcare workers in the UK: a cohort analysis 2009-2013. *Thorax* 2016; 1–6. doi:10.1136/thoraxjnl-2015-208026.

Davis, JL., Schumacher, SG., Sohn, H., Qin ZZ, Gore, G., & Denkinger, CM. (2016). Impact of Molecular Diagnostics for Tuberculosis on Patient-Important Outcomes: A Systematic Review of Study Methodologies. *PLoS ONE.* 11(3): e0151073. https://doi.org/10.1371/journal.pone.0151073.

Deffur, A., Wilkinson, RJ., & Coussens, AK. (2015). Tricks to translating TB transcriptomics. *Ann. Transl. Med,* 2015; 3: S43.

Delgado-Sánchez, G., García-García, L., Castellanos-Joya, M., Cruz-Hervert, P., Ferreyra-Reyes, L., Ferreira-Guerrero, E., Hernández, A., Ortega-Baeza, V. M., Montero-Campos, R., Sulca, J. A., Martínez-Olivares, M., Mongua-Rodríguez, N., Baez-Saldaña, R., González-Roldán, J. F., López-Gatell, H., Ponce-de-León, A., Sifuentes-Osornio, J., & Jiménez-Corona, M. E. (2015). Association of Pulmonary Tuberculosis and Diabetes in Mexico: Analysis of

the National Tuberculosis Registry 2000-2012. *PloS one*, *10*(6), e0129312. doi.org/10.1371/journal.pone.0129312.

Department of Health (1996). Joint Committee on Vaccination and Immunisation. Immunisation against infectious disease. HMSO, London.

Diabetes UK. (2019). Diabetes UK. Retrieved from https://www.diabetes.org.uk/research.

Dobler, CC., Flack, JR., & Marks, GB. (2012). Risk of tuberculosis among people with diabetes mellitus: an Australian nationwide cohort study. *BMJ Open*. 2(1):e000666. doi:10.1136/bmjopen-2011-000666.

Dodd, PJ. (2018). Commentary: The pros of plurality for tuberculosis burden estimates, *International Journal of Epidemiology*. 47 (5). 1560–1561. https://doi.org/10.1093/ije/dyy147.

Dodd, PJ., Looker, C., Plumb, ID., Bond, V., Schaap, A., Shanaube, K., Muyoyeta, M., Vynnycky, E., Godfrey-Faussett, P., Corbett, EL., & Beyers, N. (2016). Age- and Sex-Specific Social Contact Patterns and Incidence of Mycobacterium tuberculosis Infection. *Am J Epidemiol.* 183(2), 156-166.

Dodd, PJ., Yuen, CM., Becerra, MC., Revill, P., Jenkins, HE., & Seddon, JA. (2018). Potential effect of household contact management on childhood tuberculosis: a mathematical modelling study. *The Lancet Global Health*. 6(12). e1329-e1338.

Dousa, KM., De la-Hoz, A., Church, E., Onger, T., Perez, F., & Saade, E. (2019) Progressive and disseminated histoplasma infection and hemophagocytic lymphohistiocytosis in an immunocompetent adult. *Clin Case Rep*. 7(5):913-916. doi: 10.1002/ccr3.2079.

Duarte, R., Lönnroth, K., Carvalho, C., Lima, F., Carvalho, ACC., Muñoz-Torrico, M., & Centis, R. (2018). Tuberculosis, social determinants and co-

morbidities (including HIV). *Pulmonology.* 24(2). Pp 115-119. https://doi.org/10.1016/j.rppnen.2017.11.003.

Ebrahim, G. (2007). Drug Resistance in Tuberculosis, *Journal of Tropical Pediatrics*, Volume 53, 3, pp 147–149, https://doi.org/10.1093/tropej/fmm042.

Ekeke, N., Ukwaja, K. N., Chukwu, J. N., Nwafor, C. C., Meka, A. O., Egbagbe, E. E., Soyinka, F. O., Alobu, I., Agujiobi, I., Akingbesote, S., Igbinigie, O., Offor, J. B., Madichie, N. O., Alphonsus, C., Anyim, M. C., Mbah, O. K., & Oshi, D. C. (2017). Screening for diabetes mellitus among tuberculosis patients in Southern Nigeria: a multi-centre implementation study under programme settings. *Scientific reports*, *7*, 44205. https://doi.org/10.1038/srep44205.

Eshetie, S., Alebel, A., Wagnew, F., Geremew, D., Fasil, A., & Sack, U. (2018). Current treatment of multidrug resistant tuberculosis in Ethiopia: an aggregated and individual patients' data analysis for outcome and effectiveness of the current regimens. *BMC infectious diseases*, *18*(1), 486. doi:10.1186/s12879-018-3401-5.

Essam, H., Mohamed, E., Baess, AI., EL-Sayed, E., & Ahmad, MY. (2016). The role of supplementary vitamin D in treatment course of pulmonary tuberculosis. *Egyptian Journal of Chest Diseases and Tuberculosis*. 65 (3). Pp.629-635.

European Centre for Disease Prevention and Control/WHO Regional Office for Europe. Tuberculosis surveillance and monitoring in Europe 2018 – 2016 data.

European Drug Report. (2015). European Drug Report. Retrieve from http://www.emcdda.europa.eu/edr2019_en.

Eybpoosh, S., Haghdoost, A., Mostafavi, E., Bahrampour, A., Azadmanesh, K., & Zolala, F. (2017). Molecular epidemiology of infectious diseases. *Electronic physician*. *9*(8), 5149–5158. doi:10.19082/5149.

Faurholt-Jepsen, D., Range, N., PrayGod, G., Faurholt-Jepsen, M., Aabye, M., Changalucha, DC., Pipper, CB, & Krarup, H. (2011). Diabetes Is a Risk Factor for Pulmonary Tuberculosis: A Case-Control Study from Mwanza, Tanzania. *Plos.* https://doi.org/10.1371/journal.pone.0024215.

Fogel, N. (2015). Tuberculosis: a disease without boundaries. *Tuberculosis (Edinb),* 2015;95(5):527–31. 10.1016/j.tube.2015.05.017.

Fox, GJ., Dodd, PJ., and Marais, BJ. (2019). Household contact investigation to improve tuberculosis control. *Lancet Infect Dis*. 2019;19(3):235-237. https://doi.org/10.1016/S1473-3099(19)30061-1.

Gadallah, MA., Mokhtar, A., Rady, M., El-Moghazy, E., Fawzy, M., & Kandil, SK. (2016). Prognostic factors of treatment among patients with multidrug-resistant tuberculosis in Egypt. *J Formos Med Assoc*. 2016;115(11):997-1003. doi:10.1016/j.jfma.2015.10.002.

Gengiah, TN., Gray, AL., Naidoo, K., & Karim QA. (2011). Initiating antiretrovirals during tuberculosis treatment: a drug safety review. *Expert Opin. Drug Saf*. 10, 559–574. 10.1517/14740338.2011.546783.

Gil-Santana L, Almeida-Junior JL, Oliveira CAM, Hickson LS, & Daltro C. (2016) Diabetes Is Associated with Worse Clinical Presentation in Tuberculosis Patients from Brazil: A Retrospective Cohort Study. *PLOS ONE.* 11(1): e0146876. https://doi.org/10.1371/journal.pone.0146876.

Glaziou, P., Floyd, K, & Raviglione, MC. (2018). Global Epidemiology of Tuberculosis. Semin Respir *Crit Care Med*. 2018 Jun;39(3):271-285. doi: 10.1055/s-0038-1651492.

Gomez, DI., Twahirwa, M., Schlesinger, LS., & Restrepo, BI. (2013). Reduced *Mycobacterium tuberculosis* association with monocytes from diabetes patients that have poor glucose control. *Tuberculosis (Edinb)*. 93(2):192-7. doi: 10.1016/j.tube.2012.10.003.

Gomez, GB., Dowdy, DW., & Bastos, ML. (2016). Cost and cost-effectiveness of tuberculosis treatment shortening: a model-based analysis. *BMC Infect Dis* 16, 726 (2016) doi:10.1186/s12879-016-2064-3.

González-Ochoa, E., Brooks, JL., Matthys, F., Calisté, P., Armas, L. & Van der Stuyft, P. (2009). Pulmonary tuberculosis case detection through fortuitous cough screening during home visits. *Tropical Medicine & International Health*. 14: 131-135. doi:10.1111/j.1365-3156.2008.02201.x.

Grosset, J. H., & Chaisson, R. E. (2017). Handbook of Tuberculosis. Springer International Publishing. https://doi.org/10.1007/978-3-319-26273-4.

Gunda, D.W., Nkandala, I., Kilonzo, SB., Kilangi, BB., & Mpondo, B. C. (2017). Prevalence and Risk Factors of Mortality among Adult HIV Patients Initiating ART in Rural Setting of HIV Care and Treatment Services in North Western Tanzania: A Retrospective Cohort Study. *Journal of sexually transmitted diseases*, doi:10.1155/2017/7075601.

Guzman, EP., Quintas, SC., Crespo, BG., Etxeberria, L., Maestre, UKJ., Iñiguiz, MI., Aguirrezabala, AS., & Zubiaurre, PA. (2013). Futile thoracotomy in lung cancer.

Simon, S, Alimuddin I. Zumla, John M. Grange, Mario C. Raviglione, Wing Wai Yew, Jeffrey R. Starke, Madhukar Pai, & Peter R. Donald. (2009). Tuberculosis. W.B. Saunders.

Hajizadeh, R., Sato, H., Carlisle, J., Nadaf, MT., Evans, W., Shepherd, BE., Miller, RF., Kalams, SA., & Drake, WP. (2014). *Mycobacterium tuberculosis* Antigen 85A induces Th-1 immune responses in systemic sarcoidosis. *J Clin Immunol,* 27(4):445-54. doi: 10.1007/s10875-007-9080-4.

Hanif, W & Susaria, R. (2018). Diabetes abd cardiovascular risj in UK South Asians: an overview. BJC. 25(2). 8–13. doi:10.5837/bjc.2018.s08

Haraldsdottir, TL., Rudolf, F., & Bjerregaard-Andersen M. (2015). Diabetes mellitus prevalence in tuberculosis patients and the background population in Guinea-Bissau: a disease burden study from the capital Bissau. *Trans R Soc Trop Med Hyg*. 109(6):400-407. doi:10.1093/trstmh/trv030.

Hargreaves, JR., Boccia, D., Evans, CA., Adato, M., Petticrew, M., & Porter, JD. (2011). The social determinants of tuberculosis: from evidence to action. *Am J Public Health,* 101(4):654-62. doi: 10.2105/AJPH.2010.199505.
Hargreaves, JR., Boccia, D., Evans, CA., Adato, M., Petticrew, M., & Porter, JD. (2011). The social determinants of tuberculosis: from evidence to action. *Am J Public Health,*101(4):654-62. doi: 10.2105/AJPH.2010.199505.

Harries, A. D., Kumar, A. M., Satyanarayana, S., Lin, Y., Zachariah, R., Lönnroth, K., & Kapur, A. (2016). Addressing diabetes mellitus as part of the strategy for ending TB. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, *110*(3), 173–179. https://doi.org/10.1093/trstmh/trv111.

Hayward, S., Harding, RM., McShane, H., & Tanner, R. (2018). Factors influencing the higher incidence of tuberculosis among non-UK born and ethnic minorities in the UK. *F1000Research* 2018, 7:461.

Heemskerk, D., Caws, M., & Marais, B. Tuberculosis in Adults and Children. London: Springer; 2015.

Hermosilla, S., You, P., & Aifah, A. (2017). Identifying risk factors associated with smear positivity of pulmonary tuberculosis in Kazakhstan. *PLoS One*. 12(3):e0172942. doi:10.1371/journal.pone.0172942.

Herrera, MT., Gonzalez, Y., & Hernández-Sánchez, F. (2017). Low serum vitamin D levels in type 2 diabetes patients are associated with decreased mycobacterial activity. *BMC Infect Dis* 17, 610. doi:10.1186/s12879-017-2705-1.

Heysell, SK., Moore, JL., Staley, D., Dodge, D., & Houpt, ER. (2013). Early therapeutic drug monitoring for isoniazid and rifampin among diabetics with newly diagnosed tuberculosis in Virginia, USA. *Clinical Study.* https://doi.org/10.1155/2013/129723.

Ho, MJ. (2004). Sociocultural aspects of tuberculosis: a literature review and a case study of immigrant tuberculosis. *Soc Sci Med,* 59(4):753–62. 10.1016/j.socscimed.2003.11.033.

Holtz, TH., Sternberg, M., Kammerer, S., Laserson, KF., Riekstina, V., Zarovska, E., & Leimane, V. (2006). Time to sputum culture conversion in multidrug-resistant tuberculosis: predictors and relationship to treatment outcome. *Ann Intern Med*. doi: 10.7326/0003-4819-144-9-200605020-00008. PubMed PMID: 16670134.

Houben, RM & Dodd, PJ. (2016). The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. *PLoS Med.* 13(10):e1002152 (https://www.ncbi.nlm.nih.gov/pubmed/27780211.

Howell, E.M., Kigozi, N.G., & Heunis, J.C. (2014). Community-based directly observed treatment for TB patients to improve HIV services: a cross-sectional study in a South African province. *BMC Health Serv Res* 18, 255. doi:10.1186/s12913-018-3074-1.

Huang, LK., Wang, HH., Lai, YC., & Chang, SC. (2017). The impact of glycemic status on radiological manifestations of pulmonary tuberculosis in

diabetic patients. *PLoS ONE*. 12(6): e0179750. https://doi.org/10.1371/journal. pone.0179750.

Huang, SJ., Wang, XH., Liu, ZD., Cao, WL., Han, Y., Ma, AG., & Xu, SF. (2016). Vitamin D deficiency and the risk of tuberculosis: a meta-analysis. *Drug design, development and therapy*, *11*, 91–102. doi:10.2147/DDDT.S79870.

International Diabetes Federation. (2014). IDF Diabetes Atlas Ninth Edition. https://www.idf.org/e-library/epidemiology-research/diabetes-atlas.

International Diabetes Federation. (2015). IDF Diabetes Atlas Tenth Edition. https://www.idf.org/e-library/epidemiology-research/diabetes-atlas/13-diabetes-atlas-seventh-edition.html.

Jeon, CY & Murray, MB. (2008). Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. *PLoS Med*, 5(7):e152. doi: 10.1371/journal.pmed.0050152.

Jerene, D., Hiruy, N., Jemal, I., Gebrekiros, W., Anteneh, T. Habte, D., Melese, M. Suarez, P., & Sangiwa, G. (2017). The yield and feasibility of integrated screening for TB, diabetes and HIV in four public hospitals in Ethiopia, *International Health*, 9 (2).
100–104, https://doi.org/10.1093/inthealth/ihx002.

Jiménez-Corona, ME., Cruz-Hervert, LP., & García-García, L. (2013). Association of diabetes and tuberculosis: impact on treatment and post-treatment outcomes. *Thorax,* 13;68:214-220.

Joint Tuberculosis Committee of the British Thoracic Society. (2000). Control and prevention of tuberculosis in the United Kingdom: code of practice. *Thorax*, 55(11): 887-901.

Juan-García J., García-García, S., Guerra-Laso, JM., Raposo-García, S., Diez-Tascón, C., Nebreda-Mayoral, T., & Rivero-Lezcano, OM. (2017). In vitro infection with *Mycobacterium tuberculosis* induces a distinct immunological pattern in blood from healthy relatives of tuberculosis patients. *Pathog Dis.* doi: 10.1093/femspd/ftx109.

Jurado, L & Palacios, D. (2018). Tuberculosis: A Risk Factor Approach. *Intechopen.* http://dx.doi.org/10.5772/intechopen.73538.

Kadam, P., & Bhalerao, S. (2010). Sample size calculation. *Int J Ayurveda Res,* 1(1):55-7. doi: 10.4103/0974-7788.59946.

Karim, A., Naidoo, SS., Grobler, K., Padayatchi, A., Baxter, N., & Gray, A. (2010). Timing of initiation of antiretroviral drugs during tuberculosis therapy. *The New England journal of medicine*, *362*(8), 697–706. doi:10.1056/NEJMoa0905848.

Kartik, K., & Onn, K. (2017). Diagnosis and treatment of tuberculosis: latest developments and future priorities. *Annals of Research Hospitals*. doi: 10.21037/arh.2017.08.08.

Karyadi, E., Schultink, W., Nelwan, RH., Gross, R., Amin, Z., Dolmans, WM., & West, CE. (2000). Poor micronutrient status of active pulmonary tuberculosis patients in Indonesia. *J Nutr.,* 130(12):2953-8. doi: 10.1093/jn/130.12.2953.

Kato-Maeda, M., Ho, C., Passarelli, B., Banaei, N., Grinsdale, J., Flores, L., Anderson, J., & Hopewell, PC. (2013). Use of whole genome sequencing to determine the microevolution of *Mycobacterium tuberculosis* during an outbreak. *PLoS One,* 2013;8(3): e58235. doi: 10.1371/journal.pone.0058235.

Kedzierska, K., Crowe, SM., Turville, S., & Cunningham, AL. (2003). The influence of cytokines, chemokines and their receptors on HIV-1 replication in monocytes and macrophages. *Rev Med,* 13 (39).

Kendall, EA., Fojo, AT., & Dowdy, DW. (2017). Expected effects of adopting a 9-month regimen for multidrug-resistant tuberculosis: a population modelling analysis. *The Lancet, Respiratory medicine*, *5*(3), 191–199. doi:10.1016/S2213-2600(16)30423-4.

Kent, RJ., Uttley, AHC., Stoker, NG., Miller, R., & Poznaik, AL. (1994). Transmission of tuberculosis in a British care centre for patients infected with HIV. *BMJ*, 309: 639-640.

Kenyon, TA., Valway, SE., Ihle, MPA., Onorab, IM., & Castro, KG. (1996). Transmission of multi-drug resistant *Mycobacterium tuberculosis* during a long air-plane flight. *New England Journal of Medicine.* 334: 933-938.

Khalil, N & Ramadan, R. (2016). Study of risk factors for pulmonary tuberculosis among diabetes mellitus patients. *Egyptian Journal of Chest Diseases and Tuberculosis,* 65(4), 817-823.

Khandkar, C., Harrington, Z., Jelfs, PJ., Sintchenko, V., & Dobler, CC. (2015). Epidemiology of Peripheral Lymph Node Tuberculosis and Genotyping of M. tuberculosis Strains: A Case-Control Study. *PLoS One*. 2015;10(7): e0132400. doi:10.1371/journal.pone.0132400.

Kiboi, NG., Nebere, SN., & Karanja, JK. (2016). Immunological Interactions of Tuberculosis with Drugs and Substance Use: A Systematic Review and Update. *J Pulm Respir Med,* 6:326. doi:10.4172/2161-105X.1000326.

Kibret, K. T., Moges, Y., Memiah, P., & Biadgilign, S. (2017). Treatment outcomes for multidrug-resistant tuberculosis under DOTS-Plus: a systematic review and meta-analysis of published studies. *Infectious diseases of poverty*, *6*(1), 7. https://doi.org/10.1186/s40249-016-0214-x.

Knight, GM., McQuaid, CF., Dodd, PJ., & Houben, RMGJ. (2019). Global burden of latent multidrug-resistant tuberculosis: trends and estimates based

on mathematical modelling. *The Lancet Infectious Diseases, 19(8), 903-012.* doi: 10.1016/S1473-3099(19)30307-X.

Knudsen, N., Nørskov-Lauritsen, S., Dolganov, Schoolnik, G., Lindenstrøm, T., Andersen, P., Agger, E., & Aagaard, C. (2014). Fusion of ESX substrates protects against TB. *Proceedings of the National Academy of Sciences,* 111 (3), 1096-1101. DOI:10.1073/pnas.1314973111.

Kornfeld, H., West, K., Kane, K., Martinez-Balzano., Li, W., & Viswanathan, V. (2016). High Prevalence and Heterogeneity of Diabetes in Patients with TB in South India. Chest Infections. 149(6). 1501-1508, JUNE 01, 2016.

Kota, SK., Jammula, S., Kota, SK., Tripathy, PR., Panda, S., & Modi, KD. (2011). Effect of vitamin D supplementation in type 2 diabetes patients with pulmonary tuberculosis. *Diabetes Metab Syndr,* 5(2):85-9. doi: 10.1016/j.dsx.2012.02.021.

Ku, CC., & Dodd, PJ. (2019). Forecasting the impact of population ageing on tuberculosis incidence. *PLoS One*. 14(9):e0222937. doi:10.1371/journal.pone.0222937.

Ku, N., S., Oh., Shin, SY., Kim, SB., Kim, HW., & Jeong, SJ. (2013). Effects of tuberculosis on the kinetics of CD4(+) T cell count among HIV-infected patients who initiated antiretroviral therapy early after tuberculosis treatment. *AIDS research and human retroviruses*, *29*(2), 226–230. doi:10.1089/AID.2012.0192.

Kumpatla, S., Sekar, A., Achanta, S., Sharath, BN., Kumar, AM., Harries, AD., & Viswanathan, V. (2013). Characteristics of patients with diabetes screened for tuberculosis in a tertiary care hospital in South India. *Public health action*, *3*(Suppl 1), S23–S28. doi:10.5588/pha.13.0035.

Kwan, CK & Ernst, JD. (2011) HIV and tuberculosis: a deadly human syndemic. *Clin Microbiol Rev.* 24(2):351-76. doi: 10.1128/CMR.00042-10.

Lachmandas, E., van den Heuvel, C. N., Damen, M. S., Cleophas, M. C., Netea, M. G., & van Crevel, R. (2016). Diabetes Mellitus and Increased Tuberculosis Susceptibility: The Role of Short-Chain Fatty Acids. *Journal of diabetes research*, *2016*, 6014631. https://doi.org/10.1155/2016/6014631.

Lawn, S. D., & Nicol, M. P. (2011). Xpert® MTB/RIF assay: development, evaluation and implementation of a new rapid molecular diagnostic for tuberculosis and rifampicin resistance. *Future microbiology*, *6*(9), 1067–1082. doi:10.2217/fmb.11.84.

Lee, M. R., Huang, Y. P., Kuo, Y. T., Luo, C. H., Shih, Y. J., Shu, C. C., Wang, J. Y., Ko, J. C., Yu, C. J., & Lin, H. H. (2017). Diabetes Mellitus and Latent Tuberculosis Infection: A Systematic Review and Metaanalysis. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*, *64*(6), 719–727. https://doi.org/10.1093/cid/ciw836.

Lee, PH., Fu, H., Lai, TC., Chiang, CY., Chan, CC., & Lin, HH. (2016). Glycemic Control and the Risk of Tuberculosis: A Cohort Study. *PLoS Med,* 2016 Aug;13(8): e1002072. doi: 10.1371/journal.pmed.1002072.

Leegaard, A., and Riis A., & Kornum, JB. (2011). Diabetes, glycemic control, and risk of tuberculosis: a population-based case-control study. *Diabetes Care*. 34(12):2530-2535. doi:10.2337/dc11-0902.

Lerner, TR., Borel, S., & Gutierrez, MG. (2015). The innate immune response in human tuberculosis. *Cell Microbiol.* 17(9), pp. 1277-85. doi: 10.1111/cmi.12480.

Leung, CC., Chee, C., & Zhang, Y. (2017). Tuberculosis updates 2018: Innovations and developments to end TB. *Respirology*, 23: 356– 358., doi: 10.1111/resp.13244.

Lönnroth, K., Castro, KG., Chakaya, JM., Chauhan, LS., Floyd, K., Glaziou, P., & Raviglione, MC. (2010). Tuberculosis control and elimination 2010-50: cure, care, and social development. *Lancet.* 375(9728):1814-29. doi: 10.1016/S0140-6736(10)60483-7.

Lonnroth, K., Williams, BG., Cegielski, P., & Dye, C. (2010). A consistent log-linear relationship between tuberculosis incidence and body mass index. *Int. J. Epidemiol.* 39:149–155. doi: 10.1093/ije/dyp308.

Loutet, MG., Burman, M., Jayasekera, N., Trathen, D., Dart, S., Kunst, K., & Zenner, D. (2018). National roll-out of latent tuberculosis testing and treatment for new non-UK born in England: a retrospective evaluation in a high-incidence area. *European Respiratory Journal,* 51 (1) 1701226; DOI: 10.1183/13993003.01226-2017.

Lowe, DM., Redford, PS., Wilkinson, RJ., & O'Garra, A. (2012). Martineau AR. Neutrophils in tuberculosis: friend or foe? *Trends Immunol.* 33:14–25. doi: 10.1016/j.it.2011.10.003.

MacDonald, E & Izzo, A. (2014). Tuberculosis Vaccine Development — Its History and Future Directions. DOI: 10.5772/59658.

Madley-Dowd, P., Hughes, R., Tilling, K., & Heron, J. (2019). The proportion of missing data should not be used to guide decisions on multiple imputation. *Journal of Clinical Epidemiology.* 110. 63-73.https://doi.org/10.1016/j.jclinepi.2019.02.016.

Magliano, D., Chen, L & Zimmet, PZ. (2019). The worldwide epidemiology of type 2 diabetes mellitus-present and future perspectives. *Nature Reviews Endocrinology,* 8(4) pp. 228–236.

Mahishale, V., Avuthu, S., Patil, B., Lolly, M., Eti, A., & Khan, S. (2017) Effect of Poor Glycemic Control in Newly Diagnosed Patients with Smear-Positive

Pulmonary Tuberculosis and Type-2 Diabetes Mellitus. *Iranian journal of medical sciences*, *42*(2), 144–151.

Majumder, A., RoyChaudhuri, S., & Sanyal, D. (2019). A Retrospective Observational Study of Insulin Glargine in Type 2 Diabetic Patients with Advanced Chronic Kidney Disease. *Cureus*, *11*(11), e6191. doi:10.7759/cureus.6191.

Martinez, N & Kornfeld, H. (2014). Diabetes and immunity to tuberculosis. *Eur J Immunol.* 44(3), 617-26. doi: 10.1002/eji.201344301.

Martinez, N., Ketheesan, N., West, K., Vallerskog, T., & Kornfeld H. (2016). Impaired recognition of *Mycobacterium tuberculosis* by alveolar macrophages from diabetic mice. *J. Infect. Dis,* 214:1629–1637. doi: 10.1093/infdis/jiw436.

McDonald, J.H. 2014. Handbook of Biological Statistics (3rd ed.). Sparky House Publishing, Baltimore, Maryland.

Menon, M., Blair, PA., Isenberg, DA., & Mauri, C. (2016). A Regulatory Feedback between Plasmacytoid Dendritic Cells and Regulatory B Cells Is Aberrant in Systemic Lupus Erythematosus. *Immunity,* 44(3):683-697. doi: 10.1016/j.immuni.2016.02.012.

Merdith DS, Watson JM., & Citron, KM. (1996). Are healthcare workers in England and Wales at increased risk of tuberculosis? *BMJ*. 313: 522-525.

Michele TM, Cronin WA, & Graham, NMH. (1997). Transmission of Mycobacterium *tuberculosis* by fiber-optic bronchoscope: Identification by DNA fingerprinting. J*AMA,* 278:1093-1095.

Mishkin, K., Alaei, K., Alikeyeva, E., Paynter, C., Aringazina, A., & Alaei, A. (2018). Association between antiretroviral therapy and antitubercular drug resistance in TB treatment outcome among Kazakh TB/HIV co-infected

patients. *J Glob Antimicrob Resist*, 14:104-108. doi: 10.1016/j.jgar.2018.02.015.

Moreira, J., Rodolfo, C., Lamas, C., Ribeiro, S., Grinsztejn, B., & Veloso, VG. (2017). Hyperglycaemia during tuberculosis treatment increases morbidity and mortality in a contemporary cohort of HIV-infected patients in Rio de Janeiro, Brazil. *International Journal of Infectious Disease*. 69, 11-19. https://doi.org/10.1016/j.ijid.2017.12.014.

Moreira, W., Santhanakrishnan, S., Ngan, GJY., Low, CB., Sangthongpitag, K., Poulsen, A., Dymock, BW., & Dick, T. (2017). Towards Selective Mycobacterial ClpP1P2 Inhibitors with Reduced Activity against the Human Proteasome. *Antimicrob Agents Chemother*, 61(5). doi: 10.1128/AAC.02307-16.

Moreno-Martínez, A., Casals, M., Orcau, À., Gorrindo, P., Masdeu, E., & Caylà, JA. (2013). Factors associated with diabetes mellitus among adults with tuberculosis in a large European city, 2000-2013. *Int J Tuberc Lung Dis*, 19(12):1507-12. doi: 10.5588/ijtld.15.0102.

Mukhtar, F & Butt, ZA. (2018). Risk of adverse treatment outcomes among new pulmonary TB patients co-infected with diabetes in Pakistan: A prospective cohort study. *PLoS One,* 13(11):e0207148. doi: 10.1371/journal.pone.0207148. eCollection 2018.

Munoz-Torrico, M., Salazar, MA., Millán, M., Orozco, J., Diaz, LN., Pilar, M., & Migliori, GB. (2018). *European Respiratory,* 51 (3) 1702267. DOI: 10.1183/13993003.02267-2017.

Murphy, M., Robertson, W., & Oyebode, O. (2017). Obesity in International Migrant Populations. *Current obesity reports*, *6*(3), 314–323. doi:10.1007/s13679-017-0274-7.

National Institute for Health and Care Excellence. (2016). Tuberculosis Guidelines NG33 (2016) Clinical diagnosis and management of tuberculosis and measures for its prevention and control. Retrieved from https://www.nice.org.uk/guidance/ng33/evidence/full-guideline-80851860868.

National Institute for Health and Care Excellence. (2017). Tuberculosis Guidelines NG33 (2017) Clinical diagnosis and management of tuberculosis and measures for its prevention and control. Retrieved from https://www.nice.org.uk/guidance/cg117.

Narasimhan, P., Wood, J., Macintyre, C. R., & Mathai, D. (2013). Risk factors for tuberculosis. *Pulmonary medicine*, *2013*, 828939. https://doi.org/10.1155/2013/828939.

Nathella, KP & Babu, S. (2017). Influence of diabetes mellitus on immunity to human tuberculosis. *Immunology,* 152: 13-24. doi:10.1111/imm.12762.

National Health Service Executive. (1995). Hospital Infection Control: guidance on the control of infections in hospitals. HSG(95): 10. Retrieved from https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/148493/HFN_30_-_Infection_control.pdf.

NHS Newham CCG. (2018). Commissioning for value long term condition pack. Retrieved from https://www.england.nhs.uk/rightcare/wp-content/uploads/sites/40/2016/08/cfv-newham-ltc.pdf.

Niazi, AK., & Kalra, S. (2012). Diabetes and tuberculosis: a review of the role of optimal glycemic control. *J Diabetes Metab Disord,*11(1):28. doi: 10.1186/2251-6581-11-28.

Nickerson, HD &, Dutta, S. (2012). Diabetic complications: current challenges and opportunities. *J. Cardiovasc. Transl. Res.* 5:375–379. doi: 10.1007/s12265-012-9388-1.

Nijland, HM., Ruslami, R., Stalenhoef, JE., Nelwan, EJ., Alisjahbana, B., Nelwan, RH., & Crevel, R. (2006). Exposure to rifampicin is strongly reduced in patients with tuberculosis and type 2 diabetes. *Clin Infect Dis,* 1;43(7):848-54. doi: 10.1086/507543.

Nissapatorn, V., Kuppusamy, I., Jamaiah, I., Fong, MY., Rohela, M., & Anuar, AK. (2005). Tuberculosis in diabetic patients: a clinical perspective. *Southeast Asian J Trop Med Public Health*, 36 Suppl 4:213-20.

Nnadi, CD., Anderson, LF., & Armstrong, LR. (2016). Mind the gap: TB trends in the USA and the UK, 2000–2011. *Thorax,* 71:356-363.

Noémie, BB., Kaushik, LM., Mganga, M., Minja, LT., Bovet, P., Schindler, C., Eckardstein, AV., Gagneux, S., Daubenberger, C., Reither, K., & Probst-Hensch, N. (2016). Transient Hyperglycemia in Patients With Tuberculosis in Tanzania: Implications for Diabetes Screening Algorithms, *The Journal of Infectious Diseases*, 213 (7), 1163–1172, https://doi.org/10.1093/infdis/jiv568.

Noubiap, J., Nansseu, J., Nyaga, U., Nkeck, J., Endomba, FT., Kaze, AD., Agbor, VN., & Bigna, JJ. (2019). Global prevalence of diabetes in active tuberculosis: a systematic review and meta-analysis of data from 2·3 million patients with tuberculosis. *The Lancet,* 9(4) DOI:https://doi.org/10.1016/S2214-109X(18)30487-X.

Office for National Statistics. (2017). UK Census report 2017. https://www.ons.gov.uk/census/censustransformationprogramme/testingthecensus/2017test/2017censustestreport.

Olayinka, A. O., Anthonia, O., & Yetunde, K. (2013). Prevalence of diabetes mellitus in persons with tuberculosis in a tertiary health centre in Lagos, Nigeria. *Indian journal of endocrinology and metabolism*, *17*(3), 486–489. https://doi.org/10.4103/2230-8210.111646.

Oni, T., Berkowitz, N., Kubjane, M., Goliath, R., Levitt, NS., & Wilkinson, RJ. (2017). Trilateral overlap of tuberculosis, diabetes and HIV-1 in a high-burden African setting: implications for TB control. *The European respiratory journal*, *50*(1), 1700004. doi:10.1183/13993003.00004-2017.

Palomino, JC., & Martin, A. (2014). Drug Resistance Mechanisms in *Mycobacterium tuberculosis*. Antibiotics (Basel). 3(3):317-40. doi: 10.3390/antibiotics3030317. *Review.* PubMed. PMC4790366.

Pan, D., Palittapongarnpim, P., & Chaiprasert, A. (2019). Infectivity of *Mycobacterium tuberculosis* Genotypes and Outcome of Contact Investigation in Classroom in Guangxi, China. *BioMed Research International.* https://doi.org/10.1155/2019/3980658.

Pan, SC., Chen, YC., Wang, JY., Sheng, WH., Lin, HH., & Fang, CT. (2015). Tuberculosis in Healthcare Workers: A Matched Cohort Study in Taiwan. *PLoS ONE*, 10(12): e0145047. https://doi.org/10.1371/journal.pone.0145047.

Pandey, M., Talwar, S., & Bose, S. (2018). Iron homeostasis in *Mycobacterium tuberculosis* is essential for persistence. *Sci Rep* 8, doi:10.1038/s41598-018-35012-3.

Paralija, B & Mujakovic, A. (2018). Impact of diabetes mellitus on pulmonary tuberculosis clinical presentation and treatment outcomes. *European Respiratory Journal,* DOI: 10.1183/13993003.congress-2018.PA2712.

Pealing, L., Wing, K., Mathur, R., Prieto-Merino, D., Smeeth, L., & Moore, DA. (2015). Risk of tuberculosis in patients with diabetes: population based cohort study using the UK Clinical Practice Research Datalink. *BMC medicine*, *13*, 135. doi:10.1186/s12916-015-0381-9.

Pealing, L., Wing, K., Mathur, R., Prieto-Merino, D., Smeeth, L., & Moore, D. A. (2015). Risk of tuberculosis in patients with diabetes: population based

cohort study using the UK Clinical Practice Research Datalink. *BMC medicine*, *13*, 135. https://doi.org/10.1186/s12916-015-0381-9.

Pedrazzoli, D., Boccia, D., Dodd, PJ., Lonnroth, K., Dowdy, DW., Siroka., & Houben, RMGJ. (2017). Modelling the social and structural determinants of tuberculosis: opportunities and challenges. The International Journal of Tuberculosis and Lung Disease*,* 21(9), 957-964. doi: 10.5588/ijtId.16.0906.

Pérez-Guzmán, C., Vargas, MH., Torres-Cruz, A., & Villarreal-Velarde, H. (2001). Does aging modify pulmonary tuberculosis?: A meta-analytical review. *Chest,* 6(4):961-7. doi: 10.1378/chest.116.4.961.

Perez-Navarro, LM., Restrepo, BI., & Fuentes-Dominguez, FJ. (2017). The effect size of type 2 diabetes mellitus on tuberculosis drug resistance and adverse treatment outcomes. *Tuberculosis (Edinb)*. 103:83-91. doi:10.1016/j.tube.2017.01.006.

Pizzol., D., Gennaro, FD., Chhaganial., KD., Fabrizio, C., Monno, L., Putoto, G., & Saracino, A. (2016). Tuberculosis and diabetes: surrent state and future perspectives. *Tropical Medicine and International health.* 21(6), 674-701. doi:10.1111/tmi.12704.

Ponce-De-Leon, A., Garcia-Garcia, L., Garcia-Sancho, MC., Gomez-Perez, FJ., Valdespino-Gomez, JL., Olaiz-Fernandez., & Sifuentes-Osornio, J. (2004). Tuberculosis and diabetes in southern Mexico. *Diabetes Care*, 27(7):1584-90. doi: 10.2337/diacare.27.7.1584.

Prada-Medina, CA., Fukutani, KF., Pavan, Kumar., Gil-Santana, L., Babu, S., & Kornfeld, H. (2017). Systems Immunology of Diabetes-Tuberculosis Comorbidity Reveals Signatures of Disease Complications. *Sci Rep,* 17;7(1). doi: 10.1038/s41598-017-01767-4.

Prasad, R., Gupta, N., & Banka, A. (2018). Multidrug-resistant tuberculosis/rifampicin-resistant tuberculosis: Principles of management. *Lung India,* 35(1):78-81. doi: 10.4103/lungindia.lungindia_98_17.

Public Health England (2015). Collaborative tuberculosis strategy for England: 2015- 2020. https://www.gov.uk/government/publications/collaborative-tuberculosis- strategy-for-england.

Public Health England. (2016) Collaborative tuberculosis strategy for England: 2015 to 2020. Public Health England, London.

Public Health England. (2016) Technical document for the diabetes prevalence model for England. Public Health England, London.

Public Health England. (2017) Tuberculosis in the London Centre: Annual review, (2016 data). Public Health England, London.

Public Health England. (2018) Tuberculosis in England: 2017. Public Health England, London.

Public Health England. (2019) Tuberculosis in England: 2018. Public Health England, London.

Public Health England. (2015) Latent TB testing and treatment for non-UK born. A practical guide for commissioners and practitioners. Retrieved from www.gov.uk/government/uploads/system/uploads/attachment_data/file/442192/030615 _LTBI_testing_and_treatment_for_migrants_1.pdf.

Radtke, KK., Dooley, KE., Dodd, PJ., Garcia-Prats, AJ., McKenna, L., Hesselingm AC., & Savic, RM. (2019). Alternative dosing guidelines to improve outcomes in childhood tuberculosis : a mathematical modelling study. *The Lancet Child & Adolescent Health.* https://doi.org/10.1016/S2352-4642(19)30196-8.

Rajapakshe, W., Isaakidis, P., Sagili, K. D., Kumar, A. M., Samaraweera, S., Pallewatta, N., Jayakody, W., & Nissanka, A. (2015). Screening patients with

tuberculosis for diabetes mellitus in Ampara, Sri Lanka. *Public health action*, *5*(2), 150–152. https://doi.org/10.5588/pha.15.0006.

Ramos, RDLG., Goodwin, RC., Abu-Bonsrah, N., Bydon, A., Witham, TF., Wolinsky, JP, & Sciubba, DM. (2017). The epidemiology of spinal tuberculosis in the United States: an analysis of 2002–2011 data. J Neurosurg Spine 26:507–512.

Ratnawati, BE., Intani, CN., Handayani, H., & Nurwidya, F. (2019). Comparison of tuberculin skin test and interferon-gamma release assay in the diagnosis of latent tuberculosis infection among indonesian health-care workers. *J Nat Sc Biol Med.* http://www.jnsbm.org/text.asp?2019/10/1/53/251508.

Restrepo B. I. (2016). Diabetes and Tuberculosis. *Microbiology spectrum*, *4*(6), 10.1128/microbiolspec.TNMI7-0023-2016.https://doi.org/10.1128/microbiolspec.TNMI7-0023-2016.

Restrepo, BI., Camerlin, AJ., & Rahbar, MH. (2011). Cross-sectional assessment reveals high diabetes prevalence among newly-diagnosed tuberculosis cases. *Bull World Health Organ*. 89(5):352-359. doi:10.2471/BLT.10.085738.

Riza, A. L., Pearson, F., Ugarte-Gil, C., Alisjahbana, B., van de Vijver, S., Panduru, N. M., & van Crevel, R. (2014). Clinical management of concurrent diabetes and tuberculosis and the implications for patient services. *The lancet. Diabetes & endocrinology*, *2*(9), 740–753. doi:10.1016/S2213-8587(14)70110-X.

Ruslami, R., Nijland, HM., & Adhiarta, IG. (2010). Pharmacokinetics of antituberculosis drugs in pulmonary tuberculosis patients with type 2 diabetes. *Antimicrob Agents Chemother*. 54(3):1068-1074. doi:10.1128/AAC.00447-09.

Said, K., Hella, J., & Mhalu, G. (2017). Diagnostic delay and associated factors among patients with pulmonary tuberculosis in Dar es Salaam, Tanzania. *Infect Dis Poverty,* 6, 64. doi:10.1186/s40249-017-0276-4.

Schepisi, MS., Miah, J., Kaluzhenina, A., Manika, KM., Pontali, E., Prego, MR., & Girardi, E. (2017, February) *THE DIABETES-TUBERCULOSIS CO MORBIDITY AMONG PERSONS WITH HIV*. Poster session presented at the 2017 Conference on Retroviruses and Opportunistic Infections (CROI). In Seattle, Washington.

Schepisi, MS., Navarra, A., Gomez, MNA., Dudnik, A., Dyrhol-Riise, AM, Esteban, J., & Girardi, E. (2019). Burden and Characteristics of the Comorbidity Tuberculosis—Diabetes in Europe: TBnet Prevalence Survey and Case-Control Study. *Open Forum Infectious Diseases*, 6(1) 337. https://doi.org/10.1093/ofid/ofy337.

Seung, KJ., Keshavjee, S., & Rich, ML. (2015). Multidrug-Resistant Tuberculosis and Extensively Drug-Resistant Tuberculosis. *Cold Spring Harb Perspect Med,* 5(9): a017863. doi: 10.1101/cshperspect.a017863. Review. PubMed PMID: 25918181; PubMed Central PMCID: PMC4561400.

Shariff, NM., & Safian, N. (2015). Diabetes mellitus and its influence on sputum smear positivity at the 2nd month of treatment among pulmonary tuberculosis patients in Kuala Lumpur, Malaysia: A case control study. *Int J Mycobacteriol,* 4(4):323-9. doi: 10.1016/j.ijmyco.2015.09.003.

Sherwani, S. I., Khan, H. A., Ekhzaimy, A., Masood, A., & Sakharkar, M. K. (2016). Significance of HbA1c Test in Diagnosis and Prognosis of Diabetic Patients. *Biomarker insights*, *11*, 95–104. https://doi.org/10.4137/BMI.S38440.

Shewade, HD., Gupta, V., Satyanarayana, S., Kharate, A., Sahai, KN., Murali, L., & Chadha, SS. (2018). Active case finding among marginalised and vulnerable populations reduces catastrophic costs due to tuberculosis

diagnosis. *Glob Health Action,* 11(1):1494897. doi: 10.1080/16549716.2018.1494897.

Shin, JH., Yang, JY., Jeon, BY., Yoon, YJ., Cho, SN., Kang, YH., Ryu, DH., & Hwang, GS. (2011). HNMR-based metabolomic profiling in mice infected with *Mycobacterium tuberculosis*. *J Proteome Res,* 10(5):2238-47. doi: 10.1021/pr101054m.

Siddique, A., Schnitzer, M. E., Bahamyirou, A., Wang, G., Holtz, TH., & Migliori, GB. (2018). Causal inference with multiple concurrent medications: A comparison of methods and an application in multidrug-resistant tuberculosis. *Statistical Methods in Medical Research*, *28*(12), 3534–3549. https://doi.org/10.1177/0962280218808817.

Siddiqui, A., Khayyam, KU., & Sharma, M. (2016). Effect of Diabetes Mellitus on Tuberculosis Treatment Outcome and Adverse Reactions in Patients Receiving Directly Observed Treatment Strategy in India: A Prospective Study. *BioMed Research International,* https://doi.org/10.1155/2016/7273935.

Silva, DR., Dalcolmo, M., Tiberi, S., Arbex, MA., Munoz-Torrico, M., Duarte, R., & Migliori, GB. (2018). New and repurposed drugs to treat multidrug- and extensively drug-resistant tuberculosis. *J Bras Pneumol,* 44(2):153-160. doi: 10.1590/s1806-37562017000000436.

Sita-Lumsden, A., Lapthorn, G., Swaminathan, R., & Milburn, HJ. (2007). Reactivation of tuberculosis and vitamin D deficiency: the contribution of diet and exposure to sunlight. *Thorax,* 62(11):1003-7. doi: 10.1136/thx.2006.070060.

Skowronski, M., Zozulinska-Ziolkeiwciz, D., & Barinow-Wojewodzki, A. (2013). Tuberculosis and diabetes mellitus – an underappreciated association. *Arch Med Sci*. 5: 1019–1027 DOI: 10.5114/aoms.2014.46220.

Skowroński, M., Zozulińska-Ziółkiewicz, D., & Barinow-Wojewódzki, A. (2014). Tuberculosis and diabetes mellitus - an underappreciated association. *Archives of medical science AMS*, *10*(5), 1019–1027. doi:10.5114/aoms.2014.46220.

Snow, KJ., Cruz, AT., Seddon, JA., Ferrand, RA., Chiang, SS., Hughes., & Denholm. (2019). Adolescent tuberculosis. *The Lancet Child & Adolescent Health.* https://doi.org/10.1016/S2352-4642(19)30392-X.

Story, A., Murad, S., Roberts, W., Verheyen, M., & Hayward, AC. (2007). London Tuberculosis Nurses Network. Tuberculosis in London: the importance of homelessness, problem drug use and prison. *Thorax,* 62(8):667-71. http://dx.doi.org/10.1136/thx.2006.065409.

Swapnil, Nimkar. (2019) Prevalence of chest symptomatic of tuberculosis among diabetes patients in Udupi taluk. *Clinical Epidemiology and Global Health*. https://doi.org/10.1016/j.cegh.2019.06.010.

Tahir, Z., Ahmad, M. U., Akhtar, A. M., Yaqub, T., Mushtaq, M. H., & Javed, H. (2016). Diabetes mellitus among tuberculosis patients: a cross sectional study from Pakistan. *African health sciences*, *16*(3), 671–676. https://doi.org/10.4314/ahs.v16i3.5.

Takasaki, J., Manabe, T., Morino, E., Muto, Y., Hashimoto, M., Iikura, M., Izumi, S., Sugiyama, H., & Kudo, K. (2018). Sensitivity and specificity of QuantiFERON-TB Gold Plus compared with QuantiFERON-TB Gold In-Tube and T-SPOT.TB on active tuberculosis in Japan. *J Infect Chemother,* 24(3):188-192. doi: 10.1016/j.jiac.2017.10.009.

Tiberi, S., Carvalho, AC., Sulis, G., Vaghela, D., Rendon, A., Mello, FC., & Pontali, E. (2017). The cursed duet today. *Tuberculosis and HIV-coinfection.* doi: 10.1016/j.lpm.2017.01.017.

Vallerskog, T., Martens, GW., & Kornfeld H. (2010). Diabetic Mice Display a Delayed Adaptive Immune Response to *Mycobacterium tuberculosis*. *J. Immunol,* 2010;184:6275–6282. doi: 10.4049/jimmunol.1000304.

Vassall, A., Siapka, M., Foster, N., Cunnama, L., Ramma, L., Fielding, K., & Sinanovic, E. (2017). Cost-effectiveness of Xpert MTB/RIF for tuberculosis diagnosis in South Africa: a real-world cost analysis and economic evaluation. *Lancet Glob Health,* 5(7): e710-e719. doi: 10.1016/S2214-109X(17)30205-X.

Walker, C., & Unwin, N. (2010). Estimates of the impact of diabetes on the incidence of pulmonary tuberculosis in different ethnic groups in England. *Thorax*. 65(7):578-581. doi:10.1136/thx.2009.128223.

Wang, C., Liu, CM., & Wei, LL. (2016). A Group of Novel Serum Diagnostic Biomarkers for Multidrug-Resistant Tuberculosis by iTRAQ-2D LC-MS/MS and Solexa Sequencing. *Int J Biol Sci*. 12(2):246-256. doi:10.7150/ijbs.13805.

Wang, Y. (2019). Importance of tuberculosis vaccination targeting older people in China. *The Lancet Global Health,* Volume 7, Issue 2, e165 - e166.

Wong, TY., Cheung, CM., Larsen, M., Sharma, S., & Simo, R. (2016). Diabetic retinopathy. *Nat. Rev. Dis. Primers,* 2:16012. doi: 10.1038/nrdp.2016.12.

Workneh, M.H., Bjune, G.A. & Yimer, S.A. (2016). Diabetes mellitus is associated with increased mortality during tuberculosis treatment: a prospective cohort study among tuberculosis patients in South-Eastern Amahra Region, Ethiopia. *Infect Dis Poverty* **5,** 22 https://doi.org/10.1186/s40249-016-0115-z.

Workneh, MH., Bjune, GA., & Yimer, SA. (2017). Prevalence and associated factors of tuberculosis and diabetes mellitus comorbidity: A systematic review. *PLoS One*, 12(4):e0175925. doi: 10.1371/journal.pone.0175925.

Workneh, MH., Bjune, GA., & Yimer, SA. (2016). Assessment of health system challenges and opportunities for possible integration of diabetes mellitus and tuberculosis services in South-Eastern Amhara Region, Ethiopia: a qualitative study. *BMC Health Serv Res*. 16:135. doi:10.1186/s12913-016-1378-6.

World Health Organisation. (2010). Global tuberculosis control: WHO report 2010. Retrieved from https://www.who.int.

World Health Organisation. (2013). Global tuberculosis control: WHO report 2013. Retrieved from https://www.who.int.

World Health Organisation. (2017). Global Tuberculosis Report, 2017, Retrieved from https://www.who.int.

World Health Organization 2015. *Gobal Tuberculosis Report 2015* WHO Press, Geneva (2015).

World Health Organization. (2015). Global tuberculosis report 2015, 20th ed. World Health Organization. https://apps.who.int/iris/handle/10665/191102.

World Health Organization. *Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycaemia* WHO Press, Geneva (2006).

World Health Organization. Implementing the end TB strategy: the essentials. World Health Organization; 2015.

Wu, YC., Lo, HY., Yang, SL., Chu, DC., & Chou, P. (2015). Comparing the Factors Correlated with Tuberculosis-Specific and Non-Tuberculosis-Specific Deaths in Different Age Groups among Tuberculosis-Related Deaths in Taiwan. *PLoS ONE.* 10(3): e0118929. https://doi.org/10.1371/journal.pone.0118929.

Xu, P., Wu, J., & Yang, C. (2016). Prevalence and transmission of pyrazinamide resistant Mycobacterium tuberculosis in China. *Tuberculosis (Edinb)*. 2016;98:56-61. doi:10.1016/j.tube.2016.02.008.

Yamashiro, S., Kawakami, K., Uezu, K., Kinjo, T., Miyagi, K., Nakamura, K., & Saito, A. (2005). Lower expression of Th1-related cytokines and inducible nitric oxide synthase in mice with streptozotocin-induced diabetes mellitus infected with *Mycobacterium tuberculosis. Clin Exp Immunol.* 139(1):57-64. doi: 10.1111/j.1365-2249.2005.02677.x.

Yang, C. (2016). Transmission of multidrug-resistant *Mycobacterium tuberculosis* in Shanghai, China: a retrospective observational study using whole-genome sequencing and epidemiological investigation. *The Lancet Infectious Diseases*, 17(3), 275 – 284.

Yang, Z., Susan, V., Shengfen, W., Yu, P., Bing, Z., Hui, X., & Yang, Z. (2017). Association between genotype and drug resistance profiles of *Mycobacterium tuberculosis* strains circulating in China in a national drug resistance survey. *Plos.* https://doi.org/10.1371/journal.pone.0174197.

Yew, WW., Lange, C., & Leung, CC. (2011). Treatment of tuberculosis: update 2010. *Eur Respir J,* 37(2):441-62. doi: 10.1183/09031936.00033010. Epub 2010 Sep 16. PubMed PMID: 20847074.

Zhao X, Yuan Y, Lin Y, Zhang T, & Bai Y. (2018) Vitamin D status of tuberculosis patients with diabetes mellitus in different economic areas and associated factors in China. PLOS ONE 13(11): e0206372. https://doi.org/10.1371/journal.pone.0206372.

Zheng, C., Hu, M., & Gao, F. (2017). Diabetes and pulmonary tuberculosis: a global overview with special focus on the situation in Asian countries with high TB-DM burden. *Glob Health Action*.10(1):1-11. doi: 10.1080/16549716.2016.1264702.

Zhou, H., Yang, X., Zhao, S., Pan, X. & Xu, J. (2016). Spatial epidemiology and risk factors of pulmonary tuberculosis morbidity in Wenchuan earthquake-stricken area. *Journal of Evidence-Based Medicine*, 9: 69-76. doi:10.1111/jebm.12196.

Appendix – 1 – Quality Improvement Registration Form

Quality Improvement Registration Form

(7489) Tuberculosis and Diabetes Mellitus Management

Barts Health NHS
NHS Trust

Section 1: The Project

Audit ID	7489
Application Date	23/08/2016 13:29
Submitted By	Jalal Miah
Audit Title	Tuberculosis and Diabetes Mellitus Management
Reaudit Of	N/A
Audit Type	Regular
Intended Start Date	23/08/2016
Data Collection By	31/12/2016
Report Expected By	04/04/2017
Primary Specialty	Infection Control
Secondary Specialties	Clinical Microbiology
Status	Pending Endorsement
Paused?	No

Section 2: Project Team

Project Lead	Jalal Miah
Audit Team	Simon Tiberi
Are you receiving financial reward for participation in this project?	No

Section 3: Why is the project important?

Background of the project - why have you chosen this topic?	Rationale / Background There is a strong evidence to suggest diabetes mellitus (DM) as a risk factor for acquiring tuberculosis (TB) disease. Published data show individuals affected with type 2 DM have triple the risk of developing active TB disease compared to those without DM within a population (Sulaiman et al. 2011). DM has been shown to modify the presenting features of TB including pulmonary TB and is more commonly associated with atypical radiological presentation, patients are more likely to have suboptimal TB treatment outcomes, increased reactivation of disease following treatment, and an increased risk of death (Wang, Yang, and Chen, 2009). In recent decades, the increasing prevalence of TB, including Multi Drug Resistant TB (MDR-TB), and DM cases in the world, makes the argument for these two conditions be the evaluated as bi-directional risk factors for acquiring TB disease only, or TB-DM, or DM only, which pose a significant public health problem. NICE guidelines identifies diabetes as a risk factor for TB disease, however, no national or international guidelines on TB management or Endocrinology state to screen TB patients for DM or to implement a joint care for TB patients in relation to DM.

Quality Improvement Registration Form

(7489) Tuberculosis and Diabetes Mellitus Management

Barts Health NHS
NHS Trust

	There is no formal screening of DM in TB patients nationally, and lack of UK understanding of the prevalence of TB-DM patients and the characteristics of disease, disease outcome, and treatment efficacy in this risk group.
Aims of the project?	This study aims to describe the epidemiology and clinical presentation of patients with tuberculosis and diabetes in Newham, and how they are managed in line with NICE TB guidelines. Objectives: 1. To determine the prevalence of DM among TB patients in Newham. 2. To analyse epidemiological and demographic variables associated with DM among TB patients. 3. To describe clinical presentation of TB-DM and diagnosis of DM in TB patients.

Section 4: Guidelines/standards you are auditing against

Type	Standard	Reference
NICE Guidance	(CG117) Tuberculosis	CG117

Section 5: Use of electronic health records for data collection

Data Source(s)	From an existing Trust database: EPR
Describe the sample	Patient diagnosed with only TB and TB-Diabetes Mellitus confirmed cases will be included in the sample.
Sample data period	2009-2014
Site(s)	Newham
Population size	Approximately 1600
Sample size	1600
Age of patients	> 18 years of age
Does the audit include patients aged 16 or under?	No
Exclusions	< 18 years of age

Section 6: Support

Do you require assistance with obtaining data from electronic records?	No
Do you require assistance with case note retrieval?	No

Section 7: Completing the project

Audience	Agreed With	Presentation Date

Quality Improvement Registration Form

(7489) Tuberculosis and Diabetes Mellitus Management

Barts Health NHS
NHS Trust

Section 8: Data collection files

File name	Type	Description
TBnetStudy-53_Appendix1_V1-0.docx (21kb)	Other	

Section 9: Project Agreement

(a) I agree to undertake this project in accordance with the Trust Clinical Audit policy, adhering to information governance and confidentiality principles.

(b) I understand that I am accountable for completion of the project. The report and recommendations must be presented in Trust format. (Contact clinical.effectiveness@bartshealth.nhs.uk for advice)

(c) I agree to report any concerns about quality and safety of practice.

(d) I undertake to discuss this project with colleagues and to share the conclusions in an appropriate manner.

(e) On completion of the project I shall agree actions with the team and ensure implementation. This will be recorded in the project summary and shared with clinical.effectiveness@bartshealth.nhs.uk

(f) I confirm that I have declared any financial recompense from an external company for completion of the project.

(g) I agree to handover this project if I am unable to complete it.

Agreement	Name	Date
Project Lead	Jalal Miah	23/08/2016

Endorsement	Name	Date
Clinical Effectiveness Lead	Victoria Thickett	Not Yet
Line Manager	Simon Tiberi	23/08/2016

Provisional Quality Improvement Action Plan (Pending Review)

(7489) Tuberculosis and Diabetes Mellitus Management

Barts Health NHS
NHS Trust

Section 1: The Project

Audit ID	7489
Reaudit Of	N/A
Audit Title	Tuberculosis and Diabetes Mellitus Management
Audit Team	Jalal Miah (Project Lead), Simon Tiberi
Primary Specialty	Infection Control
Secondary Specialties	Clinical Microbiology
Aims	This study aims to describe the epidemiology and clinical presentation of patients with tuberculosis and diabetes in Newham, and how they are managed in line with NICE TB guidelines. Objectives: 1. To determine the prevalence of DM among TB patients in Newham. 2. To analyse epidemiological and demographic variables associated with DM among TB patients. 3. To describe clinical presentation of TB-DM and diagnosis of DM in TB patients.
Method	From an existing Trust database: EPR
Assurance Level (Overall)	Significant
Start Date	23/08/2016
End Date	03/12/2018
Reaudit intention:	No intention to reaudit. Reason: Highlighting new risk factor

Section 2: Findings

Finding #1: Age: TBDM Cohort

RAG	Site	Standard	Findings
	NUH	(CG117) Tuberculosis	In the TB only cohort 40% of the TB cases was diagnosed in the age group of 19-30 years old compared to TB-DM cohort where a 36% of the TB occurred in the age group between 31 – 45 years old. The Skewness value of 0.42 and a Kurtosis value of 2.18 suggest a normal distribution of cases. The statistical test using chi-square and Fisher's Exact test shows a significant p-value of <0.05, which signifies that age is associated with the development of TB in those with coinfection of TB-DM.

Finding #2: Gender: TBDM Cohort

RAG	Site	Standard	Findings
	NUH	(CG117) Tuberculosis	In the TB only and TB-DM cohort male are more likely to be diagnosed with TB than female; 65% and 64% respectively. Females in the TB only cohort represent 35% and in the TB-DM cohort 36%. A Skewness value of 0.66 and Kurtosis value of 1.80 a normal distribution pattern follows. The statistical test using chi-Square and Fisher's Exact test with a p-value of <0.05 show's gender has no association in increases the risk of developing TB in those with DM.

Finding #3: Co-morbidity: TBDM Cohort

RAG	Site	Standard	Findings
	NUH	(CG117) Tuberculosis	In the TB only cohort a 2.8% had a co-morbidity risk factor compared to 13.8% in the TB-DM cohort. The Skewness value of -1.19 and Kurtosis value of 2.42 demonstrates a normal distribution. The statistical test using chi-square (p-value <0.05) and Fisher Exact test (p- <0.05) shows a significance result and that co-morbid risk factor increases the risk of acquiring TB in those with co-infection.

Finding #4: Symptoms: TBDM Cohort

RAG	Site	Standard	Findings
	NUH	(CG117) Tuberculosis	Cough In the TB only cohort 89 (18%) of the individuals presented with a cough as a symptom compared to 152 (31%) cases reported in the TB-DM cohort. The Skewness value of -1.39 and Kurtosis value of 2.93 shows a

			normal distribution. The statistical chi-square and Fisher's Exact test of p-value <0.05 shows a significance, TB-DM cohort are more likely to present with a cough as a symptom. Fever In the TB only cohort 18% had fever as a symptom compared to the 21% in the TB-DM cohort, the statistical significance test with a p-value <0.05 using both chi-square and Fisher's Exact test shows a significance. The Skewness value of -1.30 and Kurtosis value of 2.71 suggest a normal distribution of the population. Fever is more likely to present in TB-DM cohort. Weight loss In the TB-DM cohort 25% reported to have weight loss as a symptom compared to 11% in the TB only cohort, the statistical test using chi-square and Fisher's Exact test of a p-value of <0.05 suggests a significance association. Weight loss is more common symptom in those with TB-DM. The Skewness value of -1.39 and Kurtosis value of 2.93 suggest a normal distribution of sample. Haemoptysis In the TB only cohort 3% reported to have haemoptysis as a symptom compared with 5% in the TB-DM cohort. Using Fisher Exact test with a p-value of <0.05 suggest haemoptysis is a more likely to present as a symptom in the TB-DM. The Skewness value of -1.11 and Kurtosis value of 2.25 values suggest a normal distribution. Night Sweats In the TB-DM cohort a 102 (20%) individuals had night sweats as a symptom compared to 51 (10%) cases from the TB only cohort. The statistical test using chi-square p-value of <0.05 showed significant test. Night sweat is more common in those with TB-DM. The Skewness value of 0.04 and Kurtosis value of 1.00 values suggest of a normal distribution.

Finding #5: Steroids Use, Vit D deficient, and HbA1c Levels in TB DM Cohort			
RAG	**Site**	**Standard**	**Findings**
	NUH	(CG117) Tuberculosis	In the TB only cohort 88 (27.4%) of the cases reported to be vitamin D deficient compared to 36 (21.4%) in the TB-DM cohort. The statistical

			significant test using chi-square showed no statistical significance between TB only and TB-DM cohort. Spearman's Rho showed no association between Vitamin D and TB development. In the TB only cohort 44 (13.7%) of the cases reported to have been prescribed systemic steroids compared to 25 (14.9%) of the TB-DM cohort. The significant statistical test using chi-square p-value of 0.723 showed statistical significance and Spearman's Rho should no association. In the TB only cohort 23 (7.2%) of the cases reported to have HbA1c levels between 4.8-7.7 compared to 64 (38.1%) cases in the TB-DM. In the TB only cohort 1 (0.3%) reported a HbA1c levels between 7.8-10.3 compared to 6 (3.6%) cases in the TB-DM cohort. In the TB only cohort 0 reported a HbA1c levels between 10.4-18.4 compared to 9 (5.4%) cases in the TB-DM cohort. The statistical significance test using chi-square showed no significance, however, Spearman's Rho used to test the measurement of strength of association between the two variables shows a significance with a p-value of <0.05.

Assurance Level	Description
Full/Significant	The standard is consistently adhered to and assurance is given to mitigate the risk of non-compliance. Evidence of a well designed process is evident. (Usually 95-100% compliance.)
Reasonable	There is reasonable evidence of compliance, but improvement is needed (85 – 94% compliance).
Limited	There is some evidence of compliance, but significant service improvement is necessary (Usually below 85% compliance).
None	No evidence of compliance. There are serious, fundamental weaknesses due to an absence of an adequate process. Urgent attention is required to address non compliance (zero compliance).
Not sure	Unable to map findings to an assurance level.

Action	The screening procedures will include all of the patients which attend the Trust as an inpatient or in an outpatient TB clinic, each patient to be asked about their history of DM. Patients not aware of their status to be offered one HbA1c or fasting blood glucose level (FBG) during TB treatment. Patients with known DM and newly diagnosed DM to be referred to the diabetes clinic for further management. Testing for human immunodeficiency virus (HIV) infection to be offered as routine to TB patients.
Staff Involved	Jalal Miah, Dr Simon Tiberi
Owner	Jalal Miah
Deadline	31/12/2018
Implementation Status	In Progress
Comments	Implement finding to screen all TB patients for DM.

Section 4: Audit Meetings

Audience	Agreed With	Date
TB Awareness Day	Simon Tiberi	25/11/2018

Section 3: Recommendations

Recommendation #1	
Recommendation	All consecutively diagnosed TB patients aged ?18 years who attended the Trust either as an inpatient or to the TB clinic to be screened for DM, as NICE guidelines recognises DM as a risk factor.

MRC Medical Research Council

NHS Health Research Authority

Do I need NHS REC approval?

To print your result with title and IRAS Project ID please enter your details below:

Title of your research:

Characteristic of Tuberculosis-Diabetes Mellitus in the London Borough of Newham

IRAS Project ID (if available):

Your answers to the following questions indicate that you **do not need NHS REC approval for sites in England.** However, you may need other approvals.

Appendix 3 – Data collection variables

Section 1 "Sociodemographic data"

Center free text field (specify)

ID Patient Code institute code and 4-digit progressive serial number

Hospitalized from – to date field: format DD MM YY- DD MM YY

Date of birth date field: format DD MM YY

Country of birth date field: format DD MM YY

Length of stay in the host country numeric field 3 digits (months)

Gender curtain drop-down menu (one choice): 1) F (female), 2) M (male)

Education curtain drop-down menu (one choice): 1) none (no formal education), 2) primary education (≤ 7 years), 3) higher education (>7 years including vocational training, secondary, high school and college/university).

Employment curtain drop-down menu (one choice): 1) street seller, 2) self-employed (sales person, craftsman), 3) employee, 4) caretaker, baby-sitter, 5) housekeeper, 6) health care worker, 7) student, 8) restaurant staff, 9) farmer, 10) construction worker, 11) industry worker, 12) other, 13) unemployed.

Section 2 "Clinical data"

ID Patient Code institute code and 4-digit progressive serial number

Weight numeric field 3 digits (kilograms)

Height numeric field 3 digits (cm)

Tobacco use curtain drop-down menu (one choice): 1) yes, 2) no, 3) nr

Tobacco intake numeric field 3 digits (cigarettes per day)

Alcohol use curtain drop-down menu (one choice): 1) yes, 2) no, 3) nr

Alcohol intake numeric field 3 digits (drinks per week)

Drug abuse curtain drop-down menu (one choice): 1) yes, 2) no, 3) nr

Type of drug free text field (specify)

HIV+ curtain drop-down menu (one choice): 1) yes, 2) no, 3) nr

Date diagnosis date field: format DD MM YY

CD4+ at diagnosis numeric field 3 digits (cell/mm3)

Date date field: format DD MM YY

Last CD4+ numeric field 3 digits (cell/mm3)

Date date field: format DD MM YY

Previous TB disease curtain drop-down menu (one choice): 1) yes, 2) no, 3) nr

Date diagnosis date field: format DD MM YY

Previous TB contact curtain drop-down menu (one choice): 1) yes, 2) no, 3) nr

Date date field: format DD MM YY

Comorbidities curtain drop-down menu (multiple choice): 1) long term steroid (inhalation corticosteoids or peroral corticosteroids), 2) cytotoxic treatment, 3) immunosuppressive medications, 4) chronic renal failure;5)chronic liver disease, 6)chronic lung diseases), 7) haematological malignancies. 8),other malignancies; 9), silicosis; 10) gastrectomy 11)anti-TNF treatment

Pregnant or lactating women curtain drop-down menu (one choice): 1) yes, 2) no, 3) nr

Symptoms curtain drop-down menu (one choice): 1) yes, 2) no, 3) nr

Persisting cough curtain drop-down menu (one choice): 1) yes, 2) no, 3) nr

Fever curtain drop-down menu (one choice): 1) yes, 2) no, 3) nr

Weight loss curtain drop-down menu (one choice): 1) yes, 2) no, 3) nr

Anorexia curtain drop-down menu (one choice): 1) yes, 2) no, 3) nr

Hemoptysis curtain drop-down menu (one choice): 1) yes, 2) no, 3) nr

Chest pain curtain drop-down menu (one choice): 1) yes, 2) no, 3) nr

Fatigue curtain drop-down menu (one choice): 1) yes, 2) no, 3) nr

Night sweating curtain drop-down menu (one choice): 1) yes, 2) no, 3) nr

Other free text field (specify)

Tuberculin skin test curtain drop-down menu (one choice): 1) negative, 2) positive, 3) nr

Date date field: format DD MM YY

IGRAs curtain drop-down menu (one choice): 1) negative, 2) positive, 3) indeterminate, 3) nr

Type curtain drop-down menu (one choice): 1) QFT, 2) TSpot-TB

Date date field: format DD MM YY

TB form curtain drop-down menu (multiple choice): P=pulmonary E=extrapulmonary

Chest X-Ray curtain drop-down menu (one choice: 1) yes, 2) no, 3) nr

Date date field: format DD MM YY

CT (computed tomography scans) curtain drop-down menu (one choice): yes/no/nr

Date date field: format DD MM YY

Normal curtain drop-down menu (one choice): 1) yes, 2) no, 3) nr

Cavity curtain drop-down menu (one choice): 1) yes, 2) no, 3) nr

Localization curtain drop-down menu (one choice): U=upper M= middle L=lower

Consolidation curtain drop-down menu (one choice): 1) yes, 2) no, 3) nr

Localization curtain drop-down menu (one choice): U=upper M= middle L=lower

Miliary curtain drop-down menu (one choice): 1) yes, 2) no, 3) nr

Plural effusion curtain drop-down menu (one choice): 1) yes, 2) no, 3) nr

Localization curtain drop-down menu (one choice): M=monolateral B=bilateral

Sputum smear microscopy curtain drop-down menu (one choice): 1) yes, 2) no, 3) nr

Result curtain drop-down menu (one choice): 1) negative, 2) positive, 3) nr

Date date field: format DD MM YY

Sputum culture curtain drop-down menu (one choice): 1) yes, 2) no, 3) nr

Result curtain drop-down menu (one choice): 1) negative, 2) positive, 3) nr

Date date field: format DD MM YY

Other material smear microscopy curtain drop-down menu (one choice): 1) yes, 2) no, 3) nr

Result curtain drop-down menu (one choice): 1) negative, 2) positive, 3) nr

Date date field: format DD MM YY

Other material culture curtain drop-down menu (one choice): 1) yes, 2) no, 3) nr

Result curtain drop-down menu (one choice): 1) negative, 2) positive, 3) nr

Date date field: format DD MM YY

PCR curtain drop-down menu (one choice): 1) yes, 2) no, 3) nr

Result curtain drop-down menu (one choice): 1) negative, 2) positive, 3) nr

Date date field: format DD MM YY

Anti -TB Drug Resistance curtain drop-down menu (one choice): 1) yes, 2) no, 3) nr

Method curtain drop-down menu (one choice): 1) culture (proportion) 2) molecular **(specify)**,

Any drug resistance curtain drop-down menu (one choice): 1) yes, 2) no, 3) nr

Resistant to curtain drop-down menu (multiple choice): 1) isoniazid, 2) rifampicin, 3) pyrazinamid, 4) ethambutol, 5) streptomycin, 6) amikacyn, 7) moxifloxacin, 8) levofloxacin, 9) ethionamid/protionamyd, 10) cycloserin/terizidon,

11) PAS, 12) claritromycin, 13) amoxicillin/clavulanic acid, 14) linezolid, 15) clofazimine

Diabetes

Previous DM diagnosis curtain drop-down menu (one choice): 1) yes, 2) no, 3) nr

Type curtain drop-down menu (one choice): 1) type1, 2) type 2, 3) nr

Date date field: format MM YY

New DM diagnosis curtain drop-down menu (one choice): 1) yes, 2) no, 3) nr

Date date field: format DD MM YY

Signs and symptoms of DM curtain drop-down menu (multiple choice): 1) polyuria, 2) polydipsia, 3) poliphagia, 4) weight loss in the last 2 months

Glycemia 1 numeric field 4 digits with one decimal point (mg/dl)

Date date field: format DD MM YY

Glycemia 2 numeric field 4 digits with one decimal point (mg/dl)

Date date field: format DD MM YY

Glycemia 3 numeric field 4 digits with one decimal point (mg/dl)

Date date field: format DD MM YY

HbA1C numeric field 2 digits with one decimal point (%)

Date **date field: format DD MM YY**

Oral glucose tolerance **curtain drop-down menu (one choice):** 1) yes, 2) no, 3)

OGTT results **numeric field 4 digits with one decimal point (mg/dl)**

Date **date field: format DD MM YY**

DM treatment **curtain drop-down menu (one choice):** 1) yes, 2) no, 3) nr

Oral hypoglycaemic agents **curtain drop-down menu (one choice):** 1) yes, 2) no, 3) nr

Insulin **curtain drop-down menu (one choice):** 1) yes, 2) no, 3) nr

DM treatment change due to TB drug interaction **curtain drop-down menu (one choice):** 1) yes, 2) no, 3) nr. If yes specify interaction: **free text field (specify)**

Vitamind D Levels 1 **numeric field 4 digits with one decimal point (ng/mL)**

Date **date field: format DD MM YY**

Albumin Levels 1 **numeric field 4 digits with one decimal point (g/L)**

Date **date field: format DD MM YY**

Appendix 4 – Differential characteristic between TB and TB-DM cohort

Characteristics	TB	TB-DM
Age	Equally to occur in all age groups	More common with older age
Gender	Men more likely affected	Men more likely affected
Symptoms (cough, fever, haemoptysis, weight loss, night sweat)	Symptoms range from non-specific to severe	Symptoms more severe
PTB / EPTB	Involves both	Significantly higher EPTB involvement
Chest x-ray	Upper-lobe infiltrates with less cavitation	Greater cavitation
AFB Smear Grade	Less higher grade positivity	Greater higher grade positivity
Culture conversion & infectivity	< 2months for culture conversion, less infectious	>2 months for culture conversion, more infectious
Haemoglobin level	Normal	HbA1c level higher

Appendix 5 – Therapeutic Drug Monitoring for Antimicrobials in Tuberculosis

This is a quality improvement project undertaken to improve the therapeutic drug monitoring (TDM) for TB patients prescribed rifampicin and isoniazid containing medication, and other antimicrobials (levofloxacin, moxifloxacin and linezolid). This is secondary to evidence to suggest that TB patients with co-morbidities, including DM are likely to have a different pharmacokinetics to these drugs, leading to under-dosing, reduced effectiveness and higher rates of treatment failure. Under-dosing should also be considered in any patient with suspected treatment failure irrespective of whether they have comorbidities.

Rifampicin and Isoniazid

Preparations:

- Rifampicin alone: **Rifampicin, Rifampin, Rifadin, Rimactane**
- Isoniazid alone: **Isoniazid**
- Rifampicin with isoniazid: **Rifinah**
- Rifampicin with isoniazid and pyrazinamide: **Rifater**
- Rifampicin isoniazid, pyrazinamide and ethambutol: **Voractiv**

Patients:

- Diagnosed with TB disease (pulmonary or extra-pulmonary), prescribed one of the above preparations containing rifampicin and/or isoniazid,
- AND has been taking the medication for **2 weeks** and has:
  - Diagnosis of type 1 or type 2 diabetes
  - HIV co-infection (treated or untreated)
  - Any condition causing gastro-intestinal absorption issues (inflammatory bowel disease, coeliac disease, short bowel syndrome etc.)
  - Co-prescriptions of other medications that may interact.
- OR has been taking the medication for **2 months** (outpatient) and has a lack of clinical response to therapy or worsening clinical picture.
- OR **as soon as possible** if the patient becomes critically unwell (hospital inpatient).

Procedure:

- Identify a patient falling into the above categories.
- Check compliance with medications, including time medications are taken in relation to routine and mealtimes, and urine colour.
- If compliance poor, improve compliance prior to TDM.

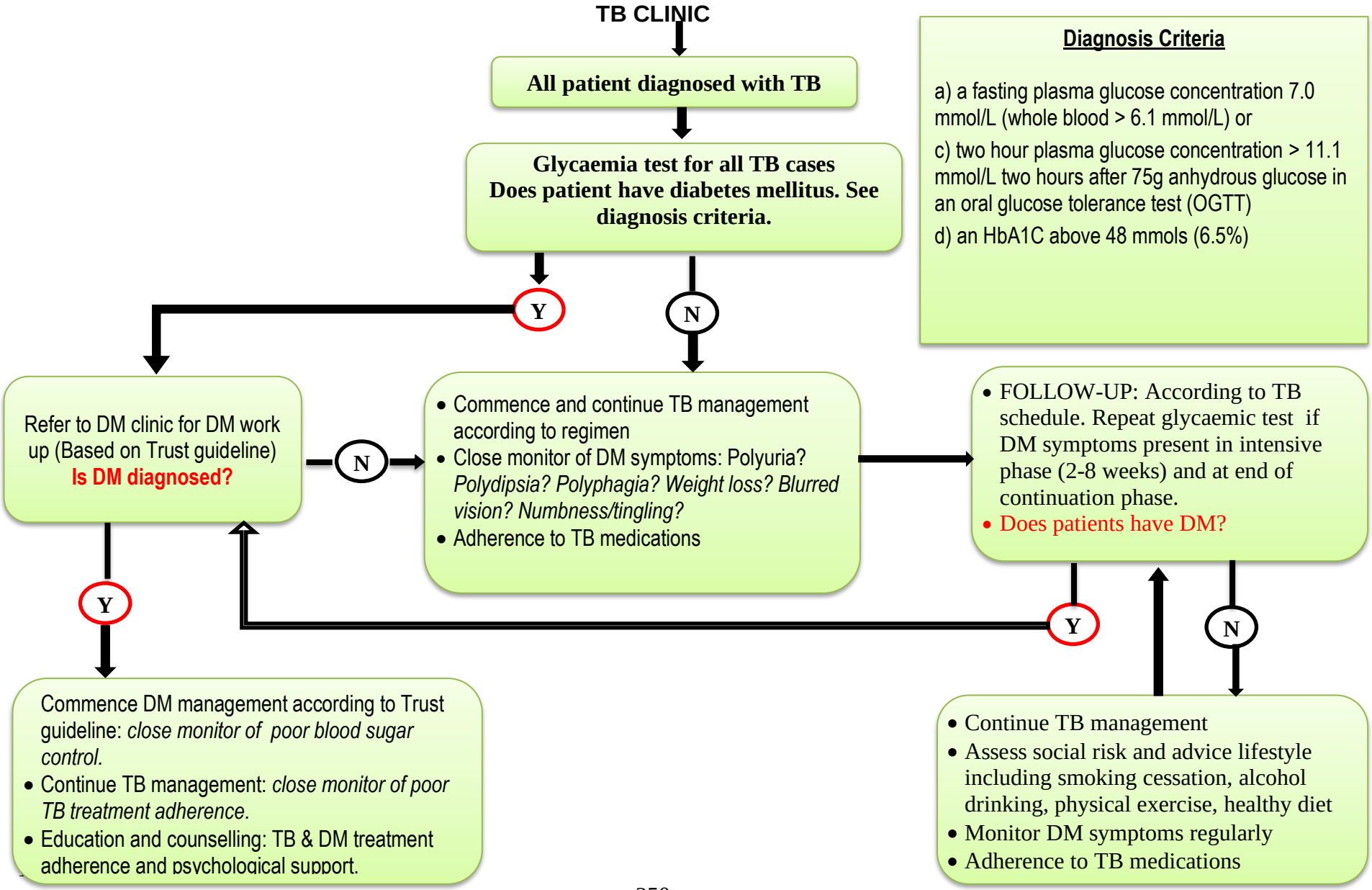
	Requests	When to take levels	Target peak (mg/L)	Subtherapeutic levels (mg/L) and actions	Toxic levels (mg/L) and actions
Rifampicin	Search for the drug serum level test on CRS and print the patient label. Take a venous sample in a GOLD TOP tube:  Stick on the CRS label and **HAND WRITE** the time of sample and time of last dose, then send to the lab.	**2hr post dose** *And 6hrs post dose in diabetics and malabsorption*	**9-24** *Note: 4-8 is low but adequate. Recheck level if no improvement*	**<4** *Requires change of dose and/or preparation**	**>24** *May require dose hold, reduction and/or change of preparation**
Isoniazid			**3-5**	**<3** *Requires change of dose and/or preparation**	**>5** *May require Dose hold, reduction and/or change of preparation**
**Please discuss the result with the TB or respiratory pharmacist/doctor to arrange a dose or preparation change.*					

Other anti-mycobacterial agents

- TDM is available for the following other antimicrobials used in TB treatment and can be sent with rifampicin and isoniazid levels if relevant to the patient.

	Requests	When to take levels	Target peak (mg/L)	Subtherapeutic levels (mg/L) and actions	Toxic levels (mg/L) and actions
Ethambutol	Search for the drug serum level test on CRS and print the patient label. Take a venous sample in a GOLD TOF tube: Stick on the CRS label and **HAND WRITE** the time of sample and time of last dose, then send to the lab.	**2hr post dose** *And 6hrs post dose in diabetics and malabsorption*	**2-6**	**<2** *Requires change of dose and/or preparation**	**>6** *May require dose hold, reduction and/or change of preparation**
Rifabutin			**0.45-0.9**	**<0.45** *Requires change of dose and/or preparation**	**>0.9** *May require dose hold, reduction and/or change of preparation**
Levofloxacin			**8-13**	**<8** *Requires change of dose and/or preparation**	**>13** *May require dose hold, reduction and/or change of preparation**
Moxifloxacin			**3-5**	**<3** *Requires change of dose and/or preparation**	**>5** *May require dose hold, reduction and/or change of preparation**
Linezolid			**12-26**	**<12** *Requires change of dose and/or preparation**	**>26** *May require dose hold, reduction and/or change of preparation**
Please discuss the result with the TB or respiratory pharmacist/doctor to arrange a dose or preparation change.					

Appendix 6 – DM Screening pathway in TB patients



Appendix 7 – Standard TB Treatment Medication

Adult TB Medication (Standard therapy) – Daily Dosing Guide

DRUG	PREPARATION	DOSE according to PATIENT'S WEIGHT								DOSE FREQUENCY
		37 – 43.9kg	44 – 49.9kg	50 – 56.9kg	57 – 63.9kg	64 – 69.9kg	70 – 76.9kg	77 – 83.9kg	84 – 89.9kg	
2-months INITIAL PHASE										
Rifinah	**100/150** Rifampicin 150mg + Isoniazid 100mg	3 tablets	3 tablets							**All medications to be taken ONCE a DAY** (half an hour before food)
	150/300 Rifampicin 300mg + Isoniazid 150mg			2 tablets	2 tablets	2 tablets	2 tablets	2 tablets	2 tablets	
Pyridoxine	10mg tablet	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg	
Pyrazinamide	500mg tablet	1.5 g	1.5 g	2 g	2 g	2 g	2 g	2 g	2 g	
Ethambutol *	100mg, 400mg tablet	600 mg	700 mg	800 mg	900 mg	1000 mg	1100 mg	1200 mg	1300 mg	
Followed by 4-months CONTINUATION PHASE										
Rifinah	**100/150** Rifampicin 150mg + Isoniazid 100mg	3 tablets	3 tablets							**All medications to be taken ONCE a DAY** (half an hour before food)
	150/300 Rifampicin 300mg + Isoniazid 150mg			2 tablets	2 tablets	2 tablets	2 tablets	2 tablets	2 tablets	
Pyridoxine	10mg tablet	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg	

Appendix- 8 – Barts Health NHS Trust TB Policy – Contribution to development

POLICY AND PROCEDURE FOR THE PREVENTION AND CONTROL OF TUBERCULOSIS – INFECTION CONTROL POLICY

APPROVING COMMITTEE(S)	Hospital Infection Control Committee	Date approved:	xx 2018
EFFECTIVE FROM	xx 2018		
DISTRIBUTION	Emergency medicine, Acute medicine, Occupational Health, TB Nursing staff, Infection Prevention and Control Teams, Consultants Respiratory physicians and teams, Consultants in Infection and teams, site managers for Barts Health NHS Trust.		
RELATED DOCUMENTS	Hand Hygiene Policy- COR/POL/057/2012-001 Environmental Cleaning and Decontamination Isolation & management of Infectious Diseases Policy Outbreak Policy Standard precautions – the use of Protective equipment. Control of Tuberculosis(TB) in staff - COR-		

251

	POL-017/2013-001 Statutory and Mandatory Training Policy (COR/POL/026/2012-001) Production and Implementation of Trust Policies and Guidelines (COR/POL/001/2014-001)
STANDARDS	Tuberculosis - NICE Guidelines (2016) – NG33 Risk Management Standard for acute Trust (2007) (Infection Control). Department of Health (1995) Hospital Infection Control - Guidance on the control of infection on hospitals. PHLS: London. Department of Health (2003) Winning Ways – Working together to reduce Healthcare Associated Infection in England. DOH: London. The Health and Safety at Work Act, 1974.
OWNER	Deputy Director of Infection Prevention & Control (DDIPC).
AUTHORS/FURTHER INFORMATION	Deputy Director of Infection Prevention & Control (DDIPC).
SUPERCEDED DOCUMENTS	CONTROL OF TUBERCULOSIS – INFECTION CONTROL POLICY, 2013
REVIEW DUE	April 2020
KEYWORDS	Infection Control Tuberculosis, MDRTB
INTRANET LOCATION(S)	http:// [file location]

CONSULTATION	*Barts Health*	Barts Health Infection Prevention and Control Committee Occupational Health Infection Department
	Barts and the London unit (BLT)	Respiratory medicine and TB nurses
	Newham University Hospital unit (NUH)	Respiratory medicine and TB nurses Emergency medicine Infection Prevention and Control
	Whipps Cross University Hospital (WX)	Respiratory medicine and TB nurses Emergency medicine Infection Prevention and Control
	External Partner(s)	

SCOPE OF APPLICATION AND EXEMPTIONS	**Included in policy:** *For the groups listed below, failure to follow the policy may result in investigation and management action which may include formal action in line with the Trust's disciplinary or capability procedures for Trust employees, and other action in relation to organisations contracted to the Trust, which may result in the termination of a contract, assignment, placement, secondment or honorary arrangement.*
	All Trust staff, working in whatever capacity, other staff, students and contractors working within the Trust.
	Other staff, students and contractors working within the Trust
	Exempted from policy: No staff groups are exempt from this policy

1.0 INTRODUCTION AND AIMS OF POLICY

1.1 The aim of the policy is to prevent and control *Mycobacterium tuberculosis* (MTB) infection within the Trust, providing a safe working enviroment for both workers (HCWs), their patients, and visitors. Due to the Trusts geographical location in the most prevalent areas for Tuberculosis in

London and the UK as a whole, it is essential that staff are provided with clear guidance so that all patients with suspected or confirmed Tuberculosis will be appropriately assessed and managed to reduce the risk of transmission to other patients and staff in accordance with national and local guidelines. All clinical staff are involved in the assessment, treatment and management of patients with Tuberculosis.

TB is not uncommon and there is a small but constant risk of hospital-acquired infection in both patients and staff. Early identification of TB in patients or staff, and implementation of this infection control policy involving TB specialist nurses and appropriate management of TB cases is essential in the prevention of transmission.

2.0 SUMMARY

2.1 The policy describes how to apply the prevention and control measures to prevent cross infection of MTB to patients, staff and the general public within our Trust. It outlines appropriate isolation and respiratory precautions for all patients with suspected or confirmed tuberculosis (TB). This policy identifies the specific management of infectious patients with MTB disease, contact tracing and notification. The document outlines the neccessary diagnosis, specimen collection methods and the safe transportation of patients within the hospital.

- Pulmonary TB is described as smear positive when *Mycobacterium tuberculosis* bacteria are visible by microscopy of sputum smears.

- Pulmonary TB with three negative sputum smears is **minimally** infectious and described as “smear negative”.

- Non-respiratory tract TB is **NOT** infectious to others (**unless** aerosolized under unusual circumstances).

- Patients or staff may be particularly at risk if they are immunocompromised, through having illnesses such as HIV infection, chronic renal failure and diseases that require treatment with immunosuppressive drugs.

- Early identification, involving TB specialist nurses and appropriate management of TB cases is essential to the prevention of transmission.

Note: These guidelines specifically address the infection control issues of respiratory tract tuberculosis, that is laryngeal tuberculosis and pulmonary tuberculosis, the principal infectious forms of the disease. Transmission of TB is primarily person-to-person through the inhalation of infectious droplets coughed into the air by an individual with pulmonary or laryngeal TB.

Symptoms of TB include: Chest pain, persistent cough, weight loss, drenching night sweats and fevers, fatigue, haemoptysis and an abnormal chest x-ray

Tuberculosis is a notifiable disease requiring notification to Public Health England (TB nursing service will notify cases accordingly).

In cases of Paediatric TB consider the risk of the same infection in the carer's / parents – this will mean isolating the child until a risk assessment is undertaken by the clinical team caring for the child.

The BCG (Bacillus Calmette-Guerin) immunization provides a degree of protection (10-30%) against TB, however, it most definitely cannot be relied upon as a method of prevention. BCG vaccinated staff or carers will still need to adopt our Trusts infection control measures detailed in this policy. The same also applies for persons having had TB previously. Previous TB disease does not offer protection to new infection. In 2005 the UK moved from a school-aged universal BCG vaccination policy to a targeted policy towards children at high risk. Many health care workers will have evidence of vaccination, but regardless all staff, who have contact with patients or clinical specimens, require Occupational Health assessment. Any doubts regarding staff immunity should be discussed with the Occupational Health Department.

Remember that TB is common in patients presenting at Barts Trust and may occur in the presence of other diseases. If a patient is suspected to have smear positive pulmonary TB, or laryngeal TB, admit to a side room. Do not admit them to an open ward until the diagnosis has been excluded (send sputum for AFB and await result before de-isolating from a side room with respiratory precautions). Infectious TB can often be identified rapidly by microscopy of sputum but the clinical history and the chest X-Ray appearances often indicate that a high level of suspicion is required.

3.0 Definitions

Negative pressure ventilation https://hberm.com/wp-content/uploads/2015/10/HBN-04-01-Supplement-1-Isolation-facilities-for-infectious-patients-in-acute-settings-20131.pdf	A ventilation system that generates negative pressure to allow air to flow into the isolation room but not escape from the room. Prevents contaminated air flow leaving the room and entering other clinical areas and the number of air changes per hour is recommended as a minimum of 10 changes of room air per hour.
Smear positive	TB bacteria are seen on microscopy of sputum.
Smear negative and culture positive	TB bacilli are not seen on the sputum smear, but are grown on culture of the sputum/ tissue.
Susceptible (or fully sensitive) TB	*Mycobacterium tuberculosis* sensitive to first-line drug therapy
MDR TB	Multi Drug Resistant TB. Tuberculosis that is resistant to at least isoniazid and rifampicin.
XDR TB	Extensively Drug Resistant TB. MDR TB with additional resistance to fluoroquinolones and one second line injectable aminoglycoside.

PTB	Pulmonary TB, affecting the lungs.
Extra-pulmonary TB	Extra-pulmonary TB, also referred to as 'closed TB', mostly affecting organs other than the lungs.
MTB	*Mycobacterium tuberculosis*

4.0 INTRODUCTION

4.1 Tuberculosis (TB) is the leading cause of death in the world from a bacterial infectious disease, affecting approximately 10 million people a year and is the 9th most common cause of death worldwide. It is estimated that up to to one-third of the entire world's population has latent TB infection with 10% of infected persons developing the disease during their lifetimes.

4.2 TB is mainly a respiratory disease caused by the bacterium called Mycobacterium tuberculosis (MTB). MTB is the etiologic agent of tuberculosis in humans, and humans are the only reservoir for the bacterium.

4.3 TB usually causes disease of the lungs (pulmonary), but can affect any other part of the body (extra-pulmonary). Not all forms of tuberculosis are infectious. Those patients with TB in organs other than the lungs and larynx are rarely infectious to others. Extra-pulmonary TB, however, is occasionally contagious: it can be transmitted to others by inhalation of aerosols produced when pus/tissue from sites of infection are aspirated or irrigated and therefore universal precautions and the recommendations of this guideline should be followed at these times.

Predisposing factors for TB include:

- *Prolonged close contact with infectious TB disease (>8 hours cumulative)*
- *Those who have lived in, travel to or visited from a place where TB is prevalent*
- *Those who live in an ethnic minority communities originating from places where TB is prevalent*
- *Those with an immune system weakened by immunosuppressive medications, HIV infection or other acquire immunosupression, cancer, tranplantation or other medical co-morbidities like diabetes*
- *Those with chronic poor health and nutrition due to social and lifestyle problems such as homeless, drug abuse or alcoholism*
- *Those living in poor or crowded housing conditions, including those living in hostels/ prisons*

5.0 LATENT TB

5.1 TB can also present as latent TB in which people can be infected with Mycobacterium tuberculosis, but they do not have active presenting symptoms. Latent TB is not infectious and cannot infect others - See Table 1:

Table 1. Latent and Active TB

Latent TB	*Active TB (in lungs or else where)*
MTB present/was present	*MTB present*
Tuberculin skin test positive	*Tuberculin skin test positive (can be negative)*
Quantiferon or T-spot positive (IFN gamma release assay (IGRA) positive)	*Quantiferon/T-spot positive (can be negative in 30% of active cases)*
Chest x-ray normal	*Abnormal chest x-ray if TB of lungs*
No acid-fast bacilli on sputum smear and culture negative	*In pulmonary TB Acid-fast bacilli on sputum smear and or culture positive* *Or* *No acid-fast bacilli on sputum smear but culture positive* *In pulmonary TB or in extra pulm TB- other tissue samples might be smear or culture positive or histology suggesting TB*
No clinical symptoms of TB	*Clinical symptoms present including cough, fever, weight loss, night sweats, lymph node swelling, non healting ulvers or sinus tracts or joint sweellings, back pain in the case of disciitis*
Not infectious	*Often infectious prior to treatment if pulmonary or laryngeal*

6.0 TRANSMISSION OF TUBERCULOSIS

6.1 The bacterium is usually transmitted by inhalation of aerosols produced by an infectious TB patient after prolonged contact, especially in those who are more susceptible to the disease i.e. the immuno-compromised or other risk groups. Prolonged contact is defined as a cumulative 8 hours or more.

6.2 Once inhaled the bacteria reaches the lungs, and multplies over time. This stimulates an immune reaction.

6.3 The majority of persons exposed to TB bacteria can eliminate or kill the inhaled bacteria The minorityof those exposed will go on to develop infection clinical disease may then occur.

6.4 In some instances, where a long period of time elapses between infection and development of disease, the dormant bacilli are thought to remain in either the lung or other sites, these can 'reactivate' in favourable circumstances for the organism (immunosuppression, elderly age, diabetes, cancer, HIV infection).

6.5 Tuberculosis is generally spread by infectious droplets coughed or sneezed by a person with respiratory 'pulmonary' TB. Non-respiratory 'non-pulmonary' TB is less infectious but procedures which generate infectious droplets pose a risk of transmitting TB (see above). Tuberculosis can be confined to a single site (respiratory is most common site) or can affect a combination of respiratory and non-respiratory sites, or single/multiple non-respiratory sites.

7.0 PRESENTATION OF TUBERCULOSIS

Pulmonary TB (PTB)

7.1 PTB is the most significant cause of cross infection as infectious persons can release TB bacilli to the environment and to contacts readily, through aerosol producing actions i.e. coughing.

Extra-pulmonary TB

7.2 TB can be found anywhere in the body.

Miliary TB

7.3 Miliary (disseminated) TB occurs when TB bacilli is spread through the blood stream to other parts of the body and organs. May not be infectious, but isolation precautions must be followed.

Atypical mycobacterial infection or Non-Tuberculosis Mycobacteria (NTMs)

7.4 Non-tuberculous mycobacteria (NTMs) or 'atypical mycobacteria' rarely cause cross infection in normal individuals unless they are present in large numbers and the receiving patient (close contact) is severely immunocompromised. Attention however to this is necessary in Cystic Fibrosis (CF) wards and clinics where NTMs like *Mycobacterium abscessus* can be transmitted by CF patients to other CF and predisposed patients.

Multi Drug Resistant –TB (MDR-TB)

7.5 MDR-TB is usually resistant to at least two anti-TB drugs Isoniazid and Rifampicin. MDR-TB requires a more complex drug regimen, prolonged patient isolation and prolonged therapy (up to 24 months). Patients with suspected infectious MDRTB should be isolated in a negative pressure room

and discharged only after they have 3 negative smears at weekly intervals and ideally have a negative culture (https://www.nice.org.uk/guidance/ng33/chapter/recommendations#multidrugresistant-tb-2). Discuss the decision to discharge a person with suspected or known multidrug‑resistant TB with the infection control team, the local microbiologist, the local TB service and the local PHE health protection team. (see the NICE Guidance and the MDRTB discharge form in the appendix 8)

Particular risk factors for MDR-TB include:

- History of prior anti-TB treatment or prior failure of treatment
- Contact with a known case of MDR-TB
- Birth or residence for > 3 months in a country with high incidence of susceptible TB and MDR-TB. (The World Health Organisation updates MDR-TB list – 2016 WHO TB report) (LINK).
- HIV co-infection

7.6 The identification of the MDR-TB requires a rapid diagnosis, usually by a direct PCR (polymerase chain reaction) or GeneXpert test on a sputum sample to exclude Rifampicin resistance in addition to the immediate isolation in a negative pressure room.

7.7 If MDR-TB is suspected, a Consultant in Microbiology/ Infectious Diseases and / or SpRs should be consulted for rapid diagnostic tests. This includes nucleic acid amplification test (GeneXpert – Cepheid) to determine rifampicin resistance. The presence of rifampicin resistance may be used as a surrogate marker for MDR-TB.

7.8 Patients with sputum microscopy-positive MDR-TB are potentially more infectious than fully sensitive susceptible TB and offer a worse prognosis. MDR TB is more challenging to treat than drug sensitive TB.

Extensively Drug Resistant TB (XDR-TB)

7.10 XDR-TB is defined as TB which is resistant to anti-TB medication Isoniazid and Rifampicin, plus resistant to any fluoroquinolone and at least one of the three injectable second-line drugs. As XDR-TB is resistant to first-line and second-line therapy, patients are left with less effective treatment options and a worse outcome.

7.11 Both MDR-TB and XDR-TB could result from non-compliance with TB treatment, or following reactivation of the disease after an earlier TB episode treated unsuccessfully.

1.12 Persons with HIV infection or other conditions which compromise the immune system are at higher risk for MDR-TB and XDR-TB. These people

are more likely to develop TB disease once infected and have a higher risk of death from disease.

8.0 INFECTION rISK FACTORS

8.1 It is important to distinguish between respiratory and non-respiratory TB in determining the infectiousness and determining the required infection prevention and control precautions.

8.2 Untreated patients who have a positive sputum microscopy from ***spontaneously*** expectorated sputum are highly infectious and require isolation using respiratory precautions.

8.3 The majority of non-respiratory TB cases are not infectious, and can be nursed on a general ward, once PTB is excluded as a potential differential diagnosis.

8.4 Those sputum smear negative patients with bronchial washings which are smear positive should be managed as infectious immediately after the bronchoscopy (as can become smear positive – sputum samples for acid fast bacilli should be sent) once the smear comes back negative the patients can be managed as non-infectious unless:

1. The sputum is also positive or becomes so after bronchoscpy
2. Are an inpatient after bronchoscopy; if the broncho-alveolar lavage is positive, the patient should be isolated with respiratory precautions.
3. They are known or suspected of having MDR-TB or
4. They are on a ward with immunocompromised patients (i.e. HIV, rheumatology, renal, haematoncology or oncology patients)

Table 2. Infectiousness of people known to have or suspected of having TB disease

Factors associated with non-infectiousness	Factors associated with infectiousness
No cough	Presence of a cough
No cavity in the lung	Cavity in the lung
No acid-fast bacilli on sputum smear	Acid-fast bacilli on sputum smear
Extra-pulmonary (non-pulmonary) TB disease	TB disease of the lungs, airway, or larynx
Compliant with adequate treatment for 2 weeks or longer if drug sensitive, if MDRTB 3 negative smears at weekly intervals and a negative culture.	Not recieiving adequate treatment or non compliant or drug resistance to primary treatment options (MDR or XDR TB)
Not undergoing cough-inducing procedures	Undergoing cough-inducing procedures (e.g., bronochoscopy, sputum induction, and administeatrion of aerosolized medications, chest physiotherapy)
Negative sputum cultures	Positive sputum cultures

9.0 Signs and sypmtoms of TUBERCULOSIS

9.1 A diagnosis of TB should be suspected in any patient who presents with 3 or more of the following symptoms:

- A persistent cough for >3 weeks
- Haemoptysis
- Fever
- Night sweats
- Weight loss or anorexia

10.0 DIAGNOSIS AND SPECIMEN COLLECTION

10.1 DIAGNOSING PULMONARY TUBERCULOSIS

1. Chest X-ray – if suggestive of pulmonary Tuberculosis, further tests required
2. Sputum samples: at least one early morning sputum specimen, on three consecutive days should be collected and sent for acid fast bacilli (AFB) microscopy and culture.
3. Pleural biopsy and aspiration to be collected if pleural effusion is present and also sent for AFB
4. Biopsy specimens of the lung or bronchial washings take sample and send for AFB before commencing treatment, if possible, or within 7 days of starting treatment.

10.2 NON-PULMONARY TUBERCULOSIS

1. All patients with non-pulmonary TB should have a chest x-ray to exclude or confirm co-existing pulmonary TB.
2. An early morning urine specimen on three consecutive days to test when miliary or urinary tract TB or TB in a person living with HIV is suspected.
3. Pus or tissue specimen to be collected rather than swab (swabs will not be processed)
4. Liver and bone marrow biopsy specimens are rarely indicated but may be sent for AFB when miliary TB is suspected particularly in patients with chronic pyrexia of unknown origin. Blood cultures for TB may also be sent when disseminated TB disease present.
5. Peritoneal biopsy specimens are to be collected during laparotomy when TB peritonitis is suspected.
6. A lumbar puncture to obtain cerebrospinal fluid must be collected when TB meningitis is suspected. An MRI of the brain is favoured over CT brain.

10.3 If patients with X-ray changes cannot expectorate sputum for microscopy, culture, and sensitivity a bronchoscopy may be indicated in order

to obtain the sample and confirm a diagnosis. If the broncho-alveolar lavage is positive, the patient should be isolated with respiratory precautions

10.4 Specimens should be obtained in a safe manner, by expectoration in a single/side or negative pressure room and sent to the laboratory for smear examination. The TB team and IP&C teams should be informed to make them aware and discuss patient management.

10.5 Specimens must be sealed securely; ensuring the outside of the container is not contaminated. Specimens should be obtained and placed in a specimen bag within the room. The request on electronic patient system must specify what examination is requested for the laboratory and the suspected diagnosis. As with any respiratory samples these must NOT go in the pneumatic tube system.

10.6 Patients with non-respiratory TB do not need isolation, but disposable gloves and apron must be worn when handling potentially contaminated materials, e.g. urine, pus or wound dressings. Abscess or wound irrigation can generate aerosols and such procedures should be carried out in a separate facility under strict infection control measures, visor, apron, gloves and face mask.

11.0 OTHER TESTING - TUBERCULOSIS PATIENTS

11.1 HIV testing as well as hepatitis B and C testing should be performed in all patients when a diagnosis of TB is made, and this should only be undertaken after informed consent has been obtained from the patient. Vitamin D should also be requested. Liver function tests and an eye examination should be requested preferably at the start of TB treatment.

12.0 TREATMENT

12.1 Once the diagnosis of TB is made, the clinician responsible for care should refer to the person to the adult TB Team will supervise the treatment of all cases of adult TB. Children aged under 16 should be referred to the paediatric TB team.

12.3 TB is curable with a combination of specific anti TB medication. The duration of treatment for drug sensitive TB disease is at least 6 months and for MDR-TB it can be up to 24 months. This prolonged period of infectivity and prolonged duration of treatment of MDR-TB are reasons for requiring strict infection prevention and control measures (i.e. negative pressure rooms) to minimize person to person transmission and outbreaks.

13.0 ISOLATION PRECAUTIONS

13.1 Patients with infectious TB disease are isolated to prevent cross-infection, via the respiratory tract or direct contact, to other patients and health care workers.

13.2 Patients who are suspected or confirmed as having pulmonary tuberculosis should be admitted to a side room, until their sputum status is known and risk assessment is made regarding infectiousness of the patient. The door should remain closed and a respiratory isolation notice must be displayed on the door.

13.3 Children with tuberculosis, whether infectious or not, and their visitors should be segregated from the rest of the ward until visitors have been screened to exclude them as a source of infection.

13.4 Do not admit patients with suspected infectious or confirmed pulmonary TB to a ward containing people and patients who are immunocompromised, such as transplant recipients, people living with HIV and those on anti-tumour necrosis factor alpha or other biologicals, unless they can be cared for in a negative pressure room in the same ward. Tuberculosis patients should not be mixed because these groups of immunocompromised patients can get severe disease if infected.

13.5 If the sideroom is in or adjoining / adjacent / to a ward or area in which significantly immunocompromisd, especially HIV infected patients are nursed, the isolation room must have negative air pressure with more than 10 air changes per hour with continous monitoring. Please also refer to HTM.

13.6 If an appropriate side-room is not available on the ward then this must be escalated to a senior nurse or the Clinical Site Manager.

14.0 MDR-TB

14.1 Patients suspected or confirmed as having MDR-TB should be transferred to a negative pressure room on 13F ward at the Royal London Hospital and notify Public Health England local public protection team.

14.2 If none are available locally, transfer them to a hospital that has these facilities and a clinician experienced in managing complex drug-resistant cases.

14.3 Carry out care in a negative pressure room for people with:

1. Suspected MDR-TB, until resistance has been ruled out
2. Confirmed MDR-TB, 3 negative smears at weekly intervals and a negative culture (absolute minimum requirement).
3. Seek the local Public Health protection teams advice prior to discharge (Public Health England) for agreement with the above as a case by case basis. The MDRTB discharge form (Appendix 8) can be used to document the rational for a decision to discharge such patients.
4.

15.0 DURATION OF ISOLATION

15.1 Patients with smear positive disease not known or suspected to have MDR-TB, are usually non-infectious to others after two weeks of continous appropriate treatment. If there is extensive pulmonary disease with cavities, diabetes and immunosuppression this may not be the case.

15.2 Consider de-escalating isolation after 2 weeks of treatment, taking into account the risk and benefit:

- *The person is taking and tolerating the prescribed treatment*
- *There is a agreement to continued adherence to treatment*
- *Diabetic patients and immunocompromised patients may require more than 2 weeks before they are no longer infectious*
- *There are not immunocompromised patient, such as tranplant recipients, people with HIV and those on anti-tumour necrois factor on the open ward.*
- *Patients with smear grades which are higher than 2 may require more time to become sputum smear negative*
- *There is not an extensive pulmonary involvment, including cavitation*
- *There is no laryngeal TB*

15.3 The final decision to move a patient out of isolation should be made following discussion with the Respiratory or Clinical Infection (ID) Consultant, TB team and the Infection Prevention and Control Team.

15.4 The decision to discharge the patient should be a multidisciplinary team approach, which includes provision for directly observed therapy, if required, and regular follow-up to supervise treatment compliance.

16.0 RESPIRATORY MASKS

Fit testing (at least once) should be performed by all staff working in bronchoscopy suites and nurses and medical staff working in 13F ward with TB and MDR-TB patients. This should be arranged by the charge nurse in co-ordination with Infection control.

16.1 Staff and visitors attending the patient should wear FFP 3 masks before entering the room to a susceptible or resistant TB patient.

16.2 The masks should be discarded outside the room into clinical waste and hands decontaminated, all masks are single use.

16.3 Staff having contact with a suspected / confirmed MDR-TB and suctioning or carrying out bronchoscopy should wear FFP 3 masks which meet the European standard EN149:2001 published by the Health and Safety Executive (2005).

16.4 Patients with or suspected to have MDR-TB should remain in isolation for the duration of their admission or until reviewed and advised otherwise by a specialist TB Consultant.

16.5 Gloves and aprons should be worn when handling sputum or infected body fluids. Visors should also be worn if performing suctioning, intubation, chest surgery, bronchoscopy, gastric lavage or nasogastric tube placement.

16.6 The smear-positive TB patient should be advised on good cough hygiene (cover their cough, through away infectious waste) and wear a surgical mask (not an FFP3) when the patient leaves their room (cough etiquette) e.g. for X-ray (as they may come into contact with other susceptible patients) for the first 2 weeks of treatment.

16.7 Other considerations:

- Staff suffering from any underlying immune dysfunction either innate or acquired or due to chemotherapy or undergoing immunosuppressive treatment and pregnant staff should be excluded where possible from managing TB patients.
- Aerosol generating procedures (suctioning, bronchoscopy) must be performed only when using a FFP3 mask

17.0 NEGATIVE PRESSURE ROOM

17.1 Isolate all patients known or suspected to have infectious TB. A negative pressure room is one where the air from the room is removed by dedicated ducting through a filter and into the outside air, at a distance from all other air intakes. The pressure should be 5 Pascals below the ambient air pressure of surrounding areas and have at least 10 air changes per hour. Please also refer to HTM for more details.
Bronchoscopy suites carrying out bronchoscopy for patients suspected or confirmed with having MDR-TB should be carried out in negative pressure endoscopy suites and be last on list so that a deep clean will be ensured.

17.2 Bronchoscopy for known or suspected MDR/XDR-TB patients should take place in a negative bronchoscopy suite room.

18.0 VISITING OTHER DEPARTMENTS and SITES and TRUSTS

18.1 If an infectious patient is to attend other departments/theatres/suites, the appropriate Manager/Head Nurse/ Senior Nurse must be notified so that arrangements can be made for the patient to be seen last on the list to allow time for appropriate cleaning to be carried out after the patient.

Transport and Ambulances should also be notified so that they can also arrange appropriate protective wear for staff as well as book and arrange cleaning.

19.0 WASTE

19.1 Sputum should be expectorated into a disposable sputum container/ receptacle ideally with a tight fitting lid and then either handed to staff for transport to pathology or discarded into a yellow clinical waste bag.

19.2 Used tissues and other waste must be disposed into the clinical waste stream within the room.

20.0 LINEN

20.1 Treat all soiled or infected laundry as clinically infected and dispose in a red alginate bag then into a clear bag.

21.0 FOODS AND DRINKS

21.1 It is not neccessary to use disposable crockery and cutlery as routine washing in a dishwasher will eliminate Mycobacterium tuberculosis.

22.0 CLEANING

22.2 The domestic cleaning the room is not at increased risk but should wear PPE as advised. The room should be cleaned with Hypocholite solution 1000 ppm ensuring that all surfaces are cleaned daily.

Tuberculosis may be transmitted via inadequately disinfected endoscopes. The correct decontamination processes of these instruments are identified in the Trust Endoscope Disinfection Policy.

23.0 SCREENING WHEN PATIENT ON OPEN WARD HAS INFECTIOUS TB DISEASE

23.1 If patients are exposed to a patient/member of staff who has smear positive pulmonary TB >8 hours (or less for those particularly at risk, e.g. neonates, severly immunosuppressed patients) then they need to be assessed by their medical team regarding whether or not they are at increased risk of developing TB and treated accordingly. They will then be offered screening by the TB team in conjunction with the patients' medical teams and the Infection Prevention and Control Team.

23.3 Staff contacts will be followed up by the Occupational Health Department with advice and support from both TB Team and Microbiology/ID Consultant.

23.4 Exposure on a ward is a Serious Incident (link to Adverse Incident Policy). A Datix and SI proforma must be completed and an incident meeting should take palce within 10 working days of the incident being declared. See Appendix 3: Algorithm For Dealing With TB Related Infection Control Incidents Within Barts Health Trust.

23.5 A formal risk assessment needs to be carried out by the the Infection Prevention & Control Team in conjunction with the TB service of both other patients, members of staff and visitors. This should highlight any persons in these groups that are at risk, what the level of risk is, and whether they simply need to be advised about their exposure or screened by the TB service.

A follow up meeting should take place 6-8 weks later to ensure that all the appropriate persons have been screen and to discuss the outcome of screening. This should include discussion on whether screening needs to be extended. A short formal report should be produced outling the incident and the numbers of staff, patients and visitors offered screening.

STAFF

Employees new to the NHS who will be working with patients or clinical specimens should not start work until they have completed a TB screen or health check, or documentary evidence is provided of such screening having taken place within the preceding 12 months. Employees new to the NHS who will not have contact with patients or clinical specimens should not start work if they have signs or symptoms of TB. Health checks for employees new to the NHS who will have contact with patients or clinical materials should include:

- *assessment of personal or family history of TB*
- *asking about symptoms and signs, possibly by questionnaire*
- *documentary evidence of TB skin (or interferon‑gamma release assay) testing within the past 5 years and/or BCG scar check by an occupational health professional, not relying on the applicant's personal assessment.*

Employees who will be working with patients or clinical specimens and who are Mantoux‑ or interferon‑gamma release assay‑negative (see section

1.2.1) should have an individual risk assessment for HIV infection before BCG vaccination is given - https://www.nice.org.uk/guidance/ng33/chapter/recommendations#preventing-infection-in-specific-settings

All new staff are screened on commencement at work for TB. The online pre-placment health questionnaire asks them to indicate any history of TB, history of vaccination and to complete a symptoms check list. Any indication of past history of TB or current symptoms will result in further enquiry. In addition all new NHS staff who will be working with patients or clinical specimens will be invited to attend Occupational Health (OH) for blood screening with an Interferon gamma release assay test – (T-spot – Oxford immunotec) and clearance is not issued until the results are received in OH and any clinically indicated follow up or treatment has been completed or established and advise to inform OH that they are fit for work has been received by the TB Nurses.

23.5 For staff whose role involves them working directly with patients or with specimens and who do not have a visible BCG scar, documentary evidence of having received a BCG vaccination or who are able to give a clear history of being vacciated, the BCG vaccine will be offered (when available). These staff will be initially tested for T.Spot and HIV blood test is also taken with consent of the staff member prior to immunisation with the BCG.

23.6 Any staff member whoes role involves direct patient contact or contact with specimens who declines the BCG vaccine, if offered as part of work protection immunisations would be required to complete a disclaimer, and their manager informed that they are not agreed to have the vaccine so that appropriate risk assessments can be completed in relation to the infection risks in the specific work environment.

23.5 It is not common for hospital staff to acquire tuberculosis from patients but is most definitely possible, and it is also well documented that patients can and staff can acuire TB infection from staff with unrcognised active TB disease, hence awareness and vigilance is required at all times.

23.6 Staff in contact with infectious TB patients and inappropriate protection – a cumulative close contact of 8 hours or more or contact for a week or more with a known TB case, or who may have undertaken mouth-to-mouth resusitation without appropriate protection or prolonged care of a high dependency patient. In these circumtances, staff should be considered as close contacts and standard procedures be followed which includes counselling the member/s of staff and referring to Occupational Health, who will in turn arrange initial screening at 8-10 weeks post the exposure to the patient/ colleague with diagnosed TB. The initial screening is by T-Spot and a symptoms check list. Those with symptoms suggestive of TB and/or a positive T-Spot result are referred to the TB Nurses clinic. The OH department will also refer the staff member with a positive T-Spot for a chest x-ray in all cases. Those with a chest x-ray result consistent with active TB disease should be removed from work immediately until evaluated by the TB team.

23.7 Staff with less than 8 cumulative hours with a case of smear positive TB should be reassured that the risk of acquiring TB disease is minimal however they should be reminded of the possible symptoms of TB e.g. night sweats, fevers, cough for more than 2 weeks, weight loss, haemoptysis) and the importance of reporting such symptoms promptly to the Occupational Health Department. If a member of staff had less than 8 hours of contact but is immunosuppressed or living with HIV the screening for latent TB should be offered.

23.8 Staff who have regular contact with tuberculosis patients and laboratory workers who handle TB specimens are at higher risk and should have regular education about the signs and symptoms of active TB and screen as necessary. Should any protective measures in the laboratory fail, members of staff should be counselled and referred to occupational health.

23.9 BCG does not confer satisfactory protection and therefore tuberculosis most definitely can still occur in vaccinated healthcare workers.

23.1.1 Staff working in high risk areas (respiratory and TB wards, A and E, medical admission unit, bronchoscopy suites, radiology, laboratory) should have periodic mask fit testing and appropriate advice on protective measures when looking after TB patients.

New and existing staff, particularly those who have recently travelled to high TB incidence areas of the world, should undertake new employment screening for TB in Occupational Health, or screening as a returning traveller, which starts with a questionaire and may lead to IGRA testing and referral to the TB clinic if there is evidence of active or latent TB, so as to protect their patients (especially if these are neonates, children or the immunocompromised), colleagues, community and family.

23.1.2 Staff with TB symptoms should seek immediate advice from Occupational Health or from their own GP so that they do not expose patients or colleagues to infection.

PATIENTS

23.1.3 A formal risk assessment needs to be carried out by the the Infection Prevention & Control Team in conjunction with the TB service. The risk assessment will include:

1. *The degree of the infectivity of the index case*
2. *The duration and proximity of contact*
3. *The susceptibility of other patients*

23.1.4 Contact tracing and testing will be undertaken in patients at significant risk. Identified patients will be managed as houshold contacts if exposed for long enough to be equivalent, or are particulary susceptible to infection.
23.1.5 Patients are considered at risk if they spend more than 8 hours in the same open bay as a patient with sputum smear-positive TB and a cough. For these patients, such contacts should be documented in the notes, the patient should be informed, as should their GP and named Consultant.

24.0 STAFF WITH TUBERCULOSIS
24.1 Refer to Tuberculosis in Staff policy (LINK). When a healthcare worker is diagnosed with tuberculosis, whether occupationally acquired or not, liason is important between the treating physician, the Occupational Health Department, and the Infection Prevention and Control Team. If the worker has been at work while infectious, it is neccesary to identify patients and colleagues who have had significant contact and manage them with support from the patients' Consultants, Occupational Health and the TB Team. Exposure on a ward is a Serious Incident (link to Adverse Incident Policy). A Datix and SI proforma must be completed and an incident meeting should take place within 10 working days of the incident being declared (see above, as per screening an infectious patient).

25.0 SPECIFIC MANAGEMENT- PAEDIATRIC CASES
25.1 All paediatric cases of suspected or confirmed TB must be isolated in a side room. Any visitors of a child with TB in hospital should be screened as part of contact tracing and kept separate from other patients until they have been excluded as source of infection.

25.2 Children with confirmed or suspected MDR TB will require isolation in a negative pressure side-room.

26.0 PROTECTING VULNERABLE INPATIENTS
26.1 Immunocompromised in-patients are at an increased risk of developing active TB; care must be taken to avoid exposure to persons with TB disease.

- HIV positive
- Patients who have had solid organ transplantation
- Patients with haematological malignancy
- Patients with chronic renal failure/ receiving haemodialysis
- Patients who are receiving anti-TNF alfa treatment

27.0 SPECIAL CIRCUMSTANCES

27.1 Intensive Care Units - Patients with MDR-TB should be nursed in a negative pressure facility. If not available then the patient should be transferred to a facility that has negative pressure rooms.

27.2 Risk is greatest during intubation and extubation; once the patient is on a closed suction system then risk to others is greatly reduced and should then be considered minimal. However, it is recommended that staff should wear FFP 3 masks for suseptible TB and MDR-TB. Masks must be worn at all times when administering patient care. During procedures such as intubation and extubation in addition to the FFPs mask full PPE (impermeable/water proof gown, visor and hair cap) should be worn in a suitable facility (side room, side room with ante room or negative pressure room) and should be used regardless of drug resistance status. On ITU patients should be isolated in a side room, negative pressure room, please see section 27.3 for operating theatre. With regards to operating theatres patients should preferably be last on list so that a terminal clean and minimum 4 hours of non use can occur.

The TB Infection Control precautions in an ICU are similar to anywhere else in the hospital - all respiratory precautions. Fit tested respirators (FFP3) are essential. If the patient is known to have TB and on effective therapy, the risk is minimal for transmission. However, the ICU is a place where TB can be missed, and those untreated patients pose a major risk. Periodic IGRA testing of staff should be considered.

The main issue here is the ventilator, the endotracheal tube or tracheostomy tube and the need for regular suctioning, which generates cough and aerosol. Unless gas flows are stopped for longer than one hour between cases, *M. tuberculosis* has been shown to be able to pass through the anaesthetic machine. The presence of a soda lime canister does not guarantee eradication, as desiccated soda lime is not bactericidal. Therefore, it is recommended that a bacterial/HEPA filter is placed both by the patient's airway (endotracheal tube) and on the expiratory limb of the circuit (ventilator). These should be able to filter more than 99.97% of particles greater than 0.3μm. While not specially advocated by ASA, it would be good practice to sterilise the circuits after such a case. If heat disinfection or ethylene oxide for reprocessing disposable filters should be changed.

The usual 10 air changes per hour are recommended, preferably the patient is cared for in a side room, but with a closed circuit this is not absolutely required. A deep clean is all that is required after the room is vacated, there is no role for fumigation. Routine surface cleaning targeting important droplet spread bacteria and viruses is, of course, recommended, as is hand washing (for other pathogens, not TB). Administrative, environmental, and respiratory protection interventions - especially early diagnosis and effective treatment are necessary for instituting good preventive measures and preventing nosocomial spread of TB.

27.3 Theatres – If possible, non-urgent surgical procedures should be postponed until the patient is recorded to be converted/non-infectious (sputum smear and culture negative), if the patient necessitates an urgent operation the patient should be seen last on list and all theatre staff should wear PPE

(gown, visor, gloves, FFP3 and hair cap). The operating room air flow can be set to neutral or negative pressure for an operation involving an MDR or XDR TB patient. The theatre will then require a deep clean. If surgery does not involve to respiratory tree or an area of TB infection and the patient is intubated, positive pressure can be used as once the patient is intubated and airways are sealed using the circuit and the filter and closed suctioning – there is sufficient protection. TB patients should be on closed suctioning and disposable ventilator circuits. Operating theatres also have significant air dilution which is approximately 25 air changes per hour- which is nearly an airchange every 2 minutes- which reduces any risk even further. The theatre will then require a terminal clean. UV lamps can also be considered for sterilization of the theatre post op.

27.4 If an emergency then the surgical procedure should be scheduled at the end of the day to maximize the time available for removal of airborne contamination prior to the next case. The patient should be brought straight to theatre, rather than wait in a central waiting area where exposure to other patients could potentially occur. The anaesthetist should ensure adequate anaesthesia and muscle relaxation to ensure that the patient does not cough on intubation. FFP3 masks should be worn by all staff during the procedure this is especially true for high-risk procedures, such as intubation and bronchoscopy. And staff fit tested for the mask. Movement inside the theatre should be minimised to essential staff with a minimum number of door openings and the names of all those present recorded.

27.5 Ideally, the patients should be recovered in a private room, rather than in the central recovery area. Practically, this may mean that he or she will need to recover in theatre before going back to the ward directly. The surgical mask (changed at hourly intervals if necessary) should be placed back on the patient as soon as active airway management is no longer required. If FFP 3 masks are used on a patient, consider increases in airway flow resistance by approximately 120% and that they should not be worn by the patient if he or she is hypoxic or in respiratory distress. Similarly, if hypoxia or respiratory distress occurs while wearing the mask, it should be removed.

28.0 Visitors

The nurse in charge of the ward has the overall responsibility to advise vistors of the risk of TB, however all members of staff should be share this responsibility and give a consistent message to members of the public.

28.1 It is important to distinguish between household close contacts and other visitors. Household contacts are defined as those who share a bedroom, kitchen, bathroom and/or living room and frequent visitors to the home of the patient. Household close contacts should be allowed access to the patient, as household contacts are actively followed up by the TB team. Other visitors should generally be discouraged to visit pulmonary TB cases while under respiratory precautions.

28.2 Visitors other than household contacts should be discouraged from visiting; it is advisable that children should not visit.

28.3 Household contacts and any other visitor should be asked to follow the isolation precautions on the door signage which includes wearing an FFP 3 mask, visitors and household contacts should be taught and given assistance in wearing their mask correctly.

29.0 TRANSPORT OF PATIENTS

29.1 Inpatients with smear positive pulmonary tuberculosis should be asked (with explanation) to wear a **surgical mask** (changed at hourly intervals if necessary) whenever they leave their room to other hospital departments until they are deemed non -infectious and are de-isolated. FFP3 masks with filters should NEVER be given to patients (the masks are designed to protect not to capture, the valve eliminates unfiltered air including the infectious TB bacilli).

29.2 Transport delays to other departments should be minimized by liaising with porters and other departmental staff. Patients undergoing x-rays should not wait in radiology department corridors and must be prioritized to minimize the contact with other patients. Patients should not wait in discharge lounges for transport to home or other accommodation.

29.3 Inter hospital transfers - Ambulance staff need sufficient information for organizing appropriate vehicle in addition to their own protection. As with visits to other departments, patients with smear-positive pulmonary TB should wear a surgical mask (changed at hourly intervals if necessary) during ambulance transport – if the patient has not completed 2 weeks of appropriate anti tuberculous treatment. If the patient is known or suspected to be infected with MDR-TB, then advice on transport should be sought on an individual basis from the IPCT, Respiratory Physician, or an ID physician. Standard procedures and close liaison with ambulance trust is necessary for contact tracing for ambulance staff who have been inadvertently in contact with a patient with confirmed infectious or potentially infectious pulmonary tuberculosis and will be covered by ambulance trust policies.

30.0 TRAINING AND AWARENESS

30.1 All Infection Prevention & Control training sessions for clinical staff contain a section on TB. Infection Prevention and Control training is part of the Trust mandatory training programme. Managers are responsible for identifying staff training requirements, booking and following up attendance/non-attendance of Infection Control mandatory training.

31.0 NOTIFICATION

31.1 Tuberculosis is a statutory notifiable disease; the TB team at the Trust will notify the appropriate external contacts.

31.2 In all cases where TB is considered in the differential diagnosis the appropriate chest or infectious diseases team should be contacted for a

consult if an in-patient or referred to the TB service if an out-patient. The TB nursing team will co-ordinate case management including contact tracing.
31.3 The doctor making the diagnosis is legally responsible for ensuring the TB team is notified. Contact tracing is organised by the TB nurse specialist. Notification triggers contact tracing procedures and also provides surveillance data to detect outbreaks and monitor epidemiological trends in incidence and drug resistance.

32.0
Executive summary protocol for the admission and management of patients with confirmed or potential smear positive respiratory tract tuberculosis

Admission of new patients.
1. Patients presenting to A&E where respiratory tract tuberculosis is a differential diagnosis should be isolated in a side room if possible. Patients attending outpatient clinic who require admission with suspected smear positive respiratory tract tuberculosis should be isolated until a suitable room is available (see below).

2. Unless there is a clear clinical or public health need, such as homelessness, people with suspected or confirmed respiratory tract TB should not routinely be admitted to hospital for diagnostic tests or for care.

3. Sputum specimens should be obtained from patients with suspected respiratory tract tuberculosis in the A&E Dept before admission and labelled as **"URGENT"** with an appropriate contact bleep number. Samples should be taken immediately to pathology at all sites by a doctor or nurse in attendance. Out of hours, the on-call microbiology technician should be bleeped when the specimen has arrived. A result will usually be available within hours of the specimen arriving in the laboratory. In the case of young children, a gastric aspirate should be sent to the laboratory. Samples must **not** be sent using the pneumatic tube system.

4. If sputum smear is positive for acid fast bacilli and there is a risk of MDR TB (request microbiology to perform a GeneXpert molecular test for detection of *Mycobacterium tuberculosis* and rifampicin resistance mutations. This is a same day test during normal working hours and weekdays.

5. Multiple-drug resistant (MDR) TB refers to TB caused by an isolate of M. tuberculosis that is resistant to both isoniazid and rifampicin and possibly additional agents. MDR TB is difficult to manage and is being seen with increased frequency in London. All patients with **known or suspected** multiple-drug resistant TB (MDR TB) – **must** be admitted directly to a negative pressure room (13F ward at the Royal London). On Paediatric Wards the child will need to be admitted to a negative pressure side room in a paediatric ward.

Risk factors for drug-resistance include: a history of previous TB treatment; prior anti-tuberculous treatment failure or poor compliance with therapy;

contact with a known drug-resistant case; birth or residence in a country in which the World Health Organization reports that a high proportion (5% or more) of new TB cases are multidrug‑resistant.

Patients with pulmonary MDR-TB must be admitted to a negative pressure room. Out of hours, the Site Nurse Practitioner(SNP) or other appropriate person **must** discuss the management of the case with the on-call doctor for Infectious Diseases/ Microbiology and/or Respiratory Medicine.

6. If sputum is smear-positive and MDRTB is **not** suspected then admit as follows.

Admit to a single/side room

For Paediatric cases admit to a single/side room on a paediatric Ward

Patients who are sputum smear-positive must **never** be admitted to a ward where immunocompromised patients are also located except if they are in a negative pressure single room.
Neutral pressure siderooms can be used provided:
The sideroom is not intentionally ventilated to positive pressure

The sideroom has an en-suite

The door to the side room is kept closed with a green respiratory precautions sign on the door and FFP3 masks available at the entrance.

The patient does not have a productive cough

The patient is not considered to be an MDR TB case

In the event of it being necessary to enact this guidance it will be necessary once the patient and side room has been identified, for a member of the IPC team to visit the ward to ensure that ward staff have the appropriate facilities and give any training that is necessary to ensure that the patient can be safely cared for; out of hours it will be the responsibility of the SNP to fulfil this requirement.

. Paediatric cases should be admitted to a side room in a paediatric ward.

- **Children under 10 years** with pulmonary TB are unlikely to be infectious, however the child should be isolated in a single room until the Paediatric Infectious Disease/Respiratory doctor has reviewed and advised on isolation requirements.
- **Children under 5 years** isolation with respiratory precautions however the use of masks is **not required** but consider risk from parent/ carer until they are seen by the TB team**.**

10. Patients admitted to a side room or negative pressure isolation with known or suspected drug-sensitive smear positive pulmonary TB should be moved only under the following circumstances:

There is laboratory confirmation of negative status (i.e. a minimum of 3 smear-negative sputa) or a revised clinical diagnosis that excludes smear positive TB. If TB is suspected clinically but the results of sputum tests are unavailable, the patient must continue to be assumed to be smear-positive.

11. If the initial sputum-smear is **negative** but pulmonary TB is still suspected, follow guidance for smear-positive patients outlined above. However, if no single rooms are available, cases must be discussed with the on-call Clinical Infection/Chest SpR before placement. Patients with suspected pulmonary TB must **never** be admitted to an open ward.

12. It is recommended that patients be admitted under the care of a Consultant from either the Infectious Disease or Respiratory Medicine teams or transferred to one of these teams as soon as possible after admission.

13. Patients already admitted within the Trust and subsequently diagnosed with, or suspected of having, smear positive pulmonary TB **must** be transferred to either a neutral pressure or negative pressure isolation room, in accordance with the above protocol.

General

1. Standard precautions should be carried out when handling body fluids and contaminated equipment. All single patient use clinical equipment should be disposed of as clinical waste and contaminated linen disposed of as infected linen. Re-usable clinical equipment must be decontaminated in accordance with the Trust decontamination policy. With MDR and XDR TB patients a stethoscope should be assigned to the patient and left in the room/ante room.

2. Staff performing invasive procedures, respiratory suctioning, bronchoscopy of TB patients **must** wear gloves; disposable long-sleeved gowns and FFP3 particulate filter respirator masks. In the event of the patient having drainage of collections potentially containing *Mycobacterium tuberculosis* bacteria (e.g. pleural effusion) specific attention must be paid to personal protection including eye protection. Staff who suspect or know they are immunosuppressed should not attend the patient without clearance from the Occupational Health Department.

3. Patients **must** wear a surgical mask if they are being transported to other areas of the hospital. Patients should be encouraged to self-isolate and use cough etiquette as is feasible.

Visitors

1. It is the responsibility of the nurse in charge of a ward to advise visitors of the risk of TB.

2. In general people who have had previous close contact (family members, including their children) with the patient can visit as long as they are fit and well and accept to use the protective measures and abide by visiting regulations. Other visitors should be discouraged whilst the patient is considered infectious.

3. Individuals (including staff members) who are immuno-suppressed must not visit. For further advice please contact a member of the Infection Control Team.

4. All visitors who are not previous close contacts must be advised to wear a FFP3 particulate filter respiratory mask.

5. Parents/ carers of children with suspected or active pulmonary TB should be kept separate from other patients until they have been excluded as a source of infection or also currently symptomatic.

Treatment

1. Treatment is multidisciplinary and must involve a Consultant with specialised training in TB (Respiratory or Infectious Diseases Physician) and the TB specialist nurses. In Paediatric cases this is led by one of the Paediatric Infection Diseases Consultants .

2. It is essential that patients comply with the multiple drug regimen prescribed, to ensure effective treatment and to minimise the risk of the development of anti-microbial resistance.

3. After a period of two weeks of therapy, patients with drug-sensitive TB should demonstrate signs of clinical improvement and will normally be no longer be infectious. Patients unlikely to be infected with Rifampicin resistant M. tuberculosis, or those with a negative molecular test for Rifampicin resistance mutations, may then leave isolation, but only on the advice of a Chest or Infectious Diseases Physician. This will not be the case for patients who have MDR-TB, who will require extended therapy and isolation.

4. It is essential that the TB nurses are informed of a patient prior to them being discharged so that follow up and contact details can be obtained.

Notification

1. Tuberculosis is a notifiable disease, and all cases **must** be notified to the Consultant in Communicable Disease Control (CCDC) for North East London Health Protection Unit (02038377084).

33.0 Duties and Responsibilities

All staff working in the Trust	This policy applies to all employees of the Trust in all locations including the Non-Executive Directors, temporary employees, locums and contracted staff.
Managers	It is the responsibility of Directors and Managers to ensure compliance with this standard.
Infection Prevention and Control Team	Responsible for updating the policy in line with new guidance issued. Ensure that staff have infection prevention and control training that includes the guidance set out in this policy. Ensure that non-compliance is addressed.

34.0 Monitoring /audit

34.1 Any instances of non-compliance with this policy will be reported as an incident on the Trust datix reporting system and investigated accordingly, where contact tracing is required this will be reported as a Serious Incident (SI) as per Trust policy.

Issue being monitored	**Monitoring method**	**Responsibility**	**Frequency**	**Reviewed by and actions arising followed up by**
New national or international guidance are updated in a timely fashion	Necessary update of new guidance	Infection Prevention & Control team (IP&C)	Generally, all policies will be updated every 3 years	IP&C team, TB team
Non-compliance with this policy will be monitored	Through incident alerting systems	Division leads, Matrons, and Ward/Department managers	On reported cases	IPCT with relevant teams involved in non-compliance.
Policy compliance	The policy and its implementation will be monitored through the Infection Control Team, Local Governance Groups and the Hospital Infection Control Committee.	IP&C team	At local Governance meetings.	IP&C team and appropriate managers.
Policy Compliance will be monitored through audit process	On single / individual cases	IP&C / and the TB teams	On reported cases. Monthly CAG Meetings	IP&C & TB Team and appropriate managers

Appendix 1: Change Log

Change Log – Management and Control of Tuberculosis		
Substantive changes since previous version	**Reason for Change**	**Author & Group(s) approving**

		change(s)
Change of layout and content	To reflect latest NICE guidelines 2016	Infection Prevention and Control Team Infection Prevention and Control Committee

Appendix 2: Impact assessments

Equalities impact checklist - must be completed for all new policies

equalities

Organisational impact checklist - must be completed for all new policies

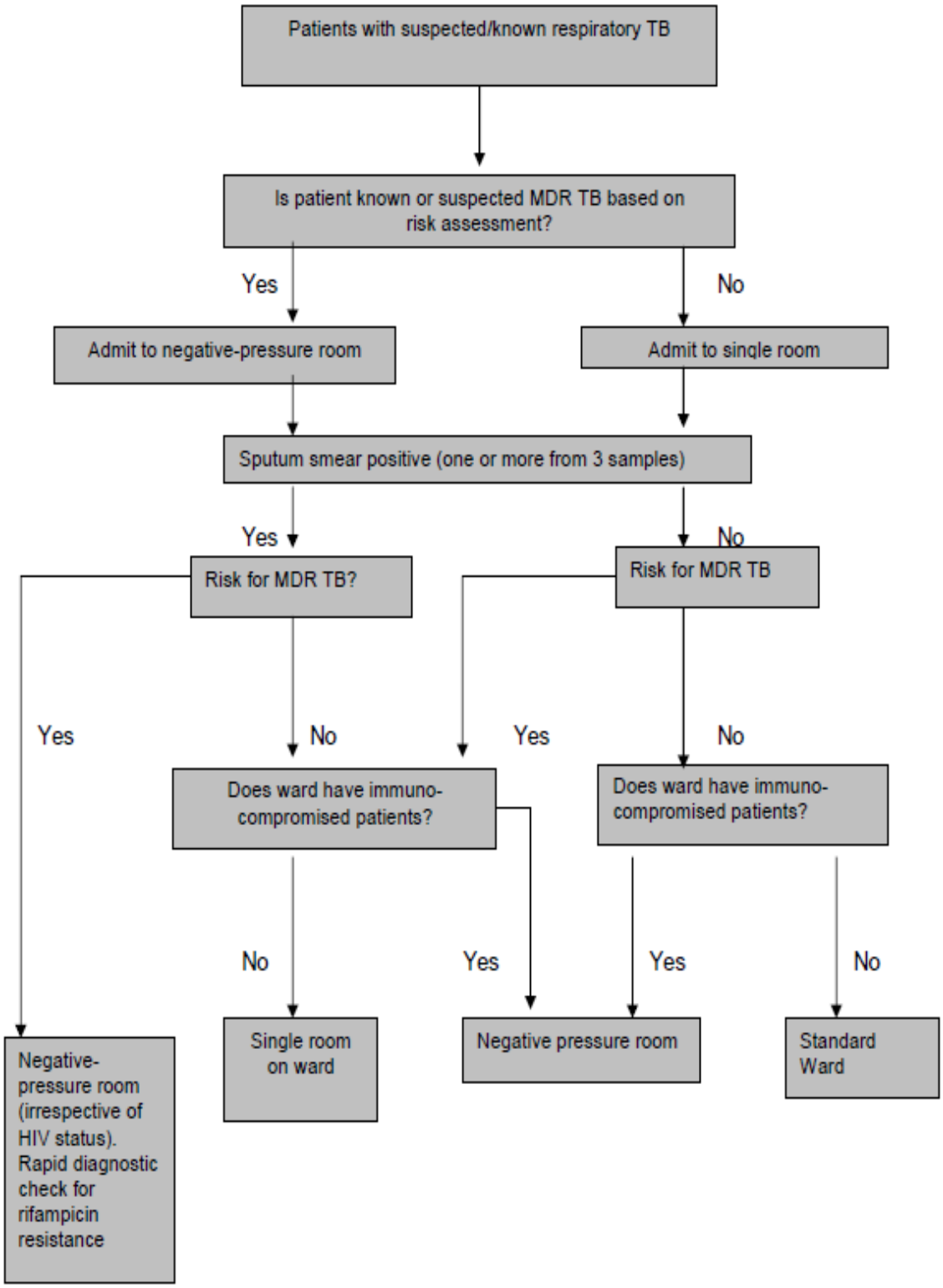
Organisational impact assessment

Appendix 3: SUPPORTING LITERATURE/ REFERENCES

1. Bhatti N, Law MR, Morris JK, Halliday R, Moore-Gillon J (1995). Increasing incidence of tuberculosis in England and Wales: a study of likely causes. BMJ 310: 967-969
2. Breathnach AS, de Ruiter A, Holdsworth GMC *et al* (1998). An outbreak of multi-drug resistant tuberculosis in a London teaching hospital. Journal of Hospital Infection 39: 111-117
3. Brewer TF, Corditz GA (1995). Bacille-Calmette-Guerin vaccination for the prevention of tuberculosis in healthcare workers. Clinical Infectious Diseases 20: 136-142
4. Centers for Disease Control and Prevention (1996). The role of BCG vaccine in the prevention and control of tuberculosis in the United States. A joint statement by the Advisory Council for the Elimination of Tuberculosis and the Advisory Committee on Immunisation Practices. MMWR;45(RR-4):1-18
5. Citron KM (1993). BCG vaccination against tuberculosis: international perspective. BMJ 306:222-223
6. Connolly M (1999). A survey of workload, resources and work practices among TB nurses in London. On behalf of The London TB Nurse Network
7. Department of Health (1996). Joint Committee on Vaccination and Immunisation. Immunisation against infectious disease. HMSO, London
8. Johnson MP et al (1992).Tuberculin skin reactivity among adults infected with human immunodeficiency virus. J Infect Dis;166:194-198
9. Joint Tuberculosis Committee of the British Thoracic Society (2000). Control and prevention of tuberculosis in the United Kingdom: code of practice. Thorax 55(11): 887-901
10. Kent RJ, Uttley AHC, Stoker NG, Miller R, Poznaik AL (1994). Transmission of tuberculosis in a British care centre for patients infected with HIV. BMJ 309: 639-640
11. Kenyon TA, Valway SE, Ihle MPA, Onorab IM, Castro KG (1996). Transmission of multi-drug resistant Mycobacterium tuberculosis during a long air-plane flight. New England Journal of Medicine 334: 933-938
12. Kritski AL et al (1996). Transmission of tuberculosis to close contacts of patients with multi-drug resistant tuberculosis. Am J Respiratory& Critical Care Med; 153:331-335
13. Merdith DS, Watson JM, Citron KM et al (1996). Are healthcare workers in England and Wales at increased risk of tuberculosis? BMJ 313: 522-525
14. Michele TM, Cronin WA, Graham NMH *et al.,* (1997). Transmission of Mycobacterium tuberculosis by fiber-optic bronchoscope: Identification by DNA fingerprinting. JAMA 278:1093-1095
15. National Health Service Executive (1995). Hospital Infection Control: guidance on the control of infections in hospitals. HSG (95): 10

16. NICE Tuberculosis Guidelines NG33 (2016) Clinical diagnosis and management of tuberculosis and measures for its prevention and control.
17. Public Health (Control of Disease) Act 1984. Sections 35, 37 and 38
18. Rouillon A, Predizet S, Parrot R (1976).Transmission of tubercle bacilli: the effects of chemotherapy. Tubercle 57: 275-299
19. Small PM, Hopewell PC, Singh SP et al (1994). The epidemiology of tuberculosis in San Francisco: a population based study using conventional and molecular methods. New England Journal of Medicine 330: 1703-1709
20. Wake D, Bowry AC, Crook B, Brown RC (1997). Performance of respiratory filters and surgical masks against bacterial aerosols. Journal of Aerosol Science 28: 1311-1129
21. Weise SE, Slocum PC, Blaise FX, King B et al (1994). The effect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis. New England Journal of Medicine 330: 1179-1184
22. World Health Organisation (2006) Tuberculosis and air travel: guidelines for prevention and control. Report WHO/HTM/TB/2006.363. Geneva, WHO
23. Mphaphlele M, Dharmadhikari AS, Jensen PA, Rudnick SN, van Reenen TH, Pagano MA, et al. Institutional Tuberculosis Transmission. Controlled trial of upper room ultraviolet air disinfection: a basis for new dosing guidelines. Am J Respir Crit Care Med. 2015;192:477–484.
24. TA Jackson & JM Thomas (2013) Tuberculosis: the implications for anaesthesia, Southern African Journal of Anaesthesia and Analgesia, 19:6, 301-305, DOI: 10.1080/22201173.2013.10872945

Appendix 1. Isolation decision for patients with suspected TB


Patients with suspected/known respiratory TB
Is patient known or suspected MDR TB based on risk assessment?
Yes
No
Admit to negative-pressure room
Admit to single room
Sputum smear positive (one or more from 3 samples)
Yes
No
Risk for MDR TB?
Risk for MDR TB
Yes
No
Yes
No
Does ward have immuno-compromised patients?
Does ward have immuno-compromised patients?
No
Yes
Yes
No
Negative-pressure room (irrespective of HIV status). Rapid diagnostic check for rifampicin resistance
Single room on ward
Negative pressure room
Standard Ward

Appendix 2:

In the event of patients identified with suspected smear positive pulmonary TB they may be isolated in a neutral pressure sideroom provided:

The sideroom is not intentionally ventilated to positive pressure
The sideroom has an en-suite
The sideroom is maintained with the door closed
The patient does not have a productive cough
The patient is not considered to be an MDRTB case
Staff caring for the patient **MUST** wear FFP3 disposable masks, and follow respiratory precautions as per the IPC policy
In the event of it being necessary to enact this guidance it will be necessary once the patient and sideroom has been identified, during normal working hours for a member of the IPC team to visit the ward to ensure that ward staff have the appropriate facilities and give any training that is necessary to ensure that the patient can be safely cared for; out of hours it will be the responsibility of the SNP to fulfil this requirement.

Appendix 3: Advice on the correct use of masks/respirators

How to put on an FFP3 mask/respirator:

- Select an FFP3 mask/respirator (NB staff have to be **fit-tested** for 3 respirators).
- Place over nose, mouth and chin.
- Fit flexible nose piece over Nose Bridge.
- Secure on head with elastic.
- Adjust to fit.
- For non-valve masks perform a quick fit-check:
  - inhale – mask should collapse
  - exhale – check for leakage around the face

Removing an FFP3 mask/respirator

- Break ties/elastic at side to remove.
- Pull off face without touching outside of mask
- Discard mask in a clinical waste bin.
- Wash hands.

Dos and don’ts

- Do not hang the mask around your neck or rest in your pocket
- Do not handle the outside of a worn mask
- Do not re-use the mask. FFP3 masks/respirators can be worn for eight hours continuously but are single use only.
- Do not give valved masks/respirators to patients/parents

Use of masks and isolation can be discontinued when:

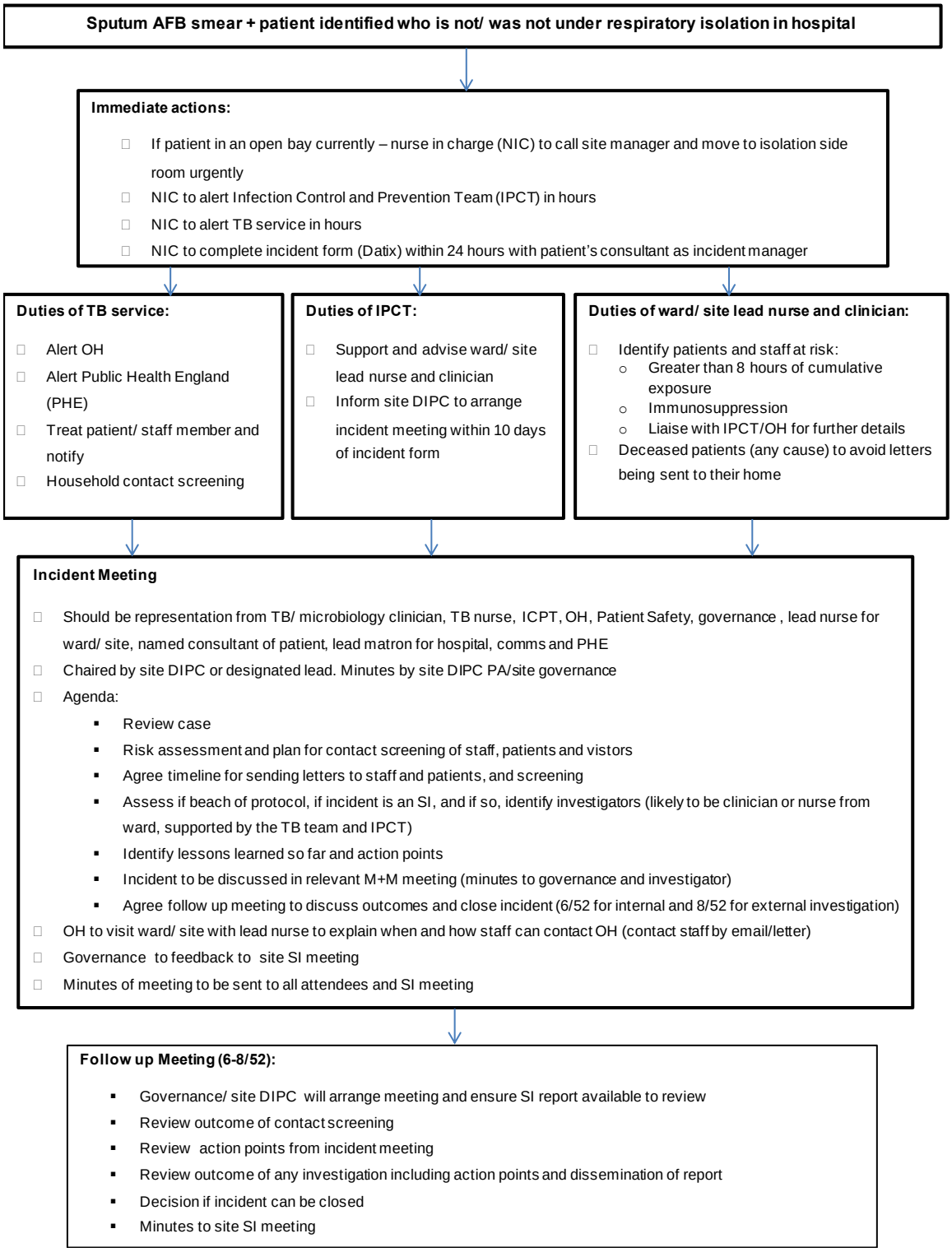
- CXR clear and where available, the sputum/gastric washings are reported to be smear negative and the patient does not have MDR TB.
- Please confer with the Infection Control and Infectious Diseases Teams on a case by case basis if the above information is not available or the results are not reported to be clear".

Members of staff who are immunosuppressed/post-transplant should avoid contact with patient with suspected or confirmed TB.

Contact Occupational Health for further information.

PPE (above standard precautions) is not required for non-pulmonary TB when chest status of patient is known to be non-TB.

Appendix 4
Algorithm For Dealing With TB Related Infection Control Incidents Within Barts Health Trust



APPENDIX 5: London Health Protection Team MDR Discharge Plan

HOSPITAL DISCHARGE PLAN: MDR Tuberculosis patient

Hospital No: …… LTBR No: ……NHS No: ……..…

Title: ...…… First Name: ……..... Last Name: ……..……

Sex: M ☐ F ☐ D.O.B. ……/……/…… Age: ……yrs

Ward: ……. Date Admitted: ……/……/…..….

Language: ……..... Translator Used: ……

UK Entry: ……/……/…… Country of Birth: ……

Country of Citizenship: ……..

Immigration status: Asylum seeker ☐ Refugee ☐ Student ☐

Visitor ☐ New entrant ☐

Prisoner / Custody: Yes ☐ No ☐

Those to be involved in the discharge of this patient include

MEMBER	NAMED CONTACT
Chest Physician	
TB Nurses	
Infection Control Team	
Outreach team	
Microbiology	
Health Protection	

Team	
Other (please specify)	

Before discharge the following sections must be completed.

SECTION	**Criteria**	**Completed (sign and date)**
1. Clinical condition	Patient is fit to be discharged.	
2. Accommodation	Suitable accommodation arrangements in place.	
Community Management	Secure arrangements in place for administration of ALL TB treatment.	
4. Risk to others	Patient is not infectious and/or poses no risk to others (Approved by local HPT).	

SECTION 1. Clinical condition

Q1. Clinical history

a.) Pulmonary or non pulmonary TB? Pulmonary ☐

Non-pulmonary ☐

b.) Date treatment started _____/____/_____

c.) Date MDR appropriate treatment started _____/____/_____

d.) Number of weeks on MDR appropriate treatment _____

Q2. Microbiological information

SMEAR RESULTS		**CULTURE RESULTS**	
DATE	RESULT	DATE	RESULT

Q3. Patient clinically fit to leave hospital Yes ☐ No ☐

Q3A. Does the patient cough? Yes ☐ No ☐

Q4. Is the patient currently infectious? Yes ☐ No ☐

Any further comment about infectiousness:

_____

_____

_____

FINAL SIGN OFF

Patient is fit to be discharged **Yes ☐**

Agreed by **Consultant ☐ TB Nurse ☐ HPT ☐**

SECTION 2. Accommodation

Q5. Issues re: immigration status? **Yes ☐** **No ☐** (go to Q 6)

If YES

Details……

……

……..

a.) Could these problems impact on eligibility for housing services?

Yes ☐ **No ☐**

(go to Q 6)

If YES Ensure there is early discussion with Outreach Team and/or Find and Treat

Q6. Eligible for social services support? **Yes ☐** **No ☐**

(go to Q 7)

If YES

Social Service Department……

Named contact……

Address……

..

Postcode…….. Telephone……..

Q7. Normal residence / accommodation:

Home setting	☐	(go to Q 8)
Flat-share	☐	(go to Q 9 overleaf)
Communal setting (student hostel)	☐	(go to Q 9 overleaf)
Communal setting (residential hostel)	☐	(go to Q 9 overleaf)
Communal setting (other)	☐	(go to Q 9 overleaf)
None (rough sleeper)	☐	

Q8. Further details on HOME accommodation

a.) Are any members in the household immunocompromised? **Yes ☐ No ☐**

*If **YES** discuss with local HPT*

……

b.) Will the patient have their own room? **Yes ☐ No ☐**

*If **NO** discuss with local HPT*

……

……

Q9. Further details on HOSTEL accommodation

a.) Are any members in the hostel immunocompromised? **Yes ☐ No ☐**

*If **YES** discuss with local HPT*

……

……

b.) Will the patient have their own room? **Yes ☐ No ☐**

*If **NO** discuss with local HPT*

……

……

c.) Will the patient have access to a fridge? **Yes ☐ No ☐ Not applicable ☐**

*If **NO** (and needed) discuss with social service*

……

……

Please list details of household contacts and their screening results:

Relation	Age	Screened (Y/N) and methods (CXR, TST, IGRA)	Result: (active TB, LTBI, discharged)

FINAL SIGN OFF

Suitable accommodation arrangements in place **Yes** ☐

Address: ……..

Postcode: …… Telephone: ……..

Agreed by **Consultant** ☐ **TB Nurse** ☐ **HPT** ☐

SECTION 3. Community management

Q10. Nurses are required to do home visits*? Yes ☐

No ☐

** For OPAT (Outpatient Parenteral Antimicrobial Therapy) or DOT (directly Observed Therapy)*

*If YES, b*y whom? .....

Date arranged? .....

Q11. Infection risk to nurses on home visits? Yes ☐

No ☐

<u>Directly observed treatment (DOT) arrangements</u>

DOT <u>must be</u> arranged if the patient diagnosed with MDR TB.

Q12. Named DOT supervisor……..

Contact details: Tel……..Mobile……..

Address……

…….……Postcode……..…….

Q13. Role of DOT Supervisor:

TB nurse ☐ Community nurse ☐ Social worker ☐ Family member ☐

Other ☐ *Details*……..

Q14.Where / how DOT to be delivered?

…….

<u>Clinical assessment arrangements</u>

Q15. Follow up appointment arranged? Yes ☐ No ☐

*If **NO** discuss with TB nurses*

Date of first follow up appointment ……..

Q16. Patient eligible for hospital transport? Yes ☐ No ☐

*If **NO** provide info. on travel arrangements*…….

FINAL SIGN OFF

Secure arrangements are in place for administration of TB treatment in community **Yes ☐**

Agreed by **Consultant ☐ TB Nurse ☐ HPT ☐**

SECTION 4. Risk to others

Q18. Is the patient infectious now (section 1)? Yes ☐

No ☐

*If **YES***

a.) Date 6 wk culture result will be available? -

……

Q19. Are accommodation arrangements agreed (section 2)? Yes ☐

No ☐

Q20. Is there any risk of infection to household/hostel contacts (section 2)?

Yes ☐ No ☐

Q21. Are robust arrangements for community treatment and follow up in place (section 3)? Yes ☐ No ☐

Q22. Is there any risk of infection to support staff (section 3)? Yes ☐

No ☐

Q23. Is the patient due to fly home? Yes ☐

No ☐

Q24. Is the patient due to be deported / incarcerated? **Yes ☐**

No ☐

Q25. Has all necessary contact tracing (household and close contacts and extended screening if required) been undertaken? **Yes ☐**

No ☐

Outcome and agreed Plan - Complete after discussion with HPT:

☐ 1. Patient is ready to be discharged.
☐ 2. Patient can be discharged when culture results are ready & discussed with HPT.
☐ 3. More information is needed.
☐ 4. Teleconference / case discussion is needed. (Arranged for:……

FINAL SIGN OFF

Patient is not infectious and/or poses no risk to others **Yes ☐**

Agreed by **Consultant ☐** **TB Nurse ☐** **HPT ☐**