Workplace risk factors associated with extra-pulmonary tuberculosis among healthcare workers in eThekwini health district, KwaZulu-Natal

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REMARK

This thesis is submitted in the form of a research article.

DECLARATION

This Master of Medical Science (Occupational and Environmental Health) is my own work, and all primary and secondary sources have been appropriately acknowledged. The dissertation has not been submitted to any other institution as part of an academic qualification.

This dissertation is prepared in fulfilment of the requirement of the Master of Medical Science (Occupational and Environmental Health) at the School of School of Nursing and Public Health University of KwaZulu-Natal, Durban, South Africa.

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I dedicate this dissertation to my late parents, Eunice Memela and Moses Memela. The first time I saw my father's pay slip, I cried, wondering how he managed to provide for all our needs. Their love, warmth, dedication and support will always be appreciated, Gambu, Msuthu kaLanga. To my late father-in-law and mother-in-law, for all your prayers and support that kept me going. To my loving husband, Philani Bhengu, for keeping the family together and for your encouragement when I thought it was impossible. To my kids Sibusisiwe, Sibongakonke and Siyanda to whom I deprived time and many play dates to focus on my studies.

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ACRONYMS AND ABBREVIATIONS

ART – Antiretroviral Therapy

aOR – adjusted odds ratio

CI – Confidence Interval

EPTB – extra-pulmonary tuberculosis

HCW – healthcare worker

HIV – Human Immunodeficiency Virus

OR – odds ratio

PPE – personal protective equipment

PTB – pulmonary tuberculosis

RPE – respiratory protective equipment

TB – tuberculosis

WHO – World Health Organisation

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ABSTRACT / SUMMARY

Background

Tuberculosis (TB) can be categorized as pulmonary tuberculosis (PTB) and extra-pulmonary tuberculosis (EPTB) involving other organs besides the lungs. Healthcare workers (HCWs) are at increased risk of tuberculosis exposure. The average burden among healthcare workers is 2% compared to 0.9% in the general population. EPTB constitutes about 16% of all TB cases. This study aimed to examine occupational, environmental, and demographic risk factors associated with EPTB among healthcare workers

Methods

This was a retrospective case referent type study with two control groups (one without tuberculosis and the other with pulmonary tuberculosis) and cases defined as those with EPTB. 282 records of healthcare workers were reviewed from January 2009 to December 2017.The study reviewed available medical records of healthcare workers from various categories and departments, both clinical and non-clinical. in health facilities within eThekwini Health District, Durban, South Africa. Data was analysed using a chi-square test, t- test and multivariet analysis.

Results

The mean incidence of TB in 2016 was 908/100 000 and for EPTB, was estimated at 87.2/100 000 HCWs in eThekwini Health District. Cases without respiratory protective equipment (RPE) use were more than three-fold suceptible (aOR 3.5 95%CI 1.0 – 11.4) compared to a PTB control. Working in a clinical department increased the odds for developing EPTB almost three-fold when compared to those with PTB (aOR 2.9 95% CI 0.6 – 13.2) than among those with no TB (aOR 1.4 95%CI 0.1– 13.8). As expected, HCWs diagnosed with HIV were almost two-fold likely to be exposed to EPTB when compared to thosed with PTB (aOR: 1.9 95% CI 0.9 – 4.0), however, when comparing EPTB to no TB, HIV positivity had a wide confidence interval (aOR: 23.4 95% CI 8.1 – 67.7) rendering the results indeterminate.

Conclusion

Occupational risk factors for EPTB are similar to that of pulmonary tuberculosis, however, risk estimates may be greater than those for PTB. Human immunodeficiency virus/ acquired immunodeficiency syndrome (HIV/AIDS) infection increases the odds of exposure to EPTB in HCWs.

CHAPTER I: INTRODUCTION

Tuberculosis (TB) is one of the major global public health concerns, claiming an estimated 1.4 million lives in 2019.[1,2] According to WHO Global Report 2020, South Africa's TB incidence was 615 /100 000, the 2nd highest incidence after Lesotho[2]. South Africa was among the eight countries that accounted for two-thirds of the global total in 2019 and contributed 3.6% of global infections.[2] Healthcare workers (HCWs) contributes 0.4% to the risk groups with prevalence of 1470/100 00 and incidence of 1133/100 000, contributing 1% to the overall tb epidemic.[3]

The transmission of mycobacterium tuberculosis occurs through infected air droplets from patients with active pulmonary tuberculosis (PTB), affecting the lungs, thus referred to as PTB, or it may affect other organs besides the lungs and is referred to as extra-pulmonary tuberculosis (EPTB).[4] The mechanism of spread of Mycobacterium tuberculosis to other organs is via the lymphohaematogenous route, within an immunocompromised context.[5] However, there is evidence to suggest that different Mycobacterium tuberculosis lineages and macrophage responses may increase risk for EPTB.[5] Unlike PTB, screening and diagnosing EPTB, especially without concomitant pulmonary involvement, may be challenging since patients are likely to have negative sputum smear.[5] This may result in life-threatening complications due to delayed treatment, resulting in affected employees seeking sick leave negatively impacting service delievery.[6]

The transmission mode of TB renders healthcare workers at greater risk of infection since they constantly interact with undiagnosed and highly infectious patients and simultaneously are exposed in their communities.[1,7] The average burden of TB in South African HCWs is higher than that of the general population, estimated to be two to three times greater.[8] Furthermore, it was reported that in South Africa, TB in HCWs was the third-highest commonly reported occupational disease submitted to the Compensation Fund, despite it being generally underreported.[7]

Researchers have found human immunodeficiency virus (HIV) infection to be the leading independent risk factor for tuberculosis.[9] Although the HIV prevalence among HCWs in South Africa is not well documented, it is estimated to be between 11% to 20%.[7,9] Additionally, the risk for tuberculosis is up to >20 times more in those living with HIV, consequently increasing

the risk of TB in HCWs.[9] Other significant risk factors include job designation, time spent with patients, duration of service, work location, failure to wear personal protective equipment (PPE) and poor implementation and enforcement of infection control and prevention measures by the management at the health facility. [9,10,11,12]

This study aimed to determine the occupational, environmental, and demographic risk factors associated with EPTB among healthcare workers in public healthcare facilities in eThekwini health district.

LITERATURE REVIEW, BACKGROUND AND SIGNIFICANCE

EPTB pathogenesis

Tuberculosis (TB) is a life-threatening bacteriological infection that may display a multi-systemic involvement, whereby *M. tuberculosis* bacilli spread into the bloodstream and lymphatic system resulting in extra-pulmonary tuberculosis (EPTB).[13,14,15] These bacilli spread and develop an inflammatory response to form protective immunity against the bacteria.[14,15] This phenomenon results in the formation of encapsulated granuloma containing viable bacilli, which can occur any time after primary infection, even decades later, depending on the individual immune response mechanisms.[14] The change in the immune mechanism that results from granuloma formation predisposes the reactivation of latent TB and the development of active TB infection in any organ or tissue except for the hair, nails, and teeth.[14] EPTB involvement may present with or without pulmonary infection. [14,15,16]

Incidence of TB and EPTB

Despite reports that the incidence of TB is decreasing worldwide, it remains one of the biggest world threats and ranks alongside HIV as a leading cause of death worldwide.[13,17] In South Africa, although tuberculosis remained the leading cause of death in the reporting period 2016 to 2018, the proportion of deaths had declined to 6.0% in 2018 from 6.5% in 2016.[18] Of note, Stats SA reported that in 2018, for the first time since 1997, TB was dethroned by forms of heart diseases as the leading underlying cause of death in KwaZulu-Natal.[18] South Africa was among the seven high TB burden countries that reached the 2020 TB milestone which was a 20% reduction in TB incidence between 2015 and 2020.[19]

The majority of research on TB focuses on PTB because it is highly contagious and requires public health interventions.[20,21] EPTB, which is less contagious, is generally underreported both within communities or as an occupational disease.[20,21] Globally, the proportion of EPTB has increased from 14% in 2014 to 16% in 2020.[12] EPTB represented 16% of the 7.1 million

incident cases that were notified in 2019 Globally, ranging from 8% in the World Health Organisation (WHO) Western Pacific Region to 24% in the Eastern Mediterranean Region with the African region presenting 16%.[19] The 15 years and above age group survey conducted in South Africa in 2018, reported that a proportion of 9.7% of notified TB cases were EPTB.[22,23] Furthermore, in a systematic review and meta-analysis of EPTB among People Living with HIV/AIDS (PLWHA) in Sub-Saharan Africa, 10% of reported EPTB cases in South Africa were HIV positive.[24]

According to WHO, in Africa, the proportion of EPTB had declined from 16% in 2014 to 15% in 2020.[25] Contrary to this, in South Africa, the rate of EPTB has decreased from one in every 6 TB patients in 2003 to one in every nine TB patients in 2015 despite South Africa having the third highest incidence of TB and HIV globally.[26] This decline has been partly attributed to the upscaling of antiretroviral therapy (ART), through providing ART immediately to people living with HIV without contraindications, regardless of CD4 cell count and clinical stage.[27] In a study conducted in the rural Mopani district in South Africa, where the ART coverage was <5% in 2009 and 41% in 2013, there was a 13% reduction in the total number of TB cases, EPTB cases declined (n=399 in 2009 vs n=336 in 2013; P<0.01).[28]

There have been limited studies focusing on EPTB in healthcare workers. However, based on the study by Tudor (2016), which compared the difference in TB incidence among HCWs with a history of working in TB wards versus without a history of working in TB wards, of the 112 healthcare workers diagnosed with TB 16% had EPTB, 7% worked in the TB ward and 17% worked in non TB wards.[6]

EPTB Diagnosis

EPTB is often challenging to diagnose by microscopy because tissue can be difficult to sample, and the bacillary tissue burden is usually low, making it hard to identify.[5] Therefore, the available estimation of the epidemiology of EPTB may be unreliable, and many cases may remain undiagnosed, especially in developing countries.[13] In these countries, diagnosis is based on probable and circumstantial evidence, with the consequence of possible misdiagnosis.[29] It is therefore, likely that the actual proportions of EPTB are much higher than was reported, given the plight of HIV in developing countries.[30]

The most common sites for EPTB, depending on social or environmental factors, are lymph nodes, pleura, cutaneous tissue, abdomen, peritoneum, bones and gastrointestinal system.[31] In a study conducted in China ,TB pleura (49.8%) accounted for half of the case.[32] Followed by bronchial TB (14.8%), TB Meningitis (7.5%) TB Lymphadenitis of the neck (7.3%), TB

peritoneum (4.8%), the rest of the site were less than 3 %.[32] Table 1 below tabulate the common EPTB sites, in terms of description,clinical features and diagnostics.

Table 1 The most common EPTB sites.[31,33]

Disease site	Description	Clinical features	Diagnostics
TB pleural effusion	A manifestation of paucibacillary mycobacterial infection within the pleural space, which is acquired from initial parenchymal lesions and results in an immunological response that both decreases pleural fluid removal and increases the pleural fluid formation	Fever, cough, chest pain, dyspnoea sometimes associated with loss of appetite, weight loss and malaise.	- Chest X-ray - Pleural aspiration - Xpert MTBRIF may be requested on pleural biopsies to confirm
Tuberculous pericardial effusion	Usually develops by retrograde lymphatic spread of *M tuberculosis* from peribronchial, peritracheal, or mediastinal lymph nodes or by hematogenous spread from primary tuberculous infection.	fever, cough, weight loss, , chest pain, night sweats, and breathlessness, along with moderate to high pericardial effusion	- Chest X-ray - ECG
TB of the spine and bone	Spinal TB comprises several pathological entities, including vertebral osteomyelitis, spondylitis, and discitis The most common site of infection is the spine followed by other large joints such as the shoulder, knee and hip	Features include reluctance to bend the back, stiff back, back pain ,localised swelling, sometimes with a noticeable lump or abnormal curvature of the spine A possibility of a cold abscess developing behind the sternocleidomastoid muscle Localised back pain due to the involvement of the thoracic vertebrae, Lower back pain due to involvement of the lumbar vertebrae results. A "cold abscess" from here can drain along the psoas muscle towards the inguinal area	- X-rays of the spine - Biopsy of cold abscess - MRI
TB lymphadenitis	Often Painless and usually represents reactivation of latent TB, although the cervical disease can be caused by local spread from direct infection of the tonsils or adenoids The most common sites are anterior or posterior cervical and submandibular nodes	Distinct wheeze or typical harsh cough due to large mediastinal lymph nodes squeezing the airways rapidly growing firm to fluctuant painless lymph nodes (>2cm) Associated systemic features include fever, weight loss, night sweats and	- Chest x-rays for diagnosing mediastinal TB lymphadenopathy - Ultrasound or CT scan for intra-abdominal lymphadenopathy - Exuding caseous material through a fistula can be sent to the laboratory for TB investigations

Disease site	Description	Clinical features	Diagnostics
TB Meningitis	Is characterized by inflammation of the membranes (meninges) around the brain or spinal cord	Present with gradual onset of headache, confusion, malaise, reduced consciousness and occasionally vomiting Examination reveals neck stiffness and a positive Kerni's sign	- Lumbar puncture (Cerebrospinal fluid (CSF) examination)
Peritoneal tuberculosis	Has a predilection for the terminal ileum	Clinical features include systemic features and ascites with no signs of portal hypertension. There may be palpable abdominal masses (mesenteric lymph nodes). Bowel obstruction may develop from the adhesion of caseous nodules to the bowel.	- Ascitic tap - Abdominal ultrasound
Disseminated/miliary TB	Regularly associated with immunodeficiency and results from lympho-haematogeneous spread throughout the body.	Health deteriorates, presenting with high fever, shortness of breath, night sweats, and weight loss.	- Chest X-ray - Full blood count - Liver function test

EPTB Treatment

Like PTB, the duration of treatment of EPTB is six months, except for TB meningitis, TB bones/joints, and miliary TB, which is nine to 12 months of therapy, and the treatment regimens are the same.[14,16,21,34] The intensive phase (rifampicin, isoniazid, pyrazinamide and ethambutol) remains two months and the continuation phase (rifampicin and isoniazid) is four months, but can be prolonged to seven months.[14,16,34] Adjunctive treatment, like pyridoxine, is recommended to prevent peripheral neuropathy in adult patients, and steroids are recommended in EPTB patients, particularly with TB meningitis and TB pericarditis.[33,34] However, bacteriological evaluation of the response to treatment is often limited by the difficulty in obtaining follow-up specimens.[32] Response is usually ruled on the basis of clinical and radiographic findings.[34] Furthermore, with EPTB, it is difficult to define if the person has been cured as there are no established criteria for the end treatment.[34]

Delayed Treatment complications

Several studies have proven that EPTB effects have devastating results, and patients who are delayed treatment may suffer high morbidity and mortality e.g. TB meningitis which has proved

to be life-threatening with serious complications if not treated promptly.[33,35] A study in Zanzibar reported an up to 76 delays of TB treatment.[35] In a retrospective cohort study of patients treated for EPTB in the state of Texas between January 2000 and December 2005, TB meningitis and peritoneal TB had a very poor long term outcomes.[14] Furthermore, in a multicohort study, TB meningitis was associated with higher mortality ratecompared to PTB (aOR 1.9 95% CI: 1.0 – 3.1).[36] Neurological infestation resulting from compression of the spinal cord and other nerve routes is approximately 50% of spinal TB patients, with incidences around 40% to 50%.[37] Ten to 27% of patients with cervical or thoracic spinal TB commonly develop paraplegia or tetraplegia.[37]

Risk Factors for EPTB

Different authors have listed the most common risk factors for EPTB compared to PTB.[20,38,39] In a tranversal study conducted in a TB reference center in northern Portugal, females were more likely to have EPTB (OR 1.63; 95%CI 1.02–2.6).[40] In a meta-analysis of observational studies which analysed evidence on the association between HIV and EPTB, there was a significant association between HIV and EPTB (OR 1.3 95%CI 1.05 – 1.6) I^2 : 0%.[38] Previous history of TB had a significant association with EPTB (OR 4.77 95% CI 1.86 – 12.24) in a cross-sectional study of n=344 subjects that assessed the prevalence and possible risk factors of smear-positive EPTB among suspect patients at the University of Gondar Hospital in North West Ethiopia.[39] In a study conducted in Texas, USA, immunosuppression (aOR 1.31 95% CI 1.00 – 1.77), and end stage renal disease (a OR 3.42 95% CI 2.39 – 4.88), significantly increased the risk of EPTB.[17] A cohort study in the US State of Georgia found TB patients with diabetes (aOR 1.55 95% CI 0.65 - 3.69) having an increased probability of developing EPTB as opposed to PTB.[37]

Problem statement

The incidence of TB among health care workers (HCWs) in high-burden countries (>100 cases/100,000 population) is 8·4% greater (95% CI 2·7% - 14·0%) than the general population.[41] In South Africa it is estimated that the burden of TB in HCWs is two to three times higher than that of the general public.[8] In 2015 the incidence of TB in South Africa was at 454/100 000 with KwaZulu-Natal having the second highest incidence in the country of 685/100 000 and eThekwini municipality recording 698/100 000.[2,42] According to the service delivery improvement plan 2015/2016, TB was by far the leading immediate cause of death in

KwaZulu-Natal by 16%, eThekwini Municipality was at 21% and EPTB accounted for 6.3% deaths in the province.[43]

The eThekwini Health district is the largest in the KwaZulu-Natal.[44] It has 18 public hospitals, three of which are specialised TB hospitals, eight community health centers, and 110 primary health care facilities, including 57 clinics under local authority.[44] The district serves a population of 3 442 361 (which is 33.5% of the KZN population) with a staff complement of approximately 18950.[44]

Overall Objective

To determine whether the occupational factors increase the risk for extra-pulmonary tuberculosis among health care workers.

Specific Aims

- To describe the demographic and occupational profiles in a sample of health care workers in the eThekwini Health District, KwaZulu-Natal with pulmonary tuberculosis, extra-pulmonary tuberculosis and without these diseases
- To determine whether occupational profiles vary across these three groups
- To determine whether occupational factors increase the risk of extra-pulmonary tuberculosis
- To calculate a minimum incidence of EPTB

Overview of methodology

We conducted a retrospective case-referent type study with two control groups (one without tuberculosis ("no TB") n=94 and the other with PTB n=94 and a case (those with EPTB) n=94. In the selection of cases, all medical records of health care workers with extra pulmonary tuberculosis were reviewed. PTB controls were selected based on the medical records of HCWs diagnosed with PTB for each case of EPTB sampled, closest to the month in which a case of EPTB was diagnosed from the same institution. For controls with no TB, A systematic random sampling strategy was undertaken where every third medical records of HCWs who were screened for TB and found to be without TB were sampled. Using a data collection tool, we extracted data from the medical records of healthcare workers (HCWs) in public health facilities within eThekwini Health District. Analysis was done using Statistical Package STATA (version 13). Characteristics of the study population were summarised using frequencies and percentages

for categorical values and mean and standard deviation (SD) for continuous variables. Bivariate analysis was performed using a chi-square test for categorical values and a t-test for continuous variables. Multivariate analysis was performed to identify independent risk factors for having EPTB, using a stepwise logistic regression. Three models were run: EPTB vs. all controls; EPTB vs. PTB and EPTB vs. no TB. Crude odds ratio, adjusted odds ratio (aOR) and 95% confidence interval (CI) were calculated and the results were considered statistically significant at $p<0.05$.

CHAPTER II: MANUSCRIPT

Workplace risk factors associated with extra-pulmonary tuberculosis among healthcare workers in eThekwini health district, KwaZulu-Natal.

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Contribution of Authors and co-authors

Author: Nontuthuzelo Bhengu contributions: conceived and implemented the study design; collected and analysed data; wrote manuscript drafts.

Co-Author: Prof. Rajen N Naidoo contributions: assisted in conceiving and implementing the study design; provided feedback on statistical analyses; commented on manuscript drafts.

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Institution and Ethics approval

In compliance with ethical standards, the study was approved by the Biomedical Research Ethics Committee (BREC) of the University of KwaZulu-Natal, South Africa (Reference number BE326/19).

Conflict of interest and Disclosure

The authors declare that they have no conflict of interest.

Disclaimer

This article is my own original work and has not been submitted to any other journal for consideration.

ABSTRACT

Background

Tuberculosis (TB) can be categorized as pulmonary tuberculosis (PTB) and extra-pulmonary tuberculosis (EPTB) involving other organs besides the lungs. Healthcare workers (HCWs) are at increased risk of tuberculosis exposure. The average burden among healthcare workers is 2% compared to 0.9% in the general population. EPTB constitutes about 16% of all TB cases. This study aimed to examine occupational, environmental, and demographic risk factors associated with EPTB among healthcare workers

Methods

This was a retrospective case referent type study with two control groups (one without tuberculosis and the other with pulmonary tuberculosis) and cases defined as those with EPTB. 282 records of healthcare workers were reviewed from January 2009 to December 2017.The study reviewed available medical records of healthcare workers from various categories and departments, both clinical and non-clinical. in health facilities within eThekwini Health District, Durban, South Africa. Data was analysed using a chi-square test, t- test and multivariet analysis.

Results

The mean incidence of TB in 2016 was 908/100 000 and for EPTB, was estimated at 87.2/100 000 HCWs in eThekwini Health District. Cases without respiratory protective equipment (RPE) use were more than three-fold suceptible (aOR 3.5 95%CI 1.0 – 11.4) compared to a PTB control. Working in a clinical department increased the odds for developing EPTB almost three-fold when compared to those with PTB (aOR 2.9 95%CI 0.6 – 13.2) than among those with no TB (aOR 1.4 95%CI 0.1– 13.8). As expected, HCWs diagnosed with HIV were almost two-fold likely to be exposed to EPTB when compared to thosed with PTB (aOR: 1.9 95%CI 0.9 – 4.0), however, when comparing EPTB to no TB, HIV positivity had a wide confidence interval (aOR 23.4 95% CI8.1 – 67.7) rendering the results indeterminate.

Conclusion

Occupational risk factors for EPTB are similar to that of pulmonary tuberculosis, however, risk estimates may be greater than those for PTB. Human immunodeficiency virus/ acquired immunodeficiency syndrome (HIV/AIDS) infection increases the odds of exposure to EPTB in HCWs.

INTRODUCTION

Tuberculosis (TB) is one of the major global public health concerns, claiming an estimated 1.4 million lives in 2019.[1,2] According to World Health Organisation (WHO) Global Report 2020, South Africa's TB incidence was 615 /100 000, the second highest incidence after Lesotho[2]. South Africa was among the eight countries that accounted for two-thirds of the global total in 2019 and contributed 3.6% of global infections.[2] The transmission of mycobacterium tuberculosis occurs through infected air droplets from patients with active pulmonary tuberculosis (PTB). Spread may affect the lungs, thus referred to as PTB, or it may affect other organs besides the lungs and is referred to as extra-pulmonary tuberculosis (EPTB).[3] The mode of transmission of TB renders healthcare workers at greater risk of infection since they constantly interact with undiagnosed and highly infectious patients and simultaneously are exposed in their communities.[1,4] The average burden of TB in South African HCWs is estimated to be two to three times higher than that of the general population.[5] Furthermore, it was reported that in South Africa, TB in HCWs was the third-highest commonly reported occupational disease submitted to the Compensation Fund, despite it being generally underreported.[4]

Researchers have found human immunodeficiency virus (HIV) infection to be the leading independent risk factor for tuberculosis.[6] Although the HIV prevalence among HCWs in South Africa is not well documented, it is estimated to be between 11% to 20%.[4,6] Additionally, the risk for tuberculosis is up to >20 times more in those living with HIV, consequently increasing the risk of TB in HCWs.[6] Other significant risk factors include job designation, time spent with patients, duration of service, work location, failure to wear personal protective equipment (PPE) and poor implementation and enforcement of infection control and prevention measures by the management at the health facility. [6,7,8,9]

The majority of research on TB focuses on PTB because it is highly contagious and requires public health interventions.[10] EPTB, which is less contagious, is generally underreported both within communities or as an occupational disease.[10,11] Globally, the proportion of EPTB has increased has increased from 14% in 2014 to 16% in 2020.[11,12] On the contrary, the the proportion of EPTB in Africa has decereased from 16% in 2014 to 15% in 2020.[12] In South Africa, the proportion is lower compared globally and Africa, recording 11% in 2015.[13] despite South Africa having the second highest incidence of TB and HIV globally.[2,13] This decline has been partly attributed to the up scaling of antiretroviral therapy (ART).[14] In a study conducted at rural Mopani district in South Africa where the ART coverage was <5% in 2009 and 41% in 2013, there was a 13% reduction in the total number of TB cases and a statistically significant reduction in EPTB cases from 399 in 2009 to 336 in 2013.[14]

Various studies have documented risk factors for EPTB, including female sex (OR 1.27 95% CI 1.21 - 1.32) p<0.001, HIV status (OR 1.3: 95% CI 1.05 – 1.6) I^2=0%, past history of TB (OR 4.77 95% CI 1.86 – 12.24) p<0.001, immunosuppression (aOR 1.31 95% CI 1.00 – 1.77) p=0.01, end stage renal disease (a OR 3.42 95% CI 2.39 – 4.88) p<0.01, diabetes (aOR 1.55 95% CI 0.65 - 3.69) and non-smoking (OR 0.57 95%CI 0.34–0.95) p=0.03.[15,16,17,18] We were not able to identify studies which have investigated EPTB and occupational risk. Although there is limited biological rationale for occupational exposure increasing the risk for EPTB beyond that of PTB, the limited investigation in the literature makes this a critical area of research.

This study aimed to determine the occupational, environmental, and demographic risk factors associated with EPTB among health care workers

METHODS

Study Design and Data Source

This study was a retrospective case-referent type study with two control groups (one without tuberculosis ("no TB") and the other with PTB and cases defined as those with EPTB. Data was extracted from the medical records of healthcare workers (HCWs) in all public health facilities within eThekwini Health District. Institutions that had no EPTB case during the study period and those that chose not to participate were excluded from the study. HCWs were routinely screened for tuberculosis in the remaining nine hospitals and three community health centres in the health district. The first data source was the medical records (patient files) that were filed at the occupational health clinic at these facilities. The variables extracted were age, gender, TB screening date, TB diagnostic test, diagnosis, organ affected, TB management, treatment outcomes, HIV status, diabetes status, and prescribed immunosuppressive drugs. The variables were extracted as captured by the medical doctor from the original patient file. The second data source was medical surveillance records (pre-employment/ periodical/ exit medical assessment records) filed in the occupational health clinic at the institutions. In some institutions, these were filed together with the patient files, and in others, they were filed separately. The variables extracted were job title, department working at the time of diagnosis, period of service, other departments worked at in the same facility, previous workplace, departments worked at previously, smoking status, and use of alcohol. The

third source of data was Injury on Duty and Occupational Disease (IOD/OD) files. Copies of these documents were generally filed at the occupational health clinic, and if not available, the original was obtained from the Human Resources department. The variables extracted were: the use of respiratory protection, training on respiratory protection, TB contacts at home, and environmental control. When a variable was not recorded on the source document, it was captured as "not recorded" in the data capture instruments.

Study Population and Sample Selection

The eThekwini Health district is situated in KwaZulu-Natal province of South Africa. The District comprises of 16 hospitals (one central hospital, six regional hospitals, five specialised hospitals and four district hospitals), eight community health centers and 42 primary health care facilities. Although the district is mainly urban, there are health facilities in the rural areas of the district. The district is the largest in the province and is home to one-third of the provincial population. The total number of HCWs in the district is averaged at 19 500. This figure includes clinical staff (doctors, nurses, allied professionals) and support staff (administration staff, security, porters, cleaners, laundry services, and maintenance services). All 24 institutions were invited to be part of the study. However, institutions with no EPTB cases during the study period (n=9) and those that did not agree to participate (n=3) were omitted, and the remaining 12 institutions, with a total employment of approximately 10 700, were included in the study.

According to the District Health Information System (DHIS), in eThekwini, 1 212 HCWs were diagnosed with TB between January 2009 and December 2017, 104 of these cases were of EPTB reported directly to the Occupational Health and Safety Office.[19] These numbers could be higher as inconsistent reporting by institution was noted. In 2016, the incidence of TB among HCWs in eThekwini was 712/100 000, almost two-fold the incidence of TB in the community which was 438/100 000 during the same year.[19]

Due to the limited number of EPTB cases in HCWs, all medical records of HCWs with EPTB (n=94) from January 2007 to December 2017 were selected. Controls with PTB (n=94) that were selected were diagnosed on a date closest to the month in which EPTB cases were diagnosed from the same health facility. Controls with no TB (n=94) were selected through a systematic random sampling where every third patient file of healthcare workers, at that facility, that screened negative for TB closest to the date in which EPTB was diagnosed. All healthcare workers under medical surveillance were periodically screened for TB, and results were documented in the patient file and medical surveillance forms.

Data Extraction

Study data was extracted using a specifically designed data collection tool. The data collection tool included personal information (sex, age), work information such as staff category, job title and department working; tuberculosis information included screening dates, results, TB diagnostic tests, current and past medical history and social history such as, TB contact at home and smoking status. The definition and diagnosis of EPTB and PTB were based on the National Tuberculosis Management Guidelines 2014.[20]

Statistical analysis

Data collected was captured in MS Excel, coded and exported into STATA software, version 13 (College Station, TX: StataCorp LP) for further analysis. STATA was used to check errors in coding and missing data.

Characteristics of the study population were summarised using frequencies and percentages for categorical values and mean and standard deviation (SD) for continuous variables. The following variables were generated at analysis: clinical departments; all departments that are involved in clinical care of the patients, such as medical wards, surgical wards, labour wards, theatre, ICU, etc; clinics such as TB clinic, ART clinic, Ante natal Clinic etc. Non clinical departments; included support services such as admin, maintenance, laundry, food services, mortuary, pharmacy, transport, etc. Clinical and non-clinical staff categories; represent the staff working in the departments listed above. RPE replaced PPE. Bivariate analysis was performed using a chi-square test for

categorical values such as sex, staff category, workplace type, clinical department, use of respiratory protective equipment, ventilation methods, past TB history, HIV positive, etc. and a t-test for continuous variables such as age. Multivariate analysis was performed to identify independent risk factors for having EPTB, using a stepwise logistic regression. The following variables were a priori considered in the logistic regression model: age greater than 60 years, sex, workplace (hospitals vs. community health centres), working department (clinical vs. non-clinical), respiratory protection equipment use, ever smoked and HIV positive. Three models were run: EPTB vs. all controls; EPTB vs. PTB and EPTB vs. no TB. Crude odds ratio, adjusted odds ratio (aOR) and 95% confidence interval (CI) were calculated and the results were considered statistically significant at $p<0.05$. Some variables, such as, not on antiretroviral treatment, environmental controls, TB vaccination, immunosuppressive drugs, TB contact, could not be added to the regression due to small numbers.

Ethics Approval

Permission to conduct this study from the health care facilities was obtained from KwaZulu Natal's Provincial Health Research and Ethics Committee (PHREC) and thereafter from the District Health Office and various health facilities where the study was conducted. Ethical approval was obtained from the Biomedical Research Ethics Committee (BREC) of the University of KwaZulu-Natal (ref no. BE326/19).

RESULTS

There was no meaningful difference in sex and age demographics across the cases and referent groups. There was also no difference in numbers per staff category. Among cases, the most affected organs were pleura with 28.4%, followed by the abdomen at 21.1%. In combination with EPTB sites, 10 cases had evidence of PTB infection which was predominantly abdomen and 5 cases had evidence of multiple EPTB sites infection. (Table 1)

Table 1 Characteristics of the study population

Variables		EPTB (n (%)) (n=94)	PTB (n (%)) (n=94)	No TB (n (%)) (n=94)
Sex	Female	66 (70.2)	68 (72.3)	63 (67.0)
Age (years). mean(SD)		40.4 (8.8)	40.9 (9.7)	39.2 (10.5)
Staff Category	Administration	5 (5.3)	8 (8.51)	7 (7.5)
	Nursing	59 (62.8)	54 (57.5)	55 (58.5)
	Medical	3 (3.2)	2 (2.1)	6 (6.4)
	Allied Health	6 (6.4)	5 (5.3)	17 (18.1)
	Support Services	21 (22.3)	25 (26.6)	9 (9.6)
Organs affected	Lung*#	10 (9.2)	94 (100.0)	-
	Bone and Joints	4 (3.7)	-	-
	Abdomen	23 (21,1)	-	-
	Meninges	11 (10.1)	-	-
	Lymph Nodes	11(10.1)	-	-
	Spine	3 (2.8)	-	-
	Pleura	31 (28.4)	-	-
	Skin	4 (3.7)	-	-
	Neck	3 (2.8)	-	-
	Milliary	2 (1.8)	-	-
	Epididymis	1 (0.9)	-	-
	Liver	2 (1.8)	-	-
	Pericardium	1 (0.9)	-	-
	Spondylitis	1 (0.9)	-	-
	Ear	1 (0.9)	-	-
	Larynx	1 (0.9)	-	-

*Notes *10 cases had evidence of PTB infection and five cases had multiple EPTB sites infection # TB of pleura or pleural effusion was considered as EPTB of the Lung*

Although there were no statistically significant differences between cases and PTB controls with regard to the risk factors, there were differences when compared to those with no TB (Table 2). These were most evident for the use of respiratory protection

equipment (23.9% vs 9.6%), past TB history (20.9% vs 9.7%), HIV positive (68.7% vs 8.8%) and not on Anti-Retroviral Treatment (22.8% vs 16.7%) cases compared to controls with no TB respectively. Other work-related factors, such as staff category, environmental controls and clinical department, showed no significant differences with either control group.

Table 2 Risk factor differences across cases and controls

	EPTB (n=94) (n (%))	**PTB (n=94)** (n (%))	**No TB (n=94)** (n (%))
Clinical Department (vs non-clinical)	86 (91.5)	78 (83.9)	87 (93.5)
No Respiratory Protective Equipment	22 (23.9)	17 (18.3)	9 (9.6)*
Mechanical Environmental controls (vs natural/windows)	11 (52.4)	14 (58.3)	.
TB Vaccination	18 (36.0)	16 (25.8)	26 (25.8)
Past TB history	19 (20.9)	14 (14.9)	9 (9.7)*
HIV positive	57 (68.7)	43 (55.1)	6 (8.8)*
Not on Anti-Retroviral Treatment	13 (22.8)	8 (18.6)	1 (16.7)
Diabetes	14 (15.7)	15 (16.5)	10 (10.9)
Immunosuppressive drugs	2 (2.8)	3 (4.0)	0 (0.0)
TB contact	1 (1.1)	3 (3.3)	4 (5.1)
Ever smoked (vs never-smoked)	14 (16.1)	15 (17.1)	13 (14.8)

*Notes *p value<0.05 comparing EPTB with either PTB or No TB.; EPTB = extra-pulmonary TB; PTB = pulmonary TB*

The final logistic regression modelling included age≥60, sex, department working (clinical vs. non-clinical), no respiratory protection equipment, ever smoked, staff category (clinical vs. non-clinical) and HIV-positive status. HCWs without respiratory protective equipment (RPE) use were more than three-fold likely to develop EPTB compared to a PTB control (aOR 3.5 95% CI 1.0 – 11.4) and compared to no TB (aOR 2.9 95% CI 0.7 – 12.3). Although clinical staff working in a clinical department were all associated with greater odds of having EPTB (compared to both PTB and no TB, respectively), none of these work-related variables reached statistical significance. Of note, HCWs working in a clinical department were more than three-fold likely to be

exposed to EPTB when compared to those with PTB than among those with no TB (Table 3).

As expected, HCWs diagnosed with HIV were almost two-fold likely to be exposed to EPTB when compared to thosed with PTB (aOR: 1.9 95% CI=0.9 – 4.0), however, when comparing EPTB to no TB, HIV positivity had a wide confidence interval (aOR: 23.4 95% CI 8.1 – 67.7) rendering the results indeterminate. (Table 3).

Table 3 Risk factors for EPTB, compared to controls with TB and with no TB

	EPTB vs PTB		**EPTB vs No TB**	
	Crude Odds Ratio OR(95% CI)	**Adjusted Odds Ratio OR(95% CI)**	**Crude Odds Ratio OR(95% CI)**	**Adjusted Odds Ratio OR(95% CI)**
Age>=60	2.0 (0.3 – 23.0)	2.5 (0.2 – 29.8)	1.3 (0.22 – 9.4)	5.2 (0.4 – 61.4)
Sex (Male vs female)	0.9 (0.5 – 1.8)	0.6 (0.2 –1.5)	1.2 (0.6 – 2.3)	1.1 (0.4 – 3.0)
Department (Clinical vs Non-clinical)	2.1 (0.8 – 6.0)	2.9 (0.6 – 13.2)	0.7 (0.2 – 2.6)	1.4 (0.1 – 13.8)
No Respiratory Protective Equipment	1.4 (0.7 – 3.1)	3.5 (1.0– 11.4)*	3.0 (1.2 – 7.8)	2.9 (0.7 – 12.3)
Ever smoked	0.9 (0.4 – 2.2)	0.9 (0.3 – 2.6)	1.1 (0.4 – 2.7)	1.2 (0.4 – 4.5)
HIV positive	1.8 (0.9 – 3.6)	1.9 (0.9 – 4.0)	22.7 (8.2 – 70.6)	23.4 (8.1 – 67.7)*
Staff category (clinical vs non-clinical)	1.4 (0.7 – 2.8)	1.7 (0.6 – 4.8)	0.5(0.2 – 1.1)	1.6 (0.4 – 6.7)
Past TB History	0.7 (0.3 – 1.5)	1.1 (0.5 – 2.8)	0.4 (0.2 – 1.0)	1.1 (0.3 – 4.6)

*Notes *p value<0.05 comparing EPTB with either PTB or No TB.; EPTB = extra-pulmonary TB; PTB = pulmonary TB. All variables indicated above where included in the regression models. Two separate models were run, for each control group.*

DISCUSSION

Our findings provide evidence that workplace factors increase the risk of developing EPTB among healthcare workers. Although strongly driven by HIV status, factors such as use of RPE, working in a clinical department or having a clinical job description suggest an increased risk when compared to those with PTB or no TB.

To our knowledge, despite the large volume of literature about TB risks faced by healthcare workers, there are no studies published showing the association between occupational risk factors and EPTB among HCWs. Research on occupational TB focuses on PTB because it is highly contagious, with severe consequences and interventions are available. However, as our data shows EPTB although less contagious,[10,11] is nevertheless work-related. More importantly, in our sample, the work-related risk for EPTB is greater than the risk for PTB. This has not been previously reported.

In addition, although up to 16% of all notified TB cases globally are EPTB, the lower absolute numbers at health facility levels create challenges in research among healthcare workers.[12] For example, in the eThekwini district, employing over 19 500 healthcare workers across 68 facilities including clinics, only 104 cases of EPTB were diagnosed over a seven-year period. Despite this, we were able to describe that work-related factors, such as working in a clinical department, are likely to create a three-fold greater increase in risk for EPTB as compared to PTB.

Although confidence intervals not always excluding the null value, all the work-related risk factors (facility type, RPE use, departmental type and job category) showed increased odds ratios. These risk estimates were always greater when comparing EPTB to PTB controls, rather than when compared to those with no TB. We, a priori, expected that a dilution of the effect estimate will occur among those with PTB because of similarity in risk factors for both outcomes. However, the greater odds ratios seen among PTB controls as compared to the no TB controls, implies that the relationship between the workplace and EPTB is likely to be independent of the risk for PTB.

Our logistic regression model suggested that although clinical staff working in clinical departments were more likely to be exposed to EPTB compared to both PTB and no TB. A systematic review of tuberculosis in healthcare workers in South Africa reported only a single study that found differences in incidence across various occupational categories.[4] Similarly, a study from South Africa found no significant difference between the department worked and the risk for TB.[6] There may be several reasons for occupational categories of health workers not being consistently identified as a risk factor. Exposure misclassification in epidemiological studies is probably a key explanation. Most health care workers work in a variety of exposure zones within their health facilities, independent of the specific job-title, and therefore job-title becomes an inadequate proxy for exposure. It is also likely that increased risk prevention strategies are present among higher exposed occupational categories. For example, those working in outpatient departments or medical wards are more likely to wear appropriate RPE as compared to those in perceived lower risk environments.

Our results suggested that HCWs without RPE use were more than three-fold likely to be exposed to EPTB (aOR 3.5 95%CI 1.1– 11.5) compared to a PTB control. Respiratory protection programmes recommended particulate respirators to reduce M. tuberculosis transmission to health workers.[22] Most studies in a systematic review assessing the effectiveness

of respiratory protection in reducing the risk of M. tuberculosis, found a reduction in the tuberculin skin test (TST) conversion rate with the use of particulate respirators by health workers, suggesting a reduction in the number of new TB infections.[22] The effectiveness of the personal respirator is maximised if routinely used, fitted and used properly to prevent face-seal leaks, and therefore can, in theory, significantly minimise the chance that inhaled air will contain infectious tubercle bacilli.[23] However, it is not clear why the risk for EPTB among non-mask users is greater than for PTB, given that the exposure pathways for both are inhalational. We hypothesise that non-mask use acts as a proxy for other unmeasured variables, or that the pathogenic mechanisms vary across the disease presentations, and that mask wearing is of greater benefit in protection against EPTB. [16,24]

The pathogenesis of EPTB needs greater investigation. It is hypothesised that mechanism of spread for EPTB disease is via the lymphohaematogenous route, within an immunocompromised context.[24] However, there is evidence to suggest that different M.tuberculosis lineages and macrophage responses may increase risk for EPTB.[24]

In our study, pleura (28.4%), was the most common site of EPTB. This has been reported in several other studies including South Africa, Spain, Pakistani and South Korea, reporting a range from 33.3% in Pakistani to 47% in South Korea.[10,14,25,26] In another study in South Africa which also identified pleura as the common EPTB site, the authors suspected a diagnosis bias, sighting that it was difficult to accurately assess the anatomical distribution of the diseases, attributed to inadequate diagnostic tools, therefore other organs may be missed.[27] The pleura as the common site could be attributed to its location, anatomically it is very close to the lungs, and pleural effusion is caused by the fluid collection due to the rupture of the sub-pleural focus causing an interaction between the tubercle bacilli inducing a delayed hypersensitivity reaction.[28,29] Pleural effusion in adults occur mostly due to reactivation disease.[28]

As expected, HCWs diagnosed with HIV were almost two-fold likely to be exposed to EPTB when compared to thosed with PTB (aOR 1.9 95% CI 0.9 – 4.0), however, when comparing EPTB to no TB, HIV positivity had a wide confidence interval (aOR 23.4 95% CI 8.1 – 67.7) rendering the results indeterminate. This is in agreement with several studies notably, those conducted in developing countries such as South Africa (OR 2.15 95% CI 2.09 – 2.21), Ghana (aOR 3.19 2.69 – 3.79), and a study conducted in a large tertiary hospital in South India reported that EPTB showed an increasing trend among HIV infected patients.[1,14,30]

Our study has several strengths. The study was able to determine the incidence of EPTB in health care workers for the past eight years and compared risk factors for pulmonary and EPTB which has never been profiled. It will also able to determine the role of HIV in TB, particularly EPTB in HCWs in eThekwini Health District. Another strength of our study was the ability to calculate a minimum incidence of EPTB on a well described denominator. Data was obtained from original source documents which included medical files, medical surveillance files and employment records, eliminating the possibility of either misclassification of outcome or exposure.

The key limitation in our study was the dependence on extracting risk factor data from a secondary database and clinical files. These records were not collected with a view of identifying risk factors, but for administrative purposes. The following risk factors of interest were not analysed due to limited data: environmental controls, i.e., type of ventilation, and administrative controls i.e., training on respiratory protection, hour spent with the patient, type of home dwelling, mode of transport. Another limitation was the small sample size of the control groups, therefore, our findings may differ from the findings of studies with larger groups. Inconsistency in record management in the institutions resulted in missing health records. There was no standardised information system and various data sources were used, some of which had incomplete information. The stigma attached to TB contributes to health care workers seeking treatment outside the facility at which they are employed. This information may not be relayed back to the occupational health services of the facilities. Therefore the true prevalence and incidence of EPTB was not known, however, our case-control study design limits the effects of this non-reporting.

In conclusion, this study provides evidence that occupational factors have a role to play in increasing the risk for EPTB, and this risk may be greater than that for PTB alone. Thus, medical surveillance among healthcare workers must take EPTB into consideration, and measures to protect workers against all forms of TB are of critical importance.

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CHAPTER III: SYNTHESIS, BIAS AND LIMITATIONS

Our study aimed to determine whether occupational factors increase the risk for EPTB among health care workers. To our knowledge, despite the large volume of literature about TB risks faced by healthcare workers, there are no studies published showing the association between occupational risk factors and EPTB among HCWs. Occupational risk factors studied were staff categories comparing clinical and non-clinical, departments comparing clinical and non-clinical and the use of respiratory protection equipment. All these factors were associated with EPTB when compared to PTB.

Our study, associated clinical staff working in the clinical department with an increased risk of EPTB compared to both PTB and no TB, although not statistically significant. There is strong evidence, across the world, that that the specific work locations and occupational categories of HCWs were associated with a higher risk of acquiring TB disease.[7,23] Enforcement of adherence to TB infection control measures in healthcare settings is a crucial predictor of disease.[9] Studies conducted in South Africa, suggested that HCWs working in clinical departments such as TB clinics and medical wards were more likely to practice TB infection and prevention control measures compared to non-clinical areas such pharmacy departments.[7] The latter studies investigated PTB. However, because EPTB has the same route of exposure as PTB, we can conclude that our findings of the association for EPTB and work is consistent.

Another crucial occupational risk factor was use of RPE: our study suggested that cases without RPE use had more than three-fold increased risk compared to PTB control. A systematic review on the use of personal protective equipment to protect against respiratory infections in Pakistan reported that studies on the use of RPE were mostly observational and the few randomized clinical trials were conducted in high/middle income countries and data from low income high TB burdened countries was limited.[45] A systematic review assessing the effectiveness of respiratory protection in reducing the risk of M. tuberculosis suggested a reduction in new TB infection as determined by the tuberculin skin test.[24] In our study, HIV-infected HCWs had increased odds of developing EPTB compared to PTB. It is likely that immunocompromised HCWs not using RPE had a greater risk for EPTB, compared to those who did use RPE.

BIAS AND LIMITATIONS

Although data was collected on environmental factors such as ventilation and administrative factors such as time spent with the patient and training on use, we were not able to analyse it further due to approximately 60% of data missing from the source documents for each variable and some variables having no data at all (22% of 50 variables had no data).

Measures of reduction in selection bias was minimised in this study because all medical files of healthcare workers diagnosed with EPTB were reviewed. PTB controls were selected based on the medical records of HCWs diagnosed with PTB for each case of EPTB sampled, closest to the month in which a case of EPTB was diagnosed from the same institution. For controls with no TB, a systematic random sampling strategy was undertaken where every 3rd medical records of HCWs who were screened for TB and found to be without TB were sampled. Data were obtained from original source documents, which included medical files, medical surveillance files and employment records, eliminating the possibility of recall bias. A standard data extraction tool was used to collect information from the medical files, thus reducing information bias. Multivariate analyses were done to minimise the effect of confounding variables. The strategies for minimizing selection and information bias improved the generalizability of findings to healthcare workers in healthcare facility settings.

The key limitation in our study was the dependence on extracting risk factor data from a secondary database and clinical files. These records were not collected with a view of identifying risk factors, but for administrative purposes. These risk factors of interest included environmental controls, i.e., type of ventilation, and administrative controls i.e., training on respiratory protection and hour spent with the patient, which were not analysed due to limited data. There is a chance that both cases and referents may not have disclosed their actual smoking status since it is associated with an unhealthy lifestyle and could have been recorded as non-smokers even though they smoked. However, this is unlikely to impact the results as this could be random in both cases and referents.

Inconsistency in record management in the institutions resulted in missing health records. There was no standardised information system, and various data sources were used, some of which had incomplete information.

The stigma attached to TB contributes to HCWs seeking treatment outside the facility at which they are employed. Especially HCWs who are already diagnosed with HIV and are not ready to

disclose their status in an environment where they are known. Consequently, when they experience TB-related symptoms, they prefer to be diagnosed and managed elsewhere rather than at the Occupational Health Clinic. This information may not be relayed back to the occupational health services of the facilities. Therefore the true prevalence and incidence of EPTB were not known, however, our case-control study design limits the effects of this non-reporting.

CHAPTER IV: CONCLUSIONS AND RECOMMENDATIONS

In conclusion, this study provides evidence that occupational factors, such as staff category, department working, and use of RPE, increase the risk for EPTB, and this risk may be greater than that for PTB alone. Thus, medical surveillance among healthcare workers must take EPTB into consideration, and measures to protect workers against all forms of TB are of critical importance. Further research is required to investigate all factors in depth which may look at social factors, environmental factors; infection, prevention and control implementation and adherence thereof.

Recommendations

- HIV prevention programs must be implemented in health facilities
- Measures to promote confidentiality of HIV clients must be put in place, such as using codes instead of the names of the healthcare worker on the patient file. OHNs must collect prepacked ARVs from pharmacy instead of the patient. Code protected Tier.Net system (patient information system) must be installed in all occupational health clinics to ensure that no staff patient file leaves the clinic for data capturing.
- Employees susceptible to EPTB e.g. HIV positive, on immunosuppressive medication, uncontrolled diabetes must not be placed in high exposure areas, e.g. TB ward, therefore this requires management to have systems in place to assess vulnerable employees.
- Rigorous programs must be implemented to educate employees on medical surveillance, the importance of employees presenting themselves for it, and the implications of failure to do so.
- Risk Assessment is crucial to gather information on the hazards and what outcomes are associated with the hazards. This information must be further analysed to prevent and protect HCWs against occupationally related diseases and physical injury
- Another crucial element is the investigation following the diagnosis of TB case and recording of findings to determine if the control measures are in place, sufficient, and well maintained.

- There is a greater need to re-enforce infection and prevention control measures that are meant to minimise exposure to TB in the workplace and extend this training to general TB prevention strategies even in the community.
- A high index of suspicion is required when screening employees for TB so that no potential cases are missed.
- Occupational Health Clinics must be equipped with sufficient and appropriate resources, including human resources. The clinics must further ensure confidentiality and ethical consideration for employees to trust the program and utilize the services instead of external service providers.

Comments on data management/file management

Although this was not the focus of the study, these were important aspects that limited the proper evaluation of the files, and therefore attention should be paid to the following:

- Filing and storing systems of medical files of healthcare workers in institutions must be standardised across the district. A decision should be taken on the system that will be adopted to manage healthcare workers' health records.
- Medical file audits should be conducted periodically to ensure the correctness and completeness of the information.
- The data collected in institutions for the District Health Information System (DHIS) should further disaggregate TB cases to show EPTB cases, and verification of this data must be strengthened
- The department must invest in an online based system that will assist in ensuring correct data.

CHAPTER V

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APPENDICES

APPENDIX A

Data Collection tool

Name of Health facility _____

File identification number /code

A. Personal Information

1. Gender

a) Male	
b) Female	
c) Not recorded	

2. Date of birth (dd/mm/yyyy)

_____

B. Work Information

Current

3. Qualification

_____

4. In which staff category do you fall?

a) Administration	
b) Nursing	
c) Doctor	
d) Allied health(e.g. physio, radiographer, etc)	
e) Support services (e.g. laundry, maintenance, food services, cleaning, etc)	
f) Other (specify)	
g) Not recorded	

5. Job title

Enrolled nursing assistant	
Enrolled nurse	
Registrar	
Professional nurse	

Nursing manager	
Part-time medical officer (OPD)	
Full-time medical officer (OPD) Ward medical officer	
Intern	
Junior consultant	
Senior consultant/Departmental Head	
Pharmacist	
Pharmacy assistant	
Laboratory technician	
Radiographer	
Physiotherapist	
Occupational Therapist	
Dentist	
Administrator	
Ward clerk	
OPD Clerk	
Lay counsellor	
HR Officer	
Finance Officer	
Security	
Laundry worker	
Artisan	
Handyman	
Porter	
Cleaner	
General assistant (please specify type) _____	
Other (please specify) _____	

6. Department/ward working in,
_____

7. Period of service in this department/ward?

years	Months

8. Hours spent with the patient per day?

hours	Minutes

9. Is PPE provided

a) Yes	
b) No	
c) Not recorded	

10. Respiratory protection used

a) N95 mask	
b) Surgical mask	
c) Other	
d) Don't use mask	
e) Not recorded	

11. Respiratory protection frequency of use

a) All the time	
b) Specific task	
c) Specific areas only	
d) Never	
e) Not recorded	

12. Respiratory protection replacement patterns

a) use once and discard	
b) re use and discard it at the end of the shift (daily)	
c) reuse and discard at the end of the week (weekly	
d) Anytime a fresh one is needed	
e) Other, please specify	

f) Not applicable	
g) Not recorded	

13. Respiratory protection storage in case of reuse

a) In a plastic bag	
b) In the brown paper bag	
c) Bare in the cupboard	
d) Bare on the table in the duty room	
e) Other, please specify	
f) Not applicable	
g) Not recorded	

14. Training on N95

a) Yes	
b) No	
c) Not applicable	
d) Not recorded	

15. Other departments/wards worked at in the same facility_____

Details of workplace at time of diagnosis of TB.

16. workplace at which TB was diagnosed

_____

17. Departments/wards worked at in this workplace?

_____

18. Period of service in this department/ward?

Years	Months

19. Hours spent with the patient per day?

Hours	Minutes

20. Respiratory protection used

a) N95 mask	
b) Surgical mask	
c) Other	
d) Don't use mask	
e) Not recorded	

21. Respiratory protection frequency of use

a) All the time	
b) Specific task	
c) Specific areas only	
d) Never	
e) Not Applicable	
f) Not recorded	

22. Respiratory protection replacement patterns?

a) use once and discard	
b) re use and discard it at the end of the shift (daily)	
c) reuse and discard at the end of the week (weekly	
d) Anytime a fresh one is needed	
e) Other, please specify	
f) Not applicable	
g) Not recorded	

23. Respiratory protection storage in case of reuse

a) In a plastic bag	
b) In the brown paper bag	
c) Bare in the cupboard	
d) Bare on the table in the duty room	
e) Other, please specify	
f) Not applicable	
g) Not recorded	

24. Environmental controls

a) Open window policy	
b) Cross ventilation	
c) Propeller fans	
d) Exhaust ventilation system	
e) Hepa filters	
f) UVGI lights	
g) Air conditioners	
h) Not recorded	

C. Tuberculosis Information

25. Tb screening date _____

26. TB Screening results

a) TB suspected	
b) TB not suspected [if no, then skip to Question 35]	
c) Not recorded	

27. If TB was suspected, where was your first diagnosis of TB

a) Private doctor	
b) Occupational health clinic	
c) Other Public health facility	
d) Never been diagnosed	
e) Not applicable	
f) Not recorded	

28. Tb diagnostic test

a) Acid fast bacilli (AFB)	
b) Gene Xpert	
c) x-ray	
d) CAT scan	
e) Biopsy	
f) Other (specify)	
g) Not applicable	
h) Not recorded	

29. Diagnosis

a) Afb +	
b) Afb ++	
c) Afb +++	
d) Gene Xpert positive	
e) X-ray positive	
f) Other (specify)	
g) Not Applicable	
h) Not recorded	

30. Part of organ affected

a) Lung	
b) Bone and joints	
c) Abdomen	
d) Meninges	
e) Lymph nodes	
f) Spine	
g) Other, specify	
h) Not applicable	
i) Not recorded	

31. Put on treatment

a) Yes	
b) No	
c) Not applicable	
d) Not recorded	

32. Treatment outcome

a) Cured	
b) Completed treatment	
c) Defaulted/ interrupted	
d) Treatment failure	
e) Died	
f) Not recorded	

33. TB Vaccination

a) Yes	
b) No	
c) Not recorded	

34. Past Tb History

a) Yes	
b) No	
c) Not recorded	

If yes:

35. How many episodes (including the current one)

_____

36. Duration of treatment for each episode

_____

_____

D. Medical History

37. HIV status

a) HIV -	
b) HIV +	
c) Not recorded	

If answerd b), please answer question 38 below

38. On anti-retroviral treatment?

a) Yes	
b) No	
c) Not recorded	

39. Diabetes

a) Yes	
b) No	
c) Not recorded	

If answered a), please answer question 40 below

40. On treatment?

a) Yes	
b) No	
c) Not recorded	

41. Use of immunosuppressive drugs

a) Yes	
b) No	
c) Not recorded	

E. Social lifestyle

42. Type of home dwelling living in?

a) Formal house	
b) RDP house	
c) Informal house (shack)	
d) Other (please specify)	
e) Not recorded	

43. Number of rooms? (including the kitchen, lounge and bedrooms)

_____

44. Number of people staying with at home?

_____

45. Tb contact at home

a) Yes	
b) No	
c) Not recorded	

46. What mode of transport do you use?

a) Own car	
b) Taxi	
c) Bus	
d) Train	
e) Motor Bike	
f) Walk	

g) Other (specify)	
h) Not recorded	

47. Alcohol use

a) Never consumed alcohol	
b) Consume alcohol frequently	
c) Consume alcohol every weekend	
d) Consume alcohol on special occasions	
e) Ex drinker	
f) Not recorded	

48. Smoking status

a) Current smoker	
b) Ex-smoker	
c) Never smoked	
d) Not recorded	

If a current smoker, please answer questions 49

If an ex-smoker, please answer question 50

49. No. of cigarettes/joints of tobacco smoked a day

_____

50. How long has it been since the last cigarette/joint of tobacco?

Years	Months	Days

- END –

APPENDIX B

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

08 July 2019

Mrs NG Bhengu
School of Nursing and Public health
College of Health Sciences
Nontuthuzelo.Bhengu@kznhealth.gov.za

Dear Mrs Bhengu

Protocol: Risk factors associated with extra-pulmonary tuberculosis among health care workers in eThekwini Health District, KwaZulu-Natal
Degree: MMedSc **BREC Ref No: BE326/19**

EXPEDITED APPLICATION: APPROVAL LETTER

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 15 April 2019.

The study was provisionally approved pending appropriate responses to queries raised. Your response received on 27 June 2019 to BREC letter dated 18 June 2019 has been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have been met and the study is given **full ethics approval** and may begin as from 08 July 2019. **Please ensure that site permissions are obtained and forwarded to BREC for approval before commencing research at a site.**

This approval is valid for one year from **08 July 2019.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **noted** by a full Committee at its next meeting taking place on **13 August 2019.**

Yours sincerely

Prof V Rambiritch
Chair: Biomedical Research Ethics Committee

cc: postgrad admin: ramlalm@ukzn.ac.za Supervisor: naldoon@ukzn.ac.za

Biomedical Research Ethics Committee
Professor V Rambiritch (Chair)
Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban 4000
Telephone: +27 (0) 31 260 2486 **Facsimile:** +27 (0) 31 260 4609 **Email:** brec@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

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APPENDIX C

health
Department:
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PROVINCE OF KWAZULU-NATAL

DIRECTORATE: CORPORATE SERVICES

83 King Cetshwayo Highway
Mayville, Durban, 4001
Tel: 031 240 5455 Email:
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ETHEKWINI HEALTH DISTRICT OFFICE

6th June 2019

Dear Nontuthuzelo Bhengu

Re: Permission To Conduct Research at eThekwini District Facilities.

This letter serves to confirm that your application to conduct the research study titled, "Risk factors associated with extra-pulmonary tuberculosis among health care workers in eThekwini Health District, KwaZulu-Natal " in the eThekwini district at the following health care facilities has been recommended:

1. Addington Hospital
2. Charles James Hospital
3. Clairwood Hospital
4. Don McKenzie Hospital
5. Ekuhlengeni Psychiatric Hospital
6. Hillcrest Hospital
7. Inkosi Albert Luthuli Central Hospital
8. King Edward VIII Hospital
9. King Dinuzulu Hospital Complex
10. Mahatma Ghandi Hospital
11. Mc Cord Eye Hospital
12. Osindisweni Hospital
13. Prince Mshiyeni Memorial Hospital
14. RK Khan Hospital
15. St. Aidan's Hospital
16. Wentworth Hospital
17. Cator Manor CHC
18. Hlengisizwe CHC
19. Inanda C CHC
20. KwaDabeka CHC
21. KwaMashu CHC
22. Newtown A CHC
23. Phoenix CHC
24. Tongaat CHC.

Kindly upload this letter together with your application as required to the Health Research and Knowledge Unit for the KZN Department of Health for Approval.

Please also note the following:

1. This research project should only commence after final approval by the KwaZulu-Natal Health Research and Knowledge Unit, and full ethical approval, has been granted,
2. That you adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
3. All research activities must be conducted in a manner that does not interrupt clinical care at the health care facility,
4. Ensure that this office is informed before you commence your research
5. The District Office/Facility will not provide any resources for this research
6. All logistical details must be arranged with the CEO/medical manager /operational manager of the facility,
7. You will be expected to provide feedback on your findings to the District Office/Facility

Yours sincerely

Dr N Green(District Research Coordinator)
Pp Ms. T. P. Msimango
Chief Director (Acting)
eThekwini Health District

- KINDLY RETURN **ALL DOCUMENTATION** WHEN REPLYING

APPENDIX D

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Physical Address: 330 Langalibalele Street, Pietermaritzburg
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Email:
www.kznhealth.gov.za

DIRECTORATE:
Health Research & Knowledge Management

NHRD Ref: KZ_201906_020

Dear Mrs NG Bhengu (UKZN)

Approval of research

1. The research proposal titled **'Risk factors associated with extra pulmonary tuberculosis among health care workers in eThekwini Health District, KZN'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at Addington, Charles James, Clairwood, Don McKenzie, Ekuhlengeni Psychiatric, Hillcrest, Inkosi Albert Luthuli, King Edward VIII, King Dinuzulu Hospital Complex, Mahatma Gandhi, McCord Eye, Osindisweni, Prince Mshiyeni Memorial, RK Khan, St Aidan's and Wentworth Hospital; Cato Manor, Hlengisizwe, Inanda C, KwaDabeka, KwaMashu, Newtown A, Phoenix and Tongaat CHC.

2. You are requested to take note of the following:
   a. Kindly liaise with the facility manager BEFORE your research begins in order to ensure that conditions in the facility are conducive to the conduct of your research. These include, but are not limited to, an assurance that the numbers of patients attending the facility are sufficient to support your sample size requirements, and that the space and physical infrastructure of the facility can accommodate the research team and any additional equipment required for the research.
   b. Please ensure that you provide your letter of ethics re-certification to this unit, when the current approval expires.
   c. Provide an interim progress report and final report (electronic and hard copies) when your research is complete to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za.

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

Elutge

Dr E Lutge
Chairperson, Health Research Committee
Date: 27/06/19

Fighting Disease, Fighting Poverty, Giving Hope