PREVALENCE AND SPECTRUM OF CUTANEOUS TUBERCULOSIS IN PATIENTS AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

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Submitted to the University of the Witwatersrand, Faculty of Health Sciences, towards the fulfilment of the requirements for the degree of Master of Medicine in Dermatology

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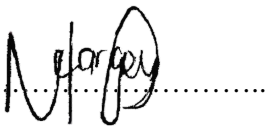
Declaration

I, Naima Hargey, declare that this research report (in the format of a "submissible" paper) is my own, unaided work. It is being submitted for the degree of Master of Medicine in the branch of Dermatology at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.



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24 day of November 2023

Contribution of the Candidate to the Paper

Declaration: Student's contribution to article(s) and agreement of co-author(s)

I, Naima Hargey, student number 2367015, declare that this research report is my own work and that I contributed significantly towards research findings presented in the paper intended for the publication below.

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Agreement by co-authors: By Signing this declaration, the co-authors listed below agree to the use of the article(s) by the student as part of her Research Report. In cases where the student is not the 1st author of a published article, the primary supervisor must explain (under comments) why the student is entitled to use the paper for his/her degree purposes.

Article Title: Prevalence and spectrum of Cutaneous Tuberculosis in patients at Charlotte Maxeke Johannesburg Academic Hospital

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Dedication

This research report is dedicated to my loving and supportive parents, Majied and Zaiboon, my husband, Waseem, and my children, Farhaan and Zayd.

Acknowledgments

I wish to express my sincere thanks to Dr Lushen Pillay and Dr Chioma Ede for their supervision, insight and support.

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Nomenclature

AARMs – Academic Affairs and Research Management System
AFB – Acid Fast Bacilli
AIDS – Acquired Immunodeficiency Syndrome
ARV – Anti-Retro Viral
BCG - Bacillus Calmette – Guerin
CMJAH - Charlotte Maxeke Johannesburg Academic Hospital
EI - Erythema Induratum
HIV - Human Immunodeficiency Virus
INH – Isoniazid
IRIS - Immune Reconstitution Inflammatory Syndrome
LV – Lupus Vulgaris
LS – Lichen Scrofulosorum
LI - Lymphocytic Infiltrate
M.Tuberculosis - Mycobacterium Tuberculosis
NI - Neutrophilic infiltrate
NHLS – National Health Laboratory Services
P - Panniculitis
PCR – Polymerase Chain Reaction
PH - Pseudoepitheliomatous hyperplasia
PNT – Papulonecrotic Tuberculid
TB – Tuberculosis
VC - TB Verrucosa Cutis
WHO - World Health Organization
WN - Wedge Necrosis

Prevalence and spectrum of Cutaneous Tuberculosis in patients at Charlotte Maxeke Johannesburg Academic Hospital

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The authors declare that there is no conflict of interest.

Abstract

Introduction

Tuberculosis (TB) is a communicable disease that belongs in the top 10 causes of death worldwide. World Health Organization (WHO) indicated that 90% of the world's TB cases occurred in 30 countries, with South Africa being one of the countries listed. Cutaneous TB comprises 1-2% of the extrapulmonary TB cases. Cutaneous TB is a chronic skin infection mainly caused by Mycobacterium Tuberculosis.

Aims

The aim of this study was to investigate the prevalence and spectrum of Cutaneous TB in patients at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

Methods

A retrospective study of 69 patients were confirmed on histopathology with cutaneous TB. This was further sub-divided into true TB and tuberculid forms. These forms were correlated with histopathological and clinical findings as well as the patient's HIV status.

Results

The average age (SD) of the 69 patients was 39(12). Females were more common than males in the study (ratio 7.625:1). The average disease duration (SD) of 17(22) months.

Tuberculids (81.2%) were the most common form of cutaneous TB with Erythema Induratum (76.8%) being the most common tuberculid. The most common form of true cutaneous TB was that of Lupus Vulgaris (13%).

Acid fast bacilli stains were the most common histopathological investigation done on tissue biopsies. Panniculitis (35.4%) was the most common histological feature.

The most common clinical manifestation was that of nodules (59.3%). Few patients presented with polymorphic manifestations (20.3%). The lower limbs were the most common affected site in cutaneous TB particularly Erythema induratum ($p<0.001$). Other key findings for Erythema Induratum were its prevalence in females ($p<0.001$), histopathological findings of granulomas, vasculitis, panniculitus and AFB negativity ($p<0.001$).

33 of the 69 patients were HIV positive but the HIV status did not show a relationship with any form of cutaneous TB ($p=0.971$). Erythema Induratum patients who were HIV positive, were more likely to be on ARV's ($p<0.001$).

Conclusion

Despite South Africa being at the forefront of the HIV/TB epidemic, cutaneous TB remains uncommon.

The advent of ARVs being prescribed to all HIV positive patients may have played a role in these patients presenting in a similar clinical and histopathological manner as HIV negative patients.

Introduction and Literature Review, Aim and Objectives

Introduction

Tuberculosis (TB) is a communicable disease that belongs in the top 10 causes of death worldwide. It is the leading cause of death from a single infectious agent. TB is caused by an Acid-fast bacillus (AFB) organism known as Mycobacterium Tuberculosis (M.Tuberculosis).
The World Health Organization (WHO) indicated that 90% of the world's TB cases occurred in 30 countries, with South Africa being one of the countries listed [1] accounting for 3.6% of the TB cases. In 2018, South Africa was estimated to have 390,000 TB cases [2]. Statistics South Africa reported that TB was the leading cause of death in 2015[3].
M. Tuberculosis usually affects the lungs but can also cause extrapulmonary TB which is around 8-10% of all TB cases [4]
Cutaneous TB comprises 1-2% of those extrapulmonary cases[4]. Cutaneous TB is a chronic skin infection mainly caused by M. tuberculosis.

Literature Review

Cutaneous TB was first described in 1826 by Laennec as a warty lesion, but the organism M. tuberculosis was only identified in 1882[5].
The development of Cutaneous TB depends on:

1) Host factors **-** such as age, gender, immune competency (Human immunodeficiency virus/HIV status)[6];
2) Environmental factors **-** areas of high prevalence
3) Mycobacterium factors [7].

According to Nguyen et al., 80% of TB cases fall in low-middle income populations[8] and South Africa is a country that exhibits this population category.
The most universally used cutaneous TB classification is based on the route of bacilli infection[6]. Tuberculids are not considered a true form of Cutaneous TB as it occurs from a hypersensitivity reaction to the mycobacterial antigens derived from other organs infected with TB[9]. The spectrum of Cutaneous TB clinically presents with various manifestations (see Table 1). Patients may also present with polymorphic (2 or more) manifestations [7].
Cutaneous TB may mimic many conditions therefore it is imperative to evaluate a patient with diagnostic tests alongside their history and clinical examination.

Table 1: Cutaneous TB variants alongside Clinical and Histopathological findings [6,7,10]

TB Type	**Clinical Findings and Sites**	**Histopathological Findings**
Lupus Vulgaris (LV)	• Plaque, Nodules and Ulcerations • Head and Neck, Extremities	• Seldom AFB + • Seldom PCR + • Culture positivity 50% • Granulomas
Tuberculosis Chancre	• Papules, Ulceration • Extremities	• AFB+ • Neutrophilic infiltrate (NI)
TB Verrucosa Cutis (VC)	• Plaques, Verrucous • Extremities	• Seldom AFB+ • Culture positivity 50% • Pseudoepithelial hyperplasia (PH) • Granulomas
Orificial TB	• Ulcerations • Genital, Oral, Urinary orifices	• AFB + • Granulomas
Scrofuloderma (S)	• Nodules, Sinuses, Suppuration, Ulceration • Head & neck	• AFB + • Culture positivity 50% • NI • Granulomas
Miliary TB	• Papules, Pustules, Nodules,	• AFB + • NI

	• Widespread	• Vasculitis
TB Gumma	• Nodules, Ulceration, Suppuration • Torso, Extremities	• Granulomas • AFB +
Lichen Scrofulosorum (LS)	• Minute Papules • Torso	• AFB - • Granuloma
Papulonecrotic Tuberculid (PNT)	• Pustules, Papules • Head and Neck, Extremities	• Granulomas • Wedge Shape Necrosis • PCR positivity in 50% • AFB -
Erythema Induratum (EI)	• Nodules, Ulcers • Extremities	• Granulomas • Vasculitis • Panniculitis • Lymphocytic Infiltrate (LI) • AFB – • Culture -

According to the WHO, in 2017, 920000 HIV positive patients developed TB and a third of these patients succumbed to TB that year[11]. 31% of TB patients in a systematic review, done in Sub-Saharan Africa over a 27 year period were HIV positive. [12]. South Africa exhibits the largest HIV epidemic in the world[13].

The initiation of antiretroviral therapy may lead to an unmasking of subclinical infections or paradoxical worsening of existing Cutaneous TB[14]. HIV may also allow for atypical presentations of cutaneous lesions.

Below is a tabulated summary of the most common findings in studies on Cutaneous TB worldwide:

Table 2: Worldwide Cutaneous TB studies[15–19]

Country	Most Common TB Type	Type of Study	Number of patients
Nepal	• True TB – LV • Tuberculid – PNT	Retrospective	47
India	• True TB – Scrofuloderma • Tuberculid – LS	Retrospective	131
Brazil	• True TB – Scrofuloderma • Tuberculid – EI	Retrospective	75
Tunisia	• True TB - Scrofuloderma • Tuberculid – EI	Retrospective	137
South Africa	• True TB - Scrofuloderma • Tuberculid – EI	Prospective	74

Despite South Africa being at the forefront of the HIV/TB epidemic and the known associated morbidity of Cutaneous TB, there is a paucity of recent data published on the prevalence, clinical and histopathological findings of Cutaneous TB and its relationship with HIV in Johannesburg, South Africa. The prevalence data on Cutaneous TB needs to be updated especially after the advent of antiretroviral therapy regardless of the CD4 count which was introduced in September 2016[20].

The aim of this study is thus to investigate the prevalence and spectrum of Cutaneous TB in patients at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

The study objectives are as follows:

1) Primary Objective: To determine the prevalence and spectrum of Cutaneous TB in patients at CMJAH;
2) Secondary Objectives: To correlate positive laboratory results in the diagnosis of Cutaneous TB and to describe the clinical presentation of lesions (as per the histopathology form)
3) Tertiary Objectives: To assess the correlation of HIV in Cutaneous TB;

Materials and Methods

Study Design

This study is a retrospective review of histologically proven cutaneous TB in patients who had attended CMJAH between 1st January 2011 and 31st December 2020.
In total 69 cases were identified.
CMJAH is a tertiary hospital that serves as a referral unit for the surrounding regional hospitals and to a community that can be described as low-middle income.

Patients

Inclusion Criteria

1) Patients older than 18 years of age, with confirmed Cutaneous TB infection on histopathology both as inpatients and outpatients at CMJAH;
2) Patients diagnosed between 1st January 2011- 31st December 2020.

Exclusion Criteria

1) Patients with inconclusive histology results
2) Patients younger than 18 years of age
3) Patients diagnosed outside the stipulated timeframe.

Methods of Data Extraction

An Academic Affairs and Research Management System (AARMS) application was lodged with the National Health Laboratory Service (NHLS) to release histopathological reports of confirmed cutaneous TB patients.
Search terms used were that of the classifications for true and tuberculid forms of cutaneous TB.
NHLS approval was followed by the release of de-identified data. However, race classification was missing from all reports.
Demographic (Age and Gender), Clinical (HIV Status, ARV usage, disease duration, site, morphology) and Histopathological (Tissue Features and Culture, Stains and PCR) data was extracted from the histopathological reports.
Appendix 1 displays the data capture sheet used to record data.

Ethics

Before the extraction of data, permission was obtained from the relevant authorities at CMJAH and ethics approval from the Human Research Ethics Committee at the University of Witwatersrand.

Statistical Methods

The patients were broadly divided into 2 groups of:

a. True cutaneous TB and;
b. Tuberculids.

These patients were further subdivided into the different forms of true cutaneous TB and tuberculids.
Descriptive statistics were conducted on demographics, clinical and histopathological results. Numerical variables were calculated on data and where applicable, mean and standard deviations were determined.
Associations between pairs of categories and their statistical significance were determined using the Pearson's Chi-Square test for numbers greater than 5 in a category.
A p-value of ≤ 0.05 was used as the measure of statistical significance.

Results

Primary Objective

69 patients were identified with cutaneous TB between the period of 1st January 2011 and 31st December 2020. Table 3 below provides a detailed description of the patient demographics. Female patients were more likely to develop cutaneous TB than males (p<0.001).

Table 3: Demographic Statistics of Patients

Demographic Data (n=69)	
Age at initial Presentation (SD) (years)	39 (12)
Females	61
Males	8
Female: Male Ratio	7.625:1
Duration of Disease (SD) (months)	17 (23)
HIV Status	N (%)
HIV +	33 (47.8)
HIV -	22 (31.9)
HIV Unknown	14 (20.3)

Table 4: Prevalence and Spectrum of Cutaneous TB in Males and Females

Patients (n=69)		**Total**	**Male**	**Female**	**p-value**
		N (%)	**N (%)**	**N (%)**	
True TB	VC	1 (1.4)	1 (1.4)	-	-
	LV	9 (13.0)	4 (5.8)	5 (7.2)	0.739
	S	3 (4.3)	-	3 (4.3)	-
Total True TB		13 (18.8)	5 (7.2)	8 (11.6)	
Tuberculid	PNT	1 (1.4)	-	1 (1.4)	-
	EI	53 (76.8)	1 (1.4)	52 (75.4)	**<0.001**
	LS	2 (2.9)	2 (2.9)	-	-
Total Tuberculid		56 (81.2)	3 (4.3)	53 (76.8)	

Table 4 above depicts the most common form of cutaneous TB was Tuberculids of which 76.8% was EI.

The most common true form of cutaneous TB was LV accounting for 13% of total patients, however, it was not found to be statistically significant.

No cases of TB Gumma, Miliary TB, TB Chancre and Orificial TB were present in this group of patients that were assessed.

Female patients were statistically more likely to develop EI (p<0.001).

Secondary Objective

Table 5: Correlation of Histopathological Laboratory Results of Cutaneous TB

		Acid Fast Bacilli		PCR		Tissue Culture		p-value
		AFB -	AFB +	PCR +	PCR -	Positive	Negative	
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	
	Total	53 (72.6)	5 (6.8)	1 (1.4)	2 (2.7)	6 (8.2)	6 (8.2)	
True TB	VC	-	-	-	-	-	-	-
	LV	4 (5.5)	3 (4.1)	1 (1.4)	-	5 (6.8)	4 (5.5)	0.248
	S	1 (1.4)	2 (2.7)	-	1 (1.4)	1 (1.4)	2 (2.7)	-
Tuberculid	PNT	1 (1.4)	-	-	-	-	-	-
	EI	45 (61.6)	-	-	-	-	-	**<0.001**
	LS	2 (2.7)	-	-	1 (1.4)	-	-	-

In Table 5 above, AFB stains were the most common histopathological test performed in cutaneous TB, however, 91.4% of the AFB test results were negative.
AFB negative was the most commonly associated laboratory result with EI ($p<0.001$).
Tissue cultures done were most commonly performed for LV.
PCR was the least common laboratory test performed.

Table 6 below indicates that panniculitis was the most common histopathological finding in cutaneous TB. Panniculitis and vasculitis were only present in EI.
Granulomas was found to be a common feature but not isolated to EI. Findings of granulomas, vasculitis and panniculitis were more likely to be associated with EI ($p<0.001$).
LV ($p<0.001$) also had granulomas occurring frequently.

Table 6: Correlation of Histopathological Findings of Cutaneous TB

		PH*	Granulomas	Vasculitis	NI**	LI***	P****	WN*****	p-value
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	
	Total	1 (0.7)	47 (32.0)	20 (13.6)	10 (6.8)	16 (10.9)	52 (35.4)	1 (0.7)	
True TB	VC	-	1 (0.7)	-	1 (0.7)	1 (0.7)	-	-	-
	LV	1 (0.7)	9 (6.1)	-	1 (0.7)	4 (2.7)	-	-	**<0.001**
	S	-	3 (2.0)	-	-	1 (0.7)	-	-	-
Tuberculid	PNT	-	-	-	1 (0.7)	1 (0.7)	-	1 (0.7)	-
	EI	-	32 (21.8)	20 (13.6)	7 (4.8)	8 (5.4)	52 (35.4)	-	**<0.001**
	LS	-	2 (1.4)	-	-	1 (0.7)	-	-	-

*Pseudoepitheliomatous hyperplasia
**Neutrophilic infiltrate
***Lymphocytic Infiltrate
****Panniculitis
*****Wedge Necrosis

Table 7: Correlation of the Clinical Presentations in Cutaneous TB

		Papules	**Nodules**	**Ulcerations**	**Plaques**	**Verrucous**	**p-value**	**Polymorphic Patients**
		N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**		
	Total	4 (4.7)	51 (59.3)	9 (10.5)	17 (19.8)	5 (5.8)		14 (20.3)
True TB	VC	-	-	-	1 (1.2)	1 (1.2)	-	1 (7.1)
	LV	1 (1.2)	4 (4.7)	3 (3.5)	8 (9.3)	4 (4.7)	0.165	8 (57.1)
	S	-	2 (2.3)	3 (3.5)	-	-	-	2 (14.3)
Tuberculid	EI	-	45 (52.3)	3 (3.5)	8 (9.3)	-	**<0.001**	3 (21.4)
	LS	2 (2.3)	-	-	-	-	-	0 (0.0)
	PNT	1 (1.2)	-	-	-	-	-	0 (0.0)

Table 7 above shows the most common clinical presentation in cutaneous TB was nodules. 52.3% of all 86 presentations were nodules associated with EI ($p<0.001$).

14 of the 69 patients presented with polymorphic lesions and this was mainly seen in LV.

Table 8: Correlation of Sites in Cutaneous TB

		Head and Neck	**Torso**	**Upper Limbs**	**Lower Limbs**	**Unknown**	**p-value**
		N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	
	Total	10 (14.5)	4 (5.8)	2 (2.9)	52 (75.4)	1 (1.4)	
True TB	VC	-	-	-	-	1 (1.4)	-
	LV	9 (13.0)	-	-	-	-	**<0.001**
	S	1 (1.4)	2 (2.9)	-	-	-	-
Tuberculid	PNT	-	1 (1.4)	-	-	-	-
	EI	-	-	2 (2.9)	51 (73.9)	-	**<0.001**
	LS	-	1 (1.4)	-	1 (1.4)	-	-

Table 8 above shows that 75.4% of all cutaneous TB occurred on the lower limbs.
The most common site in LV was the head and neck ($p<0.001$).
In EI the most common site was the lower limbs with ($p<0.001$).

Tertiary Objective

Table 9: Correlation of HIV and ARVs in cutaneous TB

		HIV +	HIV -	HIV Unknown	p-value	ARV			p-value
		P	N	Unknown		Y	N (%)	Unknown	
		N (%)	N (%)	N (%)		N (%)	N (%)	N (%)	
	Total	33 (47.8)	22 (31.9)	14 (20.3)		26 (78.8)	2 (6.1)	5 (15.2)	
True TB	VC	1 (1.4)	-	-	-	-	-	1 (3.0)	-
	LV	5 (7.2)	1 (1.4)	3 (4.3)	0.264	4 (12.1)	1 (3.0)	-	-
	S	1 (1.4)	1 (1.4)	1 (1.4)	-	1 (3.0)	-	-	-
Tuberculid	PNT	1 (1.4)	-	-	-	-	-	1 (3.0)	-
	EI	24 (34.8)	19 (27.5)	10 (14.5)	0.058	20 (60.6)	1 (3.0)	3 (9.1)	**<0.001**
	LS	1 (1.4)	1 (1.4)	-	-	1 (3.0)	-	-	-

Table 9 above shows that no relationship was found between the HIV status and cutaneous TB. HIV positive patients with EI were more likely to be on ARVs ($p<0.001$).

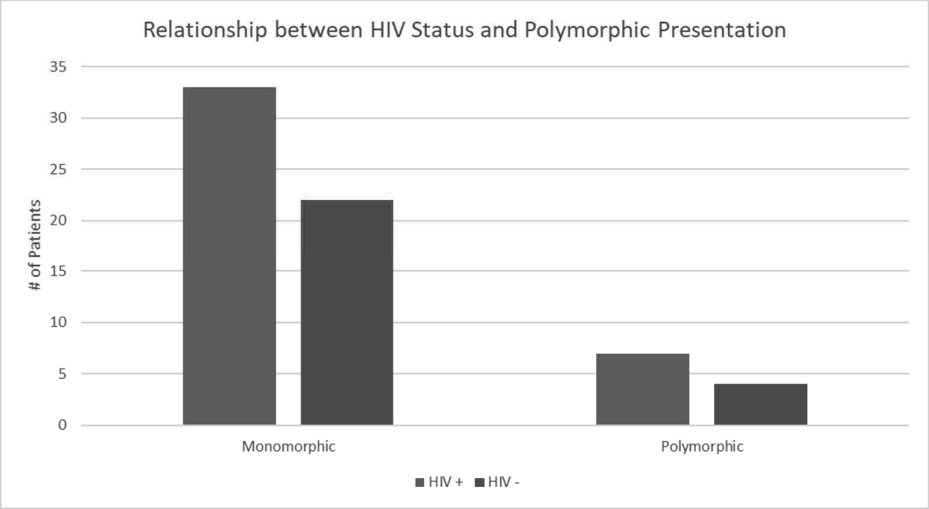

Fig. 1: Relationship between HIV Status and Polymorphic Presentation

Fig. 1 shows that no relationship was found between HIV status and polymorphic presentations in cutaneous TB ($p = 0.971$).

Discussion

This retrospective study aimed to determine the prevalence and spectrum of cutaneous TB at CMJAH in patients diagnosed by histopathological confirmation between 1st January 2011 and 31st December 2020.
69 patients were identified with cutaneous TB. Tuberculids forms were seen in 81.2% (n 56) of the patients compared to true forms which comprised 18.8% (n 13) of all cutaneous TB.

Demographic data showed that females were more common than males in the study (ratio 7.625:1). Female dominance was also noted in the previous South African[15], and Tunisian[19] studies. This finding could be explained in our setting by the higher 51.1% population of females in South Africa[21] or differences in health seeking behaviours between genders[22].

The average age (SD) of the 69 patients was 39(12) and therefore quite similar to the mean age of 32 in Moches's study[15].

The average disease duration (SD) of 17(22) months highlights the chronicity of cutaneous tuberculosis, lack of awareness, low access to medical care (due to socio-economics or logistics) and delayed health-seeking behaviour amongst our community.

Tuberculids represented 81.2% of all cases in keeping with the study conducted by Moche, who reported a majority prevalence of 51.3%[15]. This was not noted in the studies of Abdel Malek or Mathur & Pandey where true forms of cutaneous TB (Scrofuloderma[19] & Lupus Vulgaris[16]) were more common. This could indicate that the South African population with cutaneous TB has higher immunity and therefore tuberculids are more common.
Erythema induratum (76.8%) was the most common form of cutaneous TB and tuberculid. Female patients were more likely to develop EI ($p<0.001$), in keeping with the literature, describing it as a disease mainly in adult females[23].

The most common true form in our study was Lupus Vulgaris with 13%, followed by Scrofuloderma with 4.3%. This is different to the study completed by Moche and Varshney & Goyal, where Scrofuloderma (29%[15] and 36.5%[17]) accounted the most for true cutaneous TB.
Lupus Vulgaris is a disease of high immunity[6]. Improved immunity may be seen in our population with the advent of ARVs, nutritional programmes, BCG vaccines and pre-exposure to TB.

AFB stains (79.4%) were the most common histopathological test performed but 72.6% were negative. It was mainly performed in tuberculid cases (82.7% out of 58 total AFB stains) which is known to exhibit a low presence of bacilli on tissue[6]. Consequently, EI showed an association with AFB negativity ($p< 0.001$). 50% of 12 tissue cultures done were positive, in keeping with the literature[6] with the majority of positive cultures seen in LV. Very few PCR tests, 3(4.1%), were performed and this may be due to high costs, poor documentation or lack of awareness.

Granulomatous histopathological findings, comprising 32%, presented significantly in LV ($p<0.001$) and EI ($p<0.001$). However, panniculitis was the most common histopathological finding (35.4%), presenting exclusively in cases of EI. This study's findings suggests that once panniculitis is detected in cutaneous TB, the most likely diagnosis is EI.

Nodules accounted for 51 (59.3%) of all 86 clinical presentations and were the most common clinical finding in EI.
This highlights the lack of specificity of cutaneous TB lesions and diagnostic dilemmas in clinical presentation. Regardless, nodules showed a significant relationship with EI ($p<0.001$) as seen globally[5,7,26]. However, our patients with EI did not tend to ulcerate as seen in Varshney & Goyal[17] which could be attributed to a better immune system in our patients. Polymorphic clinical presentations were uncommon, accounting for 14 (20.3%) of the 69 patients and when present, seemed to be in cases of LV. This was also seen in a 14 LV case patient study conducted in India, where presentations varied between ulceration, plaques, nodules and verrucosity[25].

The most common site affected was the lower limbs, which comprised 75.4% of cases. This was also seen in the Mathur & Pandey[16] and Moche[15] studies. However, compared to the Abdel Malek[19] study, the most common site of head and neck. The explanation of lower limbs being dominant for this study can be explained by the majority of cases being EI (73.9%). EI naturally shows a predilection for the lower limbs[24]. LV cases had a significant relationship with Head and Neck sites ($p<0.001$). this was also noted in LV cases in the Moche[15] and Varshney[17] study.

Less than half of the patients were HIV positive (47.8%) and in correlating the HIV status with cutaneous TB, HIV positive patients were no more likely to develop any form of cutaneous TB (no significant p-value reported in Table 9), than HIV negative patients. However, of the HIV positive patients who were on ARVs (78.8%), a relationship ($p<0.001$) was noted between these patients and EI. This may indicate the use of ARVs boosts patients' immune systems[26], allowing HIV patients on ARVs to develop diseases of high immunity.

Despite the possibility that HIV may allow for unusual and polymorphic clinical presentations[27]in many diseases, this study showed no relationship between polymorphic lesions in HIV positive vs HIV negative patients ($p=0.971$) with cutaneous TB.
One could speculate the effects of ARVs (which were taken in the majority of our HIV positive patients), could explain the similar behaviour of clinical presentations in these 2 groups.

In considering this study's findings, the following limitations were experienced:

1) Incomplete NHLS reports e.g. missing race, patient history, diagnoses
2) Inconclusive biopsies
3) Inadequate tissue biopsies, lowering the number of cases resulting in under or over-reporting of findings.
4) De-identified data restricted access to rechecking missing histological, demographic, clinical information e.g. race, PCR, cultures etc.
5) Possibility of patients being treated by other clinicians and never referred to dermatology for biopsies
6) Certain sub-categories had overall small numbers leading to statistical inaccuracy.
7) No differentiation was made between patients before, during and after the Covid-19 pandemic.
8) The study was a single snapshot and therefore did not look at the evolving nature of cutaneous TB and a single site for data collection allows for lower numbers.

Conclusions and Recommendations

The prevalence of cutaneous tuberculosis is still uncommon despite South Africa being at the forefront of the HIV/TB epidemic.
Females accounted for the majority of patients and patients generally presented with a prolonged disease duration suggesting possible lack of awareness or access to healthcare.

The most common form of cutaneous TB was tuberculids, specifically EI while the most common true form of cutaneous TB was LV.
Fatally ill forms of cutaneous Miliary TB were not seen in the study.

AFB negativity in EI probably suggests that the test can be omitted during histological evaluation as it adds no diagnostic value, and this will reduce histological expenditure.
The presence of panniculitis in a patient with cutaneous TB was a clear indicator of EI ($p<0.001$), while granulomas histopathologically featured across the spectrum of cutaneous TB.
The most common site affected was that of the lower limbs particularly in EI ($p<0.001$) followed by head and neck in LV ($p<0.001$).
Nodules accounted for 59.3% of all clinical presentations. Since nodules present in many dermatological conditions (syphilis, sarcoid, deep fungal infections, malignancies etc), this suggests that cutaneous TB is clinically non-specific and may be a mimicker. It therefore requires heightened clinical suspicion in order to investigate and treat.

The advent of ARVs in all HIV positive patients may have played a role in these patients presenting in a similar clinical and histopathological manner as HIV negative patients as well as developing diseases of high immunity (EI).

Data from this study can be used to increase clinical awareness (in patients and clinicians) of cutaneous TB leading to prompt presentation, diagnosis and treatment thereby decreasing morbidity, mortality and spread of this communicable disease.

Lastly, this study may serve as a platform for future research on cutaneous TB e.g., looking at extracutaneous forms, response to TB medication etc.

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Appendix 1

Data Collection Sheet

#	Age	Age Group	Gender	HIV	ARV	Morphology of lesions	Duration of lesions	Polymorphic (Y/N)	Sites	Histology	Tissue Culture	Final Diagnosis

Appendix 2

Ethics Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Naima Hargey

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M210858

NAME: (**Principal Investigator**)	Dr Naima Hargey
DEPARTMENT:	Internal Medicine – Dermatology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Prevalence and spectrum of Cutaneous Tuberculosis in patients at Charlotte Maxeke Johannesburg Academic Hospital
DATE CONSIDERED:	27/08/2021
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr L. Pillay
APPROVED BY:	CB Penny Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	03/09/2021

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions.Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **August** and will therefore be due in the month of **August** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Hargey

Principal Investigator Signature

2021/09/06

Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 3

SAMJ Guidelines

Author Guidelines

Author Guidelines

The *SAMJ* has launched a new submission and tracking system. Authors will be required to register a profile on the in order to submit a manuscript.

To submit a manuscript, please proceed to: https://samajournals.co.za/index.php/samj

To access and submit an article already in production, please see the guidelines here.

Author Guidelines

Please watch the Author Tutorial for guidance on how to submit.

Please take the time to familiarise yourself with the policies and processes below. If you still have any questions, please do not hesitate to ask our editorial staff (tel.: +27 (0)21 532 1281, email: publishing@samedical.org).

SAMJ policies

- Types of articles considered by the SAMJ
- Article Processing Charges
- Authorship
- Conflict of interest
- Research ethics committee approval
- Clinical trials
- Protection of patient's rights to privacy
- Copyright notice
- Privacy statement
- Ethnic classification
- CPD

Manuscript preparation

- Preparing an article for anonymous review
- General article format/layout
- Preparation notes by article type
- Illustrations
- Tables
- References

From submission to acceptance

- Submission and peer-review
- Production process
- Changing contact details or authorship

Publication

- Online versus print
- Errata and retractions
- Indexing

SAMJ Policies

Type of articles considered by the SAMJ

The *SAMJ* will no longer limit the articles accepted to those that have 'general medical content', but is intending to capture the spectrum of medical and health sciences, grouped by relevance to the country's burdens of disease. This content will include research in the social sciences and economics that is relevant to the medical issues around our burden of disease. Please see 'A new vision for the *SAMJ* – and a call for papers' for a full discussion of the new directions for the *SAMJ*.

We accept the following types of articles:

- Research
- Reviews
- Clinical trials
- Editorials
- In Practice (Previously Forum incl. Case Reports)
- Correspondence
- Obituaries
- Book reviews
- Ad hoc supplements e.g. guidelines, conference/congress abstracts, Festschrifts*

The following articles are by invitation only:

- Guest editorial
- Continuing Medical Education (CME)

*Contact claudian@hmpg.co.za for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, Festschrifts, etc.

Publication Fees

All articles published in the *South African Medical Journa*l are open access and freely available online upon publication. This is made possible by applying a business model to offset the costs of peer review management, copyediting, design and production, by charging a publication fee of R7 440 (VAT incl.) for each research and In Practice article published. The publication fee is standard and does not vary based on length, colour, figures, or other elements.

The publication fee is payable when your manuscript is editorially accepted and before production commences for publication. The submitting author will be notified that payment is due and given details on the available methods of payment. Prompt payment is advised; the article will not enter into production until payment is received.

Authorship

Named authors must consent to publication. Authorship should be based on: (*i*) substantial contribution to conceptualisation, design, analysis and interpretation of data; (*ii*) drafting or critical revision of important scientific content; or (*iii*) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org)

If authors' names are added or deleted after submission of an article, or the order of the names is changed, all authors must agree to this in writing.

Please note that co-authors will be requested to verify their contribution upon submission. Non-verification may lead to delays in the processing of submissions.

Author contributions should be listed/described in the manuscript.

Conflicts of interest

Conflicts of interest can derive from any kind of relationship or association that may influence authors' or reviewers' opinions about the subject matter of a paper. The existence of a conflict – whether actual, perceived or potential – does not preclude publication of an article. However, we aim to ensure that, in such cases, readers have all the information they need to enable them to make an informed assessment about a publication's message and conclusions. We require that both authors and reviewers declare all sources of support for their research, any personal or financial relationships (including honoraria, speaking fees, gifts received, etc) with relevant individuals or organisations connected to the topic of the paper, and any association with a product or subject that may constitute a real, perceived or potential conflict of interest. If you are unsure whether a specific relationship constitutes a conflict, please contact the editorial team for advice. If a conflict remains undisclosed and is later brought to the attention of the editorial team, it will be considered a serious issue prompting an investigation with the possibility of retraction.

Research ethics committee approval

Authors must provide evidence of Research Ethics Committee approval of the research where relevant. Ensure the correct, full ethics committee name and reference number is included in the manuscript.

If the study was carried out using data from provincial healthcare facilities, or required active data collection through facility visits or staff interviews, approval should be sought from the relevant provincial authorities. For South African authors, please refer to the guidelines for submission to the National Health Research Database. Research involving human subjects must be conducted according to the principles outlined in the Declaration of Helsinki. Please refer to the National Department of Health's guideline on Ethics in Health research: principles, processes and structuresto ensure that the appropriate requirements for conducting research have been met, and that the HPCSA's General Ethical Guidelines for Health Researchers have been adhered to.

Clinical trials

As per the recommendations published by the International Committee of Medical Journal Editors (ICMJE), clinical trial research is any research that assigns individuals to an intervention, with or without a concurrent comparison/control group to study the cause-and-effect relationship between the intervention and health outcomes. All clinical trials should be registered with the appropriate national clinical trial registry (or any international primary register, if relevant), and the trial registration number should be cited at the end of the abstract. All clinical trial reports must also contain a data sharing statement as per the recommendations of the ICMJE. Statements are to indicate:

- whether individual deidentified participant data will be shared;
- what data in particular will be shared; whether additional, related documents will be available;
- when the data will become available and for how long; by what access criteria data will be shared.

Please see the ICJME announcement for further details and illustrative examples of data sharing statements: ICMJE Data Sharing Statements for Clinical Trials

Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register. The SAMJ therefore requires that clinical trials be registered in the relevant public trials registry at or before the

time of first patient enrollment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Please refer to the general guidelines for all papers at the top of this article for additional requirements with respect to ethics approval, funding, author contributions, etc. The format of original research articles should be followed for reporting of clinical trial results.

Patient Consent

Information that would enable identification of individual patients should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) has given informed written consent for publication and distribution. We further recommend that the published article is disseminated not only to the involved researchers but also to the patients/participants from whom the data was drawn. Refer to Protection of Research Participants. The signed consent form should be submitted with the manuscript to enable verification by the editorial team.

Other individuals

Any individual who is identifiable in an image must provide written agreement that the image may be used in that context in the *SAMJ.*

Copyright notice

Copyright remains in the Author's name. The work is licensed under a Creative Commons Attribution - Noncommercial Works License.

Material submitted for publication in the *SAMJ* is accepted provided it has not been published or submitted for publication elsewhere. Please inform the editorial team if the main findings of your paper have been presented at a conference and published in abstract form, to avoid copyright infringement. All research already published as 'Conference proceedings' needs to be substantially re-written, with a new title, a new abstract and new and important results to back up any study before it will be considered for a new publication. The *SAMJ* does not hold itself responsible for statements made by the authors.

Previously published images

If an image/figure has been previously published, permission to reproduce or alter it must be obtained by the authors from the original publisher and the figure legend must give full credit to the original source. This credit should be accompanied by a letter indicating that permission to reproduce the image has been granted to the author/s. This letter should be uploaded as a supplementary file during submission.

Privacy statement

The *SAMJ* is committed to protecting the privacy of its website and submission system users. The names, personal particulars and email addresses entered in the website or submission system will not be made available to third parties without the user's permission or due process. By registering to use the website or submission system, users consent to receive communication from the *SAMJ* or its publisher SAMA on matters relating to the journal or associated publications. Queries with regard to privacy may be directed to publishing@hmpg.co.za.

Ethnic/race classification

Use of racial or ethnicity classifications in research is fraught with problems. If you choose to use a research design that involves classification of participants based on race or ethnicity, or discuss issues with reference to such classifications, please ensure that you include a detailed rationale for doing so, ensure that the categories you describe are

carefully defined, and that socioeconomic, cultural and lifestyle variables that may underlie perceived racial disparities are appropriately controlled for. Please also clearly specify whether race or ethnicity is classified as reported by the patient (self-identifying) or as perceived by the investigators. Please note that is not appropriate to use self-reported or investigator-assigned racial or ethnic categories for genetic studies.

Continuing Professional Development (CPD)

SAMJ is an HPCSA-accredited service provider of CPD materials. Principal authors can earn up to 15 CPD continuing education units (CEUs) for publishing an article; co-authors are eligible to earn up to 5 CEUs; and reviewers of articles can earn 3 CEUs. Each month, *SAMJ* also publishes a CPD-accredited questionnaire relating to the academic content of the journal. Successful completion of the questionnaire with a pass rate of 70% will earn the reader 3 CEUs. Administration of our CPD programme is managed by Medical Practice Consulting. To complete questionnaires and obtain certificates, please visit MRP Consulting

Manuscript preparation

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this are Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

- An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
- Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
- Mask self-citations by referring to your own work in third person.

General article format/layout

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state 'none'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).

- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. μ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.

- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

**NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'

- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

- Research
- Editorials
- CME
- In Practice and Case reports
- Reviews
- Clinical trials
- Correspondence
- Obituaries
- Book reviews
- Guidelines

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been

published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text .

Structured abstract

- This should be 250-400 words, with the following recommended headings:

o **Background:** why the study is being done and how it relates to other published work.

o **Objectives:** what the study intends to find out

o **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.

o **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.

o **Conclusion:** must be supported by the data, include recommendations for further study/actions.

- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Here is an example of a good abstract.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.

- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Editorials

Guideline word limit: 1 000 words

These opinion or comment articles are usually commissioned but we are happy to consider and peer review unsolicited editorials. Editorials should be accessible and interesting to readers without specialist knowledge of the subject under discussion and should have an element of topicality (why is a comment on this issue relevant now?) There should be a clear message to the piece, supported by evidence.

Please make clear the type of evidence that supports each key statement, e.g.:

- expert opinion
- personal clinical experience
- observational studies
- trials
- systematic reviews.

CME (by invite only)

CME is intended to provide readers with practical, up-to-date information on medical and related matters. It is aimed at those who are not specialists in the field.

From January 2016, all CME articles will be printed in full in the *SAMJ*. Please try to adhere strictly to the guidelines on word count as we have a page limit for the print issue of the *SAMJ*. We reserve the right to place some tables and reference lists online if this is necessary for space.

In practice, this means that each CME topic usually covers two issues of the print issue of the *SAMJ*.

The guest editor, in consultation with the editor, is responsible for convening a team of authors, deciding on the subjects to be covered and for reviewing the manuscripts submitted. The suggestion is for 4 - 5 articles, although there is some room for flexibility contingent on discussions with the editor.

For queries about these guidelines please feel free to contact the CME editor, Dr Bridget Farham, by email (ugqirha@iafrica.com) or telephone (+27 (0)82 452 2860)

Review process

The guest editor reviews the articles and returns them to the CME editor for review and final approval.

Guest editorials

Guideline word limit: 1 000 words

- Include the guest editor's personal details (qualifications, positions, affiliation, e-mail address, and a short personal profile (50words)).
- If possible, include a photograph of the author(s) at high enough resolution for print. It is preferable to provide two guest editorials, one for each issue, so that the content of the articles in each issue is covered.

Articles

Guideline word limit: 2 000 - 3 000 words

- Each article requires an abstract of ±200 words.
- The editor reserves the right to shorten articles but will send a substantially shortened article back for author approval.

Personal details

Please supply: Your qualifications, position and affiliations and MP number (used for CPD points); Address, telephone number and fax number, and your e-mail address; and a short personal profile (50words)and a few words about your current fields of interest.

In Practice

Guideline word limit: 2 000 - 3 000words

This section includes articles that would previously have been accepted into the Forum section, and case reports.

In practice articles are those that draw attention to specific issues of clinical, economic or political interest regarding medicine and healthcare in southern Africa. They are assigned to a topic:

- Case report
- Clinical practice
- Clinical alert
- Issues in medicine
- Issues in public health
- Healthcare delivery
- Medicine and the environment
- Medicine and the law
- Cochrane corner

An In Practice article should follow the following format – sub-headings are not necessary, but may be used for clarity:

- Author affiliations and qualifications: to be the same as for Research. Provide all authors' names and initials, qualifications and full affiliations, and corresponding author.
- Short abstract: does not need to be structured, but should capture the essential features of the article
- Introduction: the reason for the article and the issue being addressed
- Recent research, discussion, local policy around the issue – include your own research where appropriate
- All statements should be referenced and, if opinion only, this should be stated
- Discussion: how this article adds to the discussion around a particular topic
- If a clinical practice or policy point is at issue, this needs to be emphasised, using a box with highlights if appropriate.

Essentially In practice is an opportunity for a more discursive approach to topics of clinical, economic or political importance in southern African health systems. It is not an opportunity to put forward unsubstantiated opinions!

Case reports

The *SAMJ* has recently started to accept case reports. The cases must come from Africa, preferably southern Africa unless the condition is common to all African countries, and must be either a completely new description of a clinical condition or result (use Google!) or a case that highlights important practice or management issues.

Please use the following format for case reports:

- Title of case: do not include the words 'a case report' in the title
- Summary/abstract: up to 150 words summarising the case presentation and outcome
- Background: why is this case important and why did you write it up?
- Case presentation: presenting features, medical, social, family history as appropriate
- Case management: should be according to best practice, and if not, please explain why
- Investigations, if relevant: save space by simply saying 'normal' if, for example, renal function was completely normal, rather than listing normal results, highlight the abnormal – or indeed the normal if this is clinically significant
- Differential diagnosis, if relevant
- Treatment, if relevant
- Outcome and follow-up
- Discussion – a VERY BRIEF review of similar published cases
- Teaching points: 3 - 5 bullet points
- References: as per the *SAMJ* house style

- Tables and figures: keep to a minimum. Use clinical images where relevant – we need hi-res versions for print, and identifiable persons must have a consent form
- Patient consent: please include a statement about patient consent to a written case report. This should be uploaded as a supplementary file.

Clinical trials

Guideline word limit: 4000 words

As per the recommendations published by the International Committee of Medical Journal Editors (ICMJE), clinical trial research is any research that assigns individuals to an intervention, with or without a concurrent comparison/control group to study the cause-and-effect relationship between the intervention and health outcomes. All clinical trials should be registered with the appropriate national clinical trial registry (or any international primary register, if relevant), and the trial registration number should be cited at the end of the abstract. Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register.
The *SAMJ* therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrollment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Please refer to the general guidelines for all papers at the top of this article for additional requirements with respect to ethics approval, funding, author contributions, etc. The format of original research articles should be followed for reporting of clinical trial results.

Review articles

Guideline word limit: 4 000 words

These are welcome, but should be either commissioned or discussed with the Editor before submission. A review article should provide a clear, up-to-date account of the topic and be aimed at non-specialist hospital doctors and general practitioners.

Please ensure that your article includes:

- Abstract: unstructured, of about 100-150 words, explaining the review and why it is important
- Methods: Outline the sources and selection methods, including search strategy and keywords used for identifying references from online bibliographic databases. Discuss the quality of evidence.
- When writing: clarify the evidence you used for key statements and the strength of the evidence. Do not present statements or opinions without such evidence, or if you have to, say that there is little or no evidence and that this is opinion. Avoid specialist jargon and abbreviations, and provide advice specific to southern Africa.
- Personal details: Please supply your qualifications, position and affiliations and MP number (used for CPD points); address, telephone number and fax number, and your e-mail address; and a short personal profile (50 words) and a few words about your current fields of interest.

Correspondence (Letters to the Editor)

Guideline word limit: 500 words

Letters to the editor should relate either to a paper or article published by the SAMJ or to a topical issue of particular relevance to the journal's readership

- May include only one illustration or table
- Must include a correspondence address.

Book reviews

Guideline word limit: 400 words

Should be about 400 words and must be accompanied by the publication details of the book. Provide a hi-res image of the cover if possible (with permission from the copyright holder).

Obituaries

Guideline word limit: 400 words

Should be offered within the first year of the practitioner's death, and may be accompanied by a photograph.

Guidelines

Guidelines should always be discussed with the Editor prior to submission.

Because of the intensive review process required to ensure Guidelines are independent, evidence-based and free from commercial bias, they are usually published as a supplement to the *SAMJ*, the costs of which must be covered by sponsorship, advertising or payment by the guideline authors/association. We will provide a quote based on the expected length of the guideline and whether it is to appear online only, or in print, which must be accepted by the body putting the guidelines together before submitting the work to the SAMJ.

The Editor reserves the right to determine the scheduling of supplements. Understandably, a delay in publication must be anticipated dependent upon editorial workflow.

All guidelines should include a clear, transparent statement about all sources of funding and an explicit, clear statement of conflicts of interest of any of the participants in the guidelines about industry funding for lectures, research, conference participation etc.

All guidelines should be structured according to Agree II.

Please access this website before putting the guidelines together, download the Agree 11 instrument and use this to put the guidelines together.

All submitted guidelines will be sent to the local Agree II appraisal committee for review and must be endorsed by an appropriate body prior to consideration and all conflicts of interest expressed.

A structured abstract not exceeding 400 words (recommended sub-headings: *Background, Recommendations, Conclusion*) is required. Sections and sub-sections must be numbered consecutively (e.g. 1. Introduction; 1.1 Definitions; 2.etc.) and summarised in a Table of Contents.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF or jpeg form.

- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make 'new rows':

Rather:
Each row of data must have its own proper row:

Do not: use separate columns for *n* and %:

Rather:
Combine into one column, *n* (%):

Do not: have overlapping categories, e.g.:

Rather:
Use <> symbols or numbers that don't overlap:

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must* ***not*** *be used.*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]

- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:

o On the Crossref homepage, paste the article title into the 'Metadata search' box.
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Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx.doi.org/10.1000/hgjr.182
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references

- Government Gazettes:

National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

- Provincial Gazettes:

Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

- Acts:

South Africa. National Health Act No. 61 of 2003.

- Regulations to an Act:

South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

- Bills:

South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

- Green/white papers:

South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

- Case law:

Rex v Jopp and Another 1949 (4) SA 11 (N)

Rex v Jopp and Another: Name of the parties concerned

1949: Date of decision (or when the case was heard)

(4): Volume number

SA: SA Law Reports

11: Page or section number

(N): In this case Natal - where the case was heard. Similarly, (C) woud indicate Cape, (G) Gauteng, and so on.

NOTE: no . after the v

- *Other references (e.g. reports) should follow the same format:* Author(s). Title. Publisher place: Publisher name, year; pages.
- Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.
- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

From submission to acceptance

Submission and peer-review

To submit an article:

- Please ensure that you have prepared your manuscript in line with the SAMJ requirements.
- The following are required for your submission to be complete:

o Anonymous manuscript (unless otherwise stated)

o Manuscript

o Any supplementary files: figures, datasets, patient consent form, permissions for published images, etc.

- Once the submission has been successfully processed, it will undergo a technical check by the Editorial Office before it will be assigned to an editor who will handle the review process. If the author guidelines have not been appropriately followed, the manuscript may be sent back to the author for correcting.

Peer-review process

Production process

Please note that there is a 6-month waiting time for publication, once an article has been sent to the production team.

The following process will follow:

1. An accepted manuscript is passed to a Managing Editor to assign to a copyeditor (CE).

2. The CE copyedits in Word, working on house style, format, spelling/grammar/punctuation, sense and consistency, and preparation for typesetting.

3. If the CE has an author queries, he/she will contact the corresponding author and send them the copyedited Word doc, asking them to solve the queries by means of track changes or comment boxes.

4. The authors are typically asked to respond within 1-3 days. Any comments/changes must be clearly indicated e.g. by means of track changes. Do not work in the original manuscript - work in the copyedited file sent to you and make your changes clear.

5. The CE will finalise the article and then it will be typeset.

6. Once typeset, the CE will send a PDF of the file to the authors to complete their final check, while simultaneously sending to the 2nd-eye proofreader.

7. The authors are typically asked to complete their final check and sign-off within 1-2 days. No major additional changes can be accommodated at this point.

8. The CE implements the authors' and proofreader's mark-ups, finalises the file, and prepares it for the upcoming issue.

Changing contact details or authorship

Please notify the Editorial Department of any contact detail changes, including email, to facilitate communication.

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The *SAMJ* is an online journal. The online version of the journal is the one that has the widest circulation, is indexed by bibliographic databases including PubMed and SciELO, and is accessible in academic libraries. A printed edition , containing material selected by the Editor is also published each month and distributed to the membership of the South African Medical Association.

Online

- The full text of all accepted articles is published in full online, open access.
- Citation information of each article is based on its online publication.
- You may want to make use of the advantages of online publication e.g. specify web links to other sources, images, data or even a short video.

Print

- Not all articles will be selected for print.
- An article may be selected for print in a different month from that in which it was published online.
- Research articles will appear *in abstract form only*, if selected for a print edition.

Errata and retractions

Errata

Should you become aware of an error or inaccuracy in yours or someone else's contribution after it has been published, please inform us as soon as possible via an email to publishing@samedical.org, including the following details:

- Journal, volume and issue in which published
- Article title and authors
- Description of error and details of where it appears in the published article
- Full detail of proposed correction and rationale

We will investigate the issue and provide feedback. If appropriate, we will correct the web version immediately, and will publish an erratum in the next issue. The correction will be indexed, as PubMed has a function for linking errata back to the original article. All investigations will be conducted in accordance with guidelines provided by the Committee on Publication Ethics (COPE).

Retractions

Retraction of an article is the prerogative of either the original authors or the editorial team of SAMA. Should you wish to withdraw your article before publication, we need a signed statement from all the authors.

Should you wish to retract your published article, all authors have to agree in writing before publication of the retraction.

Send an email to publishing@hmpg.co.za, including the following details:

- Journal, volume and issue to which article was submitted/in which article was published
- Article title and authors
- Description of reason for withdrawal/retraction.

We will make a decision on a case-by-case basis upon review by the editorial committee in line with international best practices. Comprehensive feedback will be communicated with the authors with regard to the process. In case where there is any suspected fraud or professional misconduct, we will follow due process as recommended by the Committee on Publication Ethics (COPE), and in liaison with any relevant institutions.

When a retraction is published, it will be linked to the original article.

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Published articles are covered by the following major indexing services. As such articles published in the *SAMJ* are immediately available to all users of these databases, guaranteed a global and African audience:

- Index Medicus (Medline/PubMed)
- ExcerptaMedica (EMBASE)
- Biological Abstracts (BIOSIS)
- Science Citation Index (SciSearch)
- Current Contents/Clinical Medicine
- Scopus
- AIM
- AJOL
- Crossref
- Sabinet
- Scielo

Appendix 4

Turnitin Report

Appendix 5

Approved Research Protocol with expanded Literature review

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APPLICATION FOR CHANGE OF APPROVED SUPERVISOR(S) OF RESEARCH REPORT, DISSERTATION OR THESIS

Please indicate: Additional Supervisor ☒ Withdrawal of Supervisor ☐

Motivation / Reason for addition / withdrawal of Supervisor:
Recommended by post-graduate comittee
To assist principal supervisor

Recommendation of Department / School:
Department of internal medicine

Student Full name(s) and Surname	Naima Hargey		
Student Number	2367015		
Degree: Masters in medicine	Department: Dermatology, internal medicine		
Title: Prevalence and spectrum of cutaneous tuberculosis in patient at charlotte Maxeke Johannesburg Academic Hospital			
Dr.			
Current Supervisor (Full name &Surname)	Lushen Pillay	**Supervision %**	50 %
Supervisor Qualifications	MBChB (UP), FCDerm (SA), MMed (Wits).		
Supervisor Department/Address	Head of dermatology Helen Joseph Hospital		
Supervisor Telephone	084 800 35	E-mail	lushen@mweb.co.za

Withdrawing Supervisor (Full name &Surname)	N/A.	**Supervision %**	
Supervisor Qualifications			
Supervisor Department/Address			
Supervisor Telephone		E-mail	

Additional Supervisor (Full name &Surname)	Chioma Ede	**Supervision %**	50%.
Supervisor Qualifications	MBBS, FCDerm (SA), MMed (Wits).		
Supervisor Department/Address	Dermatology, Helen Joseph Hospital		
Supervisor Telephone	072 381 6532	E-mail	drchumzy@gmail.com

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UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

CANDIDATE'S SURNAME: [Please print] **Hargey**		FIRST NAME/S: **Naima**	STUDENT NUMBER: **2367015**
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DEGREE FOR WHICH PROTOCOL IS BEING SUBMITTED: **Masters in Medicine Dermatology**			
PART-TIME OR FULL-TIME: **Full Time**			
FIRST REGISTERED FOR THIS DEGREE:	TERM : **2nd**		YEAR: **2019**
DEPARTMENT: **Department of Dermatology**			
TITLE OF PROPOSED RESEARCH: **Prevalence and spectrum of Cutaneous Tuberculosis in patients at Charlotte Maxeke Johannesburg Academic Hospital**			
CANDIDATE'S SIGNATURE:			DATE:
SUPERVISOR 1 (NAME & SURNAME): **Lushen Pillay**			**50%** Supervision
SUPERVISOR'S QUALIFICATIONS **MBChB (UP), FCDerm (SA), MMed (Wits)**			
SUPERVISOR'S DEPARTMENT Head of Dermatology – **Helen Joseph Hospital**			
SUPERVISOR'S ADDRESS / TEL / E-MAIL: **Helen Joseph Hospital, Rossmore Johannesburg. Tel: 084 800 0035 Email: lushen@mweb.co.za**			
SUPERVISOR 2 (NAME & SURNAME): Chioma Ede			50% Supervision
SUPERVISOR'S QUALIFICATIONS: **MBBS, FCDerm SA, MMed (Wits)**			
SUPERVISOR'S ADDRESS / TEL / E-MAIL: **Helen Joseph Hospital, Rossmore Johannesburg.** Email: drchumzy@gmail.com **Tel: 072 381 6532**			
SUPERVISOR 3 (NAME & SURNAME):			% Supervision
SUPERVISOR'S QUALIFICATIONS			
SUPERVISOR'S ADDRESS / TEL / E-MAIL:			

SYNOPSIS OF RESEARCH:(Brief summary of proposed research project; between 200-300 words only; with sub-headings: an introduction and justification for study, aim/s, proposed methodology and expected outcome/s)
[Use reverse side of this page if more space is required]

Introduction
Tuberculosis (TB) is a communicable disease that belongs in the top 10 causes of death worldwide. It is the leading cause for death from a single infectious agent. South Africa accounts for 3.6% of the majority of TB cases worldwide. Cutaneous TB comprises 1-2% of extrapulmonary TB and is a chronic skin infection mainly caused by Mycobacterium Tuberculosis.

Justification

Below is a tabulated summary of the most common findings in studies on Cutaneous TB worldwide:

Country	True cutaneous TB	Tuberculid
India	Scrofuloderma and Lupus Vulgaris	Papulonecrotic Tuberculid
Brazil	Scrofuloderma	Erythema Induratum
Nepal	TB Verrucosa Cutis and Lupus Vulgaris	Papulonecrotic Tuberculid
South Africa	Scrofuloderma	Erythema Induratum

The last dated study related to cutaneous TB was conducted in 2008 by Moche.

Despite South Africa being at the forefront of the TB pandemic and the associated morbidity of Cutaneous TB, there is paucity of recent data published on the prevalence of Cutaneous TB in Johannesburg, South Africa.

Aims
The aim of this study is thus to investigate the prevalence and spectrum of Cutaneous TB in patients at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

Proposed methodology
This will be a retrospective, descriptive study of adult patients seen at CMJAH with proven Cutaneous TB infection on skin biopsy from 1st January 2011- 31st December 2020.
Every patient's histology report fulfilling the inclusion and exclusion criteria will be included in the study.
The histology reports will be obtained from the Department of Anatomical Pathology at CMJAH using the National Health Laboratory Services.
Data will be captured on Microsoft excel and the relevant statistical analysis will be done.

Expected outcomes
The results and analysis on this study which will look at the frequency of Cutaneous TB in patients under various data variables can be used for future research, improving clinical acumen and institutionalize preventative measures.

WITS ETHICS NOT REQUIRED: Yes No WITS ETHICS PENDING: Yes No WITS ETHICS APPROVED: Yes No (circle appropriate symbol)* ***Please note the final human ethics clearance certificate or animal ethics certificate must be available prior to starting research**		IF Y SUPPLY ETHICS CLEARANCE CERTIFICATE AS ATTACHMENT AND INCLUDE ETHICS NUMBER HERE:
As supervisor/s, I/we confirm that I have read the protocol which has been submitted for assessment.		
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SIGNATURE PG OFFICE STAFF	REGISTERED	STAMP
.....	YES____ NO____	

SYNOPSIS OF RESEARCH CONTINUED

11 March 2019/MP

Naima Mmed - TurnitIn Final version.docx

by Naima Hargey

Submission date: 02-Oct-2023 12:42AM (UTC+0200)
Submission ID: 2182384845
File name: Naima_Mmed_-_TurnitIn_Final_version.docx (98.3K)
Word count: 3985
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Chapter One: Introduction and Literature Review, aims and Objectives

Introduction

Tuberculosis (TB) is a communicable disease that belongs in the top 10 causes of death worldwide. It is the leading cause of death from a single infectious agent. TB is caused by an Acid-fast bacillus (AFB) organism known as Mycobacterium Tuberculosis (M.Tuberculosis). In 2019, 10 million people worldwide fell ill with TB and approximately 1.4 million deaths were recorded that year [1].

World Health Organization (WHO) indicated that 90% of the world's TB cases occurred in 30 countries, with South Africa being one of the countries listed [1] accounting for 3.6% of the TB cases.

In 2018, South Africa was estimated to have 390,000 TB cases [2]. Statistics South Africa reported that TB was the leading cause of death in 2015[3].

M. Tuberculosis usually affects the lungs but can also cause extrapulmonary TB (sites other than the lungs), which is around 8-10% of all TB cases [4]

Cutaneous TB comprises 1-2% of those extrapulmonary cases[4]. Cutaneous TB is a chronic skin infection mainly caused by M. tuberculosis but also rarely by the Bacillus Calmette - Guerin (BCG) Vaccine which is an attenuated strain of Mycobacterium Bovis [5]. However, BCG vaccine-induced cutaneous TB will not be reviewed in this study.

Literature Review

Cutaneous TB was first described in 1826 by Laennec as a warty lesion, but the organism M. tuberculosis was only identified in 1882[6].

The development of Cutaneous TB depends on:

1) Host factors - such as age, gender, anatomical location, immune competency (Human immunodeficiency virus/HIV status, malignancy, diabetes, immunosuppressants) and nutritional status[7];
2) Environmental factors - areas of high prevalence e.g. South America, Asia, Southern Africa, and overpopulation[5];
3) Mycobacterium factors - such as route of its infection, virulence of the bacilli, and bacilli resistance to drugs[5].

According to Nguyen et al., 80% of TB cases fall in low-middle income populations[8] and South Africa is a country that exhibits this population category.

The pathogenesis of TB usually begins with pulmonary inhalation of the mycobacteria which is taken up by alveolar macrophages. This results in an interplay between cellular immunity alongside the production of cytokines against mycobacteria. The inflammatory response through the formation of granulomas and tissue necrosis, follows in an effort to contain the mycobacteria[5]. At this point, containment may cause latent TB infection or cure. If it fails to contain the bacilli, this leads to active disease and possible dissemination of the mycobacteria.

The most universally used cutaneous TB classification is based on the route of bacilli infection[7]:

1) Exogenous Cutaneous TB: TB Chancre and TB Verrucosa Cutis;
2) Endogenous Cutaneous TB via contiguity: Scrofuloderma, Orificial TB, Lupus Vulgaris;

3) Endogenous Cutaneous TB via haematogenous/lymphatic spread: Lupus Vulgaris, TB Gumma, Miliary TB;
4) Tuberculids: Papulonecrotic Tuberculid, Lichen Scrofulosorum and Erythema Induratum.
5) Rarely Cutaneous TB secondary to the BCG vaccination[5].
6) True forms of Cutaneous TB include 1, 2, and 3 above, however, Tuberculids are not considered a true form of Cutaneous TB as it occurs from a hypersensitivity reaction to the mycobacterial antigens derived from other organs infected with TB[9].

The spectrum of Cutaneous TB clinically presents with various manifestations (see Table 1). Patients may also present with polymorphic (2 or more) manifestations [5].
Cutaneous TB may mimic many conditions such as atypical TB, deep fungal infections, sarcoid, syphilis, malignancies etc.[7]. Therefore it is imperative to evaluate a patient with diagnostic tests alongside their history and clinical examination.

Mycobacteria detection on skin tissue may be done by sending a specimen for culture. This is documented to be the gold standard for diagnosing Cutaneous TB. The Ziehl Neelson stain may be used to identify the acid-fast bacilli (AFB) in tissue. Tissue may also be sent off for the detection of M. tuberculosis DNA via a polymerase chain reaction (PCR).[5].
Lesional skin biopsies are examined for the histopathological findings of Cutaneous TB (see Table 1).

Table 1: Cutaneous TB variants alongside Clinical and Histopathological findings [5,7,10]

TB Type	Clinical Findings and Sites	Histopathological Findings
Lupus Vulgaris (LV)	• Plaque, Nodules and Ulcerations • Head and Neck, Extremities	• Seldom AFB + • Seldom PCR + • Culture positivity 50% • Granulomas
Tuberculosis Chancre	• Papules, Ulceration • Extremities	• AFB+ • Neutrophilic infiltrate (NI)
TB Verrucosa Cutis (VC)	• Plaques, Verrucous • Extremities	• Seldom AFB+ • Culture positivity 50% • Pseudoepithelial hyperplasia (PH) • Granulomas
Orificial TB	• Ulcerations • Genital, Oral, Urinary orifices	• AFB + • Granulomas
Scrofuloderma (S)	• Nodules, Sinuses, Suppuration, Ulceration • Head & neck	• AFB + • Culture positivity 50% • NI • Granulomas

Miliary TB	• Papules, Pustules, Nodules, • Widespread	• AFB + • NI • Vasculitis
TB Gumma	• Nodules, Ulceration, Suppuration • Torso, Extremities	• Granulomas • AFB +
Lichen Scrofulosorum (LS)	• Minute Papules • Torso	• AFB - • Granuloma
Papulonecrotic Tuberculid (PNT)	• Pustules, Papules • Head and Neck, Extremities	• Granulomas • Wedge Shape Necrosis • PCR positivity in 50% • AFB -
Erythema Induratum (EI)	• Nodules, Ulcers • Extremities	• Granulomas • Vasculitis • Panniculitis • Lymphocytic Infiltrate (LI) • AFB – • Culture -

Cutaneous TB can be acquired from other tuberculoid-infected organs(lungs, lymph nodes etc.)[7] and therefore one should investigate for extracutaneous TB as it plays a role in the morbidity and mortality in these patients.

According to the WHO, in 2017, 920000 HIV positive patients developed TB and a third of these patients succumbed to TB that year[11]. 31% of TB patients in a systematic review, done in Sub-Saharan Africa over a 27 year period, were HIV positive[14]. South Africa exhibits the largest HIV epidemic in the world[13]. Cutaneous TB is believed to be on the rise in HIV-positive populations[14] and is a WHO clinical stage 4 AIDS defining illness.
The initiation of antiretroviral therapy may lead to an unmasking of subclinical infections or paradoxical worsening of existing Cutaneous TB[15].
HIV also allows for the atypical presentation of cutaneous lesions. Yet there is a lack of published data regarding HIV and Cutaneous TB in South Africa.

In South Africa, a small case series was published in 2018 describing only 3 patients with cutaneous TB at a primary healthcare facility[16].
A South African study by John Moche from the University of Witwatersrand was conducted at Chris Hani Baragwanath Academic Hospital, Helen Joseph Hospital and Charlotte Maxeke Johannesburg Academic Hospital in 2008 over a 3-and-a-half-year period[17].

Below is a tabulated summary of the most common findings in studies on Cutaneous TB worldwide:

Table 2: Worldwide Cutaneous TB studies[17–21]

Country	Most Common TB Type	Type of Study	Number of patients
Nepal	• True TB – LV • Tuberculid – PNT	Retrospective	47
India	• True TB - Scrofuloderma • Tuberculid – LS	Retrospective	131
Brazil	• True TB – Scrofuloderma • Tuberculid – EI	Retrospective	75
Tunisia	• True TB - Scrofuloderma • Tuberculid – EI	Retrospective	137
South Africa	• True TB - Scrofuloderma • Tuberculid – EI	Prospective	74

The above-mentioned studies captured demographic, clinical and histopathological data which will be described in the Chapter Four: Discussion.

Despite South Africa being at the forefront of the TB pandemic and the known associated morbidity of Cutaneous TB, there is a paucity of recent data published on the prevalence, clinical and histopathological findings of Cutaneous TB in Johannesburg, South Africa.
Data published may be used to improve clinical acumen amongst clinicians since cutaneous TB is probably missed due to its non-specific nature and low positivity of tissue culture and stains. Lastly, the prevalence data on Cutaneous TB needs to be updated in South Africa, especially after the advent of antiretroviral therapy regardless of the CD4 count which was introduced in September 2016[22].

The aim of this study is thus to investigate the prevalence and spectrum of Cutaneous TB in patients at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

The study objectives are as follows:

1) Primary Objective
   a) To determine the prevalence and spectrum of Cutaneous TB in patients at CMJAH;
2) Secondary Objectives
   a) To correlate positive laboratory results in the diagnosis of Cutaneous TB (as described in the histopathology form);
   b) To describe the clinical presentation of lesions (as described in histopathology form).
3) Tertiary Objectives
   a) To assess the correlation of HIV in Cutaneous TB;

Chapter Two: Materials and Methods

Study Design

This study is a retrospective review of histologically proven cutaneous TB in patients who had attended CMJAH between 1st January 2011 and 31st December 2020.
In total 69 cases were identified.
CMJAH is a tertiary hospital that serves as a referral unit for the surrounding regional hospitals and to a community that can be described as low-middle income.

Patients

Inclusion Criteria

1) Patients older than 18 years of age, with confirmed Cutaneous TB infection on histopathology both as inpatients and outpatients at CMJAH;
2) Patients diagnosed between 1st January 2011- 31st December 2020.

Exclusion Criteria

1) Patients with inconclusive histology results
2) Patients younger than 18 years of age
3) Patients diagnosed outside the stipulated timeframe.

Methods of Data Extraction

An Academic Affairs and Research Management System (AARMS) application was lodged with the National Health Laboratory Service (NHLS) to release histopathological reports of confirmed cutaneous TB patients.
Search terms used were that of the classifications for true and tuberculid forms of cutaneous TB.
NHLS approval was followed by the release of de-identified data. However, race classification was missing from all reports.
Demographic (Age and Gender), Clinical (HIV Status, ARV usage, disease duration, site, morphology) and Histopathological (Tissue Features and Culture, Stains and PCR) data was extracted from the histopathological reports.

Error! Reference source not found. displays the data capture sheet used to record data.

Ethics

Before the extraction of data, permission was obtained from the relevant authorities at CMJAH and ethics approval from the Human Research Ethics Committee at the University of Witwatersrand.

Statistical Methods

The patients were broadly divided into 2 groups of:

a. True cutaneous TB and;
b. Tuberculids.

These patients were further subdivided into the different forms of true cutaneous TB and tuberculids.
Descriptive statistics were conducted on demographics, clinical and histopathological results. Numerical variables were calculated on data and where applicable, mean and standard deviations were determined.
Associations between pairs of categories and their statistical significance were determined using Pearson's Chi-Square test.

To test for frequency and statistical significance of continuous variables (age and disease duration), the t-test was used.
A p-value of ≤0.05 was used as the measure of statistical significance for both the t-test and Pearson's Chi-Square test.

Chapter Three: Results

Primary Objective

69 patients were identified with cutaneous TB between the period of 1st January 2011 and 31st December 2020. Table 3 below provides a detailed description of the patient demographics. Female patients were more likely to develop cutaneous TB than males (p<0.001).

Table 3: Demographic Statistics of Patients

Demographic Data (n=69)	
Age at initial Presentation (SD) (years)	39 (12)
Females	61
Males	8
Female: Male Ratio	7.625:1
Duration of Disease (SD) (months)	17 (23)
HIV Status	N (%)
HIV +	33 (47.8)
HIV -	22 (31.9)
HIV Unknown	14 (20.3)

Table 4: Prevalence and Spectrum of Cutaneous TB in Males and Females

Patients (n=69)		**Total**	**Male**	**Female**	**p-value**
		N (%)	**N (%)**	**N (%)**	
True TB	VC	1 (1.4)	1 (1.4)	-	0.317
	LV	9 (13.0)	4 (5.8)	5 (7.2)	0.739
	S	3 (4.3)	-	3 (4.3)	0.083
Total True TB		13 (18.8)	5 (7.2)	8 (11.6)	
Tuberculid	PNT	1 (1.4)	-	1 (1.4)	0.317
	EI	53 (76.8)	1 (1.4)	52 (75.4)	**<0.001**
	LS	2 (2.9)	2 (2.9)	-	0.157
Total Tuberculid		56 (81.2)	3 (4.3)	53 (76.8)	

Table 4 above depicts the most common form of cutaneous TB was Tuberculids of which 76.8% was EI.
The most common true form of cutaneous TB was LV accounting for 13% of total patients, however, it was not found to be statistically significant.
No cases of TB Gumma, Miliary TB, TB Chancre and Orificial TB were present in this group of patients that were assessed.
Female patients were statistically more likely to develop EI (p<0.001).

Secondary Objective

Table 5: Correlation of Histopathological Laboratory Results of Cutaneous TB

		Acid Fast Bacilli		PCR		Tissue Culture		p-value
		AFB -	AFB +	PCR +	PCR -	Positive	Negative	
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	
	Total	53 (72.6)	5 (6.8)	1 (1.4)	2 (2.7)	6 (8.2)	6 (8.2)	
True TB	VC	-	-	-	-	-	-	-
	LV	4 (5.5)	3 (4.1)	1 (1.4)	-	5 (6.8)	4 (5.5)	0.248
	S	1 (1.4)	2 (2.7)	-	1 (1.4)	1 (1.4)	2 (2.7)	0.787
Tuberculid	PNT	1 (1.4)	-	-	-	-	-	0.416
	EI	45 (61.6)	-	-	-	-	-	**<0.001**
	LS	2 (2.7)	-	-	1 (1.4)	-	-	0.221

In Table 5 above, AFB stains were the most common histopathological test performed in cutaneous TB, however, 91.4% of the AFB test results were negative.
AFB negative was the most commonly associated laboratory result with EI ($p<0.001$).
Tissue cultures done were most commonly performed for LV.
PCR was the least common laboratory test performed.

Table 6 below indicates that panniculitis was the most common histopathological finding in cutaneous TB. Panniculitis and vasculitis were only present in EI.
Granulomas was found to be a common feature but not isolated to EI. Findings of granulomas, vasculitis and panniculitis were more likely to be associated with EI ($p<0.001$).
LV ($p<0.001$) and Scrofuloderma ($p=0.036$) also had granulomas occurring frequently.

Table 6: Correlation of Histopathological Findings of Cutaneous TB

		PH*	Granulomas	Vasculitis	NI**	LI***	P****	WN*****	p-value
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	
	Total	1 (0.7)	47 (32.0)	20 (13.6)	10 (6.8)	16 (10.9)	52 (35.4)	1 (0.7)	
True TB	VC	-	1 (0.7)	-	1 (0.7)	1 (0.7)	-	-	0.677
	LV	1 (0.7)	9 (6.1)	-	1 (0.7)	4 (2.7)	-	-	**<0.001**
	S	-	3 (2.0)	-	-	1 (0.7)	-	-	**0.036**
Tuberculid	PNT	-	-	-	1 (0.7)	1 (0.7)	-	1 (0.7)	0.677
	EI	-	32 (21.8)	20 (13.6)	7 (4.8)	8 (5.4)	52 (35.4)	-	**<0.001**
	LS	-	2 (1.4)	-	-	1 (0.7)	-	-	0.193

*Pseudoepitheliomatous hyperplasia
**Neutrophilic infiltrate
***Lymphocytic Infiltrate
****Panniculitis
*****Wedge Necrosis

Table 7: Correlation of the Clinical Presentations in Cutaneous TB

		Papules	Nodules	Ulcerations	Plaques	Verrucous	p-value	Polymorphic Patients
		N (%)	N (%)	N (%)	N (%)	N (%)		
	Total	4 (4.7)	51 (59.3)	9 (10.5)	17 (19.8)	5 (5.8)		14 (20.3)
True TB	VC	-	-	-	1 (1.2)	1 (1.2)	0.558	1 (7.1)
	LV	1 (1.2)	4 (4.7)	3 (3.5)	8 (9.3)	4 (4.7)	0.165	8 (57.1)
	S	-	2 (2.3)	3 (3.5)	-	-	0.092	2 (14.3)
Tuberculid	EI	-	45 (52.3)	3 (3.5)	8 (9.3)	-	**<0.001**	3 (21.4)
	LS	2 (2.3)	-	-	-	-	0.092	0 (0.0)
	PNT	1 (1.2)	-	-	-	-	0.406	0 (0.0)

Table 7 above shows the most common clinical presentation in cutaneous TB was nodules. 52.3% of all 86 presentations were nodules associated with EI (p<0.001).
14 of the 69 patients presented with polymorphic lesions and this was mainly seen in LV.

Table 8: Correlation of Sites in Cutaneous TB

		Head and Neck	**Torso**	**Upper Limbs**	**Lower Limbs**	**Unknown**	**p-value**
		N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	
	Total	10 (14.5)	4 (5.8)	2 (2.9)	52 (75.4)	1 (1.4)	
True TB	VC	-	-	-	-	1 (1.4)	0.406
	LV	9 (13.0)	-	-	-	-	**<0.001**
	S	1 (1.4)	2 (2.9)	-	-	-	0.255
Tuberculid	PNT	-	1 (1.4)	-	-	-	0.406
	EI	-	-	2 (2.9)	51 (73.9)	-	**<0.001**
	LS	-	1 (1.4)	-	1 (1.4)	-	0.558

Table 8 above shows that 75.4% of all cutaneous TB occurred on the lower limbs.
The most common site in LV was the head and neck (p<0.001).
In EI the most common site was the lower limbs with (p<0.001).

Tertiary Objective

Table 9: Correlation of HIV and ARVs in cutaneous TB

		HIV +	HIV -	HIV Unknown	p-value	ARV			p-value
		P	N	Unknown		Y	N (%)	Unknown	
		N (%)	N (%)	N (%)		N (%)	N (%)	N (%)	
	Total	33 (47.8)	22 (31.9)	14 (20.3)		26 (78.8)	2 (6.1)	5 (15.2)	
True TB	VC	1 (1.4)	-	-	0.368	-	-	1 (3.0)	0.368
	LV	5 (7.2)	1 (1.4)	3 (4.3)	0.264	4 (12.1)	1 (3.0)	-	0.074
	S	1 (1.4)	1 (1.4)	1 (1.4)	1.000	1 (3.0)	-	-	0.368
Tuberculid	PNT	1 (1.4)	-	-	0.368	-	-	1 (3.0)	0.368
	EI	24 (34.8)	19 (27.5)	10 (14.5)	0.058	20 (60.6)	1 (3.0)	3 (9.1)	**<0.001**
	LS	1 (1.4)	1 (1.4)	-	0.607	1 (3.0)	-	-	0.368

Table 9 above shows that no relationship was found between the HIV status and cutaneous TB. HIV positive patients with EI were more likely to be on ARVs (p<0.001).

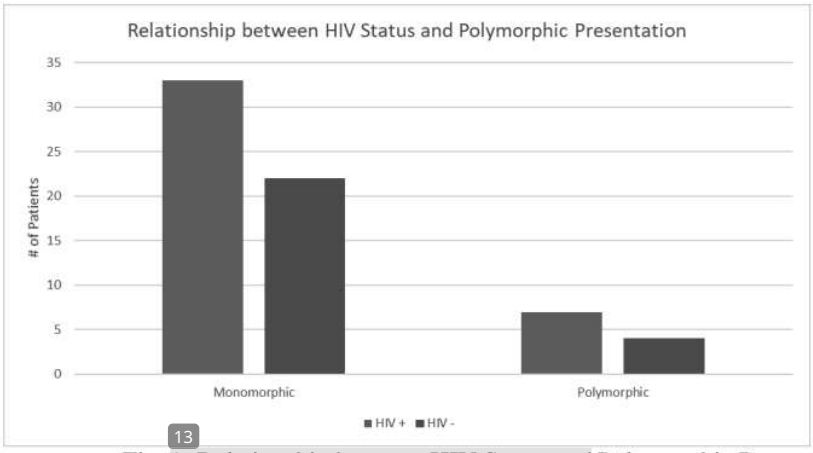

Fig. 1: Relationship between HIV Status and Polymorphic Presentation

Fig. 1 shows that no relationship was found between HIV status and polymorphic presentations in cutaneous TB ($p = 0.971$).

Chapter Four: Discussion

This retrospective study aimed to determine the prevalence and spectrum of cutaneous TB at CMJAH in patients diagnosed by histopathological confirmation between 1st January 2011 and 31st December 2020.
69 patients were identified with cutaneous TB. Tuberculids forms were seen in 81.2% (n 56) of the patients compared to true forms which comprised 18.8% (n 13) of all cutaneous TB.

Demographic data showed that females were more common than males in the study (ratio 7.625:1). Female dominance was also noted in the previous South African[17], and Tunisian[21] studies. This could be explained by the higher 51.1% population of females in South Africa[23] or differences in health seeking behaviours between genders[24].

The average age (SD) of the 69 patients was 39(12) and therefore quite similar to the mean age of 32 in John Moches's study[17].

The average disease duration (SD) of 17(22) months highlights the chronicity of cutaneous tuberculosis, lack of awareness, low access to medical care (due to socio-economics or logistics) and delayed health-seeking behaviour.

Tuberculids represented 81.2% of all cases in keeping with the study conducted by Moche, who reported a majority prevalence of 51.3%[17]. This was not noted in the studies of Abdel Malek or Mathur & Pandey where true forms of cutaneous TB (Scrofuloderma[21] & Lupus Vulgaris[18]) were more common. This could indicate that the South African population with cutaneous TB has higher immunity and therefore tuberculids are more common.
Erythema induratum (76.8%) was the most common form of cutaneous TB and tuberculid. Female patients were more likely to develop EI ($p<0.001$), in keeping with the literature, describing it as a disease mainly in adult females[25].

The most common true form in our study was Lupus Vulgaris with 13%, followed by Scrofuloderma with 4.3%. This is different to the study completed by Moche and Varshney & Goyal, where Scrofuloderma (29%[17] and 36.5%[19]) accounted the most for true cutaneous TB.
Lupus Vulgaris is a disease of high immunity[7]. Improved immunity may be seen in our population with the advent of ARVs, nutritional programmes, BCG vaccines and pre-exposure to TB.

AFB stains (79.4%) were the most common histopathological test performed but 72.6% were negative. It was mainly performed in tuberculid cases (82.7% out of 58 total AFB stains) which is known to exhibit a low presence of bacilli on tissue[7]. Consequently, EI showed an association with AFB negativity ($p< 0.001$).50% of 12 tissue cultures done were positive, in keeping with the literature[7] with the majority of positive cultures in LV. Very few PCR tests, 3(4.1%), were performed and this may be due to cost or lack of awareness.

Granulomatous histopathological findings, comprising 32%, presented significantly in LV ($p<0.001$), Scrofuloderma (p 0.036) and EI ($p<0.001$). However, panniculitis was the most common histopathological finding (35.4%), presenting exclusively in cases of EI. This study's findings suggests that once panniculitis is detected in cutaneous TB, the most likely diagnosis is EI.

Nodules accounted for 51 (59.3%) of all (86) clinical presentations and were the most common finding in EI.
This highlights the lack of specificity of cutaneous TB lesions and diagnostic dilemmas in clinical presentation. Regardless, nodules showed a significant relationship with EI ($p<0.001$) as seen globally[26]. However, our patients with EI did not tend to ulcerate as seen in Varshney & Goyal[19].
Polymorphic clinical presentations were uncommon, accounting for 14 (20.3%) of the 69 patients and when present, seemed to be in cases of LV. This was also seen in a 14 LV case patient study conducted in India, where presentation varied between ulceration, plaques, nodules and verrucosity[27].

The most common site was the lower limbs, which comprised 75.4% of cases. This was also seen in the Mathur & Pandey[18] and Moche[17] studies. However, compared to the Abdel Malek[21] study, the most common site of head and neck. The explanation of lower limbs being dominant for this study can be explained by the majority of cases being EI (73.9%). EI naturally shows a predilection for the lower limbs[26]. LV cases had a significant relationship with Head and Neck sites ($p<0.001$). this was also noted in LV cases in the Moche[17] and Varshney[19] study.

Less than half of the patients were HIV positive (47.8%) and in correlating the HIV status with cutaneous TB, HIV positive patients were no more likely the develop cutaneous TB (no significant p-value reported in Table 9), than HIV negative patients.
However, of the HIV positive patients who were on ARVs (78.8%), a relationship ($p<0.001$) was noted between these patients and EI. This may indicate the use of ARVs boosts patients' immune system[28], allowing HIV patients on ARVs to develop diseases of high immunity.

Despite the possibility that HIV may allow for unusual and polymorphic clinical presentations[29], this study showed no relationship between polymorphic lesions in HIV positive vs HIV negative patients ($p=0.971$).
One could speculate the effects of ARVs (which were taken in the majority of our HIV positive patients), could explain the similar behaviour of clinical presentations in these 2 groups.

In considering this study's findings, the following limitations were experienced:

1) Incomplete NHLS reports e.g. missing race, patient history, diagnoses
2) Inconclusive biopsies
3) Inadequate tissue biopsies, lowering the number of cases resulting in under or over-reporting of findings.
4) De-identified data restricted access to rechecking missing histological, demographic, clinical information e.g. race, PCR, cultures etc.
5) Possibility of patients being treated by other clinicians and never referred to dermatology for biopsies
6) Certain sub-categories had overall small numbers leading to statistical inaccuracy.

Chapter Five: Conclusions and Recommendations

The prevalence of cutaneous tuberculosis is still uncommon despite South Africa being at the forefront of the HIV/TB epidemic.
Females accounted for the majority of patients and patients generally presented with a prolonged disease duration suggesting possible lack of awareness or access to healthcare.
The most common form of cutaneous TB was tuberculids, specifically EI while the most common true form of cutaneous TB was LV.
Fatally ill forms of cutaneous Miliary TB were not seen in the study.

AFB negativity in EI probably suggests that the test can be omitted during histological evaluation as it adds no diagnostic value, and this will reduce histological expenditure.
The presence of panniculitis in a patient with cutaneous TB was a clear indicator of EI ($p<0.001$), while granulomas histopathologically featured across the spectrum of cutaneous TB.
The most common site affected was that of lower limbs particularly in EI ($p<0.001$) followed by head and neck in LV ($p<0.001$).
Nodules accounted for 59.3% of all clinical presentations. Since nodules present in many dermatological conditions (syphilis, sarcoid, deep fungal infections, malignancies etc), this suggests that cutaneous TB is clinically non-specific and may be a mimicker. It therefore requires heightened clinical suspicion in order to investigate and treat.

The advent of ARVs in all HIV positive patients may have played a role in these patients presenting in a similar clinical and histopathological manner as HIV negative patients as well as developing diseases of high immunity (EI).

Data from this study can be used to increase clinical awareness (in patients and clinicians) of cutaneous TB leading to prompt presentation, diagnosis and treatment thereby decreasing morbidity, mortality and spread of this communicable disease.

Lastly, this study may serve as a platform for future research on cutaneous TB e.g., looking at extracutaneous forms, response to TB medication etc.

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Appendix 5

Approved Research Protocol with expanded Literature review

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APPLICATION FOR CHANGE OF APPROVED SUPERVISOR(S) OF RESEARCH REPORT, DISSERTATION OR THESIS

Please indicate: Additional Supervisor ☒ Withdrawal of Supervisor ☐

Motivation / Reason for addition / withdrawal of Supervisor:
Recommended by post-graduate comittee
To assist principal supervisor

Recommendation of Department / School:
Department of internal medicine

Student Full name(s) and Surname	Naima Hargey		
Student Number	2367015		
Degree: Masters in medicine	Department: Dermatology, internal medicine		
Title: Prevalence and spectrum of cutaneous tuberculosis in patient at Charlotte Maxeke Johannesburg Academic Hospital			
Dr.			
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Supervisor Qualifications	MBChB (UP), FCDerm (SA), MMed (Wits).		
Supervisor Department/Address	Head of dermatology Helen Joseph Hospital		
Supervisor Telephone	084 800 35	E-mail	lushen@mweb.co.za

Withdrawing Supervisor (Full name &Surname)	N/A.	**Supervision %**	
Supervisor Qualifications			
Supervisor Department/Address			
Supervisor Telephone		E-mail	

Additional Supervisor (Full name &Surname)	Chioma Ede	**Supervision %**	50%.
Supervisor Qualifications	MBBS, FCDerm (SA), MMed (Wits).		
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1

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

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DEGREE FOR WHICH PROTOCOL IS BEING SUBMITTED: **Masters in Medicine Dermatology**			
PART-TIME OR FULL-TIME: **Full Time**			
FIRST REGISTERED FOR THIS DEGREE:	TERM : **2nd**		YEAR: **2019**
DEPARTMENT: **Department of Dermatology**			
TITLE OF PROPOSED RESEARCH: **Prevalence and spectrum of Cutaneous Tuberculosis in patients at Charlotte Maxeke Johannesburg Academic Hospital**			
CANDIDATE'S SIGNATURE:			DATE:
SUPERVISOR 1 (NAME & SURNAME): **Lushen Pillay**			**50%** Supervision
SUPERVISOR'S QUALIFICATIONS **MBChB (UP), FCDerm (SA), MMed (Wits)**			
SUPERVISOR'S DEPARTMENT Head of Dermatology – **Helen Joseph Hospital**			
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SUPERVISOR 2 (NAME & SURNAME): Chioma Ede			50% Supervision
SUPERVISOR'S QUALIFICATIONS: **MBBS, FCDerm SA, MMed (Wits)**			
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SUPERVISOR 3 (NAME & SURNAME):			% Supervision
SUPERVISOR'S QUALIFICATIONS			
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SYNOPSIS OF RESEARCH:(Brief summary of proposed research project; between 200-300 words only; with sub-headings: an introduction and justification for study, aim/s, proposed methodology and expected outcome/s)
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Introduction
Tuberculosis (TB) is a communicable disease that belongs in the top 10 causes of death worldwide. It is the leading cause for death from a single infectious agent. South Africa accounts for 3.6% of the majority of TB cases worldwide. Cutaneous TB comprises 1-2% of extrapulmonary TB and is a chronic skin infection mainly caused by Mycobacterium Tuberculosis.

Justification

Below is a tabulated summary of the most common findings in studies on Cutaneous TB worldwide:

Country	True cutaneous TB	Tuberculid
India	Scrofuloderma and Lupus Vulgaris	Papulonecrotic Tuberculid
Brazil	Scrofuloderma	Erythema Induratum
Nepal	TB Verrucosa Cutis and Lupus Vulgaris	Papulonecrotic Tuberculid
South Africa	Scrofuloderma	Erythema Induratum

The last dated study related to cutaneous TB was conducted in 2008 by Moche.

Despite South Africa being at the forefront of the TB pandemic and the associated morbidity of Cutaneous TB, there is paucity of recent data published on the prevalence of Cutaneous TB in Johannesburg, South Africa.

Aims
The aim of this study is thus to investigate the prevalence and spectrum of Cutaneous TB in patients at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

Proposed methodology
This will be a retrospective, descriptive study of adult patients seen at CMJAH with proven Cutaneous TB infection on skin biopsy from 1st January 2011- 31st December 2020.
Every patient's histology report fulfilling the inclusion and exclusion criteria will be included in the study.
The histology reports will be obtained from the Department of Anatomical Pathology at CMJAH using the National Health Laboratory Services.
Data will be captured on Microsoft excel and the relevant statistical analysis will be done.

Expected outcomes
The results and analysis on this study which will look at the frequency of Cutaneous TB in patients under various data variables can be used for future research, improving clinical acumen and institutionalize preventative measures.

WITS ETHICS NOT REQUIRED: Yes No WITS ETHICS PENDING: Yes No WITS ETHICS APPROVED: Yes No (circle appropriate symbol)* ***Please note the final human ethics clearance certificate or animal ethics certificate must be available prior to starting research**		IF Y SUPPLY ETHICS CLEARANCE CERTIFICATE AS ATTACHMENT AND INCLUDE ETHICS NUMBER HERE:
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SYNOPSIS OF RESEARCH CONTINUED

11 March 2019/MP

Research Proposal with Expanded Literature Review

Prevalence and spectrum of Cutaneous Tuberculosis in patients at Charlotte Maxeke Johannesburg Academic Hospital

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List of Abbreviations

AFB – Acid Fast Bacilli

AIDS – Acquired Immunodeficiency Syndrome

BCG - Bacillus Calmette – Guerin

CMJAH - Charlotte Maxeke Johannesburg Academic Hospital

HIV - Human Immunodeficiency Virus

IFN γ - Interferon Gamma

IGRA - Interferon Gamma Release Assay

INH – Isoniazid

IRIS - Immune Reconstitution Inflammatory Syndrome

M.Tuberculosis - Mycobacterium Tuberculosis

PCR – Polymerase Chain Reaction

TB – Tuberculosis

TNF α - Tumor Necrosis Factor Alpha

TST - Tuberculin Skin Test

WHO - World Health Organization

1 Introduction

Tuberculosis (TB) is a communicable disease that belongs in the top 10 causes of death worldwide. It is the leading cause for death from a single infectious agent. TB is caused by an Acid fast bacillus organism known as Mycobacterium Tuberculosis (M.Tuberculosis). It is estimated that 25%of the world's population is infected with M.Tuberculosis. In 2019, 10 million people worldwide fell ill with TB and approximately 1.4 million deaths were recorded that year (World Health Organization, 2020).

World Health Organization (WHO) indicated that 90% of the world's TB cases occurred in 30 countries, with South Africa being one of the countries listed (World Health Organization, 2020) accounting for 3.6% of the TB cases.

In 2018, TB disease in South Africa was estimated to be 390,000 cases (Mlambo, 2021). Statistics South Africa reported that TB was the leading cause of death in 2015 (Statistics South Africa, 2015). TB usually affect the lungs but can also cause extrapulmonary TB (sites other than the lungs), which is around 8-10% of all TB cases (van Zyl, et al., 2015)

Cutaneous TB comprises 1-2% of those extrapulmonary cases (van Zyl, et al., 2015). Cutaneous TB is a chronic skin infection mainly caused by M.Tuberculosis but also rarely by the Bacillus Calmette - Guerin (BCG) Vaccine which is an attenuated strain of Mycobacterium Bovis (Belo dos Santos, et al., 2014).

2 Literature Review

Cutaneous TB was first described in 1826 by Laennec as a warty lesion, but the organism M.Tuberculosis was only identified in 1882 (MacGregor, 1995).

The primary focus of TB tends to be pulmonary following inhalation of the mycobacteria which is taken up by alveolar macrophages. The pathogenesis of the disease is a result of an interplay between cellular immunity of the macrophages, lymphocytes and neutrophils alongside the production of cytokines such as interferon gamma (IFN γ) and tumor necrosis factor alpha (TNF α) against mycobacteria. This leads to an inflammatory response and tissue damage through the formation of the epithelioid and giant cells as well as granulomas in the effort to contain the mycobacteria (Belo dos Santos, et al., 2014). At this point containment may cause latent TB infection or cure. If it fails to contain the bacilli, this leads to active disease and dissemination of the mycobacteria.

Cutaneous TB can be acquired from either haematogenous spread, inoculation from an exogenous source or inoculation from an endogenous source via contiguous spread of the bacillus (James, et al., 2020).

Development of Cutaneous TB depends on:

1) Host factors **-** such as age, gender, anatomical location, immune competency (Human immunodeficiency virus status, malignancy, diabetes, immunosuppressants) and nutritional status (James, et al., 2020);
2) Environmental factors **-** areas of high prevalence e.g. South America, Asia, Southern Africa and areas of overpopulation (Belo dos Santos, et al., 2014);
3) Mycobacterium factors **-** such as route of its infection, virulence of the bacilli and bacilli resistance to drugs (Belo dos Santos, et al., 2014).

Clinically Cutaneous TB presents with various manifestations such as papules, plaques, pustules, ulcerations and nodules. Lesions may be suppurative and/or warty in appearance. Patients may present with polymorphic lesions as well (Belo dos Santos, et al., 2014).

The most universally used classification is based on the route of infection:

1) Exogenous Cutaneous TB: TB Chancre and TB Verrucosa Cutis;
2) Endogenous Cutaneous TB via contiguity: Scrofuloderma, Orificial TB, Lupus Vulgaris;
3) Endogenous Cutaneous TB via haematogenous dissemination: Lupus Vulgaris, TB Gumma, Acute Miliary TB;
4) Tuberculids: Papulonecrotic Tuberculid, Lichen Scrofulosorum and Erythema Induratum.
5) Rarely Cutaneous TB secondary to the BCG vaccination (Belo dos Santos, et al., 2014).

True forms of Cutaneous TB include 1, 2 and 3 above, however Tuberculids are not considered a true form of Cutaneous TB as it occurs from a hypersensitivity reaction to the mycobacterial antigens (MacGregor, 1995).
Classification may also be based on the bacterial load in the skin. Paucibacillary Cutaneous TB includes: TB Verrucosa Cutis and Lupus Vulgaris whereas multibacillary Cutaneous TB includes: TB Chancre, Scrofuloderma, Orificial TB, Miliary TB and TB Gumma (Bravo & Gotuzzo, 2007).

Cutaneous TB may present with polymorphic lesions and it may mimic other conditions such as atypical TB, deep fungal infections, leprosy, sarcoid, syphilis, malignancies, lupus etc. (James, et al., 2020). It is therefore imperative to evaluate a patient with diagnostic tests alongside their history and clinical examination to confirm Cutaneous TB.
Immunological evidence of M.Tuberculosis can be determined with a Tuberculin Skin Test (TST) and Interferon Gamma Release Assay (IGRA). TST identifies individuals who are sensitized to M.Tuberculosis and is performed by injecting 0.1ml of purified protein

derivative into the forearm. The reaction is read 48-72 hours later by measurement of an induration. The results of the measurements are as follows:

1) ≥ 5mm in HIV positive patients, indicates a positive result;
2) ≥ 10mm in other patients, indicates a positive result (Pillay, 2015)

IGRA such as QuantiFERON-TB gold measures serum levels of IFN γ produced after exposure to the M.Tuberculosis antigens (Pillay, 2015).

Mycobacteria detection on tissue may be done via sending a specimen for culture. This is documented to be the gold standard for diagnosing Cutaneous TB. Cultures can also be done on exudations from lesions. The Ziehl Neelson stains may be used to identify the acid-fast bacilli in tissue or exudate. Tissue may be sent off for the detection of M.Tuberculosis DNA via polymerase chain reaction e.g. GeneXpert test (Belo dos Santos, et al., 2014).

Lesional skin biopsies are examined for the histopathological findings of Cutaneous TB (see Table 1).

Table 1: Cutaneous TB variants alongside Clinical and Histopathological findings (James, et al., 2020)

TB Type	Clinical Findings and Sites	Histopathological Findings
Lupus Vulgaris (LV)	• Plaque, Nodules and Ulcerations • Head and Neck, Extremities	• Seldom AFB + • Seldom PCR + • Culture positivity 50% • Granulomas
Tuberculosis Chancre	• Papules, Ulceration • Extremities	• AFB+ • Neutrophilic infiltrate (NI)
TB Verrucosa Cutis (VC)	• Plaques, Verrucous • Extremities	• Seldom AFB+ • Culture positivity 50% • Pseudoepithelial hyperplasia (PH) • Granulomas
Orificial TB	• Ulcerations • Genital, Oral, Urinary orifices	• AFB + • Granulomas

Scrofuloderma (S)	• Nodules, Sinuses, Suppuration, Ulceration • Head & neck	• AFB + • Culture positivity 50% • NI • Granulomas
Miliary TB	• Papules, Pustules, Nodules, • Widespread	• AFB + • NI • Vasculitis
TB Gumma	• Nodules, Ulceration, Suppuration • Torso, Extremities	• Granulomas • AFB +
Lichen Scrofulosorum (LS)	• Minute Papules • Torso	• AFB - • Granuloma
Papulonecrotic Tuberculid (PNT)	• Pustules, Papules • Head and Neck, Extremities	• Granulomas • Wedge Shape Necrosis • PCR positivity in 50% • AFB -
Erythema Induratum (EI)	• Nodules, Ulcers • Extremities	• Granulomas • Vasculitis • Panniculitis • Lymphocytic Infiltrate (LI) • AFB – • Culture -

Histopathological features may be specific to certain variants but generally range from surface ulcerations, caseating necrosis, tuberculoid granulomas, neutrophilic or lymphocytic infiltrates, epidermal hyperplasia and suppuration (Emanuel, 2013). Extracutaneous TB should be ruled out in these patients through systemic examinations and additional tests such as sputum cultures and radiological tests (Menzies, 2021).

Treatment of Cutaneous TB follows the same general approach to that of systemic TB (Handog, et al., 2008). It involves the use of a multidrug regimen including Rifampicin, Isoniazid (INH), Ethambutol and Pyrizanamide. Surgical excision and reconstruction may be beneficial in certain cases of scrofuloderma and lupus vulgaris. In cases where Cutaneous TB

cannot be confirmed, a trial of treatment should be commenced as a response is expected within 6 weeks (Ramam, et al., 2005). Failure of a treatment response should alert one to possible drug resistance, diagnosis re-evaluation or poor compliance.

The Human Immunodeficiency Virus (HIV) population poses an increased risk of developing Cutaneous TB. According to the WHO, in 2017, 920000 HIV positive patients developed TB and a third of these patients succumbed to TB that year (World Health Organization, 2019). South Africa had an estimated 7.4 million HIV positive patients in 2018 and exhibits the largest HIV epidemic in the world (The South African National Aids Council, 2018). Cutaneous TB is believed to be on the rise in HIV positive populations (Mwiru, et al., 2018) and is a WHO clinical stage 4 AIDS defining illness.

The initiation of antiretroviral therapy may lead to an unmasking of subclinical infections or paradoxical worsening of existing Cutaneous TB. This phenomenon is known as the Immune Reconstitution Inflammatory Syndrome (IRIS) (Wolfe, 2019). A CD4 count of less than 200 is also known to increase the risk of extrapulmonary TB such as Cutaneous TB (Jaryal, et al., 2011).

HIV also allows for the atypical presentation of cutaneous lesions. Yet there is a lack of published data regarding HIV and Cutaneous TB in South Africa, which is needed to increase awareness, prompt clinical diagnosis and treatment.

In South Africa, a small case series was published describing only 3 patients with cutaneous TB abscesses concurrently with pulmonary TB in 2018 at a primary healthcare facility (Tshisevhe, et al., 2019).

Below is a tabulated summary of the most common findings in studies on Cutaneous TB worldwide:

Table 2: Worldwide Cutaneous TB studies

Country	**Most Common TB Type**	**Type of Study**	**Number of patients**	**Reference**
Nepal	• True TB – LV • Tuberculid – PNT	Retrospective	47	(Mathur 2014)
India	• True TB - Scrofuloderma • Tuberculid – LS	Retrospective	131	(Varshney, 2011)
Brazil	• True TB – Scrofuloderma • Tuberculid – EI	Retrospective	75	(Mann, 2019)
Tunisia	• True TB - Scrofuloderma • Tuberculid – EI	Retrospective	137	(AbdelMalek, 2013)
South Africa	• True TB - Scrofuloderma • Tuberculid – EI	Prospective	74	(Moche, 2010)

In Table 2, the South African study by John Moche from University of Witwatersrand was conducted at Chris Hani Baragwanath Academic Hospital, Helen Joseph Hospital and Charlotte Maxeke Johannesburg Academic Hospital with a total of 74 patients in 2008 (Moche, 2009).

As previously mentioned, cutaneous TB can be acquired from different sources including haematogenous spread, which suggests that there is underlying TB involving other organs such as the lungs, lymph nodes, bones, meninges etc. (James, et al., 2020).

Despite South Africa being at the forefront of the TB pandemic and the known associated morbidity of Cutaneous TB, there is paucity of recent data published on the prevalence of Cutaneous TB in Johannesburg, South Africa.

Data published may be used to improve clinical acumen as Cutaneous TB is often misdiagnosed. Treatment can be efficiently initiated thereby leading to cure of the disease and consequently decrease associated morbidity and mortality. This research can be used to institutionalize preventative measures as Cutaneous TB is a communicable disease. The prevalence data on Cutaneous TB needs to be updated in South Africa, especially after the advent of antiretroviral therapy regardless of the CD4 count. Lastly, this study may be beneficial for future research on Cutaneous TB.

The aim of this study is thus to investigate the prevalence and spectrum of Cutaneous TB in patients at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

3 Study Objectives

3.1 Primary Objective

1) To determine the prevalence and spectrum of Cutaneous TB in patients at CMJAH;

3.2 Secondary Objectives

1) To correlate positive laboratory results in the diagnosis of Cutaneous TB (as described in the histopathology form);
2) To describe the clinical presentation of lesions (as described in histopathology form).

3.3 Tertiary Objectives

1) To assess the correlation of HIV in Cutaneous TB;

4 Methodology

4.1 Study Design

This will be a retrospective, descriptive study of patients seen at CMJAH with proven Cutaneous TB infection on skin biopsy from 1st January 2011- 31st December 2020. The histology report will have the patient's demographic data, medical history (HIV status), clinical presentation and laboratory results including the histological confirmation of Cutaneous TB. All this information will be obtained from the Department of Anatomical Pathology at CMJAH using the National Health Laboratory Services.

4.2 Study Population

4.2.1 Inclusion criteria

- All adult patients (>18 years of age) with confirmed Cutaneous TB infection on histopathology both inpatients and outpatients at CMJAH;
- Patients diagnosed between 1st January 2011- 31st December 2020.

4.2.2 Exclusion criteria

- Patients diagnosed outside the above time frame;
- Patients younger than 18 years of age.

4.3 Site of study

It will be conducted at CMJAH, Parktown, South Africa which has 1000+ beds for treating patients within the public sector. Sample size of the study is expected to be at least 75 patients because 75 patients in the John Moche study over a period of 3 ½ years.

4.4 Data Variables

The following categories and variables will be collected as part of data collection. Refer to Appendix 1 on page 15 for the data collection sheet that will be used. For a full list of sub variables, refer to Appendix 2 on page 16.

Table 3: Data Categories and Variables

Category	**Variable 1**	**Variable 2**	**Variable 3**	**Variable 4**
Demographic	Age	Gender	Race	
HIV History	HIV Status	ARV treatment		
Clinical	Morphology of lesions	Polymorphic lesions	Duration	Sites
Laboratory Investigations	Histology	Tissue Culture		
Diagnosis	Cutaneous TB Diagnosis			

4.5 Data Processing and Analysis

Descriptive statistics on general characteristics/demographics of patients such as age, gender and race will be collected. Categorical data such as the HIV status, clinical presentation, laboratory results and the spectrum of Cutaneous TB will be described using frequencies and percentages. Frequency tables, bar graphs and pie charts will be used to present these variables. Relationships will be determined by the use of the Chi-square Test or where applicable the Fishers' Exact Test. A statistically significant p-value of less than 0.05 will be considered. All data will be stored in a Microsoft Excel program.

5 Limitations

Inaccuracy of records and missing information

Patients may be excluded from the study due to inconclusive histopathology results

6 Ethics

Permission will be obtained from CEO /Medical Superintendent of CMJAH as well as the Anatomical Pathology head of unit. The study proposal will be sent to the Human Resources Ethics Committee of the University of Witwatersrand.

7 Funding

This Masters will be self-funded.

Printing	R500
Binding	R200
Telephone calls	R100

8 Work Plan

	April - May 2021	**June-August 2021**	**September-December 2021**	**January-April 2022**	**May-June 2022**	**July – September 2022**
Research protocol						
Protocol assessment and ethics application						
Data collection						
				Part 2 studies		
Data analysis						
Writing up						

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10 Appendix 1

#	Age	Gender	Race	HIV	ARV	Morphology of lesions	Duration of lesions	Polymorphic (Y/N)	Sites	Histology	Tissue Culture	Final Diagnosis

11 Appendix 2

1. Demographic Variables:

Age: In years

Gender:

- Female
- Male

Race:

- White
- Black,
- Coloured,
- Indian,
- Other

2. HIV Status Variables:

HIV:

- Positive
- Negative

ARV:

- Yes
- No

3. Clinical Variables:

Morphology of lesions:

- Papules
- Pustules
- Nodules

- Abscesses
- Ulcerations
- Plaques
- Verrucous

Polymorphic:

- Yes
- No

Duration of lesions: In months

Sites involved:

- Head and Neck
- Orificial
- Torso
- Upper Limbs
- Lower Limbs
- Extensive surfaces
- Genitals

4. Laboratory Investigations

Histology:

- Acid Fast Bacilli
- PCR
- Pseudoepitheliomatous hyperplasia
- Suppuration
- Caseous granulomas
- Ulcerations
- Neutrophilic infiltrate

- Lymphocytic infiltrate

Tissue culture:

- Positive
- Negative
- Not done

5. Diagnostic Variables

Final Diagnosis:

True form of Cutaneous TB:

- Lupus vulgaris
- TB verrucosa cutis
- TB Gumma
- Miliary TB
- Orificial TB
- TB chancre
- Scrofuloderma

Tuberculid:

- PNT
- Erythema Induratum
- Lichen Scrofulosorum