The Use of Genexpert MTB/RIF® compared to Microscopy Culture and Sensitivity for the diagnosis of Hand and Wrist Tuberculosis

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Declaration

I Wofhatwa Solomon Ndou declare that this Research Report is my own, unaided work. It is being submitted for the Degree of Master of Medicine in the branch of Orthopaedic Surgery at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

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(Signature of candidate)

……12……day of ……May……20…20…in…Johannesburg……

Dedication

They say you can't teach an old dog new tricks but on the contrary one can argue that determination and the will to succeed can achieve anything. The true inspiration to complete my Masters report comes from my mother Mrs N.F Ndou whom at the age of 45 completed an education based Master's degree in Learner Curriculum Management. I also dedicate this Masters report to my lovely wife and children who saw me through the long hours, long nights and weekends to completion of this degree. Last but not least I would like to thank Professor M.T Ramokgopa for all the encouragement and to my Mentor and supervisor Dr M.C Sathekga, thank you for believing in me and all the support through the tough times.

Abstract

Purpose:

The global burden of Tuberculosis (TB) is ever increasing; the burden in Sub-Saharan Africa is further compounded by the rising number of Human Immunodeficiency Virus (HIV) infections, poverty and overcrowding. Musculoskeletal TB makes up 1% of all infections with spinal, hip and knee involvement being the commonest manifestations. Hand and wrist TB is a far less frequent presentation but with far reaching and devastating complications as the hand is important for prehension and interaction with the environment. The challenges in making a definitive diagnosis of TB are well established, failure to grow the mycobacterium under laboratory culture media may delay initiation of treatment even in the face of symptomatology suggestive of infection. The purpose of the study was to compare the conventional Microscopy culture and sensitivity method with the newer Genexpert MTB/RIF test looking at the sensitivity and specificity, the turnaround time and to report the number of drug resistant cases.

Materials and Methods:

A retrospective review of all hand and wrist TB cases was performed from 01 October 2012 until 31 December 2016. All cases diagnosed with hand and wrist TB were included, demographic data, laboratory results including HIV status, Microscopy culture and sensitivity, Genexpert as well as histology results were collected. The sensitivity, specificity and time taken to diagnosis or results between MC&S and Genexpert were analysed, therefore, resistant strains of TB were also reported.

Results and conclusion:

The overall sensitivity and specificity for Genexpert were 86% (95% CI, 48.7 to 97.4) and 33% (95% CI, 13.8 to 60.9) respectively, the positive predictive value (PPV) was 43% and the negative predictive value (NPV) was 80%. There were eight false-positive Genexpert tests and one false-negative Genexpert test. The mean turnaround time of one Genexpert result was two days, that of Microscopy was five days and that for culture was 21 days.

Genexpert and Microscopy had a significantly shorter turnaround time (two and five days, respectively) compared to culture with 21 days. Two cases were rifampicin resistant.

Conclusion:

Genexpert MTB/RIF is a reliable and rapid test to timeously diagnose TB. However, the test needs to be correlated with clinical symptoms. Although culture remains the gold standard, prolonged time to diagnosis may delay commencement of therapy.

Acknowledgements

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Nomenclature

CHBAH	Chris Hani Baragwanath Academic Hospital
CD4	Cluster of Differentiation 4
CRP	C-Reactive Protein
DNA	Deoxyribonucleic Acid
ESR	Erythrocyte Sedimentation Rate
HIV	Human Immunodeficiency Virus
MGIT	Mycobacteria Growth Indicator Tube
NHLS	National Health Laboratory Services
NPV	Negative Predictive Value
PCR	Polymerase Chain Reaction
PPV	Positive Predictive Value
TB	Tuberculosis
Vs.	Versus

CHAPTER 1

1 Introduction and literature review

1.1 Background

TB has a very ancient origin, which to this day cannot be accurately pinpointed. Dating back to 2400 BC, Egyptian mummies and art work demonstrate skeletal deformities typical of TB such as the Pott's lesions of the spine (1). The infectious origin of TB was conjectured by Benjamin Marten in 1720 and became popularly known as 'consumption', high mortality rates saw TB receive other descriptions such as 'The white Plague' and more dramatically 'Captain of all these men of death' (1). It was only in 1882 when Dr Robert Koch isolated the tubercle Bacillus using methylene blue staining, since then advances in the development of vaccines and anti-Tuberculosis treatment has seen declines in TB infections and mortality. It is the year 2019, and we face an organism that has borne resistant strains, co-partnered with HIV posing an even bigger challenge requiring more effective eradication strategies.

Mycobacterium TB is a common infection in third world countries, with an ever increasing burden in Sub-Saharan Africa. The World Health Organisation (WHO) statistics from 2015 report 10.4 million new cases of TB with 1.8 million deaths, six countries including South Africa accounting for 60% of all new cases (2). Poverty, low socio-economic status and HIV co-infection further increase the burden and pose a challenge on the diagnosis and treatment of TB.

The hand and wrist are important for prehension and human interaction with the environment. This interaction and complex anatomy of the hand and wrist renders this region of the body susceptible to a myriad of infections. From the synovial lining of the wrist joint to the midpalmar and thenar spaces, bacterial and non-bacterial infections may spread between the

hand and wrist. Flexor and extensor tendons are lined by tendon sheaths which are potential sites of infections, these can present as volar or dorsal hand infections (3).

1.2 Literature review

The commonest musculoskeletal manifestations include TB of the spine, hip and knee (4), and much of what is known about hand and wrist involvement has been published in case series and reports. TB of the hand and wrist is a rare form of musculoskeletal TB, and is often missed or misdiagnosed. The diagnostic dilemma arises as TB can mimic other infectious diseases. Hand and wrist TB may present as arthritis or tenosynovitis with common symptoms such as wrist pain and swelling are non-specific and pose a diagnostic challenge.

Bush et al. (2005) reported on 11 cases of hand and wrist TB and highlighted that there was a delay in the diagnosis from the onset of symptoms to initiation of therapy (5). Le Meur et al. (2005) reported a case of wrist TB in a heart transplant patient who was on immunosuppressive therapy and was treated with anti-inflammatories for four months prior to a diagnosis (6). Much of the diagnostic dilemma is due to the fact that symptoms of hand and wrist TB are non-specific and mimic other causes of wrist tenosynovitis such as seropositive or seronegative inflammatory arthropathy.

Preceding pulmonary infection may be present, which would assist in confirming a diagnosis. Benkeddache et al. (1982) in their series of 27 cases of hand and wrist TB reported 10% rate of pulmonary infection (7). Blood investigations may also aid in the diagnosis such as elevated levels of Erythrocyte Sedimentation rate (ESR) and C-reactive protein (CRP), however, these are non-specific as they are also elevated in inflammatory arthritides.

Musculoskeletal TB arises from haematogenous seeding of the bacilli soon after initial pulmonary infection (8, 9). Osteoarticular TB usually starts as an osteomyelitis in the growth plates of long bones where there is good blood supply, followed by infection of the synovium which causes synovitis (10,11). Osteomyelitis and destruction of carpal bones, metacarpals and phalanges may be seen on X-rays (see Figure 1.1), however, lytic lesions, sclerosis and osteopenia are non-specific and can be seen with other causes of osteomyelitis such as pyogenic infection (4). Delayed diagnosis and initiation of anti-TB therapy may result in

devastating complications such as wrist joint instability, stiffness, hand dysfunction and amputation.

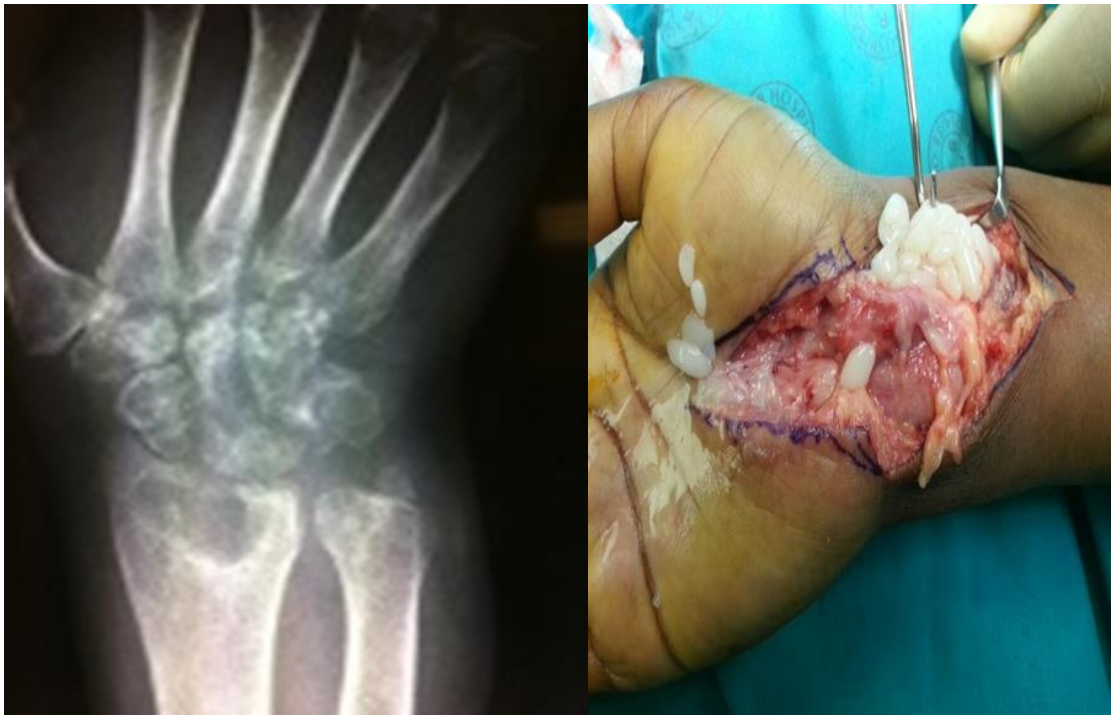

Figure 1.1: Left - X-ray showing lytic lesions in the distal radius and carpal destruction. **Right -** Clinical picture demonstrating rice bodies at biopsy

A tissue diagnosis from a biopsy and microbiological analysis remains the mainstay of confirming an infection with TB. The finding of rice bodies at biopsy may be suggestive of TB but they are non-specific. Rice bodies (see Figure 1.1) were first described in 1895, they are however not specific for TB as conditions such as Rheumatoid arthritis, Osteoarthritis and Systemic lupus erythematosus may have a similar presentation (5). The aetiology of rice bodies has been associated to multiple theories, but the evidence suggests that micro-infacts around the synovium and synovitis is the most probable cause (12).

The isolation of acid fast bacilli under different staining methods has posed a challenge in making a diagnosis. Negative results, however, do not exclude the presence of TB infection. The purified protein derivative or Mantoux skin test has been used with differing outcomes as a positive test demonstrated by a wheel or swelling at the site of injection may indicate latent or a previous infection with TB (11). Newer Deoxyribonucleic acid (DNA) based nucleic

amplification assays have shown good results in isolating different species of Mycobacterium, including Mycobacterium TB and other Mycobacteria (13).

In December 2010, the WHO endorsed the scale-up of Genexpert and recommended its use as the initial test in patients co-infected with HIV and TB (2). The Genexpert MTB/RIF is a cartridge-based fully automated nucleic acid amplification test, it purifies, concentrates, amplifies and identifies targeted nucleic acid sequences in the TB genome (2). In HIV infected patients, the test has a rate of case detection that is increased by 45%, as compared with smear Microscopy (13).

Much of the early successes of the test were seen when the test was used to make a rapid diagnosis of pulmonary TB, however recent studies have evaluated the use of Genexpert in extrapulmonary TB (14, 15). Kivhya-Nyugga et al. (2004) conducted a comparison between the routine use of Microscopy and Polymerase Chain Reaction (PCR) to diagnose pulmonary TB in a population with high TB and HIV prevalence. The study had 1398 patients who gave three sputum samples. The study reported that PCR was found to have a sensitivity of 93% and specificity of 84% with smear Microscopy having a sensitivity of 60% and specificity of 98% (15). This highlights that PCR is a reliable and test in diagnosing TB. In a laboratory based study by Hajia et al. (2009) the authors looked at 2123 specimens that included pulmonary and extrapulmonary TB and they found PCR to have a 70% sensitivity compared to 40% with routine Microscopy in diagnosing extrapulmonary TB (16). More recently Pandey et al. (2017) reported a sensitivity of 98.6% and specificity of 100% with Genexpert MTB/RIF compared to conventional culture methods in 85 pulmonary TB samples (17).

The emergence of resistance to first and second line anti-TB therapy has proven challenging. Currently there are no studies that demonstrate the incidence of resistant strains of TB in the hand and wrist. In a prospective study done by Held et al. (2014), the authors assessed the use of Genexpert MTB/RIF in 69 patients with suspected spinal TB. They were able to detect a 5.8% rate of multidrug resistant TB with 95.6% sensitivity and 96.2% specificity (18). The same authors in a subsequent study used Genexpert to diagnose musculoskeletal TB in children. The study analysed 109 samples from 102 patients, the mean time taken to reach a positive result was 0.8 days (range: 0.46 - 1.4 days) using Genexpert MTB/RIF compared to 21 days (range: 19 – 30 days) when culture methods were used (19).

The cost of Genexpert MTB/RIF has been extensively scrutinised, with most arguments supporting that the benefits of the test far outweigh the costs. In 2012 the National Health Laboratory Services (NHLS) price for a Genexpert cartridge was R110.00 and R162.20 including performing the test, while Microscopy and culture priced at R44.54 and R88.71 respectively while drug sensitivity testing to Isoniazid and Rifampicin cost an added R304.09 (20). Schnippel et al. (2013) performed a cost analysis study in diagnosing pulmonary TB in initial sputum negative patients by Genexpert MTB/RIF, they found that the cost of TB patient initiated on treatment using two Genexpert tests is R2682 compared to Genexpert and culture which cost R3046 (20). The proposed model of two consecutive Genexpert tests was 12% less than the traditional single Genexpert and culture (20). This further highlights the benefit of rapid diagnosis and accelerated treatment initiation.

1.3 Study Aim and Objectives

Aim:

To compare Genexpert MTB/RIF and MC&S in diagnosing hand and wrist TB

Objectives of this study are to:

- To compare the sensitivity and specificity of the two tests in diagnosing hand and wrist TB
- To assess the impact of HIV co-infection on both diagnostic modalities
- To document the number of drug resistant cases from hand and wrist TB
- To compare the cost of both investigations *viz* Genexpert MTB/RIF against MC&S

CHAPTER 2

2 Methodology

2.1 Research Question

Is Genexpert MTB/RIF a superior investigative technique to MC&S when used to diagnose hand and wrist TB?

2.2 Research Design

The study is a retrospective study of all suspected cases of hand and wrist TB from 01 October 2012 to 31 December 2016.

2.3 Materials and Method

In order to compare two diagnostic modalities in diagnosing hand and wrist TB, retrospective analysis of existing data from the hand masses and lumps at Chris Hani Baragwanath Academic Hospital (CHBAH) was done. All records including clinical data, blood investigations and biopsy results were collected and recorded using excel spread sheet (see appendix A).

2.4 Sample

For the purpose of this study, the principal researcher enrolled all patients (n = 22) diagnosed with hand and wrist TB from the existing database from the Hands unit at CHBAH. However, the final number of patients with adequate information for data analysis was n = 19.

2.5 Data Collection

All data were collected from an existing database from the Hands unit at CHBAH, blood results as well as biopsy results were collected and verified from the NHLS results database. Ethics approval was obtained from the hospital ethics board as well as the Human Research Ethics Committee (HREC) (Medical) of the University of the Witwatersrand (see Appendices section).

2.5.1 Selection Criteria

Inclusion criteria:

All hand and wrist masses and infections diagnosed on history, clinical examination, laboratory investigations and X-rays to be TB.

Exclusion criteria:

Hand masses and infections other than TB.

2.6 Data Analysis

Statistical analysis of the data was conducted with statistical package for the social science system version SPSS 23.0. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with 95% confidence intervals and Kappa value of Genexpert and Microscopy were calculated using culture of Mycobacteria growth indicator tube (MGIT) culture as the gold standard. The difference between the three (3) test methods were compared using the $\chi 2$, $p < 0.05$ were considered to be statistically significant. Turnaround time is presented as mean ± standard deviation (SD).

2.7 Limitations

The limitations encountered in the study largely emanated from the rare occurrence of hand and wrist TB, the initial expected number of 30 patients was not reached and therefore, rendering a small sample size of 22 patients. Furthermore, three patient samples were excluded from the study due to contamination of samples and therefore, not suitable for laboratory analysis by culture methods and comparison to Genexpert MTB/RIF.

CHAPTER 3

3 Results

A total number of n = 22 patient samples were evaluated for Genexpert, Microscopy and MGIT culture tests. However, three samples had contaminated MGIT cultures as a result excluded. Thus, n = 19 eligible patient samples were included in this analysis. Of the 19 patients, 13 presented with a volar mass while five involved the dorsum of the hand and one patient presenting with dactylitis involving the fingers.

Overall, 11/19 (58%) of patients were HIV Infected, 8/19 (42%) were not infected (see Figure 3.1 and Table 3.1).

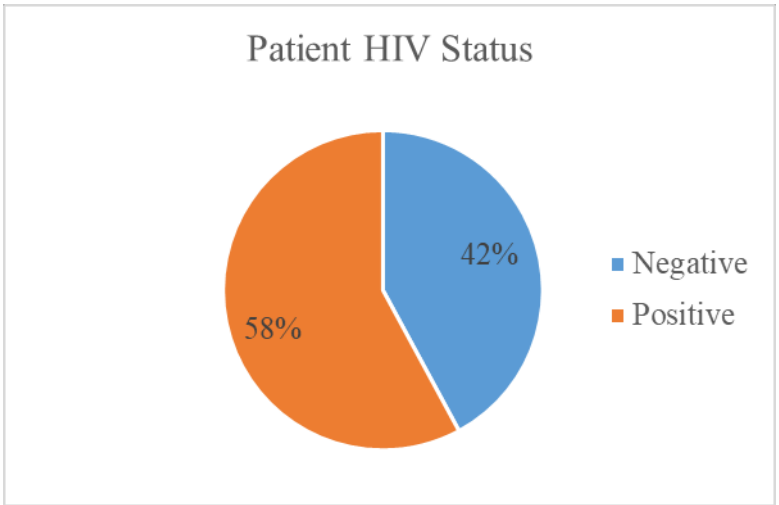

Figure 3.1: HIV results of patients

Table 3.1: HIV results vs. Genexpert test

Test	Result	Genexpert		Total
		Positive	Negative	
HIV	Positive	10	1	11
	Negative	4	4	8
	Total	14	5	19

Of the nineteen (19), three (16%) samples were positive and three (16%) were negative by all three test methods used in this study. Only two cases were detected to be rifampicin resistant by Genexpert test, one case did not have positive MGIT culture result whilst the other case had positive MGIT culture result. Of the 19 patients, two patients were detected to be rifampicin resistant by Genexpert test. Moreover, both of these rifampicin resistant patients were HIV positive. The two (2) patients that were rifampicin resistant, one patient did not have positive MGIT culture result whilst the other patient had positive MGIT culture result.

By taking Microscopy and MGIT culture methods as reference (see Table 3.2), samples that were positive and negative in microscopy and culture were considered true positive and true negative. Culture negative and Genexpert positive samples were taken as false positive samples. Genexpert negative and culture positive samples were considered false negative, the same applies with Genexpert vs. Microscopy.

Table 3.2: Contingency Table for calculating PPV and NPV

	Disease	No disease	Totals
Test Outcome Positive	a (True Positive)	b (False Positive)	$n_1=a+b$
Test Outcome Negative	c (False Negative)	d (True Negative)	$n_2=c+d$
Totals	$m_1=a+c$	$m_2=b+d$	$N=n_1+n_2$

The overall sensitivity and specificity for Genexpert (see Table 3.3) were 86% (95% CI, 48.7 to 97.4) and 33% (95% CI, 13.8 to 60.9) respectively, the PPV was 43% and the NPV was 80%.

Table 3.3: Sensitivity and specificity results for MTB/RIF Genexpert vs. Culture

Test	**Result**	**MGIT culture**		**Total**	**Sensitivity (%; 95% CI)**	**Specificity (% ; 95% CI)**	**PPV %**	**NPV %**
		Positive	**Negative**					
Genexpert	Positive	6	8	14	86 (48.7 - 97.4)	33 (13.8 - 60.9)	43	80
	Negative	1	4	5				
	Total	7	12	19				

There were eight false-positive Genexpert test and one false-negative Genexpert test (see Table 3.3). Among the HIV positive patients, sensitivity for Genexpert (see Table 3.4) was 100% (95% CI, 51.0 to 100) while it was 50% (95% CI, 9.5 - 90.5) (see Table 3.5) for non-HIV infected patients. The sensitivity for culture was lower than that of Genexpert at 57.1% (95% CI, 0.25 - 0.68) and a specificity of 41.7% (0.19 - 0.68) in HIV positive patients (see Table 3.6).

Table 3.4 Sensitivity and specificity for Genexpert in HIV positive patients

HIV positive patients (*n* = 11)

Test	Result	MGIT Culture		Total	Sensitivity (% ; 95% CI)	Specificity (% ; 95% CI)	PPV %	NPV %
		Positive	Negative					
Genexpert	Positive	4	6	10	100 (51.0 - 100)	14.3 (2.6 - 51.3)	40	100
	Negative	0	1	1				
	Total	5	6	11				

Table 3.5 Sensitivity and specificity for Genexpert in HIV negative patients

HIV negative patients (*n* = 8)

Test	Result	MGIT Culture		Total	Sensitivity (% ; 95% CI)	Specificity (% ; 95% CI)	PPV %	NPV %
		Positive	Negative					
Genexpert	Positive	1	3	4	50 (9.5 - 90.5)	50 (18.8 - 81.2)	33,3	75
	Negative	1	3	4				
	Total	2	6	8				

Table 3.6: Sensitivity and Specificity for MGIT culture vs. HIV

Test	Result	MGIT Culture		Total	Sensitivity (% ; 95% CI)	Specificity (% ; 95% CI)	PPV %	NPV %
		Positive	Negative					
HIV	Positive	4	7	11	57.1 (0.25 - 0.84)	41.7 (0.19 - 0.68)	36,4	62,5
	Negative	3	5	8				
	Total	7	12	19				

There was no statistical significant difference between Genexpert and MGIT culture and between Genexpert and Microscopy ($\chi^2 = 0.82$, $p = 0.36$ and $\chi^2 = 0.42$, $p = 0.52$). However, there was a slight agreement between the Genexpert and the MGIT culture results with a Kappa value of 0.16 (95% CI, 0.16 to 0.48) using Kappa statistics. The mean turnaround time of Genexpert result was two days, that of Microscopy was 5 ± 3 days and that for culture was 21 ± 12 days. The average time taken to process specimens and testing time of the Genexpert was two days, that of Microscopy was five days and that of culture was 21 days, i.e. Genexpert and Microscopy had a shorter turnaround time compared to culture results.

CHAPTER 4

4 Discussion

A thorough history and clinical examination remain central in clinching a diagnosis. There is a paucity of literature specifically looking at hand and wrist TB, however much of our understanding of musculoskeletal TB emanates from studies of spinal and hip infection. Obtaining a tissue (see Figure 4.1) specimen remains the gold standard in clinching a diagnosis, however, laboratory isolation of TB remains a challenge, whereby commencing empiric TB treatment becomes the norm than the exception.

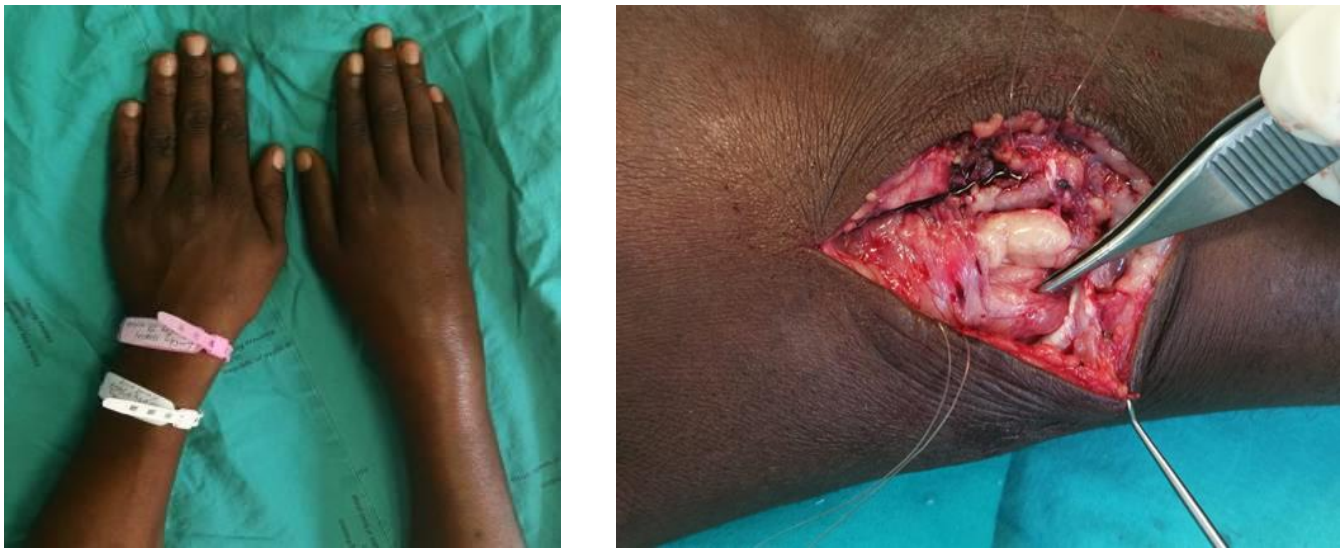

Figure 4.1: Left: Clinical images showing right dorsal wrist swelling. **Right:** Clinical picture at surgical biopsy showing synovitis

The yield with percutaneous spinal biopsies for spinal TB is 50 - 83%. Watt et al. (2014) performed a multicentre retrospective review of 44 patients with suspected spinal TB not requiring open spinal biopsy, they reported a 59% yield with percutaneous biopsies. They

attributed their results to specimen decontamination prior to culture and prior TB treatment (21).

The sensitivity and usefulness of the Genexpert MTB/RIF is limited in extrapulmonary and smear negative samples due to fewer TB bacilli. Held et al. (2014) in their study of 69 patients with spinal TB had showed a 95.6% sensitivity using the Genexpert MTB/RIF and similarly 96.2% specificity (18), results coming from our study were limited by the small sample size and further limited by contaminated specimens. Although the study had very few cases, much can be deduced from the results obtained. The Genexpert MTB/RIF had a 33% specificity and high sensitivity of 86%, further more we also noticed a significant difference between HIV positive and negative patients. Among the HIV positive patients, sensitivity for Genexpert MTB/RIF against MGIT culture was 100% (95% CI, 51.0 to 100) while it was 50 (95% CI, 9.5 - 90.5) for non-HIV infected patients. The study did not further explore the Cluster of differentiation 4 (CD4) cell counts in the HIV positive group, but from existing data it is even more difficult to culture TB in severely immunocompromised patients and hence the potential value of the Genexpert MTB/RIF in diagnosing TB (2). Held et al. in 2017 further the diagnostic accuracy of Genexpert MTB/RIF in musculoskeletal TB comparing tissue samples from HIV-infected and HIV-uninfected patients. The study showed 96.9% sensitivity in HIV positive patients compared to 89.6% in HIV negative patients, and specificity of 100% in HIV positive patients compared to 98.3% in HIV negative patients. They further compared the accuracy in spinal and extraspinal TB and found a much higher sensitivity and specificity of 93.8% and 97.6% respectively in spinal TB compared to 81.8% sensitivity and 100% specificity in extraspinal TB. The findings of a lower sensitivity in extraspinal TB are similar to the results in our study of 86% sensitivity, this finding could possibly be explained by lower TB bacilli in extraspinal cases (22). The burden of HIV and TB co-infection in the South African setting make the diagnosis of TB more challenging, and furthermore TB infection accelerates HIV progression.

One of the most significant findings in our study was that in terms of getting results from the three methods used, Genexpert MTB/RIF was found to have a much faster turnaround time as compared to the other two methods with a mean time of two days. It was followed by Microscopy with an average of 5 ± 3 days and 21 ± 12 days for culture. The time taken to

diagnosis could have been confounded by laboratory factors such as delay in processing of specimens and the number of TB specimens being processed by the NHLS at CHBAH.

The growing problem of drug resistance in South Africa further impacts on effecting treatment, from Multidrug resistant TB (MDR-TB) to extensively drug-resistant TB (XDR-TB) the cost burden to the health system keeps escalating. Our study found two (2/19) MDR-TB cases all identified by Genexpert MTB/RIF, thus constituting 11% of the sample.

The South African Health system is under considerable financial strain, rising cost to treat communicable diseases is further compounding the issue. Historical migration patterns still exist in South Africa as well as communities comprising of largely poor income households, access to Tertiary and Quaternary health centres further imposes a cost burden to patients from travelling to hospital bills. The current cost of a single Genexpert test is R201.56 while TB MC&S is R28.37, using the 19 patients in our study the total cost of Genexpert and MC&S would be R3829.64 and R255.33, respectively.

Although the Genexpert MTB/RIF is more expensive than Microscopy culture and sensitivity, our study further demonstrates that the benefits of the Genexpert MTB/RIF far outweigh its cost. Making a rapid diagnosis leads to early commencement of therapy which ultimately leads to fewer hospital visits to follow up results. Prevention remains the primary focus in decreasing the burden of TB, but early case detection and commencement of TB treatment is fundamental in reducing transmission and complications of TB infection.

4.1 Recommendations

Hand and wrist TB remain a relatively rare presentation, but can lead to devastating complications and functional deficits if not treated timeously. Our study had a small sample size but from our results we recommend first line Genexpert MTB/RIF testing for suspected hand and wrist TB cases, with significant sensitivity and specificity in HIV positive patients. The turnaround time of Genexpert MTB/RIF is by far quicker than that of Microscopy culture and sensitivity, this aids in timely commencement of anti-TB therapy. Due to the small

sample size, we further recommend further studies with larger sample sizes into hand and wrist TB cases.

CHAPTER 5

5 Conclusion

The global burden of TB is on the rise, Sub-Saharan Africa carries the bulk of this burden. Spinal and hip TB remain the leading manifestations of musculoskeletal TB, hand and wrist TB remain relatively rare but with potential devastating complications. Diagnosing TB remains a challenge; culture remains the gold standard but may take as long as eight weeks for a result. Our study sample size was small but from our results we conclude that Genexpert MTB/RIF is superior to Microscopy culture and sensitivity with a higher sensitivity and quicker turnaround time. We also conclude from our results that Genexpert MTB/RIF is a significantly useful test in HIV positive patients.

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Appendices

Appendix A: Data Collection Sheet.

Study number	**HIV status**	**Genexpert Result**	**Time to Genexpert result (days)**	**Microscopy Result**	**Time to Microscopy result (days)**	**Culture Result**	**Time to Culture result (days)**	**Histology**
1								
2								
3								
4								
5								
6								
7								
8								
9								

Appendix B: Hand Unit.

Register of masses excised

Age _____ Sex_____

GT
_____RHD/LHD Occupation_____
__

History_____
_____
_____
_____

Exam_____
_____
_____
_____

Differential
Diagnosis_____

Surgery_____Date_____

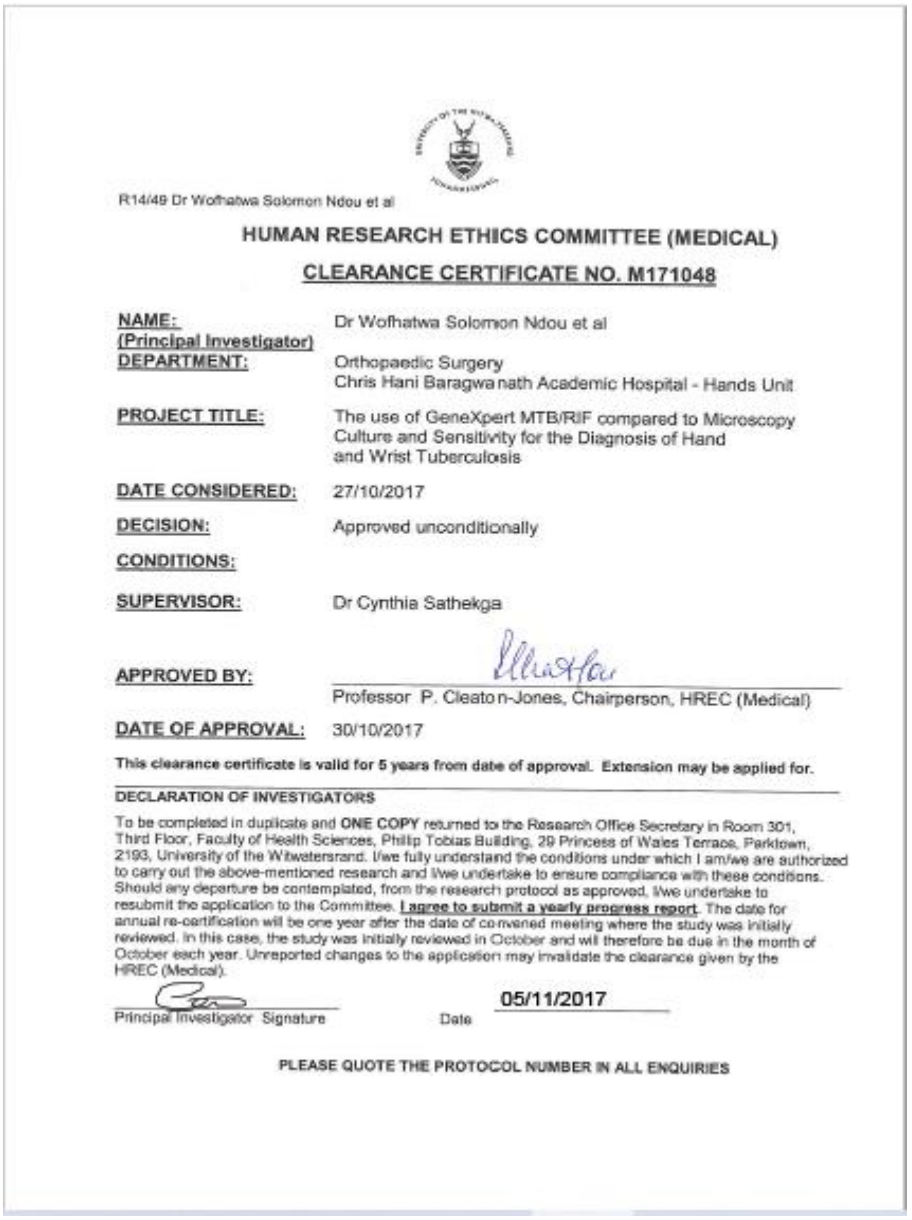
Diagnosis_____

Histology
Number_____

Histology Diagnosis
_____
_____
_____

_____

Appendix C: Human Research Ethics Clearance Certificate.



R14/49 Dr Wofhatwa Solomon Ndou et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M171048

NAME: (Principal Investigator)	Dr Wofhatwa Solomon Ndou et al
DEPARTMENT:	Orthopaedic Surgery Chris Hani Baragwanath Academic Hospital - Hands Unit
PROJECT TITLE:	The use of GeneXpert MTB/RIF compared to Microscopy Culture and Sensitivity for the Diagnosis of Hand and Wrist Tuberculosis
DATE CONSIDERED:	27/10/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Cynthia Sathekga
APPROVED BY:	Professor P. Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	30/10/2017

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 in Room 301, 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 October and will therefore be due in the month of October each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 05/11/2017

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES