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Periprosthetic joint infection: a South African perspective

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PERIPROSTHETIC JOINT INFECTION: A SOUTH AFRICAN PERSPECTIVE



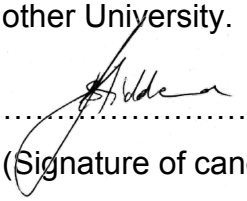
Jan Siebrand Hiddema

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Medicine

Johannesburg, 2022

Declaration

I, Jan Hiddema, 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 Orthopaedic Surgery at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



……

(Signature of candidate)

……7th……day of ……November……20……22……in……Johannesburg……

Dedication

This Masters of Medicine is dedicated to the late Professor Dick Ronald Van der Jagt. Professor Van der Jagt inspired generations of orthopaedic surgeons with his patient and kind disposition and meticulous attention to detail. He will be missed by patients and colleagues alike, however his influence lives on in the peoples who's lives he touched.

In memory of Professor Dick Ronald Van der Jagt

15 December 1952 – 31 December 2021

Acknowledgements

I would like to thank all my supervisors and research co-ordinators, Dr. Allan Sekeitto, Dr. Jacques du Toit, Prof. Dick Van der Jagt, Dr. Maxwell Jingo and Dr. Brenda Milner for all their time and effort in guiding and teaching me throughout this research project. Without you it would not have been possible.

I would also like to thank Kaeri Van der Jagt, Hanan Wilson and Carl-Adriaan Hugo in assisting me in the completion of this research report.

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Nomenclature

A. baumannii	**Acinetobacter baumannii**
ALC	**Antibiotic-loaded cement**
CEO	**Chief executive officer**
CMJAH	**Charlotte Maxeke Johannesburg Academic Hospital**
CoNS	**Coagulase Negative Staphylococci**
CRP	**C-Reactive protein**
DAIR	**Debridement, antibiotics and implant retention**
ESR	**Erythrocyte Sedimentation rate**
g	**gram**
hr	**hour**
HREC	**Human research ethics committee**
I&D	**Irrigation and debridement**
IDSA	**Infectious Diseases Society of America**
IV	**Intravenous**
l	**liter**
MC+S	**Microscopy, culture and sensitivity**
mg	**milligram**
mm	**millimeter**
PJI	**Periprosthetic joint infection**
PMMA	**Polymethyl methacrylate**
S. aureus	**Staphylococcus aureus**
THA	**Total hip arthroplasty**

TJA	**Total joint arthroplasty**
TKA	**Total knee arthroplasty**
WITS	**University of the Witwatersrand**

“Submissible” format of a paper

Periprosthetic joint infection: A South African perspective

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Keywords: Hip periprosthetic joint infection, Knee periprosthetic joint infection, periprosthetic joint infection epidemiology.

Level of evidence: 4

Abstract

Background: South African data on the bacteriology and sensitivity profile of periprosthetic joint infection is lacking. Our aim is to determine the characteristics of periprosthetic joint infection in a South African clinical setting by identifying the most common microorganisms cultured and establishing their antibiotic sensitivities in order to propose the most appropriate empiric antibiotic treatment regimen.

In the case of two-stage revision procedures with positive cultures during the second stage, we aim to compare the microorganisms cultured during the first stage *versus* the second stage. Furthermore, we aim to correlate the bacterial culture during the second stage with the erythrocyte sedimentation rate/ C-reactive protein result.

Patients and Methods: We performed a retrospective cross-sectional study looking at all hip and knee periprosthetic joint infections in patients 18 years and older, treated at a government institution and a private revision practice in Johannesburg, South Africa between January 2015 and March 2020. Data were collected from the Charlotte Maxeke Johannesburg Academic Hospital hip and knee and the Johannesburg Orthopaedic hip and knee databanks.

Results: We included 69 patients whom underwent 101 procedures relating to periprosthetic joint infection. Positive cultures were found in 63 samples and 81 different microorganisms were identified. The most common microorganisms cultured were *Staphylococcus aureus* (*n* = 16, 19.8%) and *Coagulase negative Staphylococcus* (*n* = 16, 19.8%), followed by *Streptococci* species (*n* = 11, 13.6%). The positive yield in our cohort was 62.4% (*n* = 63). A polymicrobial growth was found in 19% (*n* = 12) of the culture-positive specimens. Of all the microorganisms cultured, 59.2% (*n* = 48) were Gram-positive *versus* 35.8% (*n* = 29) Gram-negative. The remainder were fungal and anaerobic microorganisms at 2.5% (*n* = 2) each. Gram-positive microorganisms displayed 100% sensitivity to Vancomycin and Linezolid, whereas Gram-negative microorganisms displayed 82% sensitivity towards Gentamycin and 89% sensitivity towards Meropenem respectively.

Conclusion: Our study identifies the bacteriology of periprosthetic joint infections and their sensitivities in a South African clinical setting. We recommend that antibiotic-loaded cement spacers and systemic antibiotic regimens should consist of Meropenem or Gentamycin; Vancomycin and Rifampicin to achieve the broadest spectrum of coverage and most likely success in eradicating infection.

Introduction

Primary Total Joint Arthroplasty (TJA) is one of the most common orthopaedic procedures performed worldwide. According to Sloan et al., total hip arthroplasty (THA) will grow by 71%, to 635 000 procedures per year, whereas total knee arthroplasty (TKA) will grow by 85%, to 1.26 million procedures per year by 2030 in the United States of America alone (1). One of the most common complications of TJA, requiring revision surgery, is periprosthetic joint infection (PJI) (2). The incidence of PJI is 1 − 2% in primary and 4% in revision arthroplasties, respectively (3).

With the increase in TJA procedures being performed worldwide, there will also be the inevitable increase in PJI (4). This creates a significant financial burden on global healthcare with the cost for revision Arthroplasty being up to 76% higher than for primary TJA (5). Klouche et al. demonstrated that the cost of revision for infection is 2.57 times higher than the cost of revision for non-infective causes (6). There is also a five-fold increase in mortality in revision procedures for PJI *versus* revision procedures for aseptic failures (7). The five-year survival rate for PJI is lower than that of female breast cancer (8,9). Helwig et al. has shown that subjective quality of life in patients following PJI is significantly reduced (10).

Current operative methods for treating PJI include debridement, antibiotics and implant retention (DAIR) for acute and acute delayed PJI, whereas chronic PJI is most commonly treated with either a single-stage revision procedure, or the gold standard two-stage revision procedure (11).

According to the Infectious Diseases Society of America (IDSA), the medical treatment following DAIR, one-stage revision, two-stage revision or resection arthroplasty entails the initiation of intravenous (IV) broad-spectrum antibiotics if the microorganism and anti-microbial sensitivities are not known. Once the causative microorganism and anti-microbial sensitivities are known, the treatment can be adjusted accordingly. For *Staphylococcal* PJI, the recommended treatment is two to six weeks of IV antibiotics in combination with oral Rifampicin twice daily (11). The duration of antibiotic therapy is, however, controversial.

A recent paper by Bernard et al. showed that 12 weeks duration of antibiotic therapy was superior to 6 weeks duration (12).

After completion of systemic therapy, antibiotics are stopped for two weeks, which is also commonly known as an antibiotic holiday, whereafter serological markers of inflammation and nutrition are obtained (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and Serum Albumin). In the event that these markers have normalised, the second stage can usually be performed by inserting a new cemented prosthesis (13). IDSA recommends that a suitable oral antibiotic, such as Ciprofloxacin or Levofloxacin, in combination with oral Rifampicin is then used for an additional three months in THA, whereas TKA requires treatment for six months. For non-Staphylococcal PJI, four to six weeks of targeted IV antibiotics or highly bio-available oral antibiotics is recommended (11).

The chances of successful treatment of PJI are greatly increased when the causative microorganism is correctly identified and treated with the appropriate antibiotics. However, in 2 – 36% of cases, the causative microorganism cannot be identified (14). Culture-negative PJI is defined, according to the Musculoskeletal Infection Society criteria, as PJI where no microorganism has been cultured. Hersh et al. performed an observational study on culture-negative PJI treated with irrigation and debridement (I&D). Failure of treatment was defined as the need for any subsequent surgery or a positive culture within two years of the initial I&D. Of these failures, 53.33% became culture-positive. Staphylococcus species were the causative microorganisms in 62.5% of all these cases (15). When the microorganism is unknown, a typical empiric IV antibiotic regimen consists of a Carbapenem and Vancomycin (16,17). This broad-spectrum regimen is aimed at effective coverage of resistant microorganisms.

The most common antibiotics used in antibiotic-loaded cement (ALC) spacers are Gentamycin, Vancomycin, Tobramycin and Clindamycin (18). These antibiotics comply with the pre-requisites of an antibiotic to be used in an ALC spacer: it must be heat stable, hydrophilic, bactericidal and have high elusion rates from polymethyl methacrylate (PMMA) that is maintained above the minimum inhibitory concentration and must be available in powder form. Furthermore, it must be safe at high tissue concentrations and have a broad spectrum of anti-microbial coverage or be effective against the most likely microorganisms involved (19). A typical broad-spectrum mixture can consist of 3g Vancomycin and 2g Gentamycin added to 40g Palacos® cement (13). Examples of commercially available ALC

are Copal® G+C and Copal® G+V from Heraeus medical which consists of 40g PMMA bone cement mixed with 1g Gentamycin and 1g Clindamycin or 0.5g Gentamycin and 2g Vancomycin respectively.

Until now, the epidemiology of PJI in South Africa has not been studied. Local treatment guidelines are derived from international literature and it is unknown if the local microbiological aetiology of PJI is similar to that of the international community.

The primary aim of this study was to determine the most common microorganisms cultured in PJI in a South African clinical setting.

Secondary aims of the study were:

- To describe positive culture results and their local antibiotic sensitivities in order to propose the most appropriate empiric antibiotics to be used in ALC spacers and systemic therapy
- To describe the microorganisms cultured during the first stage versus the second stage in the case of two-stage revision procedures
- To describe the positive bacterial culture results from second-stage procedures and to correlate these results with the ESR/CRP values

Methodology

We performed a retrospective cross-sectional study of all adult patients (18 years of age and older) treated surgically for PJI at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) orthopaedic unit and a private revision arthroplasty practice (Mediclinic Sandton), from 1st January 2015 – 31st March 2020.

Patients treated for infections not related to joint arthroplasty and patients where the microorganisms cultured were described on the microbiology report as likely being a contaminant, were excluded from the study.

Ethics approval was obtained from the University of the Witwatersrand (WITS) Human research ethics committee (HREC) (Medical) for the Johannesburg Orthopaedic hip and knee

databank, as well as the CMJAH hip and knee arthroplasty databanks. (Ethics clearance certificate number: M200838)

Furthermore, permission has been obtained from the Chief executive officers (CEO's) of CMJAH and Mediclinic Sandton, respectively, to conduct research at these facilities

Data were collected from the CMJAH hip and knee arthroplasty databanks, as well as the Johannesburg orthopaedic hip and knee databank. Only data from patients who were diagnosed with PJI were collected. These data included the patients' personal details such as age, gender, type of surgery and stage. The patients' microbiology results, antibiotic sensitivities, as well as their CRP and ESR results were collected from the aforementioned databanks. The data were then captured in a Microsoft Excel® (Microsoft Corp, Redmond, Was) spreadsheet for comparison and statistical analysis. All the patients were assigned to unique participant numbers to maintain confidentiality and anonymity.

The data were then transferred to the Stata version 14.0 statistics software package (Stata Corp, College Station, TX) which was used for data cleaning and analysis.

Descriptive statistics were used to analyse the demographic profile of the participants, common microorganisms, and sensitivities of these microorganisms. These were reported as percentages and frequency.

Inferential statistics was carried out using Pearson's Chi-square test for the following: To compare the number of microorganisms cultured in a public hospital to those cultured in a private hospital; to compare the microorganisms cultured during the first stage *versus* the second stage in cases of two-stage revision procedures; and to correlate the bacterial culture during the second stage with the ESR and CRP result.

P-values < 0.05 were considered significant.

Results

Within our study period, 69 patients met the inclusion criteria; 40 females and 29 males. A Combined total of 101 surgical procedures were performed for PJI, of which 65 were related to knees and 36 to hips (*Figure 1*).

Eight patients underwent a DAIR revision procedure, while 93 staged revision procedures were performed. All staged revision procedures were part of a two-stage technique and no

single stage revisions were done. Of these two-stage procedures, 69 were first-stage and only 24 were second-stage procedures (*Figure 1*). Six patients had one or more repeat first-stage procedure. Only 19 patients completed both their first and second stage revision procedures at our institutions during the specified study period.

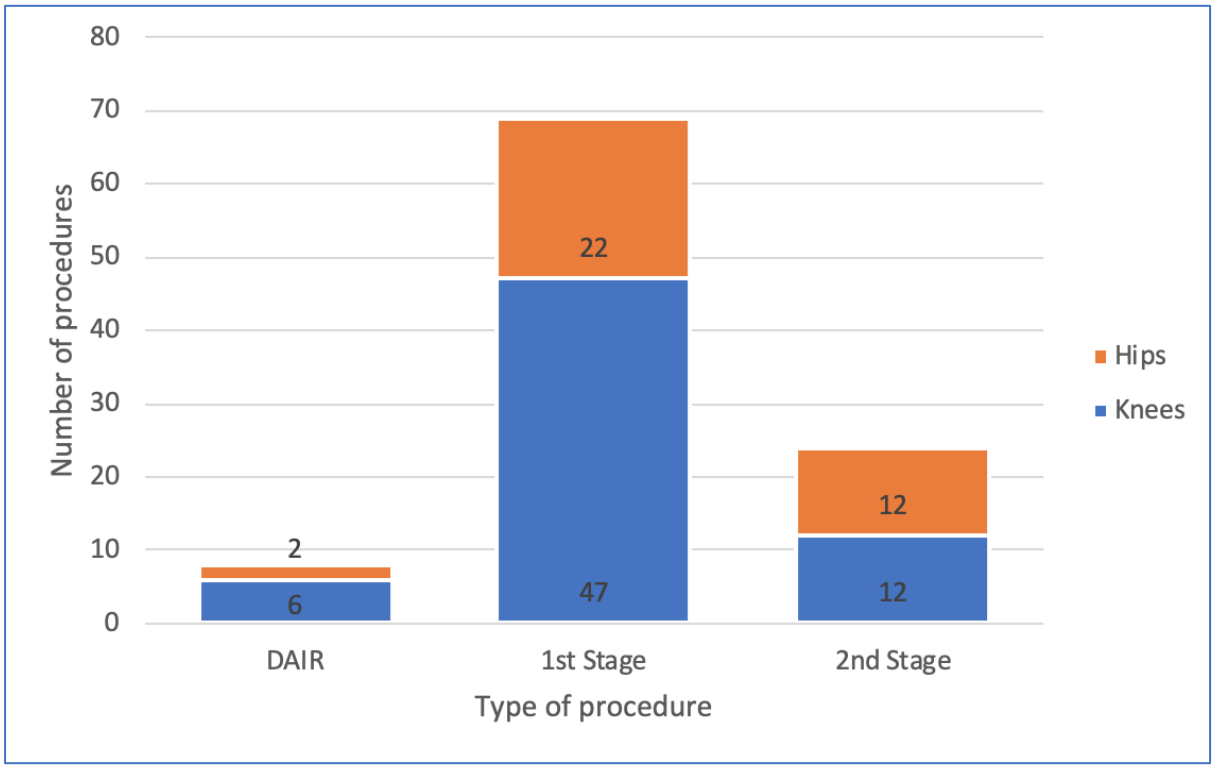


Figure 1. Total surgical procedures performed (*n* = 101)

Of the 101 procedures, 63 had a positive bacterial growth on microscopy, culture and sensitivity (MC+S) and 38 had a negative growth, thus an overall culture-positive yield in our cohort of 62.4%. The majority of the positive bacterial cultures were from first-stage revision procedures (n = 48), whilst second-stage revision procedures yielded 11 positive cultures. DAIR procedures yielded 4 positive cultures. The culture-positive yield for first- and second-stage revision procedures were 69.6% and 45.8%, respectively. DAIR procedures demonstrated a 50% positive yield (n = 4). A total number of 81 microorganisms were cultured from the 63 culture-positive specimens (*Table I*).

Table I: Number and frequency of microorganisms cultured

	Frequency	
	n	**%**
GRAM-POSITIVE		
Staphyloccus aureus	16	19.8
Coagulase negative staphylococcus	16	19.8
Streptococcus viridans	7	8.6
Streptococcus mitis/oralis	2	2.5
Enterococcus feacalis	2	2.5
Streptococcus anginosus	2	2.5
Streptococcus pyogenes	1	1.2
Cutibacterium acnes	1	1.2
Corynebacterium striatum	1	1.2
GRAM-NEGATIVE		
Klebsiella pneumoniae	7	8.6
Escherichia coli	5	6.2
Proteus mirabilis	4	4.9
Enterobacter cloacae	3	3.7
Pseudomonas stutzeri	3	3.7
Acinetobacter baumannii	2	2.5
Klebsiella oxytoca	2	2.5
Acinetobacter radioresistens	1	1.2
Proteus vulgaris	1	1.2
Pseudomonas aeruginosa	1	1.2
FUNGI		
Candida albicans	2	2.5
ANAEROBE		
Prevotella melaninogenica	1	1.2
Enterococcus casseliflavus	1	1.2
TOTAL	81	99.9*

Percentages may not total 100 due to rounding

Gram-positive microorganisms were found in 59.3% (*n* = 48) of cultures *versus* 35.8% (*n* = 29) Gram-negative microorganisms. The remainder were fungal (*n* = 2) and anaerobic microorganisms (*n* = 2) at 2.5%, respectively (*Figure 2*).

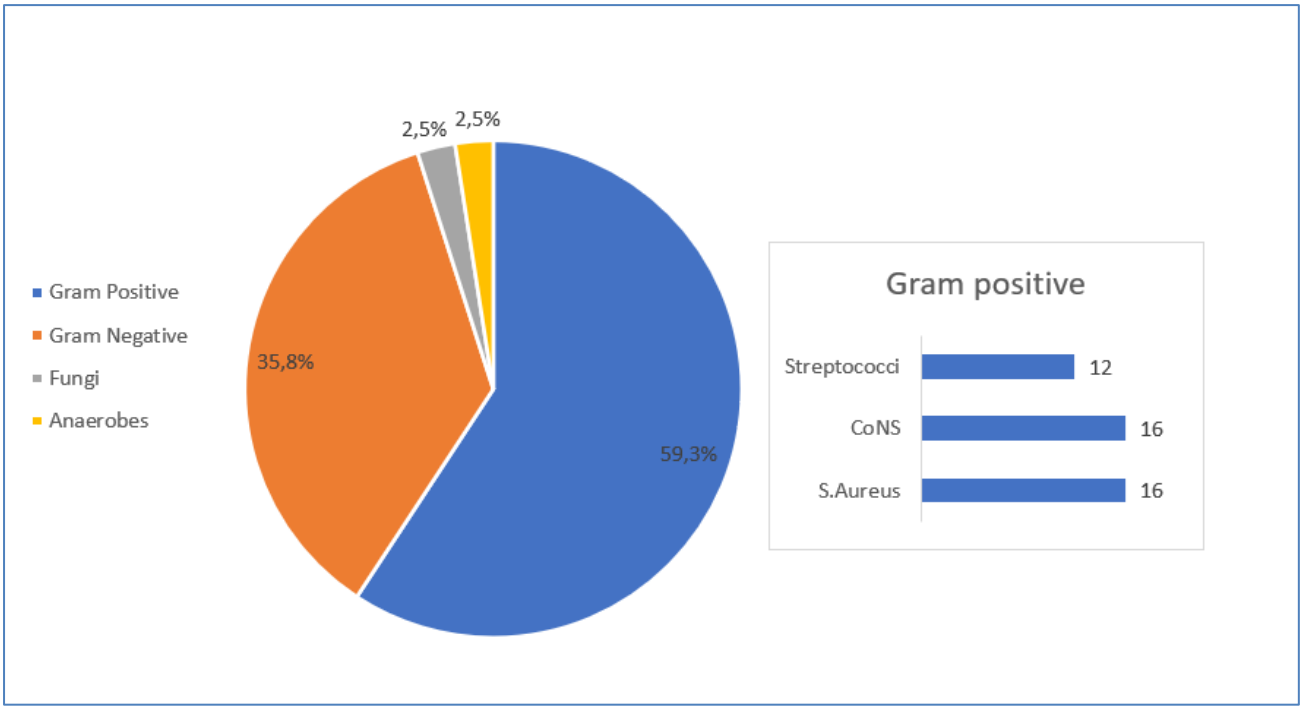


Figure 2. Culture groups and most common microorganisms cultured

Overall, the most common microorganisms cultured were *Staphylococcus aureus (S. aureus)* (*n* = 16, 19.8%) and *Coagulase negative Staphylococcus (CoNS)* (*n* = 16, 19.8%), followed by *Streptococci species (n* = 12, 14.8%).

Of the Gram-negative microorganisms cultured, Klebsiella Pneumoniae was the most prevalent and represented 8.6% (*n* = 7) of all cultures.

Twelve of the samples yielded a polymicrobial growth (19.0%). As depicted in *Table II*, more polymicrobial growth was found in the private sector (*n* = 10) as compared to the public sector (*n* = 2), *p-value* = 0.024. Further logistic regression analysis showed that samples from the private sector were six times more likely to yield a polymicrobial growth compared to the samples from the public sector (Odds ratio 6.1, *p*-value 0.028, 95% CI 1.2 – 30.6).

Table II: Comparing mono-microbial *versus* poly-microbials from public and private hospitals

	Public		**Private**			
	n	**%**	***n***	**%**	**Total**	***p-value***
Number of microorganisms cultured						0.024
Mono-microbial	28	54.9	23	45.1	51	
Poly-microbials	2	16.7	10	83.3	12	

Of the 29 Gram-negative microorganisms cultured, only 11 were tested for Gentamycin sensitivity, of which 81.8% (n = 9) were sensitive and 18.2% (n = 2) were resistant. Amikacin had a similar pattern with 81.3% sensitivity amongst Gram-negative microorganisms tested (*Table III, Figure 3*). Tobramycin sensitivity was only reported in one case, which was a multi-drug resistant strain of Acinetobacter baumannii (A. baumannii) and only sensitive to Colistin. Notably, of the samples tested for Ciprofloxacin sensitivity, a mere 47.4% were sensitive in the Gram-negative cohort.

Meropenem proved to be the most efficacious antibiotic towards Gram-negative microorganisms, with a sensitivity of 88.9% (*Table III, Figure 3*). Again, the two microorganisms that displayed resistance to Meropenem were two multi-drug resistant *A. baumannii* strains.

Table III: Sensitivity profile of Gram-negative microorganisms

Microorganism	**Gentamycin**			**Amikacin**			**Meropenem**			**Ciprofloxacin**	
	Sensitive	Resistant		Sensitive	Resistant		Sensitive	Resistant		Sensitive	Resistant
	n (%)										
Proteus mirabilis	1			1	1		2			1	1
Proteus vulgaris				1			1				
Klebsiella pneumoniae	1	1		5	1		3			2	4
Enterobacter cloacae	1						2			1	
Pseudomonas stutzeri										1	
Acinetobacter baumannii		1			1			2			2
Escherichia coli	3			3			4			1	2
Acinetobacter radioresistens				1			1			1	
Klebsiella oxytoca	2			1			2			2	
Pseudomonas aeruginosa	1			1			1			0	1
TOTAL	**9 (81.8)**	**2 (18.2)**		**13 (81.3)**	**3 (18.7)**		**16 (88.9)**	**2 (11.1)**		**9 (47.4)**	**10 (52.6)**

Note: *This table represents the number of microorganisms that were sensitive or resistant to each antibiotic. One microorganism could display multiple sensitivities and not all microorganisms were tested against all the antibiotics.*

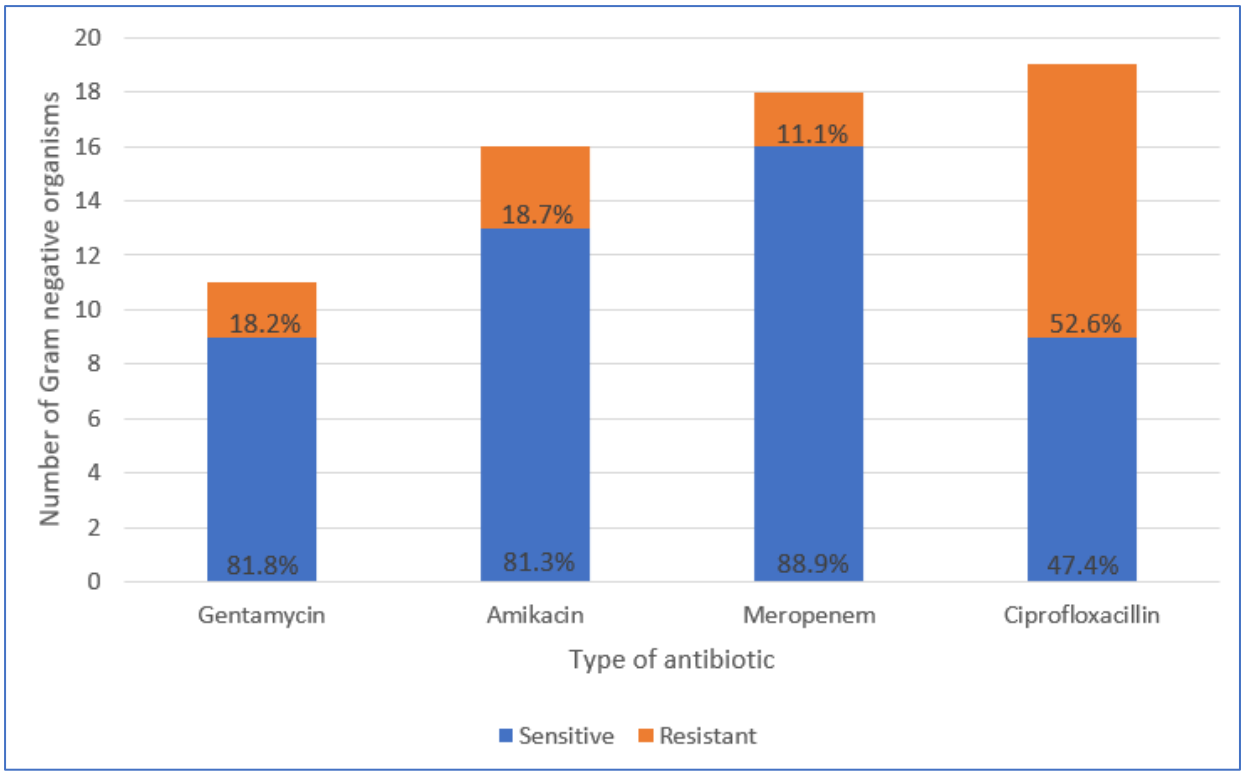


Figure 3. Sensitivity profile for Gram-negative microorganisms

Gram-positive microorganisms displayed 81.8% (*n* = 18) Methicillin sensitivity i.e., towards Cloxacillin (Figure 4), with four microorganisms (*S. aureus* [*n* = 2], *CoNS* [*n* = 2]) showing resistance. Gram-positive microorganisms showed 100.0% sensitivity towards Vancomycin (*n* = 28) and Linezolid (*n* = 20) respectively (*Table IV, Figure 4*).

Table IV: Sensitivity profile of Gram-positive microorganisms

Microorganism	**Cloxacillin**			**Vancomycin**			**Linezolid**		
	Sensitive	**Resistant**		**Sensitive**	**Resistant**		**Sensitive**	**Resistant**	
	n (%)								
Staphylococcus aureus	11	2		6			7		
Streptococcus anginosus	1			1					
Streptococcus mitis/oralis				1					
Streptococcus viridans				6			4		
Enterococcus faecalis				1					
Corynebacterium striatum				1					
Coagulase negative staphylococcus	6	2		12			9		
TOTAL	**18 (81.8)**	**4 (18.2)**		**28 (100.0)**	**0 (0.0)**		**20 (100.0)**	**0 (0.0)**	

Note: *This table represents the number of microorganisms that were sensitive or resistant to each antibiotic. One microorganism could display multiple sensitivities and not all microorganisms were tested against all the antibiotics.*

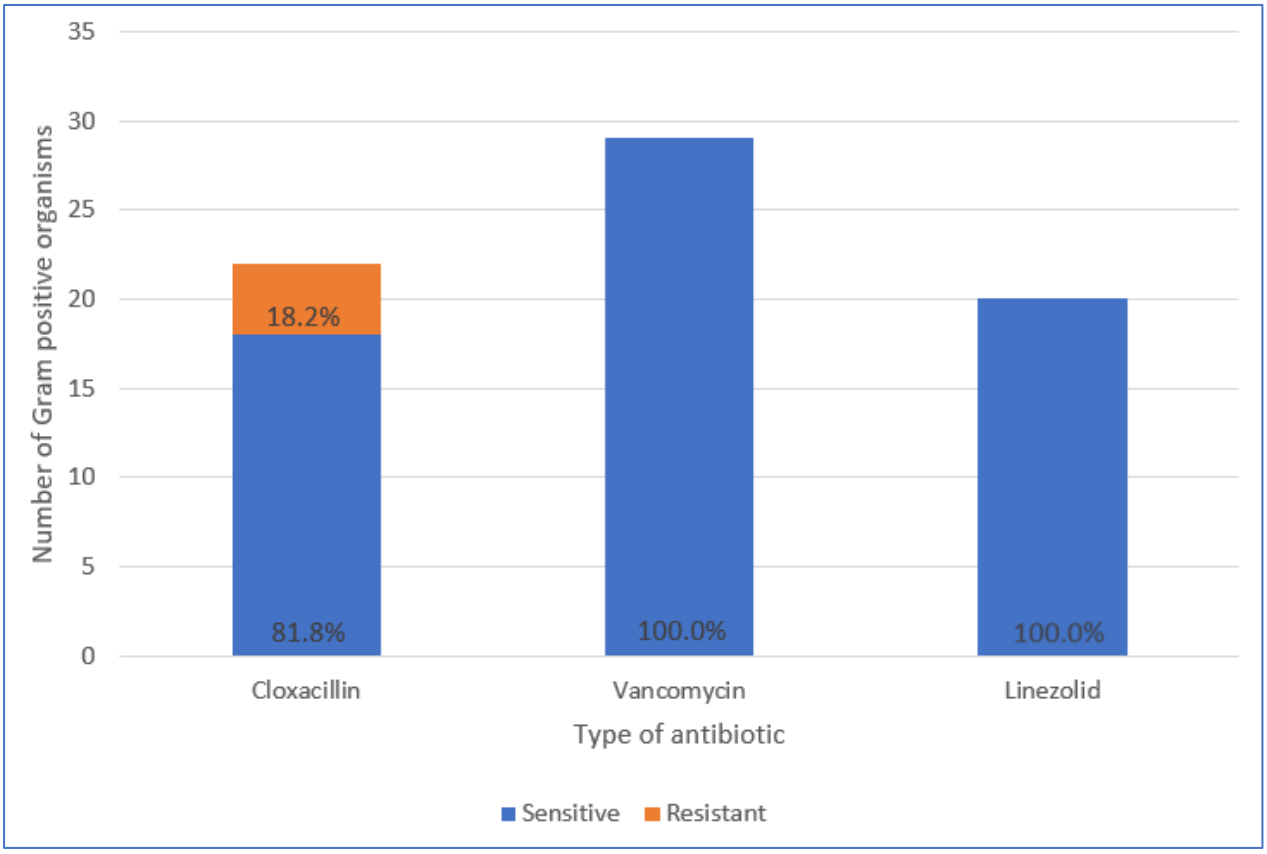


Figure 4. Sensitivity profile for Gram-positive microorganisms

When comparing microorganisms cultured during the first stage *versus* the second stage of the two-stage revision procedures, there was no statistically significant difference (*Table V*).

Table V: Comparison of microorganisms cultured during the 1st stage (*n* = 48) *versus* the 2nd stage (*n* = 11)

	First stage *n* (%)	**Second stage *n* (%)**	***p-value***
Gram-Positive			
Staphylococcus aureus			0.091
Not cultured	38 (86.4)	6 (13.6)	
Cultured	10 (66.7)	5 (33.3)	
Coagulase negative staphylococcus			1.000
Not cultured	36 (80.0)	9 (20.0)	
Cultured	12 (85.7)	2 (14.3)	
Streptococcus viridans			0.582
Not cultured	42 (79.3)	11 (20.8)	
Cultured	6 (100.0)	0 (0.0)	
Streptococcus mitis/oralis			0.341
Not cultured	47 (82.5)	10 (17.5)	
Cultured	1 (50.0)	1 (50.0)	
Enterococcus faecalis			1.000
Not cultured	46 (80.7)	11 (19.3)	
Cultured	2 (100.0)	0 (0.0)	
Streptococcus anginosus			1.000
Not cultured	47 (81.0)	11 (19.0)	
Cultured	1 (100.0)	0 (0.0)	
Cutibacterium acnes			0.186
Not cultured	48 (82.8)	10 (17.2)	
Cultured	0 (0.0)	1 (100.0)	
Corynebacterium striatum			1.000
Not cultured	47 (81.0)	11 (19.0)	
Cultured	1 (100.0)	0 (0.0)	
Gram-Negative			
Klebsiella pneumoniae			1.000
Not cultured	42 (80.8)	10 (19.2)	
Cultured	6 (85.7)	1 (14.3)	
Enterobacter cloacae			1.000
Not cultured	46 (80.7)	11 (19.3)	
Cultured	2 (100.0)	0 (0.0)	
Acinetobacter baumannii			1.000
Not cultured	46 (80.7)	11 (19.3)	
Cultured	2 (100.0)	0 (0.0)	
Escherichia coli			1.000
Not cultured	43 (81.1)	10 (18.9)	
Cultured	3 (75.0)	1 (25.0)	

Pseudomonas stutzeri			0.468
Not cultured	46 (82.1)	10 (17.9)	
Cultured	2 (66.7)	1 (33.3)	
Acinetobacter radioresistens			1.000
Not cultured	47 (81.0)	11 (19.0)	
Cultured	1 (100.0)	0 (0.0)	
Klebsiella oxytoca			0.341
Not cultured	47 (82.5)	10 (17.5)	
Cultured	1 (50.0)	1 (50.0)	
Pseudomonas aeruginosa			1.000
Not cultured	47 (81.0)	11 (19.0)	
Cultured	1 (100.0)	0 (0.0)	
Fungus			
Candida albicans			1.000
Not cultured	46 (80.7)	11 (19.3)	
Cultured	2 (100.0)	0 (0.0)	

Of the 19 patients who completed both stages of their two-stage revision procedures during the specified study period, 8 yielded a culture-positive specimen during the second-stage. Six of these 8 patients cultured different microorganisms during the first stage *versus* the second stage, with the remaining two patients showing recurrent growth of the same microorganism.

We also found no correlation between the ESR/CRP level and the microorganism cultured during the second stage (p = 1.000).

Of the 11 culture-positive second-stage procedures, eight CRP results and five ESR results were available (*Table VI*). Of the available results, the CRP results were abnormal (>10mg/l) in 7 (87.5%) of the 8 patients, and the ESR results were abnormal (>30mm/hr) in 4 (80.0%) of the 5 patients.

Table VI: Comparison of ESR and CRP results in culture-positive first-stage and second-stage procedures

	First-stage *n* (%)	**Second-stage *n* (%)**	***p*-value**
ESR			1.000
Normal (<30mm/hr)	8 (34.8)	1 (20)	
Abnormal (≥30mm/hr)	15 (65.2)	4 (80)	
CRP			1.000
Normal (<10mg/l)	6 (20.7)	1 (12.5)	
Abnormal (≥10mg/l)	23 (79.3)	7 (87.5)	

Discussion

Multiple international studies have established the commonly isolated microorganisms in PJI. Throughout these studies *S. aureus* has been the most prevalent microorganism, followed by *CoNS* and *Streptococci* (16,19 - 22). In keeping with the international literature, we have found the Gram-positive microorganisms (*S. aureus*, *CoNS* and *Streptococci species*) to be the most prevalent followed by the Gram-negative *Klebsiella pneumoniae.*

We have found a 2.5% incidence of fungal growth with Candida albicans being the only fungus cultured (n = 2). Internationally, the incidence is reported to be between one and three percent with Candida albicans also being the most common (23-26). Although rare, there is an increase in fungal PJI worldwide and these infections are particularly difficult to treat with high failure rates (27). This is partly due to the fact that fungi form a very complex biofilm and also because these patients are usually immunocompromised (28).

Anti-microbial resistance is of great concern in PJI and the medical fraternity as a whole (29). Internationally there is a rise in anti-microbial resistance, which may require a change in the choice of antibiotics used (30,31). This change in empiric antibiotic therapy should, however, be made with antibiotic stewardship in mind (32). The incidence of Methicillin resistance varies greatly in the literature (19–22). In a study by Peel et al. conducted in Australia, almost half of the *S. aureus* isolates were Methicillin resistant which was also in keeping with an American study done by Pulido (20,21). Benito found a 28% Methicillin resistance amongst *S. aureus* PJI (16). Another study conducted by Moran et al. in the United Kingdom had just over 15% incidence of Methicillin resistance amongst their *S. aureus* isolates (16). This is also in keeping with our findings of 18.8% Methicillin resistance. None of the Gram-positive isolates showed resistance to Vancomycin.

With regards to Gram-negative microorganisms, Gentamycin sensitivity was 81.8%. Interestingly, we have observed a significant resistance towards Ciprofloxacin by Gram-negative microorganisms of 47.4%. This might be a significant finding, as Ciprofloxacin is a commonly used antibiotic for enteral continuation therapy in PJI, due to its favourable reduction in biofilm production (33). Meropenem had the best sensitivity profile against Gram-negative microorganisms of 88.9%. Meropenem is a suitable antibiotic for use in ALC spacers because it comes in powder form, is heat stable and has good elusion characteristics (34,35). Meropenem might thus be the antibiotic of choice for empiric Gram-negative coverage.

An increased ESR/CRP result at the time of the second-stage revision procedure has been associated with an increased reinfection rate (36). A normal ESR/CRP result, however, does

not always exclude PJI (37). We thus tried to determine whether certain microorganisms were more likely to be cultured with a normal ESR/CRP result during the second-stage of two-stage revision procedures. We could not find any correlation in our study. However, due to our small sample size, we cannot make any conclusion in this regard and further research is needed. Despite this, we still support and recommend a 2-week antibiotic holiday, followed by a repeat joint aspiration and tissue biopsy prior to commencing the second stage.

Furthermore, in cases of two-stage revision procedures, there was also no statistically significant difference between microorganisms cultured during the first stage *versus* microorganisms cultured during the second stage.

The culture-negative PJI rate in our study was 37.6%, which is slightly higher than the expected range reported in the literature of 2–36% (14). The high culture-negative rate could possibly be due to an inadequate number of specimens; the use of a suboptimal culture medium in specimens taken for MC+S during surgery; or antibiotic therapy initiated by referring physicians prior to sampling. It is recommended that at least three, but ideally five to six, tissue samples be taken during surgery for MC+S to increase the chances of a positive yield (11). We would like to emphasise the importance thereof to increase the culture-positive yield.

When looking at the culture-positive yield during second-stage procedures, it was found to be 45.8% (*n* = 11), which is much higher than the incidence (12-25%) reported in the literature (38-40). There could be many contributing factors to this finding. One reason could be that the microorganisms cultured during the second stage were skin contaminants i.e., *S. aureus* which was the most common microorganism cultured in our cohort. Another possible reason could be that the infection was not completely eradicated by the time of re-implantation. This was, however, not the case in our study as there was no statistically significant correlation between microorganisms cultured during the first *versus* the second stage procedures (Table V).

When comparing the samples cultured in different laboratories, samples cultured in the private laboratories were six times more likely to result in a polymicrobial growth than microorganisms cultured in the government laboratory. The reasons for this discrepancy are unknown and will need further investigation and research; however, we postulate that this finding could possibly be due to a shorter incubation time in the government laboratories due to systemic constraints, whereas longer incubation times are common practice in private laboratories. Differences in sampling protocols between institutions, i.e., the number of samples taken for MC+S and the culture medium that samples are sent in to the laboratory may, once again, explain this finding.

According to our knowledge, this is the first study on the bacteriology and the characteristics of PJI in South Africa. This study has, however, a few limitations. One of the limitations of our study was the small sample size, which might compromise statistical significance. Despite the small sample size, however, our findings were still very similar to international studies with much larger cohorts. Another limitation was the low number of patients that completed both stages of their two-stage revision procedures during the study period (n = 19, 27.5%). This might be attributed to patients receiving their first-stage revision procedures before the specified study period (cross-sectional nature of the study); or at a different institution before being referred to our institutions for their second-stage procedures; or the incomplete capturing of data in our data banks.

Due to these limitations, we believe that there is definitely a need for future research on PJI and antibiotic sensitivity in South Africa with larger sample sizes. We recommend that laboratories adopt a standard set of antibiotics to test sensitivities of PJI microorganisms against, as we have found that many microorganisms were not tested for sensitivity against the most commonly used antibiotics in ALC spacers (18). One such example is Tobramycin, where only one Gram-negative microorganism was tested against, out of a possible 29. We further recommend that Ceftazidime/ Avibactam, Linezolid, Tigecycline and Rifampicin be tested in addition to the standard battery of antibiotics for PJI.

Conclusion

According to our results and findings, we recommend that empiric ALC spacers and empiric IV antibiotic regimens should consist of Meropenem or Gentamycin; Vancomycin and Rifampicin to achieve the broadest spectrum coverage and most likely success in eradicating infection. We believe that knowing the bacteriology profiles in your demographic area is of utmost importance because of the high culture-negative yield rate from culture specimens in PJI, in which case empiric antibiotic strategies should be implemented.

Author contributions

Dr Hiddema: Substantial contributions to the conception and design of the work, and the acquisition, analysis and interpretation of data for the work, drafting the work and revising it critically for important intellectual content. Drs Sekeitto and du Toit: Substantial contributions to the conception and design of the work, and the acquisition, analysis and interpretation of data for the work and revising it critically for important intellectual content. Prof Van der Jagt: Substantial contributions to study conceptualisation and design and data collection and contribution.

Conflict of interest

The authors declare they have no conflicts of interest that are directly or indirectly related to the research.

Ethics statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

For this study formal consent was not required.

Funding sources

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Appendices

Appendix A: Data collection sheet

Appendix B: Ethics clearance certificate

Appendix C: CEO permission letters

Appendix D: Journal guidelines (SAOJ)

Appendix E: Student's contribution to the research and writing of the "submissible" paper

Appendix F: Databanks Permission letters

Appendix G: Plagiarism/turn-it-in report cover page

Appendix H: Research protocol

Appendix A: Data Collection sheet

PJI data collection form

Hospital:

Patient Name:	Study nr:	Age:	Sex:	Comorbidities:	Procedure:	Proc. date:	Cult type:	Cult. Date:	Stage:	Pathogen:	Sensitivity:	CRP:	ESR:

Appendix B: Ethics clearance certificate

UNIVERSITY OF THE
WITWATERSRAND
JOHANNESBURG

R14/49 Drs J Hiddema and J du Toit

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M200838

NAME: (Principal Investigator)	Drs J Hiddema and J du Toit
DEPARTMENT:	School of Clinical Medicine Department of Surgery Division of Orthopaedic Surgery Medical School University
PROJECT TITLE:	Peri-prosthetic joint infection: A South African perspective
DATE CONSIDERED:	2020/08/28
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Professor R Van der Jagt and Dr A Sekeitto
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2020/10/20

This clearance certificate is valid for 5 years from the 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 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
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 submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **August** and will therefore reports and re-certification will be due early in the month of **August** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

25/10/2020
Date

Appendix C: CEO Permission letters

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Ms. X Dhlamini
Office of the Clinical Director
Email: xolisane.dhlamini@gauteng.gov.za
Tel: (011): 488-3710
18 June 2020

Dear Dr J Hiddema

STUDY TITLE: Peri- Prosthetic joint infection: A South Africa perspective

Permission to conduct the above-mentioned study is provisionally approved. Your study can only commence once Ethics approval is obtained. Please forward a copy of your Ethics Clearance Certificate as soon as the study is approved by the Ethics Committee for the CEO's office to give you the final approval to conduct the study.

Supported / not supported

Dr. PN Africa
Acting Clinical Director
DATE: 19/06/2020

Approved / not approved

Ms. G. Bogoshi
Chief Executive Officer
DATE: 30.06.2020

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Our ref: Final approval 25 (25)

04 November 2020

Dr JS Hiddema
7 Zambesi Road
Emmerentia
Randburg
2195

E-mail: jshiddema@gmail.com

Dear Dr Hiddema

PERMISSION TO CONDUCT RESEARCH AT MEDICLINIC SANDTON

Your research proposal entitled "*Peri-prosthetic joint infection: A South African perspective*" refers.

It is in order for you to conduct your research at Mediclinic Sandton.

I wish you success with this project and we look forward to sharing in the results of your research.

Yours sincerely

Estelle Coustas

DR ESTELLE COUSTAS
Nursing Executive

Appendix D: Journal guidelines (SAOJ)

Instructions for Authors

Authors submitting articles for consideration for publication by the journal are required to familiarise themselves with the journal Ethics and Malpractice policy prior to submission. The policy is available on the journal website: https://www.saoj.org.za

Criteria for publication

- The article falls within the scope of the journal.
- Methods, statistics, and other analyses are performed to a high technical standard and are described in sufficient detail.
- Results reported have not been published elsewhere.
- Conclusions are presented appropriately fashion and are supported by the data.
- The article is presented in an intelligible fashion and is written in standard English (British usage).
- The research meets all applicable ethical standards.
- The article adheres to guidelines provided in the instructions for authors section.

Guidelines for authorship

- Each author should participate and is responsible for the content and design of the study, the preparation of the manuscript and its revisions, and final approval.
- In order to qualify for authorship, authors should satisfy all four the criteria for authorship as specified by the ICMJE:
    1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
    2. Drafting the work or revising it critically for important intellectual content; AND
    3. Final approval of the version to be published; AND
    4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- Other ‘contributors’ or ‘collaborators’ can be acknowledged at the end of the manuscript together with their contribution. Those whose contributions do not justify authorship may be acknowledged individually or together as a group under a single heading (e.g., “Clinical Investigators” or “Participating Investigators”), and their contributions should be specified (e.g., “served as scientific advisors,” “critically reviewed the study proposal,” “collected data,” “provided and cared for study patients”, “participated in writing or technical editing of the manuscript”.
- The South African Orthopaedic Journal accepts a maximum of 8 authors per article. If there are more than eight authors, the first eight authors must be listed along with the group name at the end. The remaining authors and their affiliations must then be listed in an appendix.

- On submission of your article, the ORCID (Open Researcher and Contributor ID) identifier of at least the corresponding author will be required. ORCID provides a persistent digital identifier that distinguishes you from every other researcher and supports automated linkages between you and your professional activities, ensuring that your work is recognised. To register and find more information, please visit: http://orcid.org

Registration of clinical trials

- A clinical trial is defined as any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects of health outcomes. Interventions include drugs, surgical procedures, devices, behavioural treatments, dietary interventions, and process-of-care changes.
- Clinical trials should be registered in a public trials registry in accordance with International Committee of Medical Journal Editors
- Trials must be registered and approved by the relevant authorities before the onset of patient enrolment.
- The Medicines Control Council (MCC) reference number and the SA National Clinical Trial Register (SANCTR) registration number should be included at the end of the abstract of the article.
- Purely observational studies (those in which the assignment of the medical intervention is not at the discretion of the investigator) do not require registration.

Reporting guidelines

- All articles should be prepared in accordance with the guidelines relevant to the study design, as described in the Equator Network Guidelines (https://www.equator-network.org/reporting-guidelines/)
- Randomised trials should be accompanied by a flow diagram that illustrates the progress of patients through the trial, including recruitment, enrolment, randomisation, withdrawal and completion, and a detailed description of the randomisation procedure.

Reporting of statistics

In terms of the statistical reporting, the Equator Network advises on the use of the SAMPL guideline: https://www.equator-network.org/2013/02/11/sampl-guidelines-for-statistical-reporting/

The SAMPL guidelines provide two guiding principles

1. *"Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results."* When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as *P* values, which fail to convey important information about effect size.

2. *Provide enough detail that the results can be incorporated into other analyses.* This requires reporting the descriptive statistics from which other statistics are derived, such as the numerators and denominators of percentages, especially in risk, odds, and hazards ratios. Likewise, P-values are not sufficient for re-analysis. Needed instead are descriptive statistics for the variables being compared, including sample size of the groups involved, the estimate (or effect size) associated with the P-value, and a measure of precision for the estimate, usually a 95% confidence interval.

Some specific guidelines applicable to the SAOJ:

- Consistency is one of the most important factors in presenting a well-formatted, professional manuscript.
- The nature of the measurements and variables reported on will often dictate the amount of precision required. Report numbers - especially measurements? with an appropriate degree of precision. For ease of comprehension and simplicity, round to a reasonable extent.
- The recommendation is to report the number of decimals that have both clinical and statistical meaning and consistently reporting all other variables in the same manner.
- Note: Generally, for descriptive purposes, percentages are reported as whole numbers except when dealing with really large sample sizes
- At least for the primary outcomes, report a measure of precision (a confidence interval).
- Although not preferred to confidence intervals, if desired, *p* values should be reported as equalities to three decimal places (e.g., $p = 0.031$ and not as inequalities: e.g., $p < 0.05$). Do NOT report NS; give the actual *P-value*. The smallest *P*-value that needs to be reported is $P < 0.001$.
- Report numerators and denominators for all percentages
- Summarize data that are approximately normally distributed with means and standard deviations (SD). Use the format: mean (SD) not mean ?
- Summarize data that are not normally distributed with medians and interpercentile ranges, ranges, or both.
- Do NOT use the standard error of the mean (SE) to indicate the variability of a data set. Use standard deviations, inter-percentile ranges, or ranges instead.

Formatting examples:

- $p = 0.028$ or $p < 0.001$
- (43% vs 21%; $p = 0.002$)
- (odds ratio (OR) 0.38; 95% confidence interval (CI) 0.71 to 1.82; $p = 0.822$) or after first use (OR 1.62; 95% CI 1.41 to 1.86; $p < 0.001$)
- *Descriptive stats normal distribution:* mean age 36 years (SD 4 years) or 36 years (SD 4; range 40 to 97 years)
- *Descriptive stats non-normal distribution:* median age 36 years (IQR 44 to 88 years) or 36 years (IQR 44 to 88 years; range 40 to 97 years)
- *Descriptive stats percentage:* (149 of 202; 74%)

Formatting of submissions

Text formatting

- Use Helvetica or Arial font, size 11.
- Use double line spacing throughout the document.
- Number the pages of the blinded manuscript consecutively.
- Use italics for emphasis.
- When referring to an article with multiple authors, please use the following format: Rabinowitz et al. published their retrospective review.
- Do not use field functions.
- Use tab stops or other commands for indents, not the space bar.
- Use the table function, not spreadsheets, to make tables.
- Use the equation editor or MathType for equations.
- Save your file in docx format (Word 2007 or higher) or doc format (older Word versions).

Headings

- Use no more than three levels of displayed headings.

Abbreviations

- Define abbreviations and acronyms at first mention and use consistently thereafter.

Units

- Follow internationally accepted rules and conventions: use the international system of units (SI). If other units are mentioned, please give their equivalent in SI.

Figures

- Figures should be numbered consecutively with illustration Arabic numbers 1, 2, 3, etc.
- The figure should be listed in the text as follows: … wound irrigation and splinting (*Figure 1*).
- Figures should be clear and easily understandable with a full descriptive legend stating any areas of interest and explaining any markings, letterings or notations. All figures and figure legends should be understandable as a stand-alone item, without having to read the main body of the text.
- For radiographs, please ensure you state the view used and the time point at which it was taken, as well as the demographic details of the patient if applicable.
- Please submit the original JPEG (300 dpi) or TIFF of all photographs, as well as the figure saved as a Word document. The Word version of the figure should be complete with the legend and any necessary markings such as letters or arrows.
- Figures such as graphs and algorithms should be in Word or PowerPoint in order to be editable.

- Figures should not be imbedded in the text file but should be submitted as separate individual files. Each figure should be a separate file, entitled Figure 1, Figure 2, etc.
- Remove all markings, such as patient identification, from radiographs before photographing. Clinical photos must be adequately anonymised.
- A statement of patient consent for clinical photographs must be provided on the title page.
- In images depicting X-rays of children there should exhibit adequate shielding of radiation.
- All line or original drawings must be done by a professional medical illustrator.
- We accept a maximum of six figures. You may apply to the Editor-in-Chief for permission to include more figures if considered critical to the clarity and completeness of the submission.
- Do not submit any figures, photos, tables, or other works that have been previously copyrighted or contain proprietary data unless you have obtained and can supply written permission from the copyright holder to use that content.

Tables

- Tables should carry uppercase Roman numerals, I, II, III, etc.
- Tables should always be cited in the text in consecutive numerical order.
- The table should be identified in the text as follows: Details of results are listed in *Table I*. Or, alternatively,? high-energy trauma that is often associated with these fractures (*Table II*).
- Tables should be used to present information in a clear and concise manner. All tables should be understandable without the main text.
- For each table, please supply a table heading explaining the components of the table.
- Identify any previously published material by giving the original source in the form of a reference at the end of the table heading.
- Footnotes to tables should be indicated by superscript lower-case letters and included beneath the table body.
- Please submit tables as editable text and not as images. They should be created using the Table tool in Word.
- Do not embed tables in the text file but submit them as separate individual files. Each table should be a separate file, entitled Table I, Table II, etc.
- We accept a maximum of eight tables.
- Do not duplicate information given already in the text.
- Do not submit any figures, photos, tables or other works that have been previously copyrighted or contain proprietary data unless you have obtained and can supply written permission from the copyright holder to use that content.

References

- References should be numbered consecutively in the order that they are first mentioned in the text and listed at the end in numerical order of appearance.

- Identify references in the text by Arabic numerals in superscript after punctuation.
- References should not be a listing of a computerised literature search but should have been read by the authors and have pertinence to the manuscript.
- Accuracy of references is the authors' responsibility, and the author is to verify the references against the original documents.
- Manuscripts in preparation, unpublished data (including articles submitted but not in the press) and personal communications may not be included in the reference listing. They may be listed in the text in parentheses only if absolutely necessary to the contents and meaning of the article.
- The titles of journals should be abbreviated according to the style used in Index Medicus, obtainable through the website http://www.nlm.nih.govshould
- The following format should be used for references:

Journal article:

Sidhu GS, Ghag A, Prokuski V, Vaccaro AR, Radcliff KE. Civilian gunshot injuries of the spinal cord: a systematic review of the current literature. *Clin Orthop Relat Res* 2013;**471**:3945-55.

Ideally, the names of all authors should be provided, but the usage of *et al*. in long author lists (more than six authors) will also be accepted: Fong K, Truong V, Foote CJ, *et al*. Predictors of nonunion and reoperation in patients with fractures of the tibia: an observational study. *BMC Musculoskelet Disord* 2013;**14**:103.

Online journal article:

Caetano-Lopes J, Lopes A, Rodrigues A, *et al*. Upregulation of inflammatory genes and downregulation of sclerostin gene expression are key elements in the early phase of fragility fracture healing. *PLoS One* 2011;**6**:e16947.

Web reference (with authors):

Cierny G, DiPasquale D. Adult osteomyelitis protocol. http://www.osteomyelitis.com/pdf/treatment_protocol.pdf.

(date last accessed 05 March 2013).

Web reference (no authors listed):

No authors listed. International commission on radiological protection. http://www.icrp.org (date last accessed 20 September 2009).

Chapter in a book:

Young W. Neurophysiology of spinal cord injury. In: Errico TJ, Bauer RD, Waugh T (eds). *Spinal Trauma*. 3rd ed. Philadelphia: JB Lippincott; 1991: 377-94.

Dissertation:

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

Abstract:

Peterson L. Osteochondritis of the knee treated with autologous chondrocyte transplantation [abstract]. ISAKOS Congress, 2001.

Structure and content of submission

- We accept a maximum of 3 500 words, including the abstract and body of the text (excluding references).
- Exceptions to this rule may be made for systematic reviews and meta-analysis at the discretion of the Editor-in-Chief.
- Please follow the following structure when preparing your submission. Each of the following should be submitted as a separate file.
- Title page (title, authors and affiliations, corresponding author and declarations)
- Blinded manuscript (Abstract, keywords, introduction, methods, results, discussion, funding sources, conflict of interest statement, ethics statement, acknowledgements and references)
- Tables (with headings), each table as a separate file.
- Figures (with legends), each figure as a separate file.

Title page

Title

- The title should be concise and informative.

Author names and affiliations

- Please provide the following information for each author:
    - Full names and surname, as well as title
    - Qualifications
    - Designation
    - Affiliation and address
    - ORCID ID (see Article Submission section)
- Please check that all names are accurately spelled.
- Indicate all affiliations with a lower-case superscript letter immediately after the author's name and in front of the appropriate affiliation details.
- Provide the full postal address of each affiliation, including the country name and, if available, the e-mail address of each author.

Corresponding author

- Clearly indicate who will handle correspondence at all stages of refereeing and publication, including post-publication.

- Ensure that the e-mail address and permanent address is given and that contact details are kept up to date by the corresponding author.
- Please note that the corresponding author's contact details will be provided in the final article.
- Provide the following information for the corresponding author:
    - Full names and title
    - Affiliation
    - Physical address
    - Postal address
    - Telephone number
    - E-mail address

Declarations

Authors are to insert a section at the end of the title page entitled declarations (please provide the author's name, signature and date). The following statements are required under the declarations section:

Authorship

The authors confirm that all authors have made substantial contributions to all of the following:

- The conception and design of the study, or acquisition of data, or analysis and interpretation of data.
- The drafting of the article or its critical revision for important intellectual content.
- Final approval of the version to be submitted.

Sound scientific research practice

The authors further confirm that:

- The manuscript, including related data, figures and tables, has not been previously published and is not under consideration elsewhere.
- No data have been fabricated or manipulated (including images) to support conclusions.
- This submission does not represent part of a single study that has been split up into several parts to increase the quantity of submissions and submitted to various journals or to one journal over time (e.g. 'salami-publishing').

Plagiarism

The authors confirm that the work submitted is original and does not transgress the plagiarism policy of the journal.

- No data, text or theories by others are presented as if they were the authors' own.

- Proper acknowledgements of others' work have been given (this includes material that is closely copied, summarised and/or paraphrased); quotation marks are used for verbatim copying of material.
- Permissions have been secured for copyrighted material.

Conflict of interest statement

A conflicting interest exists when professional judgment concerning a primary interest (such as the patient's welfare or the validity of research) may be influenced by a secondary interest (such as financial gain or personal rivalry). It represents a situation in which financial or other personal considerations from authors, reviewers or editors have the potential to compromise or bias professional judgment and objectivity. It may arise for the authors when they have a financial interest that may influence their interpretation of their results or those of others. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, grants or other funding. All potential conflicts of interest need to be declared. The conflict of interest statement should list each author separately by name, e.g.,

'Author A.B. (*use initials of relevant author, not full name in order for the document to remain blinded*) has received research grants from Company A. Author B.C. has received a speaker honorarium from Company X and owns stock in Company Y. Author C.D. is a member of committee Z.'

If no conflicts of interest exist, state this as follows:

'The authors declare they have no conflicts of interest that are directly or indirectly related to the research.'

Funding sources

All sources of funding should be declared. Also, define the involvement of study sponsors in the study design, collection, analysis and interpretation of data; the writing of the manuscript; and the decision to submit the manuscript for publication.

List all funding sources as follows:

'This work was supported by the xxxx (grant numbers xxxx, yyyy).'

When funding is from a block grant or other resources available to a university, college or other research institution, submit the name of the institute or organisation that provided the funding.

If no funding was received, state as follows:

'No funding was received for this study.'

Compliance with ethical guidelines

- For all publications:

‘The author/s declare that this submission is in accordance with the principles laid down by the Responsible Research Publication Position Statements as developed at the 2nd World Conference on Research Integrity in Singapore, 2010.’

Available from: http://publicationethics.org/resources/international-standards-for-editors-and-authors

Institutional Review Board (IRB) ethical approval must have been given if the study involves human subjects or animals. Please provide the approval number. IRB documentation should be available upon request.

‘Prior to the commencement of the study ethical approval was obtained from the following ethical review board: *Provide name and reference number’*

- For studies with human subjects include the following:

‘All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.’

‘Informed written consent was or was not obtained from all patients for being included in the study.’

‘Consent was obtained from patients for the use of clinical photographs and these images were adequately anonymised.'

- For studies with animals, include the following sentence:

‘All institutional and national guidelines for the care and use of laboratory animals were followed.’

- For articles that do not contain studies with human or animal subjects:

‘This article does not contain any studies with human or animal subjects.’

- If doubt exists whether the research was conducted in accordance with the Helsinki Declaration, the authors must explain the rationale for their approach and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study. If any identifying information about patients is included in the article, the following sentence should also be included: Additional informed consent was obtained from all patients for which identifying information is included in this article. The Helsinki Declaration 2008 can be found at http://www.wma.net/en/30publications/10policies/b3/

Please provide the names and email addresses of two reviewers.

Title Page Example

Title of Submission

John Smith*

MBChB, FC Orth SA, MMed (Ortho)

University of South Africa, 123 High Street, Pretoria

ORCID ID 1234-1234-1234-1234

Paula Taylor

MBChB, FC Orth SA

University of South Africa, 123 High Street, Pretoria

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University of South Africa

123 High Street, Waterkloof, Pretoria, South Africa, 0001

POBOX 1001, Waterkloof, Pretoria South Africa, 0001

Tel: 012 123 4567

e-mail: johnsmith@unisa.ac.za

Declarations:

Authorship

The authors confirm that all authors have made substantial contributions to all of the following:

- The conception and design of the study, or acquisition of data, or analysis and interpretation of data.
- The drafting of the article or its critical revision for important intellectual content.
- Final approval of the version to be submitted.

Sound scientific research practice

The authors further confirm that:

- The manuscript, including related data, figures and tables, has not been previously published and is not under consideration elsewhere.
- No data have been fabricated or manipulated (including images) to support conclusions.
- This submission does not represent part of a single study that has been split up into several parts to increase the quantity of submissions and submitted to various journals or to one journal over time (e.g. 'salami-publishing').

Plagiarism

The authors confirm that the work submitted is original and does not transgress the plagiarism policy of the journal.

- No data, text or theories by others are presented as if they were the authors' own.
- Proper acknowledgements of others' work have been given (this includes material that is closely copied, summarised and/or paraphrased); quotation marks are used for verbatim copying of material.
- Permissions have been secured for copyrighteed material.

Conflict of interest statement

John Smith declares that he has no conflict of interest. Paula Taylor has received research grants from Drug Company A.

Funding sources

No funding was received for the purposes of performing this study.

Compliance with ethical guidelines

The author/s declare that this submission is in accordance with the principles laid down by the Responsible Research Publication Position Statements as developed at the 2nd World Conference on Research Integrity in Singapore, 2010.

Prior to the commencement of the study ethical approval was obtained from the following ethical review board: *Provide name and reference number.*

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Informed written consent was or was not obtained from all patients for being included in the study.

Consent were obtained from patients for the use of clinical photographs/ and these images were adequately anonymised.

Author Name **Signature** **Date**

J Smith	15/8/2017
P Taylor	16/8/2017

Blinded manuscript

To ensure a blinded review, the main body of the manuscript should not contain any identifying information, including author's names, institutions or affiliations. Please do not include the name of the ethics committee, this information should be provided in the title page.

Abstract

- A structured abstract (maximum of 350 words) summarising the most important points in the article is required.
- The abstract consists of four paragraphs with the subheadings:
    - Background (must include the aim of the study)
    - Patients and methods
    - Results
    - Conclusion
- References should be avoided. Avoid uncommon abbreviations. If essential, they must be defined at their first mention in the abstract itself.

Keywords

- Immediately after the abstract, provide a maximum of six keywords using standard searchable terms. These keywords will be used for indexing purposes.

Level of evidence

- Level 1 to 5.
- Please follow the level of evidence guidelines provided by the Oxford Centre for Evidence-Based Medicine (OCEBM); version 2.1.
- Available from: OCEBM Levels of Evidence Working Group. 'The Oxford Levels of Evidence 2'.Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

Introduction

- The introduction should contextualise the study by providing the background to the research; explain the problem that is to be addressed, and provide the rationale for the study.
- Briefly outline the relevance of the study with respect to the current literature. Avoid a detailed literature survey or a summary of the results.
- The last sentence should outline the research question or hypothesis.

Patients (or Materials) and methods

- State the methods, outcome measures, and selection criteria. The following aspects need to be described:
    - The study design and research methodology
    - Whether randomisation (with methods) was applied
    - If case-controlled, how the controls were selected
    - The time period under review
    - Number of patients/subjects under investigation and why this number was chosen
    - Inclusion and exclusion criteria
    - Case and outcome definitions
    - A description of the procedure or intervention, including post-operative protocol
    - The outcome measures or scores used
    - The minimum follow-up period
    - Statistical analysis paragraph. This should be included at the end of this section to detail statistical tests and package used, the reasons why these tests were used, and what p-value was considered statistically significant. A power analysis is recommended for studies comparing two or more groups.
- Provide sufficient detail so that another researcher can replicate the study.
- The reader should understand from this description all potential sources of bias such as referral, diagnosis, exclusion, recall or treatment bias. This includes the manner in which investigators selected the patients. Consecutive inclusion implies all patients with a given diagnosis are included, while selective implies patients with a given diagnosis but selected according to certain explicit criteria (e.g., state of disease, choice of treatment).
- Do not describe standard procedures for common operations. Only include new procedures or adaptations to standard procedures.
- If you name any specific product, it requires the manufacturer's name, city and state/country.
- Present information in the narrative format and use the past tense.
- Where relevant, tables or figures may be included to provide information more clearly.
- Generally, no data should be presented in this section.

Results

- Describe the relevant results and analysis thereof.
- Provide details of the number of patients included and excluded, as well as the reason for exclusion.
- It is important to state the follow-up period (mean and range).
- The results can be broken down into separate sections, e.g. Treatment, Functional outcome, Complications, etc.
- Tables may be used but avoid repeating data reported in the text in the tables.
- All appropriate data should be presented as means with ranges, not with standard deviations (SDs). Medians should only be used when the data is skewed, accompanied by an interquartile range (IQR).

- Avoid using percentages in studies involving well under 100 subjects.
- All results must be backed up with p-values or survivorship analysis. All Kaplan-Meier data should be presented with confidence intervals. Always present exact absolute p-values, whether significant or not, unless $p<0.001$.
- However, *P-values* do not always convey the entire picture and where relevant, the confidence interval will also be required (in addition to the power of the study reported in the methods section).

Discussion

- The question or hypothesis stated at the end of the introduction should be discussed and either supported or rejected.
- The results must be interpreted clearly, and any deficiencies expressed. All possible confounding factors, sources of bias or weaknesses in the study should be identified.
- Explore the significance of the results of the work rather than repeating the results.
- The discussion must point out the relevance of the work described in the paper and its contribution to current knowledge.
- Explain what can be deduced from the results and how will it affect clinical practice.
- Include a review of the relevant literature, placing the results of the study in the context of previous work in this area.
- Discussion of relevant prior research and references must be concise. Avoid extensive citations and discussion of published literature emphasize previous findings that agree (or disagree) with those of the present study.
- Do not repeat the introduction.
- Present the limitations of the study and suggest how the study could have been improved for a future study.
- Avoid making inferences from non-significant trends unless you believe your study is adequately powered to answer the question; in that case, provide a power analysis.

Conclusion

- Provide a summary statement that conveys the conclusions of the findings.
- Do not draw conclusions not supported by the data obtained from the specific study presented.

Ethics statement

- For studies involving human subjects, please include an ethics statement as follows: ‘All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.’
- For animal studies, please include the following ethical statement: ‘All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.’

- If the study did not involve human or animal subjects, state that: ‘This article does not contain any studies with human participants or animals performed by any of the authors.’
- Please also include an informed consent statement: ‘Informed consent was obtained from all individual participants included in the study.’
- Alternatively, for retrospective studies, please add the following sentence: ‘For this study formal consent was not required.’
- If identifying information about participants is available in the article, the following statement should be included: ‘Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.’

Acknowledgements

- Acknowledgements should be placed at the end of the discussion and before the references.
- In this section, persons who were involved but did not earn authorship can be acknowledged.
- Statements should be brief. A person can be thanked for assistance or comments.
- Do not include contributions by editors or referees.

Author contributions

- Please state the contributions of each author
- For example: ‘A.B contributed to the study conceptualisation, design, data analysis and manuscript preparation. C.D. contributed to data collection and manuscript preparation. E.F. contributed to ....’
- The types of contributions are:
    - Conceptualisation and design
    - Data collection or contribution
    - Data analysis
    - Manuscript preparation
    - Other contributions (please specify)

References

- Please refer to the section on Formatting of submissions.

<u>Tables and figures</u>

- Tables and figures should not be imbedded in the text file but should be submitted as separate individual files. Each table should be a separate file, entitled Table I, Figure 2, etc.
- Each table and figure should be provided with a heading or legend.
- Please refer to the ‘Formatting of submission’ section for further guidelines.

Appendix E: Student's contribution to the research and writing of the "submissible" paper

Division of Orthopaedic Surgery

Faculty of Health Sciences, 4M Room 12, Wits Medical School, 7 York Road, Parktown 2193
• Tel: +27 11 717-2538 • Fax: +27 11 717-2551

07 November 2022

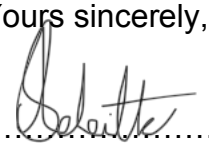
Faculty of Health Sciences, University of the Witwatersrand

RE: JAN SIEBRAND HIDDEMA'S CONTRIBUTION TO THE RESEARCH AND WRITING OF THE "SUBMISSIBLE" PAPER

To whom it may concern,

This letter serves to confirm that the co-authors of the "submissible" research paper have agreed to its use by Jan Siebrand Hiddema, student number 2272778, as part of his MMed research report. Jan Siebrand Hiddema made a substantial contribution to conducting the research study and writing the manuscript.

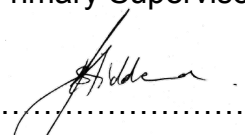
Yours sincerely,



……

Dr. Allan Roy Sekeitto

Primary Supervisor



……

Dr. Jan Siebrand Hiddema

MMed Candidate

Appendix F: Databanks Permission letters

Division of Orthopaedic Surgery

Faculty of Health Sciences, JM Room 12, Wits Medical School, 7 York Road, Parktown 2193
• Tel: +27 11 717-2558 • Fax: +27 11 717-2551

UNIVERSITY OF THE
WITWATERSRAND
JOHANNESBURG

Herewith I, Professor Dick Ronald Van der Jagt, in my capacity as gatekeeper of the Johannesburg Orthopaedic hip and knee databank, give permission to Dr. Jan Siebrand Hiddema, student nr: 2272778, to use this databank in his Mmed (Ortho) Research project titled: "Peri-prosthetic joint infection: A South African perspective".

Kind Regards,

Prof. DR Van der Jagt

Division of Orthopaedic Surgery

Faculty of Health Sciences, 4M Room 12, Wits Medical School, 7 York Road, Parktown 2193
• Tel: +27 11 717-2538 • Fax: +27 11 717-2551

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

Herewith I, Professor Mmampapatla Ramokgopa, in my capacity as gatekeeper of the Wits, Hip Arthroplasty databank and Wits, Knee Arthroplasty Databank, give permission to Dr. Jan Siebrand Hiddema, student nr: 2272778, to use these databanks in his Mmed (Ortho) Research project titled: "Peri-prosthetic joint infection: A South African perspective".

Kind Regards,

Prof. MT Ramokgopa

Appendix G: Plagiarism/turn-it-in report cover page

Appendix H: Research protocol