STAPHYLOCOCCUS AUREUS COLONIZATION AND SURGICAL SITE INFECTION IN PATIENTS ADMITTED TO A SOUTH AFRICAN ACADEMIC HOSPITAL FOR ELECTIVE TOTAL JOINT ARTHROPLASTY

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DECLARATION

I, Jurek Rafal Tomasz Pietrzak, declare that this research report is my own work. It is willingly being submitted for the degree of Master of Medicine in Orthopaedic Surgery at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signature of Candidate

26th day of April 2021 in Bryanston, Johannesburg, RSA

DEDICATION

This is for my mom and dad.

Thank you for your unwavering support and continued love and dedication. I am what I am thanks to you.

ABSTRACT

***STAPHYLOCOCCUS AUREUS* COLONIZATION AND SURGICAL SITE INFECTION IN PATIENTS ADMITTED TO A SOUTH AFRICAN ACADEMIC HOSPITAL FOR ELECTIVE TOTAL JOINT ARTHROPLASTY**

Introduction

Peri-prosthetic joint infections (PJIs) are a major source of morbidity and mortality for patients undergoing Total Joint Arthroplasty (TJA). *Staphylococcus aureus (S. aureus)* colonization, either Methicillin Sensitive *S. aureus* (MSSA) or Methicillin Resistant *S. aureus* (MRSA) is an independent, modifiable risk factor for PJIs. Post-operative infections are reported to be ten times greater in *S. aureus* carriers than in non-carriers in developed countries though recorded data is lacking for the developing world. This study aims to determine the prevalence of *S. aureus* colonization in patients awaiting TJA in South Africa.

Materials and Methods

We prospectively assessed 119 patients awaiting Total Knee Arthroplasty (TKA) and Total Hip Arthroplasty (THA) between October and December 2016. We screened three separate anatomical sites, namely the axilla, groin and anterior nares, on each patient for both MSSA and MRSA. Patients with positive cultures were treated with intra-nasal mupirocin ointment and chlorhexidine body wash. All patients were followed up for 30-, 60- and 90-days re- admissions and subsequently for a minimum of two years for any evidence of complications. Univariate and comparative statistical analyses to determine risk factors for colonization were conducted using t-test, Fisher's exact test, and chi squared analyses.

Results

The overall prevalence of MSSA-colonization was 31.9% (n = 38). There were no patients colonized with MRSA. Nasal swabs returned a yield of 81.6% (n = 31), with groin swabs and axillary swabs at 39.5% (n = 15) and 28.9% (n = 11), respectively. Eradication was successful in 94.74% (n = 36) after five days treatment. All patients (100%) were decolonized after counseling and repeat eradication treatment. The overall complication rate was 7.6% (n = 9). The 30-days re-admission rate in the *S.*

aureus -colonized group was 7.9% (n = 3) as opposed to 7.4% (n = 6) in the non-colonized cohort. There were no 60- and 90-days re-admissions and no cases were revised at a mean follow-up of 2.26 years.

Conclusion

The rate of *S. aureus* colonization in patients undergoing elective TJA in a developing country was 31.9% and is equivalent to reported rates in developed countries. We recommend that the anterior nares should always be included in the sites being analyzed for colonization. The combination of intra-nasal mupirocin ointment and chlorhexidine baths is an effective decolonization strategy for eradicating *S. aureus* colonization.

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LIST OF ABBREVIATIONS

Body Mass Index	**BMI**
Brain Heart Infusion broth	**BHI**
Charlotte Maxeke Johannesburg Academic Hospital	**CMJAH**
Centre for Disease Control and Prevention	**CDC**
Deep Vein Thrombosis	**DVT**
General Practitioner	**GP**
Gross Domestic Product	**GDP**
Haemoglobin	**Hb**
High care area	**HCA**
Human Research Ethics Committee	**HREC**
Infectious Diseases	**ID**
Intensive care unit	**ICU**
Lower than detectable level	**LDL**
Methicillin resistant *Staphylococcus aureus*	**MRSA**
Methicillin-sensitive *Staphylococcus aureus*	**MSSA**
Microscopy, Culture and Sensitivity	**MC&S**
Myocardial Infarct	**MI**
National Healthcare Safety Network	**NHSN**
Neck of Femur	**NOF**
Odds Ratio	**OR**
Tuberculosis	**TB**
Polymerase Chain Reaction	**PCR**
Primary	1°
Principal Investigator	**PI**
Prosthetic joint infection	**PJI**
Rheumatoid arthritis	**RA**
Secondary	2°
National Health Laboratory Services	**NHLS**
Staphylococcus aureus	***S. aureus***
Surgical joint infection	**SSI**
Infection Control	**IC**
Total Hip Arthroplasty	**THA**

Total Joint Arthroplasty	**TJA**
Total Knee Arthroplasty	**TKA**
Tumour Necrosis Factor inhibitors	**TNFi**
Urinary microscopy, culture and sensitivity	**u. MC&S**
Viral load	**VL**
World Health Organization	**WHO**

Contents

1. INTRODUCTION

1.1 Introduction

Total Joint Arthroplasty (TJA) represents one of the greatest developments in modern orthopaedic surgery. TJA includes Total Hip Arthroplasty (THA) and Total Knee Arthroplasty (TKA). Both THA and TKA provide reliable and reproducible pain relief and functional improvement in patients afflicted with end-stage hip and knee joint degeneration (1). The demand for THA and TKA is increasing worldwide. The number of TKA and THA procedures in the United States of America (USA) is projected to increase by 673% and 174%, respectively by the year 2030 (1). Correspondingly, the need for TJA in South Africa is expected to increase accordingly.

TJA is, however not an innocuous surgical procedure and may be complicated by adverse events. Infection after TJA is one such devastating complication. Peri-prosthetic joint infection (PJI) is the foremost cause of failure of both primary TKA and THA (2–5). The infection rates for TKA have been reported as 0.68 – 1.6%. Similarly, 0.67 – 2.4% of all THA may be complicated by infections. There has been an increase in the incidence of peri-prosthetic joint infection (PJI) complicating primary (1°) TJA globally (6) in the last decade. It has been reported that one in every 50 patients undergoing 1° TJA will develop a surgical site infection (SSI) (1,7,8). The resultant economic burden of treating PJI is immense and increasing.

Over time, a number of preventative strategies have evolved to eliminate the risk of PJI. These precautionary approaches have focused upon the timely administration of prophylactic antibiotics, the use of antibiotic-loaded cement, contained surgeon exhaust surgical suits, laminar airflow, pre-operative surgical site preparation, ultra-violet light and careful and meticulous optimization of a sterile theatre environment and precise surgical technique (7,8). Recently, greater attention has been given to the role patient-related factors play in the evolution of PJI. Patient-related factors have been implicated in the increased incidence of PJI. Patient-related factors have subsequently been divided into modifiable and non-modifiable risk factors. Non-modifiable risk factors include diabetes mellitus, rheumatoid arthritis, immune-

compromised state, tobacco use and obesity. Pre-operative nasal colonization with S. aureus has been recognized as an independent modifiable risk factor for SSI (7–9). The association between nasal colonization with *S. aureus* and infection was first made as early as 1931 (10). *S. aureus* is responsible for the majority of SSIs in orthopaedic surgery (11). In the early 1990s *S. aureus* accounted for 20% of SSIs in the USA. However, the National Healthcare Safety Network (NHSN) data reported by 2010 the frequency of SSIs as a result of *S. aureus* had increased to 30.4% (12). *S. aureus* is the infective organism responsible for more than 60% of SSIs complicating THA or TKA (12).

It has been reported that nasal carriers of *S. aureus* are approxiamtely two to nine fold more likely to be complicated by a SSI than patients that are non-carriers of *S. aureus* (13). Correspondingly, the strain of *S. aureus* isolated in SSIs is often the same as that strain found in the noses of colonized patients (9). Methicillin resistant *S. aureus* (MRSA) is the more virulent sub-type of the organism. There is an increase in MRSA infections worldwide (14). The likelihood of infection in patients colonized with MRSA-colonized is more significant than in patients that are not colonized with MRSA (14). Additionally, the length of hospital stay linked to SSIs as a result of MRSA is almost twice as long as those as a result of non-MRSA infections (14). *S. aureus* is an asymptomatic, skin comensal in as many as one third of people globally (9). The nares are the most common site of colonization by *S. aureus* (9). Extra-nasal sites of *S. aureus* colonization includes the inguinal area, the rectum, axilla and throat (15). The literature has demonstrated widespread topographical variation in the incidence of *S. aureus* nasal colonization (14). Price et al. (16) , in a series of 284 pre-operative orthopaedic patients in the USA, showed a colonization rate of 30%.

The incidence of MRSA nasal colonization reported in the literature is also variable and incidences ranging from 1.1 – 25% have been reported (17,18). In a cohort of 2432 patients in Japan, Yano et al. demonstrated a MRSA nasal colonization rate of 2.6% (15). In France, Berthelot et al. showed that 20% of 3908 patients were nasal carriers of *S. aureus,* yet only 0.6% carried MRSA (19). *S. aureus* and MRSA surveillance data from African countries, however, is scanty (20). *S. aureus* colonization occurred in 56.1% of 132 patients that were admitted to hospital in

Senegal (21). MRSA colonization and carriage rates from different African countries have demonstrated variability. Subsequently, MRSA carriage rates have been reported as 3.7% in Gabon(18) in 2014, 14.8% in Madagascar and 23% among Ethiopian prisoners and children (18,19). A single report from South Africa showed MRSA in 27% of clinical isolates (18).

Additionally, the spectrum of *S. aureus* related infections in Africa differs from those presenting in other parts of the world (22). A remarkable feature of African MRSA in urban areas is the high-levels of resistance to penicillin (73.7 – 100%), co-trimoxazole (15 – 89.1%) and tetracycline (21.8 – 92%) (22). Sub-Saharan Africa, however, has lower rates of resistance to fucidic acid (0 – 2%) than reported in North Africa (13 – 62%) (22). Risk factors reported in the literature for *S. aureus* colonization include: age, gender, ethnicity, diabetes, immune-compromised state, renal disease, dermatologic conditions and obesity (23). Geographic variation consequently exists for both the prevalence and risk factors for *S. aureus* colonization (22,24). In Africa, additional risk factors for *S. aureus* colonization include Human Immunodeficiency Virus (HIV) infection (22), frequent hand-washing (more than three times daily), living in rural areas and previous hospitalization in surgical wards exists (24).

1.2 Problem statement

An association exists between pre-operative colonization with *S. aureus* and Peri-prosthetic Infections (PJI), including SSI and deep infections. Pre-operative *S. aureus* colonization in patients undergoing 1° TJA has been recognized as a modifiable risk factor for PJIs post-operatively. Amongst other factors, geographic variation influences the incidence of *S. aureus* colonization. However, there is limited information about the epidemiology of *S. aureus* colonization in the general South African population. To the best of our knowledge, there are no published findings on the incidence of *S. aureus* colonization in South African patients undergoing 1° TJA. Furthermore, the literature is also scanty on the *S. aureus* colonization rates in developing countries.

Pre-operatively, the practice in the Arthroplasty Unit at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Johannesburg, South Africa, at the time of the initiation of our study, did not include the routine testing of patients undergoing 1° TJA for *S. aureus* colonization. Furthermore, there was no eradication treatment prescribed for potential *S. aureus* colonization in any patients prior to elective 1° TJA. Therefore, definite recommendations did not exist for either pre-operative testing for *S. aureus* colonization or the prescription of universal eradication therapy in patients undergoing 1° TJA.

1.3 Aim

To assess the prevalence of *S. aureus* colonization in patients admitted to a South African academic hospital for elective primary Total Joint Arthroplasty (TJA).

1.4 Objectives

Firstly, this study will determine the prevalence of *S. aureus* colonization of patients undergoing elective 1° TJA in our institution. Secondly, it will seek to determine potential risk factors associated with *S. aureus* colonization of patients in this population group. Thirdly, it will assess the effect of a decolonization treatment strategy, including topical intranasal mupirocin and chlorhexidine baths, on the eradication of *S. aureus* colonization. Lastly, it will attempt to determine whether any correlation exists between pre-operative *S. aureus* colonization and early- and mid-term complications after 1° elective TJA.

1.5 Significance of study

The rate of PJI complicating 1° elective TJA has remained relatively consistent worldwide despite numerous developments in surgical techniques and the evolution of instruments and implants attempting to assuage the complication rate. The need for revision TJA for PJI remains alarmingly high. Subsequently, attention has shifted decidedly to the optimization and management of those patient factors which potentially contribute to early and late infective complications and consequently lead to unplanned hospital re-admissions and re-operations. Pre-operative colonization

with *S. aureus* in patients undergoing TJA has been associated with an increased risk of PJI. Testing, treating and eradication protocols remain controversial in the literature. This study seeks to determine the prevalence of *S. aureus* colonization in a South African population group presenting for both elective 1° THA and TKA. Understanding the potential magnitude of this problem may enable the Arthroplasty unit to formulate future population-specific, bespoke management and treatment strategies to optimize patient care while still controlling costs within the context of a South African system.

1.6 Hypothesis

S. aureus colonization is low amongst patients presenting for elective 1° TJA to a South African academic, referral institution. Local MRSA colonization rates are lower than rates reported in developed countries.

2. LITERATURE REVIEW

2.1 Introduction

The prevalence of MSSA colonization in the general population has been reported as 20 – 36.4% (10,12,25–27).The discrepancy in the prevalence of *S. aureus colonization* may be associated with differences in the presence of various potential risk factors including diabetes mellitus, immunosuppression, age, gender and living conditions (28). As a consequence, it is imperative that the incidence of *S. aureus* colonization in population groups with inherently diverse population characteristics is explored (28). The role of pre-operative screening for *S. aureus* colonization is controversial and the World Health Organization (WHO) and the Centre for Disease Control and Prevention (CDC) have yet to offer any definite recommendations (24). The WHO, however, makes a strong recommendation for eradicating known nasal *S. aureus* carriers with mupirocin pre-operatively (29).

2.2 Importance of this study

The contribution of *S. aureus* to PJI, including SSI and deep PJI, is considerable (27,30). The total number of revision TJAs secondary to deep SSIs in the USA has been projected to be 70 000 each year by 2020, at a cost of $1.62 billion annually (25,26). Furthermore, by 2030, the incidence of PJIs may be as many as 270 000 per year (5,31). The treatment cost of a single case of deep PJI is $60,000 to $110,000. In the event that the infective pathogen is MRSA rather than MSSA, the costs are almost doubled especially as the length of hospital stay is far greater (12,32). On average, the duration of hospital admission may be seven to 10 days longer as a consequence of PJI (33).

In the United Kingdom (UK), the National Joint Registry (NJR) has exposed and highlighted the significant burden of PJI on revision TJA (34). In the 13th Annual Report of the NJR revision for PJI made up 14% of all revision THA and 23% of all revision TKA cases, respectively (13th Annual Report National Joint Registry for England, Wales, Northern Ireland and the Isle of Man, n.d.). The five-year survival

rate of PJI is 87.3% (27,35). The survival rate of PJI is subsequently poorer than that of prostate cancer (99%), breast cancer (89%) and melanoma (92%) (35). The mortality rate of patients with PJI attributed to MRSA is double that of PJI due to MSSA (36). Moreover, *S. aureus* has been shown to be the most likely bacteria to develop multi-microbial resistance in hospitals worldwide (ECDC) (37) contributing significantly to elevated morbidity and mortality rates and spiraling costs.

PJI as a result of MRSA, *Pseudomonas spp*. and *Proteus spp*. have poorer outcomes than PJI due to other infective pathogens including MSSA. Cunningham et al. demonstrated that these organisms are responsible for an increased number of surgical procedures required to eradicate subsequent infection necessitating an extended length of hospital stay (36). Additionally, the subsequent successful treatment of PJI is less likely. An important and essential strategy to mitigate the burden of revision TJA, alleviate the ensuing dire patient morbidity and mortality rates and reduce the weighty healthcare expenses is to prevent PJI (27,30,38). Pre-operative patient optimization remains a key and essential part of any strategy to limit the incidence of PJI (30).

2.3 How *S. aureus* colonization occurs

S. aureus is a gram-positive bacterium which is a common member of the commensal microbiota on the skin and upper respiratory tract (33). Most carriers are asymptomatic, however, *S. aureus* colonization may become an opportunistic pathogen when influenced by various host factors, environmental influences and bacterial interactions (39). The anterior nares are most commonly colonized by *Corynebacterium spp*., *Propionibacterium spp.* and *Staphylococcus spp.* (39–41). Colonization of the anterior nares by *Staphylococcus spp.* may be impeded by the presence of other bacterial species (39). *Streptococcus pneumoniae* and *Staphylococcus lugdunensis* inhibit *S. aureus* colonization by the secretion of bactericidal substances (39,42,43). *S. epidermidis* interferes with the ability of *S. aureus* to firmly adhere to the nasal mucosa by the production of an enzyme which restricts the adhesion properties of *S. aureus* (39,44). *Corynebacterium spp.* actively competes with *S. aureus* for binding sites in the anterior nares (39,45). Not only does

inter-species competition exist, but intra-species competition for colonization is also present. The presence of MSSA actively prevents the co-existence of MRSA (39,46).

2.4 Prevalence of S. aureus colonization

The prevalence of MSSA colonization in the general population has been reported as 20 – 36.4% (10,12,25–27). Conversely, the prevalence of nasal carriage of MRSA has been described as ranging from 0.6 – 6%. A study which pooled the results of 8350 patients from ten studies reported the prevalence of MRSA colonization as 3.1% (10). MRSA accounts for 25.5% of community acquired- S. *aureus* infections. More than two-thirds of 67.4% of hospital associated (HA) infections are caused by MRSA (25-27). Consolidated data from ten studies which included 8350 patients from the general population in countries from the developed world reported the prevalence of MRSA as 3.1%. After the elimination of risk factors, the rate fell to 2%. MRSA accounted for 25.5% of the total isolates of community acquired (CA) - *S. aureus* infections, whereas 67.4% of hospital associated (HA) infections were caused by MRSA (22). Kim et al. (47) prospectively screened and subsequently decolonized 7019 patients awaiting elective THA, elective TKA and spine surgery. In this cohort the prevalence of MSSA and MRSA colonization was 22.6% and 4.4%, respectively (47). Comparatively, in a retrospective analysis, Hacek et al. (48) reported that the prevalence of *S. aureus* colonization was 22.6% in 912 patients who underwent elective THA and TKA.

2.5 Testing for *S. aureus* colonization

Universally, there are three general patterns of S. *aureus* colonization: 20% are persistent carriers: 60% are intermittent carriers and 20% are non-carriers (12,49). The choice of which anatomical site, or combination of sites, to sample to most accurately and effectively detect *S. aureus* colonization remains controversial (50). Recommendations and subsequent sampling protocols vary globally (50). The primary and most typical reservoir of *S. aureus* colonization is the anterior nares (12,51,52). *S. aureus* also possesses the capacity to colonize a number of other mucosal sites including the oropharynx, forehead, neck, rectum and inhabit moist

areas of the skin such as the axillae, groin and the perineum (12,26,49,53). The potential of more definitively and accurately detecting *S. aureus* colonization and subsequently *S. aureus* carriers is achieved by sampling multiple anatomical sites (50,53,54). Wendt et al. (55) showed that colonization of the groin predicted positively for colonization of the skin in multiple other sites.

In a large study evaluating 403 MRSA-colonized patients, Coello et al. (56) showed that testing multiple sites in addition to the anterior nares increased the identification rates of patients colonized with MRSA. Swabs of the throat, perineum and anterior nares identified 98% of MRSA carriers in comparison with 79% of patients in which only the anterior nares were tested. Matheson et al. (54) reported that nasal screening was superior to testing the throat or axilla or perineum in detecting MRSA. Assessing multiple sites was preferred, however, as only two thirds of carriers were identified by testing the anterior nares alone. The combination of testing the nasal and perineal areas had better detection rates than combining nasal and throat tests (54). Baker et al. reported that the oropharynx is the most prevalent extra-nasal site of *S. aureus* colonizatio (57). An increased risk of extra-nasal *S. aureus* colonization is associated with nasal colonization with MRSA and severe disease (57).

The method of testing for *S. aureus* colonization may increase the possibility of more accurately recognizing true carriers. An investigation of 650 patients admitted to either the medical or surgical ICU in Taiwan showed that the detection rates of MRSA carriage may be improved by combining nasal and extra-nasal testing with the use of broth-enriched cultures (15). Almost two-thirds of cases of MRSA-carriage would have been missed had an enriched broth and extra-nasal sites not been used for cultures. The provision of broth enrichment for assessing *S. aureus* may double the sensitivity of cultures (15,58). Young et al. (51) performed a study analyzing the benefit of pooling the results from multiple anatomical sites and the findings showed that testing the anterior nares best identified *S. aureus* carriage. By combining tests of throat swabs with nasal swabs, 10% more *S. aureus* carriers were discovered (58). In 22% of cases, more than site was colonized. The detection rate of *S. aureus* by axillary swabs was only 8% and they were never the sole positive test to detect *S. aureus* colonization (51).

Hadi et al. (59) stated that the prevalence of *S. aureus* carriers in 226 patients awaiting TJA in Arak, Iran was 20.8%. Multiple sites were sampled and *S. aureus* was cultured from the anterior nares in 15.9% of cases; the throat in 4.4% and from the groin in 3.1% (59). The vast majority of participants in this paper were female (75%) and no correlation with gender and *S. aureus* colonization was found. Correspondingly, Batra et al. (60) showed that an increased MRSA detection rate was possible by sampling multiple sites. More cases of MRSA colonization were found when nasal, perineal and axillary swabs were taken as opposed to only rectal and throat swabs. Isolated sampling of wound sites was positive in only 4.7% of cases. Studies have, therefore, highlighted that as more sites are sampled, the potential for unearthing MRSA colonization increases (61).

The major concern with sampling multiple sites for determining *S. aureus,* including MRSA and MSSA, colonization is the potential for incurring additional costs and placing greater strain on the health care budget (12). It has been postulated, however, that testing only the anterior nares for nasal colonization may be sufficient to accurately assess *S. aureus* colonization (62). This is due to the fact that colonization of another site in the absence of nasal colonization is relatively uncommon (12,57).

2.6 Risk factors of *S. aureus* colonization

Risk factors for *S. aureus* colonization include: gender, age, recent hospitalization, ethnicity, genetic predisposition, diabetes mellitus, HIV, haemo-dialysis, skin infections and antibiotic treatment misuse (49,63). Contrasting reports on the influence of numerous risk factors on *S. aureus* colonization exists. There is controversy whether there is an association with patients' age and *S. aureus* colonization. There is available literature that argues that *S. aureus* colonization is more common in a younger demographic while conflicting reports exist showing that older patients are more likely to be *S. aureus* carriers (59). Bitterman et al. (50) reported that age was the most significant predictor of both MRSA nasal colonization and concurrent involvement of multiple anatomical sites. In a review of the *S. aureus* colonization rates of 924 healthy volunteers, there was no disparity in the carrier rate of individuals aged 30 – 60 years and those aged older than 80 years of age (64).

While the overall colonization rate in all age groups was 30%, the 50% incidence in the 5 – 10 years old group was the highest (64).

In comparison with colonized patients of other ages, elderly carriers are at an increased risk of developing related deep infection subsequent to *S. aureus* colonization (65,66). Concurrently, elderly patients are also more susceptible to the adverse effects of antibiotic treatment for deep infections (66,67). The impact of gender on the incidence of *S. aureus* colonization is also controversial (68). The likelihood of *S. aureus* colonization may potentially be more significant in males than females (9,68). In an evaluation of family doctor records from nine European countries, the risk of males being colonized with *S. aureus* was 1.38 times greater than females (68,69). This may due to males having more apocrine sweat glands in the nasal mucosa (9). Moreover, poorer hand hygiene in males may increase the chance of *S. aureus* colonization and ensuing infections (68).

Wang et al. (61) demonstrated that antibiotic use within the last year and living in homes with children less than seven years old were independent risk factors of MRSA colonization rather than MSSA colonization. Smoking was also shown to be protective of MRSA colonization (61). Similarly, Ellis et al. (70) supported the fundamental outcomes of these results by reporting that antibiotic use within six months and co-habitation with children less than 16 years of age were risk factors for *S. aureus* colonization in soldiers from five major training facilities in the USA. People that are carriers of MRSA represent a major risk for transmitting MRSA to others (15). The potential therefore exists that even healthcare workers may act as vectors thereby influencing both patient colonization and subsequent infection. In hospitals, poor hand hygiene and improper adherence to proper and safe barrier precautions may potentiate transmission (49,71).

Kent et al. (52) reviewed the pre-operative colonization screening results of 115 elective orthopaedic patients and reported that risk factors for *S. aureus* colonization included diabetes and male gender. In this report, males were twice as likely as females to be *S. aureus* carriers (52). Correspondingly, diabetics were at a 3.8 times greater risk of being colonized than non-diabetic patients. Interestingly, advanced age, recent antibiotic treatment and facial hair were, in fact,

protective of S*. aureus* colonization. Albert et al. found that patients inflicted with Rheumatoid arthritis (RA) did not have an increased prevalence of *S. aureus* colonization in comparison with matched, healthy controls (69). The incidence of *S. aureus* carriage in this study was 36%. Furthermore, there was no association between *S. aureus* colonization rates and the type of medication prescribed for the management of RA. Similarly, Bassetti et al. (70) showed that RA is not a risk factor for *S. aureus* colonization and that the rate of nasal and oral colonization was comparable, at 34.6%. Goodman et al. however reported that RA patients treated on biologics were at a greater risk of being colonized with *S. aureus* than RA patients on traditional disease-modifying anti-rheumatic drugs (DMARDs) (72). In RA patients, a risk of persistent *S. aureus* colonization may exist in patients being treated with tumour necrosis factor inhibitors (TNFi) (70). It is essential to note, however, that RA remains an independent risk factor for SSIs in patients undergoing TJA.

Malcolm et al. (73) reviewed the electronic records of 5678 undergoing elective TJA. There were 3927 patients that underwent pre-operative screening and 20% of patients were found to be MSSA carriers and 5% of these patients were colonized with MRSA. Male gender, lower average age of patient and different hospitals accounted for a greater risk of MSSA-colonization (73). Alternatively, MRSA colonization was significantly more likely in patients with congestive cardiac failure and hospital admission within the previous six months (73). An increased incidence of *S. aureus* colonization has been described in obese patients (74,75). This may be as a result of abnormal glucose metabolism and abnormal immune responses through pathways conducting inflammatory and sex-steroid signals (76,77). Olsen et al. (78) investigated the impact of diabetes, gender and obesity amongst other factors on *S. aureus* colonization. An increased waist circumference was connected to an increased probability of *S. aureus* colonization in both male and female patients. Olsen et al. (78) described that the likelihood of *S. aureus* colonization increased incrementally by 7% with every increase in BMI of 2.5kg/m^2 in females.

Walsh et al. (79) reported that the incidence of MSSA- and MRSA-nasal carriage in 716 patients undergoing elective TJA was 17.5% and 1.8%, respectively. There was an increased likelihood of *S. aureus* colonization in diabetic patients, patients who are immunosuppressed and patients with kidney failure (79). The increased

incidence of *S. aureus* colonization in these groups of patients are seemingly due to them being incapable of mounting a significant immune response to ward of bacterial infections effectively. Patients with Type 2 diabetes and poorly controlled serum glucose levels may have a greater risk of being colonized with *S. aureus* (79,80). In this study, Walsh et al. (79) also reported that patients who had a strong smoking history were more inclined to have colonization of their anterior nares by bacteria other than *S. aureus* (79). Limited reports in the literature evaluating the prevalence of *S. aureus* colonization in the African populace exists. In a review of 277 healthy Nigerian university students, Ayepola et al. (63) reported that 56.7% of tested individuals were nasal *S. aureus* carriers. They showed that hospitalization in the last 12 months, *S. aureus* skin infections and active participation in sports were major risk factors for subsequent colonization (63). They also presented that males were more likely than females to be carriers. The *S. aureus* nasal carriage rate in this paper was much higher than reports from other African countries including 13%, 29% and 18.3% reported in Tunisia (81), Gabon (24) and Kenya (82), respectively. This also serves to highlight the distinct geographical variation in the incidence of *S. aureus* carriers in Africa.

Subsequently, Dave et al. (36) attempted to establish whether selective screening of patients with certain risk factors only would still successfully and accurately identify MRSA colonization Sensitivity and specificity of MRSA in 429 patients was tested with both rapid polymerase chain (PCR) swabs and traditional culture and sensitivity analysis. Patients were deemed to be high risk if they had been admitted to a hospital in the previous 12 months, were transferred from another medical institution, transferred from a residential care or nursing institution, had been in close contact with someone with an MRSA-carrier or had previously been diagnosed with MRSA (36). The results showed that more than half the MRSA-carriers would not have been detected if a policy of selective testing had been performed. Subsequently, the authors advocated universal screening to identify potential carriers (36).

2.7 Eradication of *S. aureus* colonization

There are several decolonization strategies for the management of S. *aureus* (83). The most reliable and effective S. *aureus* eradication protocol include the use of intranasal mupirocin ointment (84,85). Mupirocin inhibits bacterial isoleucyl-tRNA synthetase and disrupts bacterial protein synthesis (12). Moroski et al. (83) proved that topical intra-nasal mupirocin ointment and chlorhexidine baths for eradicating nasal *S. aureus* colonization is both reliable and successful. The prevalence of nasal colonization with MSSA and MRSA in 289 consecutive patients undergoing 1° or revision TJA was 15.2% and 4.2%, respectively. The treatment of patients with both MSSA and MRSA colonization with five days of mupirocin ointment provided statistically significant eradication of *S. aureus*, yet, 5.2% of patients remained colonized despite treatment (83).

The value of mupirocin in the eradication of *S. aureus* colonization was also highlighted in a randomized control trial conducted by Perl et al. (84). The examiners discovered that the rate of *S. aureus* colonization in 3864 patients going through a variety of surgical procedures including gynaecological, general surgical, neurosurgical and cardiothoracic was 23.1%. Intra-nasal mupirocin significantly reduced the number of SSI in *S. aureus* carriers. Interestingly, in all patients however, irrespective of carrier status, there was no proven value of prescribing mupirocin as a prophylactic treatment as it had no impact on the incidence of *S. aureus*-associated SSIs (84). Buehlmann et al. (85) reported that pre-operative eradication treatment strategies to decolonize *S. aureus* nasal and groin carriers was 98% successful. However, Wendt et al. showed far poorer results of pre-admission eradication treatment especially for the anterior nares, throat and the perineum (34,94). Eradication was only optimally achieved in the groin. Poorer rates of eradication were predicted in patients with colonization of multiple sites and patients with open wounds (55).

The efficacy of eradication therapy may be dependent upon time. In a meta-analysis, the efficacy of mupirocin in the decolonization of *S. aureus* nasal carriers was reported to be 94% at one week after treatment. However, this decreased to 65%

after following the patients up for at least two weeks after treatment. The true efficacy of mupirocin eradication has, however, also been questioned. In a randomized control study in an academic hospital in which MRSA was endemic, Harbarth et al. (86), compared mupirocin with a placebo for the eradication of multisite MRSA colonization. The group of patients receiving mupirocin ointment and the group receiving the placebo both had chlorhexidine body washes simultaneously. The eradication of MRSA-colonization at multiple sites with mupirocin was not significantly better than that with a placebo. There was however an increased rate of MRSA related infections in the group that did not receive mupirocin (86).

Treatment failure risks of *S. aureus* colonization are associated with involvement of multiple anatomic sites, longer hospital stays and bacterial resistance to mupirocin (51). In a systematic review, Ammerlaan et al. reported that the successful eradication of S. aureus at one week was 95% (86). However, the eradication success rate subsequently decreased to 64% after two weeks upon follow-up review. This review reported that the resistance to mupirocin developed in 1% of patients. The evolution of mupirocin resistance is linked to extended hospital admissions and colonization of two or more sites (87). Kalmeijer et al. (88) conducted a double-blinded randomized control trial comparing the efficacy of mupirocin ointment on decreasing the incidence of both superficial and deep PJIs. There were 0.9% fewer infections in those patients receiving mupirocin eradication therapy, but this did not infer statistical significance. Chlorhexidine or triclosan body wash is employed as an supplement to mupirocin ointment (12,89,90). This serves to reduce the bacterial count and density on the skin, most notably in extra-anatomic sites (89).

2.8 Infections and *S.aureus* colonization

S. aureus colonization is a modifiable risk for SSI (49,72,88). *S. aureus* carriers have a 9 – 10 times greater likelihood of developing a SSI (88,91). In the advent that the *S. aureus* variant is MRSA, an additional four times greater risk of PJI is inferred (73,91). Skramm et al. (92) linked specific *S. aureus* subspecies cultured on pre-operative swab sampling to the matched causative pathogen for SSA in THA, TKA and spine surgery patients. Molecular typing identified that the S. *aureus* organism cultured on pre-operative nasal swabs was identical to the infective organism in

85.71% of cases of SSI (94). They also reported that endogenous transmission of *S. aureus* from reservoirs in the anterior nares and the skin may be have a more significant impact on SSIs than previously suspected (92).

In 9690 patients undergoing TJA, a screening programme and subsequent MSSA and MRSA decolonization strategy demonstrated a 69% reduction in the incidence of SSIs when compared to patients that had not been screened or decolonized (7). After this decolonization programme was introduced, the incidence of *S. aureus* cultured from subsequent SSIs also decreased significantly from 66.7% to 33.3%. This paper also highlighted the value of *S. aureus* decolonization in mitigating the infection risk after TJA(7). The implementation of an S. *aureus* screening and eradication programme for patients awaiting TJA, by Jeans et al. showed a significant reduction in the rate of PJI which decreased from 1.92% to 1.41% (31). This study found that eradication therapy was most efficacious in patients colonized with MSSA rather than MRSA undergoing THA(27). Ultimately, £1893 was saved per case by decreasing the PJI rate (27).

In a retrospective review of 13 828 consecutive patients for THA, TKA and spinal fusions, Ramos et al. (93) reported an *S. aureus* colonization prevalence of 18.21%. *S. aureus* colonization as a consequence of MRSA was 16.3% in TKA and 12.99% in THA. After receiving eradication treatment, the subsequent incidence of SSI in the colonized patients was lower than in non-colonized patients (2.39% vs 4.35%) (93). *S. aureus* colonization in patients undergoing TKA was determined to be a significant risk factor for SSI. Alternatively, an insignificant trend towards increased SSI rates was discovered for *S. aureus* colonized patients in 1° THA (93). Currently, the WHO provides a strong recommendation that *S. aureus* nasal carriers should be treated with 2% mupirocin intra-nasally to limit the impact of subsequent post-operative infections (94). However, the WHO and CDC are yet to commit on any definitive course of action regarding pre-operative screening for *S. aureus* (94).

3. METHODOLOGY

3.1 Study design

A prospective analysis of TJA patients admitted at CMJAH. Figure 3.1 shows the summary outline of the procedure of the study.

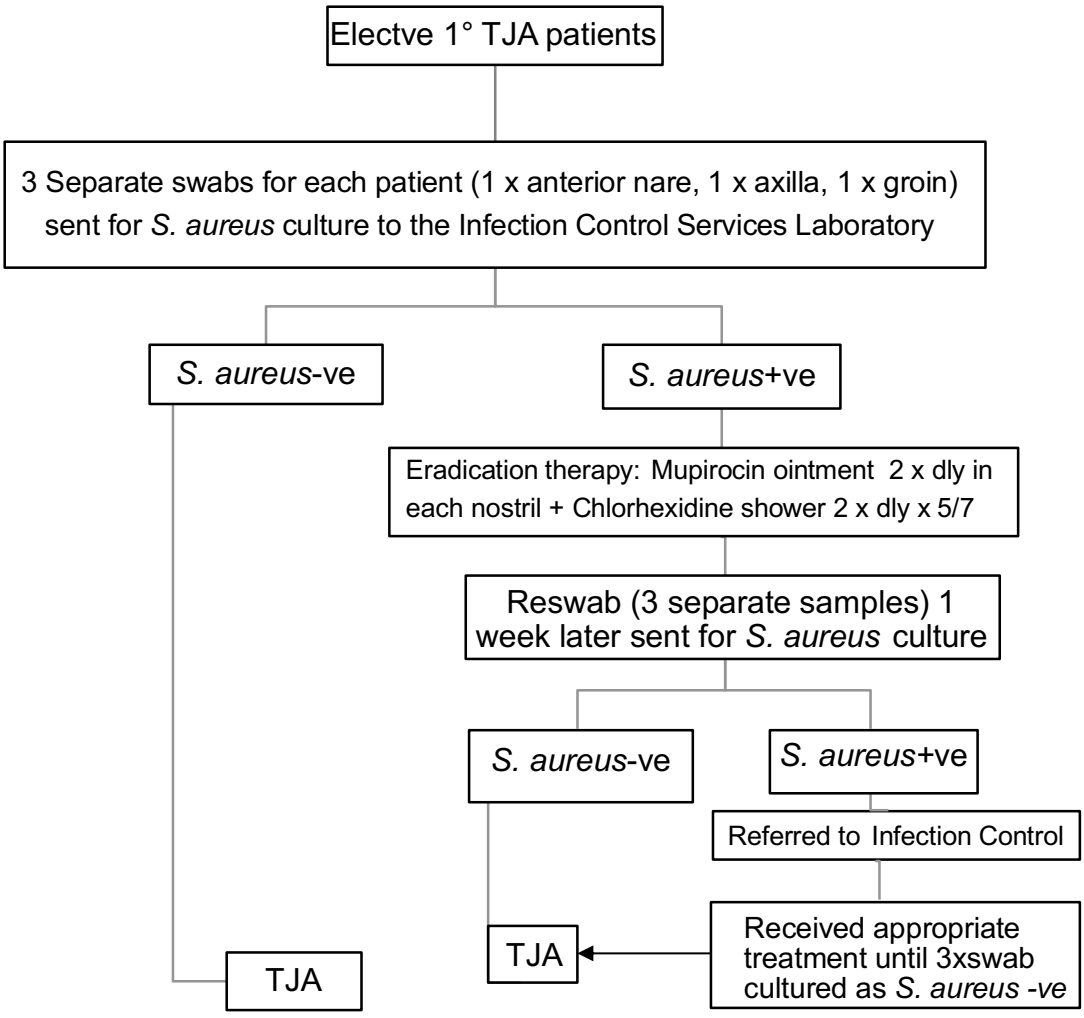

Figure 3.1: Flow diagram of study procedure

3.2 Study setting

This study was performed in the Arthroplasty Unit at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). This urban academic hospital services the greater central Johannesburg area and surrounds. The Arthroplasty Unit at CMJAH is referral-orientated and receives referrals for patients requiring elective 1° and revision THA and TKA from surrounding community-based clinics, general practitioners in Johannesburg and district hospitals in Gauteng province, Limpopo, Mpumalanga and the North-West provinces. It serves mostly South African patients, although patients from sub-Saharan Africa are also treated.

3.3 Sample selection

3.3.1 Study population

The study prospectively included patients seen in the arthroplasty clinic and admitted to the Unit for elective 1° THA or TKA. All patients that qualify for joint replacement surgery were identified at the out-patient clinic and placed on a waiting list before surgery. South African patients presenting for elective 1° TJA commonly have end-stage hip and knee degenerative pathology, significant chronic pain and functional impairment requiring surgical treatment after having failed non-operative management. The patient characteristics associated with end-stage degenerative hip and knee disease, include: a predominance of female sex, advanced age, greater body mass index (BMI) and an increased number of medical co-morbidities. Patients across all demographic categories including: age, ethnicity and domicile were represented in the randomized sample selected.

3.3.2 Sample size

A mathematical formula was used to determine the sample size needed for a prevalence study to achieve a statistical level of confidence of 95% (97). The statistical formula (97) depicted below (see equation 3.1) calculated the sample size for the study to a level of precision of 8.2% at critical region of 5% (Z = 1.96). The

sample size required was calculated to be 100 subjects given an estimated regional prevalence rate of 30% (62).

$$\text{Sample size (n)} = \frac{Z^Z\ P(1\text{-}P)}{d^Z} \quad \text{Equation (3.1)}$$

Where: *Z = Z statistic for level of confidence*

P = expected prevalence or proportion

d = precision

3.3.3 Inclusion criteria

The following inclusion criteria were applied:

- Adults of 18 years of age or older
- Patients for elective 1° TKA or THA.

3.3.4 Exclusion criteria

The following exclusion criteria were applied:

- Patients unwilling to consent for voluntarily participation in the study
- Patients who refused to undergo swabbing for *S. aureus* of their anterior nares, axilla and/or the inguinal areas pre-operatively
- Patients who presented with traumatic neck of femur (NOF) fractures for emergency 1° THA
- Patients who were incapable of assenting to the elective surgical procedure
- Patients who were unable to sign consent for participation in the study
- Patients who were unable to sign consent to undergo swabbing for *S. aureus* of their anterior nares, axilla or the inguinal area
- Patients for revision THA or TKA.

3.3.5 Ethical considerations

Medical clearance (see Appendix A) was obtained from the University of the Witwatersrand Human Research Ethics Committee (HREC) (Medical) registered with the National Health Research Ethics Council (NHREC) of the national Department of Health in South Africa.

3.4 Procedure

3.4.1 Pre-operative assessment

All patients for elective 1° THA and TKA underwent a pre-operative consultation and assessment one week prior to surgery at the CMJAH Arthroplasty Unit. The following demographic data was recorded during the pre-operative assessment: age; sex; ethnicity; co-morbidities including diabetes mellitus (DM), asthma, rheumatoid arthritis (RA), previous or current tuberculosis (TB), hypertension; cardiac disease; American Society of Anaesthesiologists (ASA) classification; tobacco and alcohol use and HIV infection. Patients with unknown HIV status were consented for HIV screening and subsequently tested. The CD4+ T-cell count (CD4+) and viral load (VL) of all HIV-positive patients was measured. The demographic data were recorded on the Pre-Operative Data Capture Sheet form (see Appendix B). The etiological diagnosis necessitating TJA was noted. Pre-operative measurements included: Body Mass Index (BMI); blood haemoglobin (Hb) and routine urine microscopy, culture and sensitivity (u. MC&S).

3.4.2 Informed consent

Informed consent was attained pre-operatively from all the patients who qualified for inclusion and were willing to participate in the study. The standardized patient information sheet and the consent form were printed in English (see Appendix C).

3.4.3 Swab collection

Three separate swabs of the anterior nares, axilla and inguinal areas for each individual patient were sampled, before their planned operative procedures. Each swab was labelled with the patient's details and the site tested. Testing multiple sites for *S. aureus* colonization increases the likelihood of identifying potential carriers (12). All samples were sent to the Infection Control Services Laboratory at the National Health Laboratory Services (NHLS). Swabs were prepared on plates and after 18 – 24 hours incubation, cultures with *Staphylococci*-resembling colonies were picked off and these isolates got manual senses performed (24). Results were ready within 72 hours of sample collection and included identification results for MSSA and MRSA sub-types. By establishing the phenotypic profile of the *S. aureus* isolates the principal investigator (PI) had the potential to illustrate a level of correlation between the colonization cultures and any future cultures from a potentially infected surgical site or septic joint.

3.4.4 Categorizing patients

The results from these swabs subsequently categorized participants into two distinct groups. The first group included participants that were colonized with *S. aureus* species (i.e. MSSA or MRSA). The first group, therefore, were to be referred to as carriers of MSSA or MRSA. This group was subsequently sub-classified as MSSA-carriers or MRSA-carriers. The second group consisted of non-carriers of *S. aureus* species. The swabs from their anterior nares, axilla and inguinal area were, therefore, all negative for MSSA and MRSA, respectively.

3.4.5 Eradication Protocol

If the swabs did not culture *S. aureus* from any of the sites those patients underwent TJA. The PI was contacted telephonically by the NHLS when any culture demonstrated positive growth for MSSA or MRSA. Patients with positive cultures were provided with mupirocin ointment and two bottles of chlorhexidine wash. Several potential decolonization strategies exist with the most consistently

successful eradication protocol involving the use of intranasal mupirocin ointment (25-26). Chlorhexidine body wash is used as an adjunct to mupirocin ointment (25-26). These patients were instructed to spray apply mupirocin intra-nasally twice per day and to apply chlorhexidine directly to the skin of their hips, knees, axilla and groin with circular movements twice daily for five days. After five days of treatment the participants were subsequently re-swabbed and tested for *S. aureus* via the same process as detailed previously. Results were reviewed and those with negative cultures then received TJA. Patients who remained culture positive received repeat counselling and were placed on the eradication protocol again. They once again returned after five subsequent days and underwent re-swabbing and re-testing of all three areas. In the event that any of the third set of swabs remained positive for MSSA or MRSA the patients would then be were referred to the Infectious Diseases Unit for further management.

3.4.6 Treatment Procedure

All elective TJA procedures were performed within one week of receiving negative swab results. Patients who underwent eradication therapy were also operated on within one week of their subsequent swabs returning with negative cultures for *S. aureus.* All participants who underwent TJA received weight-adjusted prophylactic antibiotics before their surgery. This included an intravenous infusion of cefazolin or clindamycin in cephalosporin-allergic patients. Prophylactic antibiotics were given 30 – 60 minutes before skin incision. Chlorhexidine was used for cutaneous anti-sepsis skin preparation prior to surgery. Antibiotic-loaded cement was used in those cases where implants were cemented. The peri-operative course of every patient was tracked and recorded. This included: admission post-operatively to the general ward, high care area (HCA) or intensive care unit (ICU); visits for any radiological investigations such as X-rays, ultrasonography; the number of days spent in these respective wards; the number of days post-operatively it took for the removal of the urinary catheter, the portovac drain, the intravenous access; routine movement to the smoking area and the peri-operative Hb value. The need for a peri-operative blood transfusion was also noted and recorded.

3.4.7 Post-operative evaluation

All patients had their peri-operative period closely monitored and data was recorded on the Post-Operative Data Capture Sheet (see Appendix D). The post-operative data collected and recorded included: the date of the surgical procedure; the time in minutes from prophylactic antibiotic to surgical incision; the surgical time in minutes: the type of anesthesia used; the insertion of and use of arterial lines, central venous access and urinary catheter insertion; use of antibiotic-loaded cement and if a post-operative blood transfusion was administered. Complications and adverse events of all patients who underwent TJA were recorded. Early complications were defined as those occurring within four weeks post-operatively. Late complications were those, which transpired more than four weeks after the index surgical procedure. Complications were subsequently classified according to the Clavien-Dindo Classification (95). This classification system is based on the treatment modality for the complication (95).

Participants were requested to have all surgical incision clips removed as per routine Arthroplasty Unit protocol 17 days post-operatively. Participants were closely followed up at the Arthroplasty Clinic at day 30-days, six weeks, six months, one year and annually thereafter post-operatively. Nevertheless, all patients were counselled and required to present back to the Arthroplasty Unit if there were any concerns about the surgical incision or wound ooze or drainage at any point between routine clinic visits. Preferably a pus sample or a deep swab of the wound in that event was requested as per Arthroplasty Unit protocol to the IC laboratory. These samples were to be processed as per the routine microbiological methods. Microscopy, culture and antibiotic susceptibility results were to be provided for any cultured organisms. Cultures from any potential SSI were to be correlated with pre-operative colonization culture results, patient demographic data and peri-operative clinical and procedure-related data. The 30-, 60- and 90-days re-admission rates were also assessed. Revision TJA was classified as any subsequent surgery in which one or more joint replacement components was exchanged.

3.5 Statistical analyses

Univariate and comparative statistical analyses were conducted to determine which variables were risk factors for *S. aureus* colonization by using independent samples t-test, Fisher's exact test, and chi squared analyses. Odds ratios and corresponding 95% confidence intervals were estimated using binary logistic regression analyses for S. *aureus* carriage for each potential risk factor. Statistical significance was set at $p < 0.05$.

4. RESULTS

4.1 Sample Summary

The study observed 119 consecutive patients admitted to the Arthroplasty Unit at CMJAH between October and December 2016. Figure 4.1 shows the summary of the results of the study. There were 119 patients included in the study that were subdivided into 41 patients (34.5%) for THA and 78 patients (65.5) for TKA. There were no patients colonized with MRSA and the overall TJA prevalence of MSSA-colonization was 31.9% (n = 38).

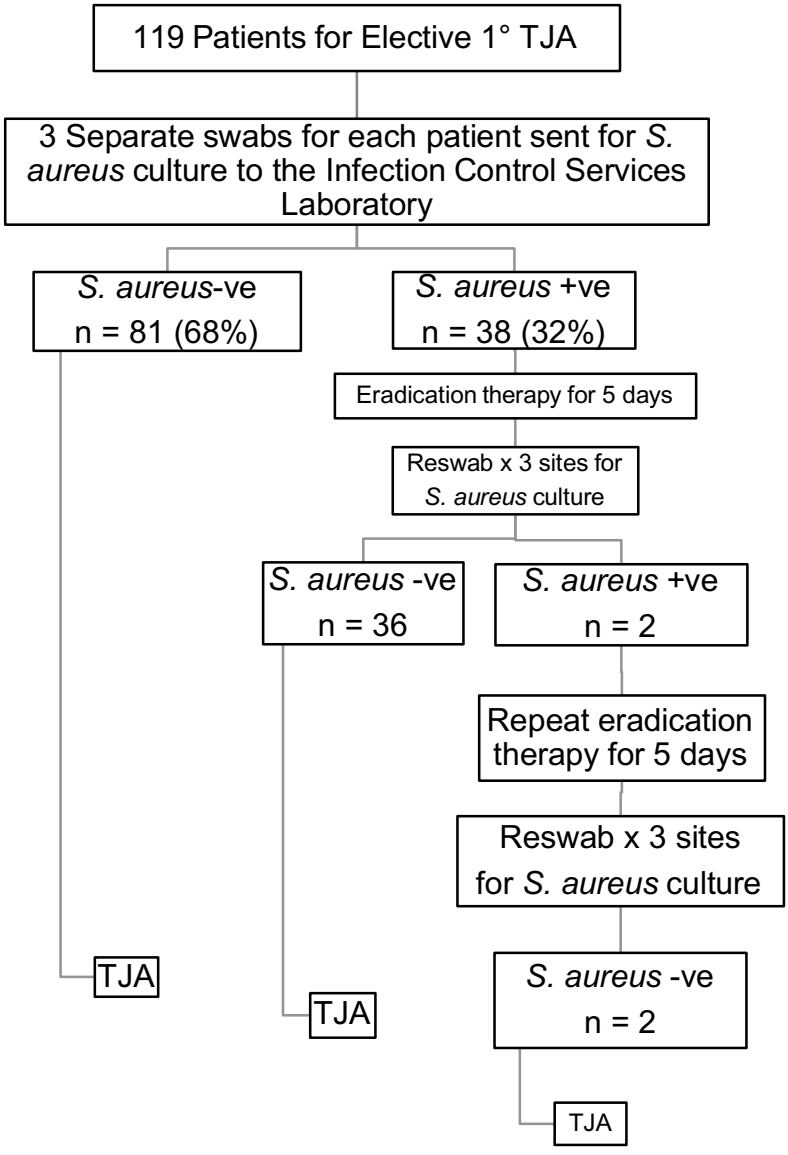

Figure 4.1: Flow diagram of study results

The results of our study are presented in more detail below. **Section 4.2** provides a summary of participant demographic information used to determine the relevant risks for *S. aureus* colonization of patients undergoing elective 1° TJA in our institution. **Section 4.3** reports the prevalence rates of *S. aureus* colonization amongst the sample of patients. A comparison is drawn by demographic group, TKA *versus* THA and site of swab taken. **Section 4.4** assesses the efficacy of the decolonization protocol used in our study for patients pre-operatively colonized with *S. aureus*. Secondly, it evaluates the association between *S. aureus* colonization and subsequent complications and re-admission rates after TJA.

4.2 Demographic data of Participants

The demographic results of our study are presented below (see Table 4.1).

Table 4.1: Demographics of study sample (96)

Demographic	Group	n	%	95% CI (%)
Age	< 50 yrs	10	8.4%	(4.4 - 14.4%)
Mean 62.69 (SD ± 9.96)	50 – 70	81	68.1%	(59.3 - 75.9%)
95% CI (60.88 - 64.50)	> 70 yrs	28	23.5%	(16.6 - 31.7%)
Sex	Male	30	25.2%	(18.1 - 33.5%)
	Female	89	74.8%	(66.5 - 81.9%)
Race	Black	79	66.4%	(57.6 - 74.4%)
	Coloured	6	5.0%	(2.1 - 10.1%)
	Indian	6	5.0%	(2.1 - 10.1%)
	White	28	23.5%	(16.6 - 31.7%)
Domicile	Rural	8	6.7%	(3.2 - 12.3%)
	City	111	93.3%	(87.7 - 96.8%)

The sample population in our study is reflective of the population that the Arthroplasty Unit in CMJAH serves. The sample is an accurate representation of the general population in South Africa. In 2018, Statistics South Africa (97) estimated

that there were 57.73 million people living in South Africa, of which 49% were male and 51% were female. The report projected that 14.7 million (25.4%) people resided in Gauteng province alone. It is estimated that 80.9% (46,682,900) of South Africans are Black, while 8.8% (5,074,300) are Coloured, 2.5% (1,448,300) are Indian/Asians and 7.8% (4,520,100) are Caucasian, respectively. There were almost 7.52 million HIV-infected people in South Africa. The overall HIV-seroprevalence is approximately 13.1%, while of 19.0% of adults aged 15 – 49 years are HIV-infected.

4.3 Prevalence rates of S. aureus colonization

4.3.1 demographic group

The prevalence of *S. aureus* colonization amongst the sample of patients is reported in Table 4.2. Overall, 31.9% (n = 38) of participants undergoing TJA were colonized with *S. aureus* pre-operatively.

Table 4.2: Prevalence of S. *aureus* colonization by demographic group (96)

Demographic	**Group**	**Sample**	***S. aureus* Prevalence**			**p-value**
		n	**n**	**%**	**95% CI (%)**	
Total sample		**119**	**38**	**31.9**	**(24.1 - 40.7)**	
Age	< 50 yrs	10	3	30.0	(9.3 - 60.6)	0.639
	50 - 70	81	28	34.6	(24.9 - 45.3)	
	> 70 yrs	28	7	25.0	(11.9 - 42.9)	
Sex	Male	30	9	30.0	(16.0 - 47.7)	0.793
	Female	89	29	32.6	(23.5 - 42.8)	
Race	Black	79	26	32.9	(23.3 - 43.7)	0.877
	Coloured	6	2	33.3	(7.7 - 71.4)	
	Indian	6	1	16.7	(1.9 - 55.8)	
	White	28	9	32.1	(17.2 - 50.5)	
Domicile	Rural	8	3	37.5	(11.9 - 70.5)	0.727
	Urban	111	35	31.5	(23.4 - 40.6)	
	No	76	23	30.3	(20.8 - 41.2)	

There were no statistically significant differences across demographic groups in the proportions of patients presenting with *S. aur*eus colonization given the overlapping of the 95% confidence intervals. An Exact Test procedure, which calculates exact *p*-values where comparative sub-sample groups are small or unbalanced, also supported the finding that no variables were significantly attributed to *S. aureus* colonization. Therefore, none of the demographic indicators were clear statistical predictors of pre-operative *S. aureus* colonization.

4.3.2 TKA/THA

The prevalence of positive of swab cultures by type of TJA is summarized in Table 4.3.

Table 4.3: Prevalence of S. *aureus* colonization by TKA/THA (96)

Demographic	**Sample (n)**	***S aureus* Prevalence**		***p*-value**
		%	**95% CI (%)**	
Total	**119**			
TJA	38	31.9	24.1 - 40.7	0.067
TKA	26	36.6	26.1 - 48.2	
THA	12	25.0	14.5 - 38.5	

Patients awaiting TKA were 1.7 times more likely to have *S. aureus* colonization than those awaiting THA (OR TKA = 0.58, OR THA = 0.33) .

4.3.3 site

The overview of yield of swab cultures done on individual culture sites on participants is summarized in Table 4.4.

Table 4.4: Swab culture results of the anatomical sites (96)

Demographic	**Sample (n)**	***S aureus* Prevalence**		***p*-value**
		%	**95% CI (%)**	
Culture positive samples	**38**			
Nasal	31	81,6	(67.2 - 91.4)	0.000
Groin	15	39,5	(25.2 - 55.3)	
Axilla	11	28,9	(16.5 - 44.5)	

Swabs from the anterior nares provide significantly better yields of *S. aureus* colonization than swabs from the axilla and groin respectively. A proportional test showed significant difference in prevalence rates with a *p*-value = 0.000. Further inspection of the results (see Figure 4.2) exposed that of the 38 patients with *S. aureus* colonization, 42.1% (n = 16) tested positive in the anterior nares only, compared to 7.9% groin only (n = 3) and 5.3% axilla only (n = 2). The remainder of cases showed: 21.1% nasal and groin (n = 8); 13.2% nasal and axilla (n = 5); 5.3% groin and axilla (n = 2); 5.3% in all three areas (n = 2). Colonization would have been identified in 81.7% of cases if only the anterior nares were tested.

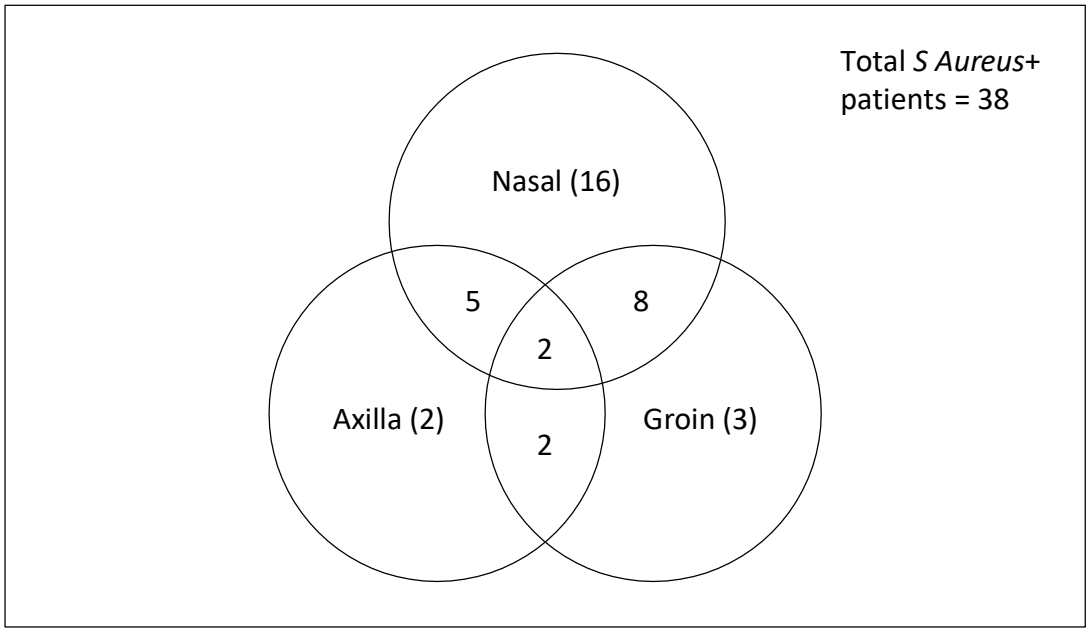

Figure 4.2: Summary of S. aureus prevalence Sensitivity according to anatomical sites screened

4.3.4 Clinical profile

The clinical profiles of our study sample are summarized in Table 4.5 (96)

Table 4.5: Prevalence of S. *aureus* colonization by clinical indicators

Demographic	Group	Sample n	Prevalence n	%	95% CI (%)	*p*-value
Diabetes	No	100	32	32.0%	(23.5 - 41.6%)	0.971
	Yes	19	6	31.6%	(14.4 - 53.9%)	
Hypertension	No	76	23	30.3%	(20.8 - 41.2%)	0.604
	Yes	43	15	34.9%	(22.0 - 49.7%)	
Thyroid	No	6	4	66.7%	(28.6 - 92.3%)	0.215
	Yes	113	34	30.1%	(22.2 - 39.0%)	
Cardiac	No	10	4	40.0%	(15.3 - 69.6%)	0.081
	Yes	109	34	31.2%	(23.1 - 40.3%)	
RA	No	17	9	52.9%	(30.3 - 74.6%)	0.45
	Yes	102	29	28.4%	(20.4 - 37.7%)	
PTB	No	1	0	0.0%		
	Yes	118	38	32.2%	(24.3 - 41.0%)	
COPD	No	10	3	30.0%	(9.3 - 60.6%)	0.664
	Yes	109	35	32.1%	(23.9 - 41.3%)	
Smoking	No	24	8	33.3%	(17.2 - 53.2%)	0.869
	Yes	95	30	31.6%	(22.9 - 41.4%)	
Alcohol	No	26	8	30.8%	(15.8 - 49.8%)	0.886
	Yes	93	30	32.3%	(23.4 - 42.2%)	
HIV	Negative	94	28	30.0%	(21.7 - 39.5%)	0.065
	Positive	25	10	42.1%	(22.3 - 64.1%)	
ASA	1	13	6	46.2%	(22.1 - 71.7%)	0.577
	2	67	22	32.8%	(22.5 - 44.6%)	
	3	39	10	25.6%	(14.0 - 40.7%)	
Previous THA/TKA	No	81	23	28.4%	(19.5 - 38.8%)	0.089
	Yes	38	15	39.5%	(25.2 - 55.3%)	
BMI	<30	44	17	38.6%	(25.3 - 53.4%)	0.484
Mean 33.46 (SD ± 6.15)	30-39	53	15	28.3%	(17.6 - 41.3%)	
95% CI (31.07 - 36.94)	>40	22	6	27.3%	(12.3 - 47.8%)	

There were no statistically significant differences across groups in the proportions of patients presenting with *S. aur*eus colonization given the overlapping of the 95%

confidence intervals. The exact *p*-values were also non-significant indicating no statistical differences in proportion. None of the co-morbidities were therefore identified as statistical predictors of pre-operative *S. aureus* colonization.

4.4 Decolonization of S. *aureus* carriers

The eradication rate of patients with pre-operative S. *aureus* colonization after five days of treatment was 94.74% (n = 36). There were two patients (5.26%) who required another one week of eradication treatment. After repeating five more days of topical intra-nasal mupirocin and chlorhexidine body washes, both patients had no subsequent growth on repeat nasal, axillary and inguinal swabs. One of these patients underwent elective 1° THA and one received elective 1° TKA, respectively. The overall eradication rate pre-operatively was therefore, 100% (n = 38).

4.4.1 Complications of TJA patients

The complications that occurred following TJA in our study sample are summarized in Table 4.6.

Table 4.6: Complications of TJA patients (96)

Pathological Cause	**Prevalence (%)**		
	Total (n = 119)	**S Aureus +ve (n = 38)**	**S Aureus -ve (n = 81)**
ALL CAUSE	7.6	7.9	7.4
Wound ooze	2.5	2.6	2.5
Deep Vein Thrombosis	2.5	2.6	2.5
Myocardial Infarction	0.84	0	1.2
Sciatic Nerve neuropraxia	0.84	0	1.2
Pneumonia	0.84	2.6	0
p-value = 0.925			

The overall complication rate of all participants who underwent TJA during our study was 7.6% (n= 9). There was no significant difference (p = 0.925) in the incidence of complications in participants with or without *S. aureus* colonization. All three wound oozes occurred in patients after 1° elective TKA. These were managed by

withholding anti-coagulation for two days and icing the affected limb. The wound ooze in all three patients had stopped before discharge. There were no reported septic sequelae, with no incidences of surgical site infections or deep infections in this cohort of patients.

4.4.2 Complications according to the Clavien-Dindo Classification

The complications that occurred following TJA of our study sample according to the Clavien-Dindo classification is summarized in Table 4.7.

Table 4.7: Incidence of complications according to the Clavien-Dindo classification (96)

	Initial Culture		
	Negative	**Positive**	**Total**
Grade I	3	0	**3**
Grade II	2	2	**4**
Grade IIIA	0	1	**1**
Grade IIIB	0	0	**1**
Grade IVA	1	0	**1**
Grade IVB	0	0	**0**
Grade V	0	0	**0**
Total	**6**	**3**	**9**

4.4.2 Re-admission rates at 30-, 60- and 90-days

The overall 30-, 60- and 90-days re-admission rates for all patients after TJA were 2.52%, 3.36% and 3.36%, respectively. There was no difference in the 30-, 60- and 90-days re-admission rates in patients colonized with S. *aureus* and those not colonized with S. *aureus*.

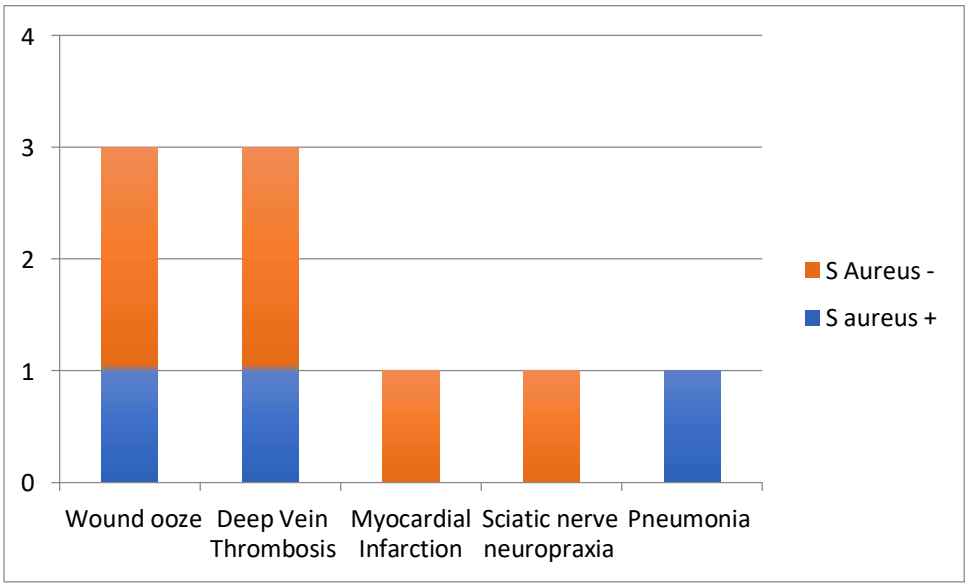

Figure 4.3: Cumulative 30-, 60- and 90-days re-admission rates and pathological causes (96)

There were three patients re-admitted with DVTs of which two patients were re-admitted within 30-days and one within 60-days. No patients were re-admitted as a result of septic complications. All four re-admissions (three DVTs and one MI) were due to medical reasons. There were no incidences in which patients were re- admitted due to joint-specific complications.

4.4.2 Survival rate of Total Joint Arthroplasty

No patients that underwent elective 1° THA or TKA in our study needed revision TJA for any reason at a mean follow-up of 37.34 months. There was, therefore, no association with early- to mid-term failure and S. *aureus* colonization. The three-year survival rate of TJA in our study is 100%.

5. DISCUSSION

5.1 Background

Our study demonstrates the prevalence of *S. aureus* colonization in patients undergoing 1° elective TJA in a South African academic, referral institution. It shows that the main reservoir of *S. aureus* colonization is the anterior nares. It highlights that improved detection rates of *S. aureus* colonization is achieved by increasing the number of anatomical sites tested. No significant risk factors for *S. aureus* colonization were identified. Furthermore, our study emphasizes the efficacy of a decolonization protocol involving a combination of intra-nasal mupirocin ointment and chlorhexidine baths. The short and long-term complication and re-admission rates in decolonized patients were found to be equivalent to patients who were not initially colonized by *S. aureus*.

5.2 Prevalence of *S. aureus* colonization

The overall prevalence of *S. aureus* colonization in patients presenting for elective 1° TJA to the CMJAH Arthroplasty Unit in Johannesburg, South Africa was 30.8%. All patients were colonized with methicillin sensitive *Staphylococcus Aureus* (MSSA). There were no cases of methicillin resistant *Staphylococcus Aureus* (MRSA) colonization. The incidence of *S. aureus* colonization in patients presenting for elective 1° THA and 1° TKA was 25.0% and 36.6%, respectively. The global prevalence of *S. aureus* colonization varies geographically (62,98). Globally, the colonization rates of MSSA in the general population have been reported to range from 20 – 36.4% (25,62,83,98–100). The colonization rates of MRSA has been reported as 0.6 – 6% in the literature (62,98).

Our study reports similar rates of *S. aureus* colonization to other studies in the literature. Moroski et al. (83) reported that 19.4% of 289 patients presenting for both 1° and revision TJA were *S. aureus* carriers. Chen et al. (100) reviewed 106 patients that underwent 1° TJA and reported that 24.8% were colonized with *S. aureus.* Kim et al. (47) reported that the incidence of *S. aureus* colonization was 27% of all orthopaedic patients. A direct comparison of our results, however, must be tempered. These studies used only nasal swabs to determine the carrier status,

whereas, our study sampled three different anatomical sites. While, our study demonstrated a prevalence of methicillin-sensitive S. *aureus* colonization in the anterior nares consistent with international studies (10,48,73,88). However, there were no patients who were colonized with MRSA in this group of patients. In contrast, an incidence of MRSA nasal colonization was found to be 2 – 6% in the USA alone (10,73). Hadley et al. (101) reviewed 1644 patients undergoing TJA and reported that 3.5% were colonized with MRSA.

The total area for the anterior nares to accommodate different bacterial genotypes is limited (102) Subsequently, there is competition between bacterial genotypes to occupy this "ecological niche" (102). Co-inhabitation of the anterior nares by MSSA and MRSA is rare (46). MSSA is more likely to inhabit and thrive in this area than MRSA. MSSA may prevent the colonization of the anterior nares by MRSA and therefore actually supplement resistance to MRSA. Our study did not investigate whether other bacterial species colonized the patients awaiting 1° TJA at our health institution. It did not examine the potential of intra-species competition. The potential for the under-reporting of bacterial colonization does, therefore, theoretically exist. This is highlighted by the work of Walsh et al. (103) who reported that while the incidence of MSSA and MRSA colonization in 716 patients undergoing 1° TJA was 17.5% and 1.8%, respectively, a significant 11.7% of these patients were colonized by other bacteria. Subsequently, a future review of South African may need to include the testing for other bacterial species.

5.3 Risk factors of *S. aureus* colonization

No significant risk factors that could potentially predict for pre-operative colonization with *S. aureus* were recognized in our study. Age, gender, race, previous TJA, BMI and any comorbid conditions including thyroid disease, cardiac disease, rheumatoid arthritis, pulmonary TB and COPD were found to have no identifiable, statistically significant impact on the risk of pre-operative *S. aureus* colonization. Unlike in our study, other studies in the literature have linked *S. aureus* colonization with various risk factors. Walsh et al. (103) were able to report that diabetes, renal insufficiency and immunosuppression were statistically significant risk factors for *S. aureus* colonization. Nasal swabs taken pre-operatively in our study, however, identified

11.70% of patients who cultured organisms other than MSSA or MRSA(104). Smoking and immunosuppression, interestingly, has been shown to predict a greater chance of colonization with bacteria other than MSSA or MRSA(104). Moroski et al. (83), meanwhile, has shown that higher ASA grading inferred a greater risk of *S. aureus* colonization.

Similar to the findings in our study, however, Price et al. (16), evaluated 264 general orthopaedic patients two weeks before surgery and discovered no discernable risk factors for MSSA colonization. Recent hospitalization and nursing home stay were, however, linked with a greater likelihood of MRSA colonization (16). Furthermore, lifestyle habits such as smoking history and alcohol use had no significant influence on carrier status in our study. Evaluation of the cohort of HIV-infected patients, albeit small, also demonstrated no difference in the incidence of *S. aureus* colonization. The literature has reported that risk factors for nasal carriage of *S. aureus* include obesity (74), rheumatoid arthritis (105), hormonal contraception use (106), skin and soft tissue infections (107), active smokers (74,108) and diabetic patients undergoing dialysis (109). Greater rates of *S. aureus* colonization have been reported in HIV-infected patients (110,111). The incidence of MRSA colonization has been reported to be as high as 31% in immunocompromised inpatients (110). A review of patients from two healthcare institutions in Botswana found the nasal colonization of *S. aureus* and MRSA was 36.9% and 3.2%, respectively, for 404 HIV-positive outpatients (111). Living with children in a high density living habitat in HIV-infected patients was reported as significant risk factor for *S. aureus* colonization.

All HIV-infected patients in our study were on HAART pre-operatively. The viral load (VL) of all patients was less than detectable (LDL) before surgery. The low incidence of HIV-infected patients colonized with *S. aureus* in our study may subsequently be as a consequence of this improved virologic control which may potentially have inferred some degree of defense from *S. aureus* colonization. Our study, however, did not assess some potential risk factors reported in the literature that have been associated with an increased incidence of *S. aureus* colonization. Jialing Lin et al. (112), for instance, reported that poor hand hygiene and infrequent baths were and important risk factors for *S. aureus* carriage amongst 2172 pregnant women evaluated. Ayepola et al. (63) reported that previous hospitalization within the last

year, sports participation and a recent skin infection contributed to positive *S. aureus* colonization in an evaluation of 277 healthy volunteers. While these reports were not in a similar population group, i.e. patients undergoing 1° TJA as in our study, they do serve to highlight the role that other factors potentially may play in increasing the possibility of *S. aureus* colonization.

5.4 Testing for *S. aureus* colonization

In our study 81.7% of identified MSSA-carriers had positive cultures from swabs taken from the anterior nares. The literature has demonstrated that the anterior nares are the primary site of MSSA and MRSA colonization (20,21,62). Other areas which may serve as alternate reservoirs of MSSA and MRSA colonization include: the oropharynx, axillae, groin, perineum, forehead, and neck (26,62,113,114). Sampling these sites to supplement the testing of the anterior nares may increase the detection rates of *S aureus* carrier status. Obviously, testing alternate areas comes with an increased financial burden. Testing only the axilla and groin areas in our study would only have identified 51.7% of *S. aureus* carriers. Adding testing of the groin to the anterior nares swabs increased the identification of *S. aureus* colonization to 94.7%. Conversely, only testing the anterior nares and the axilla would only miss 7.9% of colonized patients.

The practice of combining testing of alternate sites with the anterior nares to identify carrier status remains controversial. Colonization of secondary sites independent of the anterior nares is rare. The prevalence of MRSA and MSSA colonization in the general population may influence this decision. The CDC in the USA, which has a high rate of MRSA colonization in the general population, advocates that testing of the anterior nares alone may be sufficient (62,115). However, it has been argued that in areas with lower rates of *S. aureus* colonization such as certain Scandinavian countries, it may be pertinent to increase the number of anatomical areas tested to improve the yield (26,114).

5.5 Eradication of *S. aureus* colonization

In our study, MSSA colonization was treated and eradicated with topical mupirocin applied twice daily to the anterior nares and twice daily washes with chlorhexidine for five days. This protocol resulted in the initial, successful eradication of 93.5% of patient on subsequent testing. Ultimately, all patients were underwent effective eradication therapy using the same treatment strategy prior to surgery. Topical mupirocin is regarded as the most reliable and effective topical antibiotic option for pre-operative nasal colonization (116,117). It is also regarded as the most inexpensive option, too (91). The use of topical mupirocin has shown a five times decrease in the incidence of *S. aureus* infections in a randomized control study (88,101).

The efficacy of pre-operative decolonization treatment for MSSA and MRSA nasal carriers undergoing primary and revision TJA was appraised by Moroski et al. (83). The decolonization strategy included a five-day pre-operative course of intra-nasal mupirocin 2% twice per day in carriers. The authors demonstrated that 34% (15 of 44 patients) of MSSA carriers remained colonized despite treatment, while 92% of MRSA-carriers (11 of 12 patients) were successfully decolonized. Our study proved the efficiency of using mupirocin to facilitate nasal decolonization, however, poorer results in MSSA-carriers is noteworthy. Chen et al. (13) showed that intra-nasal mupirocin decreased the incidence of pre-operative MSSA-colonization from 22% to 2.8% post-operatively. Our study demonstrated that MRSA colonization was reduced from 4.6% pre-operatively to 0% post-operatively. The decrease in MSSA-colonization was statistically significant (17). The combination of the application of mupirocin topically to the anterior nares and full body chlorhexidine wash in this series produced postive results. Our study reinforces that the incorporation of both treatment modalities is advisable. Furthermore, it supports the good results seen in this research report.

In other studies from the literature, successful eradication of MSSA and MRSA was reported as 81.5 – 93% (84,88,118,119). Screening and treatment in these papers was generally undertaken two to four weeks before the index surgical procedure. Similarly, in our study, testing for S. *aureus* was done the week before proposed

surgery and a positive result delayed surgery while the eradication protocol was instituted. The ultimate success of the eradication strategy employed in our study was mirrored by a study by Barbero Allende et al. (120). These authors reported that a decolonization protocol combining topical mupirocin with chlorhexidine skin wash for five days produced a reduction in the incidence of SSI by 40.7%.

5.6 Correlation of *S. aureus* colonization with complications and PJI

In our study, there was no association between pre-operative *S. aureus* colonization and post-operative adverse events. There were no infective complications in either the pre-operatively colonized and non-colonized patients undergoing TJA. PJI is caused most commonly by *S. aureus* and coagulase negative Staphylococcus (73,91). In general, the three potential sources of PJI include endogenous (from the patient), exogenous (as a consequence of external contamination) and haemotogenous spread (62). Colonization with *S. aureus* has the potential to cause an endogenous infective complication. The risk of PJI is nine times greater in nasal carriers of *S. aureus* (88,121). The risk of infective complications is increased four-fold for patients with MRSA-colonization in comparison with MSSA-colonization, respectively (91). The literature reflects that the causative strain of *S. aureus* – associated PJI is identical to the strain cultured in the anterior nares of 85% of patients (88,100,121). Using innovative molecular typing techniques, Skramm et al. (92) linked the exact *S. aureus* strain in nasal carriers with the infective pathogen in 85.71% of patients with SSI after THA, TKA and spine surgery. A systematic review by Sadigursky et al. (116), including 79 studies reported in both Portuguese and English languages, evaluated the effect of routine pre-operative MRSA eradication therapy on post-operative infective complications. Sadigursky et al. (116) reported that the incidence of SSIs decreased by approximately 39% subsequent to the use of prophylactic MRSA eradication treatment. *S. aureus* colonization may additionally be attributed to a more significant rate of infections as it may be a marker of patients with an increased number of co-morbidities (122). It may also induce a pro-inflammatory biological environment making patients more vulnerable to infections (123,124).

This study showed that the incidence of adverse events, most notably post-operative infective complications, after TJA were equivocal for *S. aureus* carriers and non-carriers after successful decolonization. The value of screening for *S. aureus* carriers and subsequent decolonization of carriers, however, remains controversial. Sporer et al. (3) analyzed 9690 consecutive patients undergoing elective TJA and reported that the incidence of SSI decreased by 69% once screening for MSSA and MRSA and subsequent decolonization was added to their institution's peri-operative surgical work-up. However, screening and decolonization protocols may be beset by problems with culture interpretation, difficulties associated with patient selection for decolonization and additional costs. Subsequently, universal decolonization protocols, obviating the need for pre-operative S. aureus cultures have become more popular. Stirton et al. (126) reported that empiric treatment of patients undergoing TJA for S. aureus colonization streamlined workflow, limited the potential for clerical error, decreased the likelihood of undertreatment and did not potentiate an increase in subsequent antibiotic resistance. Proposing empiric treatment or screening for S. aureus colonization and subsequent decolonization in our institution is beyond the scope of this paper. Subsequent research will be undertaken by the author to propose best fit for his institution and TJA patient profile.

5.7 Limitations

A limitation of our study is that the testing for *S. aureus* did not utilize other methods or procedures such as polymerase chain reaction (PCR) tests or pre-plating the broth enrichment of swabs for culture to improve the yield. These have been shown to conclusively improve the detection rate of nasal MSSA colonization (125). Tsang et al. (125) reported that almost one third of both MRSA and MSSA carriers are overlooked should PCR and pre-plating of the broth enrichment of culture swabs not be added to traditional swabbing techniques. The use of PCR testing would have exacerbated the expenses of performing this research project. Some may justify the additional expense of PCR testing by an increased detection rate of MSSA and MRSA resulting in superior patient care by decreasing the transmission of MSSA and MRSA (127). The subsequent amelioration of infection rates would translate to cost reductions due to fewer cases which complicate and a lower mortality rate (47,127).

A further limitation of our study is that only consecutive patients awaiting TJA were included for testing for *S. aureus* colonization pre-operatively. As a result there was no randomized group and no control group with which to ultimately contrast and evaluate all outcomes. This would most notably have been beneficial to more clearly elucidate the impact of decolonization therapy in reducing septic sequelae in TJA. The patients included in our study were from a single health institution in Johannesburg, South Africa. Although it is a referral academic unit which attempts to meet the Arthroplasty needs of a number of surrounding hospitals and clinics from a variety of different geographic areas, it is not entirely clear whether this particularly cohort definitively represents the general South African Arthroplasty population. Furthermore, the success of eradication therapy is greatly dependent upon compliance with the prescribed eradication treatment strategy. The scope of our study, however, did not extend to explore this issue. A cautionary note should, therefore, be struck with the good eradication results reported in our study. The attainment of successful eradication therapy was only evaluated on repeat swabs taken immediately after conclusion of the eradication therapy. In a meta-analysis, Ammerlaan et al. (87,128) reported that the success rate of decolonization therapy decreased from 94% at one week to 65% after at least two weeks of eradication

therapy (127,128). The authors attributed treatment failure to increased hospital stays, colonization of multiple anatomic sites and mupirocin resistance (87,128,129).

The value of diligent adherence to a specific decolonization protocol was highlighted by Immerman et al. (119) who attributed the success of 96% of 134 patients who underwent a decolonization protocol to strict, unrelenting compliance. Patient compliance may have been artificially exaggerated in our study as all the selected patients were acutely and keenly aware that surgery was precluded entirely if post-eradication therapy cultures remained positive. The patients in our study were, therefore, more predisposed to being actively compliant with the prescribed eradication therapy. In essence, this was an observational study. While every effort was made to control for other known risk factors, further unmeasured confounders may be implicated in the evolution of adverse events especially post-operative infective complications.

6. CONCLUSION

Our study discovered that the prevalence of *S. aureus* colonization in patients undergoing TJA was 30.9%. No risk factors significantly impacted on the prevalence of *S. aureus* colonization. The anterior nares were the major reservoir of *S. aureus* colonization and nasal swabs were positively cultured in 81.7% of patients. A decolonization protocol involving intra-nasal mupirocin and chlorhexidine baths successfully eradicated 93.5% of *S. aureus* carriage. There was no difference in both the early- and mid-term complication rate in either *S. aureus* carriers or non-carriers in patients undergoing 1° elective TJA post-operatively after successful pre-operative decolonization.

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Appendix A: HREC (Medical) clearance certificate

R14/49 Dr Jurek Rafal Tomasz Pietrzak

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160870

NAME: (Principal Investigator)	Dr Jurek Rafal Tomasz Pietrzak
DEPARTMENT:	Orthopaedic Surgery Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Staphylococcus Aureaus Colonization and Surgical Site Infection in Patients Admitted to a South African Urban Academc Hospital for Elective Total Joint Arthroplasty
DATE CONSIDERED:	26/08/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Lipalo Mokete and Prof A Robertson
APPROVED BY:	Professor P Cleaton-Jones,Chairperson, HREC (Medical)
DATE OF APPROVAL:	19/09/2016

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 10004, 10th floor, Senate House/3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in August and will therefore be due in the month of August each year.

Principal Investigator Signature

Date 22/9/2016

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix B: Data collection sheet 1

Staphylococcus Sp. Colonization Study
Pre-Operative Data Capture Sheet

Name:

_____

Hospital Number:

_____

Sticker

Age: Sex:

☐M ☐F

Tel no 1:

Date of Admission:

Demographic data: ☐Black ☐Coloured ☐Indian ☐White

Domicile: ☐City ☐Town ☐Rural

Medical history:

☐Diabetes ☐Hypertension ☐Thyroid disease ☐Rheumatoid arthritis
☐Cardiac disease ☐Previous Pulmonary TB ☐Asthma/COPD/Emphysema
☐Renal disease

☐Smoking Pack years:
☐Alcohol Units/day:

RVD ☐-ve ☐+ve ☐ARVs CD4+: Viral load:

ASA rating:

Surgical history:

☐Previous THA ☐R Year: ☐L Year:

☐Previous TKA ☐R Year: ☐L Year:

Booked for:

☐R ☐L ☐THA ☐TKA Diagnosis:

Other data:

Pre-op Hb:

Weight: kg Height: m BMI:

Suprapatellar index: Urine MC & S:

Appendix C: Patient Information Sheet and Informed Consent Form for a participant

Study Title: ***Staphylococcus aureus colonization and surgical site infection in patients admitted to a South African urban academic hospital for elective Total Joint Arthroplasty.***

Hello. My name is Jurek Pietrzak. I am a Specialist Orthopaedic Surgeon. You have been booked for a Total Hip/Knee Replacement in the Arthroplasty Unit at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). This is a very good and successful operation. This operation will allow you to have a more pain free and functional life.

However, despite improvements in the quality of life that this procedure allows you, there are unfortunately many potential complications associated with it. One such complication is that your new Total Hip/Knee prosthesis can become infected.

We take many precautions to avoid this infection. These precautions include how we prepare you for theatre, what we do in theatre and things we prescribe and do for you after your operation.

Some things are, however, out of our control. One such thing is *Staphylococcus Aureus* and *Methicillin-resistant Staphylococcus Aureus* bacteria colonization. These are bacteria that may exist and live on your skin, in your nose, under your arms or on the skin in your groin. Most times these bacteria are not harmful and you can live without even noticing that they exist. However, in Total Hip/Knee Replacements these bacteria may enter the bloodstream from these areas and attach to your new prosthesis and cause an infection. This infection may result in severe consequences. These include a longer stay in hospital, more operations to clean out the infection, operations to take out the prosthesis and put new prosthesis in and even amputation of the leg.

We are able to test to see if you have these bacteria living on the skin in these areas. There are also different ways in which these bacteria can be killed. However, sometimes they may come back.

There is no clear and best way to deal with this issue. Currently, in South Africa we do not know how many patients may be waiting for a Total Hip/Knee Replacement who may be colonized with Staphylococcus Aureus and Methicillin-resistant Staphylococcus Aureus bacteria.

We would, therefore, like to test to see if you are a carrier of Staphylococcus Aureus or Methicillin Resistant Staphylococcus Aureus (MRSA) bacteria before your operation.

The test for these bacteria is not painful or uncomfortable. We will use 3 swabs testing 3 different areas of your body. These 3 areas include your nose, the skin under your arms and the skin in your groin. These swabs will be rubbed gently in your nose, under arms and in your groin individually. They will then be sent to the laboratory for testing. We will check if any bacteria are present.

A history of your condition and other illnesses will be taken. A clinical examination will be performed on you as per normal. All this information and the results of the swab tests will be kept safe and confidential.

Whatever the result of these swab tests is you will get your operation as normal. If you decide not to be part of this study you will not be prejudiced in any way. You will be treated like everyone else.

Contact Details:

If there are any problems you are more than welcome to contact Dr Jurek Pietrzak. His telephone number is 0834568090. If necessary you can mail him too on jrtpietrzak@yahoo.com alternatively my Supervisor Dr Mokete on cell: 082 570 6496.

You are also able to contact the Human Research Ethics Committee (HREC) at the University of the Witwatersrand with any questions and/ or concerns

HREC (Medical) contact details: Prof P Cleaton Jones, Tel 011 717 2301, email peter.cleaton-jones1@wits.ac.za, Mr Rhulani Mkansi Rhulani.Mkansi@wits.ac.za or Ms Zanele Ndlovu zanele.ndlovu@wits.ac.za – 011 717 1252/2700/1234/2656

Informed Consent Form for a participant

I, _ (full name and surname) agree to participate in the study titled: ***Staphylococcus aureus colonization and surgical site infection in patients admitted to a South African urban academic hospital for elective Total Joint Arthroplasty.***

☐The procedures/questionnaires have been explained to me and I understand and appreciate their purpose, any risks involved, and the extent of my involvement. I have read and understand the attached information sheet.

☐I understand that the procedures form part of a research project and may not provide any direct benefit to me.

☐I understand that all experimental procedures have been sanctioned by the Committee for Research on Human Subjects, University of the Witwatersrand, Johannesburg.

☐I understand that my participation is voluntary and that I am free to withdraw my participation from the project at any time without prejudice.

☐I understand that I have been given the contact details of Dr Pietrzak and I am aware that I may contact him at any time with any concerns, questions or complaints

_____ - _

Participant name and signature Date

_____ - _

Investigator name and signature Date

Appendix D: Data collection 2

Staphylococcus Sp. Colonization Study

Post-Operative Data Capture Sheet

Name:

_____

Hospital Number:

_____

Sticker

Age: Sex: ☐M ☐F

Tel no 1 :

Tel no 2:

Admission:

Date of Admission: Date of discharge:

_____

No of TOTAL days in hospital: days

Surgery:

Date of surgery:

No of days in hospital before surgery: days

Surgical Time start: Surgical time end:

Total surgical time: mins

Intra-operative blood transfusion: ☐Yes ☐No Units:

Cemented prosthesis: ☐Yes ☐No

Perioperative:

Type of anaesthesia: ☐GA ☐Spinal/epidural Regional ☐Intra-articular injection

Lines: ☐A-line ☐CVP line ☐urinary catheter

Hospital stay:

Post-operative admission: ☐General ward ☐HCA ☐ICU

No. of days in HCA/ICU: days

Post-operative blood transfusion: ☐Yes ☐No Units:

Routine trips to smoke: ☐Yes☐No

Days post-operatively until

Urinary catheter out: days

CVP line out: days A-line out: days ivi line out: days

Portovac drain out: days

Post-operative Hb: