

THE EPIDEMIOLOGY OF HAND
INFECTIONS AND INCIDENCE OF
*COMMUNITY ACQUIRED METHICILLIN
RESISTANT STAPHYLOCOCCUS
AUREUS* AT CHRIS HANI
BARAGWANATH ACADEMIC HOSPITAL



Dr Ashley Naidoo

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

Johannesburg, 2018

Declaration

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


.....

(Signature of candidate)

8th...day of ...June....2018.....in.....Johannesburg

In memory of my father

Morgan Naidoo

1955 - 2007

Presentations arising from research project

The content of this research project has not been presented at a recognised congress at present but shall be submitted for presentation at the 2018 SASSH congress.

Publications arising from research project

The content of this research project has not been published in an accredited journal at present. The author and supervisors wish to submit this work for publication in the future.

Abstract

Hand Infections lead to tissue destruction, disability and financial burden. Most treatment protocols underpin Methicillin based antibiotics despite rising incidence of CA-MRSA, this study aims to assess said incidence in our community and its impact on treatment. This was a prospective cross sectional analytical study performed at Chris Hani Baragwanath Academic Hospital over a 6 month period ending 31 March 2017 of all non-surgical site hand infections. Data was collected via patient questionnaire, theatre note review and microbiology results.

Our results demonstrated a predominance of *Methicillin Sensitive Staphylococcus Aureus* ($n = 121$) and an incidence of CA-MRSA of 2.5%. Our results show a statistically significant rate of repeat procedures and amputations in the CA-MRSA group especially if HIV positive ($p = 0.0125$).

Based on the above findings we cannot recommend routine empiric Oxazolidinone therapy to cover CA-MRSA. We however wish to highlight CA-MRSA as an emerging pathogen especially in the HIV positive subgroup.

Acknowledgements

I would like to acknowledge the following people for their assistance in completing this research project:

Drs T Sefeane and Dr G Biddulph (Hand unit Chris Hani Baragwanath Academic Hospital)

Dr S Pillay (Clinical Pathology Department, University of Witwatersrand)

Professor MT Ramokgopa (Orthopaedic Department, University of Witwatersrand)

Table of contents

Declaration	i
Dedication to Mr M Naidoo	Error! Bookmark not defined.
Presentations arising from research project	iii
Publications arising from research project	iii
Abstract	iv
Acknowledgements	vi
List of Figures	ix
List of Tables	x
Nomenclature	xi
CHAPTER 1.....	1
1 Introduction and literature review.....	1
1.1 Background	1
1.2 Literature review	1
1.3 Study Aim and Objectives	7
CHAPTER 2.....	8
2 Methodology	8
2.1 Research Question	8
2.2 Research Design	8
2.3 Materials and Methods.....	8
2.4 Sample	11
2.5 Data Collection	11
2.6 Data Analysis	12

2.7	Limitations	12
CHAPTER 3.....		13
3	Results	13
3.1	Epidemiology of Hand infections at Chris Hani Baragwanath Academic Hospital ..	13
3.2	Microbiology and incidence of <i>Community Acquired Methicillin Resistant Staphylococcus Aureus</i> in Hand Infections at Chris Hani Baragwanath Academic Hospital.....	16
4	Discussion	18
CHAPTER 5.....		21
5	Conclusion	21
6	References	22
7	Appendices.....	24
A	Demographic Information (Patient Questionnaire)	24
B	Microbiology Data Collection Sheet	25
C	Number needed to treat calculation i.e for Oxazolidenone empiric therapy.....	26
D	Ethics Clearance Certificate (Wits HREC M160683).....	27
E	Turnitin Report.....	28

List of Figures

Figure 1.1 Common smec types isolated in different areas of South Africa.....6

Figure 1.2 Genotype of smec IV MRSA (CA-MRSA).....6

Figure 1.3 Global burden of CA-MRSA.....6

Figure 2.1 A Mueller-Hinton agar plate showing antibiotic resistance.....10

Figure 3.1 Types of Hand Infections at CHBAH.....14

Figure 3.2 Microbiology of Hand Infections at CHBAH.....16

List of Tables

Table 2.1 Standard Operating Procedure MIC0021v9 for antibiotic sensitivity testing.....9

Table 2.2 CDC CA-MRSA Case Definition (2000).....11

Table 3.1 Aetiology of Hand Infections at CHBAH.....13

Table 3.2 Demographic data of hand infections at CHBAH.....15

Table 3.3 2X2 Contingency table of amputated *versus* non-amputated fingers (MSSA vs CA_MRSA).....17

Table 3.4 2X2 Contingency table of amputated *versus* non-amputated fingers (HIV MSSA vs HIV CA-MRSA).....17

Nomenclature

AIDS	Acquired Immunodeficiency Syndrome
CA-MRSA	Community Acquired Methicillin Resistant <i>Staphylococcus Aureus</i>
CD4	T-Helper cell count
CDC	Center for Disease Control
CHBAH	Chris Hani Baragwanath Academic Hospital
GDP	Gross Domestic Product
HIV	Human Immunodeficiency Virus
MCCS	Microscopy Culture and Sensitivity
MRSA	Methicillin Resistant <i>Staphylococcus Aureus</i>
MSSA	Methicillin Sensitive <i>Staphylococcus Aureus</i>
NHLS	National Health Laboratory Service
NICD	National Institute of Communicable Diseases
PBP	Penicillin Binding Protein
PVL	Panton Valentine Leukocidin
US FDA	United States of America Food and Drug Administration Agency
WHO	World Health Organisation

CHAPTER 1

1 Introduction and literature review

1.1 Background

Hand Infections represent a serious clinical entity which may lead to tissue destruction, functional disability and considerable financial burden. The proviso of treatment protocols under pin use of Methicillin based empirical antibiotic therapy directed against *Staphylococcus Aureus*, the commonest isolated organism. Current studies¹ support community acquired methicillin resistant *Staphylococcus Aureus* (CA-MRSA) as a causative organism with increasing incidence. Currently no studies exist in local literature to define the incidence of CA-MRSA in hand infections in South Africa. It is our goal to define the incidence of CA-MRSA within the population of hand infections treated at Chris Hani Baragwanath Academic Hospital over a five-month period, September 2016 to March 2017. Furthermore, we wish to record the aetiology, causative organism and pertinent demographics of the study population to aid future endeavours in optimising our treatment strategy

1.2 Literature review

1.2.1 Aetiology and relevant pathoanatomy of hand infections

Hand Infections represent a serious insult to human dexterity. Tissue loss, adhesions and stiffness render significant disability with ablated osteomyelitis causing disfigurement.¹

Hand infections either occur due to direct inoculation from trauma or haematogenously in immunocompromised patients.

Once local tissue infection occurs within the hand, swelling with impaired circulation and micro-vascular infarction leads to abscess formation. These collections can be sited either

superficially or deep (within deep palmar spaces). Presenting symptoms include pain, swelling, redness and occasionally a draining sinus.

In a pilot study at Dr George Mukhari Hospital Pretoria, the local population of presenting hand abscesses studied reflected the vast majority of cases being superficial collections (60%) with deep sepsis i.e. palmar space, septic arthritis, tenosynovitis and osteitis making up the latter.²

The deep palmar spaces include the thenar, hypothenar and midpalmar spaces. Collections in these spaces often confuse clinicians as the majority of swelling occurs on the dorsum due to lymphoedema.

Flexor tenosynovitis is a deep sited infection wherein pus tracks along the flexor sheath. Kannavel *et al* (1912) described pathognomic clinical signs of tenosynovitis viz, a flexed attitude, pain on passive extension, fusiform swelling and percussion tenderness along the sheath.³ The flexor sheath of the thumb and index fingers are continuous with the radial and ulna bursae respectively. Both these bursae communicate within the palm. Hence a spread of sepsis is possible across this communication. Likewise, the Space of Parona allows pus to track from the palm across the wrist joint.⁴

1.2.2 Epidemiology of hand infections

Hand sepsis represents some 20% of admissions to hand services.² It is estimated that R394550 was spent over 325 days at Pelanomi Hospital, Bloemfontein South Africa, in 2011/2012 in treating hand infections excluding the surgical costs.²

Coupled with lost time at work and reduced productivity, extrapolation of this condition on a nationwide scale can severely dampen the Gross Domestic Product (GDP). Although infections are expected to be higher in the dominant hand, Turker *et al* (2014) found equal affectation of both hands in his series of 123 cases in Arizona in the United States of America.⁵

Furthermore, Greyling *et al* (2012)² was able to show no greater incidence in manual labourers versus the unemployed in his study at Pelanomi Bloemfontein.

In 2009 it was estimated that 17.9% of South African adults (some 5.63 million) were living with the Human Immunodeficiency Virus and Acquired Immunodeficiency Syndrome (HIV/AIDS).⁶

HIV positive patients with hand sepsis have a more protracted hospital stay and require more surgeries than their HIV negative counterparts.⁷

This places further emphasis on screening voluntary counselling and testing for HIV as part of management.

Diabetes Mellitus also poses a challenge with respect to hand sepsis representing up to 10% of admissions.⁸ Often this septic process may be initial presentation of an undiagnosed diabetic in our setting and appropriate screening glucometer testing is advised.

1.2.3 Bacteriology of hand infections

Staphylococcus Aureus, a Gram Positive Coccal Bacterium and normal skin commensal, is the most common isolated organism in hand infections. Other causative organisms include *Streptococci*, Gram negatives and even fungi.

With immunocompromise, like diabetes and HIV, there is a greater likelihood of a mixed culture infection. Greyling *et al* (2012) were able to show that HIV positive patients were 5,2 times more likely to culture multiple organisms than HIV negative patients. Furthermore, Gram negative infections were increased in the HIV positive subgroup. WHO stage 3 and CDC stage B3 (i.e. CD4 < 500 with pyogenic infections) are most commonly affected by hand sepsis. There are no further stratifications of organisms by CD4 count. Therefore, the interplay between HIV and bacteriology needs further studies within our population.

Up to 60% of Diabetics with hand sepsis are more likely to develop complications including amputation.⁹ In a study at Groote Schuur Hospital, Cape Town South Africa; it was found that Diabetics, human bites and a delay to presentation represented the worst prognosis out of 42 cases studied with hand sepsis.¹⁰

Human bites are notoriously dangerous with respect to infection potential in hands, some 40%.¹⁰ The organisms cultured from these resulting abscesses are different to skin commensals in that *Streptococcus Spp* predominates (80%), with anaerobes and *Eikenella*

Corrodens being also commonly isolated. However, this may be a gross underestimation of anaerobes due to their fastidious nature and difficulty of culturing.

1.2.4 Community Acquired Methicillin Resistant *Staphylococcus Aureus* in hand infections

The clear majority of treated hand sepsis cases respond to methicillin derivatives owing to methicillin sensitivity being more common than resistance. Empiric antibiotic coverage of MSSA with Penicillin and Cephalosporins is one of the pillars of hand sepsis management.¹¹

This is however evolving in the face of increased reports of community acquired MRSA affecting many developed and developing nations.^{12, 13, 14, 15}

Risk factors for methicillin resistance includes antibiotic usage in the previous year, crowded living conditions, compromised skin, shared items and suboptimal cleanliness.¹⁶ If a person is in the at-risk group, empiric β Lactam (Methicillin) alone is no longer a reasonable choice. In Dallas Texas, Le Blanc *et al* (2007)¹² showed an increase from 55% to 78% of CA-MRSA in hand sepsis from 2001 - 2003. This varies geographically.

The component that gives CA-MRSA its ability to resist β Lactams is the *mec-A* Gene, which is responsible for producing Penicillin Binding Protein (PBP) 2a, a protein which has a low affinity for β Lactams. 66 to 100% of CA-MRSA strains express Panton-Valentine Leukocidin (PVL) which confers the ability to lyse white blood cells. PVL increases the resistance of *Staphylococcus Aureus* to conventional penicillins whilst an altered PBP due to *mec-A* Gene irregularities further deteriorates sensitivity.

The US FDA advises that in the presence of more than one risk factor, clinical suspicion or a local incidence of 10 - 15%, empiric coverage of CA-MRSA with Oxazolidinone is recommended.¹³

Downs *et al* (2007)¹⁶ showed that all recorded CA-MRSA cases in his series were started on directed therapy late. With this increasing prevalence, empiric coverage for MSSA alone will ineffectively treat the vast majority of patients. Furthermore, delay in goal directed therapy will worsen prognosis hence a high index of suspicion must be maintained if there is no

clinical improvement with Methicillin. There is no current published South African literature of incidence of CA-MRSA specifically within hand infections.

1.2.5 South African Perspective on CA-MRSA:

Very little data exists specifically to the incidence of CA-MRSA within the sphere of orthopaedic practice within the South African context.

A review of MRSA positive bacteraemia at two Gauteng province hospitals revealed a predominance of HA-MRSA (smec type III) (56%) *versus* CA-MRSA (smec type IV) (29%) and further elucidated that HIV positivity proved to be an independent risk for the development of MRSA with a higher likelihood towards increased toxin production and morbidity in CA-MRSA versus HA-MRSA.¹⁸ (Figure 1.2) 56% and 29% being in respect to all *Staphylococcus Aureus* species found sensitive and resistant. The smec subtype IV (Figure 1.2) is of most significance to denote CA-MRSA.

In a landmark paper with regard to the use of pulsed field gel electrophoresis to subtype and smec type MRSA isolates, Moodley *et al*, were able to track the most common smec types across the country and isolated CA-MRSA in Gauteng in 23%, Kwazulu Natal in 27% but just 4% in Pretoria between Steve Biko Academic Hospital.¹⁹ (Figure 1.1) Their hypothesis was that a similar species of CA-MRSA predominates the entire country but in effect they disproved this to show variations.

Owing to the high HIV prevalence in Sub-Saharan Africa, and the known interaction between poor immune status and clonal proliferation of MRSA in these hosts, one would expect our CA-MRSA burden to be on an accelerated trend.

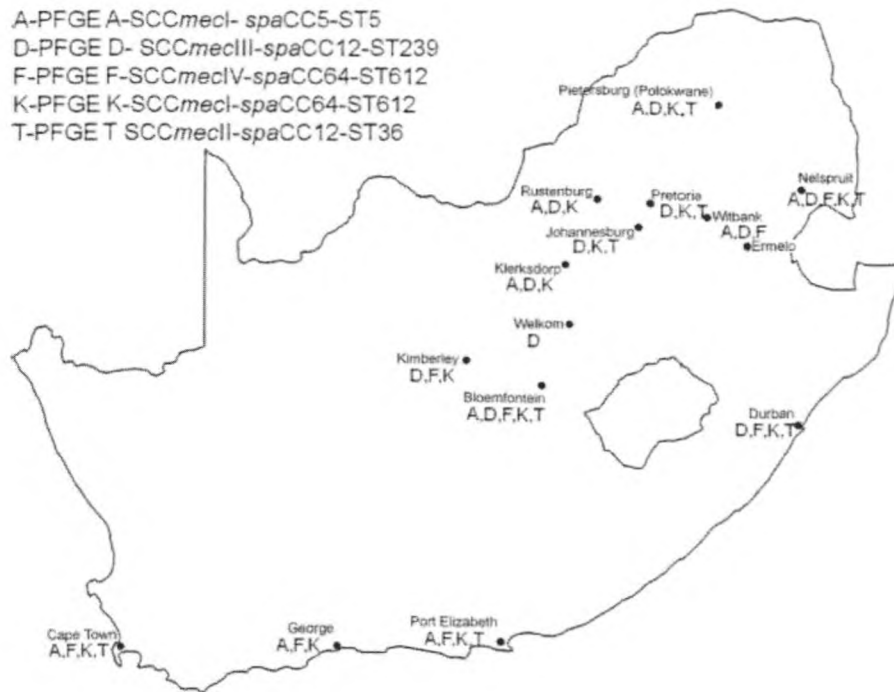


Figure 1.1 Common smec types isolated in different areas of South Africa. Special attention to smec type IV (F) which denotes CA-MRSA (A.Moodley *et al*, (2010))¹⁹

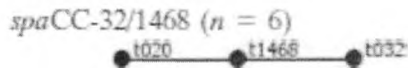


Figure 1.2 Genotype of smec IV MRSA (CA-MRSA) (A.Moodley *et al*, (2010))¹⁹

1.2.6 Global Perspective on CA-MRSA

MRSA had first emerged more than 50 years ago in the western world with much of the attention highlighting HA-MRSA over the past 30 years.²⁰

The earliest CA-MRSA endemic in modern literature points back to the 1980's in Detroit largely amongst intravenous drug abusers.²⁰ Currently in the United States of America, CA-MRSA is the commonest cause of soft tissue infections.

Peculiarly in the United Kingdom, a decline has been noted in the incidence of CA-MRSA. In Australia an increase in CA-MRSA incidence was noted from 6.6% in 2000 to 11.5% in 2010.²¹

Figure 1.3 shows the global burden of CA-MRSA and illustrates the various CA-MRSA species in the relevant continents.



Figure 1.3 Global burden of CA-MRSA (Sowash *et al*, (2014))²⁰

1.3 Study Aim and Objectives

- To explore the epidemiology of hand infections at Chris Hani Baragwanath Academic Hospital with respect to patient demographics, aetiology and causative organisms
- To determine the incidence of community acquired Methicillin Resistant *Staphylococcus Aureus* in hand infections at Chris Hani Baragwanath Academic Hospital and its impact on our current treatment protocol

CHAPTER 2

2 Methodology

2.1 Research Questions

- a) Is the epidemiology of hand infections seen at CHBAH similar to that seen in other populations?
- b) What is the incidence of *Community Acquired Methicillin Resistant Staphylococcus Aureus* in hand infections presenting to CHBAH?

2.2 Research Design

This study comprised a hospital-based, prospective cross sectional analytical study of hand sepsis patients fitting inclusion criteria at Chris Hani Baragwanath Hospital evaluated from 26 September 2016 to 28 February 2017. Patient's details were recorded on a password protected cross reference sheet only and stored on an encrypted cloud. As this was an observational capacity study, no changes were made to standard treatment guidelines and protocols. Informed consent was obtained from the patients prior to study inclusion. For minors, informed consent from parents or assent from minors were utilised as well.

2.3 Materials and Methods

Data was collected from a spectrum of sources inclusive of self-made (untested) questionnaires to define demographics and aetiology of the hand infection, laboratory results of incision and drainage microscopy culture and sensitivity and patient records for outcomes of management.

The demographic data collection sheet (Appendix A) enumerated patients by their study number to maintain confidentiality and assessed key issues such as time to presentation, type of hand abscess, aetiology and prior treatment sought. The microbiology collection sheet

(Appendix B) reported on the initial gram stain, organism(s) cultured by day 5 and their relevant sensitivities (according to Standard Operating Procedure MIC0021v9 at NHLS CHBAH) (Table 2.1)

Table 2.1 illustrates the standard antibiotic plates utilised by NHLS in our region to test sensitivities. Figure 2.1 below illustrates the appearance of antibiotic resistance on such plates denoted by the presence of continued growth in spite of appropriate local antibiotic concentration

Table 2.1 Standard Operating Procedure MIC0021v9 for antibiotic sensitivity testing based upon two plates *viz* P1 and P2 in *Staphylococcus Aureus* specimens

P1	P2
Ampicillin/ Penicillin	Chloramphenicol
Erythromycin	Ciprofloxacin
Clindamycin	Rifampicin
Cotrimoxazole	Gentamycin
Linezolid	Synercid
Vancomycin	Fusidic Acid
Cefoxitin	

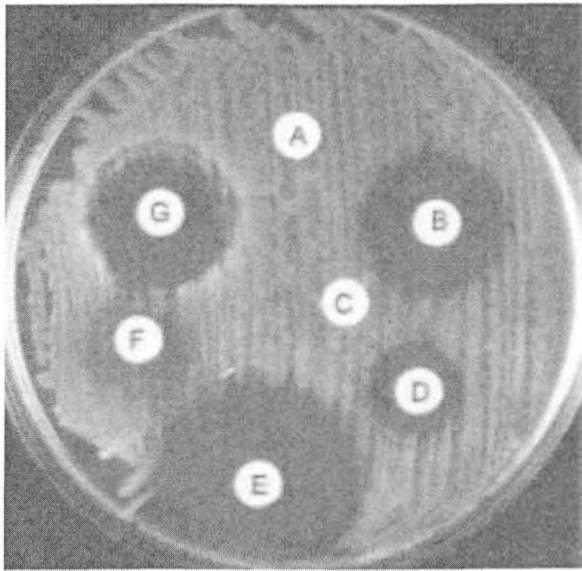


Figure 2.1 A Mueller-Hinton agar plate showing antibiotic resistance in disks A, C, F and to a lesser degree D.

(http://jameslunford.com/microunknown2_exp_explain2_files/image002.jpg)

At CHBAH, all positive culture cases of *Methicillin Resistant Staphylococcus Aureus* are referred onto the NICD for smec gene typing and PVL detection for CA-MRSA confirmation. This data is however not accessible without special clearance.

Fortuitously presence of PVL is not the most sensitive defining characteristic for CA-MRSA confirmation, as proved by Tsiodros *et al* (2014), who favours the use of the CDC case definition for CA-MRSA for its higher sensitivity. (table 2.2).²² We applied this criteria to all MRSA positive cultures to define CA-MRSA in our population. All MRSA culture positive patients not fulfilling all of the CDC case definition constituents were excluded from our study.

Table 2.2 CDC CA-MRSA Case Definition (2000)

Centre for Disease Control Case Definition <i>on Community Acquired Methicillin Resistant Staphylococcus Aureus</i> (2000)
Any MRSA infection diagnosed for an outpatient or within 48 hours of admission
No preceding haemodialysis, surgery or invasive procedure in last 1 year
No prior admission to a health care facility, residence or nursing home in preceding 1 year
Absence of an indwelling catheter or implantable device at time of culture
No prior isolation of MRSA from the index patient
Lack of exposure to antibiotics in the preceding 1 year

2.4 Sample

All patients, paediatric and adult, admitted to Chris Hani Baragwanath Academic Hospital with hand sepsis from 26 September 2016 to 28 February 2017 were invited to participate in the study. This included compos mentis adult and paediatric patients on first presentation or a repeat presentation within 1 month. We excluded all surgical site sepsis, cellulitis, chronic presentations beyond 1 month and proven hospital acquired Methicillin resistance cases. Non-compos mentis patients were excluded owing to lack of consent to participate.

Based upon a null hypothesis of no difference in epidemiology between our patients and international studies and no findings of CA-MRSA within our cultures samples or no patients found to fit the CDC case definition criteria for CA-MRSA, a sample size of 200 patients with a 95% confidence interval was determined using Stata version 12.0. This also accounts for a 5% margin of error.

2.5 Data Collection

All data was collected by the principal investigator both in person for the questionnaires and via review of the patient records and laboratory results. Data of all patients were stored in a database using Microsoft Excel® and Google Documents® and Google Drive® and only identified by their unique study number to maintain patient anonymity. Data was regularly backed up both on and off site. Access to the results was being restricted to the principal investigator (Dr A. Naidoo) and the respective supervisors only.

2.6 Data Analysis

All raw data was inputted into a data analysis sheet from which relevant totals were calculated. Demographic data was analysed categorically in terms of numbers and percentages to express proportion.

We utilised InStat® version 3 for Microsoft Windows® (Graphpad Software Inc) to perform statistical analysis of categorical variables utilising the Fisher's Exact test owing to comparisons of relatively small numbers of positive CA-MRSA cultures with that of the MSSA group. A p -value < 0.05 was considered statistically significant.

2.7 Limitations

Owing to the offsite processing of gene typing of all *Methicillin Resistant Staphylococcus Aureus* samples at the National Institute of Communicable Diseases South Africa, restrictions in access to these confirmatory tests and statistics exist. Although use of the CDC case definition criteria for CA-MRSA (2008) has been shown to be more sensitive for detection of colonisation, a confirmatory test as well as genetic typing would add more description to the organism in question in our region.

2.8 Ethics and institution approval

Ethical approval was obtained from the Human Research Ethics Committee (HREC), University of Witwatersrand, Johannesburg (Ethics clearance certificate number **M160683**, Appendix D). Institutional permission was obtained from the office of the medical superintendent of Chris Hani Baragwanath Academic Hospital.

CHAPTER 3

3 Results

3.1 Epidemiology of hand infections at CHBAH:

A total of 200 patients were assessed using the patient questionnaires, laboratory data of microscopy culture and sensitivity as well as theatre records.

The results demonstrate the majority of hand sepsis in our institution to develop spontaneously ($n = 117$) versus a definite temporal relationship to a trauma or bite wound human or animal (table 3.1).

Our study furthermore highlighted a male to female preponderance of 2.57 : 1 with a similar occurrence between the dominant and non-dominant hand being affected (Table 3.2). The majority of patients were in the 20 to 50 years old age group (68.5%, Mean age of 24 CI of 17 to 28). With respect to the types of hand infections encountered, felons, paronychia and flexor tenosynovitis predominated ($n = 49$, $n = 45$ and $n = 43$ respectively).

We had a 66.5% rate of HIV testing with consent from our subjects and our data reveals only 40% of these tests were positive but again does not discount the large proportion of subjects who refused testing ($n = 67$). Diabetics (both type 1 and 2) made up only just 18.5%. All 200 subjects had their incision and drainage in theatre. Incision and drainage in the procedure room in casualties was excluded due to lack of sample collection for MCCA. A swab or tissue specimen was sent for MCCA in all 200 theatre cases.

With regard to occupation and socioeconomic status, a statistically significant difference existed in terms of the occurrence of sepsis between manual labour and non-manual or office type jobs ($p = 0.0395$ on a 2 tailed Fisher's exact test). Furthermore, there was an unemployment rate of 29.5%.

Table 3.1 Aetiology of Hand Infections at CHBAH

Aetiology of hand infections at CHBAH	(total $n = 200$)
Spontaneous	117
Post trauma	65
Human bite	15
Animal bite	3

Types of Hand Infections at CHBAH

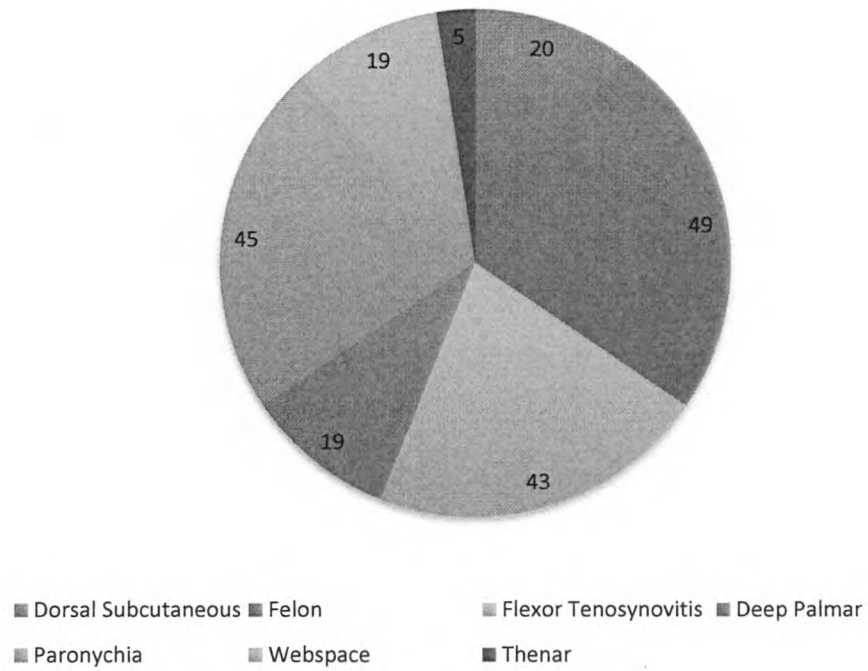


Figure 3.1 Types of Hand Infections at CHBAH

Table 3.2 **Demographic data of hand infections at CHBAH**

Demographics	total n=200
Males	144
Females	56
HIV Positive	50
HIV Negative	83
HIV Unknown/ Refused testing	67
Diabetic	37
Dominant hand involved	107
Non-dominant hand involved	93
Age < 20 years	34
Age 20 - 50 years	137
Age > 50 years	29
Labour intense occupation	56
Non-labour intense occupation	85
Unemployed	59

3.2 Microbiology and incidence of Community Acquired Methicillin Resistant *Staphylococcus Aureus* in hand infections at CHBAH:

Based upon the specimens taken intraoperatively during incision and drainage (i.e. swabs and tissue specimens), we were able to stratify the most common organisms responsible for sepsis in hand abscesses (figure 3.2). A wide spectrum of organisms was isolated including some atypical infections namely *Serratia Marcescens* ($n = 3$), *Mycobacterium Tuberculosis* ($n = 1$), *Histoplasma Capsulatum* ($n=1$) and lastly *Neisseria Gonorrhoea* ($n = 1$). A total of 18 patients had isolates of MRSA. Applying the CDC Case definition of CA-MRSA (Table 2.2), we were able to classify 5 cases out of a total of 18 confirmed MRSA specimens as CA-MRSA. The 15 that did not meet criteria was excluded from the study. We excluded these as by not meeting CDC criteria these specimens are more likely contaminants or HA-MRSA. Based upon the above we calculated the incidence proportion of CA-MRSA in hand infections at CHBAH to be 2.5%.

All of these 5 cases were confirmed as CA-MRSA *via* pulsed field gel electrophoresis, but we were however unable to attain the exact mec genes for the species isolated. Longitudinally as inpatients it was noted that all 5 of the confirmed CA-MRSA patients had repeat procedures inclusive of repeat debridement and in the case of 3 patient's amputation. We found this to be an extremely statistically significant outcome versus a total of 7 amputations in the 121 non-CA-MRSA patients ($p = 0.0034$ *via* a 2 tailed Fisher's Exact test) (Table 3.3). Consequently, all of the amputated CA-MRSA patients were also noted to be HIV positive with CD4 counts below 200 (Table 3.4).

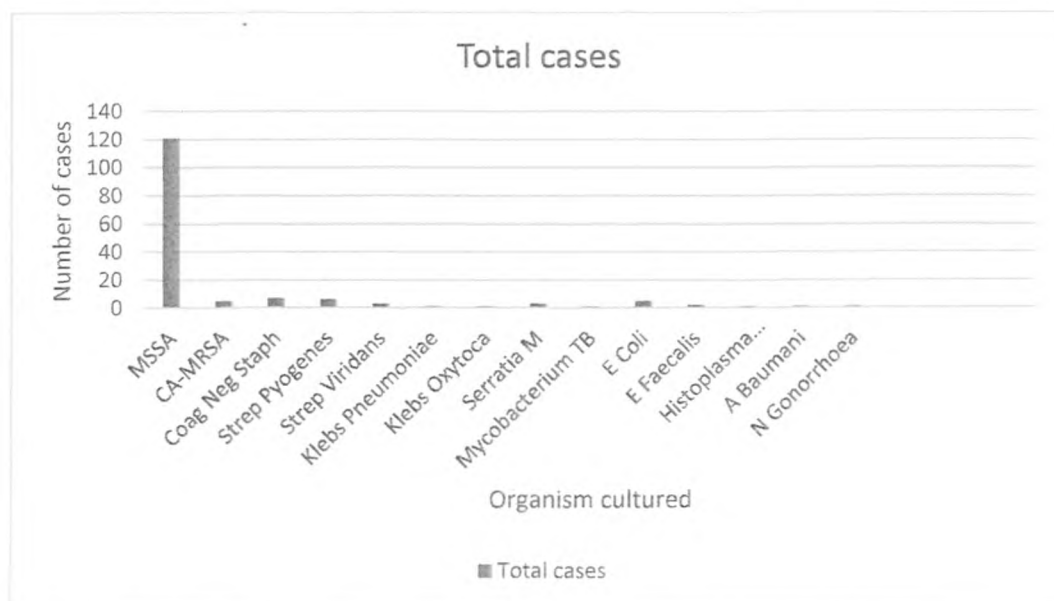


Figure 3.2 Microbiology of hand infections at CHBAH

Table 3.3 2X2 Contingency table of amputated *versus* non-amputated fingers (MSSA vs CA-MRSA) ($p = 0,0034$)

	Amputated finger	Finger not amputated	Total
MSSA	7 (5,7%)	114 (94,21%)	121
CA-MRSA	3 (60%)	2 (40%)	5
Total	10 (7,93%)	116 (92,06%)	126

Table 3.4 2X2 Contingency table of amputated *versus* non-amputated fingers (HIV MSSA vs HIV CA-MRSA) ($p = 0,0125$)

	Amputated finger	Finger not amputated	Total
MSSA+HIV	5 (17,85%)	23 (82,14%)	28
CA-MRSA+HIV	3 (100%)	0	3
Total	8 (25.80%)	23 (74,19%)	31

CHAPTER 4

4 Discussion

Hand infections form a significant burden to our institution with an estimated 400 admissions per year. Our population of 200 patients enrolled into this study highlights the diversity of presentations. With respect to the demographic findings, the mean age of 24 (95% CI 17 to 28) is no surprise as the burden of HIV is highest amongst this age group. Furthermore, they are more likely to be employed or involved in labour intensive activities and this reflects no difference to current literature. Arm dominance did not prove to be of statistical significance with respect to infection in the dominant versus non-dominant arm and again it reflects no variation to other authors findings on this detail.

The types of specimens taken, lack of specimen collection in some debridement's and turnaround time for specimens to reach the laboratory and for results to be available were some of the technical issues with this study and obviated enrolling 35 extra patients to account for numbers lost ($n = 235$).

HIV incidence in our study group was difficult to determine accurately owing to the potentially large proportion of patients refusing to be tested or not tested ($n = 67$). Nonetheless of all those tested we noted no significant difference in the organism profile save for the presence of CA-MRSA, which although just 2.5% of our population, was all found within HIV positive hosts. This is alarming owing to our high HIV burden in Sub Saharan Africa.

A major finding with respect to longitudinal course of these HIV positive, CA-MRSA isolated patients is that of the need for repeat debridement and risk of amputation (3 out of 5) which again highlights the toxin mediated tissue destruction more evident in CA-MRSA than HA-MRSA. The rate of ablation in these patients was found to be statistically significant compared to ablation rate in HIV positive MSSA isolates ($p = 0,0015$).

Although CD4 counts were available for most of our patients enrolled within the study, not all HIV positive patients had CD4 counts. Ideally stratifying the patients CD4 to the organism profile would be an ideal finding that could help identify those mainly at risk of CA-MRSA within the HIV subgroup.

Comparative to the US FDA based literature; our incidence of 2.5% is remarkably lower than the quoted 11% threshold for the institution of routine empiric antibiotic coverage for CA-MRSA. We calculated the number needed to treat based on our statistics (i.e. the number of patients with hand sepsis to receive empiric linezolid/vancomycin in order to cover 1 case of CA-MRSA) to be 400 (Appendix C). Based upon cost and risk of side effects this precludes its routine use. A more pragmatic approach would be to have a higher index of suspicion especially in HIV positive patients to the possibility of CA-MRSA and to consider addition of Oxazolidinone therapy especially in those failing to respond to the initial incision and drainage and empiric oxacillin derivative antibiotic to potentially avoid digit loss. A potential weakness was our inability to spa and smec type the strains identified in our population group. This information would have had significance with regard to comparing ourselves to the global setting and to track this species.

Current literature reports much higher incidence of CA-MRSA in soft tissue infections especially in westernised communities. Our statistics is but a small step towards defining what the CA-MRSA burden really is in our context and requires many more such studies with larger cohorts of patients to make an objective assessment. Nonetheless with an increasing HIV burden and access to similar antimicrobials like these westernised countries, South Africa may well have a much larger burden of CA-MRSA than we actually fathom.

4.1 Recommendations

Based on the results from this study the following recommendations are made:

- Firstly, we recommend the usage of Methicillin based empiric antibiotics to treat hand infections. In the event that an institutional stewardship and surveillance programme detects a CA-MRSA predominance of more than 11% then routine Oxazolidenone coverage must be instituted
- In HIV positive patients with low CD4 counts ($< 200 \text{ cells/mm}^3$) consideration should be given to the likelihood of CA-MRSA as a causative organism for hand sepsis especially if tissue destruction continues despite adequate incision and drainage and Methicillin dosing
- We recommend further research at multiple centres be conducted in order to stratify the dominant CA-MRSA strains and to get a South African perspective on true incidence

CHAPTER 5

5 Conclusion

Hand infections represent a large proportion of soft tissue septic processes encountered by the orthopaedic surgeon. Knowledge of the epidemiology and causative flora is paramount to offer patients directed therapy.

CA-MRSA is gaining recognition for its penchant for tissue destruction. Coverage empirically for CA-MRSA especially in HIV positive patients could mitigate the unacceptable high proportion of finger amputations but a larger multicentre study would be required to determine the true incidence in South Africa before a generalised recommendation can be made. This study highlights a local incidence of CA-MRSA in hand sepsis within the largest hospital on African soil and we hope to inspire many such efforts to further conceptualise the burden of CA-MRSA in hand sepsis nationwide.

Further research to subtype strains and determine PVL positivity against CD4 counts could be of value in choosing which patients would benefit from Oxazolidenone empiric therapy from the outset. This was a potential limitation of our study.

6 References

1. Mennen U, Van Velze C. *The Hand Book. A Practical approach to common hand problems*. Third Edition. Fifth Impression. South Africa. Van Schaik publishers 2015. Chapter 9:169-183.
2. Greyling J.F, Visser E, Elliot E. Bacteriology and Epidemiology of Hand Infections. *SAOJ* Autumn 2012; 11(1):57-63.
3. Kanavel AB. The symptoms, signs, and diagnosis of tenosynovitis and fascial-space abscesses. In *Infections of the Hand*. 1st ed. Philadelphia, PA: Lea & Febiger; 1912:201–226.
4. Houshian S, Seyedipour S, Wedderkopp N. Epidemiology of Bacterial Hand Infections. *Int Journal of Infectious Diseases* 2006; 10(4):315-319.
5. Turker T, Bertoch ST, Capdarest-Arest N, Bakken E.C, Hoover S.E, Zou J. Hand Infections: A Retrospective Analysis, *Peer J* 2014, 2:e513, DOI10, 7717/PeerJ.513.
6. National Strategic Plan on HIV/STI/TB, 2012-2016. www.hst.org.za/publications/national-strategic-plan-hiv-stis-tb-2012-2016. Accessed on 28 August 2016 at 21h00.
7. Ching V, Ritz M. A, Song C, De Aguir G, Mohanlal P. HIV Infection in an Emergency Hand Service; *J Hand Service Am* 1996; 21(4):696-9.
8. Thornton D, Lindau T. Hand Infections: A Mini Symposium. *J Orthopaedics and Trauma* 2010; 24(3):186-196.
9. Francel T.J, Marshall K.A, Savage R.C. Hand infections in the diabetic and the diabetic renal transplant recipient. *Annals of Plastic Surgery* 1990; 24(4):304-309.
10. Maloon S, de Beer J.D.V, Opitz M, Singer M. Acute Flexor Sheath Infections. *Journal of Hand Surgery* 1990; 15(3):474-477.
11. Visser A, Visser H.F. Biting off more than you can chew, Microbiological Flora isolated from human and animal bite wounds. *SAOJ Winter 2012*; 11(2):43-48.
12. Le Blanc, Dana M. Increasing incidence of Methicillin resistant Staph Aureus in hand infections: a 3 year country hospital experience. *Journal of Plastic and reconstructive surgery* 2007; 119(3):935-940.

13. Fowler JR. Community Associated Methicillin Resistant Staph Aureus Hand Infections in an urban setting, *Journal of Hand Surgery* 2013; 38(6):1189-1193.
14. Wilson PC, Rinker B. The incidence of Methicillin Resistant Staph Aureus in community acquired hand infections, *Annals of Plastic Surgery* 2009;62(5):513-516.
15. O Malley, Fowler J, Ilyas A.M. Community Acquired Methicillin Resistant Staph Aureus Infections of the hand: Prevalence and timelines of treatment. *Journal of Hand Surgery Am*; 2009 34(3):504-508.
16. Downs R. Timelines of appropriate antibiotics in hand infections. *Clinical Orthopaedics and Related Research* 2007; 461(1):17-19.
17. Marcotte A, Trzeciak M.A. Community Acquired MRSA: An emerging pattern in orthopaedics. *J Am Acad Orthop Surg* 2008;16(1):98-106.
18. Fortuin-de Smidt, Singh-Moodley A, Badat R, Quan V, Kularatne R, Nana T, Lekalakala R, Govender N.P, Perovic O. Staphylococcus Aureus bacteraemia in Gauteng academic hospitals in Southern Africa. *International Journal of Infectious Diseases* 2015; 30(2015): 41-48.
19. Moodley A, Oostenhuysen W.F, Duse A.G, Marais E. Molecular characterisation of clinical methicillin resistant Staphylococcus Aureus isolates in Southern Africa. *Journal of clinical microbiology* 2010; 48(12): 4608-4611
20. Sowash M.E, Uhlemann A.C. Community Acquired Methicillin Resistant Staphylococcus Aureus: South Africa case studies. *Methods in molecular microbiology* 2014; 1085(1): 25-69.
21. Coombs G.W, Georing R.V, Chua K.Y.L, Monecke S, Howden B.P, Stinear T.P, Ehrlich R, O'Brien F.G, Christensen K.J. The molecular epidemiology of the highly virulent ST-98 Australian Community acquired Methicillin Resistant Staphylococcus Aureus strain. *Plos one* 2012; 7343037 (Pubmed: 22900085).
22. Tsidrios S, Daikos G.L, Lee A, Plachouras D, Antoniadou A, Ploiarchopolou F.P, Psychogiou M, Pettrikos G, Habarth S. Risk factors for Community Acquired Methicillin Resistant Staphylococcus Aureus colonisation in a large metropolitan area in Greece: An epidemiological study using 2 case definitions. *J. Glob Antimicrob Resist* 2014; Mar 2(1): 27-33.

7 Appendices

A. Demographic Information Sheet (Sample Patient Questionnaire):

Hand Infections Epidemiology and Community Acquired Methicillin Resistant Staphylococcus Aureus incidence at the Chris Hani Baragwanath Academic Hospital		
Study Number	_____	
Date of admission	_____	
Age and Sex	_____	
Hand Dominance (L/R)	_____	
Affected Hand	_____	
Occupation	_____	
<u>Type of Hand Sepsis</u>	Dorsal Superficial	☐
(Tick)	Felon	☐
	Paronychia	☐
	Flexor Tenosynovitis	☐
	Deep Palmar Space	☐
	Webspace	☐
<u>Cause</u>	Trauma	☐
(Tick)	Spontaneous	☐
	Foreign Body	☐
	Human Bite	☐
Time to presentation	<1 week	☐
	1-2 weeks	☐
	>2 weeks	☐
Prior Treatment for infection	Clinic	☐
	Traditional Healer	☐
	Hospital	☐
Diabetes Mellitus known (Y/N)	_____	
Retroviral Disease Status (+/-/U)	_____	
CD4 Count (Date tested)	_____	
Data Collection Sheet 25/8/2016 		

B. Microbiology Data Collection Sheet:

Hand Infections Epidemiology and Community Acquired Methicillin Resistant Staphylococcus Aureus
Incidence at Chris Hani Baragwanath Academic Hospital

Study No	Culture date	Specimen Type	Gram Stain	Organism(s) Isolated	Sensitivity
A1					
A2					
A3					
A4					
A5					
A6					
A7					
A8					
A9					
A10					
A11					
A12					
A13					
A14					
A15					
A16					
A17					
A18					
A19					
A20					
A21					
A22					
A23					
A24					
A25					
A26					
A27					
A28					
A29					
A30					
A31					
A32					
A33					
A34					
A35					
A36					
A37					
A38					
A39					
A40					
A41					
A42					
A43					
A44					
A45					
A46					
A47					
A48					
A49					

C. Number needed to treat calculation i.e for Oxazolidenone empiric therapy:

$$\begin{aligned}\text{Absolute Risk Reduction} &= \text{Control event} - \text{Experiment event} \\ &= 0 - 0.0025 \\ &= -0.0025\end{aligned}$$

$$\begin{aligned}\text{Number Needed to Treat} &= 1 / \text{Absolute Risk Reduction} \\ &= 1 / 0.0025 \\ &= 400\end{aligned}$$

D. HREC Ethic Clearance Certificate M160683



R14/49 Dr Ashley Naidoo

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160683

NAME: Dr Ashley Naidoo
(Principal Investigator)
DEPARTMENT: Orthopaedic Surgery
Chris Hani Baragwanath Academic Hospital

PROJECT TITLE: Hand Infections Epidemiology and Community Acquired
Methicillin Resistant Staphylococcus Aureus Incidence
at Chris Hani Baragwanath Academic Hospital

DATE CONSIDERED: 24/06/2016

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Dr T Sefane and Dr G Biddulph

APPROVED BY:


Professor P Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 05/10/2016

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 301, Third floor, Faculty of Health Sciences, Philip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. I agree to submit a yearly progress report. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in June and will therefore be due in the month of June each year.


Principal Investigator Signature

3/1/18
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

ORIGINALITY REPORT

9%

SIMILARITY INDEX

8%

INTERNET SOURCES

5%

PUBLICATIONS

3%

STUDENT PAPERS

PRIMARY SOURCES

1	Submitted to University of Witwatersrand Student Paper	1%
2	Ravi V. Kiran. "Increased Prevalence of Community-Acquired Methicillin-Resistant Staphylococcus aureus in Hand Infections at an Urban Medical Center", Plastic and Reconstructive Surgery, 07/2006 Publication	1%
3	wiredspace.wits.ac.za Internet Source	1%
4	waikato.researchgateway.ac.nz Internet Source	<1%
5	www.ncbi.nlm.nih.gov Internet Source	<1%
6	emedicine.medscape.com Internet Source	<1%
7	M. Z. David. "Community-Associated Methicillin-Resistant Staphylococcus aureus: Epidemiology and Clinical Consequences of an	<1%

Emerging Epidemic", Clinical Microbiology
Reviews, 07/01/2010

Publication

8	espace.curtin.edu.au Internet Source	<1 %
---	---	------

9	Submitted to Auckland University of Technology Student Paper	<1 %
---	--	------

10	John R. Fowler, Dustin Greenhill, Alyssa A. Schaffer, Joseph J. Thoder, Asif M. Ilyas. "Evolving Incidence of MRSA in Urban Hand Infections", Orthopedics, 2013 Publication	<1 %
----	---	------

11	Methods in Molecular Biology, 2014. Publication	<1 %
----	--	------

12	www.ecric.org.uk Internet Source	<1 %
----	-------------------------------------	------

13	www.journals.ke-i.org Internet Source	<1 %
----	--	------

14	"Research reports from A.L. Marcotte and co- authors provide new insights into drug resistance.(Report", Health & Medicine Week, March 17 2008 Issue Publication	<1 %
----	--	------

15	mobile.wiredspace.wits.ac.za Internet Source	<1 %
----	---	------

16	iovs.arvojournals.org Internet Source	<1 %
17	www.sunstar.com.ph Internet Source	<1 %
18	open.uct.ac.za Internet Source	<1 %
19	www.rpsgb.org.uk Internet Source	<1 %
20	aap.confex.com Internet Source	<1 %
21	ir.lib.uwo.ca Internet Source	<1 %
22	www.tumori.net Internet Source	<1 %
23	Magira, Eleni E., Dimitrios Zervakis, Christina Routsis, Marina Kontogiorgi, Charis Roussos, Serafim Nanas, and Spyros Mentzelopoulos. "Community-acquired methicillin-resistant <i>Staphylococcus aureus</i> carrying Panton-Valentine leukocidin genes: A lethal cause of pneumonia in an adult immunocompetent patient", <i>Scandinavian Journal of Infectious Diseases</i> , 2007. Publication	<1 %

24	Internet Source	<1 %
25	eprints.undip.ac.id Internet Source	<1 %
26	Kroonen, Leo. "Pediatric Hand Infections", The Pediatric Upper Extremity, 2014. Publication	<1 %
27	pearl.plymouth.ac.uk Internet Source	<1 %
28	preview-www.biomedcentral.com Internet Source	<1 %
29	open.bu.edu Internet Source	<1 %

Exclude quotes On
Exclude bibliography On

Exclude matches < 3 words