Prevalence and Antimicrobial Resistance Profile of Methicillin Resistant *Staphylococcus aureus* isolates from Wound Infections in Zaria, Nigeria.

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Abstract

Methicillin Resistant *Staphylococcus aureus* (MRSA) has been a major culprit in many problematic infections especially in wound infections due to its failure to respond to antibiotics and a leading bacterial agent in community acquired infections and infections acquired in hospitals. This study investigated the prevalence and antibiotic resistant profile of MRSA in patients with wound infections in Zaria.

Two hundred and seventy-two wound swabs were collected from three hospitals in Zaria, Kaduna State. These were analyzed using standard microbiological and biochemical procedures for staphylococcal isolation. Confirmed *S. aureus* isolates were evaluated for methicillin resistance using cefoxitin disc and multidrug resistance status.

Of the 272 suspected Staphylococcal isolates analyzed, 73 (27%) were confirmed as *S. aureus* isolates, of which 63 (86 %) were MRSA. The infection rate of MRSA was found to be higher in males than in females. MRSA strains were 100 % resistant to the β-lactam antibiotics, with 57.1 % being multidrug resistant, but were susceptible to Gentamicin, Ciprofloxacin, Trimethoprim-sulphamethoxazole and Tetracycline.

We recorded a high proportion of MRSA and Multidrug resistant-MRSA isolates from wound infections in Zaria, thus, much emphasis on infection control measures should be prioritized. There is the need to increase the effectiveness of prevention and infection control measures as well as treatment of MRSA infections.

Keywords: MRSA, antibiotic resistance, wound infections

Introduction

The skin is an essential structure serving as a shield for the internal tissues of the human body against pathogens, various forms of damage such as chemical and mechanical injury, UV light among others and is considered the largest organ in the body (Yousef *et al*., 2017).An impaired skin resulting from wounding supports an impeccable milieu for the colonization, proliferation, and infection by microbes(Tsige *et al*., 2020). Common

bacteria often implicated in skin infections include *Staphylococcus aureus*, *Streptococcus* species, *Enterococcus* species *Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa*, , and *Proteus* species, (Ramsay *et al*., 2016; Tsige *et al*., 2020). Among the most frequently encountered bacteria, *S. aureus*, is implicated among aetiologies of healthcare associated infections, especially surgical wound infections, a leading cause of nosocomial infections(Sisirak*et al.*, 2010; Xu *et al*., 2021) and community acquired infections (Darboe *et al*., 2019).

Infections of wounds are re-emerging medical problem worldwide, especially because of multidrug resistance nature of their causative organism, with consequent huge economic burden, morbidity and mortality (Janssen *et al*., 2018).Identifying the aetiology of wound infections is usually tasking, requiring time and qualified professionals. Pallavaliand colleagues in 2017, documented that the most frequent bacterial isolates implicated are *S. aureus, E. coli, Klebsiella*spp,*P. aeruginosa,* and *Acinetobacter*spp, as common causes of septic wounds in their study. In the hospital environment, these bacteria tend to be multidrug resistant and difficult to control (Chudobova*et al*., 2015),this may worsen wound care in the near future (Mahmoudi and Gould 2020).

Changes in the drug susceptibility profile of *S. aureus* have been reported globally, thereby making treatment of its infections very difficult (Aslam*et al*., 2018). Wounds infections caused by*S. aureus* particularly the multidrug resistant Methicillin Resistant *Staphylococcus aureus* (MRSA) strains can be found both as community and hospitalacquired infections resulting in significant morbidity and mortality, increased length of hospital stay and cost (Negut *et al*., 2018; Dilnessa, 2019), Siddiqui and Koirala, 2020). Furthermore, MRSA tends to spread faster than other strains,and are often difficult to eradicate once established especially in the hospital. This is due to its extraordinary ability to acquire resistance to antimicrobial agents(Nehzad*et al*., 2017). MRSA transmission usually ensues from contact with colonized or infected patients or staff to other patients or staff (Yezli*et al*., 2014; Nadimpalli *et al*, 2020). In some countries, MRSA make up to three-quarter of all *S aureus* isolates in hospitals (Dilnessa and Bitew, 2016), with significant proportion seen among hospital staff in direct contact with infected patients (Siddiqui and Koirala, 2020). However, there is marked variation in the prevalence from hospitals in the same region and country, and from one country to another (Dilnessa, 2019). Thus, information from one hospital or region cannot be accurately extrapolated for other regions. Hence the need to periodically update local data on MRSA especially from wounds. This study will provide knowledge of the current drug resistance patterns which will help in developing more effective antibiotic therapy guidelines and streamline appropriate antibiotic stewardship policies to combat antibiotic resistance. This study thus aims to determine the prevalence of MRSA in wound infections and the resistance profile of *S. aureus* isolates from such wound infections obtained from some hospitals in Zaria.

Materials and Methods

Study design

A cross sectional study was conducted on two hundred and seventy-two wound swabs from

three hospitals in Zaria, Kaduna State from September 2017 to November 2018. The needed patient bio-data was also collected. This study was approved by the Committee on Use of Human Subjects for Research of the Ahmadu Bello University, Zaria, Kaduna State, Nigeria

Sample collection and bacterial identification

Wound biopsy or wound swabs samples were collected and inoculated onto Mannitol Salt Agar(Oxoid, Ltd, United Kingdom), this was incubated at 37℃ for 24hours.Colonies appearing discrete and golden yellow to yellow were presumptively identified as *S. aureus*. These were confirmed using microscopic morphology (Gram's Staining) and biochemical tests such as catalase and coagulase reaction, further confirmation was done using rapid test kits (Latex agglutination kit (oxoid) and Microgen STAPH ID system/software). Confirmed *S. aureus* isolates were sub cultured onto nutrient agar slants and incubated at 37℃ for 18 hours (Cheesebrough, 2006). The slants were then kept at 4℃ for further analysis.

Screening of Methicillin-resistance

Methicillin-resistant *S. aureus* isolates were screened using cefoxitin disc (30 µg) on Muller Hinton agar plates, with incubation at 35ºC for 16 -18 hours following theClinical and Laboratory Standards Institute guidelines (CLSI, 2018). Isolates with diameter of zones of inhibition ≤ 21mm were deemed resistant and regarded as MRSA.

Antimicrobial Susceptibility testing

All MRSA strains were subjected to antimicrobial susceptibility testing against Cefuroxime (30µg), Ceftriazone (30µg), Oxacillin (1µg), Amoxicillin (10µg), Amoxicillin/Clavulanic acid (30µg), Gentamicin (10µg), Ciprofloxacin (5µg), Erythromycin (15µg), Suphamethoxazole-Trimethoprim (25µg), Tetracycline (30µg), Linezolid (10µg) Vancomycin (30µg), and Chloramphenicol (30 µg), using the modified Kirby-Bauer disc diffusion technique on Muller Hinton agar (MHA)(Oxoid Ltd, UK) and diameter of zones of inhibition were interpreted based on the Clinical and Laboratory Standards Institute guidelines (CLSI, 2018). Briefly, discrete (three to five pure colonies) colonies from 24hour culture of the MRSA isolates on nutrient agar plates were emulsified in 5ml of sterile physiological saline and adjusted to a turbidity standard equivalent to 0.5 McFarland standard, a sterile swab was dipped in the suspension, and the entire surface of the MHA plates was swabbed in three directions with 60º rotation after each swabbing to ensure even distribution and the plates allowed to dry for 30 minutes. The antibiotic discs were then placed aseptically on the MHA plates using a multidisc dispenser, and plates were allowed to stand for 30 minutes to allow for pre diffusion of antibiotic before incubation at 37ºC for 18 - 24hrs, thereafter the diameter of zones of inhibition were measured to the nearest millimeter. Multidrug resistance (MDR) was defined as resistance to at least one agent in three or more antimicrobial categories (Magiorakos *et a*l., 2012).All the antibiotic discs used were supplied by Oxoid Ltd., Basingstoke Hampshire, England.

The data obtained were entered into Excel and analyzed using frequency distribution tables.

Results

Out of 272 specimen collected from wound infection swabs, 73 (27 %) were confirmed as *S aureus* using rapid test kits. Of these, 61.64% (45) were from males and 38.36% (28) from females, with 71. 23 % (52) from adults Table 1.

Table 1: Percentage Distribution of *Staph aureus* from Wound Infection According to Age and Gender from Three Hospitals in Zaria,

Characteristics of patients	n (%)
Age (subgroup)	
≥ 18	52 (71.23)
< 18	19 (26.03)
Unspecified	2 (2.74)
Gender	
Male	45 (61.64)
Female	28 (38.36)
Type of wound infections	
Ulcers	41 (56.16)
Surgical	4 (5.48)
Trauma	11 (15.07)
Burn	1 (1.37)
Pus	14 (19.18)
Unspecified	2 (2.74)

Proportion of MRSA

Of the 73 *S. aureus*, 63 (86 %) were identified as methicillin-resistant *S. aureus* (Fig 1), with ulcers having the highest percentage (Fig 2).

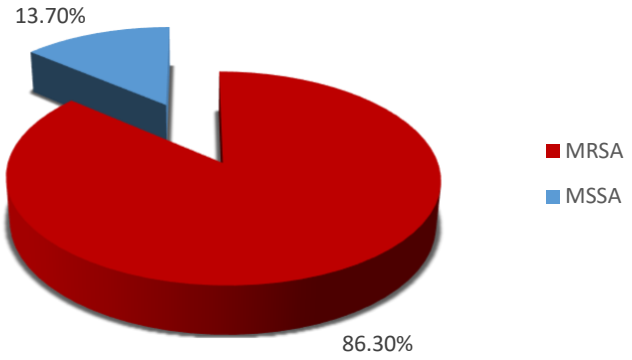


Figure 1: Proportion of MRSA among *S. aureus*isolates from wound infection in the Three Health Centres

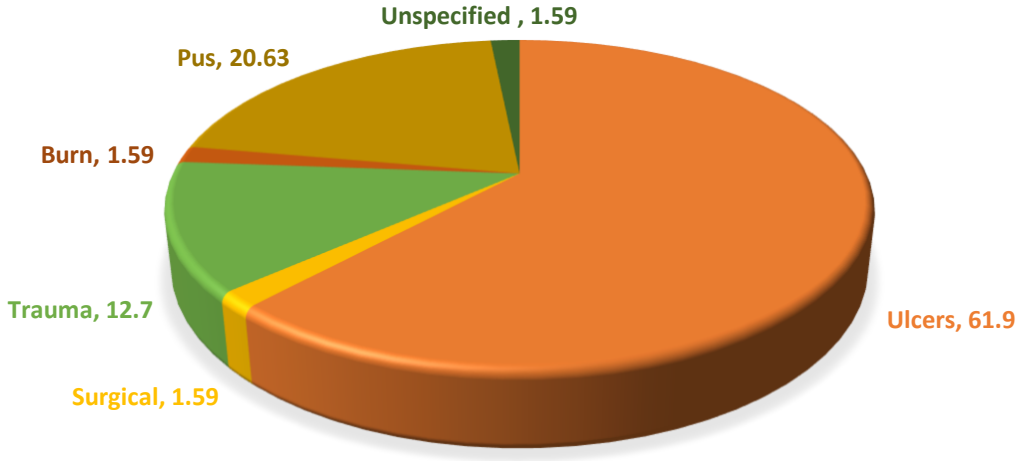


Fig 2: Percentage Distribution of MRSA Based on the Type of Wound Infections

Resistant pattern of MRSA

The methicillin-resistant *S. aureus* strains showed 100 % resistance against the β-lactam antibiotics (Amoxicillin, Amoxicillin-Clavulanate, Oxacillin, Cefuroxime, and Ceftriaxone) followed by erythromycin and linezolid (41.27%, 38.1%), Ciprofloxacin and Gentamicin (22.2%, 12.7%) Fig 3.

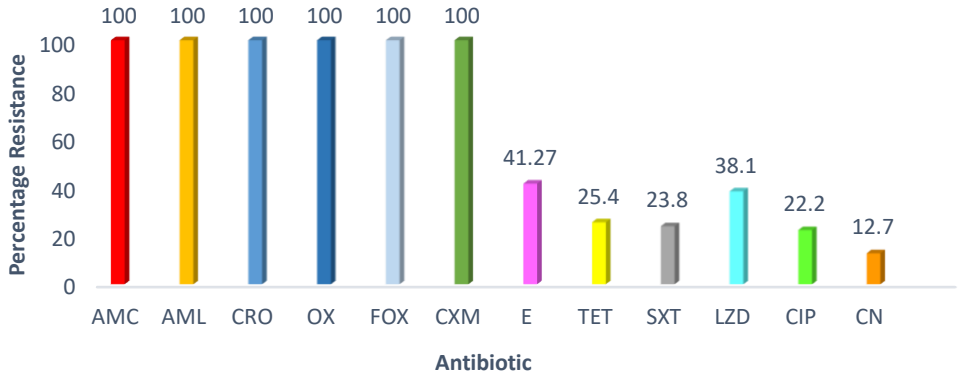


Fig 3: Antibiotic Resistance profile of MRSA Isolates from Wound Infection

Key: AMC Amoxicillin-Clavulanate, AML Amoxicillin, CRO Ceftriaxone, OX Oxacillin,, FOX cefoxitin, CXM Cefuroxime, E erythromycin, CIP Ciprofloxacin, CN Gentamicin, TET Tetracycline, SXT Trimethoprim-sulphamethoxazole, LZD linezolid

From the sixty-three MRSA isolates identified, 31 (49 %) were multidrug resistant, Fig 4 and thirty-two different phenotypic resistant pattern were observed, AMC, AML, CRO, OX, FOX, and CXM being the most common, Table 2. None of the strains were found to be resistant to all antibiotics used.

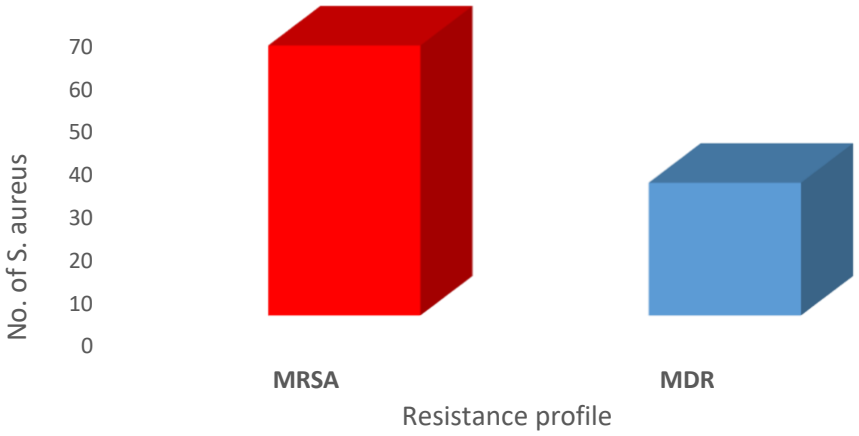


Fig 4: No of Multidrug Resistant *S. aureus* in Relation to MRSA Isolated from Wound Infection Based on their Resistance Profile

Key: MDR Multidrug Resistance**;** MRSA Methicillin-resistant *S. aureus*

Table 2: Antibiotic Resistant Phenotype of Methicillin Resistant *Staphylococcus aureus* Isolates from Wound Infections

S/No	Phenotypic Resistant Pattern	Frequency	%
1	AMC, AML, CRO, OX, FOX, CXM, KF	18	28.57
2	AMC, AML, CRO, OX, FOX, CXM, KF, VA	3	4.76
3	AMC, AML, CRO, OX, FOX, CXM, KF, VA, E	1	1.59
4	AMC, AML, CRO, OX, FOX, CXM, KF, CIP	4	6.35
5	AMC, AML, CRO, OX, FOX, CXM, KF, VA, E, CIP	1	1.59
6	AMC, AML, CRO, OX, FOX, CXM, KF, E, TET, SXT, LZD, VA, CN	1	1.59
7	AMC, AML, CRO, OX, FOX, CXM, KF, E, TET, SXT, LZD, VA	1	1.59
8	AMC, AML, CRO, OX, FOX, CXM, KF, E, TET, SXT, CN	1	1.59
9	AMC, AML, CRO, OX, FOX, CXM, KF, E	4	6.35
10	AMC, AML, CRO, OX, FOX, CXM, KF, E, CN, CIP, TET, SXT, LZD	1	1.59
11	AMC, AML, CRO, OX, FOX, CXM, KF, E, TET, SXT, LZD	3	4.76
12	AMC, AML, CRO, OX, FOX, CXM, KF, CIP, SXT, LZD	1	1.59
13	AMC, AML, CRO, OX, FOX, CXM, KF, LZD	2	3.17
14	AMC, AML, CRO, OX, FOX, CXM, KF, E, CN, CIP, TET	1	1.59
15	AMC, AML, CRO, OX, FOX, CXM, KF, CN, CIP, SXT, LZD	1	1.59
16	AMC, AML, CRO, OX, FOX, CXM, KF, E, TET, LZD	1	1.59
17	AMC, AML, CRO, OX, FOX, CXM, KF, E, CIP, TET, SXT, LZD	1	1.59
18	AMC, AML, CRO, OX, FOX, CXM, KF, E, CN, TET	1	1.59
19	AMC, AML, CRO, OX, FOX, CXM, KF, E, CN, CIP, TET, LZD	1	1.59
20	AMC, AML, CRO, OX, FOX, CXM, KF, E, VA, SXT, LZD	2	3.17
21	AMC, AML, CRO, OX, FOX, CXM, KF, CN, VA, LZD	1	1.59
22	AMC, AML, CRO, OX, FOX, CXM, KF, VA, TET	1	1.59
23	AMC, AML, CRO, OX, FOX, CXM, KF, E, VA, LZD	2	3.17
24	AMC, AML, CRO, OX, FOX, CXM, KF, LZD, CIP	1	1.59
25	AMC, AML, CRO, OX, FOX, CXM, KF, CN, CIP, LZD	1	1.59
26	AMC, AML, CRO, OX, FOX, CXM, KF, E, CIP, TET, VA, SXT, LZD	1	1.59
27	AMC, AML, CRO, OX, FOX, CXM, KF, LZD, VA	2	3.17
28	AMC, AML, CRO, OX, FOX, CXM, KF, E, TET, SXT, LZD, VA	1	1.59
29	AMC, AML, CRO, OX, FOX, CXM, KF, E, SXT, LZD, VA	1	1.59
30	AMC, AML, CRO, OX, FOX, CXM, KF, TET	1	1.59
31	AMC, AML, CRO, OX, FOX, CXM, KF, E, CN, TET, SXT	1	1.59
32	AMC, AML, CRO, OX, FOX, CXM, KF, CIP, VA	1	1.59
Total		63	100

Discussion

Staphylococcal infections have been reported to be common in developing countries and still remain globally, a significant cause of mortality and morbidity, (Almeida *et al*., 2014; Dilnessa and Bitew, 2016). Among the Staphylococci, *Staphylococcus aureus* is known to be the most virulent causing both community and healthcare related infections worldwide (Lee *et al*., 2018). Globally, wound infections are re-emerging with a consequent huge economic burden, morbidity and mortality. Due to the polymicrobial nature of infected wounds and because microbiological investigations are demanding, it is often ignored in the sub-Saharan Africa countries(Janssen *et al*., 2018).Bacteria often linked with infections of wound include *Staphylococcus aureus*, *Streptococcus* species, and *Enterococcus* species among the Gram positive pathogens, and *Pseudomonas aeruginosa*, *Klebsiellapneumoniae*, *Escherichia coli*, and *Proteus* species, among the Gram negatives(Mohammed *et al*, 2017; Janssen *et al*., 2018). Effective wound treatment often requires careful consideration, interventions necessitating several clinic or hospital visits with aconsequential costs associated with wound care (Muhammed*et al*, 2017).

In this study, *S aureus* from wound infection were higher in males 61.64%, than in females 38.36%. this is in agreement with the findings of Garoy *et al*., (2019) and Ali and Najm, (2021), who stated that isolation rate of *S aureus* from wound infectionwas higher in males than females in their study, possibly, due to the nature of their occupation.

Findings from this study showed a high percentage 86 % of *S aureus* isolates from wound infection were MRSA, such high percentage of MRSA occurrence in the study area might be due to overcrowding of the healthcare facility, shared equipment and contact with contaminated hands of the health care providers (CDC, 2019; Lena *et al*., 2021) and may result to poor clinical outcome. This rate is higher than those earlier reported in Nigeria, 22.6 % in Ebonyi by Ariom*et al*., (2019), 25 % in Sokoto, by Olowo-Okere*et al*, (2017), 26.9 % in Abuja by Abdullahi and Iregbu, (2018) and 28.6 % in Ibadan by Adetayo*et al*, (2014), other African countries such as in Egypt, 5.6 %, El Nasser *et al*, (2019); 27.8% in Kenya, Gitau *et al.*, (2018) and a pooled prevalence of 49 % in a meta-analysis from Ethiopia (Sisay*et al*, 2019), and also in other studies from other parts of the world, India (Hemamalini*et al*, 2015; Shrestha *et al*, 2018) and Iran (Nibakht*et al*, 2017). However, there are reports that are similar to the findings of this study, that show high incidence of MRSA not only in Nigeria 72 %, Udobi *et al*., (2013) but also in Eritrea 75 %, Garoy*et al*., (2019). In a systematic review conducted recently, the prevalence of MRSA was reported to be on the rise in most African countries, although the rate is still below 50%, wound specimen presents with the highest proportion of all MRSA isolates (Abubakar and Sulaiman, 2018; Almanaa *et al*., 2020). In a report, WHO highlights thedanger MRSA poses to healthcare systems in Africa, stating that, up to 80% of *S. aureus* infections in several parts of Africa, are resistant to methicillin (MRSA), making treatment with standard antibiotics ineffective (Garoy*et al*, 2019). The differences in variation in the prevalence of MRSA could be attributed to many factors such as differences in types of specimen, laboratory procedures (phenotypic methods, or DNA-based procedures for MRSA detection), study population and duration, among others (Garoy*et al*, 2019). MRSA

interferes with wound healing, increasing the severity of lesions and chances of other types of infection. Besides, infected lesions tend to be reservoirs for other pathogens, causing infection (Pereira-Franchi*et al*, 2017).

Among MRSA isolates in this study, 49.2 % were MDR, a figure lower than earlier reports in Uganda 95.2 % Kateete*et al*., (2019), in Ethiopia 69.2 % Tsige*et al*., 2020, in Poland, 92.9 % Kot*et al*, (2020), 68.0 % by Abdullahi and Iregbu, (2018) in central Nigeria and 71.4 % in Iran, Eftikhar*et al*., (2017). Although, a little higher than 44 % earlier documented in the same locality (Obajuluwa*et al.*, 2018). MRSA strains have been shown to exhibit resistance to several antibiotics such as β-lactam (penicillins, cephalosporins, carbapenems), fluoroquinolones, macrolides, aminoglycosides, clindamycins among others, they are now regarded as the first-class multidrug resistant pathogens (Gajdacs, 2019).MDR *S. aureus* isolates are often linked to inappropriate use of antibiotics, whether in human care as in self-medication or in veterinary, and poor or inadequate infection control and prevention practices (Garoy *et al*., 2019).

Thirty-two different phenotypic resistant pattern was observed among the MRSA, with β-lactam antibiotics being the most common resistant pattern 28.57 % this could be attributed to misuse, overuse of this class of antibiotics by their availability over the counter, without prescription and through unregulated supply chains (Ayukekbong *et al*., 2017). Antibiotic resistance pattern of the MRSA isolates showed 100% resistance to the Penicillins (Amoxicillin, Amoxicillin-Clavulanic, and Oxacillin) and Cephalosporins used, there was lower resistance to Linezolid, Erythromycin, Trimethoprim-Sulphamethoxazole, Gentamicin and Chloramphenicol. High resistance to Penicillins have also been reported in a number of studies in and outside Nigeria, Muhammed *et al*., (2013) reported 100% resistance to the Penicillins in Kano, while 61.95% resistance was reported by Olugbue *et al*, (2018) in Ebonyi, Nigeria. Similarly, Hong *et al*., (2018), in South Korea, reported an incidence of 69.9 %, Khan *et al*, (2017), reported 82% in Pakistan and in Iran, 94.7%, Nezhad *et al*., (2017). The low percentage resistance observed to Trimethoprim-Sulphamethoxazole and gentamicin in this study has also been reported by Muhammed*et al*., (2013), Hong and Sung, (2018) and Muhammed*et al*., (2018) in their centers. In contrast to findings in this study, high resistance to erythromycin have been reported by some researchers, Hong and Sung, (2018), Nehzad*et al*., (2017), Aggarwal *et al*., (2019), and similar report of high percentage resistance to Trimethoprim-Sulphamethoxazole 97.2 %, have also been documented in Ethiopia, by Kahsay*et al*., (2014) and 74 % in India, by Aggarwal *et al*., (2019). While in these studies, no resistance against linezolid was recorded, 38.35% of resistance was found in this study. However, 5.5 % was earlier reported from Iran, Arianpoor*et al*., (2015). This finding is indicative of decline in the effectiveness of drugs used in the management of infections caused by *S. aureus* in this environment representing an alarming threat to patient health, (Kumar, 2016).

The threat of antibiotic resistance in *S.aureus* has become global and has been rising in the past several years. Unfortunately, this is facilitated in developing countries by lack of or unimplemented antibiotic policies, misuse of antimicrobials especially without prescription, suboptimal or uncompleted dosing, ease of access over the counter and unregulated supply chains (Ayukekbong*et al*., 2017). In addition, there are incidences of patients abandoning their medication as result of short side effect, these patients tend to come back to the hospital with recurring infection by a more virulent and resistant

strain of the infecting bacteria. Consequently,increasing the possibilities of the surviving pathogens to acquire resistance by exposing them to sub-therapeutic concentrations of the antimicrobials,(Ayukekbong*et al*., 2017). Mass migration, rapid intercontinental travel and trade also form an important route for the spread or dissemination of resistant bacterial strains from one geographic location to another (Memish*et al*, 2003, van der Bij*et al*., 2012, Laws *et al*., 2019).

Findings from this study, suggests a high proportion 86% of Methicillin resistance *S. aureus* and MDR-MRSA isolates from wound infection, which were also resistant to other β lactam antibiotics used and a significant proportion were found resistant to erythromycin and linezolid, while sensitive to the fluoroquinolone, aminoglycoside, tetracycline, sulphonamide. This observation possibly will provide a valuable contribution to the choice of first line antibiotics in the treatment of wound infections caused by MRSA, and has also highlighted the urgent need for training and retraining on infection prevention and control, increasing surveillance for antimicrobial resistance, and instituting and improving on antibiotic stewardship. Awareness talks to patients on proper use of antibiotics, antibiotic resistance and the dangers of misuse is of paramount importance. Epidemiological studies aimed at describing the predominant resistance profile of circulating clones is necessary, thereby increasing the effectiveness of prevention and infection control measures as well as treatment of MRSA infections.

Conflict of Interest

The authors declare no conflict of interest.

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