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Distribution and Antibiotics Resistance Pattern of Community-Acquired Methicillin-Resistance *Staphylococcus aureus* in Southwestern Nigeria

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Abstract

Background Methicillin-resistant *Staphylococcus aureus* is a global public health challenge and there is a continuous increase in community-acquired infections among people in different geographical location. We sought the distribution and antibiotics pattern of community-acquired methicillin-resistant *Staphylococcus* isolates among apparently healthy residents of Ibadan, Southwestern Nigeria.

Methods Seven hundred (700) healthy volunteers residing in Ibadan metropolis, Nigeria, were enrolled in this study. Isolates from the nasal swabs were aseptically collected and characterized using standard and established microbiological methods, which included growth and fermentation on mannitol salt agar, colonial morphology, Gram-staining reaction, Microbact™ 12S identification kit and confirmed with 16SrRNA. After identification of the isolates, antimicrobial susceptibility test was performed on Mueller-Hinton agar by modified Kirby-Bauer disc diffusion method and the presence of *mecA* and *nuc* genes were detected via polymerase chain reaction assay.

Results Prevalence of *Staphylococcus aureus* nasal carriage and Methicillin-resistant *Staphylococcus* in this study was 31.9% and 9.43% respectively. The residents of Ibadan North local government area (Fisher's Exact = 1.8962, $P = .028$) and Egbeda local government area (Fisher's Exact = 2.7222, $P = .006$) are likely to carry Methicillin-resistant *Staphylococcus* than any other local government area in Ibadan, Nigeria. The antimicrobial resistance patterns of the isolates revealed high resistance to Oxacillin (96.9%). Most of the isolates were sensitive to vancomycin (92.4%). Polymerase chain reaction analysis showed that *mecA* gene was present in all 66 (100%) Methicillin-resistant *Staphylococcus aureus* isolates. Male-gender ($\varkappa^2 = 8.849$, $P = .003$), Adults; 40–50 years old ($\varkappa^2 = 9.842$, $P = .002$), low educational background ($\varkappa^2 = 36.817$, $P < .001$), recent hospital visitation ($\varkappa^2 = 8.693$, $P = .003$) are some of the factors that are observed in this study to be associated with Methicillin-resistant *Staphylococcus* infection.

Conclusion Our findings revealed the relatively high frequency of nasal carriers of

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Methicillin-resistant *Staphylococcus aureus* among the apparently healthy residents of the studied area and the advent of multidrug resistance among these isolates. Our study also supports previous findings on male-gender and low educational background as risk factors of *S. aureus* carriage. The need for rational chemotherapy, routine detection and regular surveillance of Methicillin-resistant *Staphylococcus* to limit its spread and reduce treatment failures is important.

Keywords

Antibiotic resistance · mecA gene · MRSA · Multidrug resistance · Nasal carriers · Nigeria

1 Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as an important pathogen in human medicine. MRSA was first reported in 1961, soon after the introduction of methicillin into human medicine to treat penicillin-resistant staphylococci in nosocomial infections (Conly and Johnston 2003; Lakhundi and Zhang 2018). Methicillin resistance is of great importance because it is conferred by the presence of the *mecA* gene that resides on a staphylococcal chromosomal cassette (SCC), which encodes for the production of an altered penicillin-binding protein (PBP; PBP2a or PBP2) that has a reduced affinity for all beta-lactam antimicrobials. In the past five decades, the incidences of both nosocomial and community-acquired *S. aureus* (CA-MRSA) infections have increased, while antibiotics treatment options are increasingly hampered by the spread of MRSA (Davis et al. 2007; Yarovoy et al. 2019). MRSA are resistant to a broad range of antimicrobials and are also frequently resistant to most of the commonly used antimicrobial agents such as aminoglycosides, macrolides, chloramphenicol, tetracycline, and fluoroquinolones which make MRSA particularly difficult to treat.

From the systematic review carried out by Abubakar and Sulaiman (2018), the prevalence of MRSA infection in Nigeria was about 50%. Poor infection control, inappropriate use of antibiotics and poor implementation of the developed National action plan for antimicrobial resistance could explain the rising trends of MRSA in Nigeria (FMoH 2017). However, efforts are currently being made to implement such interventions in Nigeria. The emergence of CA-MRSA has changed the epidemiology of *S. aureus* as reported by several studies (Iwao et al. 2017; Oliveira et al. 2018; Wang et al. 2016). Many studies have characterized *S. aureus* and MRSA isolates from individuals at some selected communities and hospitals but there is a paucity of information on the distribution of staphylococcal nasal carriage and MRSA among a group of communities in southwestern Nigeria particularly, in Ibadan. Therefore, we sought to determine the distribution, risk factors, and the antibiotic resistance patterns of MRSA to commonly prescribed antibiotics in these localities. This would be useful in choosing empirical therapy for the treatment of CA-MRSA infections and the enactment of infection control guidelines.

2 Methods

2.1 Ethical Approval

Ethical approval was sought from the Health Research Ethics Committee (HREC) of the Institute of Public Health, Obafemi Awolowo University, Ile-Ife, Nigeria. We obtained informed consent from all participants or their legal guardians and confidentiality of all participants and premise data was strictly maintained.

2.2 Study Population and Collection of Samples

This was a cross-sectional, multicenter study using a proportionate stratified random sampling

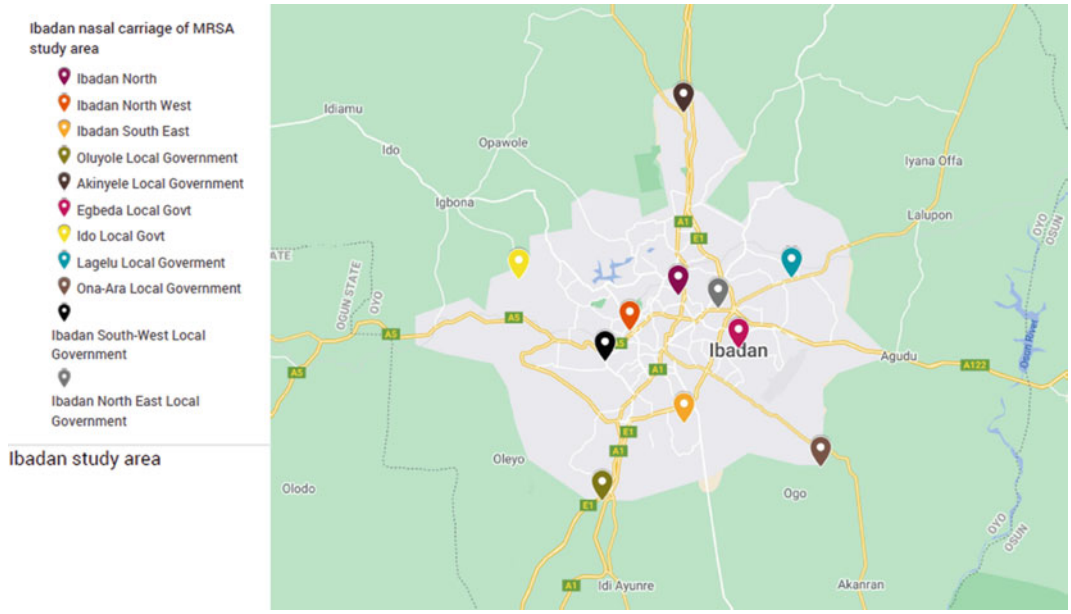

Fig. 1 Map indicating the location of the study area (Olayinka 2021)

technique. Ibadan city is the state capital of Oyo-State with over 3.7 million inhabitants. The participants were recruited from the 11 local government areas (LGAs) in Ibadan, Nigeria for a period of 9 months (Fig. 1). Nasal specimens were collected by streaking both the anterior nares of each participant using sterile swabs (Copan Diagnostics, Corona, CA, USA) moisture with sterile normal saline. The samples were transported to the laboratory aseptically within 2 h of collection.

2.3 Isolation and Identification of *Staphylococcus aureus*

All nasal swabs were inoculated onto Mannitol Salt Agar and Blood Agar (Oxoid Ltd., Hampshire, England) aseptically and incubated aerobically at 37 °C for 24–48 h. Discrete colonies of *Staphylococcus aureus* were sub-cultured on Nutrient agar (Oxoid Ltd., Basingstoke, Hampshire, England) plates incubated aerobically at 37 °C for 24 h to obtain pure culture and for further analyses. Each isolate was identified using Gram-staining, Cowan & Steel method of bacteria identification, Microbact™ 12S identification kit and confirmed via 16SrRNA gene detection.

2.4 Antimicrobial Sensitivity Testing

The susceptibility of recovered *S. aureus* isolates to various antibiotics were determined according to Kirby-Bauer disc diffusion technique and the (Clinical and Laboratory Standards Institute 2021) guideline was used to interpret the result. The tested antibiotics include Tetracycline (30 μg), Gentamicin (10 μg), Clindamycin (2 μg), Erythromycin (15 μg), Oxacillin (1 μg), Ceftaroline (30 μg), Co-trimoxazole (25 μg), Linezolid (30 μg), Vancomycin (30 μg), Cefoxitin (30 μg), and Ceftriaxone (30 μg) (Oxoid Ltd., Basingstoke, United Kingdom). We used cefoxitin discs (30 μg) (Oxoid Ltd., Basingstoke, United Kingdom) to phenotypically screen for methicillin-resistance). *S. aureus* ATCC 25923 was used for quality control.

2.5 Genomic DNA Isolation and Detection of *mecA* and *nuc* Genes

Promega (Madison, USA) genomic DNA extraction kit was according to the manufacturers' instructions using aseptic precautions. Polymerase Chain Reaction (PCR) assay was carried out for *mecA* (for detection of methicillin resistance) and *nuc gene* (for detection of *S. aureus*). The primer sequenced were as follows *mec-A1* (5′-AAA ATC GAT GGT AAA GGT TGC C-3′), *mec-A2* (5′- AGT TCT GCA GTA CCG GAT TTG C- 3′) and *nuc-A1* (5′- GCG ATT GAT GGT GAT ACG GTT-3′), *nuc-A2* (5′- AGC CAA GCC TTG AAC GAA CTA AAGC- 3′ (David et al. 2010).

2.5.1 Questionnaire Design

We developed and administered a structured questionnaire. Three independent reviewers were selected to validate the questionnaire; to assess the content validity, clarity, ease of response, scope, and face validity of the questions, We also obtained the participants' demographic characteristics (gender, education, and age group) and information on risk factors (recent antibiotics use, handwashing frequency, educational background of participants, etc.) for predisposition to colonization (Supplementary file 1).

2.5.2 Statistical Analysis

The data was summarized using Microsoft excel 2016 and subjected to further statistical analysis using Chi-Square and Fisher's Exact Probability Test in Epi-Info V.7.0 (CDC, Atlanta, USA). Inferences were made based on computed Prevalence ratios, their 95% confidence intervals and p-values. The level of significance was set at $p < 0.05$.

3 Results

Seven hundred (700) participants were included in this study from their respective LGAs; 56% (392/700) males and 44% (308/700) female participants while the age range (30–40 years) had the highest frequency of participants 20.1% (141/700). Most of the participants (62.6%, n = 438/700) had no formal/primary education (Table 1). The prevalence of *S. aureus* nasal carriage and MRSA in this study was 31.9% (223/700) and 9.43% (66/700) respectively. MRSA was well distributed in all the eleven (11) LGAs in the study area with the highest prevalence in Egbeda LGA (28.6%, n = 18/63). Results showed that methicillin-resistant *S. aureus* is significantly associated with participants that reside in Ibadan North LGA (FE = 1.8962, $P = .028$) and Egbeda LGA (FE = 2.7222, $P = .006$) (Table 2).

Table 1 Description of the study participants (n = 700)

Variables	Frequency (%)
Gender	
Female	392 (56.00)
Male	308 (44.00)
Age	
1–10	63 (9.00)
>10–20	83 (11.86)
>20–30	127 (18.14)
>30–40	141 (20.14)
>40–50	140 (20.00)
>50–60	99 (14.14)
>60–70	47 (67.14)
Educational background	
Secondary & tertiary education	262 (37.43)
No formal education & primary education	438 (62.57)

Table 2 Profile of *Staphylococcus aureus* nasal carriage (SANC) and methicillin-resistance *Staphylococcus aureus* (MRSA) isolates from Ibadan

Local govt. area N = 700	Total participants N (%)	SANC, n (%)	MRSA, n (%)	FE (P-value)
Ibadan North	190 (27.14)	71 (37.36)	31 (16.32)	**1.8962 (0.0281)***
Ibadan North East	73 (10.43)	12 (16.44)	2 (2.74)	0.5495 (0.7437)
Ibadan North West	34 (4.90)	6 (17.65)	1 (2.94)	0.5564 (1.0000)
Ibadan South East	60 (8.57)	21 (35.00)	4 (6.67)	0.6206 (0.4659)
Ibadan South West	63 (9.00)	27 (42.86)	3 (4.76)	0.3457 (0.1058)
Oluyole	46 (6.50)	21 (45.65)	2 (4.35)	0.3006 (0.1205)
Akinyele	55 (7.79)	6 (10.91)	1 (1.82)	0.5564 (1.0000)
Egbeda	63 (9.00)	27 (42.85)	18 (28.57)	**2.7222 (0.0059)***
Ido	23 (3.24)	3 (13.04)	1 (4.35)	1.1282 (1.0000)
Lagelu	33 (4.71)	7 (21.21)	1 (3.03)	0.4747 (0.6872)
Ona-Ara	60 (8.57)	22 (36.67)	2 (3.33)	0.2855 (0.1238)

FE Fisher's exact, *SANC* Staphylococcus aureus nasal carriage, *MRSA* Methicillin-resistant Staphylococcus aureus
*p < 0.05 (i.e. statistically significant)

The susceptibility pattern of nasal *S. aureus* to different antibiotics is presented in Table 3. Most of the MRSA were resistant to other antibiotics such as Oxacillin (96.9%), clindamycin (62.1%), Co-trimoxazole (59.1%) as revealed in Fig. 2. This study showed that nasal *Staphylococcus aureus* are highly multidrug-resistant as 54% were resistant to two different classes of antibiotics while 24% were resistant to three or more different classes of antibiotics. All the 66 (100%) MRSA isolates harboured the *mecA* gene (Fig. 3). In addition, 18 (27.3%) of the recovered MRSA possess the *nuc* gene (Fig. 4).

The result of this study showed that participants between 40–50 years old (34.5%, $\varkappa^2 = 9.842$, $P = .002$) and the male participants (35.3%, $\varkappa^2 = 8.849$, $P = .003$) were more likely to be carriers of MRSA (Table 4). Some of the factors that are associated with MRSA infection were tested in this study; the participants that visited the hospital recently (39.7%, $\varkappa^2 = 8.693$, $P = .003$), used antibiotics recently (61.7%, $\varkappa^2 = 7.556$, $P = .006$) and those with low educational background (3.9%, $\varkappa^2 = 36.817$, $P < .001$) are more likely to be carriers of MRSA as presented in Table 4.

4 Discussion

The epidemiological knowledge of Methicillin-resistant *Staphylococcus aureus* (MRSA) infection is very important for appropriate decision-making in the treatment of infections. Since at least 1978 when we have the first reported case of MRSA in Africa (Scragg and Appelbaum 1978), we have been attending to an increase in the number of infection episodes in healthy individuals (both adults and children) in the community (Abubakar and Sulaiman 2018). According to the review done by Abdulgader et al. (2015), only fifteen (15) out of the fifty-four (54) African countries are with reports on the molecular epidemiology of MRSA. Additionally, despite the global challenge on the burden of disease caused by CA-MRSA, in Nigeria, only a few isolated studies describing MRSA with typical community backgrounds were reported (Ghebremedhin et al. 2009). In this study, we report for the first time the prevalence, risk factors and the epidemiology of CA-MRSA infections in Ibadan as well as determine the antibiotic resistance indices of MRSA in different communities in Ibadan, Nigeria.

It has been reported that all beta-lactam antibiotics have poor affinity when penicillin-binding protein (PBP) is altered; it will be difficult to kill such microorganisms when exposed to therapeutic concentration. Methicillin resistance is mediated among *Staphylococcus aureus* by the penicillin-binding protein encoded by the *mecA* gene (Ito et al. 2014). The overall prevalence of CA-MRSA in this study was 9.43%. The MRSA prevalence reported in this study is higher than what was reported (4%) by Ajani et al. (2020) among students of a private institution in Ogun-State, Nigeria.

Table 3 Resistance profile of Nasal *S. aureus* from healthy population in Ibadan

Antibiotics	Concentrations (μg)	Resistance n (%)	Intermediate n (%)	Susceptible n (%)
Tetracycline	30	29 (13.00)	3 (1.35)	191 (85.65)
Gentamicin	10	14 (6.28)	7 (3.14)	202 (90.58)
Clindamycin	2	126 (56.50)	43 (19.28)	54 (24.22)
Erythromycin	15	85 (38.12)	35 (15.69)	103 (46.19)
Oxacillin	1	187 (83.86)	18 (8.07)	18 (8.07)
Ceftaroline	30	32 (14.35)	6 (2.69)	185 (82.96)
Co-trimoxazole	25	180 (80.72)	16 (7.17)	27 (12.11)
Linezolid	30	47 (21.08)	11 (4.93)	165 (73.99)
Vancomycin	30	8 (3.59)	9 (4.04)	206 (92.38)
Cefoxitin	30	91 (40.81)	0 (0.00)	132 (59.19)
Ceftriaxone	30	35 (15.70)	24 (10.76)	164 (73.54)

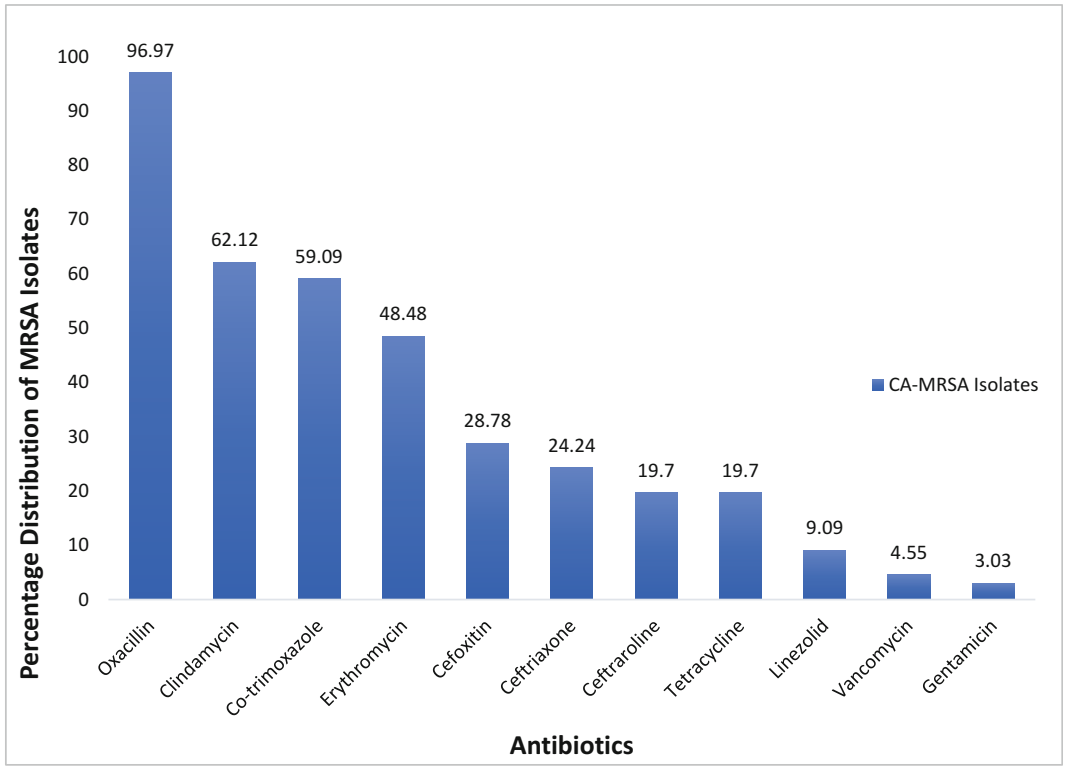

Fig. 2 Antimicrobial resistance pattern of CA-MRSA in Ibadan

We detected *nuc* genes of *S. aureus* in only 27.3% of the MRSA isolates this is probably due to the differences in the nucleotide sequence among the *nuc* genes caused by some mutation or the absence of *nuc* gene in some *S. aureus* strains (Sahebnasagh et al. 2014). The difference between the phenotypic and genotypic detection of *S. aureus* strains made it clear that, the method of identifying only *nuc* genes in *S. aureus* is not sufficient. Therefore, both phenotypic and genotypic methods should be conducted for the identification of *S. aureus* strain. Methicillin-resistant

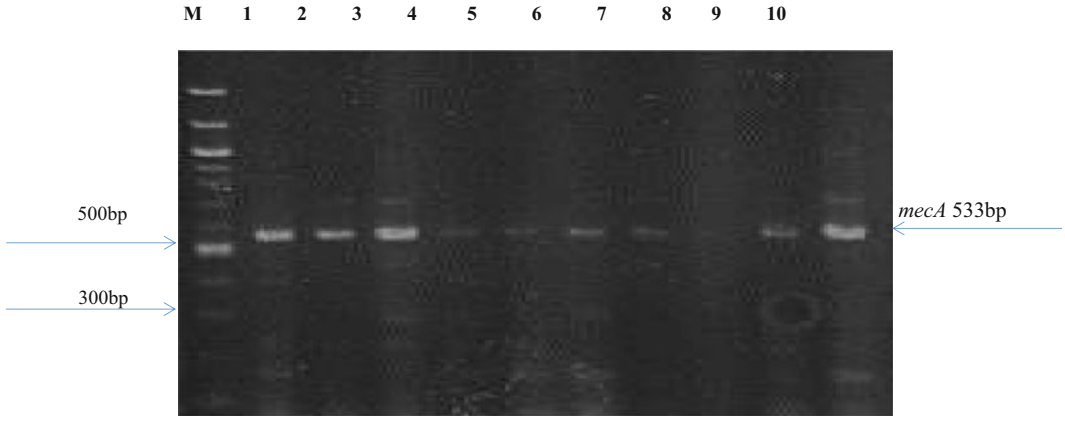

Fig. 3 PCR amplification of *MecA* gene (533 bp), 16-10-2020
Lane M: DNA molecular size marker (100 bp ladder), Lane 1: ATCC 33591 (positive control), Lane 2: Isolate 14; Lane 3: Isolate 28; Lane 4: Isolate 35; Lane 5: Isolate 38; Lane 6: Isolate 48; Lane 7: Isolate 55; Lane 8: Isolate 62; Lane 9: Isolate 69; Lane 10: Isolate 71.

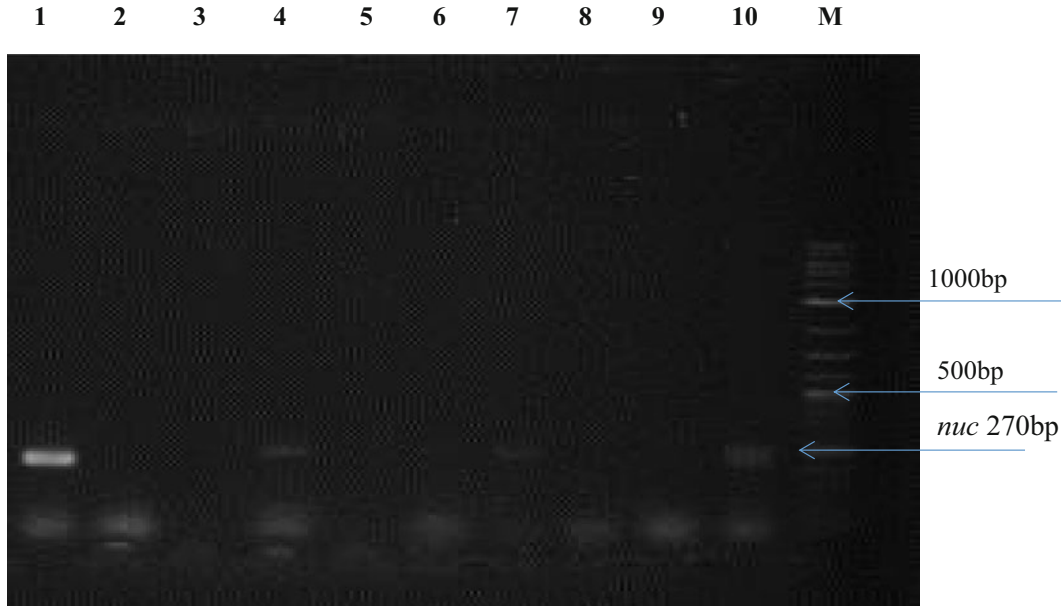

Fig. 4 Lane 1: Isolate 14, Lane 2: Isolate 16; Lane 3: Isolate 19; Lane 4: Isolate 22; Lane 5: Isolate 25; Lane 6: Isolate 27; Lane 7: Isolate 35; Lane 8: Isolate 36; Lane 9: Isolate 43; Lane 10: ATCC 29213 (positive control), Lane M: DNA molecular size marker (100 bp ladder)

Staphylococcus aureus isolates were obtained from all the 11 LGAs in Ibadan, Nigeria. Egbeda and Ibadan North LGAs presented the highest MRSA prevalence in this study. Individuals that reside in either of these LGAs (Ibadan North; FE = 1.8962, P = .028 or Egbeda; FE = 2.7222, P = .006) are more likely to carry MRSA than those in other areas. This is because the two LGAs are among the most populated LGAs in Ibadan with shared border and linked

Table 4 Bivariate analysis of risk factors for MRSA

Variable	Total participants N = 700, N (%)	SANC, n (%)	MRSA, n (%)	χ^2 (P-value)
Gender				**9.842 (0.002)***
Male	392 (56.00)	142 (36.22)	49 (34.50)	
Female	308 (44.00)	81 (26.21)	17 (20.99)	
Recent antibiotics used				**7.556 (0.006)***
Yes	205 (29.29)	47 (22.92)	29 (61.70)	
No	495 (70.71)	176 (35.56)	37 (21.02)	
Recent hospital visit (in the last 3 months)				**8.693 (0.003)***
Yes	220 (31.43)	78 (35.45)	31 (39.74)	
No	480 (68.57)	145 (30.21)	35 (24.14)	
Household members who care for sick people				0.137 (0.711)
Yes	15 (2.14)	3 (20.00)	1 (33.33)	
No	685 (97.86)	221 (32.26)	65 (29.41)	
Hand washing frequency				1.298 (0.255)
Often	576 (82.29)	197 (34.20)	51 (25.89)	
Seldom	124 (17.71)	26 (20.97)	15 (57.69)	
Educational background				**36.817 (<0.001)***
Secondary & tertiary education	262 (37.43)	51 (19.47)	2 (3.92)	
No formal education & Primary education	438 (62.57)	172 (39.27)	64 (37.21)	
Smoking habits[a]				
Ex-smoker	63 (9.00)	26 (41.27)	6 (23.08)	0.001 (0.978)
Current smoker	141 (20.14)	40 (28.37)	11 (27.50)	0.547 (0.459)
Non-smoker	496 (70.86)	157 (31.65)	49 (31.21)	0.404 (0.525)

χ^2 = Chi square, *S. aureus* nasal carriage (SANC)
*$p < 0.05$ (i.e. statistically significant)
[a]multivariate analysis was used

roadways (NPC 2006; Olayinka 2021). This result is similar to the previous MRSA prevalence range of 14.3–37% that has been reported in different communities in Nigeria (Akerele et al. 2015; Bale et al. 2019; Egwuatu et al. 2016; Ghebremedhin et al. 2009; Taiwo et al. 2005). This is not surprising as the MRSA prevalence varies greatly with geographical location and studied population (Bell et al. 2002).

Antimicrobial resistance (AMR) is one of the major threats posed by microorganisms in this twenty-first century. Despite the serious efforts employed to control AMR by aggressive infection control methods, MRSA has become one of the most frequent cause of hospital and community-acquired infections globally. MRSA has always been one of the major pathogens that possess the ability to develop resistance to newly developed antimicrobial agents (Joo et al. 2017). In this study, *Staphylococcus aureus* nasal carriage exhibited resistance to Oxacillin, Co-trimoxazole and Clindamycin but susceptible to Vancomycin, Gentamicin, Tetracycline, Ceftaroline and Linezolid in varying degrees. The MRSA isolates were also resistant to multiple antibiotics. The antimicrobial resistance patterns of the isolates revealed high (80%) multidrug resistance (resistance against at least 2 different classes of antimicrobials) rate among the MRSA isolates. Shariati et al. (2020) reported a global increase in the prevalence of vancomycin resistance in their systemic review of global prevalence and distribution of vancomycin-resistant *Staphylococcus aureus*. Therefore, the 7.6%prevalence of vancomycin resistance in this study is not surprising although it remains a major global

public health challenge. The relatively high resistance prevalence observed in both Ceftaroline and linezolid in this study are comparable with the rate of resistance reported in a neighboring town by Osinupebi et al. (2018). Many factors can be linked to the high resistance of this organism to antibiotics in these communities. Such factors include self-medication, availability and use of antibiotics without prescription, irrational consumption rate of antibiotics, over the counter accessibility without prescription and sales of fake or substandard drugs, unrestricted use of antimicrobials in farm animals (including poultries and fisheries), and transmission of resistant strains between individuals within the community (Akerele et al. 2015; Elimam et al. 2014).

One of the main reason for *mecA* gene screening by polymerase chain reaction (PCR) technique is to compare the results of antibiotic susceptibility by disc diffusion method with gene analysis results in *Staphylococcus aureus* isolates. Not all MRSA strains may be detectable with phenotypical methods as some *mecA* genes may be heterogeneously expressed. In this study, all the MRSA isolates that were cefoxitin resistant were also positive for this gene detection method confirming that they are all methicillin-resistant *Staphylococcus aureus.* The study showed a strong correlation between genotypic and phenotypic analysis and it is consistent with previous studies that reported a perfect association between the results obtained by the phenotypic antibiotic resistance determination and PCR- based assays (Bale et al. 2019; Ito et al. 2014; Strommenger et al. 2006).

The present study showed a high proportion of CA-MRSA in the male-gender than in female which agrees with previous studies (Abroo et al. 2017; Mehraj et al. 2014; Skramm et al. 2011). The microbial differences between male and female could be due to physiological factors or anatomical differences between genders (Giacomoni et al. 2009). Our findings that males were more likely to carry MRSA is consistent with other studies, which indicate a gender-specific risk factor (Andersen et al. 2013; Assafi et al. 2015; Gorwitz et al. 2008; Graham et al. 2017; Mehraj et al. 2014; Skramm et al. 2011). Some studies have reported the association of MRSA among adults and elderly as revealed in this study (Andersen et al. 2013; Gorwitz et al. 2008). This study also revealed that individuals with certain risk factors (age, male gender, recent use of antibiotics, recent hospital visitation, and level of education) were more likely to be carriers of MRSA (Abroo et al. 2017; Graham et al. 2017).

5 Conclusion

In conclusion, the strongest risk factors of CA-MRSA were male gender, low educational background, recent antibiotics used, and hospital visits. The relatively high prevalence of CA-MRSA in this study is a cause for concern. CA-MRSA showed a high resistance burden and individuals who are harboring these isolates can act as reservoirs; this may negatively influence the treatment of CA-MRSA infections. The continuous surveillance of CA-MRSA is essential to prevent transmission of *Staphylococcus aureus* from the infected carriers to others also to apply effective therapeutic options for their treatment.

Competing Interests Authors have declared that no competing interests exist.

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