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Macrolide, Lincosamides and Streptogramin-B (MLS_B) Resistance Phenotypes in Community and Hospital-Associated *Staphylococcus Aureus* in Sokoto, Nigeria.Ganau, A.M.*¹, Shuraihu, A.², Garba, M.K.¹, Imam, A.U.¹*Department of Medical Microbiology, Faculty of Medical Laboratory Sciences, Usmanu Danfodiyo University P. M. B. 2346, Sokoto Nigeria¹, Ahmadu Bello University Teaching Hospital Shika, P. M. B. 06 Zaria, Kaduna State Nigeria².**Author for Correspondence*: ahamadonline@yahoo.co.uk; mohammed.ahmed@udusok.edu.ng; +234-803-268-0096***Abstract**

The Macrolide, Lincosamides and Streptogramin-B (MLS_B) is a group of chemically distinct agents with similar mode of action and target site. In the event of failure of β -lactam antibiotics, clindamycin become the drug of choice for treating Gram positive infections. The aim of the study is to determine the patterns of MLS_B resistance in community and hospital associated *Staphylococcus aureus* in Sokoto. During the study, 272 non-repetitive specimens from hospitals (Specialist hospital Sokoto and Maryam Abacha) and apparently healthy community volunteers (Almajiri Integrated School in Denge-Shuni) were collected and analysed. Out of the 272 samples analysed 81(29.8%) *Staphylococcus aureus* isolates were recovered and identified using standard microbiological methods. Twenty-nine (35.8%) of the *Staphylococcus aureus* isolates were community-associated while 52(64.2%) were from the hospital (hospital-associated). Of the 81 isolates studied 51(63.0%) were sensitive to both erythromycin and clindamycin, 10(12.3%) exhibited constitutive resistance to both drugs while the remaining 20(24.7) exhibited erythromycin-clindamycin discordance. Out of the 20 discordant isolates 2(10.0%) tested positive for the iMLS_B phenotype, both isolates were from hospital specimens ($p=0.260$). All the iMLS_B positive *S. aureus* were isolated from the age group 0-10 years, none was isolated from the other age groups ($p=0.060$). The antibiotic susceptibility profile of the isolates showed that the most potent antibiotics were quinupristin-dalfopristin, clindamycin and gentamycin with resistance seen only in 9.9%, 14.8% and 25.9% of all isolates tested respectively. The highest resistance of 53.1% was observed in trimethoprim-sulphamethoxazole. Although the

prevalence of iMLS_B observed in this study is relatively low it still calls for vigilance on the part of both laboratory scientist and clinicians.

Key words: Macrolides, Lincosamides, MRSA, MLS_B, *Staphylococcus aureus*

Introduction

Staphylococcus aureus is one of the most common etiological agents of both community-acquired and nosocomial bacterial infections (Mohamed *et al.*, 2005). *S. aureus* causes a variety of infections, from skin and soft tissue infections (SSTIs) to life threatening endocarditis (Fiebelkorn *et al.*, 2003). The increasing incidence of *Staphylococcus aureus* infections and the changing patterns in its antimicrobial resistance have led to renewed interest in the use of macrolide-lincosamide-streptogramin B (MLS_B) antibiotics to treat such infections. However, their widespread use has led to an increase in the number of *Staphylococcus* strains resistant to MLS_B antibiotics (Saiman *et al.*, 1999).

One important resistance phenotype in *S. aureus* is that involving the 23S ribosomal subunit, the active site for the activity of a group of antibiotics that inhibit protein synthesis (Rahbar *et al.*, 2003).

The MLS_B antibiotics are chemically distinct but share a common target site and mode of action. They exhibit three major mechanisms of resistance that include target site modification, enzymatic inactivation and efflux pumps that reduce intracellular concentrations. Resistance to MLS_B antibiotics is an acquired resistance encoded in erythromycin methylase (*erm*) genes.

Three distinct methylase genes (*ermA*, *ermB* and *ermC*) have been described in *Staphylococci*. Expression of these methylases is controlled by translational attenuation (Leclercq and Courvalin, 2009). Resistance can also result due to active efflux of the antimicrobial agent by an ATP-dependent pump encoded by their gene. However, the efflux mechanism affects macrolides and streptogramins only (Richard and Fair, 2014). Other rarer macrolide resistance mechanisms include ribosomal mutations and antibiotic inactivation by specific hydrolases or phosphotransferases (Leclercq and Courvalin, 2009).

MLS_B resistance in *S. aureus* can also be described as either being constitutive or inducible. When the expression is constitutive, the bacteria are resistant to all macrolides, lincosamides and streptogramin-B antibiotics. But when the resistance expression is inducible, the organisms are resistant to 14- and 15-membered macrolides; and are sensitive to 16-membered MLS_B antibiotics in the absence of inducer erythromycin (Steward *et al.*, 2005).

There's ongoing debate over the use of clindamycin in iMLS_B phenotype infection. There is doubt in usefulness of Clindamycin for the treatment of infections by *S. aureus* exhibiting iMLS_B. Although iMLS_B resistance phenotype isolates appear susceptible to clindamycin in the absence of an inducing agent macrolide, there is widespread reluctance to prescribe clindamycin for treatment of patients with infections caused by such organisms due to the concerns that resistance to clindamycin will develop during therapy.

However, in spite of the clinical relevance of this phenomenon, studies were yet to be conducted in the study area. The study is intended to provide a baseline study on the microbial epidemiology of this form of resistance pattern in *S. aureus*.

Materials and Methods

Study Area

Sokoto state is located in the North-western geopolitical zone of Nigeria, carved out of the defunct North Western State on 3rd February 1976. It lies between longitudes 11°03' to 13°50' East and latitudes 4° to 6°40' North. It covers a

total land area of about 32,000 square kilometers within the Iullemeden Basin surrounded to the East and South by the Precambrian basement complex (Nwankwoala, 2015). The Sokoto Rima River and its tributaries form one of the most extensive Fadama areas in Nigeria. The land is rich in limestone deposits with more than 100.6 million tones of reserves in the Kalambaina axis alone (Fatoye and Gideon, 2013). The National Population Commission put population figures at 3,702,676 persons spread over an area of 33,776.89 square kilometers of land. The population mainly consists of the Hausa/Fulani ethnic groups. The main occupation of the people is farming (during the rainy season and irrigation in the dry season) and animal husbandry. The two major seasons in Sokoto are the dry and wet seasons. The dry season starts around October and may last up to May; the wet season spans between June and September, with an annual rainfall of 50 - 130 cm (Atedhor, 2015).

Study Design

The study was a cross-sectional descriptive study, conducted between January and September 2018.

Study Population

The study was designed to isolate strains of *Staphylococcus aureus* from two different sources, the community and the hospital. From the community the main targeted source of specimen was the nasal swab. Nasal colonization is one of the main sources of infection in the community. Thus, nasal swabs were collected from volunteer participants that consented to participate in the research.

In the case of hospitals, specimens were collected from patients for whom culture have been indicated already depending on the site of infection or suggestion by the attending physician. The hospitals included in the study include Maryam Abacha Women and Children Hospital and Specialists Hospital, all in Sokoto.

Inclusion Criteria

Subjects included were those that show willingness to participate by providing their consent through filling a written informed

consent form. Only one isolate per subject was included.

Exclusion Criteria

Individuals that declined to provide a written consent were excluded. Similarly, specimens were only collected from subjects within the study area.

Ethical Considerations

Approval for the research was obtained from the ethical committee of the Sokoto State Ministry of Health.

Culture and Identification of Isolates

Clinical specimens were collected using appropriate sample containers using established standard procedures. Nasal swabs were collected using sterile swab sticks. Each specimen was inoculated on a quarter plate of Mannitol Salt Agar (MSA) and blood agar (5% sheep blood) plates and incubated at 37°C in ambient air for 24 hours before examining the resulting growth on both plates. *S. aureus* was identified using standard microbiological techniques. These include colonial morphology, mannitol fermentation on MSA, Gram stain reaction, general microscopic morphology, catalase test and coagulase tests (bound and free).

Antibiotic Susceptibility Testing (AST)

Suspensions for AST were prepared by the direct colony suspension method. Three well isolated 24-hour colonies on nutrient agar plates were suspended in 5mL of normal saline. The suspension was adjusted to achieve a turbidity that is equivalent to 0.5 McFarland standard ($1-2 \times 10^8$ CFU/mL).

A sterile cotton swab was then dipped into the adjusted suspension and rotated firmly against the inside wall of the tube above the fluid level to remove excess fluid. A Mueller-Hinton agar (MHA) plate was then inoculated by streaking the swab over the entire surface of the agar. The streaking was repeated two more times with the same swab, each time rotating the plate approximately 60°, in order to obtain a bacterial lawn of uniform density. Finally, the rim of the agar was swabbed. Excess surface moisture was allowed to evaporate and the antibiotic-

impregnated disks applied. The plates were then incubated in an inverted position in ambient air at 37°C for 24 hours. Results validation for the disk diffusion AST was done using the results obtained from the control organism.

Detection of Methicillin resistance

All isolates were screened for Methicillin resistance using a 30µg cefoxitin disk (Oxoid, UK).

Detection of the iMLS_B Phenotype

S. aureus isolates that exhibit erythromycin-clindamycin discordance were further studied for inducible clindamycin resistance by disk approximation test (D test) using a 15µg erythromycin disk and a 2µg clindamycin disk according to the Clinical Laboratory Standard Institute guidelines (CLSI, 2015). A 0.5ml McFarland suspensions of the test isolate was prepared as described above and used to inoculate the surface of MHA plate (Oxoid, UK). One erythromycin disk (15µg) and one clindamycin disk (2µg) were then placed 15mm apart (edge to edge) from each other on the inoculated plates and incubated at 37°C for 24 hours.

Results

During the study 272 non-repetitive specimens from hospitals (Specialist hospital Sokoto and Maryam Abacha) and apparently healthy community volunteers from the Almajiri Integrated School in Denge-Shuni were collected and analysed. These included 129 nasal swabs from the community and 143 clinical specimens from the two hospitals included in the study. Out of the 129 nasal swabs analysed 31(24.0%) *S. aureus* were isolate. At Specialists and Maryam Abacha Hospitals 102 and 41 specimens were collected respectively. The highest prevalence of *S. aureus* isolation 48(47.1%) was from Specialists Hospital (Table 1).

Of these specimens 81(29.8%) yielded growth of coagulase positive *Staphylococcus aureus*. Out of the 20 erythromycin-clindamycin discordant isolates 2(10.0%) tested positive for the iMLS_B phenotype.

Table 1: Sample collection and *S. aureus* distribution

Study Site	Samples Collected	Culture Negative (%)	<i>S. aureus</i> (%)
Almajiri School Dange-Shuni	129	76(58.9)	31(24.0)
Specialists Hospital	102	68(66.7)	48(47.1)
Maryam Abacha Hospital	41	39(95.1)	2(4.9)
Total	272	183(67.3)	81(29.8)

We were able to isolate and identify a total of 29(35.8%) MRSA strains during the study from both community and hospital associated specimens, 25(86.2%) of these isolates were hospital-associated. Only 4(13.8%) of the MRSA were from community sources (Table 2).

Table 2: MSSA and MRSA distribution from community and hospital sources

Phenotype	Community (%)	Hospital (%)	Total	χ^2	<i>p</i> value
MSSA	27(51.9)	25(48.1)	52	11.457	0.001
MRSA	4(13.8)	25(86.2)	29		
Total	31(38.3)	50(61.7)	81(100)		

Antibiotic susceptibility profile of the isolates showed that quinupristin-dalfopristin had the highest sensitivity 86.4% followed by clindamycin, gentamycin, ceftioxin and ciprofloxacin with sensitivities seen in 74.1%, 71.6%, 64.2% and 63.0% respectively. The highest resistance level of 53.1% was observed in trimethoprim-sulphamethoxazole, followed by tetracycline with 37.0% and ceftioxin with resistance seen in 35.8% of all isolates tested (Table 3).

Table 3: Antibiotic sensitivity pattern of all *S. aureus* isolated

Antibiotics	Sensitive (%)	Intermediate (%)	Resistant (%)	Total
QD	70(86.4)	3(3.7)	8(9.9)	81
Clindamycin	60(74.1)	9(11.1)	12(14.8)	81
Gentamycin	58(71.6)	2(2.5)	21(25.9)	81
Ceftioxin	52(64.2)	0(0.0)	29(35.8)	81
Ciprofloxacin	51(63.0)	13(16.0)	17(21.0)	81
Tetracycline	47(58)	4(4.9)	30(37.0)	81
Erythromycin	39(48.1)	15(18.5)	27(33.3)	81
STX	30(37.0)	8(9.9)	43(53.1)	81

QD = Quinupristin-dalfopristin; STX = Trimethoprim- Sulphamethoxazole

The distribution of MLS_B susceptibility phenotypes showed that 51(63.0%) of all the isolates tested were sensitive to both erythromycin and clindamycin, 26(51.0%) from the community source and 25(49.0%) from the two hospitals. Twenty of the isolates showed erythromycin-clindamycin discordance, resistant to erythromycin but sensitive to clindamycin, 17(85.0%) of which were from hospital and 3(15.0%) from the community. The constitutive resistance phenotype (resistant to both antibiotics) was observed in 10(12.3%) isolates of which 8(80.0%) were from hospital and 2(20.0%) were isolated from the community (Table 4).

Table 4: Erythromycin-clindamycin susceptibility Phenotypes between community vs. hospital and MSSA vs. MRSA isolates

Source	Constitutive	Sensitive	Discordant	Total	χ^2	<i>p</i> value
Community (%)	2(20.0)	26(51.0)	3(15.0)	31(38.3)	9.485	0.009
Hospital (%)	8(80.0)	25(49.0)	17(85.0)	50(61.7)		
Total	10	51	20	81		
MSSA (%)	1(10.0)	40(78.4)	11(55.0)	52(0.0)	18.012	0.000
MRSA (%)	9(90.0)	11(21.6)	29(0.0)	29(0.0)		
Total	10	51	40	81		

The patterns of MLSB resistance between MSSA and MRSA isolates indicates that out of the 10 isolates that exhibited constitutive resistance 9(90%) were from hospital-associated sources, only 1(10%) were community –associated. However, we observed a higher recovery rate of isolates with erythromycin-clindamycin discordance from community sources than from hospital-associated specimens (11 isolates representing 55.0% versus 9 representing 45.0%).

Only 2/20(10.0%) of the isolates expressing erythromycin-clindamycin discordance were positive for the iMLS_B phenotype (Fig. 1), both of which were hospital-associated strains.

Distribution of iMLS_B phenotype among the age groups (Table 5) showed that 2(13.3%) isolates of the age group 0-10 years were iMLS_B positive. No isolate from the other age groups tested positive.

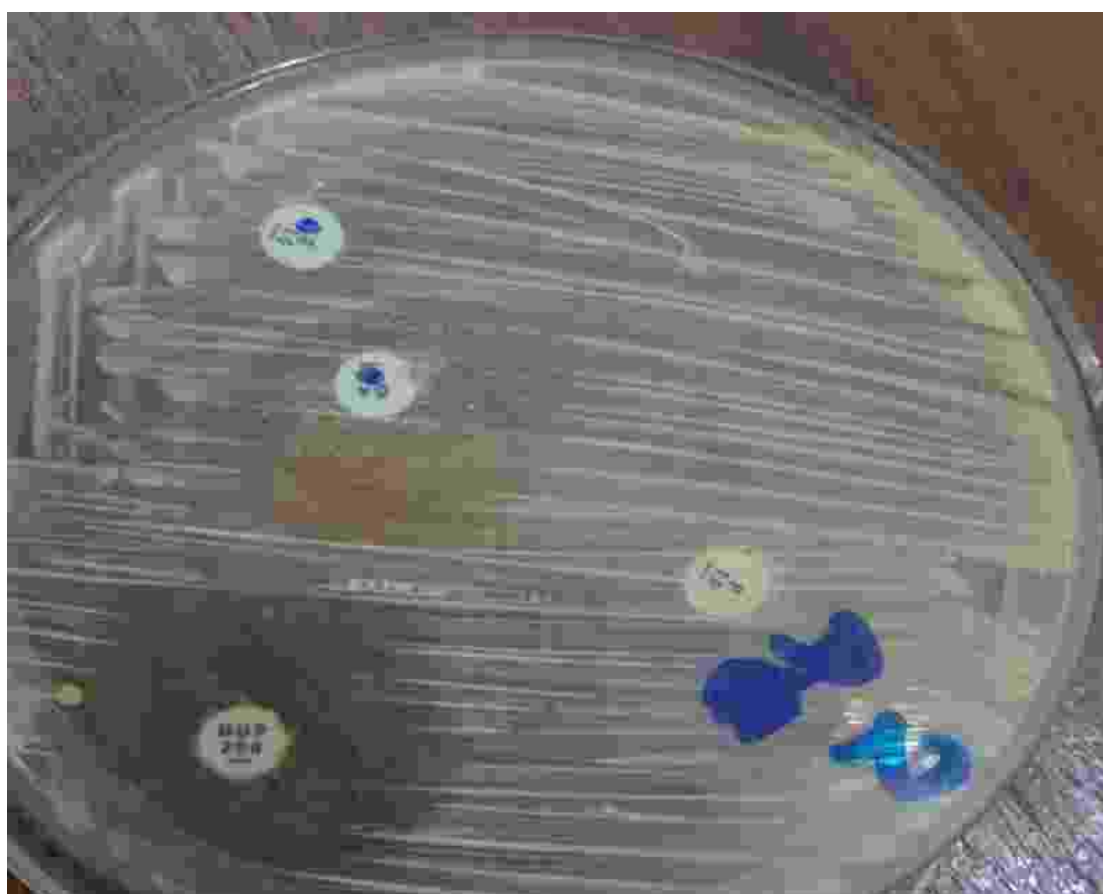


Figure 1: A D-test positive isolate

Age group-based distribution of isolates exhibiting the iMLS_B phenotype is depicted in Table 4 below. The two isolates that turned positive were all isolated from samples collected from hospitalized children within the age group 0-10 years, both from Specialists Hospital Sokoto. One of which was from a female patient (7 years old) with otitis media, the other male (5 years) with an infected wound. None of the isolates from any of the other age groups tested positive for this resistance phenotype.

Table 5: Distribution of iMLS_B phenotypes among the Age groups (Years)

Age Group (Yrs)	iMLS _B Negative	iMLS _B Positive	Total	²	p value
0 – 10	13(86.7)	2(13.3)	15(100)	9.023	0.061
11 – 20	46(100)	0(0)	46(100)		
21 – 30	13(100)	0(0)	13(100)		
31 – 40	4(100)	0(0)	4(100)		
41 – 50	3(100)	0(0)	3(100)		
Total	79(97.5)	2(2.5)	81(100)		

Discussion

As staphylococcal infections have become increasingly common in the community setting, the choice of empirical antimicrobial therapeutic strategies for *Staphylococcal* infections has become more problematic (Fridkin *et al.*, 2005). Clindamycin has long been an option for treating both MSSA and MRSA infections. However, expression of inducible resistance to clindamycin could limit the effectiveness of this drug. An important resistance phenotype in *S. aureus* is that involving the 23S ribosomal subunit that is used as the active site for the activity of a group of antibiotics that inhibit protein synthesis, including macrolides (Rahbar *et al.*, 2003). The aim of this study was to determine the patterns of macrolides lincosamides streptogramin-B (MLS_B) resistance in community- and hospital-associated *Staphylococcus aureus* in Sokoto metropolis.

Out of the 272 samples analysed 81(29.8%) *Staphylococcus aureus* isolates were recovered and identified using standard microbiological methods. Out of the 81 isolates of coagulase positive Staphylococci 29(35.8%) were from community (community-associated) and 52(64.2%) were from the hospital (hospital associated). The isolation rate of 29.8% for *S. aureus* compares favourably with the 28.95% reported from Cameroun (Bissong *et al.*, 2016). It is, however, much lower than the 48%

prevalence reported in an earlier Swedish study by Nilsson and Ripa (2006).

The most commonly used antibiotic for the treatment of such staphylococcal infections in event of failure of β -lactam antibiotics is clindamycin (owing to its excellent tissue penetration), except for the central nervous system (Sivapalasingam and Steigbigel, 2005; Fiebelkorn *et al.*, 2003). Macrolide-induced clindamycin resistance was first observed in clinical isolates of *staphylococcus* in 1968 (McGehee *et al.*, 1968).

Resistance to macrolide in *Staphylococci* is caused either by ribosomal modification by 23S *rRNA* methylases encoded by the *erm* genes or may result from active efflux by an ATP-dependent pump (Reygaert, 2009). Methylases confer inducible (iMLS_B) or constitutive (cMLS_B) resistance to macrolides, lincosamides and streptogramin agents (MLS_B resistance) (Reygaert, 2009). The efflux mechanism affects macrolides and streptogramins only (Richard and Fair, 2014). The antibiotic susceptibility profile of the studied isolates showed a 33.3% resistance to erythromycin and a 14.8% resistance to clindamycin. The resistance pattern of erythromycin compares favourably with the 33.6% resistance recorded elsewhere in Nigeria (Akanbi and Mbe, 2013). However, Mittal and Colleagues (2013), reported a higher prevalence of 44.2% to erythromycin resistance in a study

involving 99 isolate of *Staphylococcus aureus*. The overall prevalence of the iMLS_B phenotype in erythromycin-clindamycin discordant isolates in this study is 10%. This is slightly lower than the 15.4% reported from Abakaliki, South-South Nigeria (Chika *et al.*, 2018). Similarly, a higher prevalence of 17.7% was reported from the North-Central state of Plateau recently (Okojoku, *et al.*, 2018). However, our findings compare favourably with the 11.2% prevalence reported from Rivers State (Nwokah and Abbey, 2016). In an earlier study from the North-Western part of Nigeria, Kumurya (2015) identified 24.63% prevalence from Kano State. Notwithstanding, much lower prevalence of the iMLSB phenotype have been reported from studies around the world. For instance, an earlier study in Brazil reported a prevalence rate of only 3.3% (Coutinho *et al.*, 2010).

Constitutive resistance to erythromycin and clindamycin is expressed by 10(12.3%) of the 81 isolates encountered in our study. This compares to the 10.8% constitutive resistance reported elsewhere (Okojoku *et al.*, 2018). It is, however, much higher than what was reported by Nwokah and Abbey (2016), who reported a constitutive resistance of only 4.9%. Much higher prevalence of 20.5% has been reported recently (Chika *et al.*, 2018).

Initially only 12(14.8%) of the isolates encountered exhibited resistance to the lincosamide antibiotic clindamycin, however, upon performing the D-test 2 erythromycin-clindamycin discordant isolates showed positive results and as such reported as resistant to clindamycin as required (CLSI, 2015). Thus, this gives a total of 14(17.3%) resistance to clindamycin.

Out of the 20(24.7%) isolates that exhibited erythromycin-clindamycin discordance 11(55.0%) were MSSA while 9(45.0%) were MRSA. One isolate from each turned positive for the iMLS_B phenotype, both of which were hospital-associated *Staphylococcus aureus*. This gives an iMLSB prevalence of 9.1% for MSSA and 11.1% for MRSA. Thus, we observed a higher prevalence of erythromycin-clindamycin discordance in MSSA but a higher prevalence of

the iMLS_B phenotype in MRSA. Similarly, Otsuka and Colleagues (2007) reported a significantly higher prevalence of iMLSB in MRSA from Japan (38.7% in MRSA versus 94.0% in MSSA). Outcomes that agree with such findings were made elsewhere (Patel *et al.*, 2006).

However, in an earlier study by Levin and Colleagues (2005), the authors discovered that although most (72.2%) erythromycin-clindamycin discordant isolates were MRSA only 12.3% turned iMLSB positive. But of the 27.5% of the discordant isolates found among the MSSA isolates in the study 68% turned out to be iMLS_B positive (Levin *et al.*, 2005; Mahmoud *et al.*, 2015; Majhi *et al.*, 2016). A possible explanation for the disparity seen herein may be attributed to the genetics of antimicrobial resistance in *S. aureus*. The transposable genetic element designated Tn554 has been implicated in the disparity seen between HA- and CA-MRSA in terms of the expression of the iMLSB resistance phenotype (Patel *et al.*, 2006). Transposon *Tn554* harbours one of the most widespread methylases genes, *erm(A)*. However, *Tn554* is not usually found in type IV SCCmecA, the *mecA* variant common in CA-MRSA strains (McDougal *et al.*, 2003).

None of the community associated *S. aureus* isolates in this study exhibited the iMLSB phenotype even though up to 15.0% of the erythromycin-clindamycin isolates were from the community. This, probably, can be associated with the nature of specimens collected from the community settings which were nasal swabs from apparently healthy individuals. Studies that identified clinical predictors of the iMLSB phenotype associated with community associated MRSA and MSSA have identified skin and soft tissue infections and the existence of comorbidities (diabetes, trauma, burns, renal dysfunction *e.t.c.*) as being strongly associated with the iMLSB phenotype in community-associated specimens (Levin *et al.*, 2005; Patel *et al.*, 2006). None of these conditions was encountered in our community-associated specimens.

Based on the findings of this study, the

distribution of iMLS_B phenotypes among the age group were observed more in children of age between 0-10 with 2(13.3%) out of 18. One of the isolates was from a female and the other from male.

Finally, antibiotic susceptibility pattern showed that most iMLS_B positive were identified in HA S. aureus. among which the D-test positive were from age groups 0-10 years. Indiscriminate use of antibiotics is among the causative agent of a drugs resistance leading to inducible drugs resistance. This research also signals to the public that use of D-tests in routine laboratory will help in guiding the clinicians the judicious use of Clindamycin in skin and soft tissue infection as Clindamycin is not a suitable drug for D-test positive isolate but can be a drug of choice in case of D-test negative isolate.

Conclusion

In this study, the prevalence of inducible clindamycin was found to be moderate at 10.0%. The D-test is an easy, sensitive, and reliable means for detecting iMLSB resistance phenotype in the clinical laboratory, with no specialized testing equipment needed.

Recommendations

1. Molecular studies are required to further determine and characterise the genetic diversity of this resistance mechanisms.
2. There is need for increased public awareness on the impact of antibiotic resistant bacteria in order to discourage self-medication and improve compliance to prescribed drugs.
3. Since the prevalence of iMLSB and other MLSB phenotypes may change over time, periodic surveys should be performed.
4. Laboratories should perform the double disk diffusion test as a routine procedure for all erythromycin-clindamycin discordant *Staphylococci*.

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