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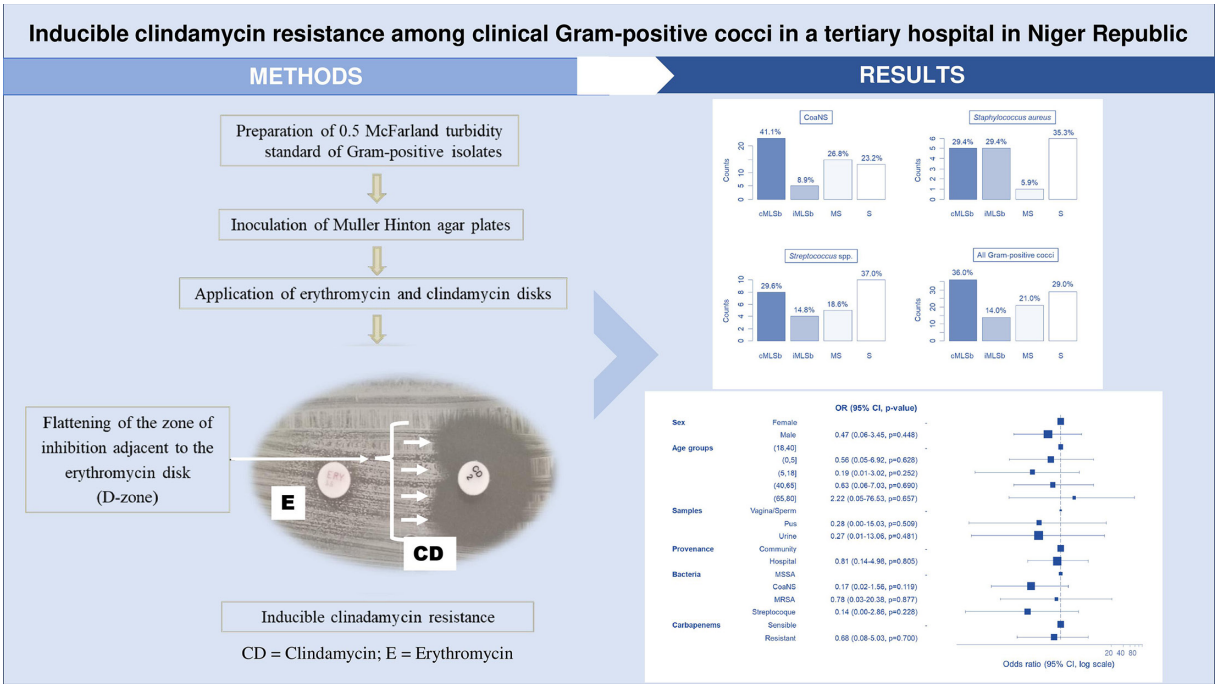
Inducible clindamycin resistance among clinical Gram-positive cocci in a tertiary hospital in Niger Republic

Abdourahamane Yacouba[1,2,*], Malika Zeidou Alassoum[1], Boubacar Marou Soumana[1,3], Sahada Moussa Saley[1,3], Abdoulaye Ousmane[4], Harouna Moussa[2], Saidou Amatagas[5], Daouda Alhousseini[1,3], Mahamadou Doutchi[5], Salao Chaibou[6], Mamane Daou[1,3], Souleymane Brah[1,2], Eric Adehossi[1,6], Ahmed Olowo-Okere[7] and Saidou Mamadou[1,2]



Graphical abstract

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Author affiliations: [1]Faculté des Sciences de la Santé, Université Abdou Moumouni, Niamey, Niger; [2]LNR-RAM-Niger, Hôpital National Amirou Boubacar Diallo, Niamey, Niger; [3]Hôpital National de Niamey, Niamey, Niger; [4]Hôpital de référence de Maradi, Université Dan Dicko Dan Kolodo, Maradi, Niger; [5]Université André Salifou, Zinder, Niger; [6]Hôpital Général de Reference, Niamey, Niger; [7]Faculty of Pharmaceutical Sciences, University of Abuja, Sokoto, Nigeria.
***Correspondence:** Abdourahamane Yacouba, abdourahamaneyacouba@yahoo.fr
Keywords: clindamycin; erythromycin; inducible resistance; MRSA; Niger.
Abbreviations: cMLSb, constitutive macrolide-lincosamide-streptogramin B (phenotype clindamycin resistant and erythromycin resistant); CoNS, coagulase-negative staphylococci; iMLSb, inducible macrolide-lincosamide-streptogramin B (phenotype clindamycin sensitive and erythromycin-resistant); MRCoNS, methicillin-resistant coagulase-negative staphylococci; MRSA, methicillin-resistant *Staphylococcus aureus*; MS, phenotype clindamycin sensitive and erythromycin resistant, with no apparent D zone; MSCoNS, methicillin susceptible coagulase-negative staphylococci; MSSA, methicillin susceptible *Staphylococcus aureus*; S, sensitive to both erythromycin and clindamycin.

Abstract

Background. Macrolide-induced resistance to clindamycin is a well-described mechanism leading to treatment failure. Herein, we determined the frequency and associated factors of inducible clindamycin resistance in Gram-positive cocci in a tertiary care hospital.

Methods. A cross-sectional descriptive study was carried out between January and December 2022. D-tests were performed as recommended by EUCAST 2021 guidelines on 100 non-duplicate clinical isolates of Gram-positive cocci to determine the prevalence of methicillin resistance and inducible clindamycin resistance among the collected isolates.

Results. Of the 100 Gram-positive cocci isolates, 56 (56.0%), 17 (17.0%) and 27 (27.0%) were respectively coagulase-negative staphylococci, *Staphylococcus aureus* and *Streptococcus* spp. Among *Streptococcus* spp., Group D Streptococci (15.0%) were the most isolated. Methicillin-resistant *Staphylococcus aureus* (MRSA) represented nine (53.0%) of the *S. aureus* isolates. Constitutive (cMLSb) and inducible clindamycin resistance (iMLSb) phenotypes were detected in 36 (36.0%) and 14 (14.0%) of the isolates, respectively. *S. aureus* exhibited 38.4% of cMLSb and 13.7% of iMLSb. The result of multivariate analysis showed that age groups, gender, type of samples, provenance, and bacteria, were not significantly associated with Gram-positive cocci iMLSb phenotype.

Conclusion. The study reported for the first time a high prevalence of inducible resistance of Gram-positive cocci strains to clindamycin in Niger Republic. This suggests the urgent need for the implementation of regular screening of these isolates and the wise use of clindamycin in clinical practice.

DATA SUMMARY

All supporting data is provided in the manuscript. The complete datasets are available online at https://figshare.com/articles/dataset/_b_Niger_data_b_b_Inducible_clindamycin_resistance_b_/25466677 (Doi: 10.6084/m9.figshare.25466677)[1].

INTRODUCTION

Gram-positive cocci (GPC) are one of the most common infectious agents in urinary tract infections [2]. The evolution and increasing antibiotic resistance among the GPC, particularly the emergence and spread of methicillin-resistant *Staphylococcus aureus* (MRSA) has become a grievous threat to the global public health. This has reduced the therapeutic options available for treating these infections, forcing clinicians to modify their treatment regimens and use reserve drugs such as clindamycin, a member of Macrolide-Lincosamide-Streptogamin b (MLSb) group of antibiotics [3, 4].

Clindamycin was developed and introduced into clinical practice in late 1960s [5]. It is a broad-spectrum antibiotic, highly effective against several GPC including MRSA [5]. Clindamycin is a crucial component in the treatment of serious infections, particularly when caused by pathogens resistant to other antibiotics [5]. Its long safety profile and tolerability makes it a drug of choice against several GPC infections, especially in children where it has been used to treat serious *S. aureus* infections for over 30 years [6, 7]. It is also useful in certain infections caused by *Streptococcus pneumoniae*, Group A *Streptococcus*, Group B *Streptococcus,* and *Enterococcus* spp. [8]. Absorption of clindamycin after oral administration is almost complete, giving serum concentrations approaching those of intravenous (IV) administration [9]. However, the widespread use of clindamycin has led to emergence of clindamycin resistant bacteria [10].

The mechanism of resistance to clindamycin has been well-described in several studies [11–15]. Mainly, this is due to constitutive or inducible expression of genes encoding methyltransferase enzymes, the *erm* genes, which methylate specific adenine residues on the 23S ribosomal RNA (*rRNA*), decreasing the binding affinity of clindamycin to the ribosome [12, 13]. Inducible resistance occurs when bacterial strains are exposed to subinhibitory concentrations of macrolides, such as erythromycin, in the environment, leading to induction of *erm* gene expression [10, 11]. On the other hand, constitutive expression of the *erm* gene results in constitutive resistance, i.e. resistance to clindamycin, even in the absence of prior exposure to macrolides [10, 11].

The prevalence of inducible clindamycin resistance varies depending on the type bacterial species and geographical regions [13]. In a systematic review summarizing the available information about the occurrence of inducible clindamycin resistance on the entire African continent, an overall prevalence of inducible clindamycin resistance among *S. aureus* isolates was reported to be 19.8% (range 2.9–44.0%) [13]. This was found to be higher among MRSA isolates (3.6–77.8%) than MSSA (0–58.8%) [13]. To the best of our knowledge, no study has investigated inducible resistance to clindamycin in Niger Republic. The study was thus designed to determine the frequency of inducible clindamycin resistance and MRSA in clinical isolates of Gram-positive cocci at the *Hôpital National Amirou Boubacar Diallo* (HNABD), Niamey, Niger Republic.

METHODOLOGY

Study design, setting and period

This cross-sectional descriptive study was carried out between January and December 2022. Samples were collected and processed in bacteriology laboratory, *Hôpital National Amirou Boubacar Diallo*.

Isolation, identification, and antibiotic susceptibility test

A total of 100 non-duplicate clinical isolates of Gram-positive cocci were isolated from different clinical samples. The isolated strains were identified by standard biochemical techniques. This includes Gram-staining, coagulase and catalase tests. Antibiotic susceptibility testing was performed using the Kirby Bauer disc diffusion method and interpreted according to EUCAST 2021 guidelines [16]. In brief, overnight culture of the test bacteria was diluted in sterile 0.85% sodium chloride solution to 0.5 McFarland standard and spread over the entire surface of a dried Mueller–Hinton Agar (MHA) medium (bioMérieux, Marcy l'Etoile, France). The following antibiotics sourced from Biomérieux were then placed on the inoculated plates: erythromycin (15 µg); clindamycin (2 µg); cefoxitin (30 µg); imipenem (10 µg); norfloxacin (10 µg); ciprofloxacin (5 µg); amikacin (30 µg); gentamicin (10 µg); kanamycin (30 µg); doxycycline (30 µg); minocycline (30 µg); cotrimoxazole (1.25, 23.75 µg); and linezolid (10 µg). The inoculated plates were thereafter inverted and incubated at 37 °C. The zone of inhibition formed after 16–18 h was measured and interpreted as susceptible, intermediate or resistant according to breakpoints defined by EUCAST 2021.

Phenotypic detection of methicillin resistance

For *Staphylococcus* spp. isolates, methicillin resistance was detected using cefoxitin disc (30 µg) diffusion method. According to EUCAST guidelines, isolates with cefoxitin inhibition zone size ≥22 mm were considered methicillin susceptible and those with cefoxitin inhibition zone size <22 mm were considered methicillin resistant [17].

Phenotypic detection of clindamycin resistance (D-test)

All Gram-positive cocci isolates were subjected to D-test on Muller Hinton agar plate as recommended by EUCAST 2021 guidelines [17]. Briefly, erythromycin (15 µg) and clindamycin (2 µg) discs were placed at a distance of 12–20 mm edge to edge on a Mueller–Hinton agar plate, previously inoculated with 0.5 McFarland standard bacterial suspensions to detect inducible resistance to lincosamides in Gram-positive cocci.

Following 18–24 h incubation at 37 °C, flattening of zone (D-shaped) around clindamycin in the area between the two discs indicated inducible clindamycin resistance (Fig. 1). Four different phenotypes were observed after testing and then interpreted: (i) isolates, which were clindamycin sensitive and erythromycin resistant, with no apparent D-zone were interpreted as MS phenotype (D-test negative); (ii) isolates which were clindamycin sensitive and erythromycin resistant with apparent D-zone were interpreted as inducible clindamycin resistance phenotype (iMLSb) (D-test positive); (iii) isolates which were resistant to both erythromycin and clindamycin interpreted as constitutive clindamycin resistance (cMLSb); (iv) isolates which were sensitive to both erythromycin and clindamycin were interpreted as S (susceptible) phenotype.

Quality control

Quality control of the discs of clindamycin and erythromycin was performed with *Staphylococcus aureus* ATCC 29213, according to EUCAST 2021 procedures [17]. Additionally, in-house *Staphylococcus aureus* and *Streptococcus pneumoniae* strains that demonstrated positive and negative D-test reactions were used to perform quality control.

Statistical analysis

Statistical analysis was done using R software version 4.0.4. Descriptive statistics: numerical presentation of data was done using frequency distribution tables. Logistic regression was performed to determine the associations between dependent and independent variables. The adjusted odds ratio and the 95% confidence interval were used to measure the strength of an association. *P* value was significant at <0.05.

Ethical consideration

Ethical approval was obtained from the Ethical Review Committee of the *Hôpital National Amirou Boubacar Diallo*, Niamey, Niger. Additionally, the study was carried out in accordance with the ethical principles of the Declaration of Helsinki on human subjects. All the study participants were informed concerning the study verbally, and a written informed consent was obtained from each participant.

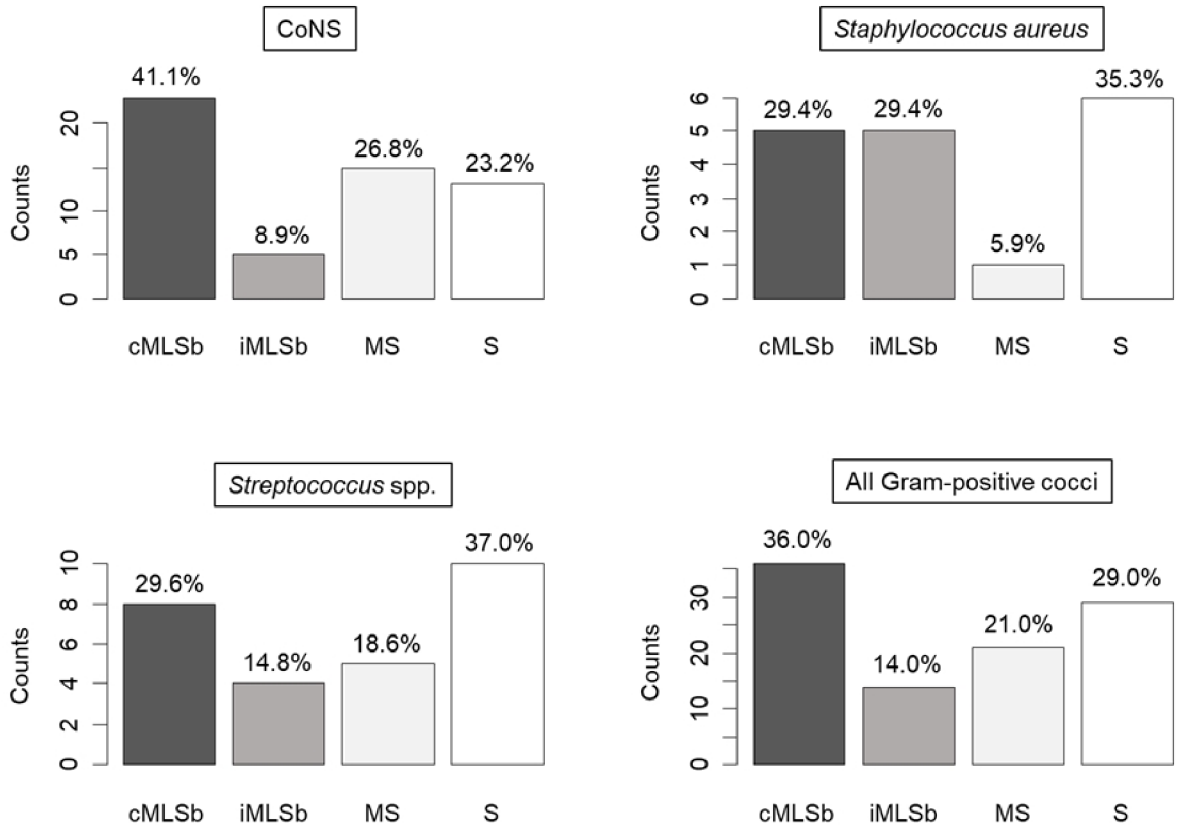

Fig. 1. Prevalence of Macrolide-Lincosamide-Streptogramin b phenotypes of resistance. CoNS: Coagulase negative Staphylococci; MS phenotype=isolates, which were clindamycin sensitive and erythromycin resistant, with no apparent D-zone were interpreted; iMLSb phenotype=isolates which were clindamycin sensitive and erythromycin resistant with apparent D-zone; cMLSb phenotype=isolates which were resistant to both erythromycin and clindamycin; S phenotype=isolates which were sensitive to both erythromycin and clindamycin.

RESULTS

Baseline characteristics of participants

In the present study, a total of 100 clinical isolates of Gram-positive cocci from 100 study participants were included and 57.0% (57/100) of whom were male. The mean age of the study participants was 25.7 (±25.3) years. The majority, 33.0% (33/100) of participants were less than 5 years old. Sixty-two percent (62/100) of the study participants were inpatients, and the rest 38.0% (38/100) of patients were outpatients. Urine was the most common specimen type 77.0% (77/100), followed by pus specimens 19.0% (19/100) (Table 1).

Gram-positive cocci isolates

Out of 100 clinical Gram-positive cocci isolated, 73.0% were *Staphylococcus* spp. and 27.0% were *Streptococcus* spp. Among *Streptococcus* spp., Group D Streptococci (15.0%) were the most isolated, followed by Group B Streptococci (6.0%) (Table 1). Among *Staphylococcus* spp., 12.3% (9/73) were MRSA.

Prevalence of Macrolide-Lincosamide-Streptogramin b phenotypes of resistance

Out of 100 Gram-positive cocci isolates, inducible and constitutive phenotypes of clindamycin resistance were shown in 14.0 and 36.0%, respectively. Among *Staphylococcus aureus* isolates, 29.4% were cMLSb and 29.4% were iMLSb; whereas in *Streptococcus* spp. isolates, cMLSb and iMLSb phenotypes were observed in 29.6 and 14.8%, respectively (Fig. 1).

Table 1. Baseline characteristics of the participants and isolates

Characteristics	Frequency	Percentage (%)
Sex		
Female	43	43.0
Male	57	57.0
Age (years)		
(0–5)	33	33.0
(5–18)	19	19.0
(18–40)	18	18.0
(40–65)	22	22.0
> 65	8	8.0
Specimens		
Urine	77	77.0
Pus	19	19.0
Sperm	3	3.0
Cervico-vaginal swab	1	1.0
Type of patient		
Outpatient	38	38.0
Inpatient	62	62.0
Strains isolated		
***Staphylococcus* spp.**	**73**	**73.0**
- Coagulase-negative staphylococci	56	56.0
- *Staphylococcus aureus*	17	17.0
***Streptococcus* spp.**	**27**	**27.0**
- Group A Streptococci	2	2.0
- Group B Streptococci	6	6.0
- Group D Streptococci	15	15.0
- Group F Streptococci	4	4.0
Methicillin susceptibility of *Staphylococcus* spp.		
MRSA	9	12.3
MSSA	8	11.0
MRCoNS	28	38.4
MSCoNS	28	38.4

MRCoNS, methicillin resistant coagulase-negative staphylococci; MRSA, methicillin resistant *Staphylococcus aureus*; MSCoNS, methicillin susceptible coagulase-negative staphylococci; MSSA, methicillin susceptible *Staphylococcus aureus*.

Associated factors with Gram-positive cocci iMLSb phenotype

In univariate (Table 2) and multivariate analysis (Fig. 2), any of the following variables, age groups, gender, type of samples, provenance, and bacteria, were not significantly associated with Gram-positive cocci iMLSb phenotype.

DISCUSSION

Clindamycin is a useful antibiotic for the treatment of skin, soft tissue and bone infections due to its tolerability profile, cost-effectiveness, and good tissue penetration [18, 19]. Also, recent guidelines recommend the use of clindamycin for the treatment of toxin-mediated infections including toxic shock syndrome and necrotizing pneumonia, due to its ability to

Table 2. Univariate analysis of factors associated with Gram-positive cocci iMLSb phenotype

Characteristics	D-Test (%)		Odd ratio	IC 95%	*P* value
	Negative	Positive			
Sex					
Female	38 (88.4)	5 (11.6)	1		
Male	48 (84.2)	9 (15.8)	0.47	0.06–3.45	0.448
Age groups					
(0–5)	29 (87.9)	4 (12.1)	0.56	0.05–6.92	0.628
(5–18)	18 (94.7)	1 (5.3)	0.19	0.01–3.02	0.252
(18–40)	15 (83.3)	3 (16.7)	1		
(40–65)	18 (81.8)	4 (18.2)	0.63	0.06–7.03	0.690
(65–80)	6 (75.0)	2 (15.0)	2.22	0.05–76.53	0.657
Samples					
Pus	17 (89.5)	2 (10.5)	0.28	0.00–15.03	0.509
Urine	66 (85.7)	11 (14.3)	0.27	0.01–13.06	0.481
Vagina/Sperm	3 (75.0)	1 (25.0)	1		
Provenance					
Community	32 (84.2)	6 (15.8)	1		
Hospital	54 (87.1)	8 (12.9)	0.81	0.14–4.98	0.805
Bacteria					
CoNS	51 (91.1)	5 (8.9)	0.17	0.02–1.56	0.119
MRSA	7 (77.8)	2 (22.2)	0.78	0.03–20.38	0.877
MSSA	5 (62.5)	3 (37.5)	1		
Streptocoque	23 (85.2)	4 (14.8)	0.14	0.00–2.86	0.228
Carbapenem					
Resistant	26 (86.7)	4 (13.3)	0.68	0.08–5.03	0.700
Susceptible	30 (83.3)	6 (16.7)	1		

CI 95%, confident interval at 95%; CoNS, coagulase negative staphylococci; MRSA, methicillin resistant *Staphylococcus aureus*; MSSA, methicillin susceptible *Staphylococcus aureus*.

inhibit bacterial toxin production [20–22]. However, the widespread use of clindamycin has led to an increase in Gram-positive cocci resistance to MLS antibiotics [13, 23–25]. Reporting Gram-positive cocci, specially *Staphylococcus aureus* as susceptible to clindamycin without checking for inducible resistance may on one hand result in use of inappropriate clindamycin therapy. On the other hand negative results for inducible clindamycin resistance confirms clindamycin susceptibility and provides a very good therapeutic option. To the best of our knowledge, there is no substantial data regarding clindamycin prescription from Niger Republic. This study aimed to determine the frequency and associated factors of inducible resistance to clindamycin in Gram-positive cocci.

Our findings showed the prevalence of inducible phenotype of clindamycin of 14.0% in Gram-positive cocci isolates, 13.7% in *Staphylococcus* spp. isolates, and 14.8% in *Streptococcus* isolates. These findings are consistent with the previous studies [12, 14]. In a recent systematic review, the authors found an overall estimated prevalence of 19.8% (range 2.9–44.0%) of inducible clindamycin resistance in *Staphylococcus aureus* in Africa [13].

In this study, any of the variables – age groups, gender, type of samples, and provenance were not significantly associated with Gram-positive cocci iMLSb phenotype. In contrast to the above findings, Nahar *et al.* [15] showed that male patients had a higher frequency of iMLSb resistance than female.

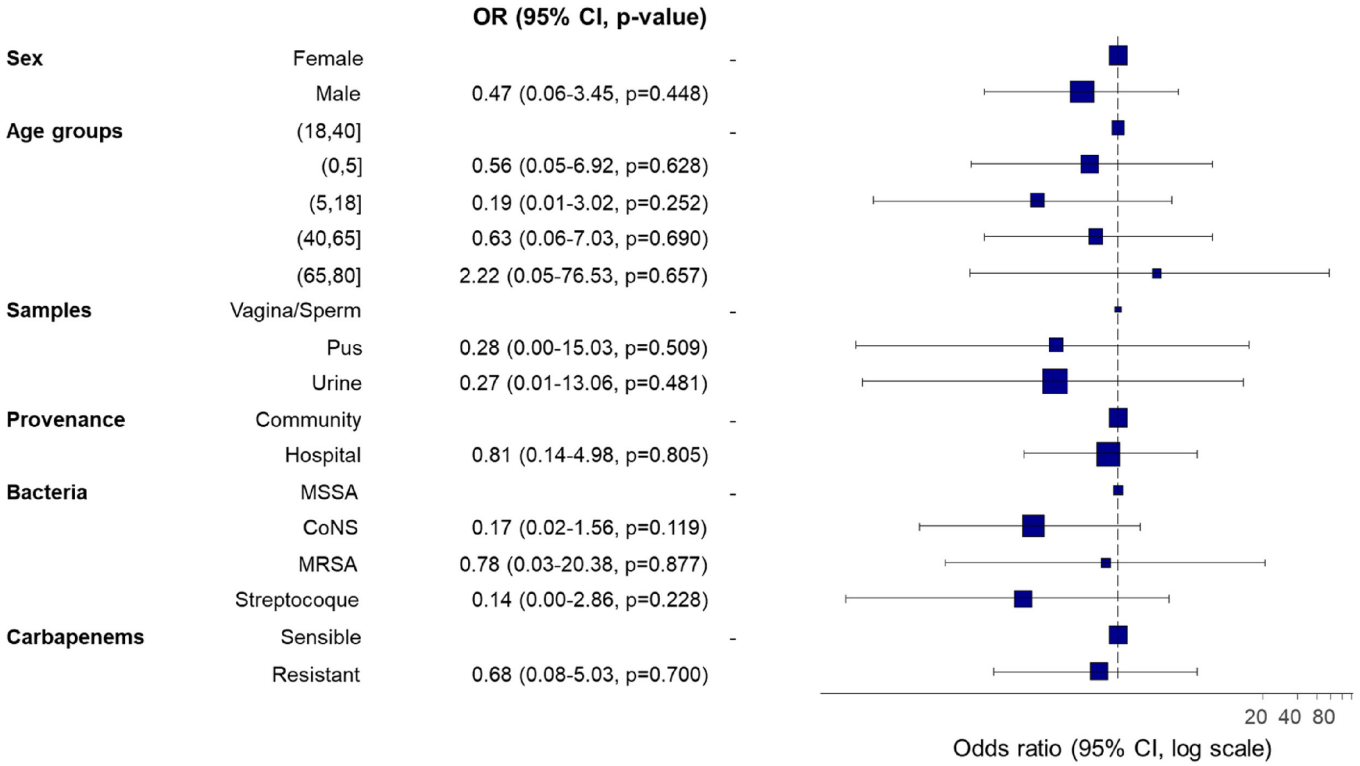

Fig. 2. Multivariate analysis of factors associated with Gram-positive cocci iMLSb phenotype. 95% CI=Confident interval at 95%; CoNS=Coagulase negative Staphylococci; MRSA=Methicillin resistant *Staphylococcus aureus*; MSSA=Methicillin susceptible *Staphylococcus aureus*.

Regarding *Staphylococcus aureus*, previous studies have shown a high frequency of inducible resistance MRSA [12, 14]. However, our findings did not report significant association between MRSA and inducible resistance in multivariate analysis. Even so, according to the authors, it should be clearly important to incorporate the methicillin resistance test and the D-zone test into the routine antibiotic susceptibility testing in hospital settings [26].

Regarding coagulase negative Staphylococci, five (8.9%) were iMLSb phenotypes in our study. This result is consistent with the previous studies as presented by Manandhar *et al.* [11], with 14.5%, and Abdollahi *et al.* [27], with 10.4%.

Group B *Streptococcus* is a continuing cause of morbidity and mortality in neonates, pregnant women, and the elderly [28]. In this study, any of six group B *Streptococcus* isolates had shown iMLSb phenotype. In a study performed in pregnant mothers, 15.5% (*n*=7) of group B *Streptococcus* isolates showed iMLSb phenotype [29].

This study is limited by the fact that the genetic diversity of antibiotic resistance genes associated with inducible clindamycin resistance was not investigated. Three major mechanisms underlie Gram-positive cocci resistance to clindamycin, including methylation of 23S ribosomal RNA, enzymatic inactivation, and active efflux [30]. In the recent study, the most common mechanism for MLSb resistance in *S. aureus* were *ermA, ermB, ermC, ermE* genes [13]. In group B *Streptococcus*, *ermTR* gene was significantly associated with iMLSb phenotype [29].

Strengths and limitations: the prospective design of the study, coupled with various specimens from a tertiary hospital, significantly bolsters the robustness of our findings. This also enables inclusion of diverse patient populations, thereby enhancing the generalizability of our results. However, the study was constrained by the unavailability of data on specific disease conditions. This limitation hinders our ability to correlate inducible clindamycin resistance with underlying clinical conditions. In addition, our inability to molecularly characterize the isolates serves as another limitation. This study however provides a valuable insights into the diversity of inducible clindamycin resistance profile of Gram-positive cocci isolates within the study population, thereby enriching our understanding of these microbial pathogens and informing targeted intervention strategies.

CONCLUSION

This study highlighted a relatively high prevalence of inducible clindamycin resistance Gram-positive cocci isolates in Niger Republic. Additionally, a relatively higher number of iMLSb phenotypes was observed in MRSA isolates. Despite the study

failing to show factors associated to inducible clindamycin resistance Gram-positive cocci isolates in multivariate analysis, there is an urgent need for the implementation of regular screening of these isolates and in the revision of clindamycin prescription in our hospital. Ongoing studies to further assess iMLSb-positive Gram-positive cocci especially genotypic detection of resistance genes are needed to characterize inducible clindamycin resistance and to minimize clindamycin treatment failure.

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Author contributions
A.Y. contributed to experimental design, routine analyses, data analysis, data interpretation and writing the first draft. M.Z.A collected samples and collected clinical information and contributed to routine analyses and writing the first draft. H.M. contributed to routine analyses. B.S.M, S.M.S, A.O, S.A, A.O-O, D.A, M.D, S.C, M.D, and S.B. contributed to critically reviewing the manuscript and data interpretation. E.A. and S.M. coordinated and directed the work. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest
The authors declare that they have no conflict of interest.

Ethical statement
All procedures were approved by the Research Ethics Committee of Amirou Boubacar Diallo National Hospital (HNABD/2022/014, approved on 11 January 2022).

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