The Molecular Epidemiology and Mechanisms of Antibiotic Resistance in Gram-positive Bacteria in Africa: A Systematic Review and Meta-Analysis from a One Health Perspective

John Osei Sekyere[ac#] and Eric Mensah[b]

Department of Pharmaceutics, Faculty of Pharmacy and Pharmaceutical Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana.[a]

Kumasi Center for Collaborative Research in Tropical medicine, School of Medical Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana.[b]

Department of Medical Microbiology, School of Medicine, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa.[c]

#Address correspondence to John Osei Sekyere, jod14139@yahoo.com

Running title: Resistance mechanisms of Gram-positive bacteria

HIGHLIGHTS

- There is substantial resistance to antibiotics among Gram-positive bacteria (GPB) in Africa
- Multidrug-resistant (MDR) *S. aureus, E. faecium, E. faecalis, S. pyogenes,* and *S. haemolyticus* of the same clones were common in humans, animals and the environment.
- MDR clones such as *S. aureus ST5* and *E. faecium ST80* were found in humans, animals and the environment.
- *mecA, ermB, ermC, tetM/K/L,* and *vanA/B/C* were common in GPB, including in VRSA.
- Meta-analysis confirmed a high mean rate of drug resistance in GPB from humans (35.68%), animals (69.63%) and the environment (88.33%) (*p*-value= 0.0301) in Africa.
- *SCCmec, IS16,* and *Tn916* mobilized *mecA, ermB* and *tetM* respectively across various GPB species in animals, humans, and the environment.
- A One Health approach to studying resistance mechanisms and molecular epidemiology of antibiotic-resistant GPB is warranted.

ABSTRACT

The emergence and dissemination of antibiotic resistance (ABR) in bacteria are being driven by antibiotics use in humans, animals and the environment, threatening global health and strengthening calls for a One Health approach to contain ABR.

A systematic search in PubMed for English research articles reporting on ABR in Gram-positive bacteria in Africa within the last ten years from 2007 to 2017 was undertaken. This finally yielded 76 articles that were included in this review and all statistical analysis.

The same ABR Gram-positive bacterial clones, resistance genes, and mobile genetic elements (MGEs) were found in humans, animals and the environment. *IS16* and *Tn916* were highly associated with *erm (B)* and *tet(M)* in *E. faecium* (*ST18, ST80* and *ST910*), *S. agalactiae* (*ST612, ST616* and *ST617*), *E. faecalis* and *S. pyogenes* (*emm18, emm42, emm76* and *emm118*) whilst *SCCmec* was associated with *mecA* in *S. aureus* (*ST5, ST80, ST8,* and *ST88*) and *S. haemolyticus*. The resistance genes, *mecA*, *erm*(B), *erm*(C), *tet*(M), *tet*(K), *tet*(L), *van*(B), *van*(A), *van*(C), and *tet*(O), were found in isolates from humans, animals and the environment. An ABR rate of 39.55% in Gram-positive bacteria is estimated in Africa. Meta-analysis reveal that isolates were most resistant to erythromycin (≥ 2 482) (37.37%), rifampicin (≥ 2 323) (33.42%), tetracycline (≥ 2 181) (40.72%), penicillin (≥ 2 127) (73.47%), sulfamethoxazole/trimethoprim (≥1 377) (45.97%), ciprofloxacin (≥846) (35.37%), gentamicin (≥805) (23.87%), vancomycin (≥712) (42.24%), ampicillin (≥691) (48.25%), streptomycin (≥551) (32.03%) and chloramphenicol (≥376) (11.50%) (p-value <0.0001).

There is substantial resistance to antibiotics among Gram-positive bacteria in clinical and environmental settings in Africa, mediated by clonal and polyclonal expansion as well as horizontal transmission of resistance genes. A One Health approach to research, surveillance, and molecular epidemiology, as well as antibiotic stewardship to contain ABR in humans, animals and the environment should be prioritised.

Keywords: *Staphylococcus spp.*; *Enterococcus spp.*; *Streptococcus spp.*; MRSA; VRE

1. INTRODUCTION

Antibiotic resistance, a threat to public health

The emergence of multiple antibiotic resistance (ABR) determinants in clinically important Gram-positive bacteria (GPB) such as *Staphylococcus spp., Streptococcus spp.,* and *Enterococcus spp.* is a major threat to the successful treatment of infectious diseases worldwide as they result in high morbidity and mortality rates, and limited therapeutic options [1–3]. A recent report projects that the current rate of 700, 000 deaths/annum caused by drug-resistant pathogens could increase to 10 million by 2050 if unchecked [4]. In the European Union (EU), methicillin-resistant *Staphylococcus aureus* (MRSA) alone affects approximately 150, 000 patients annually within the health-care sector, resulting in an expenditure of €380 million [5]. Additionally, there were 80, 461 invasive MRSA infections and 11, 285 MRSA-attributable mortality cases with an estimated annual cost of $1.4 billion to $13.8 billion in the United States of America[6]. In USA, staphylococci and enterococci together comprise 42% of all pathogens involved in device-associated and procedure-associated infections [7]. As well, 29–63% of hospital-recorded mortalities have been attributed to *S. aureus*-mediated bacteremia [8,9].

A significant increase in vancomycin-resistant *Enterococci* (VRE) has been reported in many countries recently. For instance, vancomycin-resistant *E. faecium* increased from <5% in 2001 to 14.5% in 2013 in Germany[10]. Moreover, of the 9.6% *Enterococcus spp*. isolated from all nosocomial infections in Europe, 10.2% were VRE [11]. The rate of nosocomial infections due to VRE is much higher in intensive care units with a significant mortality compared to vancomycin susceptible Enterococcus[11]. According to studies in USA, a hospital cost of between $ 9,949 and $77,558, and $12,766 was attributed to treating VRE blood stream infections and surgical site

83 infections respectively [12,13] . Puchter et al., (2018) reported a median cost of €13,147 for treating
84 a single case of nosocomial infections due to VRE [14].

85 *Streptococcus pyogenes*-associated infections and sequalae pose a devastating burden on public
86 health and national economies [11]. There are approximately 517,000 deaths annually due to severe
87 *Streptococcus pyogenes* infections such as rheumatic heart disease, post-streptococcal
88 glomerulonephritis and acute rheumatic fever globally. A prevalence of 18.1 million cases of
89 severe Streptococcus-mediated diseases has been estimated, with 1.7 million new cases reported
90 annually [15]. *S. agalactiae* is capable of causing life-threatening diseases in pregnant women,
91 newborns and patients with underlying conditions such as diabetes and liver disease [16,17]. Sepsis
92 due to *S. agalactiae* accounts for about 26% of all neonatal deaths and 10% maternal deaths in
93 Sub-Saharan Africa[18]. *Bacillus spp.*, such as *Bacillus cereus,* is among the important aetiologies
94 of foodborne diseases that threaten food security, and is capable of causing serious sequalae such
95 as neurological disorders, multi-organ damage and abortion [19].

96 Limited data in Africa makes it impossible to track and monitor the true burden of ABR.
97 According to a recent WHO report, the potential for ABR to lead to higher mortalities and
98 morbidities in low- and middle-income countries such as Africa may even be greater as a result of
99 the higher burden of bacterial infections, limited diagnostic capacity and lower access to second-
100 line antibiotics [20].
101 In a recent review, GPB were responsible for a high proportion of infections among children and
102 showed a high level of resistance to WHO-recommended drugs in Africa [21]. In some African
103 regions, as many as 80% of *S. aureus* infections are MRSA, which show resistance to most
104 standard licensed drugs including quinolones and peptides [25]. Although *Enterococcus spp.* are
105 mostly not as virulent as *S. aureus*, their multidrug resistance (MDR) propensities restrict drug

options for clinicians [2]. Patients infected with MRSA are estimated to be 64% more likely to demise than those infected with MSSA [23].

Sources and anthropogenic activities driving resistance

ABR has been reported in humans, animals and the environment at alarming proportions worldwide, with indiscriminate antibiotic use being fingered as a major contributor [24–26]. Resistance genes have been detected in surface water fed with runoff effluents from farms utilizing antibiotics, hospitals, and sewage processing plants as well as in ground water [27–29]. Furthermore, genes mediating resistance to last-resort GPB antibiotics such as vancomycin have been recovered from raw milk and animal products, pigs, wild animals (buffalo, zebra and cattle), waste water, effluents and patients, implicating veterinary and agricultural use of antibiotics as potential sources of resistance genes in humans [30–32]. Current reports reveal that global agricultural antibiotics consumption exceeds that of humans. An estimated 63, 151 tonnes of antibiotics were consumed globally in livestock production in 2010 [33–35], and a significant amount of this was used for veterinary purposes [36,37]. These reports suggest that a larger share of the antibiotics that end up polluting the environment and communities emanate from livestock production [38–40]. This interconnectivity between animals, humans and the environment, explains the need to adopt a One Health research policy.

Several studies have reported high rate of MDR among GPB isolates from humans, animals and the environment in Africa, mainly as a result of overuse, underuse and wrong choice of antibiotics [41–47]. Different factors have been implicated in the high rate of ABR to the limited drugs in Africa. These include: unrestricted access to antibiotics over-the-counter without prescription such as selling on the streets; inadequate hygienic practices; uncontrolled usage of antibiotics as growth promoters in food animals production; wrong diagnosis and prescription, off-label use and errors

in dosage regimens; use of untreated poultry and cattle manure to fertilize agriculture lands; extensive use of broad-spectrum antibiotics in poultry production; and inefficient chlorination of hospital wastewater effluents before discharge into the environment [28,41,45,48–52]. Additionally, inadequate knowledge of animals' diseases, misdiagnosis and poor antibiotic handling practices in animal production add up to the overall burden of ABR in Africa [40].

Molecular ABR mechanisms

Selective pressures exerted by various antibiotics used in human and veterinary medicine, as well as in agriculture, have resulted in the emergence and dissemination of numerous mechanisms of resistance in GPB. These mechanisms include drug target-site modification(s), enzymatic hydrolysis/inactivation of antibiotics, reduced cell wall/membrane permeability and active efflux [53–56]. Resistance is often acquired through mobile genetic elements (MGEs) such as transposons, conjugative plasmids, integrons, and insertion sequences, which are capable of mobilizing resistance genes across a wide spectrum of bacterial species. These include between commensals and medically important Gram-positive pathogens [57,58]. Tn916 and *IS*16 are notable MGEs that carry major ABR determinants and are transmissible between clones of the same or different bacteria species by a conjugative mechanism. Some MGEs are excised from donor cells and transferred during cell-to-cell contact prior to being inserted into recipient cells by a site-specific recombinase. The capability of these MGEs to pick up extra clinically relevant resistance genes contributes to the emergence of multidrug resistance [59–61].

Purpose of this review

Excellent reviews addressing antimicrobial resistance in some GPB in Africa have been published [21,62–67]. However, reviews discussing the molecular epidemiology and mechanisms of ABR in GPB

such as *Staphylococcus spp.*, *Streptococcus spp.* and *Enterococcus spp.* in Africa in the context of resistance rates, resistance mechanisms (and MGEs), clonality, and geographical distribution are non-existent, to the best of our knowledge. This review sought to identify species, clones and MGEs responsible for the spread of resistance genes in GPB in Africa from a One Health perspective. It is our aim that the geographical distribution of resistant strains and GPB resistance mechanisms in Africa presented herein will inform the choice of anti-infective agents or treatment guidelines, infection control strategies and ABR study designs.

1.1 Search strategy and inclusion criteria

Research articles published within the last ten years (2007 to January 2018) in English and indexed in PubMed were searched with the following keywords: “Enterococcus”, and “Streptococcus”, “Staphylococcus”, in permutations and combinations with “resistance AND Africa”. Studies which did not identify the underlying ABR mechanisms/genes as well as the clonality of antibiotic-resistant GPB were excluded. Thus, studies that only reported on antibiotic sensitivity testing results or undertook ABR surveillance studies without further molecular tests to characterize the ABR mechanisms and/or clonality of the isolates were excluded. All searches were undertaken independently by both authors in triplicates to ensure replication of the results.

Data extracted from the articles included year of study, country, GPB species, clones, sample sources, sample size/number of isolates, number of resistant isolates, resistance genes and MGEs such as integrons, plasmids, transposons and insertion sequences, and antibiotics to which the strains were resistant (Tables 1-5). The mean rate of ABR among GPB per country and in Africa was determined to identify countries with the highest or lowest levels of resistance in Africa. As well, the antibiotics to which the isolates were most resistant were determined to evaluate their correlation with the detected/reported resistance mechanisms.

The resistance mechanisms, as well as MGEs involved in the transmission of resistance genes per species or clone, were determined to assess the means of resistance transfer i.e., horizontal or vertical (through clonal expansion), per specimen sources (animal, human, and environment). The distribution of clones, resistance genes, and MGEs were considered to identify countries with most resistant clones, resistance genes, and their associated MGEs.

1.2 Statistical analysis.

The data was analyzed using Microsoft Excel® 2017 and Graph pad prism™ 6 (GraphPad Software, San Diego, CA, USA) (Supplementary data). Calculation for the statistical significance of the data was determined using the kolmogorov-smirnov test (with Dallal - wilkinson-Lilliefors p-value) and/or column statistics or one sample t-test, and the confidence intervals determined at 95%. The p-values were two tailed with a Gaussian approximation. A p-value of <0.05 was considered as statistically significant. Only studies that provided the required information were used in the analysis. In all, 76 articles were used for the data analysis.

2. RESULTS AND DISCUSSION

Antibiotic usage in humans, food, wild and domestic animals, as well as in agriculture, is selecting for ABR genes and resistant bacteria in hospitals, farms, and the environment [33–35,38–40,53]. The constant interactions between man, animals, food and the environment enhances the easy transmission of resistance genes and resistant bacteria between humans, animals and the environment [73,74]. Thus, ABR is not limited to clinical settings, farms, the environment or to individual countries as increased globalization, trade and international travel put all humans and animals at risk of contracting difficult-to-treat antibiotic-resistant infections [75,76]. This limitless capability for resistance genes and resistant bacteria to spread across a broad-spectrum of hosts or

196 niches makes the menace even more worrying, underscoring the need for a One Health approach
197 to contain the situation by looking at resistance from all spheres: humans, animals and the
198 environment [77,78].

199 A meta-analysis of published literature confirmed the presence of a high mean rate of drug
200 resistance in GPB from humans (35.68%), animals (69.63%) and the environment (88.33%) (*p*-
201 value= 0.0301) in Africa, albeit many studies that did not address the molecular mechanisms of
202 resistance in GPB were excluded. Obviously, the mean rate of resistance would have been higher
203 had all research articles using only phenotypic methods to describe ABR in GPB been included.
204 Interestingly, although a lesser number of GPB were isolated from environmental sources, they
205 expressed higher ABR than those from humans and animals; hence, the higher mean resistance
206 rate of 88.33%. This also underscores the fact that there is increasing ABR genes in the
207 environment, obviously due to antibiotic pollution from human activity. Evidently, ABR is high
208 among GPB in certain regions in Africa (Figure 3) and underpins the need to up the ante against
209 this menace through increased molecular surveillance research, education of clinical
210 microbiologists on ABR, and antibiotic stewardship.
211 Studies describing detailed molecular mechanisms of GPB resistance and molecular epidemiology
212 in Africa are few, making it difficult to paint a vivid comprehensive picture of ABR in Africa.
213 However, this review shows that *S. aureus ST5*, *E. faecium ST18, ST80* and *ST910, E. faecalis, S.*
214 *pneumoniae* and *S. agalactiae* harbouring *mecA, tet* and *erm* genes, were commonly found in
215 humans, animals and the environment, particularly in Northern, Western, and Southern Africa.
216 Thus, careful use of β-lactams, tetracyclines, and macrolides is warranted to prevent further
217 selection and dissemination of these resistance genes and resistant clones. Furthermore, it will be

prudent for countries within these regions to review their recommended antibiotic regimens, guidelines/protocols for infections caused by these species.

Erm(B), tet(M) and *vanA* genes were mobilized by *Tn916* and *IS16*. Moreover, *erm(B) and tet(M)* were found in *S. aureus, Enterococcus spp. and Streptococcus spp., i*ndicating horizontal transfer within same clones, different clones and species. The discovery of same clones and resistance genes in specimens from humans, animals and the environment suggest a possible transmission of these clones between humans, animals and the environment, corroborating the need for a One Health approach to infection control and management of antibiotic-resistant infections. Further molecular epidemiological surveillance in the above-mentioned states is crucial to forestall further spread of these resistant pathogenic clones both within their borders and from their borders to other countries.

2.1 Resistance rates per countries and MDR GPB species

Of the 1,466 articles returned from the systematic literature search (Fig. 1), 76 studies representing 20 out of 54 African countries were included in this review and data analysis. Tunisia (n= 19) recorded the highest number of studies followed by South Africa (n=1, 4), Egypt (n=9), Nigeria (n=7) and Algeria (n=4) (*p*-value 0.0054). Majority of the included studies were undertaken in Northern Africa (n=32, 43.83%), Southern Africa (n=16, 21.92%) and Western Africa (n=10, 12.99%). Different rates of resistance to antibiotics were reported in different countries in Africa (Tables 2-4). High mean resistance rates were reported in Nigeria, Tunisia, Algeria, and South Africa. Cross-contamination of multi-drug resistant bacteria between patients and the environment accounted for the high rate of resistance in Algeria [79,101,108–110]. The high rate of ABR in Tunisia was attributed to cross contamination between hospital patients and hospital environment, immune deficiency [111], over-consumption of antibiotics, heavy

consumption of sheep meat, which is a reservoir of MRSA, and high consumptions of antibiotics in animal feed. In Egypt, inappropriate antibiotic prescription practices [52], inadequate hygienic handling and processing of food [30], and close contact with pet dogs accounted for the high resistance [112].

The high rate of drug resistance in Nigeria has been attributed to the exchange of resistance genes between farm animals or their products and man [113,114], existence of MRSA in clinical and community settings [115], uncontrolled usage of antibiotics [116] and the presence of efflux pumps in coagulase-negative staphylococcus strains [117]. Expansion of resistant clones [80], variability of hospital acquired MRSA clones [103], consumption of unpasteurized milk or inefficient thermal processing of milk [44], shedding of resistant clones from animals to the environment and heavy consumption of antibiotics to treat TB due to high HIV burden [118], were incriminated for the high-level resistance in South Africa.

Staphylococcus spp. (*S. aureus, S. haemolyticus* and *S. saprophyticus*); *Streptococcus spp.* (*S. pyogenes and S. agalactiae*), and *Enterococcus spp.* (*E. faecium, E. faecalis, E. hirae, E. durans, E. gallinarum*) were the antibiotic-resistant GPB widely distributed in Northern, Southern, Western and Central Africa. The high number of *tet(M/L/K), erm(A/B/C), aph(3')-lll* and *van(A/B/C)* in *Staphylococcus spp*., *Enterococcus spp*., and *Streptococcus spp*. reported in Tunisia, South Africa, Nigeria, Algeria and Egypt accounted for the high rate of resistance to tetracycline (43.76%, 95% CI=34.37-52.36)(p-value=0.0001), erythromycin (42.05%, 95% CI=33.16-50.94)(p-value = .0001), kanamycin (34.99%, 95% CI=18.34-51.65%) and vancomycin (42. 24%, 95% CI=19.71-64.76) (p-value = .0001). Such resistant GPB are known to compromise the safety of invasive medical procedures such as organ transplants, orthopedic surgery, and cancer treatment. In addition, infections such as sepsis, endocarditis, deep wound infections, pneumonia,

meningitis and urinary tract infections caused by these resistant pathogens are becoming increasingly fatal due to limited treatment options [4,99]. The abuse of antibiotics as growth promoters, prophylaxis, and metaphylaxis in food animals in these countries have been implicated in the selection of resistant bacteria that can pass on to humans through food consumption, direct contact with animals and the environment, as well as trade of animals and food products between countries [100].

Approximately 26,108 GPB were isolated from humans (n=47 studies, 64.38%), animals (n=16 studies, 21.92%) and the environment (n=10 studies, 13.70%), of which 10, 326 were resistant, equivalent to 39.55% overall resistance rate in Africa (Tables 1-4). Countries such as Algeria, Egypt, Ghana, Nigeria, Uganda, Tunisia recorded at least 51% mean rates of ABR (Tables 2-4). Nigeria recorded the highest mean rates of resistant isolates (n=74.62%) followed by Egypt (n=71.79%), Ghana (n=70.41%), Tunisia (n=66.55%), Algeria (n= 57.40%), Angola (n=56.77%), Uganda (n=51.43%), Democratic Republic of Congo (49.45%), Kenya (n=37.3%), Tanzania (n=35.75%), São Tomé & Príncipe (n= 34.85%), and South Africa (n= 31.50%). Resistant isolates were reported in Angola (17.29%), Gabon (49.06%), Libya (33.69%), Morocco (83.33%), Mozambique (19.15%), Namibia (29.31%), and Senegal (100%) in single studies (Tables 1-3).

The antibiotics to which the isolates were most resistant to were erythromycin (≥ 2 482) (37.37%), rifampicin (≥ 2 323) (33.42%), tetracycline (≥ 2 181) (40.72%), penicillin (≥ 2 127) (73.47%), sulfamethoxazole/trimethoprim (≥1 377) (45.97%), ciprofloxacin (≥846) (35.37%), gentamicin (≥805) (23.87%), vancomycin (≥712) (42.24%), ampicillin (≥691) (48.25%), streptomycin (≥551) (32.03%) and chloramphenicol (≥376) (11.50%) (p-value <0.0001) (Tables 2-4). Countries with high number of studies such as Tunisia, South Africa, Egypt and Nigeria recorded high number of ABR. These countries recorded high number of *mecA*, *erm(B)*, *tet(M)*, *drfG* and *vanB* resistance

287 genes. Vancomycin resistance was reported in six studies in both animals and the environment,
288 and five studies in Humans. Vancomycin-resistant *Enterococcus spp.* (≥594 isolates) and
289 vancomycin-resistant *Staphylococcus spp.* (≥118 isolates) were reported in humans, animals and
290 the environment. Vancomycin-resistant *Staphylococcus aureus* (VRSA) was reported in animals
291 (≥47 isolates), the environment (≥15 isolates) and humans (≥2 isolates); whilst vancomycin-
292 resistant *E. faecium* was reported in the environment (n≥238 isolates), animals (≥ 330 isolates) and
293 humans (≥20 isolates).

294 *S. aureus* (≥ 24 321 isolates in 47 studies) accounted for approximately 92.55% of all GPB
295 involved in hospital- and community-acquired infections, followed by *E. faecium* (≥1 121 isolates
296 in 18 studies, 4.27%), *S. agalactiae* (≥750 in 6 studies, 2.85%) *E. faecalis* (≥284 isolates in 13
297 studies, 1.08%). Antibiotic-resistant *S. aureus* (ST5), *E. faecium* (ST18, ST80 and ST910) and *E.*
298 *faecalis* harbouring *mecA, erm(B), erm(C), tet(M), tet(K), tet(L)* and *van(B)* were isolated from
299 humans, animals and the environment, albeit in higher proportion in humans and animals than the
300 environment (Tables 1-2). For instance, Farhat et al. (2014) [79], van Rensburg *et al.* (2012) [80] and
301 De Boeck et al. (2015) [81] in Algeria, South Africa and Democratic Republic of Congo respectively,
302 reported on resistant *S. aureus ST5* in humans whilst Fall et al. (2012) [82] reported on the same
303 clone (S. *aureus* ST5) in pigs from Senegal. Further, Mariem et al. (2013) [47] isolated the same
304 clone (*S. aureus* ST5) from the environment in Tunisia, suggesting that this clone is widely
305 distributed in Africa in humans, animals and environment. It is currently not clear whether this
306 clone first emerged from humans, animals or the environment, but its presence in all three spheres
307 shows the possibility of resistant species and clones being disseminated between animals, humans
308 and the environment. Notably, *S. aureus* ST5 is among the frequently reported clones in Asia [83]

and recent evidence suggest that it has spread from hospitals into communities, resulting in community-acquired MRSA [84].

Similarly, Lochan et al. (2016) [85] in South Africa, Dziri et al. (2016) [43] and Elhani et al. (2014) [71] in Tunisia isolated resistant *E. faecium* ST80 from humans. For the first time, E. faecium ST80 was isolated from environmental samples in a hospital in Tunisia by Elhani et al. (2013) [71] and Dziri et al. (2016) [72]. Transmission of this resistant clone to animals is possible, although not yet reported. This implies that these resistant species and clones are circulating between humans, animals and the environment, underpinning the broad host range and transmissibility of these strains between animals, humans and the environment.

Although *mecA* was the predominant resistance gene, higher resistance was recorded to erythromycin probably due to lesser use of penicillin(s) in antibiotic susceptibility testing or lesser inclusion of *erm* primers in PCR analysis to detect resistance genes.

MRSA strains were the most commonly isolated strains (≥ 2,350) [86–89]. This is consistent with the global report of increasing prevalence of MRSA [90,91]. MRSA harbours the *mecA* gene, which is carried by the *SCCmec* MGE, and mediates resistance to multiple antibiotics [92]. From this review, MRSA showed resistance to eleven different antibiotic classes: aminoglycosides (gentamicin, tobramycin), β-lactams (penicillin, ampicillin, oxacillin, cefoxitin), fluoroquinolones (ciprofloxacin, levofloxacin, ofloxacin), glycopeptides (vancomycin), lincosamide (clindamycin), macrolides (erythromycin), phenicols (chloramphenicol), rifamycins (rifampicin), streptogramins (pristinamycin), sulfonamides (trimethoprim/sulfamethoxazole), and tetracyclines (tetracycline). MRSA is thus a worrying public health threat as some strains have evolved resistance to almost all licensed drugs (26).

Vancomycin-resistant Enterococci (VREs) (≥ 594), which were reported in Northern and South Africa, also pose a serious threat to public health as they are resistant to vancomycin, a glycopeptide that is reserved for fatal or life-threatening Gram-positive infections, and other important antibiotics such as ampicillin, erythromycin, fluoroquinolones (ciprofloxacin, levofloxacin), gentamicin, rifampicin, streptomycin, trimethoprim/sulfamethoxazole and tetracycline. In this study, enterococcus isolates had a resistance rate of 52.13% (95% CI=21.75 - 82.51) (p-value = 0.0006) to vancomycin. Multidrug resistance in VREs increases VRE-associated mortality rates, which is likely to increase to 75% compared with 45% from susceptible strains [31,95]. As well, evolution of macrolide resistance (45.96%, 95% CI=0.04 – 91.88) (p-value = 0.049) in drug-resistant streptococci is limiting treatment options and resulting in high mortalities [69,96,97]. In this study, MRSA, VRE and drug-resistant streptococci remain major public health threats, calling for measures to contain ABR. Novel antibiotics such as linezolid, synercid, and daptomycin should be used empirically in such infections whilst awaiting susceptibility results. The empirical therapy can be changed or maintained based on the susceptibility report [98].

2.2 Resistance rates of species per animals, humans and the environment

The rates of ABR in isolates recovered from the environment was highest, followed by isolates from animal source. Among environmental isolates, 94.30% (95% CI=83.49–105.1)(p-value = 0.0001) were resistant to penicillin, 81.99% (95% CI=40.57–123.4)(p-value 0.0082) were resistant to sulfamethoxazole/trimethoprim, 75.53% (95% CI=1.92–149.1)(p-value = 0.0480) were resistant to ampicillin, 68.30% (95% CI=23.12–104.5) (p-value = 0.0063) were resistant to ciprofloxacin, 62.78% (95% CI=-56.96–105.5)(p-value = 0.153) were resistant to clindamycin, 60.93% (95% CI=39.70–82.17)(p-value = 0.0002) were resistant to erythromycin, and 59.37% (95% CI=15.10–103.6)(p-value = 0.0183) were resistant to vancomycin.

Among animal isolates, 58.80% (95% CI=17.87–100)(p-value = 0.0148) were resistant to penicillin, 49.24% (95% CI=13.76–84.71)(p-value = 0.016) were resistant to clindamycin, 46.22% (95% CI=26.77–65.67)(p-value = 0.0017) were resistant to ciprofloxacin, 44.91% (95% CI=17.31–60.82) (p-value = 0.046) were resistant to ampicillin, 39.24% (95% CI=14.53–63.96)(p-value = 0.0081) were resistant to trimethoprim/sulfamethoxazole, 36.35% (95% CI=20–52.67)(p-value = 0.0005) were resistant to erythromycin, and 25.84% (95% CI=13.94–64.99)(p-value = 0.15) were vancomycin resistant.

The rates of resistance were much lower in humans for most of the antibiotics used. Among the various species, *Enterococcus spp*. and *Staphylococcus spp.* recorded high rates of resistance for most antibiotics. *Streptococcus spp*. reported low rates of resistance except for tetracycline that recorded a high rate of 57.60% (95% CI=25.18–90.03) (p-value = 0.065). Resistance to vancomycin was not reported in any *Streptococcus spp.* isolates.

Enterococcus spp., mainly *E. faecium* and *E. faecalis*, recorded a resistance rate of 99.38% (95% CI=91.43–107.3)(p-value = 0.004) to clindamycin, 82.26% (95% CI=43.37–121.1)(p-value = 0.0042) to trimethoprim/sulfamethoxazole, 61.39% (95% CI=44.22–78.55)(p-value = 0.0001) to erythromycin, 55.59% (95% CI=22.98–88.20)(p-value = 0.0035) to vancomycin, 54.39% (95% CI=29.17–70.52)(p-value = 0.047) to ciprofloxacin, 50.75% (95% CI=30.96-70.54)(p-value = 0.0002) to tetracycline, 47.09% (95% CI=23.65–70.52)(p-value = 0.0017) to ampicillin, 42.52% (95% CI=14.47–70.57)(p-value = 0.0089) to kanamycin, 30.93% (95% CI=10.91–50.95)(p-value = 0.007) to streptomycin and 30.07% (95% CI=18.20–41.96)(p-value = 0.0001) to gentamicin.

S. aureus showed high resistance (71.33%) to penicillin (95% CI=50.43–92.22)(p-value = 0.0001), 55.36% to ampicillin (95% CI=15.77–94.22)(p-value = 0.0156), 47.34% to streptomycin (95%

CI=60.24–154.9)(p-value = 0.20), 37.63% to tetracycline (95% CI=26.14–49.11)(p-value = 0.0001), 31.38% to trimethoprim/sulfamethoxazole (95% CI=18.01–44.76)(p-value = 0.0001), 30.37% to ciprofloxacin (95% CI=18.38–42.37)(p-value = 0.0001), 29.71% to rifampicin (95% CI=8.78–50.63)(p-value = 0.010), 27.74% to erythromycin (95% CI=17.67–37.80)(p-value = 0.0001), 25.37% to clindamycin (95% CI=12.33–38.41)(p-value = 0.128), 22.57% to gentamicin (95% CI=5.97–51.11)(p-value = 0.0003) and 18.97% to vancomycin (95% CI=5.34–43.27)(p-value = 0.096).

2.3 Resistance mechanisms, clones, and MGEs

Few studies identified the clones and MGEs in the resistant isolates. Of the 76 included studies, 32 identified the clones whilst 22 described the MGEs, which was used in the statistical analysis. The most dominant gene detected in Africa, which was widespread and responsible for resistance in GPB, was *mecA* (≥2 603), followed by *erm(B)* (≥ 984), *tet(M)* (≥620), *dfrG* (≥400), *vanB* (≥380) *blaZ* (≥362), *aph(3')-IIIa (*≥139) and *mefA/E* (≥ 47) (p-value = 0.0011) (Fig. 2a). Isolates from humans had the highest *mecA* (≥2 079), *ermB* (≥721) and *tet(M)* (≥461) (p-value = 0.048) resistance genes. This was followed by animals (*mecA* ≥ 208), *erm(B)* (≥362) and *tet(M)* (≥78) (p-value = 0.343). (Tables 1-4). The 21 studies that described the MGEs included 15 *SCC*mec(≥ 2 138) , two *IS*16 (≥18) and two *Tn*916(≥ 99)(Table 1).

Figure 2b represents MGEs per clone. *S. aureus* clones ST5, ST8, ST 80 and ST88 were highly associated with *mecA*. Resistant *S. aureus, E. faecium* and *E. faecalis* clones such as *S. aureus ST5*, and *E. faecium* clones *ST18, ST80,* and *ST16* were widely distributed in humans, animals and the environment. Similarly, *mecA, erm(B), erm(C), tet(M), tet(K), tet(L), van(B), van(A), van(C)* and *tet(O)* were reported in isolates from humans, animals and the environment (Table 1).

398 *IS16* and *Tn916* were found with the resistance genes *erm (B)* and *tet(M)* in *E. faecium* (*ST18,*
399 *ST80* and *ST910*), *S. agalactiae* (*ST612, ST616* and *ST617), E. faecalis* and *S. pyogenes (emm18,*
400 *emm42, emm76* and *emm118)* isolated from humans, animals and the environment (Tables 2-4).
401 *TetM* was associated with *Tn*916 transposon in tetracycline-resistant *S. agalactiae* [68] and *S.*
402 *pyogenes* [69] in humans in Tunisia. Fischer et al. (2013) also reported the association between *Tn*916
403 and *tetM* in tetracycline resistance *S. agalactiae* in camel in Kenya [70]. Similarly, *IS*16 element was
404 found in vancomycin-resistant *E. faecium* (ST80, ST180 and ST910) in humans and the environment
405 in Tunisia [71,72]. Investigations into the association between MGEs and resistance genes were limited
406 by few studies (n=22) on MGEs.

407 From Tables 2-4, majority of the resistance genes namely, *mecA*, *erm (B)*, *tet (M), vanA* etc. were
408 responsible for drug resistance to antibiotics such as aminoglycosides (gentamicin, streptomycin,
409 kanamycin), β-lactams (penicillins, cephalosporins), fluoroquinolones (ciprofloxacin), macrolide
410 (erythromycin), sulfamethoxazole/trimethoprim, tetracycline and glycopeptides (vancomycin)
411 respectively, were widely distributed in Northern Africa (Tunisia, Algeria, Egypt, Morocco, and
412 Libya) and Southern Africa (South Africa and Namibia). All the three different MGEs (*Tn*916,
413 *SCCmec* and *IS*16) were reported in Tunisia, with two being reported in Kenya (*SCCmec* and
414 *Tn*916). *IS*16 was only reported in an *E. faecium* infection in Tunisia (Figure 3) whilst *mecA* was
415 mostly associated with *SCCmec*. *erm (B)* and *tet (M)* were highly associated with *Tn*916 and *IS*16.

416 In Africa, different studies have reported *SCCmec*-borne *mecA* in *S. aureus* in humans, animals and
417 the environment [46,82,101–103] besides the discovery of *IS16* and *Tn916* in the environment of *erm(B)* and
418 *tetM* genes in Enterococcus and Streptococcus. These reports show that MGEs are mediating the
419 dissemination of these (and possibly other) resistance genes across different GPB clones and
420 species. MGEs-mediated mobilization of various resistance genes in different GPB clones and

421 species in humans, animals and the environment (Tables 1-4) calls for prompt measures to contain
422 ABR as the situation may worsen if additional resistance genes are acquired by the MGEs.
423 Resistance genes on MGEs can be horizontally transferred to susceptible cells or vertically
424 transferred to daughter clones [60,104,105], which can easily spread these resistance genes to
425 susceptible pathogens. The higher number of resistant Gram-positive cocci and mean resistance
426 rate in Tunisia may be due to the presence of these three MGEs in this region [69,71,72,106]

427 **2.6 Molecular epidemiology of antibiotic-resistant GPB**

428 ***Staphylococcus spp.* (*S. aureus, S. haemolyticus and S. saprophyticus*)**
429 *Staphylococcus spp.*, including *mecA*-harbouring methicillin resistant clones, have been described
430 in humans, animals and the environment in Northern, Western, Central, Eastern and Southern
431 Africa with varying but substantial frequencies and resistance rates. Common STs, resistance
432 genes and MGEs were identified in humans, animals and the environment.

433 **North Africa: Algeria, Egypt, Morocco, Tunisia, Libya**

434 ***Algeria.***
435 *S. aureus* was recovered from two different studies in Algeria. In assessing the nasal carriage of *S.*
436 *aureus* in patients with medical conditions including pneumonia, urinary tract infections,
437 osteoarthritis, heart diseases, diabetes and chronic kidney disease, Djoudi *et al.* (2014) isolated
438 MRSA [79]. They also found nasal carriage of *S. aureus* to be significantly associated with cancer
439 and previous hospitalization of patients with kidney failure due to immunological suppression and
440 hemodialysis. The nine MRSA isolates, i.e. ST80 (n=4), ST5 (n=2), ST22 (n=2) and ST535 (n=1),
441 harboured *mecA* and were resistant to tobramycin (n=6), gentamicin (n=1),
442 trimethoprim/sulfamethoxazole (n=2), tetracycline (n=3) and erythromycin (n=1). MRSA ST80 is

a well-known and frequent etiological agent of infections in North Africa and Middle-East countries[119,120]. Typing of 64 MRSA isolated from human pus (n=47), venous catheters (n=7), tracheal aspirates (n=4), punction fluids (n=3), blood (n=2) and urine (n=1) in 64 Algerian patients revealed that 50 were hospital acquired (HA-MRSA) and 14 community acquired (CA-MRSA), which were all resistant to cefoxitin and oxacillin [101]. *MecA*, mobilized by *SCCmec*, was the only detected mechanism of resistance.

Egypt

MRSA have been respectively isolated in five animal-based and two human-based studies in Egypt between 2011 to 2017. Hashem et.al (2013) isolated 94 *S. aureus* strains from blood and wounds in which 45 were MRSA while 25 were fluoroquinolone-resistant [52]. Mutations such as C**2402**T, T**2409**C, T**2460**G, T**1497**C, and A**1578**G in gyrase enzymes, which leads to fluoroquinolones' target-site alterations, were implicated in resistance to fluoroquinolones (ciprofloxacin, levofloxacin, ofloxacin). The high rate of fluoroquinolone resistance (55.56%) among MRSA infections is rather concerning as patients unable to tolerate vancomycin are treated with other antibiotics such as fluoroquinolones. Vancomycin is often reserved as a last-resort therapy for MRSA infections due to their high resistance to several antibiotics.

Multidrug resistance to drugs such as gentamicin, ampicillin, amoxicillin, cefepime, tetracycline and chloramphenicol in MRSA is mediated by diverse resistance mechanisms including impermeability effects and efflux pumps. Unrestricted access to antibiotics and inappropriate prescriptions were responsible for the high rates of drug resistance in this study [52]. In a similar study, MRSA was isolated from patients suffering from surgical wound infections, diabetic foot, abscess and burns. Although *mecA* was the only mechanism of resistance, the isolates were

multiple-resistant to several antibiotics belonging to the β-lactams, aminoglycosides, fluoroquinolones, macrolides, lincosamides, tetracyclines and glycopeptides, indicating other mechanisms of resistance [121]. It therefore implies that administration of such antibiotics will not relieve patients from *S. aureus* infections. The high rate of *S. aureus* isolation confirms it to be the most prevalent Gram-positive pathogen isolated from soft tissue and wound infections.

Al-Ashmawy *et. al*. detected a high rate of MRSA (53%) in milk and dairy products believed to originate from human contamination rather than contamination from animals. Besides being resistant to β-lactams and other antibiotics, thirty-six of the isolates were resistant to vancomycin known to be effective in treating MRSA infections [30], making milk and dairy products a significant source of multidrug-resistant and toxigenic *S. aureus* infections. The occurrence of MRSA in pets such as dogs admitted in a veterinary clinic [112] may confirm a possible route in the community transmission of this pathogen, which is emerging as a veterinary pathogen of public health importance.

In 2017, Osman and colleagues detected *Staphylococcus spp.* in imported beef meat. Sixteen of these isolates were MDR and showed resistance to different groups of antibiotics due to resistance mechanisms such as *mecA*, and mutations in *gyrA* and *gyrB.* Indeed, MRSA has made methicillin and other β-lactams antibiotics clinically useless as a result of their high MDR [122]. Imported meat acts as a transmission vector for MRSA and is worrisome as *Staphylococcus spp.* are among the most common foodborne pathogens causing food poisoning outbreaks worldwide. Of 133 *S. aureus* recovered from animal origin, more than 70% were MDR and 30 were MRSA, exhibiting high resistance to clindamycin, co-trimoxazole, tetracycline, oxacillin, cefoxitin, ceftriaxone and erythromycin; four of the isolates were resistant to vancomycin [46]. The isolates showed the maximum sensitivity to imipenem, chloramphenicol and rifamycin, which is consistent with

488 similar reports in China and Pakistan [123,124], indicating their effectiveness in treating *S. aureus*
489 infections.
490 In 2016, MRSA was isolated from chicken products mainly due to poor hygienic handling
491 processes, posing a risk to public health. The mean *S. aureus* count in the chicken products were
492 beyond the permissible limits of the Egyptian organization for Standardization and Quality Control
493 (EOSQC 2005), coupled with resistance to different antibiotics classes; thus, retail chicken
494 products could constitute a high health risk to human consumers [51]
495
496 ***Morocco***
497 In a study to assess *S. aureus* carriage among end-stage renal diseases patients undergoing
498 hemodialysis, 42.9% *were* carriers, of which only one was MRSA. The methicillin-susceptible *S.*
499 *aureus* (MSSA) was resistant to many of the local antibiotics, thus limiting the successful treatment
500 of MSSA infections. Moreover 81.8% of the MSSA were penicillin-resistant. The male gender
501 and age 30 or below were identified as risk factors of *S. aureus* nasal carriage (*P-value* < 0.001)
502 [50]. Periodic monitoring of patients with hemodialysis is crucial as they are at increased risk of *S.*
503 *aureus* infection due to periodic hospitalization, immunosuppression and high invasive vascular
504 interventions.
505
506 ***Tunisia***
507 Resistant *S. aureus* was isolated from the environment, animals and humans between 2011 to 2017.
508 Ben Said, et al. recovered 12 MSSA from wastewater samples that were resistant to penicillin
509 (n=12 isolates), erythromycin (n=7 isolates), tetracycline (n=1 isolate) and clindamycin (n=1
510 isolate) due to the presence of *blaZ* (n=7), *msr(A)* (n= 7) and *tetK*(n=1). These resistant strains
511 were of ST3245(n=7) and ST15(n=1) [41], which have been also reported in animals and humans.

In an investigation to evaluate the prevalence of coagulase-negative Staphylococcus (CoNS) in the hospital environment, MDR *S. haemolyticus* and *S. saprophyticus* were the most dominant. Methicillin resistance was detected in *S. haemolyticus*, *S. epidermidis and S. saprophyticus*. These isolates were resistant to erythromycin, tetracycline, gentamicin, kanamycin, tobramycin and streptomycin due to the presence of *msrA* (32), *ermC* (8), *tetK* and *tetM*, *aac(6´)-Ie-aph(2´´)-Ia (16),), aph(3`)-IIIa(19), ant(4´)-Ia (n=14)* and *ant(6´)-Ia (3)* [125]. The high prevalence of MDR *Staphyloccoci spp.* isolates may result from transmission between the staff, patients and the environment. Strict infection controls are needed as infections caused by CoNS are common causes of death, particularly in low-birth-weight children, and are opportunistic infections in immunocompromised patients [126].

Moreover, nasal swab from sheep detected five MRSA (*mecA*=5), which were all of ST153 and carried *blaZ*, *ant(6)-Ia*, *aph(30)-IIIa*, *erm(C)*, *tet(K)*, and *fusB* genes that respectively encoded resistance to penicillin, streptomycin, kanamycin, erythromycin, tetracycline and fusidic acid. This study shows that the nares of healthy sheep could act as reservoirs of MRSA [107].

Between 2011 to 2012, 99 MRSA strains were detected from nasal swabs, blood, catheter, wounds, pleural puncture and abscess, among which 39 were tetracycline resistant. These isolates were resistant to aminoglycosides, fluoroquinolones, macrolides and lincosamide, with mechanisms of resistance including *mecA* (n=24), *tet(K)* (n=6), *tet(L)* (n=1) *and/or tet(M)* (n=18), *erm (A)(n=14), aph(2')-acc(6')* (n=13). Identified drug-resistant strains included ST247 (n=12), ST239 (n=6), ST728 (n=2), ST241 (n=1), ST398 (n=1), ST5 (n=1) and ST641 (n=1) [111]. For the first time, clonal lineage ST398, which has been reported in pigs from several studies in USA, South America, Asia and Canada [127–130], was found in human MRSA isolates in Africa in a nasal swab of a 74-year old patient.

Additionally, 69 MRSA strains were isolated from hospital-acquired and community-acquired infections. Although *mecA* (n=59) was the only mechanism of resistance identified, the isolates were resistant to aminoglycosides, tetracycline, fluoroquinolones, macrolides and rifampicin. The resistant clones were ST80 (n=41), ST1440 (n=1), ST1 (n=2), ST5 (n=5), ST22 (n=1), ST97 (n=2), ST239 (n=4), ST241 (n=3), ST247 (n=3), ST1819 (n=3),ST153 (n=2),ST256 (n=1) [47].

Mezghani Maalej and colleagues (2012) isolated five pristinamycin-resistant *S. aureus* strains from patients with skin infections. These isolates were MDR (Table 2), being the first detection of resistance to streptogramins due to *vat(B)* and *vga(B)* resistance genes [131], which emerged due to selective pressure from the use of pristinamycin. Thirty-six methicillin-resistant *S. haemolyticus* (MRSHae) were isolated from neutropenic patients (suffering from febrile neutropenia) with hematological cancer between 2002 and 2004. These MDR isolates carried *SCCm*ec-borne *mecA* (Table 2) [132], which agrees with a report on *S. haemolyticus'* MDR capacity, particularly in immunocompromised patients [133,134]

Libya

Due to the high risk of MRSA colonization developing into infections in children, nasal samples were collected from children inpatients, their mothers, healthcare workers and outpatients' workers, which yielded a MRSA nasal carriage rate of 8.3%, 11% ,12.3% and 2.2% respectively in Libya [135]. Thus, nasal carriage of MRSA is common in inpatients children, their mothers and health workers in Libya and could be a source of MRSA infections.

West Africa: Ghana, Nigeria, Senegal

Ghana

Among 308 staphylococcus isolates collected across Northern, Central and Southern Ghana in 2013, low prevalence of antibiotic resistance was reported except for penicillin (97%), tetracycline

(42%) and erythromycin (6%) [136]. Moreover, *mecA* was detected in only nine isolates, implying the presence of other β-lactam resistance mechanisms. The MRSA clones included ST88 (n=2), ST8 (n=1), ST789 (n=1), ST72 (n=1), ST2021 (n=1), ST250 (n=2), and ST239 (n=1). In a similar study that characterized 30 MRSA isolates resistant to tetracycline, fluoroquinolones and macrolides, *tet(M)* (n=13), *tet(K)* (n=10), *aphA3* (n=7), *aacA–aphD* (n=5) *and erm(C)* (n=4) were detected. Similar and different resistant clones, viz. ST88 (n=8), ST8 (n=5), and ST247 (n=4) were detected [137], indicating high MRSA clonal diversity in Ghana. These studies show a high rate of resistance to non-β lactams that further complicate MRSA treatment. Furthermore, the isolation of USA300 and other epidemic multidrug-resistant MRSA clones calls for MRSA surveillance and adequate control measures.

Nigeria

Five different studies reported drug-resistant *S. aureus* from several human anatomical sites such as throat swabs, soft skin and tissue infection, urinary tract and respiratory infections, wound, vagina, otitis, conjunctivitis, septicemia and bronchitis. Of a total ≥602 isolates, ≥433 were resistant to several antibiotic classes (Table 1). Of note, 429 of the ≥433 drug-resistant isolates were all resistant to cotrimoxazole or trimethoprim/sulfamethoxazole (TMP/SMX). Mechanisms of resistance included *mecA* (≥54), *blaZ* (n=284), *dfrA* (≥5) and *dfrG* (≥152). *S. aureus*-resistant clones ST8, ST152, ST772, ST14, ST241, ST37, ST39, and ST88 were present. Colonized persons, including immune-compromised individuals, facilitated the spread of *S. aureus* and MRSA ST8 identified as ubiquitous in various geographic areas of Nigeria. High utilization of cotrimoxazole or TMP/SMX because of low cost and easy obtainability through lenient medication regulations were implicated for the high resistance [115]. Besides *S. aureus*, *S. haemolyticus* was the major species isolated, and is considered as the second most detected and clinically important

581 *Staphylococci spp*., particularly in immunocompromised patients [138]. All the *S. haemolyticus*
582 isolates detected were resistant to at least three antibiotics classes (Tables 2-4) [139].

583 Moreover, O. Ayepola *et al.* (2015) reported a higher rate of 20.8% *S. aureus* from UTIs than the
584 reported ranges in Africa (6.3-13.9%), and far exceed the rate reported from Europe and Brazil
585 (1.1%) [140]. None of the isolates exhibited resistance to vancomycin, linezolid, daptomycin and
586 mupirocin; indicating their usefulness in treating *S. aureus* infections. Co-trimoxazole, which was
587 previously clinically valuable in treating MRSA infections, demonstrated the highest level of
588 resistance, hence it's not recommendedble [106,115,116,139]. In a study to examine the genetic
589 mechanism(s) of resistance in CoNS in faecal samples, all the 53 islolated CoNS were Penicillin
590 V-resistant and between three to 19 exhibited multidrug resistance (Table 2); *mecA* (n=15), *ermC*,
591 *tetM* (n=4) and *tetK* (n=6) were identified [139]. CoNS isolates from faeces carrying tetracycline,
592 macrolides and aminoglycosides resistance genes may transfer them inter- and intra-species,
593 disseminating MDR in Staphylococcus.

594 ***Senegal***

595 A low prevalence of MRSA (10.52%) was reported in Senegalese pigs compared to those reported
596 in developed countries. This might be due to a lesser veterinary antibiotic use as growth promoters
597 and/or for therapy. However, all the isolates were resistant to penicillin, 27 were resistant to
598 cotrimoxazole and 16 were resistant to tetracycline [82]. Five of the MRSA were of ST5 [82], evincing
599 the spread of this clone in animals, humans [79,80], and the environment [47] ; the importance of this
600 clone as a cause of human infections is well-established [84].

601 ***Cape verde***

In Cape Verde, a low prevalence of 5.6% (6/107) MRSA nasal carriage was documented in 2015. The predominant MRSA clones was ST5 (n=3), ST88 (n=2) and ST8 (n=1). These isolates showed significant level of resistance to ERY, SXT and PEN [141] .

Central Africa: Gabon, D.R. Congo

Gabon

In Gabon, *S. aureus* isolated from colonized persons, blood, as well as soft and skin tissue infections resulted in 49% (104/212) resistance to trimethoprim: *dfrA* (n=1), *dfrG* (n=100), *dfrK+G* (n=1), *dfrB* (n=2), and *mecA* (n=1) were detected in the isolates [114]. Thus, *dfrG* is obviously the most abundant and common trimethoprim resistance mechanisms in Africa, refuting *dfrB* mutation as the main mechanism of resistance to trimethoprim [142–144].

D.R. Congo (DRC)

A total of 215 (79.34%) drug-resistant *S. aureus* isolates were collected between 2015 to 2017 from nasal swab and bloodstream infections in the D. R. Congo; 70 isolates were MRSA. Other major resistance genes mediating resistance to trimethoprim/sulfamethoxazole, aminoglycoside, macrolides, tetracycline, penicillin, and chloramphenicol were *dfrG* (≥120), *tetK* (≥98), and *femA* (≥98). MRSA showed high-level resistance to β-lactams, aminoglycoside, macrolides and tetracycline. The pathogen caused severe infections such as pneumonia, meningitis, complicated urinary tract infections, gynaecological infections and peritonitis. *S. aureus* ST8 (≥47) was the dominant clone, followed by ST152 (≥17), ST5 (≥2) and ST88 (≥2). In DRC, MRSA ST8 outnumbers the African MRSA clone ST88, which is dominant in Africa. The high-level oxacillin resistance in DRC was associated with a mutation in *femA* (Y**195**F) whist high-level trimethoprim resistance was due to the detection of *dfrG*, which is consistent with trimethoprim resistance in Africa and Asia. In Africa, TMP/SMX or cotrimoxazole is frequently administered as prophylactic

to immuno-suppressed patients such as HIV/AIDS patients to prevent opportunistic infections such as *Pneumocystis carinii* pneumonia, toxoplasmosis and bacterial pneumonia [145] Hence, prophylactic use of TMP/SMX in HIV patients may impact resistance. Additionally, there was high-level MDR among MRSA, which is a great concern as microbiological laboratories/facilities and second-line antibiotics are rare in DRC. Moreover, the detection of nasal carriage among healthcare workers' demands strict infection controls and surveillance [81,146,147].

East Africa: Kenya, Tanzania

Kenya

In contrast to earlier studies done in Kenya, Omuse and colleagues (2016) detected a wide genetic diversity of MRSA and well-established epidemic MRSA clones among clinical isolates. MRSA clonal complexes 5, 22 and 30, implicated in several outbreaks were described. These clones included ST22 (n=4), ST88 (n=1), ST789 (n=1), ST5 (n=1), ST8 (n=2), ST241 (n=12) and ST239 (n=2). Approximately 41% of the MRSA in the study were MDR (Table 2), showing resistance to clindamycin, erythromycin and TMP/SMX [102]. Detection of these clones in referral hospitals in Kenya calls for implementation of strict infection control measures to reduce the high morbidities and mortalities associated with HA-MRSA infections.

Tanzania

In a study to investigate the molecular epidemiology of trimethoprim resistance in MSSA causing skin and soft tissues infections, *dfrG* was detected in all 32-trimethoprim resistant isolates. Other reported trimethoprim resistance mechanisms such as *dfrA*, *dfrB* and *dfrK* were missing, confirming *dfrG* as the main trimethoprim resistance mechanism in Sub-Sahara Africa [114].

Uganda

A MRSA carriage of 56.1% (23/41) was detected in milk from pastoral communities in Uganda, exactly 70% of which were tetracycline-resistant. MRSA clones ST97 and ST1 were identified. Furthermore, over 90% of the isolates carried genes encoding enterotoxin that causes food-borne diseases. The weak veterinary delivery system and the high dependency on animals and animal products for food in Uganda was implicated for the high prevalence of MRSA [148].

S. aureus isolates, including 24 MRSA and 40 MSSA, were isolated from patients with surgical site infections (SSI). The MRSA isolates were MDR (including resistance to oxacillin, gentamicin, ciprofloxacin and chloramphenicol) compared to the MSSA. Inducible clindamycin resistance was found in 17.2% of the isolates, mostly in MRSA. In a multivariate analysis, inducible clindamycin resistance and cancer were identified as independent predictors of MRSA-SSI [149].

Southern Africa: Angola, Malawi, Mozambique, Namibia, South Africa

Angola

Conceica˜o et al (2014) reported a nasal *S. aureus* carriage of 23.7% (n=128), out of which 58.1% (n=77) were MRSA. Fifty-seven of the MRSA clones were of ST5, followed by ST88 (n=9), ST8 (n=5) and ST72 (n=3). This study represents the first description of the spread of MRSA ST5 in Africa. All the 77 MRSA strains were resistant to SXT, FOX and PEN [150] . In a study to identify oxacillin-susceptible *mecA*-positive *S. aureus* (OS-MRSA) for the first time in Africa, a prevalence of 17.7% was detected among healthy healthcare workers in Angola and Sa˜o Tome´ & Principe, making them potential OS-MRSA reservoirs [151]. OS-MRSA have been reported worldwide in humans, animals and food animals [152–155]. The OS-MRSA isolates expressed MDR (Table 2) and belonged to ST88 (n=15) and ST8 (n=9). In sub-Saharan Africa, the identification of clinically important *S. aureus* is heavily based on phenotypic agar-screening and oxacillin disc-diffusion methods.

Mozambique

The prevalence of HA-MRSA and CA-MRSA in Mozambique was found to be 15.1% and 1%, respectively. MRSA showed high-level resistance to penicillin, cefoxitin, gentamicin, ciprofloxacin, erythromycin, TMP/SMX, chloramphenicol and tetracycline, compared to MSSA. Additionally, inducible macrolide–lincosamide–streptogramin B (MLSB) resistance was 41.7% and 10.7% in hospital-acquired *S. aureus* (HA-SA) and community-acquired *S. aureus* (CA-SA) isolates respectively [156], further limiting therapeutic options for *S. aureus* infections. This study, which is the first to detect the emergence of HA-MRSA within post-operative abdominal wounds and burn wounds in Mozambique, reported that patients with infected burn wounds had a significantly longer hospitalisation than patients with post-operated abdominal wounds. Efforts to prevent the transmission of MDR HA-SA, such as education on proper hand-washing techniques, are urgently needed.

Namibia

The dominant resistance gene mediating trimethoprim resistance in MRSA and MSSA in Namibia was *dfrG*. This is similar to reports in other Africa countries [114]. Moreover, *dfrG* was frequently detected in *S. aureus* from SSTIs in travelers returning from other African countries, suggesting that *dfrG* can be transmitted into populations with low antifolate resistance such as North America and Europe [157,158].

South Africa

Thirty MDR *S. aureus* were recovered between April 2015 to April 2016 from ten beaches in the Eastern Cape Province, South Africa (Table 2). Notably, the isolates harbored *mecA*, *femA*, *rpoB*, *blaZ*, *ermB* and *tetM* [29], making marine environments and public beaches potential depositaries of MDR *S. aureus* that can be transmitted to animals and humans. Further, the 50% resistance to

693 vancomycin recorded is concerning to global health due to its role as a last-resort antibiotic for
694 treating MRSA infections.

695 *S. aureus* was detected in raw and pasteurized milk at an isolation rate of 75% and 29%
696 respectively, due to inefficient thermal processing and post-process contamination. A high
697 proportion (60%-100%) of these isolates showed resistance to aminoglycosides, β-lactams,
698 vancomycin, tetracycline and erythromycin, albeit only 19 *mecA* genes were present [44]. Evidently,
699 raw and pasteurized milk can harbour MDR *S. aureus*, exposing consumers to colonization and/or
700 infections. Again, *Staphylococcus spp*., including *S. aureus, S. haemolyticus, S. xylosus* and *S.*
701 *capitis* were isolated from healthy pigs and cattle, of which between 75 to 100% were resistant to
702 penicillin G, tetracycline, sulfamethoxazole and nalidixic acids, due to their use as growth
703 promoters; *MecA* and *mphC* were identified. Additionally, 12% of the isolates were resistant to
704 vancomycin and erythromycin, evincing the important role of animals in the dissemination of
705 resistance determinants and the importance of commensals to public health [118].

706 Van Rensburg et al. [80] detected 43.4% (1432/3298) and 3.1% (328/10448) rifampicin resistance
707 rate among MRSA and MSSA respectively. Similar studies in South Africa have also reported of
708 high rifampicin resistance in MRSA [159,160], obviously due to frequent use of rifampicin among
709 tuberculosis patients, who are highly prevalent in South Africa. MRSA ST5 and ST612 were
710 detected while H**481**Y/N and I**527**M mutations in *rpoB* were associated with high-level rifampicin
711 resistance, similar to reports in Italy [161]. Additionally, novel H**481**N, I**527**M, K**579**R mutations
712 were also detected.

713 Three studies reported a prevalence of 29.1% [162], 45.44% [103] and 100% [163] MRSA recovered from
714 humans, expressing resistance to macrolides, tetracycline, aminoglycoside, cotrimoxazole and
715 rifampicin. MRSA ST612, ST239, ST36 and ST5 were the dominant strains similar to other

findings in Australia and Europe[164]. The study showed that *S. aureus* bacteremia is common and account for high mortality in South Africa. For instance, in a study by Perovic et al., [162] 202 patients died from *S. aureus* bacteremia infections, with HIV patients being more likely to acquire HA-MRSA. The isolates were however susceptible to glycopeptides, fluoroquinolones, linezoid, tigecycline, fosfomycin and fusidic acid, confirming their clinical usefulness in treating MRSA infections. In a recent study, a high prevalence and genetic diversity of multi-drug efflux (MDE) resistance genes were found in clinical *S. aureus* isolates, including 81 MRSA and 16 MSSA [165]. *NorA, norB, mepA, tet38, sepA, mdeA, imrs* and *sdrM* were present in at least 86% of the isolates, predicting resistance to broad-spectrum biocides and fluoroquinolones, which is disturbing. Efforts to develop efflux pump inhibitors can mitigate such resistance mechanisms.

Sao Tome & Principe

MRSA prevalence of 26.9% [166] and 25.5% [141] was reported in nasal swabs in 2014 and 2015, respectively, in Sao Tome & Principe. Additionally, a high prevalence of oxacillin-susceptible *mecA*-positive *S. aureus* was reported in the same study in Sao Tome & Principe and Angola [151]. The most dominant MRSA clone was ST8 (n=25), followed by ST5 (n=13) and ST80 (n=13). High genetic variability was found in the MSSA strains. Both MRSA and MSSA showed different levels of resistance to SXT, ERY, CIP and TET; however, all the MRSA isolates were resistant to cefoxitin.

***Streptococcus spp.* (*S. pyogenes, S. pneumoniae and S. agalactiae*)**

Drug resistant *Streptococcus spp*. including *S. agalactiae* and *S. pyogenes* have been identified in Northern, Eastern and Southern Africa. *S. pyogenes* were reported in only humans whilst *S.*

agalactiae was reported in both animals (camels) and humans with a high rate of resistance to tetracycline and erythromycin.

North Africa: Algeria, Egypt, Morocco, Tunisia, Libya

Algeria

A sole study has so far detected 44 tetracycline (100%, 44/44)- and erythromycin-resistant (43.18%, 19/44) *S. agalactiae* from vaginal swabs; *tetM*; and *ermB* respectively mediated this resistance. A high diversity of resistant clones viz., ST1, ST19, ST10, ST158, ST166, ST233, ST460, ST521 and ST677 were detected [108], which have been reported worldwide for causing life-threatening invasive diseases such a meningitis and sepsis [167,168].

Egypt

Similarly, Shabayek et al. (2014) detected 98% and between 14-17% *S. agalactiae* resistance to tetracycline and macrolides respectively. *TetM* was detected in all the 98 tetracycline-resistant isolates whilst *ermB* and *ermA* mediated erythromycin resistance. Efflux pump genes such as *tetK* (n=12), *tetL* (n=1) and *mefA/E* (n=1) were also found [169], which reflects the increasing reports of *S. agalactiae* resistance to tetracycline and macrolides [170]. This study also showed that vancomycin and fluoroquinolones are effective replacement for erythromycin and clindamycin, and for patients allergic to penicillin. Although penicillin is the antibiotic of choice for treating *S. agalactiae* infections, reports of penicillin resistance in USA and China calls for increased surveillance in Africa [170].

Tunisia

S. agalactiae

From January 2007 to December 2009, 226 *S. agalactiae* were isolated from female genitals and gastric fluid of infected newborns. Of these, 97.35% (220/226), 40% (90/226) and 19.1% (43/226) were resistant to tetracycline, erythromycin and rifampicin respectively. Additionally, seven isolates were resistant to aminoglycoside (gentamycin and streptomycin) and chloramphenicol. *TetM* (n=205), encoding a ribosomal protection protein, which protect the ribosome from the action of tetracycline, was the main tetracycline resistance mechanism, and was significantly associated with *Tn*916 (p-value = 0.0002). Other resistance genes including *ermB* (n=79) and *tetO* (n=50) were detected. All isolates were however susceptible to β-lactams and quinupristin-dalfopristin [68]. Between 2005 and 2007, 160 erythromycin-resistant *S. agalactiae* were isolated from humans, with a high resistance rate of 84.3% (135/160) to the constitutive macrolides-lincosamides, streptogramines B (MLSB) [171].

S. pyogenes

Hraoui *et al.*, (2011) reported a low macrolide resistance rate (5%, 5/103) and a high tetracycline resistance rate (70%, 72/103) among human isolates, with *tetM*, associated with *Tn916*, being responsible for tetracycline resistance [172]. Increase tetracycline use in food animals was implicated in this instance, leading to selection and dissemination of resistance genes from animals to human. Macrolide resistance was only detected in seven isolates, which is corroborated by the findings of Ksia et al. (2010), who detected low-level macrolides resistance among Children [173].

East Africa: Kenya, Tanzania

Kenya

S. agalactiae

In the horn of Africa, camel plays a significant role in the survival of humans by providing milk, meat and transportation. In 2013, Fischer et al. detected 36% (37/92) tetracycline resistance in *S. agalactiae* isolates from camels' wound infections and mastitis that was mainly mediated by a *Tn*916-borne *tetM*. ST616 (n=22) was the major resistant clone, followed by ST612 and ST617 [174]. Shifting from tetracycline to other antibiotics is evidently necessary for effective treatment outcomes in camel infections in Kenya.

Southern Africa: Angola, Malawi, Mozambique, Namibia, South Africa

South Africa

S. agalactiae

A *S. agalactiae* colonization rate of 30.9% was detected from vaginal and rectal swabs of pregnant women. Similar to other reports in Africa, a high rate of tetracycline (94.5%, 120/128) and macrolide (21.1%, 27/128) resistance was documented. All the isolates were however sensitive to penicillin, ampicillin, vancomycin and gentamicin. Macrolide and clindamycin resistance were associated with *ermB* and *mefA* genes [175]. The study highlights the need for research on treatment options for patients allergic to penicillin due to high-level resistance in alternative drugs such as macrolides and lincosamides.

***Enterococcus spp*. (*E. faecium, E. faecalis, E. hirae, E. durans, E. gallinarum*)**

Enterococcus spp., predominately MDR and vancomycin-resistant (VR) *E. faecium* and *E. faecalis*, were isolated from humans, animals and the environment in Northern, Western, Eastern and Southern Africa. From the meta-analysis, Enterococcus isolates recorded the highest rate of resistance followed by *S. aureus.* Common resistance genes, clones and MGEs were found in humans, animals and the environment.

North Africa: Algeria, Egypt, Morocco, Tunisia, Libya

Algeria

The first study to molecularly characterize *Enterococcus spp.* from urinary tract and wound infections in Algeria revealed a high rate of resistance to erythromycin (86.4%,108/125), tetracycline (82.4,103/125), levofloxacin (71.2%,89/125) and gentamicin (54.4,68/125). Only 3.2% (4/125) were VRE, confirming glycopeptides as ideal antibiotics for treating Enterococcus infections. A mortality rate of 10% was reported due to infections caused by Enterococcus. *E. faecium*, *E. faecalis* and *E. gallinarum* were the main Enterococcus isolated. Majority of these isolates were from females (53%). *ErmB* (≥92) and *vanC1*(≥4) were the main mechanisms of resistance. A high genetic diversity among strains was seen in *E. faecium* and *E. faecalis*, with *E. faecium* ST78 being the dominant resistant strain [176], which is also prevalent in Asian (Japan, Taiwan, China and Korea) and European (Italy and Germany) countries [177–179]. A novel ST317 (n=33) clone was predominant among the *E. faecalis* isolates. Rational use of antibiotics, as well as close monitoring of the epidemiology of the strains are crucial.

Egypt

In a similar study to characterize *E. faecium* and *E. faecalis* from patients, 82% of the isolates were MDR, showing high-level resistance to aminoglycosides, β-lactams and tetracycline. *VanA* was detected in two *E. faecium* isolates, all of which were resistant to all antibiotics tested. Bioinformatic (sequence) analysis revealed that *vanA* was transmitted horizontally to *S. aureus*, showing the importance of horizontal gene transfer in ABR and subsequent management of enterococci infections such as bacteremia, endocarditis and urinary tract infections [180].

Tunisia

Antimicrobial-resistant Enterococcus was found in faeces of pet and camel, irrigation water from farm environments, food vegetables, hospital environments, animal meat and patients in Tunisia [42,45,71,181–183]. High-level resistance to vancomycin, macrolides, aminoglycosides, β-lactams and tetracycline was detected in the environment, animals and humans with majority of the isolates being *E. faecium*, followed by *E. faecalis*. *TetM, tetL, ermB, ant (6)-la, vanA* and *aph(3')-llla* were the major resistance mechanisms, with *IS16* being the main MGE disseminating the resistance genes. *E. faecium ST80, ST910* and *ST16* were the dominant resistant clones in Tunisia. The studies show that meat, animals, pets, hospital environment and wastewater used for farm irrigation play a crucial role in the spread of antibiotic resistant Enterococcus.

West Africa: Cape Verde, Ghana, Nigeria, Senegal

Nigeria

Enterococcus spp. isolated from poultry and cattle as well as their manure demonstrated high-level resistance to tetracycline, erythromycin, gentamicin, ampicillin and streptomycin. Sixty isolates were MDR, showing resistance to three or more antimicrobials [184]. The rate of MDR is a reflection of the substantial use of broad-spectrum antibiotics in Nigeria, raising major public health concerns as practices such as the use of untreated poultry and cattle manure for fertilizing agricultural soils, particularly vegetables, are a common practice in Africa. This could transfer MDR Enterococci to humans, and cause serious nosocomial infections including endocarditis, bacteremia and urinary tract infections that can result in high morbidities and mortalities.

Ngbede et al. (2017) recently characterized 63 ampicillin- and 37 gentamicin-resistant *E. faecium* from vegetables, soil, farms, animal and manure [48]. Approximately 95% (35/37) and 8% (5/63) of the aminoglycoside- and ampicillin-resistant clones were recognized as high-level aminoglycosides- and ampicillin-resistant *E. faecium* respectively. Modifying enzymes' genes

such as *aac(6')-Ie-aph(2'')-Ia)*, *aph(2')-1c,aph(3')-llla,*, and *ant(4')-la* accounted for the aminoglycoside resistance.

East Africa: Kenya and Tanzania

Tanzania

In a study to determine if cattle co-grazing with wild life influence ABR, ABR in wild animals such as buffalo, zebra and wildebeest was higher than in cattle, although wildlife is periodically treated with antibiotics. Ten VRE and ampicillin-resistant Enterococcus were found in the wild animals but not cattle. Additionally, Enterococcus isolates from wildlife were highly resistant to tetracycline, rifampicin, macrolides, aminoglycosides and cotrimoxazole [32]. *TetW* and s*ul1* were the resistance genes identified in the isolates. The practice of co-grazing possibly resulted in transmission of ABR genes from livestock to wildlife. The high presence of ABR bacteria in wildlife was likely due to contact with more environmental surfaces that have been contaminated with human, birds or animal excreta. Result from this study demonstrates the presence of ABR Enterococci in wild animals without antibiotic pressure.

Southern Africa: Angola, Malawi, Mozambique, Namibia, South Africa

South Africa

Multiple antibiotic-resistant Enterococci were isolated from borehole water, waste water, pigs and humans in South Africa. Notably, a very high-level vancomycin, aminoglycoside, β-lactam, macrolides and fluoroquinolones resistance was detected among the Enterococci isolates compared to other countries. *ErmB* (≥300), *vanC* 2/3(162), *vanB* (≥138), *vanC* (≥120), *strA* (≥120) were the major resistance genes. The vancomycin-resistant isolates were from patients with haematological malignancies, bacteremia, pigs, wastewater and underground water [27,28,49,85]. Inefficient chlorination to kill bacteria accounted for the high resistance rates in the final effluents'

discharge into the environment. Hospital wastewater is therefore a major source of MDR Enterococcus. Sub-therapeutic antibiotic usage in animal feed also accounted for the emergence of ABR in pigs whilst the construction of boreholes near pit toilets resulted in high enterococcal isolation and resistance rates in South Africa.

3. CONCLUSION AND STUDY LIMITATIONS

The high rate of ABR among GPB to important antibiotics in Africa is a major threat to clinical medicine, the economy and socio-economic development. This calls for national as well as international rules and regulations to contain resistance. Heavy consumption of antibiotics in animal feed, exchange of resistance genes between animals and food animal products to man, uncontrolled and inappropriate antibiotics prescription practices, inadequate hygienic handling and processing of food, close contact with pet dogs, shedding of resistant clones from animals to humans and the environment, as well as high consumption of antibiotics in humans, particularly in HIV patients, account for the high rate of ABR in Africa.

Effective surveillance and monitoring of antimicrobial drug usage and licensing, banning or restricting the prescription of reserved, expired and substandard drugs, periodic monitoring of pharmacies and veterinary shops, and antibiotic stewardship are recommended measures to contain ABR. Improving animal health through hygienic practices on farms, avoiding prophylactic or growth-promoting antibiotic usage in veterinary medicine, integrative efforts between human and veterinary medicine as well as environmental health are urgently needed to contain ABR. Implementation of these policies will decrease the high rate of ABR in Africa, reduce longer hospital stays and the resort to expensive but toxic antibiotic alternatives, with a concomitant reduction in morbidity and mortality rates. Few studies reporting on the molecular determinants of

ABR in GPB in Africa limited the study to 77 articles. Among these, only few studies reported on MGEs and resistant clones.

Experimental procedures used in included studies

The studies included in this review basically used the following experimental procedures. Transport media such as stuart agar, cary-blair medium, and gel transport swabs with charcoal were used to transport the samples to the laboratory [81,112]. Cotton swabs were used to swab sample specimens, tissues, surfaces, fluids, etc. and cultured on nutrient agar, blood agar, tryptone soya agar, mannitol salt-phenol red agar, brain-heart infusion broth, Slanetz-Bartley mannitol salt agar, and Edwards agar media prior to identifying the 24-hour colonies using Gram-staining and different biochemical tests such as catalase and coagulase tests, latex coagulase test and DNase agar test. Subsequently, antimicrobial susceptibility testing (AST) using disc diffusion (Kirby-Bauer method or E-test) on Mueller Hinton agar plates and a 0.5 McFarland bacterial inoculum was performed. Antibiotics such as ampicillin (AMP), amoxicillin (AMX), amikacin (AMK), ampicillin-Sulbactam (SAM), amoxicillin-clavulanic acid (AMC), azithromycin (AZI), apramycin (APR), chloramphenicol (CHL), cefoxitin (FOX), ceftazidime (CFZ), clarithromycin (CLR), ciprofloxacin (CIP), cefuroxime (CXM), clindamycin (CLI), cephalexin(LEX), cefoperazone (CFP), cefepime (FEP), cefotaxime (CTX), ceftaroline (CPT), cephalothin (CET), cloxacillin (CLX), doxycycline (DOX), erythromycin (ERY), fusidic acid (FUS), fosfomycin (Fof), gatifloxacin (GAT), gentamicin (GEN), imipenem (IPM), kanamycin (KAN), levofloxacin (LVX), linezolid (LZD), lincomycin (LIN), meropenem (MER), mupirocin (MUP), minocycline (MIC), moxifloxacin (MXF), methicillin (MET), metronidazole (MTZ), nitrofurantoin (NIT), norfloxacin (Nor), nalidixic acid (NAL), netilmicin (NEL), oxacillin (OXA), ofloxacin (OFX), perfloxacin (PF), penicillin (PEN), pristinamycin (PRI), rifampicin (RIF), streptomycin (STR), streptogramin

B (SB), sulfamethoxazole (SMZ), tetracycline (TET), teicoplanin (TEC), telithromycin (TEL), tobramycin (TOB), trimethoprim-sulfamethoxazole (SXT), and vancomycin (VAN) were mostly used for the AST. Polymerase chain reaction (PCR) was used to detect the antimicrobial resistance genes and clones (i.e. molecular typing) of the isolates.

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References

1. Witte W, Cuny C, Klare I, Nübel U, Strommenger B WG. Emergence and spread of antibiotic-resistant Gram-positive bacterial pathogens. *Int J Med Microbiol* 2008; **298(5-6)**: 365–77.

2. Witte W. 'Antibiotic resistance in gram-positive bacteria: epidemiological aspects.' *J Antimicrob Chemother* 1999; **44**, **su**: 1–9.

3. Nelson RE, Slayton RB, Stevens VW, Jones MM, Khader K, Rubin MA, Jernigan JA SM. Attributable Mortality of Healthcare-Associated Infections Due to Multidrug-Resistant Gram-Negative Bacteria and Methicillin-Resistant Staphylococcus Aureus. *Infect Control Hosp Epidemiol* 2017; **38(7)**: 848–56.

935 4. O'Neill J. 'Tackling drug-resistant infections globally: final report and recommendations.' *Rev*
936 *Antimicrob Resist* 2016.

937 5. Kluyt- mans J. EKRBKCB vanGemert-PJEHS. Methicillin-resistant Staphylococcusaureus
938 (MRSA): burden of disease and control challenges in Europe. *Euro Surveill* 2010; **15**: 19688.

939 6. Lee B.Y, Singh A, David M.Z , Bartsch S.M, Slayton R.B, Huang S.S E. The economic
940 burden of community associated methicillin-resistant Staphylococcusaureus (CA-MRSA).. *Clin*
941 *MicrobiolInfect* 2013; **19,**: 528–536. Available at: doi: 10.1111/j.1469-0691.2012.03914.x.

942 7. Hidron A, Edwards J, Patel J et al. NHSN annual update: antimicrobialresistant pathogens
943 associated with healthcare-associated infections: annual summary of data reported to the
944 National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006–
945 2007. *Infect Control Hosp Epidemiol 2008; 29* 2008; **29**: 996–1011.

946 8. Kaasch AJ, Barlow G, Edgeworth JD, Fowler VG Jr., Hellmich M, Hopkins S et al.
947 Staphylococcus aureus bloodstream infection: a pooled analysis of five prospective,
948 observational studies. *J Infect* 2014; **68(3)**: 242–51. Available at: doi: 10.1016/j.jinf.2013.10.015
949 PMID: 24247070%0A.

950 9. Fortuin-de Smidt MC, Singh-Moodley A, Badat R, Quan V, Kularatne R, Nana T et al.
951 Staphylococcus aureus bacteraemia in Gauteng academic hospitals, South Africa. International
952 journal of infectious diseases. *Int Soc Infect Dis 2015;* 2015; **30:** 41–8.

953 10. Gastmeier P, Schroder C, Behnke M, Meyer E GC. Dramatic increase in vancomycin-
954 resistant enterococci in Germany. *J Antimicrob Chemother* 2011; **69(6):** 1660–4.

955 11. Lepoutre A, Doloy A, Bidet P, Leblond A, Perrocheau A, Bingen E, Trieu-Cuot P, Bouvet A,

956 Poyart C, Lévy-Bruhl D M of the EN. Epidemiology of invasive Streptococcus pyogenes
957 infections in France in 2007. *J Clin Microbiol* 2011; **49(12)**: 4094–100.

958 12. Butler AM, Olsen MA, Merz LR, Guth RM, Woeltje KF, Camins BC FV. Attributable costs
959 of enterococcal bloodstream infections in a nonsurgical hospital cohort. *Infect Control Hosp*
960 *Epidemiol* 2010; **31(1)**: 28–35.

961 13. Kaye KS, Engemann JJ, Mozaffari E CY. Reference group choice and antibiotic resistance
962 outcomes. *Emerg Infect Dis* 2004; **10(6)**: 1125–8.

963 14. Puchter L, Chaberny IF, Schwab F, Vonberg RP, Bange FC EE. Economic burden of
964 nosocomial infections caused by vancomycin-resistant enterococci. *Antimicrob Resist Infect*
965 *Control* 2018; **7(1)**: 1.

966 15. Carapetis JR, Steer AC, Mulholland EK WM. The global burden of group A streptococcal
967 diseases. *Lancet Infect Dis* 2005; **5(11)**: 685–94.

968 16. Skoff TH, Farley MM, Petit S, Craig AS, Schaffner W G, K, Harrison LH, Lynfield R,
969 Mohle-Boetani J, Zansky S A, BA, Stefonek K, Zell ER, Jackson D, Thompson T SS. Increasing
970 burden of invasive group B streptococcal disease in nonpregnant adults, 1990–2007. *Clin Infect*
971 *Dis* 2009; **49(1)**: 85–92.

972 17. Eskandarian N, Ismail Z, Neela V, van Belkum A, DesaMN A, S N. Antimicrobial
973 susceptibility profiles, serotype distribution and virulence determinants among invasive, non-
974 invasive and colonizing Streptococcus agalactiae (group B streptococcus) from Malaysian
975 patients. *Eur J Clin Microbiol Infect Dis* 2015; **34(3)**: 579–584.

976 18. Seale AC, Mwaniki M, Newton CR BJ. Maternal and early onset neonatal bacterial sepsis:

977 burden and strategies for prevention in sub-Saharan Africa. *Lancet Infect Dis* 2009; **9(7)**: 428–
978 38.

979 19. Kuchenmüller T, Abela-Ridder B, Corrigan T TA. World Health Organization initiative to
980 estimate the global burden of foodborne diseases. *Rev Sci Tech* 2013; **32(2)**: 459–67.

981 20. World Health Organization. Antimicrobial resistance—global report on surveillance.
982 Geneva, Switzerland. *WHO* 2014.

983 21. Williams PC, Isaacs D BJ. Antimicrobial resistance among children in sub-Saharan Africa.
984 *Lancet Infect Dis* 2017.

985 22. Liu Y-Y, Wang Y, Walsh TR, Yi LX, Zhang R, Spencer J et al. Emergence of plasmid-
986 mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a
987 microbiological and molecular biological study. . *Lancet Infect Dis* 2016; **16:** 161–8. Available
988 at: doi:10.1016/S1473-3099(15)00424-7.

989 23. World Health Organization. WHO's first global report on antibiotic resistance reveals
990 serious, worldwide threat to public health. In Antimicrobial resistance–global surveillance report.
991 Virtual Press Conference 2014 Apr. *WHO* 2014; **(Vol. 30).**

992 24. Willems RJ, Hanage WP, Bessen DE FE. Population biology of Gram-positive pathogens:
993 high-risk clones for dissemination of antibiotic resistance. *FEMS Microbiol Rev* 2011; **35(5)**:
994 872–900.

995 25. Shen J, Wang Y SS. Presence and dissemination of the multiresistance gene cfr in Gram-
996 positive and Gram-negative bacteria. *J Antimicrob Chemother* **68(8)**: 1697–706.

997 26. Lebreton F, van Schaik W, McGuire AM, Godfrey P, Griggs A, Mazumdar V, Corander J,

998 Cheng L, Saif S, Young S ZQ. Emergence of epidemic multidrug-resistant Enterococcus faecium
999 from animal and commensal strains. *MBio* **4(4)**: e00534-13.

1000 27. Ateba CN, Lekoma KP KD. 'Detection of vanA and vanB genes in vancomycin-resistant
1001 enterococci (VRE) from groundwater using multiplex PCR analysis.' *J Water Health* 2013; **11.4**:
1002 684–691.

1003 28. Iweriebor, Benson Chuks, Sisipho Gaqavu, Larry Chikwelu Obi, Uchechukwu U. Nwodo
1004 and AIO. 'Antibiotic susceptibilities of Enterococcus species isolated from hospital and domestic
1005 wastewater effluents in Alice, eastern Cape Province of South Africa.' 4231-4246. *Int J Environ*
1006 *Res Public Health* **12**, no. **4**.

1007 29. Akanbi OE, Njom HA, Fri J, Otigbu AC CA. Antimicrobial Susceptibility of Staphylococcus
1008 aureus Isolated from Recreational Waters and Beach Sand in Eastern Cape Province of South
1009 Africa. *Int J Environ Res public Heal* 2017; **1;14(9)**: 1001.

1010 30. Al-ashmawy MA, Sallam KI, Abd-elghany SM. Prevalence, Molecular Characterization, and
1011 Antimicrobial Susceptibility of Methicillin-Resistant Staphylococcus aureus Isolated from Milk
1012 and Dairy Products. *FOODBORNE Pathog Dis* 2016; **13**: 156–62.

1013 31. Iweriebor BC, Obi LC OA. Virulence and antimicrobial resistance factors of Enterococcus
1014 spp. isolated from fecal samples from piggery farms in Eastern Cape, South Africa. *BMC*
1015 *Microbiol* 2015; **15(1)**: 136.

1016 32. Katakweba AA, Møller KS, Muumba J, Muhairwa AP, Damborg P, Rosenkrantz JT, Minga
1017 UM, Mtambo MM OJ. Antimicrobial resistance in faecal samples from buffalo, wildebeest and
1018 zebra grazing together with and without cattle in Tanzania. *J Appl Microbiol* 2015; **118(4)**: 966–

1019 75.

1020 33. FDA. Antimicrobials Sold or Distributed for Use in Food-ProducingAnimals. Summary
1021 Report by the Food and Drug Administration Department of Health and Human Services.
1022 *Maryland, USA Adm* 2014.

1023 34. Van Boeckel TP, Brower C GM et al. Global trends in antimicrobial use in food animals.
1024 *Proc Natl Acad Sci* 2015; **112**: 5649–54.

1025 35. Zhang QQ, Ying GG PC et al. Comprehensive evaluation of antibiotics emission and fate in
1026 the river basins of China: source analysis,multimedia modeling, and linkage to bacterial
1027 resistance. *Env Sci Technol 2015;496772–82* 2015; **49**: 67772–82.

1028 36. Oliver SP MS. Antimicrobial resistance of mastitis pathogens. *Vet Clin Food Anim Pract*
1029 2012; **28(2)**: 165–85.

1030 37. Osei Sekyere J. Current State of Resistance to Antibiotics of Last-Resort in South Africa: a
1031 Review From a Public Health Perspective. *Front Public Heal* 2016; **4**: 209.

1032 38. Osei Sekyere J. Types and selling practices of antibiotics in veterinary shops in ashanti
1033 region, GHANA. *Int J Food, Agric Vet Sci* 2014; **4(2)**: 87–96.

1034 39. Osei Sekyere, John and FA. 'Prevalence of Multidrug Resistance among Salmonella enterica
1035 Serovar Typhimurium Isolated from Pig Faeces in Ashanti Region, Ghana.' *Int J Antibiot 2015*.

1036 40. Osei Sekyere J. 'Antibiotic types and handling practices in disease management among pig
1037 farms in Ashanti Region, Ghana.' *J Vet Med 2014*.

1038 41. Said MB, Abbassi MS, Gómez P, Ruiz-Ripa L, Sghaier S, Ibrahim C, Torres C HA.

1039 Staphylococcus aureus isolated from wastewater treatment plants in Tunisia: occurrence of
1040 human and animal associated lineages. *J water Heal* 2017; **15(4)**: 638–43.

1041 42. Ben Said L, Klibi N, Dziri R, Borgo F, Boudabous A, Ben Slama K TC. 'Prevalence,
1042 antimicrobial resistance and genetic lineages of Enterococcus spp. from vegetable food, soil and
1043 irrigation water in farm environments in Tunisia.' *J Sci Food Agric* 2016; **96(5):** 1627–33.

1044 43. Dziri R, Lozano C, Said LB, Bellaaj R, Boudabous A, Slama KB, Torres C KN. Multidrug-
1045 resistant enterococci in the hospital environment: detection of novel vancomycin-resistant E.
1046 faecium clone ST910. *J Infect Dev Countries* 2016; **10(08):** 799–806.

1047 44. Akindolire MA, Babalola OO AC. 'Detection of antibiotic resistant Staphylococcus aureus
1048 from milk: A public health implication.' *Int J Environ Res Public Health* 2015; **12**, no. **9**: 10254–
1049 10275.

1050 45. Ben Said L, Dziri R, Sassi N, Lozano C, Ben Slama K, Ouzari I, Torres C KN. Species
1051 distribution, antibiotic resistance and virulence traits in canine and feline enterococci in Tunisia.
1052 *Acta Vet Hungarica* 2017; **65(2)**: 173–84.

1053 46. El-Hamid MI BM. 'Comparative phenotypic and genotypic discrimination of methicillin
1054 resistant and susceptible Staphylococcus aureus in Egypt.' *Cell Mol Biol* 2015; **61**, no. **4**: 101–
1055 112.

1056 47. Mariem BJ, Ito T, Zhang M, *et al.* Molecular characterization of methicillin-resistant Panton-
1057 valentine leukocidin positive staphylococcus aureus clones disseminating in Tunisian hospitals
1058 and in the community. *BMC* 2013; **12**: 2.

1059 48. Ngbede EO, Raji MA, Kwanashie CN, Kwaga JK, Adikwu AA, Maurice NA AA.

1060 Characterization of high level ampicillin-and aminoglycoside-resistant enterococci isolated from
1061 non-hospital sources. *J Med Microbiol* 2017; **10;66(7)**: 1027–32.

1062 49. Iweriebor BC, Obi LC OA. Virulence and antimicrobial resistance factors of Enterococcus
1063 spp. isolated from fecal samples from piggery farms in Eastern Cape, South Africa. *BMC*
1064 *Microbiol* 2015; **15**: 136.

1065 50. Oumokhtar B, Elazhari M, Timinouni M, Bendahhou K, Bennani B, Mahmoud M, El Ouali
1066 Lalami A, Berrada S, Arrayhani M SHT. Staphylococcus aureus nasal carriage in a Moroccan
1067 dialysis center and isolates characterization. *Hemodial Int* 2013; **2**: 542–7.

1068 51. El Bayomi RM, Ahmed HA, Awadallah MA, Mohsen RA, Abd El-Ghafar AE AM.
1069 Occurrence, Virulence Factors, Antimicrobial Resistance, and Genotyping of Staphylococcus
1070 aureus Strains Isolated from Chicken Products and Humans. *VECTOR-BORNE ZOONOTIC Dis*
1071 2016; **16**: 157–64.

1072 52. Hashem RA, Yassin AS, Zedan HH, Amin MA. Fluoroquinolone resistant mechanisms in
1073 methicillin-resistant Staphylococcus aureus clinical isolates in Cairo , Egypt. *J Infect Dev Ctries*
1074 2013; **7**, no. **11**: 796–803.

1075 53. Osei Sekyere J. Current State of Resistance to Antibiotics of Last-Resort in South Africa: a
1076 Review From a Public Health Perspective. *Front Public Heal* 2016; **4**: 209.

1077 54. Alekshun MN LS. Molecular mechanisms of antibacterial multidrug resistance. *Cell* 2007;
1078 **128(6)**: pp.1037-1050.

1079 55. McKeegan KS, Borges-Walmsley MI WA. Microbial and viral drug resistance mechanisms.
1080 *Trends Microbiol* 2002; **10(10)**: s8–s14.

1081 56. Osei Sekyere J, Asante J. Emerging mechanisms of antimicrobial resistance in bacteria and
1082 fungi : advances in the era of genomics. *Future Microbiol* 2018; **13**: 1–22.

1083 57. Malachowa N DF. 'Mobile genetic elements of Staphylococcus aureus.' *Cell Mol life Sci*
1084 2010; **67.18**: 3057–3071.

1085 58. Roberts AP MP. 'Tn916-like genetic elements: a diverse group of modular mobile elements
1086 conferring antibiotic resistance.' *FEMS Microbiol Rev* 2011; **35**, no. **5**: 856–871.

1087 59. Frost LS, Leplae R, Summers AO TA. 'Mobile genetic elements: the agents of open source
1088 evolution.' *Nat Rev Microbiol* 2005; **3**, no. **9**: 722–732.

1089 60. Thomas CM NK. 'Mechanisms of, and barriers to, horizontal gene transfer between
1090 bacteria.' (2005): . *Nat Rev Microbiol* 2005; **3**, no. **9**: 711–21.

1091 61. Smillie C, Garcillán-Barcia MP, Francia MV, Rocha EP de la CF. 'Mobility of plasmids.'
1092 *Microbiol Mol Biol Rev* 2010; **74**, no. **3**: 434–452.

1093 62. Bernabé KJ, Langendorf C, Ford N, Ronat JB MR. Antimicrobial resistance in West Africa:
1094 a systematic review and meta-analysis. *Int J Antimicrob agents* 2017; **50(5)**: 629–39.

1095 63. Tadesse BT, Ashley EA, Ongarello S, *et al.* Antimicrobial resistance in Africa : a systematic
1096 review. *BMC Infect Dis* 2017; **17:616**: 1–17.

1097 64. Workneh M, Katz MJ, Lamorde M, Cosgrove SE MY. Antimicrobial Resistance of Sterile
1098 Site Infections in Sub-Saharan Africa: A Systematic Review. *Open forum Infect Dis*: ofx209).
1099 US: Oxford University Press.

1100 65. Schaumburg F, Alabi AS, Peters G BK. New epidemiology of Staphylococcus aureus

infection in Africa. Clinical. *Microbiol Infect* 2014; **20(7)**: 589–96.

66. Nejad SB, Allegranzi B, Syed SB, Ellis B PD. Health-care-associated infection in Africa: a systematic review. *Bull World Heal Organ* 2011; **89(10)**: 757–65.

67. Abdulgader SM, Shittu AO, Nicol MP KM. Molecular epidemiology of Methicillin-resistant Staphylococcus aureus in Africa: a systematic review. *Front Microbiol* 2015; **6**: 348.

68. Hraoui M, Boubaker IB, Rachdi M, Slim A RS. Macrolide and tetracycline resistance in clinical strains of Streptococcus agalactiae isolated in Tunisia. *J Med Microbiol* 2017; **61**: 1109–13.

69. Hraoui M, Boubaker IB, Doloy A, Redjeb SB BA. Molecular Mechanisms of Tetracycline and Macrolide Resistance and emm Characterization of Streptococcus pyogenes Isolates in Tunisia. *Microb Drug Resist* 2011; **17(3)**: 377–82.

70. Fischer A, Liljander A, Kaspar H, Muriuki C, Fuxelius HH, Bongcam-Rudloff E, de Villiers EP, Huber CA, Frey J, Daubenberger C BR. Camel Streptococcus agalactiae populations are associated with specific disease complexes and acquired the tetracycline resistance gene tetM via a Tn 916 -like element Camel Streptococcus agalactiae populations are associated with specific disease complex. *Vet Res 2013*, 2013; **44:86**.

71. Elhani D, Klibi N, Dziri R, Hassan MB, Mohamed SA, Said LB, Mahjoub A, Slama KB, Jemli B, Bellaj R BF. 'vanA-containing E. faecium isolates of clonal complex CC17 in clinical and environmental samples in a Tunisian hospital.' *Diagn Microbiol Infect Dis* 2014; **79**, no. **1**: 60–63. Available at: http://dx.doi.org/10.1016/j.diagmicrobio.2014.01.011.

72. Dziri R, Lozano C, Said LB, Bellaaj R, Boudabous A, Slama KB, Torres C KN. 'Multidrug-

1122 resistant enterococci in the hospital environment: detection of novel vancomycin-resistant E.
1123 faecium clone ST910.' *J Infect Dev Ctries* 2016; **10**, no. **8**: 799–806.

1124 73. Mensah SE, Koudande OD, Sanders P, Laurentie M, Mensah GA AF. Antimicrobial residues
1125 in foods of animal originin Africa: public health risks. *RevSciTech* 2014; **33**: ,987–996.

1126 74. O'Neill J. Antimicrobials in Agriculture and the Environment: Reducing Unnecessary Use
1127 and Waste-The Review on Antimicrobial Resistance. 2015.

1128 75. da Costa PM, Loureiro L MA. Transfer of multi-drug resistant bacteria between intermingled
1129 ecological niches: the interface between humans, animals and the environment. *Int J Environ Res*
1130 *Public Health* 2013; **10,**: 278–294. Available at: .doi:10.3390/ijerph10010278.

1131 76. Holmes AH, Moore LS, Sundsfjord A, Steinbakk M, Regmi S, Karkey A, Guerin PJ PL.
1132 Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet* 2016; **387,**: 176–
1133 187. Available at: doi:10.1016/S0140-6736(15)00473-0.

1134 77. Hueston W, Appert J, Denny T, King L, Umber J VL. Assessing global adoption of one
1135 health approaches. *Ecohealth* 2013; **10:** 228–33. Available at: doi:10.1007/%0As10393-013-
1136 0851-5.

1137 78. Parmley J, Leung Z, Léger D, Finley R, Irwin R, Pintar K, Pollari F, Reid-Smith R, Waltner-
1138 Toews D, Karmali M ER. One health and food safety- The Canadian experience: a holistic
1139 approach toward enteric bacterial pathogens and antimicrobial resistance surveillance. In:
1140 Institute of Medicine (US). Improving Food Safety through a One Health Approach: Workshop
1141 Summary. *Natl Acad Press Washington, DC, USA* 2012.

1142 79. Djoudi F, Benallaoua S, Aleo A, Touati A, Challal M, Bonura C MC. Descriptive

1143 Epidemiology of Nasal Carriage of Staphylococcus aureus and Methicillin-Resistant
1144 Staphylococcus aureus Among Patients Admitted at Two Healthcare Facilities in Algeria.
1145 *Microb Drug Resist* 2014; **21(2):** 218–23.

1146 80. van Rensburg MJ, Whitelaw AC EB. Genetic basis of rifampicin resistance in methicillin-
1147 resistant Staphylococcus aureus suggests clonal expansion in hospitals in Cape. *BMC Microbiol*
1148 2012; **12**: 46.

1149 81. Boeck H De, Vandendriessche S, Hallin M, Batoko B, Alworonga J. Staphylococcus aureus
1150 nasal carriage among healthcare workers in Kisangani , the Democratic Republic of the Congo.
1151 *Eur J Clin Microbiol Infect Dis* 2015; **34(8)**: 1567–72.

1152 82. Fall C, Seck A, Richard V, Ndour M, Sembene M, Laurent F BS. Epidemiology of
1153 Staphylococcus aureus in Pigs and Farmers in the Largest Farm in Dakar , Senegal. *FOOD*
1154 *BORNE Pathog Dis* 2012; **9**: 962–5.

1155 83. Stefani S, Chung DR, Lindsay JA, Friedrich AW, Kearns AM, Westh H MF. 'Meticillin-
1156 resistant Staphylococcus aureus (MRSA): global epidemiology and harmonisation of typing
1157 methods.' *Int J Antimicrob Agents* 2012; **39**, no. **4**: 273–282.

1158 84. Song JH, Hsueh PR, Chung DR, Ko KS, Kang CI, Peck KR et al. Spread of methicillin-
1159 resistant Staphylococcus aureus between the community and the hospitals in Asian. *J Antimicrob*
1160 *Chemother 2011* 2011; **66**: 1061–9.

1161 85. Lochan H, Moodley C, Rip D, Bamford C, Hendricks M, Davidson A EB. 'Emergence of
1162 vancomycin-resistant Enterococcus at a tertiary paediatric hospital in South Africa.' *SAMJ South*
1163 *African Med J* 2016; **106**, no. **6**: 562–566.

1164 86. Udo EE, Pearman JW GW. Genetic analysis of community isolates of methicillin-resistant
1165 Staphylococcus aureus in Western Australia. *J Hosp Infect* 1993; **25**: 97–108.

1166 87. Salgado CD, Farr BM CD. Community-acquired methicillin-resistant Staphylococcus aureus:
1167 a meta-analysis of prevalence and risk factors. *Clin Infect Dis 2003, 36* 2003; **36**: 131–139.

1168 88. Hiramatsu K, Okuma K, Ma XX, Yamamoto M, Hori S et al: New trends in Staphylococcus
1169 aureus infections: glycopeptide resistance in hospital and methicillin resistance in the
1170 community. *Curr Opin Infect Dis 2002, 15* 2002; **15**: 407–\413.

1171 89. Chambers H. The changing epidemiology of Staphylococcus aureus? *Emerg Infect Dis* 2001;
1172 **7**: 178–182.

1173 90. Diekema DJ, Pfaller MA, Schmitz FJ, Smayevsky J, Bell J et al. Survey of infections due to
1174 Staphylococcus species: frequency of occurrence and antimicrobial susceptibility of isolates
1175 collected in the United States, Canada, Latin America, Europe, and the Western Pacific region
1176 for the SENTRY Antimicrobial Surveillanc. *Clin Infect Dis* 2001; **32 Suppl 2**: S114–132.

1177 91. NNIS. National Nosocomial Infections Surveillance (NNIS) System Report, data summary
1178 from January 1992 through June 2004. *Am J Infect Control* 2004; **2**: 470–485.

1179 92. Katayama Y, Ito T HK. A new class of genetic element, staphylococcus cassette
1180 chromosome mec, encodes methicillin resistance in Staphylococcus aureus. *Antimicrob agents*
1181 *Chemother* 2000; **44(6):** 1549–55.

1182 93. Akinkunmi E LA. Species distribution and antibiotic resistance in coagulase-negative
1183 staphylococci colonizing the gastrointestinal tract of children in Ile-Ife, Nigeria. *Trop J Pharm*
1184 *Res* 2010; **9(1)**: 35–43.

1185 94. Archer GL CM. Antimicrobial susceptibility of coagulase-negative staphylococci.
1186 *Antimicrob Agents Chemother* 1994; **38**: 2231–2237.

1187 95. Hashem YA, Yassin AS AM. Molecular characterization of Enterococcus spp. clinical
1188 isolates from Cairo, Egypt. *Indian J Med Microbiol* 2015; **33(5)**: p.80.

1189 96. Rachdi M, Boubaker IB, Moalla S, *et al.* Phenotypic and genotypic characterization of
1190 macrolide resistant Streptococcus pneumoniae in Tunisia ´ risation phe ´ notypique et ge ´
1191 notypique des souches Caracte ´ es en Tunisie de Streptococcus pneumoniae isole. 2008; **56**:
1192 125–9.

1193 97. Wolter N, Gottberg A Von, Gouveia L De, Klugman KP. Molecular basis and clonal nature
1194 of increasing pneumococcal macrolide resistance in South Africa , 2000 – 2005. *Int J Antimicrob*
1195 *Agents* 2008; **32**: 2000–5.

1196 98. Hancock RE. Mechanisms of action of newer antibiotics for Gram-positive pathogens.
1197 *Lancet Infect Dis* 2005; **5**: 209–18.

1198 99. WHO. Tackling Antibiotic Resistance from a Food Safety Perspective in Europe. *WHO-*
1199 *Europe, Denmark* 2011: 1–88.

1200 100. Cavaco LM AF. 'Resistance in bacteria of the food chain: epidemiology and control
1201 strategies.' *Microb Drug Resist Futur Med Ltd, Brastislava, Slovakia* 2013: 136–158.

1202 101. Ouchenane Z, Agabou A, Smati F, Rolain JM RD. Staphylococcal cassette chromosome
1203 mec characterization of methicillin-resistant Staphylococcus aureus strains isolated at the
1204 military hospital of Constantine / Algeria ´ risation des cassettes chromosomiques mec
1205 staphylococciques des souches Caracte ` l. *Pathol Biol* 2013; **61**: 280–1.

1206 102. Omuse G, Zyl KN Van, Hoek K, Abdulgader S, Kariuki S, Whitelaw A. Molecular
1207 characterization of Staphylococcus aureus isolates from various healthcare institutions in Nairobi
1208 , Kenya : a cross sectional study. *Ann Clin Microbiol Antimicrob* 2016; **15:51**: 1–9.

1209 103. Perovic O, Iyaloo S, Kularatne R, Lowman W. Prevalence and Trends of Staphylococcus
1210 aureus Bacteraemia in Hospitalized Patients in South Africa , 2010 to 2012 : Laboratory- Based
1211 Surveillance Mapping of Antimicrobial Resistance and Molecular Epidemiology. *PLoS One*
1212 2015: 1–14.

1213 104. Stokes HW GM. 'Gene flow, mobile genetic elements and the recruitment of antibiotic
1214 resistance genes into Gram-negative pathogens.' *FEMS Microbiol Rev* 2011; **35**, no. **5**: 790–819.

1215 105. Gogarten JP TJ. 'Horizontal gene transfer, genome innovation and evolution.' *Nat Rev*
1216 *Microbiol* 2005; **3**, no. **9**: 679–687.

1217 106. Bouchami O, Hassen AB, De Lencastre H MM. High prevalence of mec complex C and
1218 ccrC is independent of SCC mec type V in Staphylococcus haemolyticus. *Eur J Clin Microbiol*
1219 *Infect Dis* 2012; **31**: 605–14.

1220 107. Gharsa H, Slama KB, Lozano C, Gómez-Sanz E, Klibi N, Sallem RB, Gómez P, Zarazaga
1221 M, Boudabous A TC. Prevalence, antibiotic resistance, virulence traits and genetic lineages of
1222 Staphylococcus aureus in healthy sheep in Tunisia. Veterinary microbiol. *Vet Microbiol* 2012;
1223 **156(3)**: pp.367-373.

1224 108. Bergal A, Loucif L, Benouareth DE, Bentorki AA, Abat C RJ. Molecular epidemiology and
1225 distribution of serotypes, genotypes, and antibiotic resistance genes of Streptococcus agalactiae
1226 clinical isolates from Guelma, Algeria and Marseille, France. European Journal of Clinical

1227 Microbiology & Infectious Disea. *Eur J Clin Microbiol Infect Dis* 2015; **34**, no. **12**: 2339–48.

1228 109. Djahmi N, Boutet-Dubois A, Nedjai S, Dekhil M, Sotto A LJ. Molecular epidemiology of
1229 Enterococcus sp . isolated in a university hospital in Algeria. *Scand J Infect Dis* 2012; **2011**:
1230 656–62.

1231 110. Conceição T, Coelho C, de Lencastre H A-SM. Frequent occurrence of oxacillin-susceptible
1232 mecA -positive Staphylococcus aureus (OS-MRSA) strains in two African countries ´. *J*
1233 *Antimicrob Chemother 2015;* 2015; **70**: 3200–4.

1234 111. Elhani D, Gharsa H, Kalai D, Lozano C, Gómez P, Boutheina J, Aouni M, Barguellil F,
1235 Torres C SK. 'Clonal lineages detected amongst tetracycline-resistant meticillin-resistant
1236 Staphylococcus aureus isolates of a Tunisian hospital, with detection of lineage ST398.' *J Med*
1237 *Microbiol* 2015; **64**, no. **6**: 623–629.

1238 112. Abdel-moein KA, El-Hariri M SA. Methicillin-Resistant Staphylococcus aureus : An
1239 Emerging Pathogen of Pets in Egypt with a Public Health Burden. *Transbound Emerg Dis* 2012;
1240 **59**: 331–5.

1241 113. Fowoyo PT, Ogunbanwo ST. Antimicrobial resistance in coagulase - negative staphylococci
1242 from Nigerian traditional fermented foods. *Ann Clin Microbiol Antimicrob* 2017; **16:4**: 1–7.

1243 114. Nurjadi D, Olalekan AO, Layer F, Shittu AO, Alabi A, Ghebremedhin B, Schaumburg F,
1244 Hofmann-Eifler J, Van Genderen PJ, Caumes E FR. Emergence of trimethoprim resistance gene
1245 dfrG in Staphylococcus aureus causing human infection and colonization in sub-Saharan Africa
1246 and its import to Europe. *J Antimicrob Chemother* 2014; **27**: 2361–8.

1247 115. O'Malley SM, Emele FE, Nwaokorie FO, Idika N, Umeizudike AK, Emeka-Nwabunnia I,

1248 Hanson BM, Nair R, Wardyn SE ST. Molecular typing of antibiotic-resistant Staphylococcus
1249 aureus in Nigeria. *J Infect Public Health* 2015; **8**: 187–93. Available at:
1250 http://dx.doi.org/10.1016/j.jiph.2014.08.001.

1251 116. Shittu A, Oyedara O, Abegunrin F, Okon K, Raji A, Taiwo S, Ogunsola F, Onyedibe K EG.
1252 Characterization of methicillin-susceptible and -resistant staphylococci in the clinical setting : a
1253 multicentre study in Nigeria. *BMC Infect Dis* 2012; **12(1):** 286.

1254 117. Vitali LA, Petrelli D, Lamikanra A, Prenna M, Akinkunmi EO. Diversity of antibiotic
1255 resistance genes and staphylococcal cassette chromosome mec elements in faecal isolates of
1256 coagulase-negative staphylococci from Nigeria. *BMC Microbiol* 2014; **14:106**.

1257 118. Adegoke AA, Okoh AI. Species diversity and antibiotic resistance properties of
1258 Staphylococcus of farm animal origin in Nkonkobe Municipality , South Africa. *FoliaMicrobiol*
1259 2014; **59**: 133–40.

1260 119. Khalil W, Hashwa F, Shihabi A TS. Methicillin-resistant Staphylococcus aureus ST80-IV
1261 clone in children from Jordan.. *Diagn Microbiol Infect Dis* 2012; **73:** 228–230.

1262 120. Udo EE SE. The dissemination of ST80-SCCmec-IV community-associated methicillin
1263 resistant Staphylococcus aureus clone in Kuwait hospitals. *Ann Clin Microbiol Antimicrob* 2010;
1264 **9**: 1–7.

1265 121. Ahmed EF, Gad GF, Abdalla AM, Hasaneen AM AS. Prevalence of Methicillin Resistant
1266 Staphylococcus aureus among Egyptian Patients after Surgical interventions. *Surg Infect*
1267 *(Larchmt)* 2014; **15**: 404–11.

1268 122. Osman K, Alvarez-Ordóñez A, Ruiz L, Badr J, ElHofy F, Al-Maary KS, Moussa IM,

1269 Hessain AM, Orabi A, Saad A EM. Antimicrobial resistance and virulence characterization of
1270 Staphylococcus aureus and coagulase-negative staphylococci from imported beef meat. *Ann Clin*
1271 *Microbiol Antimicrob* 2017; **16(1)**: 35.

1272 123. Perveen I, Majid A, Knawal S, Naz I, Sehar S, Ahmed S RM. Biochemical characters and
1273 antibiotic susceptibility of S. aureus isolates. *Asian Pac J Trop Biomed* 2011; **1**: 212–216.

1274 124. Perveen, I., Majid, A., Knawal, S., Naz, I., Sehar, S. A, S. and Raza MA. Prevalence and
1275 antimicrobial susceptibility pattern of methicillin-resistant Staphylococcus aureus and
1276 coagulasenegative staphylococci in Rawalpindi, Pakistan. *Br J Med Med Res* 2013; **3**: 198–209.
1277 Available at: doi: 10.9734/%0ABJMMR/2013/2109.

1278 125. Dziri R, Klibi N, Lozano C, *et al.* High prevalence of Staphylococcus haemolyticus and
1279 Staphylococcus sapro- phyticus in environmental samples of a Tunisian hospital. *Diagn*
1280 *Microbiol Infect Dis* 2016; **85.2**: 136–140. Available at:
1281 http://dx.doi.org/10.1016/j.diagmicrobio.2016.03.006.

1282 126. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA ER, Lemons JA, Donovan EF,
1283 Stark AR, Tyson JE, Oh W BC, Korones SB, Shankaran S, Laptook AR, Stevenson DK, Papile
1284 LA P, WK. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD
1285 Neonatal Research Network. *J Pediatr* 2002; **110**: 285–291.

1286 127. Cui S, Li J, Hu C, Jin S, Li F, Guo Y, Ran LU MY. Isolation and characterization of
1287 methicillin-resistant Staphylococcus aureus from swine and workers in China. *J Antimicrob*
1288 *Chemother* 2009; **64**: 680–683.

1289 128. Jiménez JN, Vélez LA, Mediavilla JR, Ocampo AM, Vanegas JM, Rodríguez EA,

1290 Kreiswirth BN CM. Livestock-associated methicillin-susceptible Staphylococcus aureus ST398
1291 infection in woman, Colombia. *Emerg Infect Dis* 2011; **17**: 1970–1971.

1292 129. Khanna T, Friendship R, Dewey C WJ. Methicillin resistant Staphylococcus aureus
1293 colonization in pigs and pig farmers. *Vet Microbiol* 2008; **128**: 298–303.

1294 130. Smith TC, Male MJ, Harper AL, Kroeger JS, Tinkler GP, Moritz ED, Capuano AW,
1295 Herwaldt LA DD. Methicillin-resistant Staphylococcus aureus (MRSA) strain ST398 is present
1296 in midwestern U.S. swine and swine workers. *PLoS One* 2009; **4,**: e4258.

1297 131. Maalej SM, Malbruny B, Leclercq R HA. Emergence of Staphylococcus aureus strains
1298 resistant to pristinamycin in Sfax (Tunisia). *Pathol Biol* 2012; **60**: e71–4. Available at:
1299 http://dx.doi.org/10.1016/j.patbio.2011.10.012.

1300 132. Bouchami O, Hassen AB, De Lencastre H MM. High prevalence of mec complex C and
1301 ccrC is independent of SCCmec type V in Staphylococcus haemolyticus. *Eur J Clin Microbiol*
1302 *Infect Dis* 2012; **31(4)**: 605–614.

1303 133. Tabe Y, Nakamura A, Oguri T IJ. Molecular characterization of epidemic multiresistant
1304 Staphylococcus haemolyticus isolates. *Diagn Microbiol Infect Dis* 1998; **32**: 177–183.

1305 134. Santos Sanches I, Mato R, de Lencastre H, Tomasz A C, Collaborators C and the I. Patterns
1306 of multidrug resistance among methicillin-resistant hospital isolates of coagulase-positive and
1307 coagulase-negative staphylococci collected in the international multicenter study RESIST in
1308 1997 and 1998. *Microb Drug Resist* 2000; **6**: 199–211.

1309 135. Al-haddad OH, Zorgani A GK. Nasal Carriage of Multi-Drug Resistant Panton-Valentine
1310 Leucocidin-Positive Methicillin-Resistant Staphylococcus aureus in Children in Tripoli-Libya.

2014; **90**: 724–7.

136. Egyir B, Guardabassi L, Sørum M, Nielsen SS, Kolekang A, Frimpong E, Addo KK, Newman MJ LA. Molecular epidemiology and antimicrobial susceptibility of clinical Staphylococcus aureus from healthcare institutions in Ghana. *PLoS One*, 2014; **9(2)**: p.e89716.

137. Egyir B, Guardabassi L, Monecke S, Kwasi K, Jemima M, Rhod A. Resistance Methicillin-resistant Staphylococcus aureus strains from Ghana include USA300. *J Glob Antimicrob Resist* 2015; **3**: 26–30. Available at: http://dx.doi.org/10.1016/j.jgar.2014.11.006.

138. Bouchami O, Ben Hassen A, de Lencastre H MM. High prevalence of mec complex C and ccrC is independent of SCCmec type V in Staphylococcus haemolyticus. *Eur J Clin Microbiol Infect Dis* 2012; **31(4)**: 605–614.

139. Shittu A, Oyedara O, Abegunrin F, Okon K, Raji A, Taiwo S, Ogunsola F, Onyedibe K EG. 'Characterization of methicillin-susceptible and-resistant staphylococci in the clinical setting: a multicentre study in Nigeria.' *BMC Infect Dis* **12**, no. **1**: 286.

140. Naber KG, Schito G, Botto H, Palou J MT. Surveillance Study in Europe and Brazil on Clinical Aspects and Antimicrobial Resistance Epidemiology in Females with Cystitis (ARESC): Implications for Empiric Therapy. *Eur Urol* 2008; **54:** 1164–1178. Available at: doi: 10.1016/j.eururo.2008.05.010 PMID: 18511178.

141. Conceição T, Coelho C, Silva IS, de Lencastre H A-SM. Staphylococcus aureus in former Portuguese colonies from Africa and the Far East: missing data to help fill the world map. *Clin Microbiol Infect* 2015; **21(9)**: 842–e1.

142. Jensen SO LB. Genetics of antimicrobial resistance in Staphylococcus aureus. *Futur*

Microbiol 2009; **4**: 565–82.

143. Frey KM, Lombardo MN, Wright DL AA. Towards the understanding of resistance mechanisms in clinically isolated trimethoprim-resistant, methicillin-resistant Staphylococcus aureus dihydrofolate reductase. *J Struct Biol* 2010; **170**: 93–7.

144. Kadlec K, Fessler AT, Hauschild T SS. Novel and uncommon antimicrobial resistance genes in livestock-associated methicillinresistant Staphylococcus aureus. *Clin Microbiol Infect* 2012; **18**: 745–55.

145. Badri M, Ehrlich R, Wood R MG. Initiating co-trimoxazole prophylaxis in HIV-infected patients in Africa: an evaluation of the provisional WHO/UNAIDS recommendations. . *AIDs* 2001; **15(9)**: 1143–8.

146. Phaku P, Lebughe M, Strauß L, *et al.* Unveiling the molecular basis of antimicrobial resistance in Staphylococcus aureus from the Democratic Republic of the Congo using whole genome sequencing. *Clin Microbiol Infect* 2016. Available at: http://dx.doi.org/10.1016/j.cmi.2016.04.009.

147. Vandendriessche S, De Boeck H, Deplano A, Phoba MF, Lunguya O, Falay D, Dauly N, Verhaegen J, Denis O JJ. Characterisation of Staphylococcus aureus isolates from bloodstream infections, Democratic Republic of the Congo. *Eur J Clin Microbiol Infect Dis* 2017; **36(7)**: 1163–71.

148. Asiimwe BB, Baldan R, Trovato A CD. Prevalence and molecular characteristics of Staphylococcus aureus, including methicillin resistant strains, isolated from bulk can milk and raw milk products in pastoral communities of South-West Uganda. *BMC Infect Dis* 2017; **17(1)**:

422.

149. Seni J, Bwanga F, Najjuka CF, Makobore P, Okee M, Mshana SE, Kidenya BR, Joloba ML KD. Molecular Characterization of Staphylococcus aureus from Patients with Surgical Site Infections at Mulago Hospital in Kampala , Uganda. 2013; **8**: 1–7.

150. Conceiçao T, Coelho C, Santos-Silva I, de Lencastre H A-SM. Epidemiology of methicillin-resistant and-susceptible Staphylococcus aureus in Luanda, Angola: first description of the spread of the MRSA ST5-IVa clone in the African continent. *Microb Drug Resist* 2014; **20(5):** 441–9.

151. Conceição T, Coelho C, de Lencastre H A-SM. Frequent occurrence of oxacillin-susceptible mecA-positive Staphylococcus aureus (OS-MRSA) strains in two African countries. *J Antimicrob Chemother* 2015; **70(12):** 3200–4.

152. Hososaka Y, Hanaki H EH et al. Characterization of oxacillinsusceptible mecA-positive Staphylococcus aureus: a new type of MRSA. *J Infect Chemother* 2007; **13:** 79–86.

153. Petinaki E, Kontos F MA. Emergence of two oxacillin-susceptible mecA-positive Staphylococcus aureus clones in a Greek hospital. *J Antimicrob Chemother* 2002; **50:** 1090–1.

154. Pu W, Su Y LJ et al. High incidence of oxacillin-susceptible mecA-positive Staphylococcus aureus (OS-MRSA) associated with bovine mastitis in China. *PLoS One* 2014; **9:** e88134.

155. Corrente M, Normanno G, Martella V, Bellacicco AL, Quaglia NC, Dambrosio A, Buonavoglia D, D'Abramo M BC. Comparison of methods for the detection of methicillin resistance in Staphylococcus aureus isolates from food products. *Lett Appl Microbiol* 2007; **45**: 535–9.

156. Meeren BT, Millard PS, Scacchetti M, Hermans MH, Hilbink M, Concelho TB, Ferro JJ WP. Emergence of methicillin resistance and Panton-Valentine leukocidin positivity in hospital- and community-acquired Staphylococcus aureus infections in Beira , Mozambique. *Trop Med Int Heal Vol* 2013; **0**.

157. De Angelis G, Cipriani M, Cauda R TE. Treatment of skin and soft tissue infections due to community-associated methicillin-resistant Staphylococcus aureus in Europe: the role of trimethoprim-sulfamethoxazole. *Clin Infect Dis author reply 2* 2011; **52**: 1471–2.

158. Chua K, Laurent F CG et al. Antimicrobial resistance: not community-associated methicillin-resistant Staphylococcus aureus (CA-MRSA)! A clinician's guide to community MRSA—its evolving antimicrobial resistance and implications for therapy. *Clin Infect Dis* 2011; **52**: 99–114.

159. Marais E, Aithma N, Perovic O, Oosthuysen WF, Musenge E DA. Antimicrobial susceptibility of methicillin-resistant Staphylococcus aureus isolates from South Africa. . *SAMJ* 2009; **99**: 170–3.

160. Shittu AO LJ. Antimicrobial susceptibility patterns and characterization of clinical isolates of Staphylococcus aureus in KwaZulu-Natal province, South Africa. *BMC Infect Dis* 2006; **6**: 125.

161. Wichelhaus TA, Schafer V, Brade V BB. Molecular characterization of rpoB mutations conferring cross-resistance to rifamycins on methicillin-resistant Staphylococcus aureus. *Antimicrob Agents Chemother* 1999; **43**: 2813–2816.

162. Perovic O, Singh-Moodley A, Govender NP, Kularatne R, Whitelaw A, Chibabhai V,

1395 Naicker P, Mbelle N, Lekalakala R, Quan V SC. A small proportion of community-associated
1396 methicillin-resistant Staphylococcus aureus bacteraemia, compared to healthcare-associated
1397 cases, in two South African provinces. *Eur J Clin Microbiol Infect Dis* 2017; **36(12)**: 2519–32.

1398 163. Amoako DG, Bester LA, Somboro AM, Baijnath S, Govind CN, Essack SY. Plasmid-
1399 mediated resistance and virulence mechanisms in the private health sector in KwaZulu-Natal ,
1400 South Africa : An investigation of methicillin resistant Staphylococcus aureus (MRSA) clinical
1401 isolates col. *Int J Infect Dis* 2016; **46**: 38–41.

1402 164. Sit PS, Teh CS, Idris N, Sam IC, Syed Omar SF SH, Thong KL, Kamarulzaman A PS.
1403 Prevalence of methicillin-resistant Staphylococcus aureus (MRSA) infection and the molecular
1404 characteristics of MRSA bacteraemia over a two-year period in a tertiary teaching hospital in
1405 Malaysia. *BMC Infect Dis* 2017; **17**: 274.

1406 165. Antiabong JF, Kock MM, Bellea NM EM. Diversity of Multidrug Efflux Genes and
1407 Phenotypic Evaluation of the In vitro Resistance Dynamics of Clinical Staphylococcus Aureus
1408 Isolates Using Methicillin; a Model β-lactam. *open Microbiol journal* 2017; **11:** 132–41.

1409 166. Conceiçao T, Santos Silva I, de Lencastre H A-SM. Staphylococcus aureus nasal carriage
1410 among patients and health care workers in Sao Tome and Principe. *Microb Drug Resist* 2014;
1411 **20(1)**: 57–66.

1412 167. Sadowy E, Matynia B HW. Population structure, virulence factors and resistance
1413 determinants of invasive, noninvasive and colonizing Streptococcus agalactiae in Poland. *J*
1414 *Antimicrob Chemother* 2010; **65(9)**: 1907–1914.

1415 168. Bohnsack JF, Whiting A, GottschalkM, DunnDM, Weiss R A, PH, Philips JB 3rd, Weisman

LE, Rhoads GG LF. Population structure of invasive and colonizing strains of Streptococcus agalactiae from neonates of six U.S. Academic Centers from 1995 to 1999. *J Clin Microbiol* 2010; **46(4):** 1285–1291.

169. Shabayek S, Abdalla S. Macrolide- and tetracycline-resistance determinants of colonizing group B streptococcus in women in Egypt. *J Med Microbiol* 2014; **63**: 1324–7.

170. Verani, J. R., McGee, L., Schrag SJ. Prevention of perinatal group B streptococcal disease— revised guidelines from CDC, 2010. *MMWR Recomm Rep* 2010; **59 (RR-10)**: 1–36.

171. Rachdi M, Boubaker IB, Hraoui M RS. High rates of macrolide resistance among clinical isolates of Streptococcus agalactiae in Tunisia. *Arch Inst Pasteur Tunis* 2010; **87(1/2)**: p.35.

172. Hraoui M, Boubaker IB, Doloy A, Redjeb SB BA. 'Molecular mechanisms of tetracycline and macrolide resistance and emm characterization of Streptococcus pyogenes isolates in Tunisia.' *Microb Drug Resist* 2011; **17**, no. **3**: 377–382.

173. Ksia S, Smaoui H, Hariga D KA. Biotypes and antimicrobial susceptibility of Streptococcus pyogenes strains isolated in children in Tunis. *Bull la Société Pathol Exot* 2010; **103(2)**: pp.69-74.

174. Fischer A, Liljander A, Kaspar H, Muriuki C, Fuxelius HH, Bongcam-Rudloff E, de Villiers EP, Huber CA, Frey J, Daubenberger C BR. 'Camel Streptococcus agalactiae populations are associated with specific disease complexes and acquired the tetracycline resistance gene tetM via a Tn 916-like element.' *Vet Res* 2013; **44**, no. **1**: 86.

175. Bolukaoto JY, Monyama CM, Chukwu MO, Lekala SM, Nchabeleng M, Maloba MR, Mavenyengwa RT, Lebelo SL, Monokoane ST, Tshepuwane C MS. Antibiotic resistance of

1437 Streptococcus agalactiae isolated from pregnant women in Garankuwa , South Africa. *BMC Res*
1438 *Notes* 2015: 6–12.

1439 176. Djahmi N, Boutet-Dubois A, Nedjai S, Dekhil M, Sotto A LJ. Molecular epidemiology of
1440 Enterococcus sp. isolated in a university hospital in Algeria. *Scand J Infect Dis* 2012; **44(9),.**:
1441 pp.656-662.

1442 177. Matsushima A, Takakura S, Yamamoto M, Matsumura Y, Shirano M, Nagao M, Ito Y,
1443 Iinuma Y, Shimizu T, Fujita N IS. Regional spread and control of vancomycin-resistant
1444 Enterococcus faecium and Enterococcus faecalis in Kyoto, Japan. *Eur J Clin Microbiol Infect*
1445 *Dis* 2011.

1446 178. Fallico L, Boldrin C, Grossato A, Franchin E DCE, Tommasini T et al. Molecular
1447 epidemiology of Enterococcus faecium isolates from an Italian hospital. *Infection* 2011; **39**: 127
1448 – 33.

1449 179. Hsieh YC, Lee WS, Ou TY HP. Clonal spread of CC17 vancomycin-resistant Enterococcus
1450 faecium with multilocus sequence type 78 (ST78) and a novel ST444 in Taiwan. *Eur J Clin*
1451 *Microbiol Infect Dis* 2010; **29**: 25 – 30.

1452 180. Mardassi, Boutheina Ben Abdelmoumen, Nadhem Aissani, Imed Moalla, Douaa Dhahri,
1453 Abir Dridi and BM. 'Evidence for the predominance of a single tet (M) gene sequence type in
1454 tetracycline-resistant Ureaplasma parvum and Mycoplasma hominis isolates from Tunisian
1455 patients.' *J Med Microbiol* 2012; **61**, no. **9**: 1254–61.

1456 181. Said LB, Klibi N, Lozano C, Dziri R, Slama KB, Boudabous A TC. 'Diversity of
1457 enterococcal species and characterization of high-level aminoglycoside resistant enterococci of

1458 samples of wastewater and surface water in Tunisia.' . *Sci Total Environ* 2015; **530**: 11–7.

1459 182. Klibi N, Lagha AB, Slama KB, Boudabous A TC. 'Faecal enterococci from camels in
1460 Tunisia: species, antibiotic resistance and virulent genes.' *Vet Rec* 2013; **172**, : 213–213.

1461 183. Klibi N, Said LB, Jouini A, Slama KB, López M, Sallem RB, Boudabous A TC. 'Species
1462 distribution, antibiotic resistance and virulence traits in enterococci from meat in Tunisia.'
1463 (2013): . *Meat Sci* 2013; **93**, no. **3**: 675–80.

1464 184. Iweriebor, Benson C., Larry C. Obi and AIO. 'Virulence and antimicrobial resistance
1465 factors of Enterococcus spp. isolated from fecal samples from piggery farms in Eastern Cape,
1466 South Africa.' *BMC Microbiol* **15**, no. **1**: 136.

1467 185. Al-haddad OH, Zorgani A GK. Nasal Carriage of Multi-Drug Resistant Panton-Valentine
1468 Leucocidin-Positive Methicillin-Resistant Staphylococcus aureus in Children in Tripoli-Libya.
1469 *Am J Trop Med Hyg* 2014; **90**: 724–7.

1470 186. Ayepola OO, Olasupo NA, Egwari LO, Becker K. Molecular Characterization and
1471 Antimicrobial Susceptibility of Staphylococcus aureus Isolates from Clinical Infection and
1472 Asymptomatic Carriers in Southwest Nigeria. *PLoS One* 2015; **2304**: 4–11. Available at:
1473 http://dx.doi.org/10.1371/journal.pone.0137531.

1474 187. Mbelle NM, Maningi NE, Tshisevhe V, Modipane L, Amoako DG SJ. First Report of a
1475 Whole-Genome Shotgun Sequence of a Clinical Enterococcus faecalis Sequence Type 6 Strain
1476 from South Africa. *Genome Announc* 2017; **5(50)**: e01382-17.

1477 188. Mbelle NM, Maningi NE, Tshisevhe V, Modipane L, Amoako DG SJ. Draft Genome
1478 Sequence of a Clinical Enterococcus faecium Sequence Type 18 Strain from South Africa.

Genome Announc 2017; **5(48)**: e01381–17.

189. Kullin, B., T. Brock, N. Rajabally, F. Anwar, G. Vedantam, S. Reid, and V. Abratt. "Characterisation of Clostridium difficile strains isolated from Groote Schuur Hospital, Cape Town SA. ." European journal of clinical microbiology & infectious diseases: *Off Publ Eur Soc Clin Microbiol* 2016; **35**, no. **10**: 1709–18.

190. Marzouk M, Ferjani A, Amamou S, Alibi S, Ali MH BJ. 'Phenotype, genotype, and serotype distribution of macrolide resistant invasive and non-invasive Streptococcus pneumoniae strains, in Sousse, Tunisia.' *Med Mal Infect* 2014; **44**, no. **10**: 478–482.

191. Bouchami O, Achour W HA. 'Prevalence of resistance phenotypes and genotypes to macrolide, lincosamide and streptogramin antibiotics in Gram-positive cocci isolated in Tunisian Bone Marrow Transplant Center.' *Pathol Biol* 2011; **59**, no. **4**: 199–206.

192. Seni J, Bwanga F, Najjuka CF, Makobore P, Okee M, Mshana SE, Kidenya BR, Joloba ML KD. 'Molecular characterization of Staphylococcus aureus from patients with surgical site infections at Mulago Hospital in Kampala, Uganda.' *PLoS One* 2013; **8**, no. **6**: e66153.

193. Fischer A, Liljander A, Kaspar H, Muriuki C, Fuxelius HH, Bongcam-Rudloff E, de Villiers EP, Huber CA, Frey J, Daubenberger C BR. Camel Streptococcus agalactiae populations are associated with specific disease complexes and acquired the tetracycline resistance gene tetM via a Tn 916-like element. *Vet Res* 2013; **44(1)**: 86.

194. Ngbede EO, Raji MA, Kwanashie CN KJ. Antimicrobial resistance and virulence profile of enterococci isolated from poultry and cattle sources in Nigeria. *Trop Anim Heal Prod* 2017; **49(3)**: 451–8.

195. Akanbi OE, Njom HA, Fri J, Otigbu AC CA. Antimicrobial Susceptibility of Staphylococcus aureus Isolated from Recreational Waters and Beach Sand in Eastern Cape Province of South Africa. *Int J Environ Res public Heal* 2017; **14(9)**: 1001.

Table 1. Frequency distribution of species, clones, resistance genes and MGEs isolated from animals, humans and environmental specimens.

BACTERIAL SPECIES, CLONES, RESISTANCE GENES AND MGES		HUMANS	ANIMALS	ENVIRONMENT
SPECIES	*E. faecalis*	5	6	3
	E. faecium	8	3	7
	S. agalactiae	6	1	-
	S. aureus	26	10	2
	S. haemolyticus	2	1	1
	S. pyogenes	2	-	-
CLONES	*S. aureus ST5*	3	1	1
	E. faecium ST18, ST16, ST80, ST910	2	-	2
	S. aureus ST22, ST535	1	-	-
	E. faecium ST317, ST51, ST52, ST175, ST178, ST578, ST81	1	-	-
	S. aureus ST8, ST88	3	-	-
	S. aureus ST247, ST36	1	-	-
	S. aureus ST789, ST72, ST2021, ST250, ST239	1	-	-
	S. agalactiae ST617, ST612, ST616	-	-	1
	S. aureus ST152, ST772, ST14	1	-	-

	S. aureus ST241, ST37, ST39	1	-	-
	E. faecium ST203	1	-	-
	S. aureus ST612	1	-	-
	E. faecium ST910	-	-	1
	E. faecium ST480, ST531, ST55, ST532, ST202, ST314, ST985, ST30, ST986, ST12, ST327	-	-	1
	E. faecium ST2, ST28, ST528, ST56, ST885, ST886	-	-	1
	S. aureus ST1440, ST1, ST22, ST97, ST239, ST241, ST247, ST1819, ST153, ST256	1	-	-
	S. aureus ST253, ST700	-	1	-
	P. pyogenes emm18, emm42, emm76, emm118	1	-	-
RESISTANCE GENES	*mecA*	2370	208	25
	erm(B)	721	362	184
	erm(C)	62	5	8
	tet(M)	461	82	75
	tet(k)	90	30	68
	tet(L)	24	46	8
	Van(B)	2	320	59
	Van(A)	18	-	22
	Van(C)	7	320	55
	tet(O)	9	-	-
	dfrA/G	420	-	-
	aph(3')-IIIa	16	11	110
	aac(6')-aph(2')	84	16	71

MGE[1]	*ant(6)-la*	3	23	22
	blaZ	311	28	23
	aph(3')-llla	16	11	110
	mef A/E	136	-	-
	IS16	1	-	1
	SCCmec	12	3	-
	Tn916	1	1	-

1505

[1] Mobile genetic elements

1506 **Table 2. Geographical distribution, species, clones, and resistance mechanisms of antibiotic-resistant Gram-positive bacteria**

1507 **isolated from humans in Africa from 2007-2017**

Country (n)	Year	Organism/ Species (n)	Specimen Sources (n)	Sample size (Resistant isolates)	Resistance rate (%)	Clones (n)	Resistance genes/ mechanisms (n)	Antibiotics to which strains were resistant	MGEs [2] (n)	Reference
Algeria (4)	2015	*S. agalactiae* (44)	Vaginal swab (44)	(44)	100	ST1(9), ST19(14), ST10(4), ST158, ST166, ST233, ST460, ST521, ST677	*tetM* (44), *ermB, (19), mefA/E* (1), *ermA (1)*	TET[3](44) ERY[4](13)	ND	[108]
	2014	*S. aureus* (159)	Nasal swab (159)	159 (9)	5.66	ST80 (4), ST5 (2), ST22 (2), ST535 (1)	*mecA (9)*	GEN[5]((3), TET (3), TOB[6],(6) SXT[7] (2)	*SCC mec* (9)	[79]
	2012	*E. faecium (80), E. faecalis (39)* E. gallinarum (4), E. raffinosus (1), and E.durans(1).	Urinary (85), cutaneous (24), blood (14), pus (2)	125 (108)	87	ST 317 (33), ST51(20), ST52(11), ST175 (8), ST78(25), ST578(4), ST81(2), ST16(2)	*erm*(B) (92), *vanC1*(4)	AMP[8](38), GEN (68), TET (103), ERY (106), CAM (18), LVX ((89), NIT (24), VAN (4).	ND	[176]
	2012	*S. aureus* (64)	Pus (47), venous catheters (7 tracheal aspirates (4),	(64)	100	ND	*MecA (64)*	MET (64), OXA (64), FOX (64)	*SCC mec (46)*	[101]

[2] Mobile genetic elements: plasmids, transposons; integrons

[3] Tetracycline

[4] Erythromycin

[5] Gentamicin

[6] Tobramycin

[7] Sulphamethoxazole-trimethoprim

[8] Ampicillin

			punction fluids (3), blood (2), urine (1)							
Angola (3) and Sao Tome principe	2015	*S. aureus (164)*	Nasal swab (164)	164 (29)	17.68	ST88(15), ST8(9)	*MecA (NS)*	FOX (29), SXT (26), TET (18), ERY (16), CIP (9) and CLI (8)	*SCC mec (NS)*	110
	2015	*S.aureus (203)*	Nasal (203)	203(128)	63.05	ST8(16), ST5(83), (ST88(19), ST72(5), ST789(1), ST5/2629(2), ST30(2), ST22(1)	*MecA (127)*	SXT (136), FOX (128), TET (39), PEN (200), RIF (156), CLI (4), ERY (14), CIP (20), GEN (43), CHL (18)	*SCC mec (128)*	141
	2014	*S.aureus*	Nasal swab (128)	128(124)	96.88	ST8(57), ST88(9), ST8(5), S T72(3), ST789(1)	*MecA (77)*	PEN (124), FOX (77), SXT (80), GEN (24), RIF (97), CHL (11), CIP (10), TET (16), ERY (8)	*SCC mec (128)*	150
Cape verde	2015	*S.aureus*	Nasal swab (113)	113(16)	14.16	ST88(2), ST8(1), ST5(3)	*MecA (6)*	FOX (5), TET (5), PEN (109), CIP (2), CLI (3), SXT (12), ERY (16), (FUS (5), MUP (6)	*SCC mec (6)*	
Democratic Republic of Congo (3)	2017	*S.aureus*	blood(108)	108(27)	25	ST5(11) ,ST8(30),ST88(1), ST152(17)	*dfrG(24),aac(6')-aph(2")(25),tetK(23) ,ermC(20)*	TET(61),LIN(20),CIP(20),PEN(87),CHL(5),SXT(4),	ND	147
	2016	*S. aureus (100)*	Nasal swab (100)	100 (97)	97	ST8 (9)	*dfrG,(72),tet(K) (44), FemA (98),mecA (33)*	TMP(72), PEN (97), TET(45),GEN(25),OXA(24),ERY(20),LUV(16),RIF(7),CHL(7),CLI(4)	ND	146
	2015	*S. aureus (63)*	Nasal swabs (63)	63(10)	15.87	ST8 (8), ST5 (1), ST88 (1)	*MecA (10)*	TET(21),ERY(12),CLI(8),PG(60),CHL(9),KAN(12),GEN(12),TOB(12), SXT(6)	*SCC mec (10)*	81

Egypt (4)	2015 H	*E. faecium (26), E. faecalis (47)*	Urine (100)	(73)	100	ND	*VanA (2)*	PEN(17), AMP(38), CIP(22), GEN(41), STR(73), CHL(12), TET(50), VAN(2)	ND	95
	2014	*S. agalactiae (100)*	Vaginal swab (100)	100 (98)	98	ND	*ermB (9), ermA (1) ,mefA/E, (1) tetM (99) ,tetL (12), tetK (1) , tetO (1)*	ERY(17), CLI(14), AZI(16), TET(98) and CHL(1)	ND	169
	2014	*S. aureus (127)*	Diabetic foot ulcers (39), surgical site infection (48) and abscess infections (25), burn discharges (15).	127 (111)	87.40	ND	*mecA (29)*	AMP(111), AMX(104), OXA(31), LEX(83), CXM(67), CFP(43), FEP(56), CTX(32), SAM(37), AMC(41), AMK(3) CIP(32), NOR(37), OFX(31), LVX(11), GAT(5), ERY(59), Cli(34), TET(66), VAN(2), CHL(44), RIF(35)	ND	121
	2013	*S. aureus (94)*	Blood and wound	94 (45)	47.87	ND	*gyrA* (C2402T, T2409C, T2460G) (60), *gyrB(*T1497C, A1578G) (5)	CIP(26), LUX(26), AMC(26), FEP(24), GEN(11), TET(17),CHL(5)	ND	52]
Gabon (1)	2014	*S. aureus (212)*	Skin and soft tissue (100) and bloodstream (12)	212 (104)	49.06	ND	*dfrA (1), dfrG (100), dfrK+G (1), dfrB (2) mecA(1)*	TMP;(104), SXT(100), SMZ(6)	ND	114
Ghana (2)	2015	*S. aureus (30)*	Skin and Soft Tissue Infections (16) , bacteraemia (5), nasal swab (9)	(30)	100	ST88 (8),ST8 (5), ST247 (4)	*tet(M) (13) , tet(K) (10), aphA3 (7), aacA–aphD (5)and erm(C) (4).*	TET(20), NOR(12), MXF(11), ERY(11), CLI(9), KAN(9),GEN(9) and CPT (6)	ND	137
	2014	*S. aureus (308)*	Blood (112), SST1(173), others (23)	308 (208)	67.53	ST88 (2), ST8 (1), ST789 (1), ST72 (1), ST2021 (1), ST250 (2), ST239 (1)	*mecA (9)*	PEN(208), TET(129), and ERY(18)	ND	136
Kenya (1)	2016	*S. aureus (93)*	Blood(93)	93 (32)	34.41	ST22(4),ST88(1), ST789(1),ST5(1),	*MecA (32)*	CLI(10), ERY(9) and SXT(9),MXF(1) ,RIF(3), TET(6),LUX(5)	SCC mec (32)	102

						ST8(2),ST241(12), ST239(2)				
Libya (1)	2014	*S. aureus (208)*	Nasal swab (44)	208(70)	33.69	ND	*MecA (35)*	CIP(22), GEN(24), FUS(49)	ND	185
Morocco (1)	2013	*S. aureus (30)*	Nasal swab (30)	30 (25)	83.33	ND	*MecA (1)*	PEN(25), GEN(1), TOB(1), KAN(1), PF(1), TET(1), ERY(1), SXT(1)	ND	50
Mozambique (1)	2013	*S. aureus (24)*	Wound (24)	24 (9)	19.15	ND	*MecA (9)*	FOX(9), OXA(8)	ND	156
Namibia (1)	2014	*S. aureus (116)*	skin and soft tissue (31), urinary tract(19), respiratory tract (37), ear (7), eye (4) and bloodstream (3)	116 (34)	29.31	ND	*dfrA (14), dfrG (20) mecA (11)*	SXT(20), TMP(34) SMZ(20)	ND	114
Nigeria (5)	2015	*S. aureus (38)*	throat (40), nasal (23), wound (10)	38 (32)	84.21	ST8 (5), ST152 (1), ST772 (1), ST14(1)	*mecA(16)*	TET(32),LUX(7), GEN(5), ERY(5), PEN, SXT(29)	ND	186
	2015	*S. aureus (290)*	Skin and nasal swab (120), wounds, blood	290 (211)	72.76	ND	*mecA (7), blaZ (284))*	PEN(284), SXT(233), TET(51),OXA(7),GEN(11),TOB(11),LUX(23),MXF(21),TGC(51),	SCC mec (7)	117
	2014	S.epidermidis (20), S. haemolyticus (10), S. saprophyticus (5), S. capitis, (5), S. lugdunensis	Stool (53)	(53)	100	ND	*MecA (15), aac(6')–aph(2") (3),ermC (4), msrA(1), tetK (6) ,tetM(4)*	PEN(53), OXA(15), GEN(3), ERY(5), TET(7), SXT(19), CHL(4),AMC (31),CIP(1)	SCC mec(15)	117

		(2), S. warneri (4), S. xylosus (n4),S. cohnii (3).								
	2014	*S. aureus (183)*	Skin and soft tissue (32), urinary tract (9), ear (7), unknown site (4), oropharynx (3), eye (3) and bloodstream (1)	183 (154)	84.15	ND	*dfrA (2), dfrG (152), mecA(16)*	(TMP)(154), SXT(83),SMZ(85)	ND	114
	2012	*S. aureus (51)* S. haemolyticus (21),S. sciuri (9), S. saprophyticus (5), S. warneri (3),S. epidermidis (1) and S. hominis (1),	wounds, (11) skin and soft tissues (12), osteomyelitis (5), burns (1), urinary tract infection (6), septicaemia (17), urinary tract infection (10), otitis media (2), bronchitis (2)	91 (36)	39.56	ST241 (1), ST8 (1),ST152 (1),ST37 (37),ST39,ST88	*MecA (15), dfrA (3)*	SXT(13), PEN(15),OXA(15), GEN(6), CIP(7), MXF(1),ERY(5),CLI(4),TET(13), SXT(13), RIF(2)	*SCC mec* (15)	139
Sa˜o Tome´ Prı´ncipe (3)	2015	*S.aureus (114)*	Nasal swab (114)	114(29)	25.5	ST5(2),ST88(11), ST8(13),ST1(2),ST105(1)	*MecA(29)*	FOX(29),PEN(114),TET(30),CIP(28),RIF(6),GEN(20) ,CLIN(20),SXT(58),ERY(25),CH	SCC mec (29)	141
Sao Tome principe and Angola	2015	*S. aureus (164)*	Nasal swab (164)	164 (29)	17.68	ST88(15),ST8(9)	*MecA (NS)*	FOX(29), SXT(26), TET(18), ERY(16), CIP (9) and CLI(8)	*SCC mec (NS)*	110
		S.aureus (52)	Nasal swab (52)	52(27)	51.92	ST8(3), ST88(2),ST5(1),ST105(1)	*MecA 14*	SXT(27),ERY(11), CIP(11),TET(12),FOX(14),RIF(2)	SCC mec	166

South Africa (10)	2017	*S.aureus(1914)*	Blood (1914)	1914(557)	29.10	ST239(8),ST612(8),ST4121(1),ST36(4),ST5(4),ST33(3)	*mecA(483)*	β-lactams(557),TET(NS),aminoglycoside(NS),SXT(NS)	SCCmec (482)	162
	2017	*S.aureus(97)*	Human	97(96)	99	ND	norA(96),norB(96),mepA(95),tet38(96),sepA(94),mdeA(93),imrs(86),sdrM(83),norC(77),qacA/B(34),smr(42)	NS	ND	165
	2017	*E. faecalis (1)*	Urine (1)	1	100	ST6(1)	Aph(3')-III(1), ant(6)-Ia (1), aac(6')-aph(2") (1), isa(A)(1),mphd(1), tetM(1)	GEN(1),STR(1),ERY(1),CLI(1), TET(1),CLI(1),TET(1),CIP(1)	ND	187
	2017	*E.faecium (1)*	Urine (1)	1	100	ST18(1)	Aph(3')-III(1), ant(6)-Ia (1),tetM(1),ermB(1),msr(C)(1),tet (L)	GEN(1),STR(1),ERY(1),CLI(1), TET(1),CLI(1),TET(1),CIP(1)	ND	188
	2016	*S. aureus (27)*	Blood (5), nasal (2), CVP(2), Endotracheal tube (2), pus (2), sputum (1), wound (20), Eye (1),humerus (1), bone (1), cheek (1), buttock (1), head (1)	(27)	100	ND	*MecA (27) and blaZ (27),aac (6')–aph (2") (25),ermC (13)*	CIP(23), GEN(20), RIF(19), TET(18), ERY(17), CLI(3)	ND	189

	2016	*E. faecium (120) E. faecalis (40)*	Blood (4)	(4)	100	ST80 (1),ST203 (1),ST18 (1),ST817(1	*van A (3) and van B (1)*	VAN (4)	ND	175
	2015	*S. agalactiae (128)*	vaginal and rectal swabs (128)	128 (121)	94.53	ND	*ermB, (28),linB(48) mefA (48)*	ERY(27), CLI(32), CHL(32),TET(111),CIP(24)	ND	103
	2015	*S. aureus (2709)*	Blood (2709)	2709 (1231)	45.44	ND	*mecA (1160)*	TET(NS), RIF (NS),MUP(NS), CIP(NS) and SXT(NS) MET(1231)	SCC mec (1160)	80
	2012	*S. aureus (13746)*	Human (13746)	13746(3298)	24	ST5 (1), ST612 (44),	*RpoB (H481Y, H481N, I527M) (NS)*	RIF(1760)	ND	80
Tanzania (1)	2014	*S. aureus (87)*	Skin and soft tissue (39) and bloodstream (2)	87 (32)	36.78	ND	*dfrG (32)*	SMZ(5), TMP (32)	ND	111

Tunisia (12)	2015	*S. aureus (99)*	Human (99)	(99)	100	ST247 (12), ST239 (6), ST728 (2), ST241 (1), ST398 (1), ST5 (1) and ST641 (1)	*MecA (24), tet(K) (6), tet(L) (1) and/or tet(M)(18), erm (A), aph(2')-acc(6') (13)*	TET(24), GEN(18), ERY(15), FOF(1), CLI(14), OFX(16), TOB(20), FUS(5)	ND	[71]
	2014	*E. faeciun (13),E.gallinarum(3),*	blood (8), pus (3), urine (2) and rectal swabs (3).	(16)	100	ST18 (1)and ST80 (2)	*VanA (13),vanC1(3), erm(B) (16), tet(M)(15),tetl(1), aac(6')-aph(2")(13) aph(3')-IIIa (16),ant(6)(3)*	VAN(16),TEC(13), AMP(16),CIP(16), ERY, TET(16), KAN(13), STR(13), SXT(16), GEN(8),	*IS16 (3)*	[190]
	2013	*S. aureus (69)*	Human (69)	(69)	100	ST80 (41), ST1440 (1), ST1 (2), ST5 (5), ST22 (1), ST97 (2), ST239 (4), ST241 (3), ST247 (3), ST1819 (3),ST153 (2),ST256 (1)	*MecA (59)*	KAN(62), AMK(62(18), TETs(61), OFX(20) , CIP(31), ERY(38) , CLI(12), RIF(22)	*SCC mec* (59)	[68]
	2012	*S. agalactiae (226)*	Female genital (120), gastric fluid (106)	226 (220)	97.34	ND	*erm(B) (79), mef(A) (2), tet(M) (205), tet(L)(10) tet(O) (5), tet(T)(1)*	CHL(7), RIF(43), ERY(90) and TET(220), STR(7),GEN(7)	*Tn916*	[132]

	2012	*S. haemolyticus (46)*	Blood (19), intravascular catheters (14), others (13)	46 (36)	78.26	ND	*mecA (28)*	PEN(36), OXA(36), GEN(34), kAN(34), and TOB(34), ERY(33), SXT(32), OFX(32), CIP(32), STR(25), fusidic acid(14), TET(11),RIF(9),LIN(6(,CHL(1),FOF(1)	*SCCmec* (28)	131
	2011	*S. aureus (1463)*	Skin (1463)	160 (5)	3.13	ND	*erm(C (3)), erm(A) (1), vat(B) (5), vga(B) (5)*	PEN(5),OXA(4), GEN(4), KAN(5), TOB(4(5) and RIF(5),LIN(5)	ND	172
	2011	*S. pyogenes (103)*	skin (43), respiratory tract (41), blood (12), fluids (4), endometrium (1), vagina (1), and urine (1).	103 (72)	70	emm18 (4), emm42 (9), emm76 (6), emm118(10)	*erm(B) (50, tet(M) (63),* $\mathrm{tet(O)(3)}$	ERY(5), CLI (5), and TET(72),	*Tn916 (62)*	173
	2010	*S. pyogenes (193)*	throat (63) (32.7%), pus (89), punctures (30), blood (4), other sources (7)	193 (13)	6.74	ND	*ermB (6), mefA (2)*	ERY(7) and TET(6)	ND	171
	2010	*S. agalactiae (160)*	Urinary tract (160)	(160)	100	ND	*erm(B) (132), erm(TR) (13), mef (A) (3)*	ERY(160), LIN(135) and SB (135)	ND	191
	2009	S. epidermis (77), S. mitis (50), E. faecium (45)	blood cultures (55), central venous catheters, (22),stool cultures (40), respiratory tract (2) and different sites (3), systematic nasopharyngeal specimens (42), upper respiratory	172(95)	55.23	ND	erm (C) (18), , ermB (6), ermA(11),msrA (5)	OXA(39), AMP(28),PEN(90),ERY(119),LIN(97), PRI (3),GEN(71),RIF(78), TEC(50),	ND	96

			tract(5) and other sources (3).							
	2008									
Uganda (2)	2013	*S. aureus (64)*	Nasal swab (64)	64(24)	37.5	ND	*MecA (24)*	OXA(22), GEN(8), CIP(12), CHL(9)	*SCCmec (24)*	[192]

1517 **Table 3. Geographical distribution, species, clones, and resistance mechanisms of antibiotic-resistant Gram-positive bacteria**

1518 **isolated from animals in Africa from 2007-2017.**

Country (n)	Year	Organism/ Species (n)	Specimen Sources (n	Sample size (Resistant isolates)	Resistance rate (%)	Clones (n)	Resistance genes/ mechanisms (n)	Antibiotics to which strains were resistant	MGEs [9] (n)	Reference
Egypt (5)	2017	*S.aureus(3),S.hycus(6), S.intermedns(3) ,S.epidermis(1) ,S.hemolyticus(1), S.hominis(1), S.lugdunensis(3), S.simulans(1),S.scuri(4)*	imported beef meat (23)	23(16)	69.57	ND	mecA(5)gyrA(12), grlA(10),gyrB(6),	AMP((6),CHL(1),CIP(8),CLI(15), ERY(6),GEN(14),MET(8),OXA(13) ,PEN(22), TET(6)	ND	122
	2016	*S. aureus (30)*	raw chicken breast fillet (40), sliced luncheon meat (20), and chicken nuggets (20),Human (18)	40 (21)	33.33	ND	*mecA (10)*	DOX(31), AMX(29), OFX(10), CFP(23), CLI(21), GEN(20), APR(16), ERY(21), SXT(23), LUX(18), NAL(20), OFX(10), CIP(16).	ND	51
	2016	*S. aureus (200)*	Raw milk (40), Damietta Cheese (40), Kareish cheese (40), ice cream (40), and yogurt (40)	200 (106)	53	ND	MecA(106)	TET(270), NEL(78), AMX(230), CLX(314),STR(186),SXT(58), GEN(114), PEN(364), RIF(152), CHL(128), AMK(146), VAN(36)	ND	30
	2015	*S. aureus (133)*	cow milk samples (61), various origins (14), minced meat (6), sausage (4) and	133 (96)	72.18	ND	*mecA (30)*	CRO(96), TET(90), OXA(70), FOX(65), ERY(81),VAN(4),IPM(7),CRO(96),CHL(12) ,GEN(36),CLI(29), CIP(31),RIF (18)	SCCmec (25)	46

[9] Mobile genetic elements: plasmids, transposons; integrons

			burger (7), pus (22), sputum (17), urine (1), cerebrospinal fluid (1)							
	2011	*S. aureus (4)*	dogs swab (70), cats swab (48), human nasal and oral swabs (50).	(4)	100	ND	*mecA (4)*	OXA(4), FOX(4), AMP(3),FOX(4),RIF(3),GEN(2),CLI(2),RIF(2),CIP(2),TET(1)	ND	112
Kenya (1)	2013	*S. agalactiae (92)*	Camel(92)	92 (37)	36	ST617 (8), ST-612 (1),ST-616 (22)	*TetM (37)*	TET(37)	Tn916 (37)	193
Nigeria	2016	*E. faecium (108), E. gallinarum, (30), E. faecalis (5), E. hirae. (5) E.mundtii (12)*	Cattle (130), chickens (130),manure (130)	167 (102)	61.0	ND	tetK (NS), tetL (NS), tetM (NS), tetO (NS) and ermB (NS)	TET (102), ERY (102), CHL (13), GEN(55), STR(47),AMP(75)	ND	194
South Africa	2015	*S. aureus (211)*	Milk (211)	211 (124)	58.77	ND	*MecA (19)*	PEN (124), AMP(99), OXA (93), VAN(47), TEC(116), TET(56),ERY(56),STR(89),KAN(55),GEN(47),SXT (37)	ND	44
	2015	*E. faecalis (40), E. hirae (100), E. durans (60), E. faecium (120)*	Pigs (320)	(320)	100	ND	*vanB,(320) vanC1 (320), vanC2/3 (320), ermB, (300)*	VAN(320), STR(320) and CLX(320),STR(320),CET(286),PEN(292),CIP(248),AMO(64), AMK(272),CLI(316),ERY (280),IPM (52),	ND	31
	2013	*S. xylosus (18), S. aureus (28), S. haemolyticus (42), S . capitis (18), and other Staphylococcus spp. (14*	Animals (120)	(120)	100	ND	*mecA (NS)and mphC(NS)*	PEN (90), MER(3), VAN(14), CTX(14), CFZ(48), OXA(46), MIC(19), TET(100), ERY(14), CLI(19), NAL(120), CIP(5), OFX(6), LUX(2)	*SCCmec (*NS)	118

Senegal (1)	2012	*S. aureus (57)*	Swabs from pigs (300) and farmers	(57)	100	ST5 (5)	*mecA(6)*	PEN(57), SXT(35), TET(20)	*SCCmec (6)*	82
Tanzania (1)	2014	*E. faecium (95) E. faecalis(9) E. gallinarum (7) E. Hirae (9)*	Faecal samples of buffalo (35), wildebeest (40), zebra (40) and cattle (20)	120 (42)	35	ND	*TetW (NS)* and *sulII (NS)*	VAN(10),AMP(10),TET(40),SXT(32),RIF(53),ERY(42),GEN(35),AMP(31)	*ND*	32
Tunisia	2017	*E.faecium (31),E.faecalis (14),E.durans(6),E. casseliflavus(2),E.gallinarum (2)*	Faecal sample of cats(20), dogs(50)	58(31)	53.45	ND	ermB(22),tetM(5),tetM+tetL(16),tetL(4),ant(6')-la(11),aac(6')-le-aph(2'')-la(16),aph(3')-llla(11),catA(1)	AMP(1),ERY(26),CIP(30), PRI(9), STR(12), KAN(12),GEN(9),TET(21),CHL(7)	*ND*	45
	2013	*E. faecalis (49), E. faecium (30), E. gallinarum (12), E. hirae(12),E.casseliflavus (2),E. durans (2)*	Meat (199)	(119)	78.5	ST260(1), ST454(1), ST452(1), ST22(1),ST300(1),ST455(1),ST453(1),ST456(1)	*tet(M) (36) tet(L) (32), erm(B) (33), aac(6')-aph(2'') (1),ant(6) (7)*	TET(57), ERY(43), STR(17), CHLI(4),GEN(1)	*ND*	183
	2013	*E. mundtii, (23) E. casseliflavus (20)*, *E. hirae (19)*, *E faecalis (10)*, *E. faecium (10), E. durans (7), E. gallinarumd (7), E. dispar (2)*	Cattle (92)	92 (72)	78	ND	*erm*(B) (7), *tet*(M) (4) and/or *tet*(L)(4)	ERY(10), TET(4) and SXT(72)	*ND*	182
	2012	*S. aureus (73)*	nasal swab from sheep (73)	73 (5)	6.85	ST153(5)	*MecA (5),blaZ (28), ant(6)-Ia (5), , erm(C) (5), tet(K) (30)*	PEN(5), STR(5), KAN(5), ERY(5), TET (5), FUS(5)	ND	107

Uganda (1)	*2017*	*S.aurus*	milk(30),sour milk sample(11)	41(30)	73.17	ST97(1),ST1(2)	*mecA(23)*	TET(30),RIF(1),SXT(2),ERY(1), GEN((1),CLI(1)	*ND*	[148]

1519

1520 **Table 4. Geographical distribution, species, clones, and resistance mechanisms of antibiotic-resistant Gram-positive bacteria**

1521 **isolated from the environment in Africa from 2007-2017.**

Country (n)	Year	Organism/ Species (n)	Specimen Sources (n)	Sample size (Resistant isolates)	Resistance rate (%)	Clones (n)	Resistance genes/ mechanisms (n)	Antibiotics to which strains were resistant	MGEs[10] (n)	Reference
Nigeria (1)	2017	*E.faecium (100)*	Vegetables soil, farm, Cloacal swabs (25), Manure (8), Rectal swabs(2)	(100)	100	ND	*aac(6')-Ie-aph(2'')-Ia(35),aph(2')-1c(31),aph(3')-IIIa(32), ant(4')-Ia(14*	AMP (63), GEN(37)	ND	[48]
South Africa (3)	2017	S.aureus	Recreational waters and beach sand (30)	(30)	100	ND	mecA(5),femA(16). rpoB(11),blaZ(16),ermB(15),tetM(8)	AMP (29),PEN (29),RIF(24), CLI(24),OXA (22),ERY(21),VAN(15), TET(13),SXT(13),CIP(10),GEN(1)	ND	[195]
	2015	*E. faecium (30), E . durans. (15)*	waste water (32) and effluent (32)	(45)	100	ND	*erm(B) (40), vanB, (42) vanC1 (42), van C2/3(42)*	PEN(38), ERY(40), CTX(43), GEN(28),IPM(43), TET(45), KAN(43), CIP(43), VAN(42),CLI(45)	ND	[28]

[10] Mobile genetic elements: plasmids, transposons; integrons

	2013	*E. faecium (179)*	Borehole Water (179)	179 (172)	96.09	ND	*VanA (17) and vanB (17)*	AMP(158), VAN (166)and PEN(172),CHL(11),KAN(12),GEN(3),AMX (155), ERY(86)	ND	[27]
Tunisia (6)	2017	*S.aureus*	Wastewater	12	100	ST3245(7),ST15(1)	*blaZ(7),msrA(7),tetK(1),*	PEN(12),ERY(7),TET(1),CLI(1)	ND	[41]
	2016	*E. faecium (86),* E. faecalis(8), E.casseliflavus (6)	Hands (50), inanimate such as beds, treatment tables, toilets, faucets, wrists, sinks (250)	(100)	100	ST910 (13), ST80 (1)	*erm(B) (71), tet(M) (18), aph(3')-IIIa (27), ant(6)-Ia (15),cat(A) (4), van(C2) (6)*	ERY(73), TET(20),STR(27) and KAN(28), VAN(14),CHL(10),SXT(100), CIP(48),PRI(18)	*IS16* (14)	[43]
	2016	*S. saprophyticus, (30) S. haemolyticus (38). S. epidermidis (NS), S. cohnii (NS), S. warneri (NS), S. sciuri (NS), S. simulant (NS)s, S. pasteuri (NS), S. arlettae (NS)* and *S. xilosus(NS*	Inanimate surfaces (83	83 (32)	38.55	ND	*MecA (20), msr*(A)(32); *erm*(C)(8), *tet*(K)and/or *tet*(M)(21), *aac*(6´)-Ie-*aph*(2´´)-Ia (16),(*aph*(3`)-IIIa(19), *ant*(4´)-Ia (n=14), *ant*(6´)-Ia (3)	ERY(32), TET(21), GEN(16), KAN(19), TOB(14), STR(3),	ND	[125]
	2015	*E. faecium (34), E. hirae (23)* , *E. faecalis (4)*, and *E. casseliflavus (4)*	Vegetable food (34), soil and irrigation water (27)	65 (40)	61.54	*ST2 (5), ST16 (2), , ST528 (2), ST56 (1), ST885 (1), ST886 (1)*	*erm(B) (12), tet(M)-tet(L)(10), aph(3')-III, (10) ant(6) (2),vanC2(4)*	CIP(42), ERY(12), TET(10), KAN(10), CHL(5), STR(2), and GEN(5), VAN(4)	ND	[42]
	2015	*E. faecium (54), E. faecalis(17),E. hirae (8) E.casseliflavus (4),E.durans (2)*	waste and surface water (114)	(85)	100	ST480 (1), ST531 (1),ST55 (1),ST532(1), ST202 (1),ST314(1), ST985(1),ST30 (1),ST986 (1),ST12	*aph(3')-IIIa (22), ant(6)-Ia (4),erm(B) (34), tet(M) (13), tet(L)(8),aac(6')-Ie-aph(2')(15)*	GEN(22), KAN(22), STR(7), ERY(36), TET(13), SXT(79), CIP(6),	ND	[181]

					(1),ST296 (1),ST327(1)					
2014	*E.faecium(5),E.casseliflavus(7)*	Hospital environment((beds, treatment table, toilet, faucet, wrist and sink) (100)	(12)	100	ST80(1)	*VanA(5),vanC2(7),ermB(12),tetM(5),aph(3')-IIa(5),aac(6')-aph(2")(5)*	VAN,(12),AMP(5),CIP(12),ERY(12),TET(8), STR(6),KAN(80,SXT(11),GEN(3),TEC(5)	*IS16(1)*	[71]	

1522

1523 **Table 5. Distribution of resistance genes per clones in Africa.**

Clones	*mecA*	*vanA*	*dfrG*	*tet(K)*	*tetM*	*Aph(3)-IIIa*	*ermC*	*acc(6')-aph(2")*	*ermB*	*Van B*	*blaZ*	*femA*	*Van C1*	*MefA/E*	*GyrA*	*GyrB*
S. aureus ST5	11	-	1	2	-	-	-	1	-	-	1	-	-	-	-	-
S. aureus ST80	5	-	1	2	1	1	-	1	1	1	-	-	-	-	-	-
S. aureus ST8	10	-	2	3	1	-	2	1	-	-	-	-	-	-	-	-
S. aureus ST88	5	-	1	2	1	-	2	1	-	-	-	-	-	-	-	-
S. aureus ST22	4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
S. aureus 152	2	-	1	1	-	-	1	1	-	-	-	-	-	-	-	-
S. aureus ST247	2	-	-	1	1	-	1	-	-	-	-	-	-	-	-	-
S.aureus ST239	3	-	-	1	1	-	-	-	-	-	-	-	-	-	-	-
E.faecalis ST81	-	-	-	-	-	-	-	-	1	-	-	-	1	-	-	-
E.faecalis ST578	-	-	-	-	-	-	-	-	1	-	-	-	1	-	-	-
E.faecalisT16	-	-	-	-	1	1	-	-	1	-	-	-	1	-	-	-
E. faecium ST52	-	-	-	-	-	-	-	-	1	-	-	-	1	-	-	-
E. faecium ST51	-	-	-	-	-	-	-	-	1	-	-	-	1	-	-	-
E.faecium ST317	-	-	-	-	-	-	-	-	1	-	-	-	1	-	-	-
E.faecium S528	-	-	-	-	1	1	-	1	-	-	-	-	1	-	-	-

E.faecium ST2	-	-	-	-	1	1	-	-	2	-	-	-	2	-	-	-
E.faecium ST910	-	-	-	-	1	1	-	-	1	-	-	-	1	-	-	-
E.faecium ST18	-	2	-	-	1	1	-	1	1	1	-	-	-	-	-	-
S. agalactiae ST612	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-
S. agalactiae ST616	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-
S. agalactiae ST617	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-
S. agalactiae ST10	-	-	-	-	1	-	-	-	1	-	-	-	1	-	-	-
S. agalactiae ST19	-	-	-	-	1	-	-	-	1	-	-	-	1	-	-	-
S. agalactiae ST1	-	-	-	-	1	-	-	-	1	-	-	-	1	-	-	-

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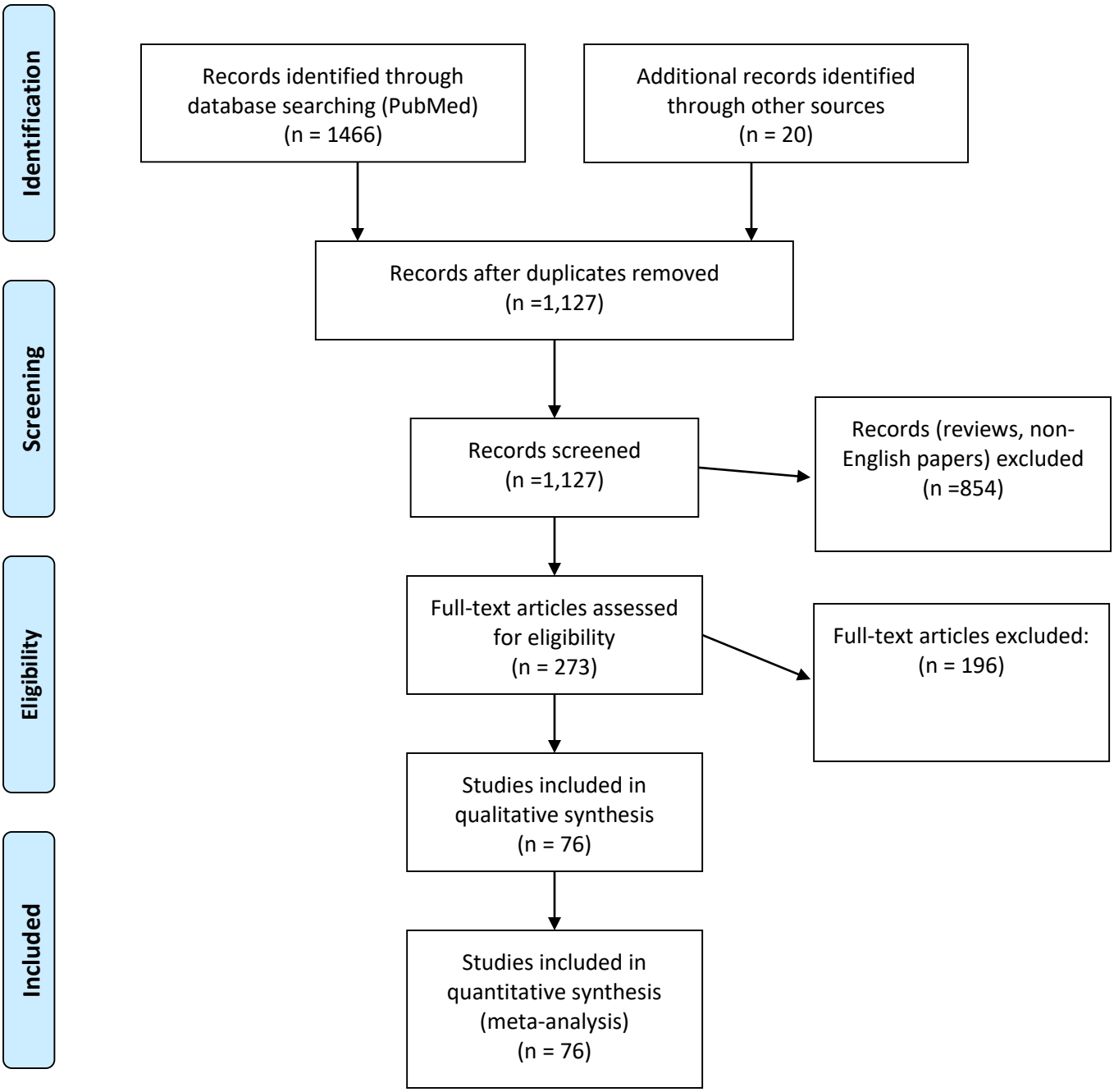
Figure 1. PRISMA-adapted flow chart showing included and excluded articles. All search was conducted on Pubmed and a final number of 77 manuscripts were used for the qualitative analysis.

Figure 2. Frequency and distribution of mobile genetic elements (MGEs), resistance genes and antibiotics with recorded resistance in Gram-positive bacteria in Africa. 2ai) Shows the frequency of the various resistance genes found in the drug-resistant Gram-Positive bacterial strains. *MecA* and *ermB* were the most dominant resistance genes detected, followed by *tetM, dfrG, vanB, vanC1* etc. 2aii) Shows the antibiotics to which the isolates were most resistant: erythromycin (ERY) was the least effective drug, followed by rifampicin (RIF), tetracycline (TET), penicillin (PEN), sulphamethoxazole/trimethoprim (SXT), ciprofloxacin (CIP), gentamicin (GEN), vancomycin (VAN), ampicillin (AMP), clindamycin (CLI), streptomycin (STR), chloramphenicol (CHL), and kanamycin (KAN). 2b) Shows the MGEs per resistant Gram-positive bacterial clones in Africa. The figure represents resistant clones and the different MGEs they carry. Each colour represent a particular resistant clone. *S. agalactiae* (ST612, ST616, ST617) and *S. pyogenes* (emm18, emm42, emm76, emm118), *E. faecium* (ST18, ST80, ST910) and *S. aureus* (ST5, ST22, ST35) were associated with *Tn916*, *IS16* and *SCCmec* respectively.

Figure 3. Frequency of resistant Gram-positive bacterial species clones and mobile genetic elements (MGEs) per country in Africa. 3a) Shows the distribution frequencies of the resistant species, clones and MGEs per country in Africa whilst 3b) shows the total frequency per clone in Africa. It is obvious that *S. aureus* ST5 is predominant in Tunisia, the DRC and Senegal whilst ST22 is highly prevalent in Algeria. *SCCmec* was the commonest MGE in most of the countries except in Tunisia where *IS16* and *Tn916* were higher in prevalence. *S. aureus* ST8 and ST80 were the most common clones reported, followed by *E. faecium* ST317.

PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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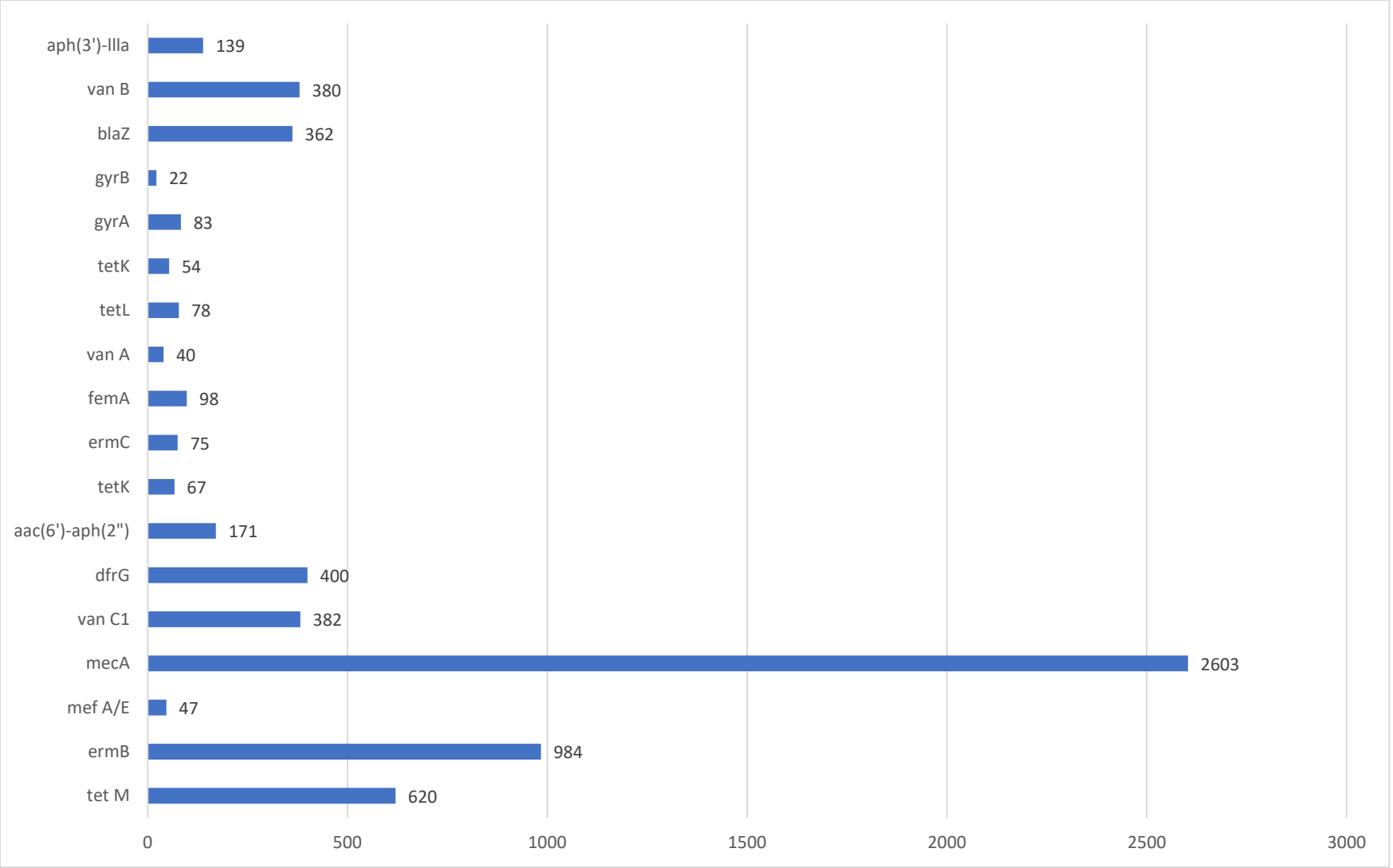

Figure 2ai. Frequency and distribution of mobile genetic elements (MGEs), resistance genes and antibiotics with recorded resistance in Gram-positive bacteria in Africa.

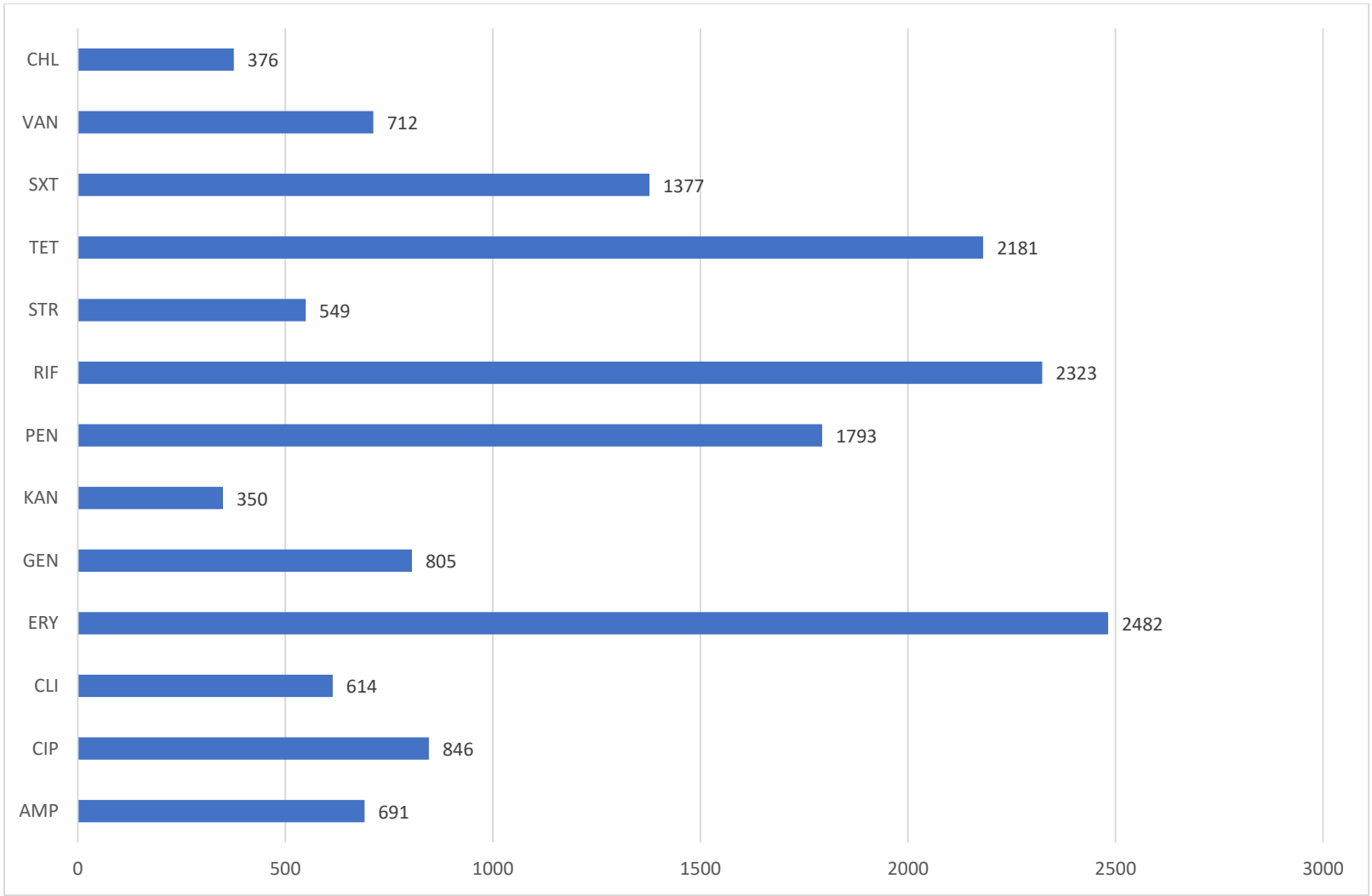

Figure 2aii. Frequency and distribution of mobile genetic elements (MGEs), resistance genes and antibiotics with recorded resistance in Gram-positive bacteria in Africa.

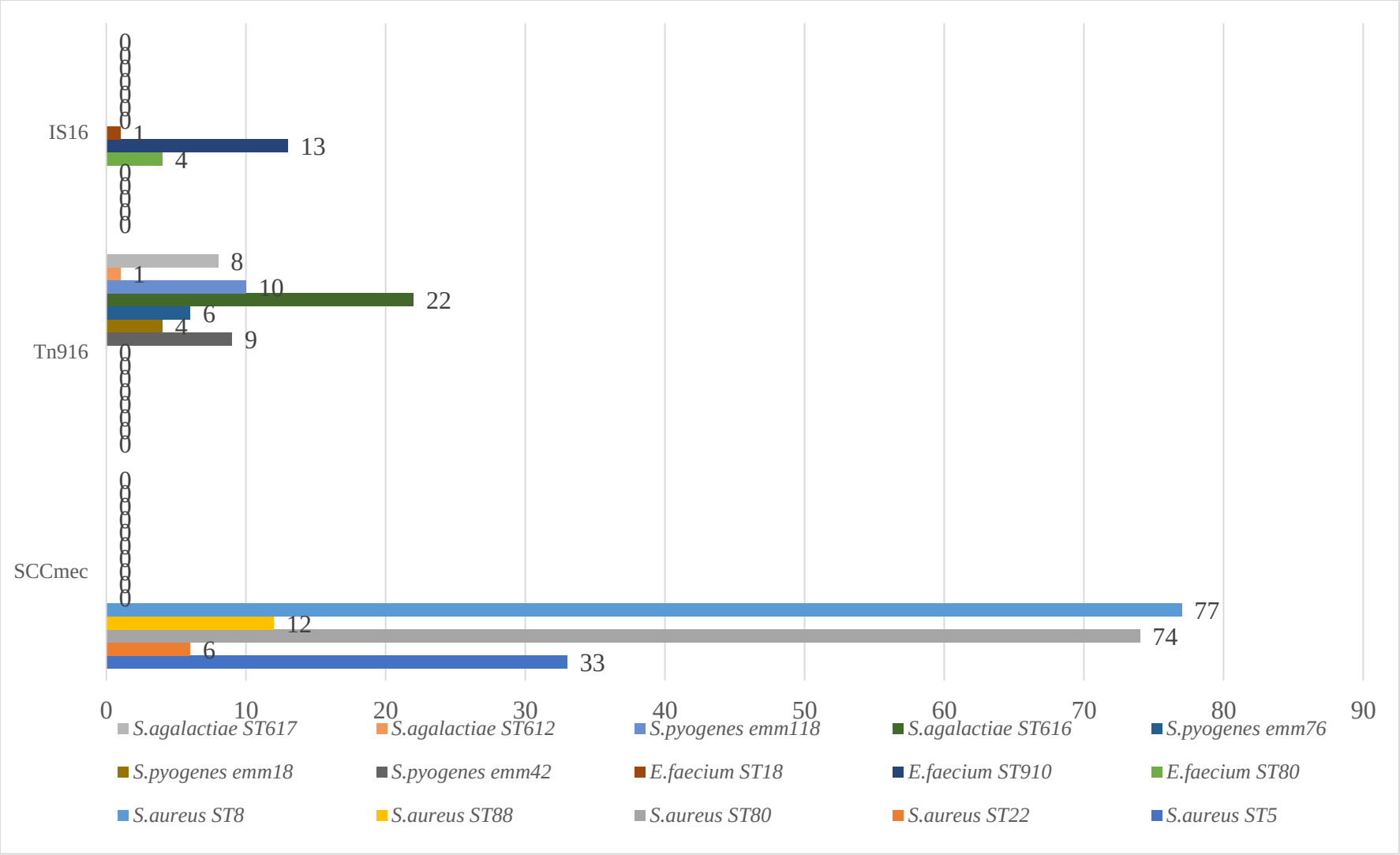

Figure 2b. Frequency and distribution of mobile genetic elements (MGEs), resistance genes and antibiotics with recorded resistance in Gram-positive bacteria in Africa.

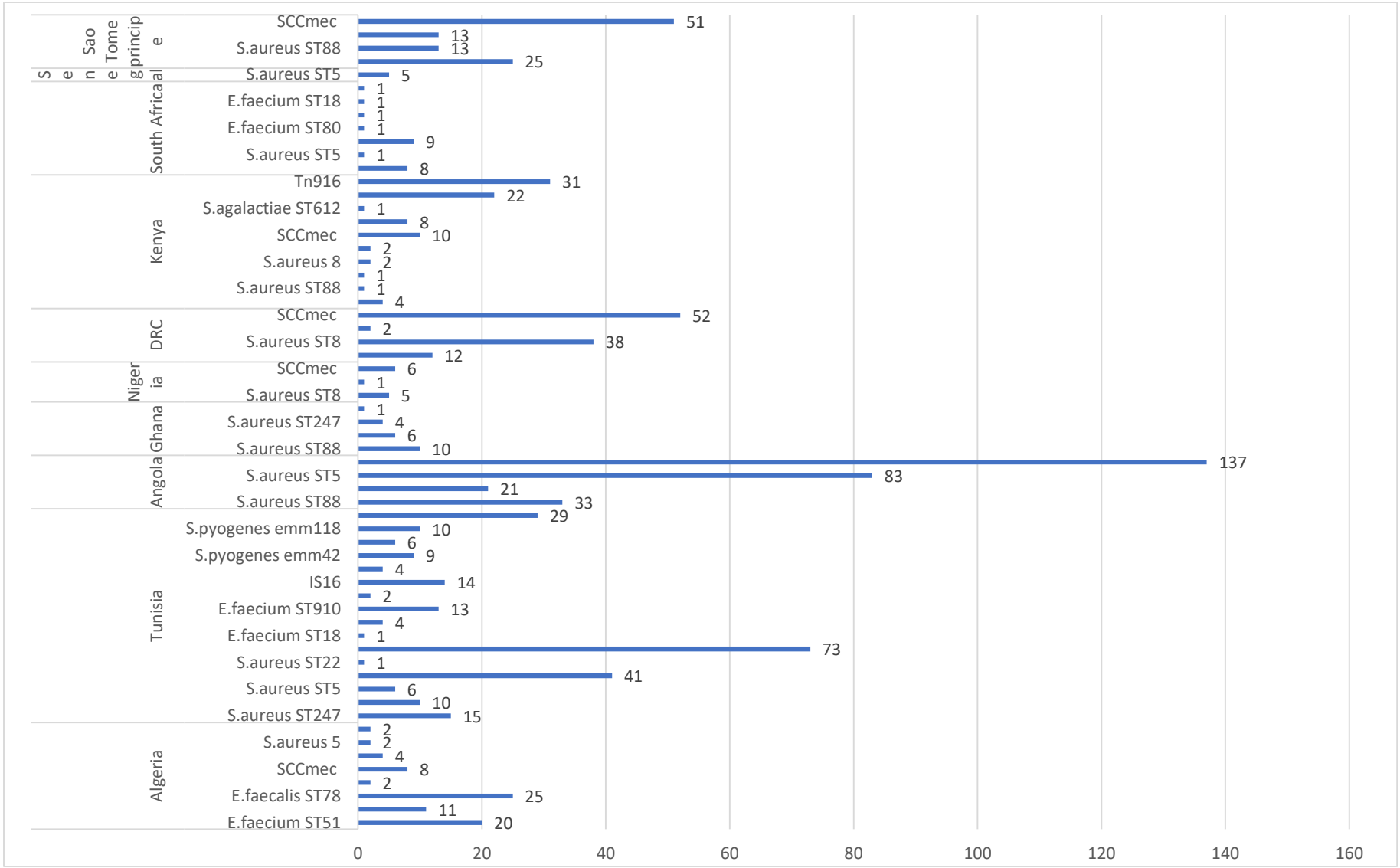

Figure 3a. Frequency of resistant Gram-positive bacterial species clones and mobile genetic elements (MGEs) per country in Africa

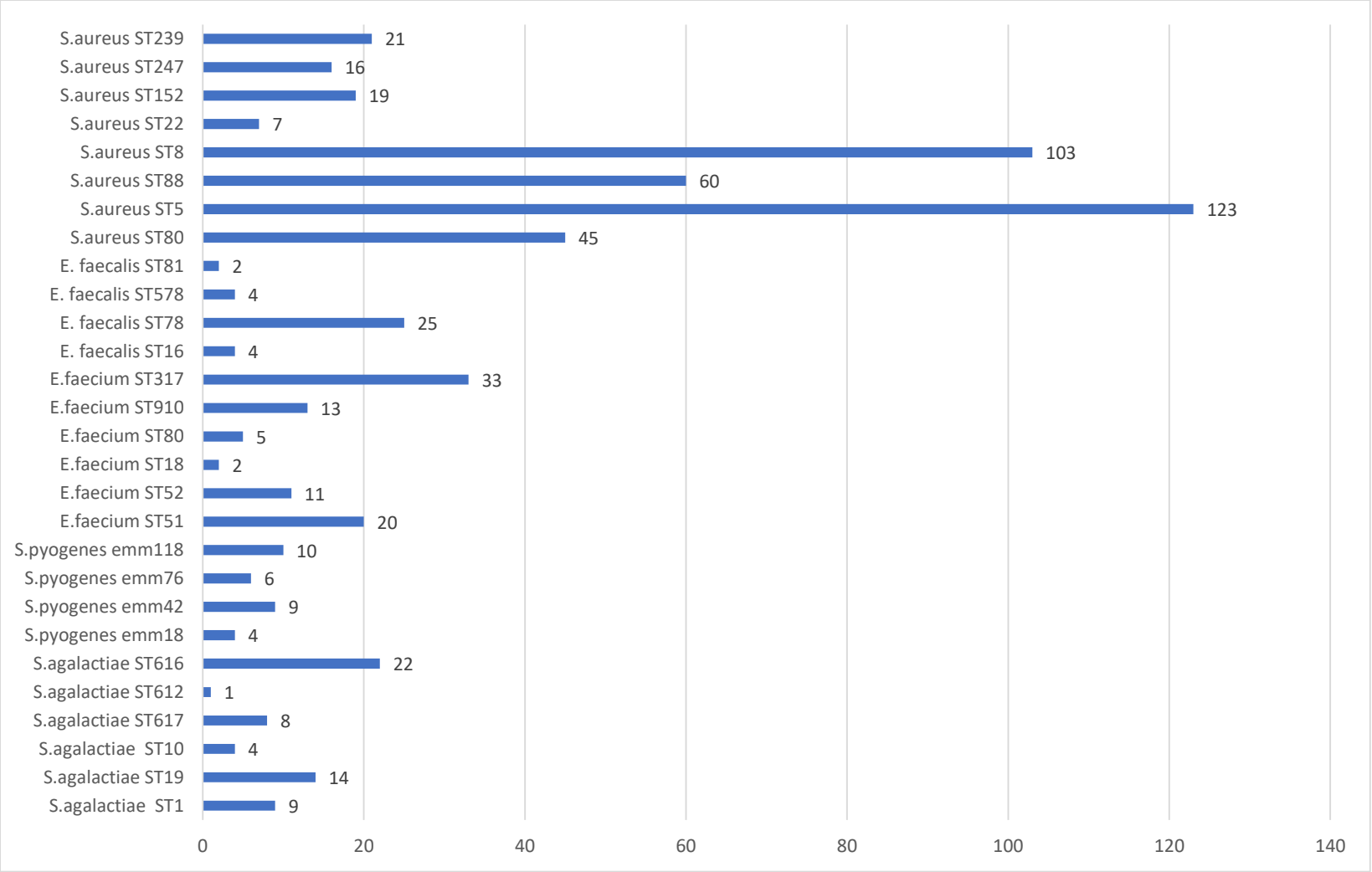

Figure 3b. Frequency of resistant Gram-positive bacterial species clones and mobile genetic elements (MGEs) per country in Africa