

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

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4                             John Osei Sekyere<sup>ac#</sup> and Eric Mensah<sup>b</sup>

5     Department of Pharmaceutics, Faculty of Pharmacy and Pharmaceutical Sciences, Kwame Nkrumah  
6     University of Science and Technology, Kumasi, Ghana.<sup>a</sup>

7     Kumasi Centre for Collaborative Research in Tropical medicine, School of Medical Sciences, Kwame  
8     Nkrumah University of Science and Technology, Kumasi, Ghana.<sup>b</sup>

9     Department of Medical Microbiology, School of Medicine, Faculty of Health Sciences, University of  
10    Pretoria, Pretoria, South Africa.<sup>c</sup>

11    #Address correspondence to John Osei Sekyere, [jod14139@yahoo.com](mailto:jod14139@yahoo.com)

12  
13    **Running title:** Resistance mechanisms of Gram-positive bacteria

21

## HIGHLIGHTS

- 22 • Gram-positive bacteria (GPB) isolated from human, animal and environmental samples were of the  
23 same clones and/or shared common resistance genes and mobile genetic (MGEs).
- 24 • Multidrug resistant (MDR) clones such as *S. aureus* ST5 and *E. faecium* ST80 were isolated from  
25 human, animal and environmental sources.
- 26 • *mecA*, *erm(B)*, *erm(C)* *tet(M/K/L)*, and *vanA/B/C* were common in GPB, including VRSA.
- 27 • Mean drug resistance rates of isolates from humans, animals and the environment were respectively  
28 62.0% (95% CI: 54.7 – 69.3%), 68.2% (95% CI: 58.0 -78.4%) and 84.6% (95% CI: 69.9 – 99.31%)  
29 (*P-value*<0.0001).
- 30 • SCC*mec*, IS*I6*, and Tn*916* mobilized *mecA*, *erm(B)* and *tet(M)* respectively across various GPB  
31 species isolated from animals, humans, and the environment.
- 32 • A One Health approach to studying antibiotic resistance mechanisms and molecular epidemiology of  
33 GPB is warranted.

## 34 ABSTRACT

35 A systematic review and meta-analysis of antibiotic-resistant Gram-positive bacteria in Africa, showing  
36 the molecular epidemiology of resistant species from animal, human and environmental sources, is  
37 lacking. Thus, the current burden, type, and sources of Gram-positive bacterial resistance and their  
38 dissemination routes from farm to fork is absent. To fill this One Health information gap, we  
39 systematically searched PubMed, Web of Science and African Journals Online for English research  
40 articles reporting on the resistance mechanisms and clonality of resistant Gram-positive bacteria in Africa  
41 within 2007 to 2018. The review and all statistical analysis were undertaken with 130 included articles.  
42 From our analyses, the same resistant Gram-positive bacterial clones, resistance genes, and mobile  
43 genetic elements (MGEs) are circulating in humans, animals and the environment. The resistance genes,  
44 *mecA*, *erm(B)*, *erm(C)*, *tet(M)*, *tet(K)*, *tet(L)*, *vanB*, *vanA*, *vanC*, and *tet(O)*, were found in isolates from

45 humans, animals and the environment. Commonest clones and mobile genetic elements identified from all  
46 three sample sources included *Staphylococcus aureus* ST5 (n=208 isolates), ST 8 (n=116 isolates), ST 80  
47 (n=123 isolates) and ST 88 (n=105 isolates), and *IS16* (n=18 isolates), *Tn916* (n=60 isolates) and  
48 *SCCmec* (n=202 isolates). Resistance to penicillin (n=4 224 isolates, 76.2%), erythromycin (n=3 552  
49 isolates, 62.6%), ampicillin (n=1 507 isolates, 54.0%), sulfamethoxazole/trimethoprim (n=2 261 isolates,  
50 46.0%), tetracycline (n=3 054 isolates, 42.1%), vancomycin (n=1 281 isolates, 41.2%), streptomycin (n=1  
51 198 isolates, 37.0%), rifampicin (n=2 645 isolates, 33.1%), ciprofloxacin (n=1 394 isolates, 30.5%),  
52 clindamycin (n=1 256 isolates, 29.9%) and gentamicin (n=1 502 isolates, 27.3%) (*p*-value <0.0001) were  
53 commonest.

54 Mean resistance rates of 14.2% to 98.5% were recorded in 20 countries within the study period, which  
55 were mediated by clonal, polyclonal and horizontal transmission of resistance genes. A One Health  
56 approach to research, surveillance, molecular epidemiology, and antibiotic stewardship to contain ABR  
57 should be prioritized.

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

## 59 1. INTRODUCTION

### 60 *Antibiotic resistance, a threat to public health*

61 Limited research and surveillance data in Africa makes it impossible to track and monitor the true burden  
62 of antibiotic resistance (ABR) <sup>1</sup>, particularly the distribution and dissemination of resistance genes  
63 between humans, animals and the environment. According to a recent WHO report, the potential for ABR  
64 to lead to higher mortalities and morbidities in low- and middle-income countries such as Africa may  
65 even be greater as a result of the higher burden of bacterial infections, limited diagnostic capacity and  
66 lower access to second-line antibiotics<sup>1,2</sup>. This makes it imperative to have a One Health analysis that  
67 describes the burden and epidemiology of resistance genes in bacteria isolated from humans, animals and  
68 the environment <sup>3</sup>.

69 In a recent review, Gram-positive bacteria (GPB) were responsible for a high proportion of infections  
70 among children and showed a high level of resistance to WHO-recommended drugs in Africa <sup>4</sup>. In some  
71 African regions, as many as 80% of *Staphylococcus aureus* infections are methicillin-resistant *S. aureus*  
72 (MRSA), which show resistance to most standard licensed drugs including quinolones and peptides <sup>25</sup>.  
73 Although *Enterococcus spp.* are mostly not as virulent as *S. aureus*, their multidrug resistance (MDR)  
74 propensities restrict drug options for clinicians <sup>7</sup>. Patients infected with MRSA are estimated to be 64%  
75 more likely to demise than those infected with methicillin-susceptible *S. aureus* (MSSA) <sup>6</sup>.  
76 Reviews addressing GPB in Africa have reported on increasing rates of ABR from blood-stream  
77 infections, pneumonia, urinary tract infections and meningitis caused by *Streptococcus agalactiae*, *S.*  
78 *aureus*, *Streptococcus pneumoniae* and *Enterococcus faecium* in both children and adults. Sepsis due to *S.*  
79 *agalactiae* accounts for about 26% of all neonatal deaths and 10% maternal deaths in Sub-Saharan Africa  
80 <sup>8</sup> However, the potential dissemination of these resistant strains from farm (environment and animals) to  
81 fork (humans), are less described.

### 82 ***Sources and anthropogenic activities driving resistance***

83 **High-level** ABR has been reported in humans, animals and the environment, with indiscriminate  
84 antibiotic use being fingered as a major contributor in Africa. Resistance genes have been detected in  
85 surface water fed with runoff effluents from farms utilizing antibiotics, hospitals, and sewage processing  
86 plants as well as in ground water <sup>9-11</sup>. Furthermore, genes mediating resistance to last-resort GPB  
87 antibiotics such as vancomycin have been recovered from raw milk and animal products, pigs, wild  
88 animals (buffalo, zebra and cattle), waste water, effluents and patients, implicating veterinary and  
89 agricultural use of antibiotics as potential sources of resistance genes in humans <sup>12-14</sup>. These reports  
90 suggest that a larger share of the antibiotics that end up polluting the environment and communities  
91 emanate from livestock production <sup>15-17</sup>. This interconnectivity between animals, humans and the  
92 environment, explains the need to adopt a One Health research policy.

93 Several studies have reported high rates of MDR among GPB isolates from humans, animals and the  
94 environment in Africa, mainly as a result of overuse, underuse and wrong choice of antibiotics<sup>18–24</sup>.  
95 Different factors have been implicated in the high rate of ABR to the limited drugs in Africa. These  
96 include: unrestricted access to antibiotics over-the-counter without prescription such as selling on the  
97 streets; inadequate hygienic practices; uncontrolled usage of antibiotics as growth promoters in food  
98 animals production; wrong diagnosis and prescription, off-label use and errors in dosage regimens; use of  
99 untreated poultry and cattle manure to fertilize agriculture lands; extensive use of broad-spectrum  
100 antibiotics in poultry production; and inefficient chlorination of hospital wastewater effluents before  
101 discharge into the environment<sup>10,18,22,25–29</sup>. Additionally, inadequate knowledge of animals' diseases,  
102 misdiagnosis and poor antibiotic handling practices in animal production add up to the overall burden of  
103 ABR in Africa<sup>17</sup>.

#### 104 ***Molecular ABR mechanisms***

105 Selective pressures exerted by various antibiotics used in human and veterinary medicine, as well as in  
106 agriculture, have resulted in the emergence and dissemination of numerous mechanisms of resistance in  
107 GPB in Africa. Commonly reported mechanisms include *blaZ*, *erm(B)*, *mecA*, *tet(M)*, *vanB* and *vanC*<sup>30–</sup>  
108 <sup>33</sup>. These resistance genes have been found to be associated with mobile genetic elements (MGEs) such as  
109 transposons, conjugative plasmids, integrons, and insertion sequences, which are capable of mobilizing  
110 resistance genes across a wide spectrum of bacterial species<sup>34,35</sup>. *SCCmec*, *Tn916* and *IS16* are notable  
111 MGEs that carry major ABR determinants in Africa and are transmissible between clones of the same or  
112 different bacteria species by a conjugative mechanism. These MGEs have the potential to thus spread  
113 resistance genes from environmental and animal bacterial hosts to human pathogens in Africa; they have  
114 therefore been analysed herein<sup>36–38</sup>.

#### 115 ***Purpose of this review***

116 Excellent reviews addressing antimicrobial resistance in some GPB and Gram-Negative ones in Africa  
117 have been published<sup>4,39-44</sup>. However, reviews discussing the molecular epidemiology and mechanisms of  
118 ABR in GPB such as *Staphylococcus spp.*, *Streptococcus spp.* and *Enterococcus spp.* in Africa in the  
119 context of resistance rates, resistance mechanisms (and MGEs), clonality, and geographical distribution  
120 from a One Health perspective are non-existent, to the best of our knowledge. This review sought to fill  
121 this gap by analyzing the burden, types, and molecular epidemiology of resistant GPB from a One Health  
122 context.

### 123 *1.1 Search strategy and inclusion criteria*

124 English research articles published within the last ten years (01/01/2007 to 07/08/ 2018) and indexed in  
125 PubMed, Web of Science and African Journals Online were searched with the following keywords:  
126 “Enterococcus”, and “Streptococcus”, “Staphylococcus”, in permutations and combinations with  
127 “resistance AND Africa”. Studies which did not identify the underlying ABR mechanisms/genes as well  
128 as the clonality of antibiotic-resistant GPB were excluded. Thus, studies that only reported on antibiotic  
129 sensitivity testing (AST) results or undertook ABR surveillance studies without further molecular tests to  
130 characterize the ABR mechanisms and/or clonality of the isolates were excluded (Figure 1). In all, 248  
131 studies were excluded because they only had MIC data (See Supplementary data 1). All searches were  
132 undertaken independently by both authors in triplicates to ensure replication of the results.

133 Data extracted from the articles included year of study, country, GPB species, clones, sample sources,  
134 sample size/number of isolates, number of resistant isolates, resistance genes and MGEs and antibiotics to  
135 which the strains were resistant (Tables 1-6; Supplementary data 2). The mean rate of ABR among GPB  
136 per country and in Africa was determined to identify countries with the highest or lowest levels of  
137 resistance in Africa (Table 5). As well, the antibiotics to which the isolates were most resistant were  
138 determined to evaluate their correlation with the detected/reported resistance mechanisms (Table 6).

139 The resistance mechanisms, as well as MGEs involved in the transmission of resistance genes per species  
140 or clone, were determined to assess the means of resistance transfer i.e., horizontal or vertical (through

141 clonal expansion), per specimen sources (animal, human, and environment) (Figures 2a & 2b). The  
142 distribution of clones, resistance genes, and MGEs were considered to identify countries with most  
143 resistant clones, resistance genes, and their associated MGEs (Figure 3a).

#### 144 *1.2 Statistical analysis.*

145 The data was analyzed using Microsoft Excel® 2017 and Graph pad prism™ 6 (GraphPad Software, San  
146 Diego, CA, USA) (Supplementary data 2). Calculation for the statistical significance of the data was  
147 determined using the kolmogorov-smirnov test (with Dallal - wilkinson-Lilliefors p-value) and/or column  
148 statistics or one sample t-test, and the confidence intervals determined at 95%. The p-values were two  
149 tailed with a Gaussian approximation. A p-value of <0.05 was considered as statistically significant. Only  
150 studies that provided the required information were used in the analysis. In all, 130 articles were used for  
151 the data analysis (Fig. 1).

## 152 **2. RESULTS AND DISCUSSION**

153 Of the 1,486 articles returned from the systematic literature search from PubMed, Web of Science and  
154 African Journals Online, 130 studies representing 20 out of 54 African countries were included in this  
155 review and data analysis (Fig. 1). A total of 249 papers were excluded because they only had MIC data.  
156 Tunisia (n=33 studies) recorded the highest number of studies followed by South Africa (n=21 studies),  
157 Egypt (n=21 studies), Nigeria (n=13 studies) and Algeria (n=7 studies), Angola (n=6 studies), Uganda  
158 (n=5 studies), Democratic Republic of the Congo (n=3 studies), Ghana (n=3 studies), Kenya (n=3  
159 studies), São Tomé and Príncipe (n=3 studies), Gabon (n=2 studies), Tanzania (n=2 studies), Cape Verde  
160 (n=1 study), Libya (n=1 study), Namibia (n=1 study), Senegal (n=1 study) and Sudan (n=1 study).  
161 Majority of the included studies were undertaken in Northern Africa (n=65 studies, 50%), Southern  
162 Africa (n=35 studies, 26.9%) and West Africa (n=18 studies, 13.9%). Different rates of resistance to  
163 antibiotics were reported in different countries in Africa (Tables 2-5; Supplementary data 1).

164 A meta-analysis of published literature confirmed the presence of a high mean rate of drug resistance in  
165 GPB isolated from humans (62.0%, 95% CI: 54.7 – 69.3%), animals (68.2%, 95% CI: 58.0 -78.4%) and  
166 the environment (84.6%, 95% CI: 69.9 – 99.3%) ( $P$ -value<0.0001) in Africa, albeit many studies that did  
167 not address the molecular mechanisms of resistance in GPB were excluded. Obviously, the mean rate of  
168 resistance would have been higher had all research articles using only phenotypic methods to describe  
169 ABR in GPB been included (Supplementary data 1). Interestingly, although a lesser number of GPB were  
170 isolated from environmental sources, they expressed higher ABR than those from humans and animals;  
171 hence, the higher mean resistance rate of 84.6%. This also underscores the fact that there is increasing  
172 ABR genes in the environment, obviously due to antibiotic pollution from human activity. Evidently,  
173 ABR is high among GPB in certain regions in Africa (Figures 3a & 3b) (Table 5) and underpins the need  
174 to up the ante against this menace through increased molecular surveillance research, education of clinical  
175 microbiologists on ABR, and antibiotic stewardship.

176 Studies describing detailed molecular mechanisms of GPB resistance and molecular epidemiology in  
177 Africa are few, making it difficult to paint a vivid comprehensive picture of ABR in Africa. However, this  
178 review shows that *S. aureus* ST5, *E. faecium* ST18, ST80 and ST910, *E. faecalis* and *S. agalactiae*  
179 harbouring *mecA*, *tet* and *erm* genes, were commonly found in humans, animals and the environment,  
180 particularly in Northern, Western, and Southern Africa. Thus, careful use of  $\beta$ -lactams, tetracyclines, and  
181 macrolides is warranted to prevent further selection and dissemination of these resistance genes and  
182 resistant clones. Furthermore, it will be prudent for countries within these regions to review their  
183 recommended antibiotic regimens, guidelines/protocols for infections caused by these species.

184 *erm*(B) and *tet*(M) were found in *S. aureus*, *Enterococcus spp.* and *Streptococcus spp.*, with *erm*(B),  
185 *tet*(M) and *vanA* genes being mobilized by Tn916 and IS16, indicating horizontal transfer within same  
186 clones, different clones and species. The discovery of same clones and resistance genes in specimens  
187 from humans, animals and the environment suggest a possible transmission of these clones between  
188 humans, animals and the environment, corroborating the need for a One Health approach to infection



189 control and management of antibiotic-resistant infections. Further molecular epidemiological surveillance  
190 in the above-mentioned states is crucial to forestall further spread of these resistant pathogenic clones  
191 both within their borders and from their borders to other countries.

### 192 ***Resistance rates per countries and MDR GPB species***

193 High mean resistance rates were reported in Sudan (98.5%), South Africa (82.7%) Nigeria (71.2%),  
194 Egypt (70.5%), Angola (66.2%), Tunisia (66.8%), Ghana (65.1%), Algeria (62.2%) etc. (Table 5). Cross-  
195 contamination of multi-drug resistant bacteria between patients and the environment accounted for the  
196 high rate of resistance in Algeria <sup>45-49</sup>. The high rate of ABR in Tunisia was attributed to cross  
197 contamination between hospital patients and hospital environment, immune deficiency <sup>50</sup>, over-  
198 consumption of antibiotics, heavy consumption of sheep meat, which is a reservoir of MRSA, and high  
199 consumptions of antibiotics in animal feed <sup>51,52</sup>. In Egypt, inappropriate antibiotic prescription practices <sup>29</sup>,  
200 inadequate hygienic handling and processing of food <sup>12</sup>, and close contact with pet dogs accounted for the  
201 high resistance <sup>53</sup>. The high rate of drug resistance in Nigeria has been attributed to the exchange of  
202 resistance genes between farm animals or their products and man <sup>54,55</sup>, existence of MRSA in clinical and  
203 community settings <sup>56</sup>, uncontrolled usage of antibiotics <sup>57</sup> and the presence of efflux pumps in coagulase-  
204 negative staphylococcus strains <sup>58</sup>. Expansion of resistant clones <sup>59</sup>, variability of hospital acquired MRSA  
205 clones <sup>60</sup>, consumption of unpasteurized milk or inefficient thermal processing of milk <sup>21</sup>, shedding of  
206 resistant clones from animals to the environment and heavy consumption of antibiotics to treat TB due to  
207 high HIV burden <sup>61</sup>, were incriminated for the high-level resistance in South Africa.

208 *Staphylococcus spp.* (*S. aureus*, *S. haemolyticus* and *S. saprophyticus*); *Streptococcus spp.* (*S. pyogenes*  
209 and *S. agalactiae*), and *Enterococcus spp.* (*E. faecium*, *E. faecalis*, *E. hirae*, *E. durans*, and *E.*  
210 *gallinarum*) were the antibiotic-resistant GPB widely distributed in Northern, Southern, Western and  
211 Central Africa. The high number of *tet*(M/L/K), *erm*(A/B/C), *aph*(3')-III and *vanA/B/C* in *Staphylococcus*  
212 *spp.*, *Enterococcus spp.*, and *Streptococcus spp.* reported in Tunisia, South Africa, Nigeria, Algeria and  
213 Egypt accounted for the high rate of resistance to tetracycline, erythromycin, kanamycin and vancomycin

214 (Figure 3a). Such resistant GPB are known to compromise the safety of invasive medical procedures such  
215 as organ transplants, orthopedic surgery, and cancer treatment. In addition, infections such as sepsis,  
216 endocarditis, deep wound infections, pneumonia, meningitis and urinary tract infections caused by these  
217 resistant pathogens are becoming increasingly fatal due to limited treatment options<sup>62,63</sup>. The abuse of  
218 antibiotics as growth promoters, prophylaxis, and metaphylaxis in food animals in these countries have  
219 been implicated in the selection of resistant bacteria that can pass on to humans through food  
220 consumption, direct contact with animals and the environment, as well as trade of animals and food  
221 products between countries<sup>64</sup>.

222 Approximately 26, 385 GPB were isolated from humans (n=83 studies), animals (n=32 studies) and the  
223 environment (n=14 studies) (Tables 1-4), with mean rates of ABR varying from 14.2% to 98.5% across  
224 the 20 included countries (Tables 2-5). The antibiotics to which the isolates were most resistant to were  
225 penicillin (n=4 224 isolates, 76.2%), erythromycin (n=3 552 isolates, 62.6%), ampicillin (n=1 507  
226 isolates, 53.9%), sulfamethoxazole/trimethoprim (n=2 261 isolates, 46.0%), tetracycline (n=3 054  
227 isolates, 42.1%), vancomycin (n=1 281 isolates, 41.2%), streptomycin (n=1 198 isolates, 37.0%),  
228 rifampicin (n=2 645 isolates, 33.1%), ciprofloxacin (n=1 394 isolates, 30.5%), clindamycin (n=1 256  
229 isolates, 29.9), and gentamicin (n=1 502 isolates, 27.3%) ( $p$ -value <0.0001) (Tables 2-4 & 6). Countries  
230 with high number of studies such as Tunisia, South Africa, Egypt and Nigeria recorded high number of  
231 ABR (Table 5) and high number of *mecA*, *erm(B)*, *tet(M)*, *drfG* and *vanB* resistance genes (Figure 3a).  
232 Vancomycin resistance was reported in seven studies each for animals and the environment, and 12  
233 studies in Humans. Vancomycin-resistant *Enterococcus spp.* (n=102 isolates) and vancomycin-resistant  
234 *Staphylococcus spp.* (n=258 isolates) were reported in humans, animals and the environment (Tables 2-4;  
235 Figures 2). Vancomycin-resistant *Staphylococcus aureus* (VRSA) was reported in animals (n=238  
236 isolates), the environment (n=15 isolates) and humans (n=5 isolates). A similar situation occurred with  
237 vancomycin-resistant *E. faecium*, which was isolated from the environment (n=306 isolates), animals (n=  
238 671 isolates) and humans (n=26 isolates) (Supplementary data 1).

239 Antibiotic-resistant *S. aureus* ST5, *E. faecium* (ST18, ST80 and ST910) and *E. faecalis* harbouring *mecA*,  
240 *erm(B)*, *erm(C)*, *tet(M)*, *tet(K)*, *tet(L)* and *vanB* were isolated from humans, animals and the environment,  
241 albeit in higher proportion in humans and animals than the environment (Tables 2-4). For instance, Farhat  
242 et al. (2014)<sup>46</sup>, van Rensburg et al. (2012)<sup>59</sup> and De Boeck et al. (2015)<sup>65</sup> in Algeria, South Africa and  
243 Democratic Republic of Congo respectively, reported on resistant *S. aureus* ST5 in humans whilst Fall et  
244 al. (2012)<sup>66</sup> reported on the same clone (*S. aureus* ST5) in pigs from Senegal. Further, Mariem et al.  
245 (2013)<sup>24</sup> isolated the same clone (*S. aureus* ST5) from the environment in Tunisia, suggesting that this  
246 clone is widely distributed in Africa in humans, animals and environment. It is currently not clear whether  
247 this clone first emerged from humans, animals or the environment, but its presence in all three spheres  
248 shows the possibility of resistant species and clones being disseminated between animals, humans and the  
249 environment. Notably, *S. aureus* ST5 is among the frequently reported clones in Asia<sup>67</sup> and recent  
250 evidence suggest that it has spread from hospitals into communities, resulting in community-acquired  
251 MRSA<sup>68</sup>.

252 Similarly, Lochan et al. (2016)<sup>30</sup> in South Africa, Dziri et al. (2016)<sup>20</sup> and Elhani et al. (2014)<sup>69</sup> in  
253 Tunisia isolated resistant *E. faecium* ST80 from humans. For the first time, *E. faecium* ST80 was isolated  
254 from environmental samples in a hospital in Tunisia by Elhani et al. (2013)<sup>69</sup> and Dziri et al. (2016)<sup>70</sup>.  
255 Transmission of this resistant clone to animals is possible, although not yet reported. This implies that  
256 these resistant species and clones are circulating between humans and the environment, underpinning the  
257 broad host range and transmissibility of these strains between humans and the environment.

258 *mecA* was the predominant resistance gene, which corresponded with the higher penicillin resistance  
259 recorded (Figure 2a<sub>ii</sub>). MRSA strains were the most commonly isolated strains ( $\geq 2,350$ )<sup>71-74</sup>. This is  
260 consistent with the global report of increasing prevalence of MRSA<sup>75,76</sup>. MRSA harbours the *mecA* gene,  
261 which is carried by the SCC<sub>mec</sub> MGE, and mediates resistance to multiple  $\beta$ -lactam antibiotics<sup>77</sup>. From  
262 this review, MRSA showed resistance to eleven different antibiotic classes: aminoglycosides (gentamicin,  
263 tobramycin),  $\beta$ -lactams (penicillin, ampicillin, oxacillin, cefoxitin), fluoroquinolones (ciprofloxacin,

264 levofloxacin, ofloxacin), glycopeptides (vancomycin), lincosamide (clindamycin), macrolides  
265 (erythromycin), phenicols (chloramphenicol), rifamycins (rifampicin), streptogramins (pristinamycin),  
266 sulfonamides (trimethoprim/sulfamethoxazole), and tetracyclines (tetracycline). MRSA is thus a  
267 worrying public health threat as some strains have evolved resistance to almost all licensed drugs (26).  
268 Vancomycin-resistant Enterococci (VREs) ( $\geq 594$ ), which were reported in Northern and South Africa,  
269 also pose a serious threat to public health as they are resistant to vancomycin, a glycopeptide that is  
270 reserved for fatal or life-threatening Gram-positive infections, and other important antibiotics such as  
271 ampicillin, erythromycin, fluoroquinolones (ciprofloxacin, levofloxacin), gentamicin, rifampicin,  
272 streptomycin, trimethoprim/sulfamethoxazole and tetracycline. In this study, enterococcus isolates had a  
273 resistance rate of 60.1% (95%, CI=32.2 -87.9) (p-value = 0.0005) to vancomycin (Table 6). Multidrug  
274 resistance in VREs increases VRE-associated mortality rates, which is likely to increase to 75% compared  
275 with 45% from susceptible strains<sup>13,80</sup>. As well, evolution of macrolide resistance (42.0%, 95% CI: 12.02  
276 – 72.1) (p-value = 0.0129) in drug-resistant streptococci is limiting treatment options and resulting in  
277 high mortalities<sup>81–83</sup>. In this study, MRSA, VRE and drug-resistant streptococci remain major public  
278 health threats, calling for measures to contain ABR. Novel antibiotics such as linezolid, synergid, and  
279 daptomycin should be used empirically whilst awaiting susceptibility results. The empirical therapy can  
280 be changed or maintained based on the susceptibility report<sup>84</sup>.

### 281 ***Resistance rates of species per animals, humans and the environment***

282 The rates of ABR in isolates recovered from the environment was highest, followed by isolates from  
283 animal sources. Among environmental isolates, 91.2% (95%, CI=78.8–103.6) were resistant to penicillin,  
284 82% (95%, CI=40.6–123.4) were resistant to sulfamethoxazole/trimethoprim, 68.5% (95%, CI=24.1–100)  
285 were resistant to ampicillin, 60.8% (95%, CI=25.0–96.6) were resistant to vancomycin, 56.9% (95%,  
286 CI=–40.7–73.2) were resistant to erythromycin, 54.5% (95%, CI=29.49–79.5) were resistant to  
287 ciprofloxacin, and 51.3% (95%, CI=21.3–100) were resistant to clindamycin (Table 6). Among animal  
288 isolates, 71.8% (95%, CI=54.9–88.73) were resistant to penicillin, 58.9% (95%, CI=36.1–81.7) were  
289 resistant to clindamycin, 58.5% (95%, CI=37.6 –79.4) were resistant to ampicillin, 49.6% (95%,

290 CI=30.1–69.1) were resistant to trimethoprim/sulfamethoxazole, 42.3% (95% CI=17.7–67.0) were  
291 resistant to vancomycin, 47.6% (95% CI=34.0–61.2) were resistant to erythromycin, and 38.8% (95%  
292 CI=21.3–56.3)(p-value = 0.15) were ciprofloxacin resistant (Table 6; Supplementary file 1).

293 The rates of resistance were much lower in humans for most of the antibiotics used (Tables 2-4). Among  
294 the various species, *Enterococcus spp.* and *Staphylococcus spp.* recorded high rates of resistance for most  
295 antibiotics (Figure 3b). *Streptococcus spp.* reported low rates of resistance except for tetracycline to  
296 which it recorded a high rate of 55.13% (95%, CI=20.63.18–89.64) (p-value = 0.006). Resistance to  
297 vancomycin was not reported in any *Streptococcus spp.* Isolate (Table 6).

298 *Enterococcus spp.*, mainly *E. faecium* and *E. faecalis*, recorded a resistance rate of 98.5% (95%,  
299 CI=94.5–102.6)(p-value = 0.0001) to clindamycin, 81.6% (95%, CI=52.1–110)(p-value = 0.0008) to  
300 trimethoprim/sulfamethoxazole, 64.0% (95%, CI=50.0–78.1)(p-value=0.0001) to erythromycin, 60.1%  
301 (95%, CI=32.2–87.9)(p-value = 0.0005) to vancomycin, 57.3% (95%, CI=24 -90.7)(p-value=0.0057) to  
302 penicillin, 51.7% (95%, CI=35.8–67.6)(p-value=0.0001) to tetracycline, 49.9% (95% CI=31.3–68.5)(p-  
303 value = 0.0001) to ciprofloxacin, 48.9% (95% CI=20.6–77.2)(p-value=0.004) to kanamycin, 47.1% (95%  
304 CI=26.7–67.7)(p-value=0.0006) to ampicillin, 40.8% (95% CI=24.3–57.4)(p-value=0.0001) to  
305 streptomycin and 34.0% (95% CI=19.7–48.4)(p-value=0.0002) to gentamicin (Table 6).

306 *S. aureus* showed high resistance (79.6%) to penicillin (95% CI=69.7–89.5)(p-value = 0.0001), 67.8% to  
307 erythromycin (95% CI=11.5–147.0)(p-value = 0.0917), 55.5% to ampicillin (95% CI=44.50–88.5)(p-  
308 value = 0.0001), 39.3% to trimethoprim/sulfamethoxazole (95% CI=39.3–47.8)(p-value = 0.0001), 36.9%  
309 to tetracycline (95% CI=29.3–44.5)(p-value = 0.0001), 35.8 to streptomycin (95% CI=14.7–57.0)(p-value  
310 = 0.004), 33.6% to rifampicin (95% CI=20.1–47.03)(p-value = 0.0001), 24.0% to clindamycin (95%  
311 CI=14.9–33.1)(p-value = 0.0001), 23.9% to ciprofloxacin (95% CI=17.6-30.2)(p-value= 0.0001), 22.7%  
312 to vancomycin (95% CI=4.3–41.2)(p-value = 0.0212) and 22.2% to vancomycin (95% CI=15.7–28.3)(p-  
313 value = 0.0001) (Table 6).

### 314 **Resistance mechanisms, clones, and MGEs**

315 Few studies identified the clones and MGEs in the resistant isolates. Of the 130 included studies, 32  
316 identified the clones whilst 22 described the MGEs, which were used in the statistical analysis. The most  
317 dominant gene detected in Africa, which was widespread and responsible for resistance in GPB, was  
318 *mecA* (n=3 547), followed by *erm(B)* (n=1 268), *vanC1/2/3* (n=971), *tet(M)* (n=720), *blaZ* ( $\geq 565$ ), *dfpG*  
319 (n=422), *vanB* ( $\geq 451$ ), *aph(3')-IIIa* ( $\geq 170$ ) and *aac(6')-aph(2')* ( $\geq 268$ ) (p-value = 0.0011) (Fig. 2a).

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

325 *IS16* and *Tn916* were found with the resistance genes *erm(B)* and *tet(M)* in *E. faecium* (ST18, ST80 and  
326 ST910), *S. agalactiae* (ST612, ST616 and ST617), *E. faecalis* and *S. pyogenes* (*emm18*, *emm42*, *emm76*  
327 and *emm118*) isolated from humans, animals and the environment (Tables 2-4; Figure 2b). *tet(M)* was  
328 associated with *Tn916* transposon in tetracycline-resistant *S. agalactiae*<sup>85</sup> and *S. pyogenes*<sup>81</sup> in humans in  
329 Tunisia. Fischer et al. (2013) also reported the association between *Tn916* and *tet(M)* in tetracycline-  
330 resistant *S. agalactiae* in camel in Kenya<sup>86</sup>. Similarly, *IS16* was found in vancomycin-resistant *E.*  
331 *faecium* (ST80, ST180 and ST910) in humans and the environment in Tunisia<sup>69,70</sup>. Investigations into the  
332 association between MGEs and resistance genes were limited by few studies (n=22 studies) on MGEs.

333 From Tables 2-4, majority of the resistance genes namely, *mecA*, *erm(B)*, *tet(M)*, *vanA* etc. were  
334 responsible for drug resistance to antibiotics such as aminoglycosides (gentamicin, streptomycin,  
335 kanamycin),  $\beta$ -lactams (penicillins, cephalosporins), fluoroquinolones (ciprofloxacin), macrolide  
336 (erythromycin), sulfamethoxazole/trimethoprim, tetracycline and glycopeptides (vancomycin). These  
337 resistance genes were widely distributed in Northern Africa (Tunisia, Algeria, Egypt, Morocco, and

338 Libya) and Southern Africa (South Africa and Namibia). All the three different MGEs (Tn916, SCCmec  
339 and ISI6) were reported in Tunisia, with two being reported in Kenya (SCCmec and Tn916). ISI6 was  
340 only reported in an *E. faecium* infection in Tunisia (Figure 3) whilst *mecA* was mostly associated with  
341 SCCmec. *erm*(B) and *tet*(M) were highly associated with Tn916 and ISI6.

342 In Africa, different studies have reported SCCmec-borne *mecA* in *S. aureus* in humans, animals and the  
343 environment<sup>23,47,60,66,87</sup> besides the discovery of ISI6 and Tn916 in the environment of *erm*(B) and *tet*(M)  
344 genes in Enterococcus and Streptococcus. These reports show that MGEs are mediating the  
345 dissemination of these (and possibly other) resistance genes across different GPB clones and species.  
346 MGEs-mediated mobilization of various resistance genes in different GPB clones and species in humans,  
347 animals and the environment (Tables 1-4; Figure 2b) calls for prompt measures to contain ABR as the  
348 situation may worsen if additional resistance genes are acquired by the MGEs. Resistance genes on MGEs  
349 can be horizontally transferred to susceptible cells or vertically transferred to daughter clones<sup>37,88,89</sup>,  
350 which can easily spread these resistance genes to susceptible pathogens. The higher number of resistant  
351 Gram-positive cocci and mean resistance rate in Tunisia may be due to the presence of these three MGEs  
352 in this region<sup>69,70,81,90</sup>

### 353 **Molecular epidemiology of antibiotic-resistant GPB**

354 *Staphylococcus spp.* (*S. aureus*, *S. haemolyticus* and *S. saprophyticus*)

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

356 **Algeria.**

357 *S. aureus* was recovered from two different studies in Algeria. In assessing the nasal carriage of *S. aureus*  
358 in patients with medical conditions including pneumonia, urinary tract infections, osteoarthritis, heart  
359 diseases, diabetes and chronic kidney disease, Djoudi *et al.* (2014) isolated MRSA<sup>46</sup>. They also found  
360 nasal carriage of *S. aureus* to be significantly associated with cancer and previous hospitalization of  
361 patients with kidney failure due to immunological suppression and hemodialysis. The nine MRSA  
362 isolates, i.e. ST80 (n=4), ST5 (n=2), ST22 (n=2) and ST535 (n=1), harboured *mecA* and were resistant to



363 tobramycin (n=6), gentamicin (n=1), trimethoprim/sulfamethoxazole (n=2), tetracycline (n=3) and  
364 erythromycin (n=1). MRSA ST80 is a well-known and frequent etiological agent of infections in North  
365 Africa and Middle-East countries<sup>91,92</sup>. Typing of 64 MRSA isolated from human pus (n=47), venous  
366 catheters (n=7), tracheal aspirates (n=4), puncture fluids (n=3), blood (n=2) and urine (n=1) in 64  
367 Algerian patients revealed that 50 were hospital acquired (HA-MRSA) and 14 community acquired (CA-  
368 MRSA), which were all resistant to ceftazidime and oxacillin<sup>47</sup>. *mecA*, mobilized by *SCCmec*, was the only  
369 detected mechanism of resistance.

### 370 ***Egypt***

371 MRSA have been respectively isolated in five animal-based and two human-based studies in Egypt  
372 between 2011 to 2017. Hashem et.al (2013) isolated 94 *S. aureus* strains from blood and wounds in which  
373 45 were MRSA while 25 were fluoroquinolone-resistant<sup>29</sup>. Mutations such as C2402T, T2409C,  
374 T2460G, T1497C, and A1578G in gyrase enzymes, which leads to fluoroquinolones' target-site  
375 alterations, were implicated in resistance to fluoroquinolones (ciprofloxacin, levofloxacin, ofloxacin). The  
376 high rate of fluoroquinolone resistance (55.56%) among MRSA infections is rather concerning as patients  
377 unable to tolerate vancomycin are treated with other antibiotics such as fluoroquinolones. Vancomycin is  
378 often reserved as a last-resort therapy for MRSA infections due to their high resistance to several  
379 antibiotics.

380 Multidrug resistance to drugs such as gentamicin, ampicillin, amoxicillin, cefepime, tetracycline and  
381 chloramphenicol in MRSA is mediated by diverse resistance mechanisms including impermeability  
382 effects and efflux pumps. Unrestricted access to antibiotics and inappropriate prescriptions were  
383 responsible for the high rates of drug resistance in this study<sup>29</sup>. In a similar study, MRSA was isolated  
384 from patients suffering from surgical wound infections, diabetic foot, abscess and burns. Although *mecA*  
385 was the only mechanism of resistance, the isolates were multiple-resistant to several antibiotics belonging  
386 to the  $\beta$ -lactams, aminoglycosides, fluoroquinolones, macrolides, lincosamides, tetracyclines and



387 glycopeptides, indicating other mechanisms of resistance<sup>93</sup>. It therefore implies that administration of  
388 such antibiotics will not relieve patients from *S. aureus* infections. The high rate of *S. aureus* isolation  
389 confirms it to be the most prevalent Gram-positive pathogen isolated from soft tissue and wound  
390 infections.

391 Al-Ashmawy *et. al.* detected a high rate of MRSA (53%) in milk and dairy products believed to originate  
392 from human contamination rather than contamination from animals. Besides being resistant to  $\beta$ -lactams  
393 and other antibiotics, thirty-six of the isolates were resistant to vancomycin known to be effective in  
394 treating MRSA infections<sup>12</sup>, making milk and dairy products a significant source of multidrug-resistant  
395 and toxigenic *S. aureus* infections. The occurrence of MRSA in pets such as dogs admitted in a veterinary  
396 clinic<sup>53</sup> may confirm a possible route in the community transmission of this pathogen, which is emerging  
397 as a veterinary pathogen of public health importance.

398 In 2017, Osman and colleagues detected *Staphylococcus spp.* in imported beef meat. Sixteen of these  
399 isolates were MDR and showed resistance to different groups of antibiotics due to resistance mechanisms  
400 such as *mecA*, and mutations in *gyrA* and *gyrB*. Indeed, MRSA has made methicillin and other  $\beta$ -lactams  
401 antibiotics clinically useless as a result of their high MDR<sup>94</sup>. Imported meat acts as a transmission vector  
402 for MRSA and is worrisome as *Staphylococcus spp.* are among the most common foodborne pathogens  
403 causing food poisoning outbreaks worldwide. Of 133 *S. aureus* recovered from animal origin, more than  
404 70% were MDR and 30 were MRSA, exhibiting high resistance to clindamycin, co-trimoxazole,  
405 tetracycline, oxacillin, cefoxitin, ceftriaxone and erythromycin; four of the isolates were resistant to  
406 vancomycin<sup>23</sup>. The isolates showed the maximum sensitivity to imipenem, chloramphenicol and  
407 rifamycin, which is consistent with similar reports in China and Pakistan<sup>95,96</sup>, indicating their  
408 effectiveness in treating *S. aureus* infections.

409 MRSA was isolated from chicken products mainly due to poor hygienic handling processes, posing a risk  
410 to public health in 2016. The mean *S. aureus* count in the chicken products were beyond the permissible  
411 limits of the Egyptian organization for Standardization and Quality Control (EOSQC 2005), coupled with

412 resistance to different antibiotics classes; thus, retail chicken products could constitute a high health risk  
413 to human consumers <sup>28</sup>

#### 414 **Morocco**

415 In a study to assess *S. aureus* carriage among end-stage renal diseases patients undergoing hemodialysis,  
416 42.9% were carriers, of which only one was MRSA. The methicillin-susceptible *S. aureus* (MSSA) was  
417 resistant to many of the local antibiotics, thus limiting the successful treatment of MSSA infections.  
418 Moreover 81.8% of the MSSA were penicillin-resistant. The male gender and age 30 or below were  
419 identified as risk factors of *S. aureus* nasal carriage (*P*-value < 0.001) <sup>27</sup>. Periodic monitoring of patients  
420 with hemodialysis is crucial as they are at increased risk of *S. aureus* infection due to periodic  
421 hospitalization, immunosuppression and high invasive vascular interventions.

#### 422 **Tunisia**

423 Resistant *S. aureus* was isolated from the environment, animals and humans between 2011 to 2017. Ben  
424 Said, et al. recovered 12 MSSA from wastewater samples that were resistant to penicillin (n=12 isolates),  
425 erythromycin (n=7 isolates), tetracycline (n=1 isolate) and clindamycin (n=1 isolate) due to the presence  
426 of *blaZ* (n=7), *msr(A)* (n= 7) and *tet(K)*(n=1). These resistant strains were of ST3245(n=7) and  
427 ST15(n=1) <sup>18</sup>, which have been also reported in animals and humans. In an investigation to evaluate the  
428 prevalence of coagulase-negative Staphylococcus (CoNS) in the hospital environment, MDR *S.*  
429 *haemolyticus* and *S. saprophyticus* were the most dominant. Methicillin resistance was detected in *S.*  
430 *haemolyticus*, *S. epidermidis* and *S. saprophyticus*. These isolates were resistant to erythromycin,  
431 tetracycline, gentamicin, kanamycin, tobramycin and streptomycin due to the presence of *msrA* (32),  
432 *erm(C)* (8), *tet(K)* and *tet(M)*, *aac(6')-Ie-aph(2'')-Ia* (16), *aph(3')-IIIa*(19), *ant(4')-Ia* (n=14) and  
433 *ant(6')-Ia* (3) <sup>97</sup>. The high prevalence of MDR *Staphylococci spp.* isolates may result from transmission  
434 between the staff, patients and the environment. Strict infection controls are needed as infections caused  
435 by CoNS are common cause of death, particularly in low-birth-weight children, and are opportunistic  
436 infections in immunocompromised patients <sup>98</sup>.

437 Moreover, nasal swab from sheep detected five MRSA (*mecA*=5), which were all of ST153 and carried  
438 *blaZ*, *ant(6)-Ia*, *aph(30)-IIIa*, *erm(C)*, *tet(K)*, and *fusB* genes that respectively encoded resistance to  
439 penicillin, streptomycin, kanamycin, erythromycin, tetracycline and fusidic acid. This study shows that  
440 the nares of healthy sheep could act as reservoirs of MRSA <sup>99</sup>.

441 Between 2011 to 2012, 99 MRSA strains were detected from nasal swabs, blood, catheter, wounds,  
442 pleural puncture and abscess, among which 39 were tetracycline resistant. These isolates were resistant to  
443 aminoglycosides, fluoroquinolones, macrolides and lincosamide, with mechanisms of resistance including  
444 *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).  
445 Identified drug-resistant strains included ST247 (n=12), ST239 (n=6), ST728 (n=2), ST241 (n=1), ST398  
446 (n=1), ST5 (n=1) and ST641 (n=1) <sup>50</sup>. For the first time, clonal lineage ST398, which has been reported  
447 in pigs from several studies in USA, South America, Asia and Canada <sup>100-103</sup>, was found in human MRSA  
448 isolates in Africa in a nasal swab of a 74-year old patient.

449 Additionally, 69 MRSA strains were isolated from hospital-acquired and community-acquired infections.  
450 Although *mecA* (n=59) was the only mechanism of resistance identified, the isolates were resistant to  
451 aminoglycosides, tetracycline, fluoroquinolones, macrolides and rifampicin. The resistant clones were  
452 ST1 (n=2), ST5 (n=5), ST22 (n=1), ST80 (n=41), ST97 (n=2), ST153 (n=2), ST239 (n=4), ST241 (n=3),  
453 ST247 (n=3), ST256 (n=1), ST1819 (n=3) and ST1440 (n=1) <sup>24</sup>.

454 Mezghani Maalej and colleagues (2012) isolated five pristinamycin-resistant *S. aureus* strains from  
455 patients with skin infections. These isolates were MDR (Table 2), being the first detection of resistance to  
456 streptogramins due to *vat(B)* and *vga(B)* resistance genes <sup>104</sup>, which emerged due to selective pressure  
457 from the use of pristinamycin. Thirty-six methicillin-resistant *S. haemolyticus* (MRSHae) were isolated  
458 from neutropenic patients (suffering from febrile neutropenia) with hematological cancer between 2002  
459 and 2004. These MDR isolates carried SCC*mec*-borne *mecA* (Table 2) <sup>105</sup>, which agrees with a report on  
460 *S. haemolyticus*' MDR capacity, particularly in immunocompromised patients <sup>106,107</sup>

461 **Libya**

462 Due to the high risk of MRSA colonization developing into infections in children, nasal samples were  
463 collected from children inpatients, their mothers, healthcare workers and outpatients' workers, which  
464 yielded a MRSA nasal carriage rate of 8.3%, 11% ,12.3% and 2.2% respectively in Libya <sup>108</sup>. Thus, nasal  
465 carriage of MRSA is common in inpatients children, their mothers and health workers in Libya and could  
466 be a source of MRSA infections.

## 467 **West Africa: Ghana, Nigeria, Senegal**

### 468 *Ghana*

469 Among 308 staphylococcus isolates collected across Northern, Central and Southern Ghana in 2013, low  
470 prevalence of antibiotic resistance was reported except for penicillin (97%), tetracycline (42%) and  
471 erythromycin (6%) <sup>109</sup>. Moreover, *mecA* was detected in only nine isolates, implying the presence of other  
472  $\beta$ -lactam resistance mechanisms. The MRSA clones included ST8 (n=1), ST72 (n=1), ST88 (n=2), ST239  
473 (n=1), ST250 (n=2), ST789 (n=1), and ST2021 (n=1). In a similar study that characterized 30 MRSA  
474 isolates resistant to tetracycline, fluoroquinolones and macrolides, *tet(M)* (n=13), *tet(K)* (n=10), *aphA3*  
475 (n=7), *aacA-aphD* (n=5) and *erm(C)* (n=4) were detected. Similar and different resistant clones, viz.  
476 ST88 (n=8), ST8 (n=5), and ST247 (n=4) were detected <sup>110</sup>, indicating high MRSA clonal diversity in  
477 Ghana. These studies show a high rate of resistance to non- $\beta$  lactams that further complicate MRSA  
478 treatment. Furthermore, the isolation of USA300 and other epidemic multidrug-resistant MRSA clones  
479 calls for MRSA surveillance and adequate control measures.

### 480 *Nigeria*

481 Five different studies reported drug-resistant *S. aureus* from several human anatomical sites such as throat  
482 swabs, soft skin and tissue infection, urinary tract and respiratory infections, wound, vagina, otitis,  
483 conjunctivitis, septicemia and bronchitis. Of a total  $\geq 602$  isolates,  $\geq 433$  were resistant to several antibiotic  
484 classes (Table 1). Of note, 429 of the  $\geq 433$  drug-resistant isolates were all resistant to cotrimoxazole or  
485 trimethoprim/sulfamethoxazole (SXT). Mechanisms of resistance included *mecA* ( $\geq 54$ ), *blaZ* (n=284),

486 *dfrA* ( $\geq 5$ ) and *dfrG* ( $\geq 152$ ). *S. aureus*-resistant clones ST8, ST14, ST37, ST39, ST88, ST152, ST241, and  
487 ST772 were present. Colonized persons, including immune-compromised individuals, facilitated the  
488 spread of *S. aureus* and MRSA ST8 identified as ubiquitous in various geographic areas of Nigeria. High  
489 utilization of co-trimoxazole or SXT because of low cost and easy obtainability through lenient  
490 medication regulations were implicated for the high resistance <sup>56</sup>. Besides *S. aureus*, *S. haemolyticus* was  
491 the major species isolated, and is considered as the second most detected and clinically important  
492 *Staphylococci spp.*, particularly in immunocompromised patients <sup>111</sup>. All the *S. haemolyticus* isolates  
493 detected were resistant to at least three antibiotics classes (Tables 2-4) <sup>112</sup>.

494 Moreover, O. Ayepola *et al.* (2015) reported a higher rate of 20.8% *S. aureus* from UTIs than the  
495 reported ranges in Africa (6.3-13.9%), and far exceed the rate reported from Europe and Brazil (1.1%) <sup>113</sup>.  
496 None of the isolates exhibited resistance to vancomycin, linezolid, daptomycin and mupirocin; indicating  
497 their usefulness in treating *S. aureus* infections. Co-trimoxazole, which was previously clinically valuable  
498 in treating MRSA infections, demonstrated the highest level of resistance, hence it's not recommendable  
499 <sup>56,57,90,112</sup>. In a study to examine the genetic mechanism(s) of resistance in CoNS in faecal samples, all the  
500 53 isolated CoNS were Penicillin V-resistant and between three to 19 exhibited multidrug resistance  
501 (Table 2); *mecA* (n=15), *erm(C)*, *tet(M)* (n=4) and *tet(K)* (n=6) were identified <sup>112</sup>. CoNS isolates from  
502 faeces carrying tetracycline, macrolides and aminoglycosides resistance genes may transfer them inter-  
503 and intra-species, disseminating MDR in *Staphylococcus*.

#### 504 ***Senegal***

505 A low prevalence of MRSA (10.5%) was reported in Senegalese pigs compared to those reported in  
506 developed countries. This might be due to a lesser veterinary antibiotic use as growth promoters and/or  
507 for therapy. However, all the isolates were resistant to penicillin, 27 were resistant to co-trimoxazole and  
508 16 were resistant to tetracycline <sup>66</sup>. Five of the MRSA were of ST5 <sup>66</sup>, evincing the spread of this clone in

509 animals, humans<sup>46,59</sup>, and the environment<sup>24</sup>; the importance of this clone as a cause of human infections  
510 is well-established<sup>68</sup>.

### 511 *Cape verde*

512 In Cape Verde, a low prevalence of 5.6% (6/107) MRSA nasal carriage was documented in 2015. The  
513 predominant MRSA clones was ST5 (n=3), ST8 (n=1) and ST88 (n=2). These isolates showed significant  
514 level of resistance to erythromycin (ERY), sulphamethoxazole-trimethoprim (SXT) and penicillin G  
515 (PEN)<sup>114</sup>.

### 516 **Central Africa: Gabon, D.R. Congo**

#### 517 *Gabon*

518 In Gabon, *S. aureus* isolated from colonized persons, blood, as well as soft and skin tissue infections  
519 resulted in 49% (104/212) resistance to trimethoprim: *dfrA* (n=1), *dfrG* (n=100), *dfrK+G* (n=1), *dfrB*  
520 (n=2), and *mecA* (n=1) were detected in the isolates<sup>55</sup>. Thus, *dfrG* is obviously the most abundant and  
521 common trimethoprim resistance mechanism in Africa, refuting *dfrB* mutation as the main mechanism of  
522 resistance to trimethoprim<sup>115-117</sup>.

#### 523 *D.R. Congo (DRC)*

524 A total of 215 (79.3%) drug-resistant *S. aureus* isolates were collected between 2015 to 2017 from nasal  
525 swab and bloodstream infections in the D. R. Congo; 70 isolates were MRSA. Other major resistance  
526 genes mediating resistance to trimethoprim/sulfamethoxazole, aminoglycoside, macrolides, tetracycline,  
527 penicillin, and chloramphenicol were *dfrG* ( $\geq 120$ ), *tet(K)* ( $\geq 98$ ), and *femA* ( $\geq 98$ ). MRSA showed high-  
528 level resistance to  $\beta$ -lactams, aminoglycoside, macrolides and tetracycline. The pathogen caused severe  
529 infections such as pneumonia, meningitis, complicated urinary tract infections, gynaecological infections  
530 and peritonitis. *S. aureus* ST8 ( $\geq 47$ ) was the dominant clone, followed by ST152 ( $\geq 17$ ), ST5 ( $\geq 2$ ) and  
531 ST88 ( $\geq 2$ ). In DRC, MRSA ST8 outnumbers the African MRSA clone ST88, which is dominant in  
532 Africa. The high-level oxacillin resistance in DRC was associated with a mutation in *femA* (Y195F) whilst

533 high-level trimethoprim resistance was due to the detection of *dfrG*, which is consistent with  
534 trimethoprim resistance in Africa and Asia. In Africa, SXT or cotrimoxazole is frequently administered  
535 as prophylactic to immuno-suppressed patients such as HIV/AIDS patients to prevent opportunistic  
536 infections such as *Pneumocystis carinii* pneumonia, toxoplasmosis and bacterial pneumonia<sup>118</sup> Hence,  
537 prophylactic use of SXT in HIV patients may impact resistance. Additionally, there was high-level MDR  
538 among MRSA, which is a great concern as microbiological laboratories/facilities and second-line  
539 antibiotics are rare in DRC. Moreover, the detection of nasal carriage among healthcare workers'  
540 demands strict infection controls and surveillance<sup>65,119,120</sup>.

#### 541 **East Africa: Kenya, Tanzania**

##### 542 *Kenya*

543 In contrast to earlier studies done in Kenya, Omuse and colleagues (2016) detected a wide genetic  
544 diversity of MRSA and well-established epidemic MRSA clones among clinical isolates. MRSA clonal  
545 complexes 5, 22 and 30, implicated in several outbreaks were described. These clones included ST5 (n=1  
546 isolates), ST8 (n=2 isolates), ST22 (n=4 isolates), ST88 (n=1 isolates), ST241 (n=12 isolates), ST239  
547 (n=2 isolates) and ST789 (n=1 isolates). Approximately 41% of the MRSA in the study were MDR  
548 (Table 2), showing resistance to clindamycin, erythromycin and SXT<sup>87</sup>. Detection of these clones in  
549 referral hospitals in Kenya calls for implementation of strict infection control measures to reduce the high  
550 morbidities and mortalities associated with HA-MRSA infections.

##### 551 *Tanzania*

552 In a study to investigate the molecular epidemiology of trimethoprim resistance in MSSA causing skin  
553 and soft tissues infections, *dfrG* was detected in all 32-trimethoprim resistant isolates. Other reported  
554 trimethoprim resistance mechanisms such as *dfrA*, *dfrB* and *dfrK* were missing, confirming *dfrG* as the  
555 main trimethoprim resistance mechanism in Sub-Sahara Africa<sup>55</sup>.

##### 556 *Uganda*

557 A MRSA carriage of 56.1% (23/41) was detected in milk from pastoral communities in Uganda, exactly  
558 70% of which were tetracycline-resistant. MRSA clones ST97 and ST1 were identified. Furthermore,  
559 over 90% of the isolates carried genes encoding enterotoxin that causes food-borne diseases. The weak  
560 veterinary delivery system and the high dependency on animals and animal products for food in Uganda  
561 was implicated for the high prevalence of MRSA <sup>121</sup>.

562 *S. aureus* isolates, including 24 MRSA and 40 MSSA, were isolated from patients with surgical site  
563 infections (SSI). The MRSA isolates were MDR (including resistance to oxacillin, gentamicin,  
564 ciprofloxacin and chloramphenicol) compared to the MSSA. Inducible clindamycin resistance was found  
565 in 17.2% of the isolates, mostly in MRSA. In a multivariate analysis, inducible clindamycin resistance  
566 and cancer were identified as independent predictors of MRSA-SSI <sup>122</sup>.

## 567 **Southern Africa: Angola, Malawi, Mozambique, Namibia, South Africa**

### 568 *Angola*

569 Conceica˜o et al (2014) reported a nasal *S. aureus* carriage of 23.7% (n=128 isolates), out of which 58.1%  
570 (n=77 isolates) were MRSA. Fifty-seven of the MRSA clones were of ST5, followed by ST88 (n=9), ST8  
571 (n=5) and ST72 (n=3). This study represents the first description of the spread of MRSA ST5 in Africa.  
572 All the 77 MRSA strains were resistant to SXT, cefoxitin (FOX) and PEN <sup>123</sup>. In a study to identify  
573 oxacillin-susceptible *mecA*-positive *S. aureus* (OS-MRSA) for the first time in Africa, a prevalence of  
574 17.7% was detected among healthy healthcare workers in Angola and Sa˜o Tome´ & Principe, making  
575 them potential OS-MRSA reservoirs <sup>124</sup>. OS-MRSA have been reported worldwide in humans, animals  
576 and food animals <sup>125–128</sup>. The OS-MRSA isolates expressed MDR (Table 2) and belonged to ST88 (n=15  
577 isolates) and ST8 (n=9 isolates). In sub-Saharan Africa, the identification of clinically important *S. aureus*  
578 is heavily based on phenotypic agar-screening and oxacillin disc-diffusion methods.

### 579 *Mozambique*



580 The prevalence of HA-MRSA and CA-MRSA in Mozambique was found to be 15.1% and 1%,  
581 respectively. MRSA showed high-level resistance to penicillin, ceftazidime, gentamicin, ciprofloxacin,  
582 erythromycin, SXT, chloramphenicol and tetracycline, compared to MSSA. Additionally, inducible  
583 macrolide–lincosamide–streptogramin B (MLSB) resistance was 41.7% and 10.7% in hospital-acquired *S.*  
584 *aureus* (HA-SA) and community-acquired *S. aureus* (CA-SA) isolates respectively <sup>129</sup>, further limiting  
585 therapeutic options for *S. aureus* infections. This study, which is the first to detect the emergence of HA-  
586 MRSA within post-operative abdominal wounds and burn wounds in Mozambique, reported that patients  
587 with infected burn wounds had a significantly longer hospitalization than patients with post-operated  
588 abdominal wounds. Efforts to prevent the transmission of MDR HA-SA, such as education on proper  
589 hand-washing techniques, are urgently needed.

#### 590 ***Namibia***

591 The dominant resistance gene mediating trimethoprim resistance in MRSA and MSSA in Namibia was  
592 *dfpG*. This is similar to reports in other Africa countries <sup>55</sup>. Moreover, *dfpG* was frequently detected in *S.*  
593 *aureus* from SSTIs in travelers returning from other African countries, suggesting that *dfpG* can be  
594 transmitted into populations with low antifolate resistance such as North America and Europe <sup>130,131</sup>.

#### 595 ***South Africa***

596 Thirty MDR *S. aureus* were recovered between April 2015 to April 2016 from ten beaches in the Eastern  
597 Cape Province, South Africa (Table 2). Notably, the isolates harbored *mecA*, *femA*, *rpoB*, *blaZ*, *erm*(B)  
598 and *tet*(M) <sup>11</sup>, making marine environments and public beaches potential depositaries of MDR *S. aureus*  
599 that can be transmitted to animals and humans. Further, the 50% resistance to vancomycin recorded is  
600 concerning to global health due to its role as a last-resort antibiotic for treating MRSA infections.

601 *S. aureus* was detected in raw and pasteurized milk at an isolation rate of 75% and 29% respectively, due  
602 to inefficient thermal processing and post-process contamination. A high proportion (60%-100%) of these  
603 isolates showed resistance to aminoglycosides,  $\beta$ -lactams, vancomycin, tetracycline and erythromycin,  
604 albeit only 19 *mecA* genes were present <sup>21</sup>. Evidently, raw and pasteurized milk can harbour MDR *S.*  
605 *aureus*, exposing consumers to colonization and/or infections. Again, *Staphylococcus spp.*, including *S.*

606 *aureus*, *S. haemolyticus*, *S. xylosus* and *S. capitis* were isolated from healthy pigs and cattle, of which  
607 between 75 to 100% were resistant to penicillin G, tetracycline, sulfamethoxazole and nalidixic acids, due  
608 to their use as growth promoters; *mecA* and *mphC* were identified. Additionally, 12% of the isolates were  
609 resistant to vancomycin and erythromycin, evincing the important role of animals in the dissemination of  
610 resistance determinants and the importance of commensals to public health <sup>61</sup>.

611 Van Rensburg et al. <sup>59</sup> detected 43.4% (1432/3298 isolates) and 3.1% (328/10448 isolates) rifampicin  
612 resistance rate among MRSA and MSSA respectively. Similar studies in South Africa have also reported  
613 of high rifampicin resistance in MRSA <sup>132,133</sup>, obviously due to frequent use of rifampicin among  
614 tuberculosis patients, who are highly prevalent in South Africa. MRSA ST5 and ST612 were detected  
615 while H481Y/N and I527M mutations in *rpoB* were associated with high-level rifampicin resistance,  
616 similar to reports in Italy <sup>134</sup>. Additionally, novel H481N, I527M, K579R mutations were also detected.

617 Three studies reported a prevalence of 29.1% <sup>135</sup>, 45.44% <sup>60</sup> and 100% <sup>136</sup> MRSA recovered from humans,  
618 expressing resistance to macrolides, tetracycline, aminoglycoside, cotrimoxazole and rifampicin. MRSA  
619 ST612, ST239, ST36 and ST5 were the dominant strains similar to other findings in Australia and  
620 Europe<sup>137</sup>. The study showed that *S. aureus* bacteremia is common and account for high mortality in  
621 South Africa. For instance, in a study by Perovic et al., <sup>135</sup> 202 patients died from *S. aureus* bacteremia  
622 infections, with HIV patients being more likely to acquire HA-MRSA. The isolates were however  
623 susceptible to glycopeptides, fluoroquinolones, linezolid, tigecycline, fosfomycin and fusidic acid,  
624 confirming their clinical usefulness in treating MRSA infections. In a recent study, a high prevalence and  
625 genetic diversity of multi-drug efflux (MDE) resistance genes were found in clinical *S. aureus* isolates,  
626 including 81 MRSA and 16 MSSA <sup>138</sup>. *norA*, *norB*, *mepA*, *tet(38)*, *sepA*, *mdeA*, *imrs* and *sdrM* were  
627 present in at least 86% of the isolates, predicting resistance to broad-spectrum biocides and  
628 fluoroquinolones, which is disturbing. Efforts to develop efflux pump inhibitors can mitigate such  
629 resistance mechanisms.

630 ***Sao Tome & Principe***

631 MRSA prevalence of 26.9%<sup>139</sup> and 25.5%<sup>114</sup> was reported in nasal swabs in 2014 and 2015, respectively,  
632 in Sao Tome & Principe. Additionally, a high prevalence of oxacillin-susceptible *mecA*-positive *S. aureus*  
633 was reported in the same study in Sao Tome & Principe and Angola<sup>124</sup>. The most dominant MRSA clone  
634 was ST8 (n=25 isolates), followed by ST5 (n=13 isolates) and ST80 (n=13 isolates). High genetic  
635 variability was found in the MSSA strains. Both MRSA and MSSA showed different levels of resistance  
636 to SXT, ERY, CIP and TET; however, all the MRSA isolates were resistant to ceftiofur.

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

638 Drug resistant *Streptococcus spp.* including *S. agalactiae* and *S. pyogenes* have been identified in  
639 Northern, Eastern and Southern Africa. *S. pyogenes* were reported in only humans whilst *S. agalactiae*  
640 was reported in both animals (camels) and humans with a high rate of resistance to tetracycline and  
641 erythromycin.

### 642 **North Africa: Algeria, Egypt, Morocco, Tunisia, Libya**

#### 643 ***Algeria***

644 A sole study has so far detected 44 tetracycline (100%, 44/44 isolates)- and erythromycin-resistant  
645 (43.18%, 19/44 isolates) *S. agalactiae* from vaginal swabs; *tet(M)*; and *erm(B)* respectively mediated this  
646 resistance. A high diversity of resistant clones viz., ST1, ST19, ST10, ST158, ST166, ST233, ST460,  
647 ST521 and ST677 were detected<sup>45</sup>, which have been reported worldwide for causing life-threatening  
648 invasive diseases such as meningitis and sepsis<sup>140,141</sup>.

#### 649 ***Egypt***

650 Similarly, Shabayek et al. (2014) detected 98% and between 14-17% *S. agalactiae* resistance to  
651 tetracycline and macrolides respectively. *tet(M)* was detected in all the 98 tetracycline-resistant isolates  
652 whilst *erm(B)* and *erm(A)* mediated erythromycin resistance. Efflux pump genes such as *tet(K)* (n=12  
653 isolates), *tet(L)* (n=1 isolates) and *mefA/E* (n=1 isolates) were also found<sup>32</sup>, which reflects the increasing  
654 reports of *S. agalactiae* resistance to tetracycline and macrolides<sup>142</sup>. This study also showed that

655 vancomycin and fluoroquinolones are effective replacement for erythromycin and clindamycin, and for  
656 patients allergic to penicillin. Although penicillin is the antibiotic of choice for treating *S. agalactiae*  
657 infections, reports of penicillin resistance in USA and China calls for increased surveillance in Africa <sup>142</sup>.

## 658 **Tunisia**

### 659 *S. agalactiae*

660 From January 2007 to December 2009, 226 *S. agalactiae* were isolated from female genitals and gastric  
661 fluid of infected newborns. Of these, 97.35% (220/226 isolates), 40% (90/226 isolates) and 19.1%  
662 (43/226 isolates) were resistant to tetracycline, erythromycin and rifampicin respectively. Additionally,  
663 seven isolates were resistant to aminoglycoside (gentamycin and streptomycin) and chloramphenicol.  
664 *tet(M)* (n=205 isolates), encoding a ribosomal protection protein, which protect the ribosome from the  
665 action of tetracycline, was the main tetracycline resistance mechanism, and was significantly associated  
666 with Tn916 (p-value = 0.0002). Other resistance genes including *erm(B)* (n=79 isolates) and *tet(O)* (n=50  
667 isolates) were detected. All isolates were however susceptible to  $\beta$ -lactams and quinupristin-dalfopristin  
668 <sup>85</sup>. Between 2005 and 2007, 160 erythromycin-resistant *S. agalactiae* were isolated from humans, with a  
669 high resistance rate of 84.3% (135/160 isolates) to the constitutive macrolides-lincosamides,  
670 streptogramins B (MLSB) <sup>143</sup>.

### 671 *S. pyogenes*

672 Hraoui *et al.*, (2011) reported a low macrolide resistance rate (5%, 5/103) and a high tetracycline  
673 resistance rate (70%, 72/103) among human isolates, with *tet(M)*, associated with Tn916, being  
674 responsible for tetracycline resistance <sup>144</sup>. Increase tetracycline use in food animals was implicated in this  
675 instance, leading to selection and dissemination of resistance genes from animals to human. Macrolide  
676 resistance was only detected in seven isolates, which is corroborated by the findings of Ksia *et al.* (2010),  
677 who detected low-level macrolides resistance among Children <sup>145</sup>.

678 **East Africa: Kenya, Tanzania**

679 **Kenya**

680 ***S. agalactiae***

681 In the horn of Africa, camel plays a significant role in the survival of humans by providing milk, meat  
682 and transportation. In 2013, Fischer et al. detected 36% (37/92) tetracycline resistance in *S. agalactiae*  
683 isolates from camels' wound infections and mastitis that was mainly mediated by a Tn916-borne *tet(M)*.  
684 ST616 (n=22) was the major resistant clone, followed by ST612 and ST617<sup>146</sup>. Shifting from tetracycline  
685 to other antibiotics is evidently necessary for effective treatment outcomes in camel infections in Kenya.

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

687 **South Africa**

688 ***S. agalactiae***

689 A *S. agalactiae* colonization rate of 30.9% was detected from vaginal and rectal swabs of pregnant  
690 women. Similar to other reports in Africa, a high rate of tetracycline (94.5%, 120/128 isolates) and  
691 macrolide (21.1%, 27/128) resistance was documented. All the isolates were however sensitive to  
692 penicillin, ampicillin, vancomycin and gentamicin. Macrolide and clindamycin resistance were associated  
693 with *erm(B)* and *mefA* genes<sup>147</sup>. The study highlights the need for research on treatment options for  
694 patients allergic to penicillin due to high-level resistance in alternative drugs such as macrolides and  
695 lincosamides.

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

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

698 **Algeria**

699 The first study to molecularly characterize *Enterococcus spp.* from urinary tract and wound infections in  
700 Algeria revealed a high rate of resistance to erythromycin (86.4%, 108/125 isolates), tetracycline (82.4,  
701 103/125 isolates), levofloxacin (71.2%, 89/125 isolates) and gentamicin (54.4, 68/125 isolates). Only

702 3.2% (4/125 isolates) were VRE, confirming glycopeptides as ideal antibiotics for treating Enterococcus  
703 infections. A mortality rate of 10% was reported due to infections caused by Enterococcus. *E. faecium*, *E.*  
704 *faecalis* and *E. gallinarum* were the main Enterococcus isolated. Majority of these isolates were from  
705 females (53%). *erm*(B) ( $\geq 92$ ) and *vanCI*( $\geq 4$ ) were the main mechanisms of resistance. A high genetic  
706 diversity among strains was seen in *E. faecium* and *E. faecalis*, with *E. faecium* ST78 being the dominant  
707 resistant strain <sup>148</sup>, which is also prevalent in Asian (Japan, Taiwan, China and Korea) and European  
708 (Italy and Germany) countries <sup>149–151</sup>. A novel ST317 (n=33) clone was predominant among the *E.*  
709 *faecalis* isolates. Rational use of antibiotics, as well as close monitoring of the epidemiology of the strains  
710 are crucial.

### 711 **Egypt**

712 In a similar study to characterize *E. faecium* and *E. faecalis* from patients, 82% of the isolates were MDR,  
713 showing high-level resistance to aminoglycosides,  $\beta$ -lactams and tetracycline. *VanA* was detected in two  
714 *E. faecium* isolates, all of which were resistant to all antibiotics tested. Bioinformatic (sequence) analysis  
715 revealed that *vanA* was transmitted horizontally to *S. aureus*, showing the importance of horizontal gene  
716 transfer in ABR and subsequent management of enterococci infections such as bacteremia, endocarditis  
717 and urinary tract infections <sup>152</sup>.

### 718 **Tunisia**

719 Antimicrobial-resistant Enterococcus was found in faeces of pet and camel, irrigation water from farm  
720 environments, food vegetables, hospital environments, animal meat and patients in Tunisia <sup>19,22,31,51,52,69</sup>.  
721 High-level resistance to vancomycin, macrolides, aminoglycosides,  $\beta$ -lactams and tetracycline was  
722 detected in the environment, animals and humans with majority of the isolates being *E. faecium*, followed  
723 by *E. faecalis*. *tet*(M), *tet*(L), *erm*(B), *ant* (6)-*la*, *vanA* and *aph*(3')-IIIa were the major resistance  
724 mechanisms, with *IS16* being the main MGE disseminating the resistance genes. *E. faecium* ST80, ST910  
725 and ST16 were the dominant resistant clones in Tunisia. The studies show that meat, animals, pets,

726 hospital environment and wastewater used for farm irrigation play a crucial role in the spread of antibiotic  
727 resistant Enterococcus.

## 728 **West Africa: Cape Verde, Ghana, Nigeria, Senegal**

### 729 **Nigeria**

730 *Enterococcus spp.* isolated from poultry and cattle as well as their manure demonstrated high-level  
731 resistance to tetracycline, erythromycin, gentamicin, ampicillin and streptomycin. Sixty isolates were  
732 MDR, showing resistance to three or more antimicrobials<sup>153</sup>. The rate of MDR is a reflection of the  
733 substantial use of broad-spectrum antibiotics in Nigeria, raising major public health concerns as practices  
734 such as the use of untreated poultry and cattle manure for fertilizing agricultural soils, particularly  
735 vegetables, are a common practice in Africa. This could transfer MDR Enterococci to humans, and cause  
736 serious nosocomial infections including endocarditis, bacteremia and urinary tract infections that can  
737 result in high morbidities and mortalities.

738 Ngbede et al. (2017) recently characterized 63 ampicillin- and 37 gentamicin-resistant *E. faecium* from  
739 vegetables, soil, farms, animal and manure<sup>25</sup>. Approximately 95% (35/37 isolates) and 8% (5/63 isolates)  
740 of the aminoglycoside- and ampicillin-resistant clones were recognized as high-level aminoglycosides-  
741 and ampicillin-resistant *E. faecium* respectively. Modifying enzymes' genes such as *aac(6')-Ie-aph(2'')-*  
742 *Ia*), *aph(2')-Ic*, *aph(3')-IIIa*., and *ant(4')-Ia* accounted for the aminoglycoside resistance.

## 743 **East Africa: Kenya and Tanzania**

### 744 **Tanzania**

745 In a study to determine if cattle co-grazing with wild life influence ABR, ABR in wild animals such as  
746 buffalo, zebra and wildebeest was higher than in cattle, although wildlife is periodically treated with  
747 antibiotics. Ten VRE and ampicillin-resistant Enterococcus were found in the wild animals but not cattle.  
748 Additionally, Enterococcus isolates from wildlife were highly resistant to tetracycline, rifampicin,  
749 macrolides, aminoglycosides and cotrimoxazole<sup>14</sup>. *tet(W)* and *sulI* were the resistance genes identified  
750 in the isolates. The practice of co-grazing possibly resulted in transmission of ABR genes from livestock

751 to wildlife. The high presence of ABR bacteria in wildlife was likely due to contact with more  
752 environmental surfaces that have been contaminated with human, birds or animal excreta. Result from  
753 this study demonstrates the presence of ABR Enterococci in wild animals without antibiotic pressure.

#### 754 **Southern Africa: Angola, Malawi, Mozambique, Namibia, South Africa**

##### 755 **South Africa**

756 Multiple antibiotic-resistant Enterococci were isolated from borehole water, waste water, pigs and  
757 humans in South Africa. Notably, a very high-level vancomycin, aminoglycoside,  $\beta$ -lactam, macrolides  
758 and fluoroquinolones resistance was detected among the Enterococci isolates compared to other countries.  
759 *erm(B)* ( $\geq 300$  isolates), *vanC* 2/3 (162 isolates), *vanB* ( $\geq 138$  isolates), *vanC* ( $\geq 120$  isolates), *strA* ( $\geq 120$   
760 isolates) were the major resistance genes. The vancomycin-resistant isolates were from patients with  
761 haematological malignancies, bacteremia, pigs, wastewater and underground water<sup>9,10,26,30</sup>. Inefficient  
762 chlorination to kill bacteria accounted for the high resistance rates in the final effluents' discharge into the  
763 environment. Hospital wastewater is therefore a major source of MDR Enterococcus. Sub-therapeutic  
764 antibiotic usage in animal feed also accounted for the emergence of ABR in pigs whilst the construction  
765 of boreholes near pit toilets resulted in high enterococcal isolation and resistance rates in South Africa.

##### 766 ***Experimental procedures used in included studies***

767 The studies included in this review basically used the following experimental procedures. Transport  
768 media such as stuart agar, cary-blair medium, and gel transport swabs with charcoal were used to  
769 transport the samples to the laboratory<sup>53,65</sup>. Cotton swabs were used to swab sample specimens, tissues,  
770 surfaces, fluids, etc. and cultured on nutrient agar, blood agar, tryptone soya agar, mannitol salt-phenol  
771 red agar, brain-heart infusion broth, Slanetz-Bartley mannitol salt agar, and Edwards agar media prior to  
772 identifying the 24-hour colonies using Gram-staining and different biochemical tests such as catalase and  
773 coagulase tests, latex coagulase test and DNase agar test. Subsequently, antimicrobial susceptibility  
774 testing (AST) using disc diffusion (Kirby-Bauer method or E-test) on Mueller Hinton agar plates and a  
775 0.5 McFarland bacterial inoculum was performed. Antibiotics such as ampicillin (AMP), amoxicillin



776 (AMX), amikacin (AMK), ampicillin-Sulbactam (SAM), amoxicillin-clavulanic acid (AMC),  
777 azithromycin (AZI), apramycin (APR), chloramphenicol (CHL), ceftazidime (CFZ),  
778 clarithromycin (CLR), ciprofloxacin (CIP), cefuroxime (CXM), clindamycin (CLI), cephalixin(LEX),  
779 cefoperazone (CFP), cefepime (FEP), cefotaxime (CTX), ceftaroline (CPT), cephalothin (CET),  
780 cloxacillin (CLX), doxycycline (DOX), erythromycin (ERY), fusidic acid (FUS), fosfomycin (Fof),  
781 gatifloxacin (GAT), gentamicin (GEN), imipenem (IPM), kanamycin (KAN), levofloxacin (LVX),  
782 linezolid (LZD), lincomycin (LIN), meropenem (MER), mupirocin (MUP), minocycline (MIC),  
783 moxifloxacin (MXF), methicillin (MET), metronidazole (MTZ), nitrofurantoin (NIT), norfloxacin (Nor),  
784 nalidixic acid (NAL), netilmicin (NEL), oxacillin (OXA), ofloxacin (OFX), perfloxacin (PF), penicillin  
785 (PEN), pristinamycin (PRI), rifampicin (RIF), streptomycin (STR), streptogramin B (SB),  
786 sulfamethoxazole (SMZ), tetracycline (TET), teicoplanin (TEC), telithromycin (TEL), tobramycin (TOB),  
787 trimethoprim-sulfamethoxazole (SXT), and vancomycin (VAN) were mostly used for the AST.  
788 Polymerase chain reaction (PCR) was used to detect the antimicrobial resistance genes and clones (i.e.  
789 molecular typing) of the isolates.

### 790 3. CONCLUSION AND STUDY LIMITATIONS

791 We report of high rate of ABR among GPB in several African countries, mediated largely by *S. aureus*  
792 ST5, ST8, and ST80, *Enterococcus faecium* and *Enterococcus faecalis* strains, *SCCmec*, Tn916 and IS16  
793 MGEs are a major threat to clinical medicine, the economy and socio-economic development. This calls  
794 for national as well as international rules and regulations to contain resistance. Heavy consumption of  
795 antibiotics in animal feed, exchange of resistance genes between animals and food animal products to  
796 man, uncontrolled and inappropriate antibiotics prescription practices, inadequate hygienic handling and  
797 processing of food, close contact with pet dogs, shedding of resistant clones from animals to humans and  
798 the environment, as well as high consumption of antibiotics in humans, particularly in HIV patients,  
799 account for the high rate of ABR in Africa.

800 Effective surveillance and monitoring of antimicrobial drug usage and licensing, banning or restricting the  
801 prescription of reserved, expired and substandard drugs, periodic monitoring of pharmacies and veterinary  
802 shops, and antibiotic stewardship are recommended measures to contain ABR. Improving animal health  
803 through hygienic practices on farms, avoiding prophylactic or growth-promoting antibiotic usage in  
804 veterinary medicine, integrative efforts between human and veterinary medicine as well as environmental  
805 health are urgently needed to contain ABR. Implementation of these policies will decrease the high rate of  
806 ABR in Africa, reduce longer hospital stays and the resort to expensive but toxic antibiotic alternatives,  
807 with a concomitant reduction in morbidity and mortality rates. Few studies reporting on the molecular  
808 determinants of ABR in GPB in Africa limited the study to 130 articles. Among these, only few studies  
809 reported on MGEs and resistant clones.

810

811 **Role of Funding Source:** Not applicable.

812 **Contributors:** JOS conceived, designed and supervised the study, analysed and vetted the results, wrote  
813 the paper, edited and formatted it for publication. EM co-conceived and co-designed the study, gathered  
814 and analysed the data and drafted the paper. Both authors approved the final version for submission.

815 **Funding:** None

816 **Declaration of interests:** The authors declare no conflict of interest.

817 **Acknowledgments:** None

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1524 **Table 1. Frequency distribution of Gram-positive bacterial species, resistance genes and MGEs**  
1525 **isolated from animals, humans and environmental specimens.**

Bacteria species, ARGs and MGEs		Human (n) <sup>1</sup>	Animal(n) <sup>2</sup>	Environment(n) <sup>3</sup>
Species	<i>E. faecalis</i>	225	129	66

<sup>1</sup> Total number of species or ARGs or MGEs in human isolates

<sup>2</sup> Total number of species or ARGs or MGEs in animal isolates

<sup>3</sup> Total number of species or ARGs or MGEs in environmental isolates

	<i>E. faecium</i>	299	577	523
	<i>S. agalactiae</i>	658	92	0
	<i>S. aureus</i>	25559	1609	65
	<i>S. haemolyticus</i>	96	43	38
	<i>S. pyogenes</i>	296	0	0
<b>ARGs</b>	<i>mecA</i>	3057	462	28
	<i>erm(B)</i>	551	520	197
	<i>erm(C)</i>	102	23	8
	<i>tet(M)</i>	524	115	81
	<i>tet(K)</i>	179	80	22
	<i>tet(L)</i>	25	57	37
	<i>vanB</i>	4	387	60
	<i>vanA</i>	23	0	23
	<i>vanC1/2/3</i>	8	862	101
	<i>dfrA/G</i>	422	0	0
<i>aph(3')-IIIa</i>	50	5	115	
<i>aac(6')-aph(2')</i>	178	17	73	
<i>ant(6)-Ia</i>	5	24	38	
<i>blaZ</i>	403	127	35	
<b>MGEs</b>	<i>IS16</i>	3	0	5
	<i>SCCmec</i>	2471	27	8
	<i>Tn916</i>	62	37	0

1526 **Table 2. Geographical distribution, species, clones, and resistance mechanisms of antibiotic-resistant Gram-positive bacteria isolated from**  
 1527 **humans in Africa from 2007-2018**

Country (n) <sup>4</sup>	Year	Organism/Species (n) <sup>5</sup>	Specimen Sources (n) <sup>6</sup>	Sample size (Resistant isolates)	Resistance rate (%)	Clones (n) <sup>7</sup>	Resistance genes/mechanisms (n) <sup>8</sup>	Antibiotics to which strains were resistant(n) <sup>9</sup>	MGEs (n) <sup>10</sup>	Reference
Algeria (6)	2015	<i>S. agalactiae</i> (44)	Vaginal swab (44)	(44)	100	ST1(9), ST19(14), ST10(4), ST158, ST166, ST233, ST460, ST521, ST677	<i>tet(M)</i> (44), <i>erm(B)</i> (19), <i>mefA/E</i> (1), <i>erm(A)</i> (1)	TET (44) ERY (13)	ND	45
	2014	<i>S. aureus</i> (159)	Nasal swab (159)	159 (9)	5.66	ST80 (4), ST5 (2), ST22 (2), ST535 (1)	<i>mecA</i> (9)	GEN ((3), TET (3), TOB(6) SXT(2)	SCC <sub>mec</sub> (9)	46
	2013	<i>S. aureus</i> (85), <i>E. faecalis</i> (7), <i>C. ONs</i> (31)	Human(123)	123(NS)	NS	NS	<i>mecA</i> (73), <i>aphA</i> (70), <i>aacA-aphD</i>	Methicillin(73)	ND	154
	2012	<i>E. faecium</i> (80), <i>E. faecalis</i> (39) <i>E. gallinarum</i> (4), <i>E. raffinosus</i> (1), and <i>E. durans</i> (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)	<i>erm(B)</i> (92), <i>vanC1</i> (4)	AMP (38), GEN (68), TET (103), ERY (106), CAM (18), LVX ((89), NIT (24), VAN (4).	ND	148
	2012	<i>S. aureus</i> (64)	Pus (47), venous catheters (7)	(64)	100	ND	<i>mecA</i> (64)	MET (64), OXA (64), FOX (64)	SCC <sub>mec</sub>	47

<sup>4</sup> Total number of studies per country

<sup>5</sup> Total number of isolates

<sup>6</sup> Total number of specimen source

<sup>7</sup> Total number of resistant clones

<sup>8</sup> Total number of resistant genes

<sup>9</sup> Total number of antibiotics to which strains were resistant to.

<sup>10</sup> Total number of MGEs

			tracheal aspirates (4), puncture fluids (3), blood (2), urine (1)						(46)	
	2010	<i>S. aureus</i> (221)	Skin and soft tissue(158),bone and joint (infection(25),bacteraemia(20),pneumonia(12),eye infection(7),meningitis(3),UTI(2)	221(41)	18.55	ST80(13),ST241(9)	<i>mecA</i> (97)	KAN(29),TET(25),ERY(25),FUS(41)	SCCmec(97)	
Angola (4) and Sao Tome principe (1)	2015	<i>S. aureus</i> (164)	Nasal swab (164)	164 (29)	17.68	ST88(15), ST8(9)	<i>mecA</i> (NS)	FOX (29), SXT (26), TET (18), ERY (16), CIP (9) and CLI (8)	SCCmec (NS)	49
	2015	<i>S. aureus</i> (203)	Nasal (203)	203(128)	63.05	ST8(16), ST5(83), (ST88(19), ST72(5), ST789(1), ST5/2629(2), ST30(2), ST22(1)	<i>mecA</i> (127)	SXT (136), FOX (128), TET (39), PEN (200), RIF (156), CLI (4), ERY (14), CIP (20), GEN (43), CHL (18)	SCCmec (128)	114
	2015	<i>S. aureus</i> (70)	Nasal swab(70)	70(61)	87.14	ST5(13),ST88(6),ST601(1)	<i>mecA</i> (20)	PEN(67),FOX(20),RIF(61),SXT(15),CHL(6),GEN(3),TET(7),FUS(1),CIP(1)	ND	155
	2014	<i>S. aureus</i>	Nasal swab (128)	128(124)	96.88	ST8(57), ST88(9), ST8(5), ST72(3), ST789(1)	<i>mecA</i> (77)	PEN (124), FOX (77), SXT (80), GEN (24), RIF (97), CHL (11), CIP (10), TET (16), ERY (8)	SCCmec (128)	123
Cape verde (1)	2015	<i>S. aureus</i>	Nasal swab (113)	113(16)	14.16	ST88(2), ST8(1), ST5(3)	<i>mecA</i> (6)	FOX (5), TET (5), PEN (109), CIP (2), CLI (3), SXT (12), ERY (16), (FUS (5), MUP (6)	SCCmec (6)	
Democratic Republic of Congo (3)	2017	<i>S. aureus</i> (108)	blood(108)	108(27)	25	ST5(11),ST8(30),ST88(1),ST152(17)	<i>dfgG</i> (24), <i>aac</i> (6')- <i>aph</i> (2'')(25), <i>tet</i> (K)(23), <i>erm</i> (C)(20)	TET(61),LIN(20),CIP(20),PEN(87),CHL(5),SXT(4),	ND	120

	2016	<i>S. aureus</i> (100)	Nasal swab (100)	100 (97)	97	ST8 (9)	<i>dfrG</i> (72), <i>tet</i> (K) (44), <i>femA</i> (98), <i>mecA</i> (33)	TMP(72), PEN (97), TET(45),GEN(25),OXA(24),ERY (20),LUV(16),RIF(7),CHL(7),CLI(4)	ND	119
	2015	<i>S. aureus</i> (63)	Nasal swabs (63)	63(10)	15.87	ST8 (8), ST5 (1), ST88 (1)	<i>mecA</i> (10)	TET(21),ERY(12),CLI(8),PG(60) ,CHL(9),KAN(12),GEN(12),TOB(12), SXT(6)	SCCmec (10)	65
Egypt (10)	2017	<i>S. aureus</i> (20), <i>S. haemolyticus</i> (9), <i>S. schleifer</i> (3), <i>S. warnei</i> (2), <i>S. lugdunensis</i> (4)	Urine(NS), Blood(NS)	58(38)	65.52	ND	<i>mecA</i> (19)	FOX(25),CIP(21),CLI(21), SXT(21),ERY(38),GEN(32),RIF(14), TET(27)	SCCmec	156
	2016	<i>E. faecalis</i> (57)	Urine(57)	57(52)	91.23	ND	<i>acc</i> (6) <i>la-aph</i> (2) <i>la</i> (21), <i>erm</i> (B)(51), <i>mef</i> (A/E) (1)	AMX(14),VAN(2),FoF(36),GEN(20), AMK(52)	ND	157
	2016	<i>Staphylococcus spp</i>	Urine(3),blood(10), pus(7),sputum(4),bronchoalveolar lavage(2)	81(26)	32.1	ND	<i>fusB</i> (8), <i>fusC</i> (9)	GEN(14),RIF(5),AMP(17)	ND	158
	2016	<i>S. aureus</i> (60)	Human(60)	60(NS)	NS	ST22(1),ST239(1)	<i>mecA</i> (14), <i>erm</i> (C)(14)	CLI(NS),CIP(NS),GEN(NS),SXT(NS), VAN(NS),OXA(NS),ERY(NS).	ND	159
	2016	<i>S. aureus</i> (64)	Sputum(18),pus(35), urine(10),CSF(1)	64(45)	69.23	ND	<i>mecA</i> (NS)	CRO(45),ERY(38),OXA(38),SXT(31), GEN(22),CIP(19),CLI(17),VAN(3)	ND	160
	2015 H	<i>E. faecium</i> (26), <i>E. faecalis</i> (47)	Urine (100)	(73)	100	ND	<i>vanA</i> (2)	PEN(17), AMP(38), CIP(22), GEN(41), STR(73), CHL(12), TET(50), VAN(2)	ND	80



	2014	<i>S. agalactiae</i> (100)	Vaginal swab (100)	100 (98)	98	ND	<i>erm</i> (B) (9), <i>erm</i> (A) (1), <i>mefA/E</i> (1), <i>tet</i> (M) (99), <i>tet</i> (L)(12), <i>tet</i> (K)(1), <i>tet</i> (O) (1)	ERY(17), CLI(14), AZI(16), TET(98) and CHL(1)	ND	32
	2014	<i>S. aureus</i> (127)	Diabetic foot ulcers (39), surgical site infection (48) and abscess infections (25), burn discharges (15).	127 (111)	87.40	ND	<i>mecA</i> (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	93
	2013	<i>S. aureus</i> (94)	Blood and wound	94 (45)	47.87	ND	<i>gyrA</i> (C2402T, T2409C, T2460G) (60), <i>gyrB</i> (T1497C, A1578G) (5)	CIP(26), LUX(26), AMC(26), FEP(24), GEN(11), TET(17), CHL(5)	ND	29
	2008	<i>S. aureus</i> (60)	Sputum(13),throat swabs(11), nasal swabs(31), blood(9)	60(31)	51.67	ND	<i>mecA</i> (18)	MET(31)	ND	161
Gabon (2)	2016	<i>S. aureus</i> (103)	Throat swab(79),skin lesions(24)	103(61)	59.22	ND	<i>mecA</i> (3), <i>blaZ</i> (90), <i>mr</i> s(A)(8), <i>aphA3</i> (1), <i>df</i> rA(2), <i>tet</i> (K)(56), <i>tet</i> (M)(6), <i>qacC</i> (4)	PEN(90), OXA(1), CXM(1), ERY(8), TET(61), SXT(51), CIP(3)	ND	162
	2014	<i>S. aureus</i> (212)	Skin and soft tissue (100) and bloodstream (12)	212 (104)	49.06	ND	<i>df</i> rA (1), <i>df</i> rG (100), <i>df</i> rK+G (1), <i>df</i> rB (2) <i>mecA</i> (1)	TMP;(104), SXT(100), SMZ(6)	ND	55
Ghana (3)	2015	<i>S. aureus</i> (30)	Skin and Soft Tissue Infections (16), bacteraemia (5), nasal swab (9)	(30)	100	ST88 (8), ST8 (5), ST247 (4)	<i>tet</i> (M) (13), <i>tet</i> (K) (10), <i>aphA3</i> (7), <i>aacA-aphD</i> (5), <i>erm</i> (C) (4).	TET(20), NOR(12), MXF(11), ERY(11), CLI(9), KAN(9), GEN(9) and CPT (6)	ND	110
	2014	<i>S. aureus</i> (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)	<i>mecA</i> (9)	PEN(208), TET(129), and ERY(18)	ND	109

	2013	<i>S. aureus</i> (105)	Nasal swab(105)	105(29)	27.62	ST88(4),ST8(1),ST172(1)	<i>mecA</i> (6)	PEN(98),FUS(13),TET(29),FOX(6),SXT(3),ERY(5),CLI(3),NOR(2),GEN(2),RIF(1),MUP(1)	SCCmec(6)	163
Kenya (2)	2016	<i>S. aureus</i> (93)	Blood(93)	93 (32)	34.41	ST22(4),ST88(1),ST789(1),ST5(1),ST8(2),ST241(12),ST239(2)	<i>mecA</i> (32)	CLI(10), ERY(9) and SXT(9),MXF(1),RIF(3),TET(6),LUX(5)	SCCmec (32)	87
	2013	<i>S. aureus</i> (82)	Boil(39),abscess(14),cellulitis(18),ulcer(11),	82(69)	84.12	ND	<i>mecA</i> (52)	ERY(56),CLI(31),CIP(55),OXA(69),FOX(69),SXT(51),GEN(69)	SCCmec	164
Libya (1)	2014	<i>S. aureus</i> (208)	Nasal swab (44)	208(70)	33.69	ND	<i>mecA</i> (35)	CIP(22), GEN(24), FUS(49)	ND	165
Morocco (2)	2013	<i>S. aureus</i> (30)	Nasal swab (30)	30 (25)	83.33	ND	<i>mecA</i> (1)	PEN(25), GEN(1), TOB(1), KAN(1), PF(1), TET(1), ERY(1), SXT(1)	ND	27
	2012	<i>S. aureus</i> (79)	Human(79)	79(43)	54.43	ND	<i>mecA</i> (28)	PEN(74),KAN(29),TOB(27),GEN(27),ERY(21),FUS(25),PF(30),TET(43),MIC(34),RIF(25),SXT(19)	ND	166
Mozambique (1)	2013	<i>S. aureus</i> (24)	Wound (24)	24 (9)	19.15	ND	<i>mecA</i> (9)	FOX(9), OXA(8)	ND	129
Namibia (1)	2014	<i>S. aureus</i> (116)	skin and soft tissue (31), urinary tract(19), respiratory tract (37), ear (7), eye (4) and bloodstream (3)	116 (34)	29.31	ND	<i>dfrA</i> (14), <i>dfrG</i> (20) <i>mecA</i> (11)	SXT(20), TMP(34) SMZ(20)	ND	55
Nigeria (9)	2015	<i>S. aureus</i> (38)	throat (40), nasal (23), wound (10)	38 (32)	84.21	ST8 (5), ST152 (1), ST772 (1), ST14(1)	<i>mecA</i> (16)	TET(32),LUX(7), GEN(5), ERY(5), PEN, SXT(29)	ND	167
	2015	<i>S. aureus</i>	Skin and nasal		72.76	ND	<i>mecA</i> (7), <i>blaZ</i>	PEN(284), SXT(233),	SCCm	58

		(290)	swab (120), wounds, blood	290 (211)			(284))	TET(51),OXA(7),GEN(11),TOB(11),LUX(23),MXF(21),TGC(51),	ec (7)	
2014	<i>S. epidermidis</i> (20), <i>S. haemolyticus</i> (10), <i>S. saprophyticus</i> (5), <i>S. capitis</i> (5), <i>S. lugdunensis</i> (2), <i>S. warneri</i> (4), <i>S. xylosus</i> (n4), <i>S. cohnii</i> (3).	Stool (53)	(53)	100	ND	<i>mecA</i> (15), <i>aac(6)</i> - <i>aph(2)</i> (3), <i>erm(C)</i> (4), <i>msrA</i> (1), <i>tetK</i> (6), <i>tet(M)</i> (4)	PEN(53), OXA(15), GEN(3), ERY(5), TET(7), SXT(19), CHL(4),AMC (31),CIP(1)	SCCmec(15)	58	
2014	<i>S. aureus</i> (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	<i>dfrA</i> (2), <i>dfrG</i> (152), <i>mecA</i> (16)	(TMP)(154), SXT(83),SMZ(85)	ND	55	
2013	<i>S. aureus</i> (61)	Human(61)	61(27)	44.26	ST39(1),ST5(2),ST241(1),ST250(1),ST88(2)	<i>mecA</i> (7)	PEN(45),TET(26),CLI(2),GEN(10),LVX(6), SXT(27)	SCCmec(2)	168	

2012	<i>S. aureus</i> (51) <i>S. haemolyticus</i> (21), <i>S. sciuri</i> (9), <i>S. saprophyticus</i> (5), <i>S. warneri</i> (3), <i>S. epidermidis</i> (1) and <i>S. hominis</i> (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	<i>mecA</i> (15), <i>dfra</i> (3)	SXT(13), PEN(15), OXA(15), GEN(6), CIP(7), MXF(1), ERY(5), CLI(4), TET(13), SXT(13), RIF(2)	SCCmec (15)	112
2011	<i>S. aureus</i>	Human(68)	68(49)	72	ND	<i>mecA</i> (11), <i>erm</i> (A)(6), <i>msrA</i> (2), <i>aacA-aphD</i> (10), <i>tet</i> (M)(11), <i>tet</i> (K)(27)	PEN(60), OXA(11), GEN(10), TET(38), CIP(20), MXF(7), SXT(49), ERY(8), CLI(6)	SCCmec(11)	169
2009	<i>S. aureus</i> (96)	Human(96)	96(12)	12.5	ST241(12)	<i>mecA</i> (12)	PEN(12), OXA(12), FOX(12), GEN(12), ERY(12), CLI(9), SXT(12), CIP(12)	ND	170
2009	<i>S. aureus</i> (346)	Human(346)	346(206)	59.54	ST5 (72), ST7 (44), ST121 (38), ST250(28), ST88 (33), ST30(26), ST8(18), ST1(20), ST15(8), ST80 (8), ST241 (7), ST25 (5), ST72 (3)	<i>mecA</i> (70)	PEN(316), SXT(206), TET(182), CIP(58), ER7(26), GEN(42)	SCCmec(70)	171

São Tome Príncipe (3)	2015	<i>S. aureus</i> (114)	Nasal swab (114)	114(29)	25.5	ST5(2),ST88(11), ST8(13),ST1(2),ST105(1)	<i>mecA</i> (29)	FOX(29),PEN(114),TET(30),CIP(28),RIF(6),GEN(20),CLIN(20),SXT(58),ERY(25),CH	SCCmec (29)	114
Sao Tome principe and Angola	2015	<i>S. aureus</i> (164)	Nasal swab (164)	164 (29)	17.68	ST88(15),ST8(9)	<i>mecA</i> (NS)	FOX(29), SXT(26), TET(18), ERY(16), CIP (9) and CLI(8)	SCCmec (NS)	49
		<i>S. aureus</i> (52)	Nasal swab (52)	52(27)	51.92	ST8(3), ST88(2),ST5(1),ST105(1)	<i>mecA</i> (14)	SXT(27),ERY(11), CIP(11),TET(12),FOX(14),RIF(2)	SCCmec	139
South Africa (11)	2017	<i>S. aureus</i> (1914)	Blood (1914)	1914(557)	29.10	ST239(8),ST612(8),ST4121(1),ST36(4),ST5(4),ST33(3)	<i>mecA</i> (483)	β-lactams(557),TET(NS),aminoglycoside(NS),SXT(NS)	SCCmec (482)	135
	2017	<i>S. aureus</i> (97)	Human	97(96)	99	ND	<i>norA</i> (96), <i>norB</i> (96), <i>mepA</i> (95), <i>tet</i> (38)(96), <i>sepA</i> (94), <i>mdeA</i> (93), <i>imrs</i> (86), <i>sdrM</i> (83), <i>norC</i> (77), <i>qacA/B</i> (34), <i>smr</i> (42)	NS	ND	138
	2017	<i>E. faecalis</i> (1)	Urine (1)	1	100	ST6(1)	<i>aph(3')-III</i> (1), <i>ant(6)-la</i> (1), <i>aac(6)-aph(2'')</i> (1), <i>isa(A)</i> (1), <i>mphd</i> (1), <i>tet(M)</i> (1)	GEN(1),STR(1),ERY(1),CLI(1),TET(1),CLI(1),TET(1),CIP(1)	ND	172
	2017	<i>E. faecium</i> (1)	Urine (1)	1	100	ST18(1)	<i>aph(3')-III</i> (1), <i>ant(6)-la</i> (1), <i>tet(M)</i> (1), <i>erm(B)</i> (1), <i>msr(C)</i> (1), <i>tet(L)</i>	GEN(1),STR(1),ERY(1),CLI(1),TET(1),CLI(1),TET(1),CIP(1)	ND	173

	2016	<i>S. aureus</i> (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	<i>mecA</i> (27) and <i>blaZ</i> (27), <i>aac</i> (6')- <i>aph</i> (2'') (25), <i>erm</i> (C) (13)	CIP(23), GEN(20), RIF(19), TET(18), ERY(17), CLI(3)	ND	174
	2016	<i>E. faecium</i> (120) <i>E. faecalis</i> (40)	Blood (4)	(4)	100	ST80 (1),ST203 (1),ST18 (1),ST817(1)	<i>vanA</i> (3), <i>vanB</i> (1)	VAN (4)	ND	147
	2015	<i>S. agalactiae</i> (128)	vaginal and rectal swabs (128)	128 (121)	94.53	ND	<i>erm</i> (B), (28), <i>linB</i> (48) <i>mefA</i> (48)	ERY(27), CLI(32), CHL(32),TET(111),CIP(24)	ND	60
	2015	<i>S. aureus</i> (2709)	Blood (2709)	2709 (1231)	45.44	ND	<i>mecA</i> (1160)	TET(NS), RIF (NS),MUP(NS), CIP(NS) and SXT(NS) MET(1231)	SCCmec (1160)	59
	2012	<i>S. aureus</i> (13746)	Human (13746)	13746(3298)	24	ST5 (1), ST612 (44),	<i>RpoB</i> (H481Y, H481N, I527M) (NS)	RIF(1760)	ND	59
	2009	<i>S. aureus</i> (17)	Human(17)	17(13)	76.47	ND	<i>mupA</i> (3)	ERY(12),CIP(10),RIF(4),CHL(4)	ND	175
	2007	<i>S. aureus</i> (3), <i>S. lugdunensis</i> (2)	Wound(4),blood(1)	5(5)	100	ND	<i>mecA</i> (5)	PEN(5), OXA(5),GEN(5),ERY(4),TET(5), SXT(5),RIF(5)	SCCmec(5)	176
Sudan(1)	2015	<i>S. aureus</i> (200)	Wound(49),ear swab(57),urine(47), nasal swab(47)	200(197)	98.5	ND	<i>mecA</i> (111)	PEN(197), AMP(197),GEN(122),KAN(136),I PM(89),AMO(87),CIP(123),CLI(113),SXT(105)	ND	177

Tanzania (1)	2014	<i>S. aureus</i> (87)	Skin and soft tissue (39) and bloodstream (2)	87 (32)	36.78	ND	<i>dfrG</i> (32)	SMZ(5), TMP (32)	ND	50
Tunisia (18)	2015	<i>S. aureus</i> (99)	Human (99)	(99)	100	ST247 (12), ST239 (6), ST728 (2), ST241 (1), ST398 (1), ST5 (1) and ST641 (1)	<i>mecA</i> (24), <i>tet(K)</i> (6), <i>tet(L)</i> (1), <i>tet(M)</i> (18), <i>erm(A)</i> , <i>aph(2')-acc(6')</i> (13)	TET(24), GEN(18), ERY(15), FOF(1), CLI(14), OFX(16), TOB(20), FUS(5)	ND	69
	2014	<i>E. faecium</i> (13), <i>E. gallinarum</i> (3)	blood (8), pus (3), urine (2) and rectal swabs (3).	(16)	100	ST18 (1)and ST80 (2)	<i>vanA</i> (13), <i>vanC1</i> (3), <i>erm(B)</i> (16), <i>tet(M)</i> (15), <i>tet(L)</i> (1), <i>aac(6')-aph(2'')</i> (13) <i>aph(3')-IIIa</i> (16), <i>ant(6)</i> (3)	VAN(16),TEC(13), AMP(16),CIP(16), ERY, TET(16), KAN(13), STR(13), SXT(16), GEN(8),	<i>IS16</i> (3)	178
	2013	<i>S. aureus</i> (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)	<i>mecA</i> (59)	KAN(62), AMK(62(18), TETs(61), OFX(20) , CIP(31), ERY(38) , CLI(12), RIF(22)	<i>SCCmec</i> (59)	85
	2013	<i>S. aureus</i> (64)	Pus(53)pus, blood culture (6), articular Puncture (4), venous catheter r(1).	(64)	100	ST80(64)	<i>mecA</i> (64)	PEN(64),OXA(64),FOX(64),AMK (64),KAN(63),ERY(13),TET(3),LIN(3)	<i>SCCmec</i> (64)	179
	2012	<i>S. agalactiae</i> (226)	Female genital (120), gastric fluid (106)	226 (220)	97.34	ND	<i>erm(B)</i> (79), <i>mef(A)</i> (2), <i>tet(M)</i> (205), <i>tet(L)</i> (10), <i>tet(O)</i> (5), <i>tet(T)</i> (1)	CHL(7), RIF(43), ERY(90) and TET(220), STR(7),GEN(7)	<i>Tn916</i>	105

2012	<i>S. haemolyticus</i> (46)	Blood (19), intravascular catheters (14), others (13)	46 (36)	78.26	ND	<i>mecA</i> (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)	SCC <i>mec</i> (28)	104
2011	<i>S. aureus</i> (1463)	Skin (1463)	160 (5)	3.13	ND	<i>erm</i> (C)(3), <i>erm</i> (A)(1), <i>vat</i> (B)(5), <i>vga</i> (B)(5)	PEN(5), OXA(4), GEN(4), KAN(5), TOB(4) and RIF(5), LIN(5)	ND	144
2011	<i>S. pyogenes</i> (103)	skin (43), respiratory tract (41), blood (12), fluids (4), endometrium (1), vagina (1), and urine (1).	103 (72)	70	<i>emm</i> 18 (4), <i>emm</i> 42 (9), <i>emm</i> 76 (6), <i>emm</i> 118(10)	<i>erm</i> (B)(5), <i>tet</i> (M)(63), <i>tet</i> (O)(3)	ERY(5), CLI (5), and TET(72),	<i>Tn</i> 916 (62)	145
2011	<i>S. epidermidis</i> (34), <i>S. haemolyticus</i> (10), <i>S. hominis</i> (1)	Blood(45)	45(42)	93.33	ND	<i>mecA</i> (43), <i>mrsA</i> (13), <i>erm</i> (C)(7), <i>erm</i> (B)(2), <i>erm</i> (A)(6), <i>aac</i> (6')- <i>le-aph</i> (2'')(35), <i>ant</i> (4')- <i>la</i> (18), <i>aph</i> (3')- <i>lla</i> (4), <i>tet</i> (K)(6), <i>tet</i> (M)(1)	PEN(45), OVA(43), GEN(35), KAN(42), TOB(40), ERY(25), CLI(11), TET(5), CHL(3), RIF(15), SXT(31), CIP(25), FUS(27), FOF(18)	SCC <i>mec</i> (43)	180
2010	<i>S. pyogenes</i> (193)	throat (63), pus (89), punctures (30), blood (4), other sources (7)	193 (13)	6.74	ND	<i>ermB</i> (6), <i>mefA</i> (2)	ERY(7) and TET(6)	ND	143
2010	<i>S. aureus</i> (55)	Nasal swab(55)	55(19)	35.55	ST80(1)	<i>mecA</i> (1), <i>ant</i> (6)- <i>la</i> (3), <i>tet</i> (K)(7), <i>aph</i> (3')- <i>lla</i> (4), <i>dfrA</i> (1), <i>tet</i> (M)(1), <i>tet</i> (L)(1)	PEN(54), OXA(19), FOX(1), TET(11), STR(5), KAN(3) CIP(8)	SCC <i>mec</i> (1)	181
2010	<i>S. agalactiae</i> (160)	Urinary tract (160)	(160)	100	ND	<i>erm</i> (B) (132), <i>erm</i> (TR) (13), <i>mef</i> (A) (3)	ERY(160), LIN(135) and SB (135)	ND	182



	2010	<i>S. aureus</i> (13)	Pus(32),blood(16), catheter(12)	72(42)	58.33	ND	<i>mecA</i> (13)	PEN(65),STR(11),GEN(4),KAN(11), OXA(13),TOB(4),LIN(3),TET(42)ERY(11),RIF(6),CHL(2),CIP(5),FUS(8),FOF(1)	ND	183
	2009	<i>S. epidermidis</i> (77), <i>S. mitis</i> (50), <i>E. faecium</i> (45)	blood cultures (55), central venous catheters, (22),stool cultures (40), respiratory tract (2) and different sites (3), systematic nasopharyngeal specimens (42), upper respiratory tract(5)	172(95)	55.23	ND	<i>erm</i> (C) (18), <i>erm</i> (B) (6), <i>erm</i> (A)(11), <i>mrsA</i> (5)	OXA(39), AMP(28),PEN(90),ERY(119),LIN(97),PRI (3),GEN(71),RIF(78),TEC(50),	ND	82
	2007	<i>E. faecalis</i> (34), <i>E. faecium</i> (12)	Blood(10), pus(26),catheter(7) ,plural aspirate(2)	46(46)	100	ND	<i>aac</i> (6)- <i>aph</i> (2)(46)	GEN(46),KAN(46),PEN(12),ERY(45),CHL(25),TET(32),STR(26)	ND	184
	2007	<i>E. faecium</i> (2)	Urine(2)	2	-	ND	<i>vanA</i> (2)	STR(2), ERY(2),CIP(2),VAN(2)	ND	156
	2007	<i>S. epidermidis</i> (346)	Human(346)	346(7)	2.02	ND	<i>erm</i> (A)(6), <i>erm</i> (C)(1), <i>vga</i> (7)	PRI(7),OXA(7),GEN(7),ERY(7),LIN(7),RIF(7),SXT(7)TEC(1)	ND	185
	2007	<i>S. epidermidis</i> (34)	Blood(55), urine(22)	(34)	100	ND	<i>icaA</i> (26), <i>erm</i> (C)(18), <i>erm</i> (A)(11), <i>mrsA</i> (5), <i>vga</i> (3),	ERY(34),OXA(28),GEN(34),LIN(33),OFX(33),RIF(28)	ND	186
Uganda (4)	2013	<i>S. aureus</i> (64)	Nasal swab (64)	64(24)	37.5	ND	<i>mecA</i> (24)	OXA(22), GEN(8), CIP(12), CHL(9)	SCCmec (24)	187
	2012	<i>S. epidermidis</i> (50)	Nasal swab(20),catheter(14),blood(9),wound(3)	50(26)	52	ND	<i>aph</i> (-) <i>lla</i> (28), <i>blaZ</i> (2), <i>mecA</i> (3), <i>vanA</i> (3), <i>vanB1</i> (3),	ERY(20),GEN(26),PEN(32),TET(15),SXT(17),OXA(6)	IS256(33)	188
	2011	<i>S. aureus</i> (122)	pus	122(48)	39.34	ND	<i>mecA</i> (2)	AMP(48),CHL(42),CIP(1),ERY(5),TET(29),SXT(320)	ND	189
	2009	<i>S. aureus</i> (54)	Human(54)	54(15)	27.78	ND	<i>mecA</i> (17)	CIP(12),GEN(10),SXT(15),CHL(15),ERY(15)	NG	190

1529 **Table 3. Geographical distribution, species, clones, and resistance mechanisms of antibiotic-resistant Gram-positive bacteria isolated from**  
 1530 **animals in Africa from 2007-2018.**

Country (n) <sup>11</sup>	Year	Organism/Species (n) <sup>12</sup>	Specimen Sources (n) <sup>13</sup>	Sample size (Resistant isolates)	Resistance rate (%)	Clones (n) <sup>14</sup>	Resistance genes/mechanisms (n) <sup>15</sup>	Antibiotics to which strains were resistant (n) <sup>16</sup>	MGEs (n) <sup>17</sup>	Reference
Angola(1)	2015	<i>E. faecium</i> (3)	Pig faeces(1), Chicken faeces(2)	3	-	ST971, ST245(2)	<i>tet(L)</i> (1), <i>tet(M)</i> (2), <i>erm(B)</i> (2)	CIP(1),TET(3),ERY(2),STR(2),NIT(2),Q/D(2)	ND	191
Egypt (10)	2017	<i>S. aureus</i> (3), <i>S. hycus</i> (6), <i>S. intermedius</i> (3), <i>S. epidermis</i> (1), <i>S. hemolyticus</i> (1), <i>S. hominis</i> (1), <i>S. lugdunensis</i> (3), <i>S. simulans</i> (1), <i>S. scuri</i> (4)	imported beef meat (23)	23(16)	69.57	ND	<i>mecA</i> (5), <i>gyrA</i> (12), <i>griA</i> (10), <i>gyrB</i> (6),	AMP((6),CHL(1),CIP(8),CLI(15), ERY(6),GEN(14),MET(8),OXA(13), PEN(22), TET(6)	ND	94
	2017	<i>S. aureus</i> (84)	Milk(84)	84(80)	95.23	ND	<i>mecA</i> (42), <i>blaZ</i> (67)	AMX(54), SXT(66),GEN(20),CIP(12),CHL(58),PEN(70), RIF(32),AMK(14), VAN(64),STR(50),TET(44),ERY(40), AMP(80),OXA(42)	ND	192
	2016	<i>S. aureus</i> (73)	Animal(73)	73(NS)	NS	ST113(1), ST80(1)	<i>mecA</i> (14), <i>erm(C)</i> (14)	CLI(NS),CIP(NS),GEN(NS),SXT(NS),OXA(NS), ERY(NS)	ND	159

<sup>11</sup> Total number of studies per country

<sup>12</sup> Total number of bacteria isolated

<sup>13</sup> Total number of Specimen source

<sup>14</sup> Total number of resistant clones

<sup>15</sup> Total number of resistant genes

<sup>16</sup> Total number of isolates resistant to antibiotics

<sup>17</sup> Total number of mobile genetic elements: plasmids, transposons, integrons

2016	<i>S. aureus</i> (30)	raw chicken breast fillet (40), sliced luncheon meat (20), and chicken nuggets (20), Human (18)	40 (21)	33.33	ND	<i>mecA</i> (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	28
2016	<i>S. aureus</i> (70)	Bovine(70)	70(41)	58.57	ND	<i>mecA</i> (NS)	CRO(41), ERY(35), OXA(41), SXT(14), GEN(14), CIP(11), CLI(8), VAN(1)	ND	160
2016	<i>S. aureus</i> (40)	Milk(30), meat(10)	40(22)	55	ND	<i>erm</i> (A)(18), <i>mrs</i> (A)(4), <i>mphC</i> (6), <i>erm</i> (B)(3)	ERY(22), CLI(4), TET(24), CIP(4), CHL(5), AMX(26), FOX(22), SXT(1), RIF(5), GEN(4), CRO(14)	ND	193
2016	<i>S. aureus</i> (200)	Raw milk (40), Damietta Cheese (40), Kareish cheese (40), ice cream (40), and yogurt (40)	200 (106)	53	ND	<i>mecA</i> (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	12
2015	<i>S. aureus</i> (133)	cow milk samples (61), various origins (14), minced meat (6), sausage (4) and burger (7), pus (22), sputum (17), urine (1), cerebrospinal fluid (1)	133 (96)	72.18	ND	<i>mecA</i> (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)	23
2015	<i>S. aureus</i> (288)	Chicken(288)	288(256)	88.89	ND	<i>mecA</i> (76)	PEN(269), AMP(256), CLX(240), AMX(224), ERY(212), TET(197), STR(150), RIF(113), AMK(99), CH	ND	194

								L(91),GEN(70),CIP(39),NEL(48),SXT(39),VAN(17)		
	2011	<i>S. aureus</i> (4)	dogs swab (70), cats swab (48), human nasal and oral swabs (50).	(4)	100	ND	<i>mecA</i> (4)	OXA(4), FOX(4), AMP(3),FOX(4),RIF(3),GEN(2),CLI(2),RIF(2),CIP(2),TET(1)	ND	53
Kenya (1)	2013	<i>S. agalactiae</i> (92)	Camel(92)	92 (37)	36	ST617 (8), ST-612 (1),ST-616 (22)	<i>tet(M)</i> (37)	TET(37)	Tn916 (37)	195
Nigeria(3)	2017	<i>S. aureus</i> (30), <i>S. epidermidis</i> (16), <i>S. saprophyticus</i> (2), <i>S. sciuri</i> (1), <i>S. xylosum</i> (1)	Pork(26),beef(14),chicken(10)	50(48)	96	ND	<i>mecA</i> (49)	PEN(48),CLI(48),CHL(46),SXT(46),KAN(46),AMX(460)	ND	156
	2016	<i>E. faecium</i> (108), <i>E. gallinarum</i> , (30), <i>E. faecalis</i> (5), <i>E. hirae</i> . (5) <i>E. mundtii</i> (12)	Cattle (130), chickens (130),manure (130)	167 (102)	61.0	ND	<i>tet(K)</i> (NS), <i>tet(L)</i> (NS), <i>tet(M)</i> (NS), <i>tet(O)</i> (NS) and <i>erm(B)</i> (NS)	TET (102), ERY (102), CHL (13), GEN(55), STR(47),AMP(75)	ND	196
	2014	<i>Coagulase negative staphylococcus</i> (16)	Groin swab of dogs(16)	(16)	100	ND	<i>mecA</i> (16), <i>blaZ</i> (1), <i>tetK</i> (12), <i>tet(M)</i> (8), <i>erm(B)</i> (3), <i>aacA-aphD</i> (11)	PEN(16),OXA(16),FOX(16),TET(13),ERY(9),CLI(9),GEN(5),KAN(12),TOB(1),SXT(10),CHL(7)	ND	197
South Africa (6)	2017	<i>E. faecium</i> (180), <i>E. durans</i> (80), <i>E. hirae</i> (29), <i>E. casseliflavus</i> (20)	Cattle (241)	100	100	ND	<i>vanB</i> (67), <i>vanC1</i> (85), <i>vanC2/3</i> (137), <i>erm(B)</i> (137)	ERY(338),CLI(330),VAN(341),PEN(310),CET(300),STR(320),CLX(100),AMK(252),CIP(41)	ND	198
	2017	<i>S. aureus</i> (104)	Chicken(104)	(104)	100	ND	<i>mecA</i> (45), <i>blaZ</i> (12), <i>tet(K)</i> (32)	AMP(46),GEN(29),ERY(64),FOX(71),KAN(52),STR(57),TET(82),VAN(43)		156
	2015	<i>S. aureus</i> (211)	Milk (211)	211 (124)	58.77	ND	<i>mecA</i> (19)	PEN (124), AMP(99), OXA (93), VAN(47), TEC(116), TET(56),ERY(56),STR(89),KAN(55),GEN(47),SXT (37)	ND	21

	2015	<i>E. faecalis</i> (40), <i>E. hirae</i> (100), <i>E. durans</i> (60), <i>E. faecium</i> (120)	Pigs (320)	(320)	100	ND	<i>vanB</i> ,(320), <i>vanC1</i> (320), <i>vanC2/3</i> (320), <i>erm</i> (B)(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	13
	2014	<i>Staphylococcus spp</i> (120)	Pigs(30),cattle(30),cows(30),goats(30)	120(53)	44.17	ND	<i>mecA</i> (12)	VAN(12),CRO(12),CFZ(37),CTX(19),SAM(13),PEN(53),MER(4)	ND	199
	2013	<i>S. xylosus</i> (18), <i>S. aureus</i> (28), <i>S. haemolyticus</i> (42), <i>S. capitis</i> (18), and other <i>Staphylococcus spp.</i> (14)	Animals (120)	(120)	100	ND	<i>mecA</i> (NS), <i>mphC</i> (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)	61
Senegal (1)	2012	<i>S. aureus</i> (57)	Swabs from pigs (300) and farmers	57(35)	61.40	ST5 (5)	<i>mecA</i> (6)	PEN(57), SXT(35), TET(20)	SCCmec (6)	66
Tanzania (1)	2014	<i>E. faecium</i> (95) <i>E. faecalis</i> (9) <i>E. gallinarum</i> (7) <i>E. Hirae</i> (9)	Faecal samples of buffalo (35), wildebeest (40), zebra (40) and cattle (20)	120 (42)	35	ND	<i>tet</i> (W) (NS), <i>sull</i> (NS)	VAN(10),AMP(10),TET(40),SXT(32),RIF(53),ERY(42),GEN(35),AMP(31)	ND	14
Tunisia (8)	2017	<i>E. faecium</i> (31), <i>E. faecalis</i> (14), <i>E. durans</i> (6), <i>E. casseliflavus</i> (2), <i>E. gallinarum</i> (2)	Faecal sample of cats(20), dogs(50)	58(31)	53.45	ND	<i>erm</i> (B)(22), <i>tet</i> (M)(5), <i>tet</i> (M), <i>tet</i> (L)(16), <i>tet</i> (L)(4), <i>ant</i> (6)- <i>la</i> (11), <i>aac</i> (6)- <i>le-aph</i> (2")- <i>la</i> (16), <i>aph</i> (3)- <i>lla</i> (11), <i>catA</i> (1)	AMP(1),ERY(26),CIP(30),PRI(9),STR(12),KAN(12),GEN(9),TET(21),CHL(7)	ND	22
	2017	<i>E. faecalis</i> (2), <i>E. faecium</i> (NS), <i>Enterococcus spp</i> (NS)	Urban wastewater (5)	5(2)	40	ST86(2)	<i>optrA</i> (2), <i>erm</i> (A), <i>erm</i> (B), <i>tet</i> (M)(1), <i>tet</i> (L)(1), <i>aac</i> (6)- <i>aph</i> (2")	CHL(2),CIP(2),ERY(2),TET(1),GEN(1),STR(2)	ND	200

2015	<i>S. aureus</i> (43)	Chicken(19), Veal (9), sheep(14), horse(1)	43(13)	30.23	ST30(1), ST398(1)	<i>tet(M)</i> (2), <i>erm(C)</i> (4), <i>erm(A)</i> (2), <i>erm(T)</i> (1), <i>tet(K)</i> (6), <i>tet(L)</i> (3), <i>tet(M)</i> (2), <i>aph(3')</i> - <i>IIIa</i> (4), <i>ant(4)-Ia</i> (1), <i>mrsA</i> (4)	PEN(41), OXA(2), FOX(2), KAN(4), TOB(1)	SCCmec(2)	201
2015	<i>S. aureus</i> (17)	Goat, cats dogs(17)	17(7)	41.18	ST45(1), ST15(1), ST6(1), ST21(1), ST188(1)	<i>blaZ</i> (7), <i>tet(M)</i> (1), <i>erm(A)</i> (1), <i>ant(6)-Ia</i> (1)	PEN(6), TET(1), ERY(1), STR(1), CIP(1)	ND	202
2013	<i>E. faecalis</i> (49), <i>E. faecium</i> (30), <i>E. gallinarum</i> (12), <i>E. hirae</i> (12), <i>E. casseliflavus</i> (2), <i>E. durans</i> (2)	Meat (199)	(119)	78.5	ST260(1), ST454(1), ST452(1), ST22(1), ST300(1), ST455(1), ST453(1), ST456(1)	<i>tet(M)</i> (36), <i>tet(L)</i> (32), <i>erm(B)</i> (33), <i>aac(6)-aph(2)</i> (1), <i>ant(6)</i> (7)	TET(57), ERY(43), STR(17), CHL(4), GEN(1)	ND	51
2013	<i>E. mundtii</i> , (23) <i>E. casseliflavus</i> (20), <i>E. hirae</i> (19), <i>E. faecalis</i> (10), <i>E. faecium</i> (10), <i>E. durans</i> (7), <i>E. gallinarum</i> (7), <i>E. dispar</i> (2)	Cattle (92)	92 (72)	78	ND	<i>erm(B)</i> (7), <i>tet(M)</i> (4), <i>tet(L)</i> (4)	ERY(10), TET(4) and SXT(72)	ND	52
2012	<i>S. aureus</i> (73)	nasal swab from sheep (73)	73 (5)	6.85	ST153(5)	<i>mecA</i> (5), <i>blaZ</i> (28), <i>ant(6)-Ia</i> (5), <i>erm(C)</i> (5), <i>tet(K)</i> (30)	PEN(5), STR(5), KAN(5), ERY(5), TET (5), FUS(5)	ND	99
2012	<i>S. aureus</i> (50)	Nasal swab of donkey(50)	50(30)	60	ST133(15), ST1738(4), ST1(2), ST6(4), ST2057(4), ST2110(1), ST2181(1), ST1660(1)	<i>baZ</i> (12), <i>erm(A)</i> (8), <i>erm(C)</i> (2), <i>tet(M)</i> (1), <i>fusC</i> (1)	PEN(12), ERY(8), TET(1), Fusic acid(12),	ND	203

Uganda (1)	2017	<i>S. aureus</i> (41)	milk(30),sour milk sample(11)	41(30)	73.17	ST97(1),ST1(2)	<i>mecA</i> (23)	TET(30),RIF(1),SXT(2),ERY(1),GEN((1),CLI(1)	ND	121
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1531

1532 **Table 4. Geographical distribution, species, clones, and resistance mechanisms of antibiotic-resistant Gram-positive bacteria isolated from**  
 1533 **the environment in Africa from 2007-2017.**

Country (n) <sup>18</sup>	Year	Organism/Species (n) <sup>19</sup>	Specimen Sources (n) <sup>20</sup>	Sample size (Resistant isolates)	Resistance rate (%)	Clones (n) <sup>21</sup>	Resistance genes/mechanisms (n) <sup>22</sup>	Antibiotics to which strains were resistant(n) <sup>23</sup>	MGEs (n) <sup>24</sup>	Reference
Angola	2015	<i>E. faecium</i> (5)	Chicken farm facility(4), water from hospital and community(1)	5(4)	80	ST245(1), ST650(2)	<i>tet</i> (M)(4), <i>erm</i> (B)(4), <i>tet</i> L(2)	TET(4),ERY(4),STR(4),NIT(2),Q/D	ND	191
Egypt	2016	<i>S. aureus</i> (23)	Food sample(23)	23(NS)	NS	ST689(1)	<i>mecA</i> (3), <i>vanA</i> (1), <i>vanB</i> (1)	VAN(NS), CIP(NS), GEN(NS),SXT(NS),OXA(NS),ERY(NS)	ND	159
Nigeria (1)	2017	<i>E. faecium</i> (100)	Vegetables soil, farm, Cloacal swabs (25), Manure (8), Rectal swabs(2)	(100)	100	ND	<i>aac</i> (6')- <i>le-aph</i> (2')- <i>la</i> (35), <i>aph</i> (2')- <i>1c</i> (31), <i>aph</i> (3')- <i>IIIa</i> (32), <i>ant</i> (4')- <i>la</i> (14)	AMP (63), GEN(37)	ND	25
South Africa (4)	2017	<i>S. aureus</i>	Recreational waters and beach sand (30)	(30)	100	ND	<i>mecA</i> (5), <i>femA</i> (16), <i>rpoB</i> (11), <i>blaZ</i> (16), <i>ermB</i> (15), <i>tet</i> (M)(8)	AMP (29),PEN (29),RIF(24), CLI(24),OXA	ND	204

<sup>18</sup> Total number of studies per country

<sup>19</sup> Total number of isolates

<sup>20</sup> Total number of specimen source

<sup>21</sup> Total number of resistant clones

<sup>22</sup> Total number of resistant clones

<sup>23</sup> Total number of isolates resistant to antibiotics

<sup>24</sup> Total number of mobile genetic elements : plasmids,transposons, integrons

								(22), ERY(21), VAN(15), TET(13), SXT(13), CIP(10), GEN(1)		
	2016	<i>E. faecium</i> (30), <i>E. faecalis</i> (37) <i>E. mundtii</i> (36), <i>E. casseliflavus</i> (14), <i>E. gallinarum</i> (5), <i>E. hirae</i> (1), <i>E. sulfureus</i> (1)	Surface water(124)	124(86)	69.35	ND	<i>tet</i> (L)(17), <i>msrC</i> (9)	AMP(59), AMX(53), PEN(87), STR(8), VAN(86), CHL(23), CIP(47)  ERY(68), TET(59)	ND	205
	2015	<i>E. faecium</i> (30), <i>E. durans.</i> (15)	waste water (32) and effluent (32)	(45)	100	ND	<i>erm</i> (B) (40), <i>vanB</i> , (42), <i>vanC1</i> (42), <i>vanC2/3</i> (42)	PEN(38), ERY(40), CTX(43), GEN(28), IPM(43), TET(45), KAN(43), CIP(43), VAN(42), CLI(45)	ND	10
	2013	<i>E. faecium</i> (179)	Borehole Water (179)	179 (172)	96.09	ND	<i>vanA</i> (17) and <i>vanB</i> (17)	AMP(158), VAN (166)and PEN(172), CHL(11), KAN(12), GEN(3), AMX (155), ERY(86)	ND	9
Tunisia (7)	2017	<i>S. aureus</i> (12)	Wastewater	12	100	ST3245(7), ST15(1)	<i>blaZ</i> (7), <i>msrA</i> (7), <i>tet</i> (K)(1)	PEN(12), ERY(7), TET(1), CLI(1)	ND	18
	2016	<i>E. faecium</i> (86), <i>E. faecalis</i> (8), <i>E. casseliflavus</i> (6)	Hands (50), inanimate such as beds, treatment tables, toilets, faucets, wrist, sinks (250)	(100)	100	ST910 (13), ST80 (1)	<i>erm</i> (B) (71), <i>tet</i> (M) (18), <i>aph</i> (3')-IIIa (27), <i>ant</i> (6)-Ia (15), <i>cat</i> (A) (4), <i>vanC2</i> (6)	ERY(73), TET(20), STR(27) and KAN(28), VAN(14), CHL(10), SXT(100), CIP(48), PRI(18)	IS16 (14)	20
	2016	<i>S. saprophyticus</i> (30), <i>S. haemolyticus</i> (38), <i>S. epidermidis</i> (NS), <i>S. cohnii</i> (NS), <i>S. warneri</i> (NS), <i>S. sciuri</i> (NS), <i>S. simulant</i>	Inanimate surfaces (83)	83 (32)	38.55	ND	<i>mecA</i> (20), <i>msrA</i> (32), <i>erm</i> (C)(8), <i>tet</i> (K)and/or <i>tet</i> (M)(21), <i>aac</i> (6')-Ie- <i>aph</i> (2')-Ia (16), ( <i>aph</i> (3')-IIIa(19), <i>ant</i> (4')-Ia (n=14), <i>ant</i> (6')-Ia (3)	ERY(32), TET(21), GEN(16), KAN(19), TOB(14), STR(3),	ND	97



		(NS)s, <i>S. pasteurii</i> (NS), <i>S. arlettae</i> (NS) and <i>S. xilosus</i> (NS)								
	2015	<i>E. faecium</i> (34), <i>E. hirae</i> (23), <i>E. faecalis</i> (4), and <i>E. casseliflavus</i> (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)	<i>erm</i> (B) (12), <i>tet</i> (M)- <i>tet</i> (L)(10), <i>aph</i> (3')-III, (10) <i>ant</i> (6) (2), <i>vanC2</i> (4)	CIP(42), ERY(12), TET(10), KAN(10), CHL(5), STR(2), and GEN(5), VAN(4)	ND	19
	2015	<i>E. faecium</i> (54), <i>E. faecalis</i> (17), <i>E. hirae</i> (8) <i>E. casseliflavus</i> (4), <i>E. durans</i> (2)	waste and surface water (114)	(85)	100	ST480 (1), ST531 (1),ST55 (1),ST532(1),ST202 (1),ST314(1), ST985(1),S T30 (1),ST986 (1),ST12 (1),ST296 (1),ST327(1)	<i>aph</i> (3')-IIIa (22), <i>ant</i> (6)- <i>la</i> (4), <i>erm</i> (B) (34), <i>tet</i> (M) (13), <i>tet</i> (L)(8), <i>aac</i> (6')- <i>le-aph</i> (2')(15)	GEN(22), KAN(22), STR(7), ERY(36), TET(13), SXT(79), CIP(6),	ND	31
	2015	<i>S. aureus</i> (12)	Hospital environment(12)	12(6)	50	ST247(2)	<i>blaZ</i> (12), <i>erm</i> (A), <i>tet</i> (M)(2), <i>aac</i> (6')- <i>aph</i> (2')(2),	STR(2),KAN(2),ERY(2),CL I(2),TET(2),FUS(2),TOB(2),GEN(2),AMK(2),OXA(6),PEN(12),FOX(2)	SCCmec(2)	206
	2014	<i>E. faecium</i> (5), <i>E. casseliflavus</i> (7)	Hospital environment((beds, treatment table, toilet, faucet, wrist and sink) (100)	(12)	100	ST80(1)	<i>vanA</i> (5), <i>vanC2</i> (7), <i>ermB</i> (12), <i>tetM</i> (5), <i>aph</i> (3')-IIIa(5), <i>aac</i> (6')- <i>aph</i> (2')(5)	VAN,(12),AMP(5),CIP(12), ERY(12),TET(8), STR(6),KAN(80,SXT(11),GEN(3),TEC(5)	<i>IS16</i> (1)	69

1534

1535 **Table 5. Mean antibiotic resistance rates per country in Africa**

Country	No. of studies N=130	Mean rate of ABR (%)	95% CI	P-value
Algeria	7	62.24	4.76 - 119.7	0.03
Angola	6	66.19	9.98 – 122.4	0.03
Cape Verde	1	14.16	-	-
Democratic Republic of the Congo	3	45.96	-	-
Egypt	21	70.49	59.30 – 81.68	0.0001
Gabon	2	54.14	-	-
Ghana	3	65.05	-	-
Kenya	3	51.51	-	-
Libya	1	33.69	-	-
Morocco	2	68.88	-	-
Mozambique	1	19.15	-	-
Namibia	1	29.31	-	-
Nigeria	13	71.23	54.81 – 87.65	0.0001
São Tome´ Pri´ncipe	3	31.70	12.87 – 76.27	0.092
South Africa	21	82.72	70.73 – 94.69	0.0001
Sudan	1	98.5	-	-
Tanzania	2	35.89	24.58 – 47.00	0.016
Tunisia	33	66.82	54.73 – 78.91	0.0001
Uganda	5	45.96	24.25 – 67.66	0.0042
Senegal	1	61.40	-	-

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**Table 6: Antibiotic resistance rates of various Gram-positive bacterial species isolated from humans, animals and the environment in Africa between 2007 and 2018.**

Species	Total isolates	Antibiotic resistance rate (%)											
		AMP <sup>25</sup>	CIP <sup>26</sup>	CLI <sup>27</sup>	ERY <sup>28</sup>	GEN <sup>29</sup>	KAN <sup>30</sup>	PEN <sup>31</sup>	RIF <sup>32</sup>	STR <sup>33</sup>	TET <sup>34</sup>	SXT <sup>35</sup>	VAN <sup>36</sup>
<b>Human</b>													
<i>E. faecalis</i>	179	30.4	26.3	-	91.35	77.2	100	26.0	-	56.5	76.0	19.30	52.6
<i>E. faecium</i>	205	56.1	19.0	-	88.0	61.4	90.6	21.5	-	70.3	75.5	100	51.3
<i>S. agalactiae</i>	658	-	18.8	19.5	50.6	3.1			19.0	3.1	68.8	-	-
<i>S. aureus</i>	24160	64.7	24.1	16.3	82.4	20.3	32.9	81.5	31.2	12.2	35.4	40.5	3.13
<i>S. haemolyticus</i>	91	-	62.6	24.4	63.7	75.9	73.9	78.3	31.2	12.2	35.4	69.2	-
<i>S. pyogenes</i>	148	-	-	4.9	5.8	-	-	-	-	-	36.5	-	-
<b>Animal</b>													
<i>E. faecalis</i>	129	24.2	64.6	98.8	43.5	19.5	20.7	16.6	44.17	16.7	32.7	52.5	50.1
<i>E. faecium</i>	577	31.4	43.7	97.8	57.5	23.0	20.7	53.7	44.2	37.9	43.9	52.5	66.7
<i>S. aureus</i>	1601	62.8	23.1	39.3	32.7	28.9	36.8	69.5	33.5	45.3	42.2	37.6	24.4
<i>S. haemolyticus</i>	43	-	-	-	-	-	-	59.6	-	-	-	83.3	-
<b>Environment</b>													
<i>E. faecalis</i>	66	47.6	47.6	-	45.7	20.5	23.1	70.2	-	17.0	23.6	96.5	29.8
<i>E. faecium</i>	523	59.2	69.2	100	64.6	26.1	39.7	83.6	-	29.1	49.3	94.9	62.7
<i>S. aureus</i>	77	96.7	25	35	48.2	10.0	16.67	98.9	80.0	16.7	25.8	43.0	50.0

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<sup>25</sup> Ampicillin  
<sup>26</sup> Ciprofloxacin  
<sup>27</sup> Clindamycin  
<sup>28</sup> Erythromycin  
<sup>29</sup> Gentamicin  
<sup>30</sup> kanamycin  
<sup>31</sup> Penicillin  
<sup>32</sup> Rifampicin  
<sup>33</sup> Streptomycin  
<sup>34</sup> Tetracycline  
<sup>35</sup> Sulphamethoxazole-trimethoprim  
<sup>36</sup> Vancomycin

1540 **Figure 1.** PRISMA-adapted flow chart showing included and excluded articles. All search were conducted on PubMed, Web of Science and African Journals  
1541 Online, and a final number of 130 articles were used for the quantitative analysis.

1542 **Figure 2.** Frequency and distribution of resistance genes, antibiotics, and mobile genetic elements (MGEs) with recorded resistance in Gram-positive bacteria in  
1543 Africa. 2ai) Shows the frequency of the various resistance genes found in the drug-resistant Gram-Positive bacterial strains. *mecA* and *erm(B)* were the most  
1544 dominant resistance genes detected, followed by *tet(M)*, *dfrG*, *vanB*, *vanC1* etc. 2aii) Shows the antibiotics to which the isolates were most resistant:  
1545 erythromycin (ERY) was the least effective drug, followed by rifampicin (RIF), tetracycline (TET), penicillin (PEN), sulphamethoxazole/trimethoprim (SXT),  
1546 ciprofloxacin (CIP), gentamicin (GEN), vancomycin (VAN), ampicillin (AMP), clindamycin (CLI), streptomycin (STR), chloramphenicol (CHL), and  
1547 kanamycin (KAN). 2b) Shows the MGEs per resistant Gram-positive bacterial clones in Africa. The figure represents resistant clones and the different MGEs  
1548 they carry. Each colour represent a particular resistant clone. *S. agalactiae* (ST612, ST616, ST617) and *S. pyogenes* (*emm18*, *emm42*, *emm76*, *emm118*), *E.*  
1549 *faecium* (ST18, ST80, ST910) and *S. aureus* (ST5, ST22, ST35) were associated with *Tn916*, *IS16* and *SCCmec* respectively.

1550 **Figure 3.** Frequency distribution of resistant Gram-positive bacterial species, clones and mobile genetic elements (MGEs) per country in Africa. 3a) Shows the  
1551 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  
1552 *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  
1553 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.*  
1554 *faecium* ST317.

1555 **Supplementary data 1.** List of excluded articles on the basis of only phenotypic (antibiotic sensitivity) tests.

1556 **Supplementary data 2.** Raw data and analysis of extracted information from included articles.

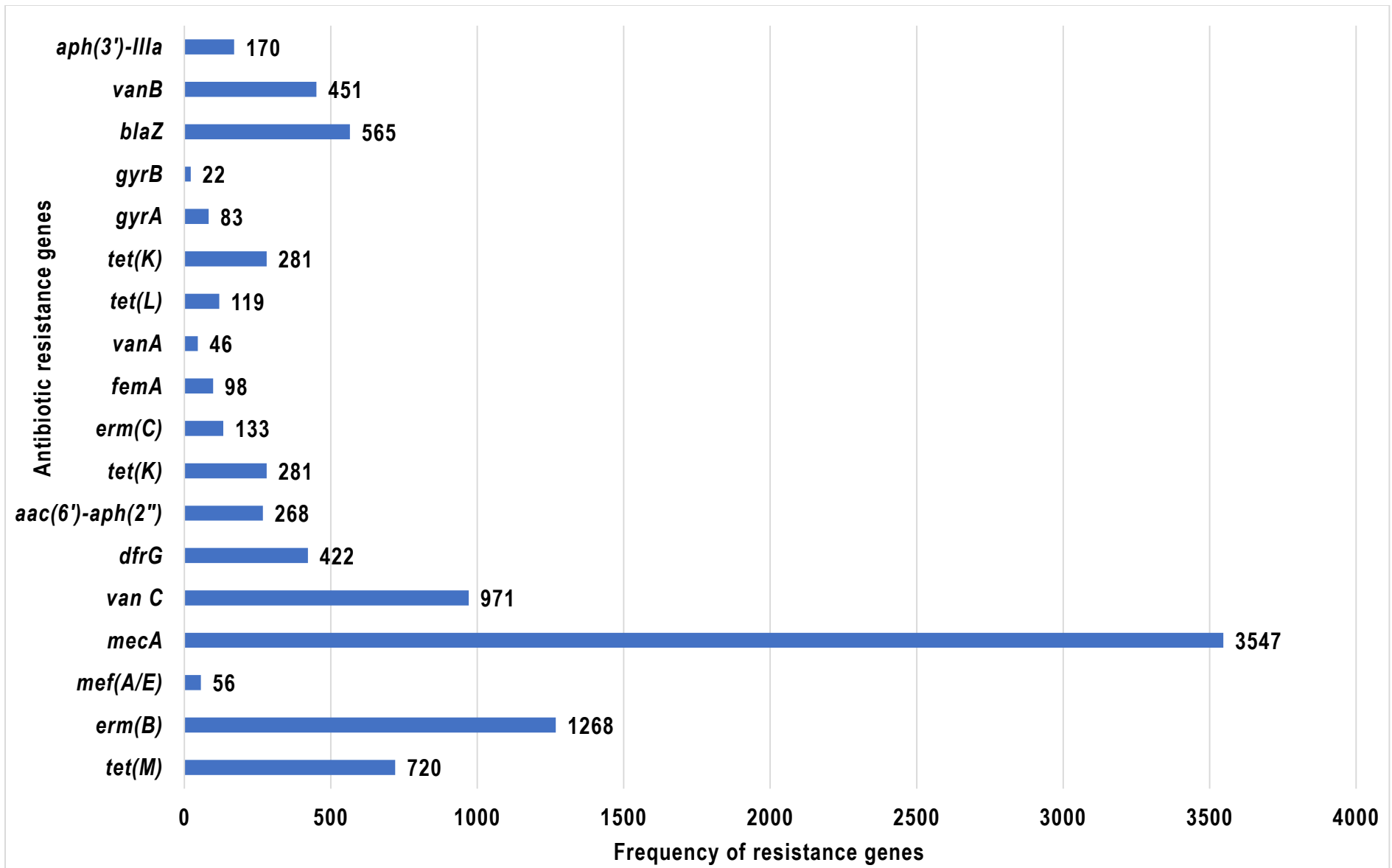


Figure 2ai. Frequency of resistance genes conferring resistance to antibiotics in Gram-positive bacteria in Africa.

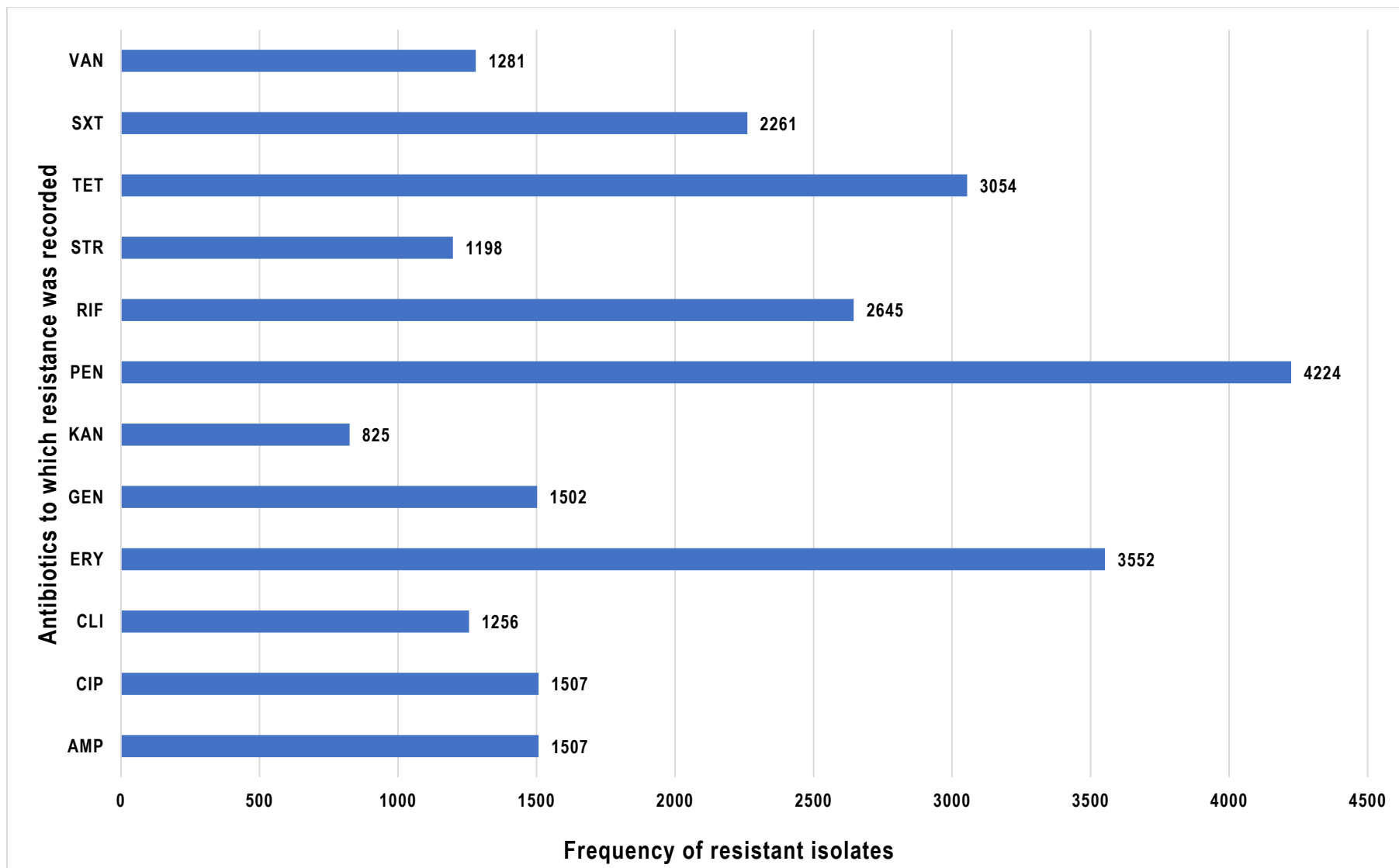


Figure 2aii. Frequency of antibiotics to which Gram-positive bacteria were resistant to in Africa.

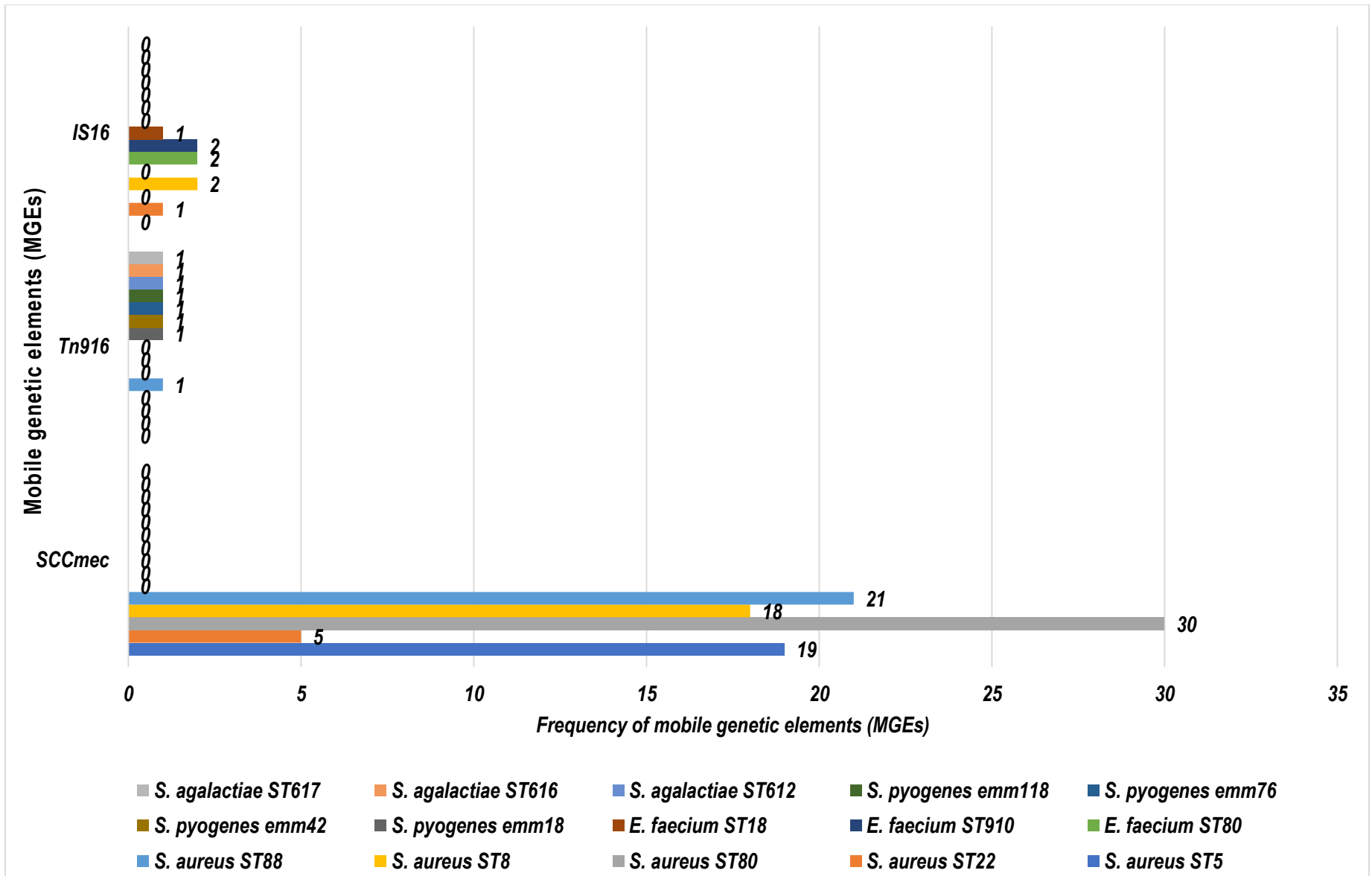


Figure 2b. Frequency and distribution of mobile genetic elements (MGEs) and resistant clones in Gram-positive bacteria in Africa.

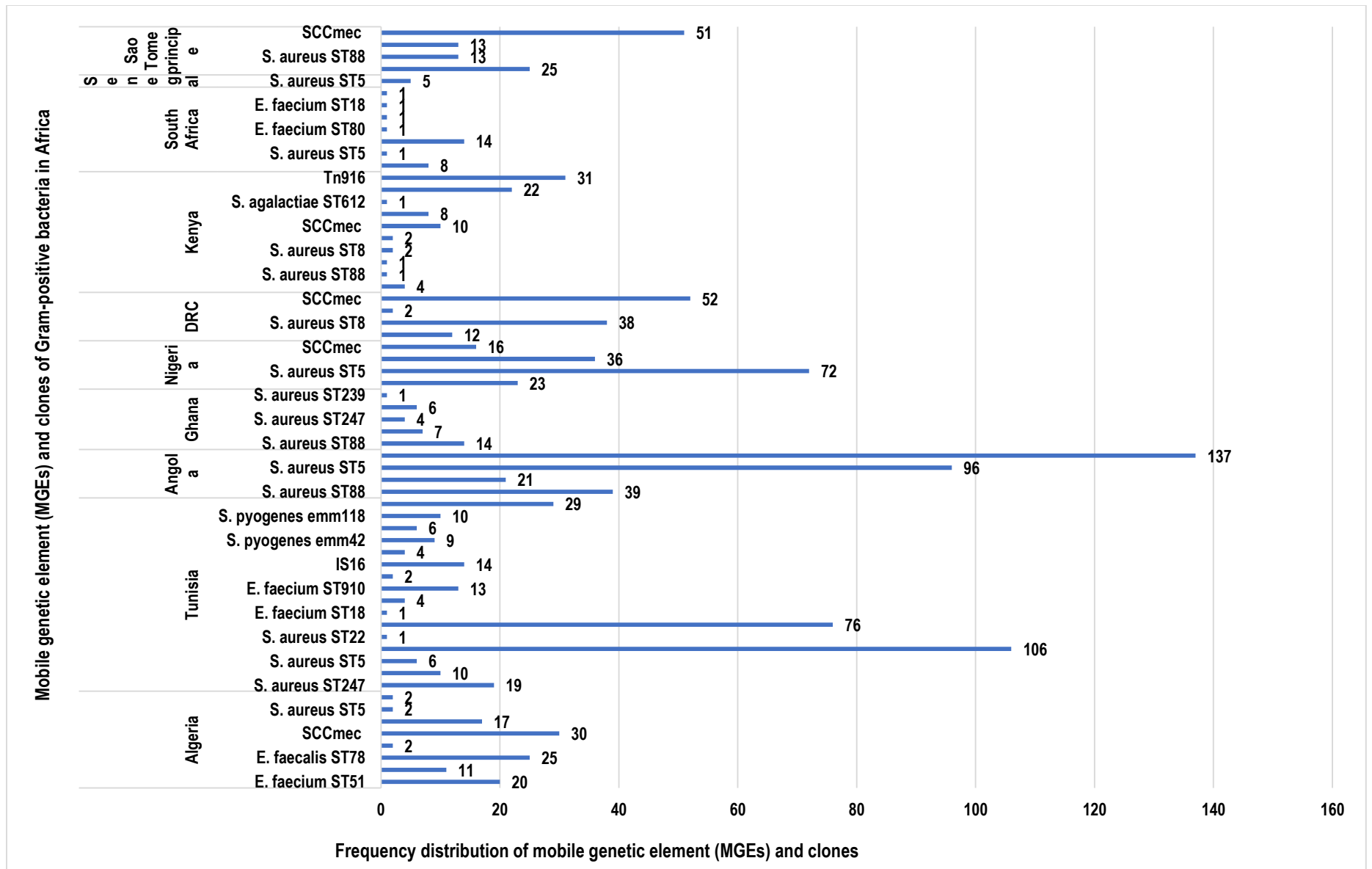


Figure 3a. Frequency distribution of resistant Gram-positive bacterial species, clones and mobile genetic elements (MGEs) per country in Africa.



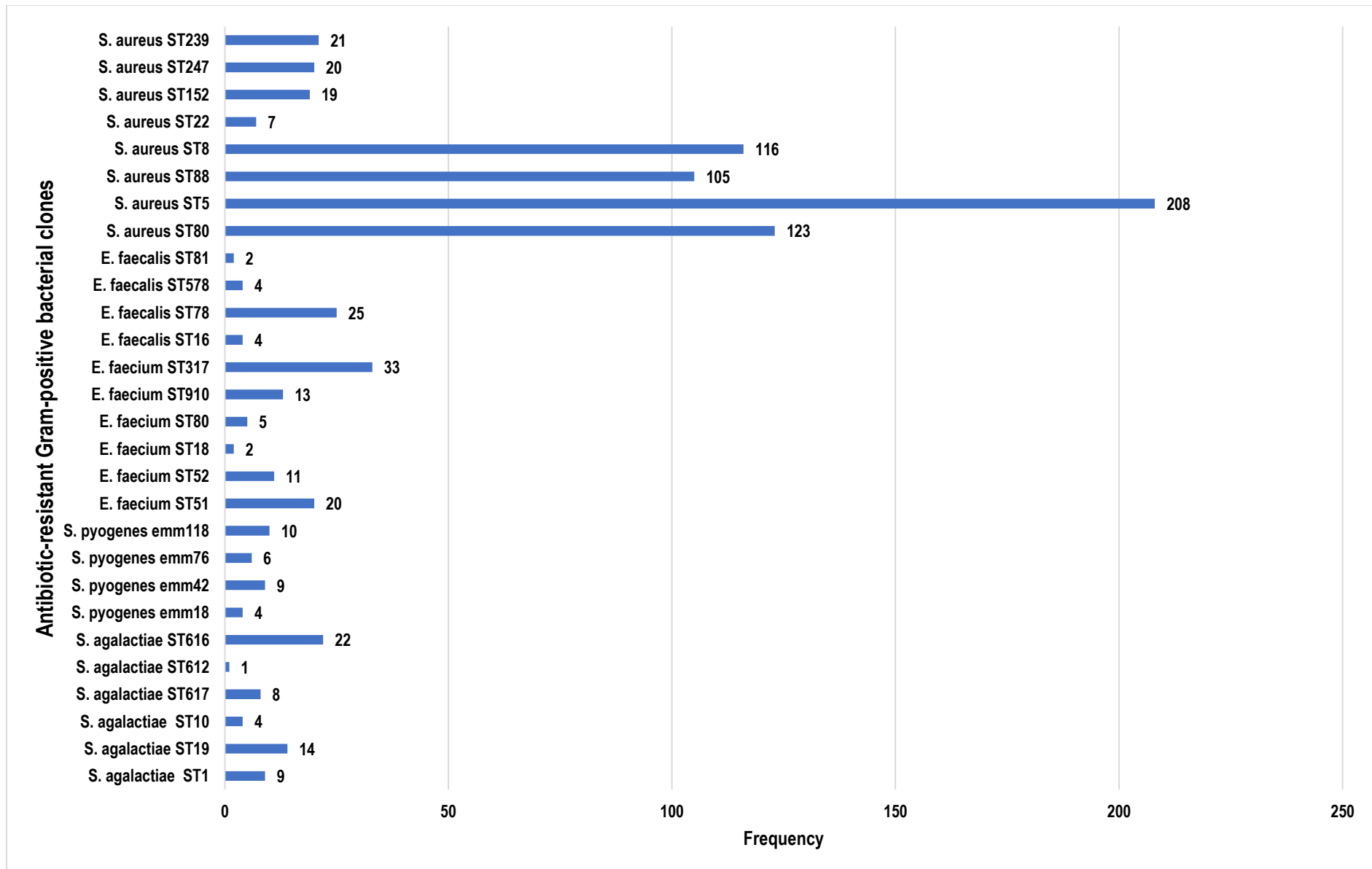


Figure 3b. Frequency of resistant Gram-positive bacterial species, clones and mobile genetic elements (MGEs) per country in Africa.