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Antimicrobial resistance prevalence of *Escherichia coli* and *Staphylococcus aureus* amongst bacteremic patients in Africa: a systematic review

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A B S T R A C T

Objectives: Antimicrobial resistance (AMR) is a global concern among infectious diseases. Bloodstream infections can potentially become life-threatening if they become untreatable with conventional antimicrobials. This review aims to provide an understanding of the AMR prevalence and trends of common bacteremic pathogens, namely *Escherichia coli* and *Staphylococcus aureus* in the World Health Organization (WHO) Africa region.
Methods: PubMed and Google Scholar were searched using relevant keywords for published human studies (excluding case reports and reviews) reporting bacteremic AMR data on the pathogens of interest between 2008 and 2019. Two reviewers independently screened the articles against a pre-defined eligibility criterion. Data extraction and analysis were achieved with different platforms: Covidence, Excel, R version 3.6.3, and QGIS v3.4.5. The pooled prevalence, 95% confidence intervals, and I^2 index (a measure of heterogeneity) were calculated for the various pathogen-antibiotic combinations.
Results: Five hundred sixty-two papers were retrieved, with 27 papers included in the final analysis. Only 23.4% (11/47) of member states of the WHO African region had reports on AMR in bacteremia. The Clinical and Laboratory Standards Institute (CLSI) (78.5%) was the most common standard used in the region. For *E. coli*, the pooled resistance was: cefotaxime (42%), imipenem (4%), meropenem (0%), and colistin (0%). For *S. aureus*, the calculated pooled resistance was cloxacillin (34%), oxacillin (12%), and vancomycin (0%). There was a high degree of variation across studies ($I^2 > 90\%$).
Conclusion: The pooled resistance rates indicate a concerning degree of methicillin-resistant and Extended Spectrum-ß-lactamase–producing pathogens. The paucity of AMR data also presents challenges for a comprehensive understanding of the situation in the region. Continent-wide and standardized surveillance efforts therefore need strengthening.

1. Introduction

Antimicrobial resistance (AMR) is recognized as a global health problem [1–4]. AMR is a multifaceted problem that affects the entire spectrum of microbes (e.g. bacteria, viruses, fungi, and parasites) [5,6] across the human, animal, and environmental health sectors [7–9].

The global proportion of Disability-Adjusted Life Year (DALY) was comprised of 63.8% non-communicable diseases; 26.4% communicable, maternal, neonatal, and nutritional diseases; and 9.8% injuries. However, the burden of communicable disease is considerably high in sub-Saharan Africa (i.e. accounting for 62.35% of the total DALY) [10]. Amongst communicable diseases, bloodstream or invasive infections are associated with high fatality rates and have

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a significant effect on healthcare operations [11,12]. The continued rise of multidrug-resistant (MDR) bacteria [13] may pose a threat to the management of bacteremic and septic cases.

The main etiological agents of bloodstream infections are *Staphylococcus aureus, Escherichia coli, Klebsiella* Spp., *Streptococcus pneumoniae*, and *Salmonella* Spp. [14–18]. Because of the emergence of resistance, the management of infections involving these pathogens with empiric and broad spectrum antibiotics may inadvertently harm patients [11]. This harm may be even greater when pathogens are resistant to last-resort antibiotics [19–23].

In this review, we focus on bacteremic organisms *Staphylococcus aureus* and *Escherichia coli.* These organisms have various resistance mechanisms that render them resistant to multiple antimicrobials. This results in therapeutic challenges, as alternative antimicrobials have become limited. Examples are methicillin-resistant *S. aureus* [24,25] and *E. coli* exhibiting extended-spectrum-ß–lactam or carbapenem resistance [26–28].

AMR rates vary across geographical settings, syndromes, and pathogens [11,29,30]. Thus, surveillance efforts need to take the aspects previously mentioned into consideration to achieve a comprehensive understanding of the AMR situation and provide therapeutic management of resistant pathogens.

This systematic literature review focuses on analysis of antimicrobial resistance levels of *S. aureus* and *E. coli* isolated from blood cultures within the World Health Organization (WHO) African region during a 12-year period.

2. Methodology

2.1. Literature search strategy

Google Scholar and PubMed were searched for publications reporting resistance between the years 2008 and 2019. Studies carried out before 2007 but published from 2008 onwards were excluded. The search was carried out between March 28, 2019 to August 8, 2019, and the results were recorded in an Excel Search diary. The following search strings were used: ‘Antimicrobial or antibiotic’, ‘Susceptibility’, ‘testing’, ‘non-susceptibility’, ‘*Escherichia coli* (*E. coli*)’, ‘*Staphylococcus aureus* (*S. aureus*)’, ‘bacteremia*’, ‘bacteremic infections’, ‘blood culture’, ‘bloodstream infection’, ‘sepsis’, ‘surveillance’, ‘epidemiology’, ‘epidemiological’, ‘Africa’, and specific names of all countries within the WHO African region.

2.2. Article screening and eligibility criteria

All publications were imported into the Covidence online platform (Covidence Systematic Review Software, Veritas Health Innovation, Melbourne, Australia; available at www.covidence.org). The articles were blindly and independently screened, assessed, and validated against a pre-defined eligibility criterion (Appendix 1) by two reviewers.

2.3. Data extraction

Fig. 1 below provides a summary of the number (n) of publications at the various stages of identification, screening, eligibility, and final inclusion. The variables extracted from the papers that were eligible for inclusion were the year, country, age or age group (i.e neonates, geriatrics, etc.), sex, laboratory standard/guideline, the total number of isolates (N), proportion of resistant isolates, and percentage resistant (%R) or percentage susceptible (%S). Information was extracted for pathogen-antimicrobial combination groups as recommended by the Global Antimicrobial Surveillance System (GLASS) (Appendix 2).

2.4. Data analysis

Descriptive summaries on the number of publications by country and year, as well as the laboratory testing standards/guideline, were reported. QGIS version 3.4.5-Madeira was used to visually represent the number of publications by country on a map of Africa. The pooled prevalence of resistance and 95% confidence intervals (CIs) were calculated for the pathogen-antibiotic combinations using a random-effects model in R 3.6.3 (2020-02-29). Resistance rates reported for less than 30 isolates for a given pathogen-antibiotic combination were excluded from the analysis.

3. Results

3.1. Descriptive characteristics

There are 54 countries in continental Africa, with 47 being part of the World Health Organization (WHO) Africa region. PubMed and Google Scholar searches yielded 562 publications (see Fig. 1), with 27 included in the final analysis. The eligible publications were from 23% (11/47) member states of the WHO African region (Fig. 2). During the period from 2008 to 2019, the published papers were mainly from Ghana (5), Nigeria (4), and Tanzania (4). In addition, 63% (17/27) of the papers were published in the years 2015 (8) and 2016 (9) (Appendix 3, Appendix 4).

The majority of publications (n = 22, 81.5%) reported AMR data on both organisms, whilst 2 (7.4%) and 3 (11.1%) reported exclusively on *E. coli* and *S. aureus*, respectively (Fig. 3). Furthermore, the CLSI (78%) was the most common guideline used in antimicrobial susceptibility testing (Appendix 5). The five reports of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) as the laboratory standard were from five different countries (i.e. there was one report from each of the five countries; Guinea-Bissau and Mali exclusively reported EUCAST as the laboratory standard used, whereas Uganda, Ghana, and Tanzania have also reported CLSI in separate studies) (Appendix 4).

3.2. Antimicrobial resistance rates

3.2.1. Overall and Country-Specific Antimicrobial Resistance Rates: S. aureus

The majority of the bacteremic isolates (N = 2651) were tested against the following antimicrobial agents: cefuroxime (n = 521), oxacillin (n = 427), and cloxacillin (n = 339).

The forest plot in Fig. 4 shows that the antibiotic, ampicillin, had the highest pooled resistance rate of 85% (95% CI 0.41–0.98). In Kenya, this rate stood at 45% (73 of 162 isolates) in the year 2010. Ghana recorded 90% (234/260) and 100% (34/34) resistance in 2016 and 2017, respectively. A moderate pooled resistance rate of 46% (95% CI: 0.07–0.92) against co-trimoxazole was found. Ceftriaxone resistance was 20% in Nigeria in 2010. Cefuroxime (n = 521) pooled resistance was 24% (95% CI: 0.07–0.58), which is comprised of the composite data from Kenya (2010), Nigeria (2011), and Ghana (2016). Oxacillin resistance was 21% and 23% in Kenya and Ghana in the years 2010 and 2016, respectively. The pooled resistance rate for oxacillin was 18% (95% CI: 0.09–0.31).

In Ghana, no *S. aureus* were found to be resistant to vancomycin (0/144) in 2016. Overall, we note a high variation between antimicrobial groups and years (i.e. I^2 of between 74%–98%) (Fig. 4).

3.2.2. Overall and Country-Specific Antimicrobial Resistance Rates: E. coli

For *E.coli* (N = 3447), the highest testing was among the following antibiotics: ciprofloxacin (n = 618), co-trimoxazole (n = 422), and ceftriaxone (n = 416). A pooled high resistance was found for

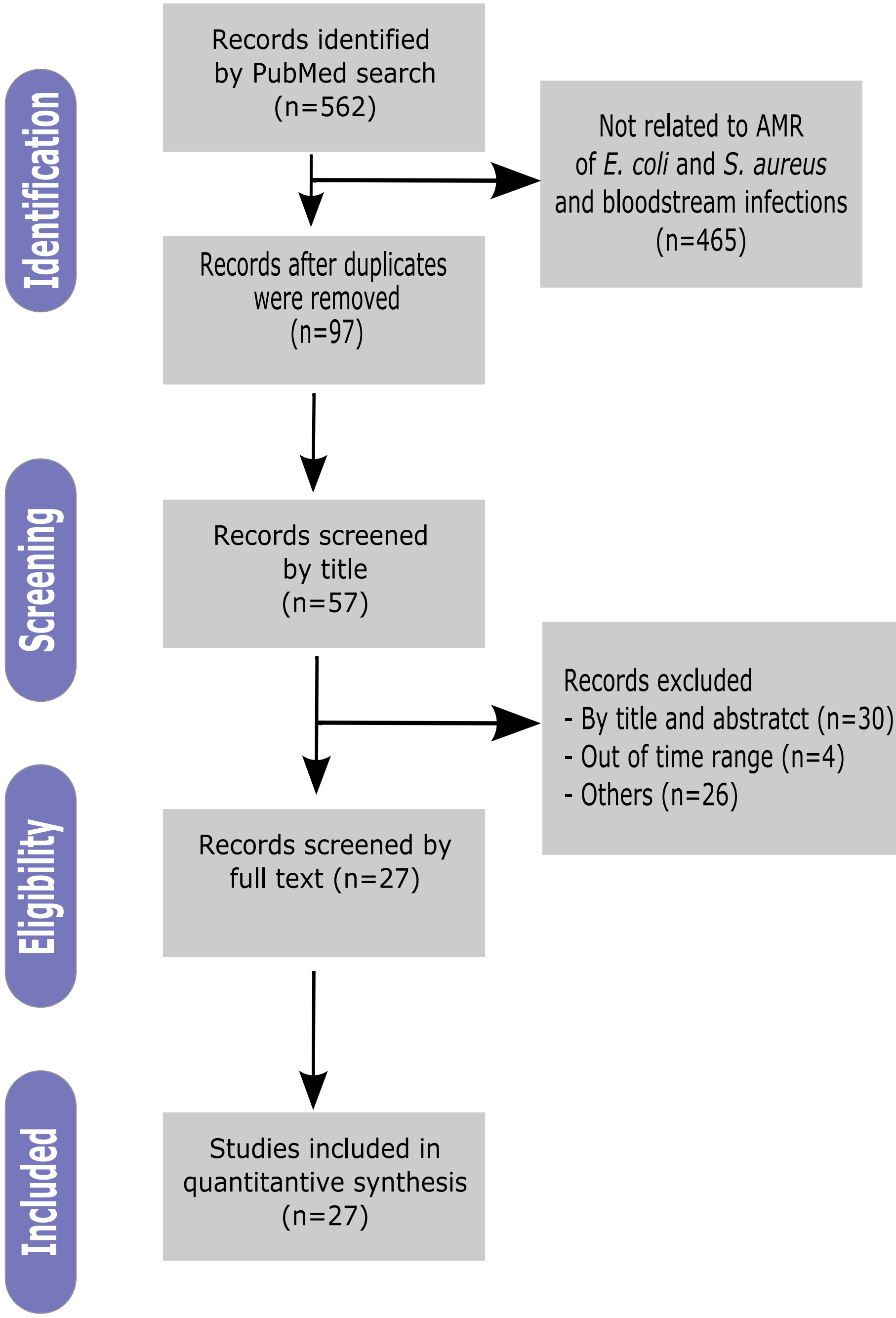

Fig. 1. PRISMA flow diagram for retrospective systematic review on antimicrobial resistance prevalence.

co-trimoxazole and ampicillin: 75% (95% CI: 0.57–0.87) and 87% (95% CI: 0.46–0.98) (Fig. 5), respectively.

Moderate resistance was found among the cephalosporins group. The median resistance for the second-generation cephalosporin, cefuroxime, was 58 (95% CI: 0.47–0.69), with high resistance of 70% (73/104) found in Ghana in 2016. The median resistance and 95% CI for the third generation cephalosporins were 32% (95% CI: 0.09–0.69) and 42% (95% CI: 0.28–0.58) for ceftriaxone and cefotaxime, respectively. Ceftazidime median resistance was 19% (95% CI: 0.05–0.52) (Fig. 5).

Fluoroquinolone (i.e. ciprofloxacin) resistance was also found to be high, with a median of 44% (95% CI: 0.23–0.67). In general, resistance to colistin and the carbapenems, ertapenem and meropenem, was zero except for imipenem. Imipenem median resistance was 4% (95% CI: 0.00–0.64). Imipenem resistance was 0% in South Africa (0/90) and 19% in Uganda (9/47) in 2017 and 2018, respectively (Fig. 5).

4. Discussion

In this review, we report a lack of publications on the AMR situation of severe infections, such as bacteremia/sepsis, within the WHO African region. Reports from the years 2010 to 2019 could only be found for 23% of the African countries. During the period under review, the majority (63%) of the papers were published between 2015 and 2016. This seems to have coincided with the launch of the WHO Action Plan on AMR in 2015 and the declaration of AMR as a global crisis by a United Nations General Assembly in 2016 [31–34]. The MRSA rates found were generally comparable to those of other countries and the European region

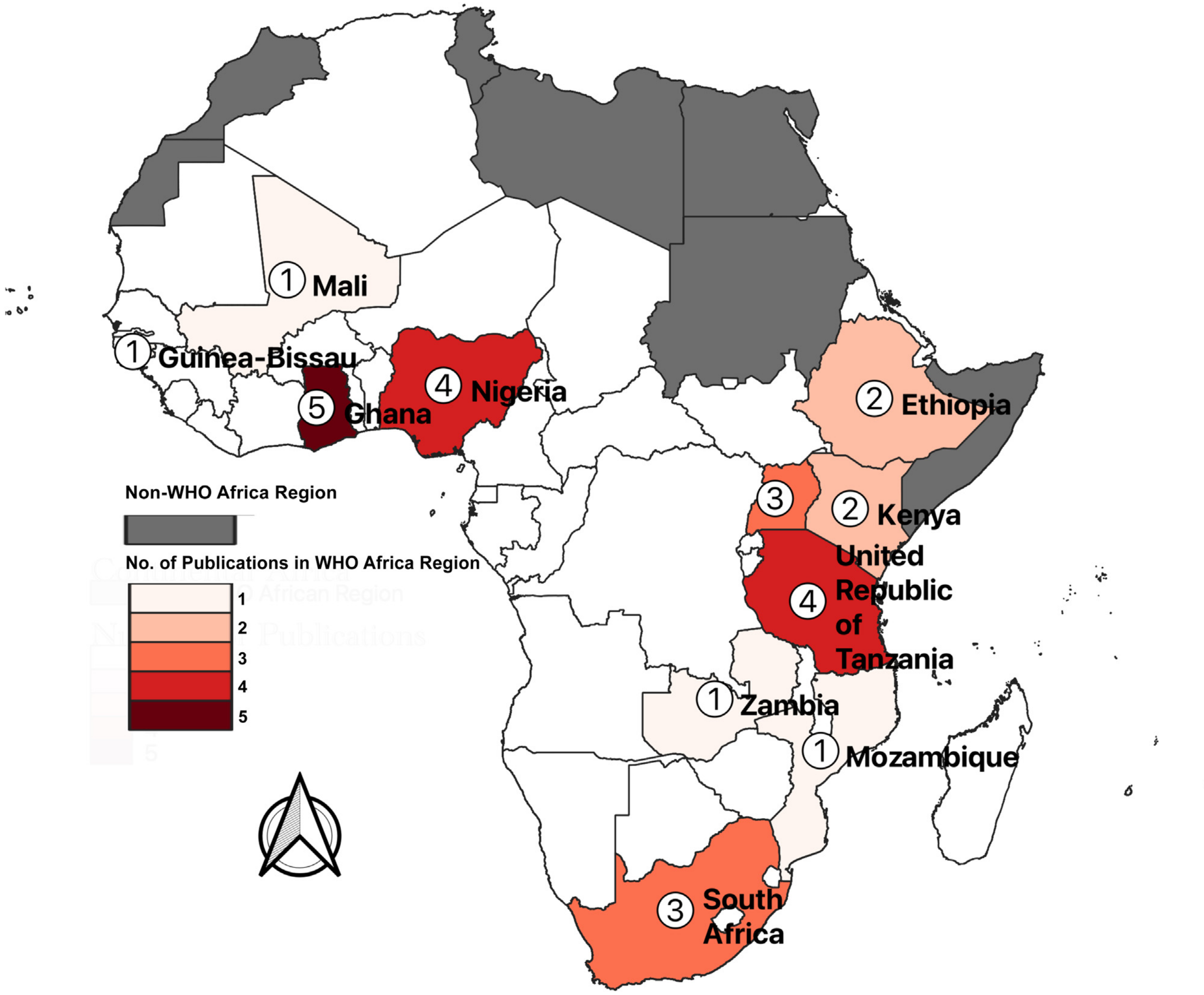

Fig. 2. Number of publications (2008–2019) by country reporting on the antimicrobial resistance prevalence of bacteremic Escherichia coli and Staphylococcus aureus in Africa.

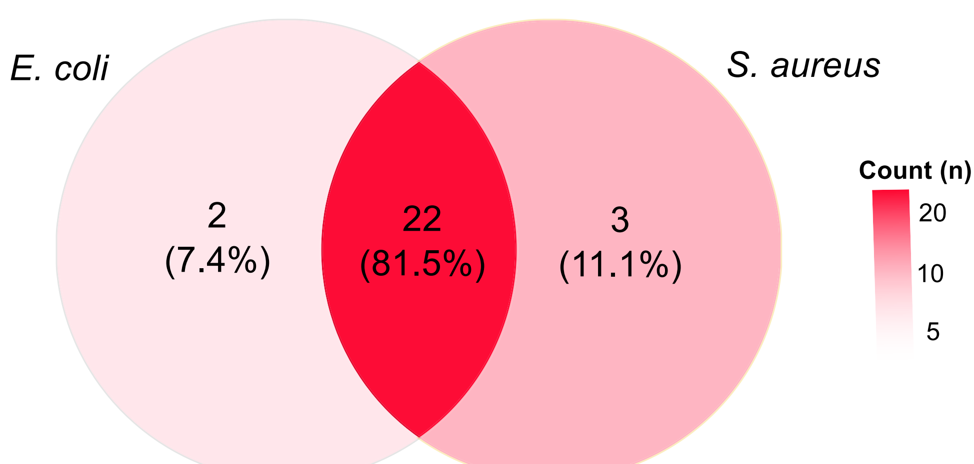

Fig. 3. An illustration of the distribution of organisms by identity in the published bacteremic antimicrobial resistance studies (i.e. the commonalities and differences by study).

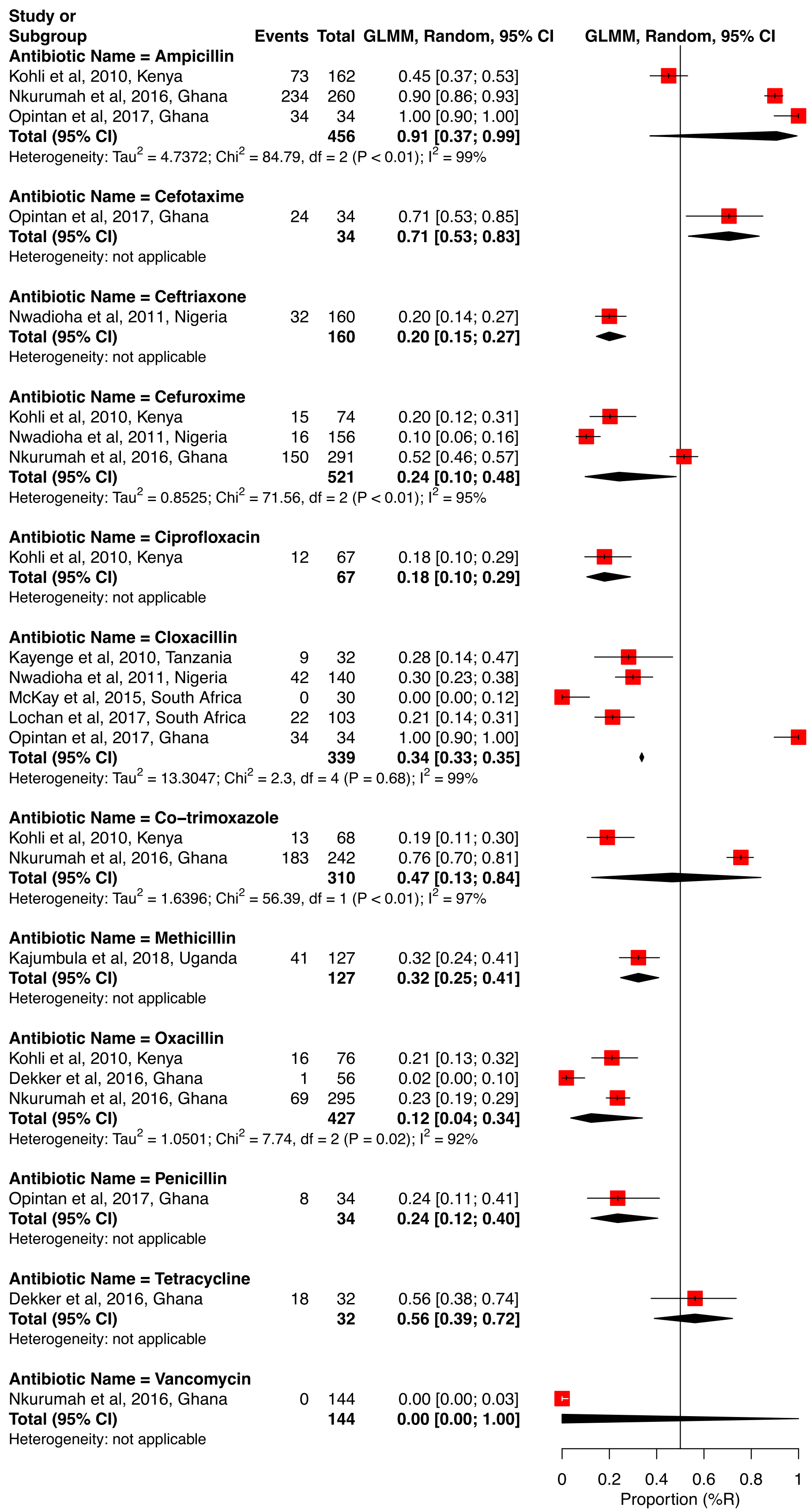

Fig. 4. Forest plot of antimicrobial resistance rates among *Staphylococcus aureus* given by antibiotic grouping and country.

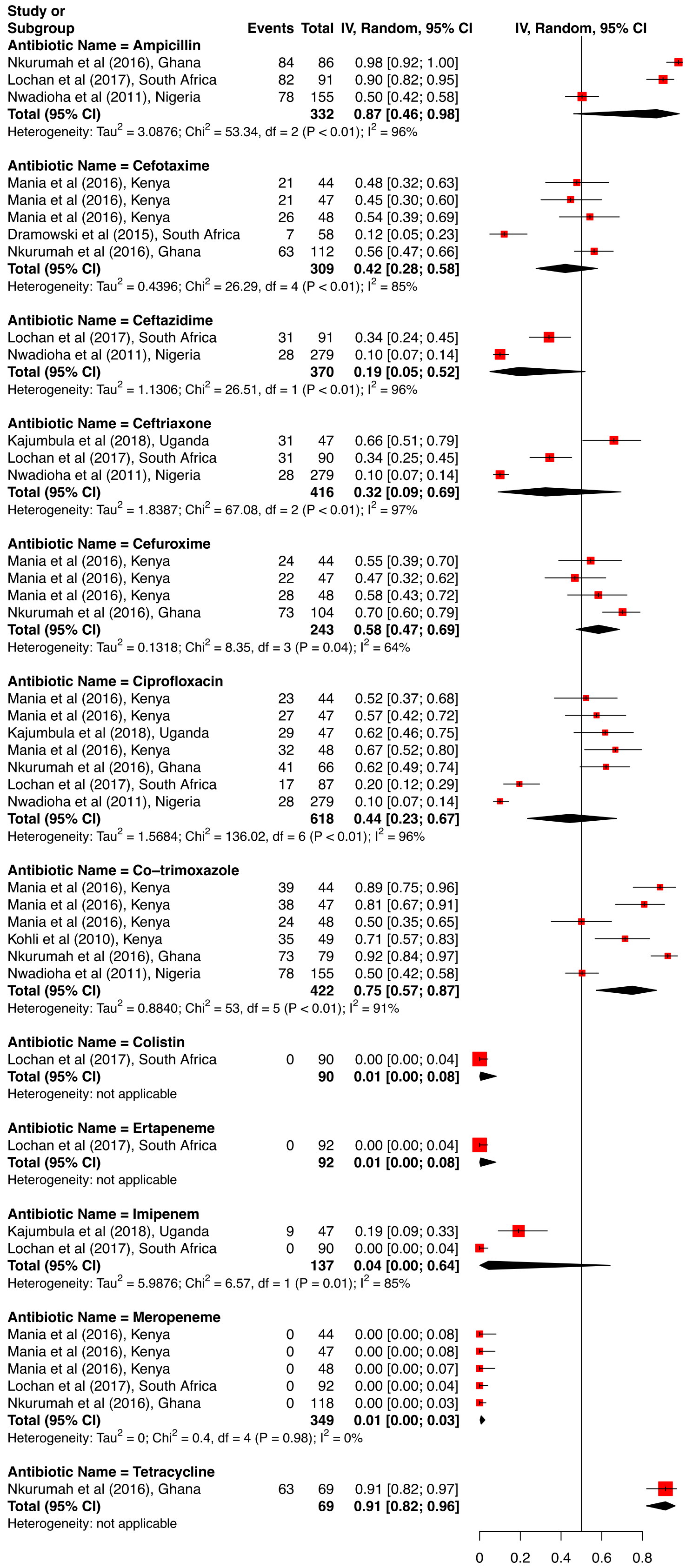

Fig. 5. Forest plot of antimicrobial resistance rates among Escherichia coli given by antibiotic grouping and country.

(i.e. below 32%). Overall, *E. coli* showed moderate to high resistance against commonly-used therapeutic agents, such as third-generation cephalosporins (resistance [R]: 19–58%), ciprofloxacin (R: 45%), co-trimoxazole (R: 75%), and tetracycline (R: 91%). However, carbapenem and colistin resistance were largely absent (i.e. resistance was 0.01%).

We inferred MRSA resistance from oxacillin and cloxacillin despite the CLSI standard and EUCAST recommendation to use cefoxitin for this since 2008 and 2009, respectively. Whilst many African countries used the CLSI standard, cefoxitin resistance data was not regularly reported in publications included in our review.

Oxacillin resistance was reported from Kenya and Ghana, whereas cloxacillin resistance was reported from four countries (Ghana, Tanzania, Nigeria, and South Africa). However, the majority of isolates were tested against the former (n = 427). There was variation across settings for oxacillin and cloxacillin (i.e. $I^2 = 74\%$ and 81%, respectively). Similar to our study, heterogeneity was also found by [35] in a review on MRSA proportions within the Asia Pacific region. The overall MRSA rates that can be inferred from oxacillin and cloxacillin were thus 18% (95% CI: 0.09–0.31) and 29% (95% CI: 0.15–0.48), respectively. The overall bacteremic MRSA rate of 18% (as inferred from oxacillin) found in our review (2008–2019) was within the range of 16 to 55% reported in an earlier study (2002–2011) on the prevalence of MRSA in Africa [36]. A systematic review conducted [37]during the years 2000 to 2010 in Western European healthcare settings found the MRSA prevalence to vary widely (between 1% and over 20%) . Wide ranges have also been reported in the Asia Pacific region, where the proportion of MRSA infections was between 0 and 98.4% between 2000 and 2016 [35]. Similarly, the European region reported MRSA resistance of 19% in 2015 with a decline to 15.5% by 2019 [38]. Our study primarily focused on blood culture isolates and many other studies did not make this distinction (i.e. specimen characteristics); the findings were nonetheless both comparable, and, in certain instances, widely varied [35]. This variation may be explained by the country's income status and patient or sample characteristics [35]. The unharmonized definitions of measuring resistance as proportions or prevalence also introduce incomparability of the data across settings [39].

Among *E. coli*, Extended Spectrum-ß-lactamase (ESBL) producers ranged from 19 to 42%, inferred from resistance to third-generation cephalosporins. These were ceftazidime (19%, 95% CI: 0.05–0.52), ceftriaxone (32%, 95% CI: 0.09–0.69), and cefotaxime (42%, 95% CI: 0.25–0.58). Between 2005 and 2013, the bacteremic ESBL-producing Enterobacteriaceae in Africa varied from 0.7% to 75.8% [40–42]. By 2019, in Europe, the population-weighted resistance of third-generation cephalosporins among invasive *E. coli* isolates was 15.1%. The lowest resistance rate stood at 6.2% in Norway and the highest rates were above 30% in Italy and Bulgaria [43]. In Eurasia (India, Thailand, Vietnam, China, and Russia), the proportion of *E. coli* ESBL phenotypes collected from 2015 to 2019 was reported to have exceeded 50% [44]. In Japan (2008–2013), 30 of 115 (26,1%) *E. coli* bacteremia cases were caused by ESBL-producing *E. coli* [45]. Between 2012 and 2017, the distribution of ESBL prevalence ranged from 11.9% to 15.7% in the United States [46,47]. In the Middle East (January 2012–January 2017), resistance to ceftazidime and ceftriaxone was 49.1% and 51.7%, respectively, among pediatric patients in Turkey [48].

Although trend analysis was not possible with our study materials, there has lately been growing evidence for increasing ESBL resistance rates [49–51]. For example, a study from Turkey found that bloodstream ESBL *E. coli* producers increased from 23% to 48% between 2014 and 2016 [52]. In Nepal, in two separate years (i.e. 2015 and 2017) among various clinical specimens, the *E. coli* ESBL prevalence was 38% (46/121) and 43% (130/302), respectively [53,54]. Also, ESBL *E. coli* bacteremic prevalence increased from 5.2% (2005) to 13.5% (2009) in five yrs in a French hospital [55].

Carbapenems are recommended as therapy for severe infections involving ESBL-producing Enterobacteriaceae [56]. Carbapenem and colistin resistance were generally low albeit a few publications in our study reporting on them. This finding is consistent with studies elsewhere, in which resistance to carbapenems and colistin was absent/low for both ESBL-producing and non-ESBL–producing *E. coli* alike [50,57,58]. However, carbapenem resistance was more likely to be encountered in hospital settings [59], as it was found in a tertiary hospital in Uganda (i.e imipenem resistance of 19%) within our study materials [60].

The widespread use of ciprofloxacin and co-trimoxazole is responsible for increasing resistance and its subsequent preclusion as an empiric therapeutic regimen [60,61]. In the present review, high resistance to co-trimoxazole and ciprofloxacin (i.e. pooled resistance: 75% and 44%) was found. Haindongo et al. (2022) reported high resistance in Namibia to these two antimicrobial agents among urinary *E. coli* from 2016 to 2017. Ciprofloxacin resistance of 44% was comparable to that reported elsewhere [18,62,63]. Resistance to ciprofloxacin was found to be higher in Africa than in Asia (36.7% vs. 0%). Within the European Union, fluoroquinolone resistance (23.8%) was reported to be second-highest, after resistance to aminopenicillins (57.1%) [43].

There have been some noticeable variations in resistance between the type of specimen and the patient groups under study. For example, a 5 month study in 2013 in Nottingham, United Kingdom [64] reported a higher ciprofloxacin resistance rate among bacteremic *E. coli* than among urinary *E. coli* (25.7% vs. 8.8%; $P < 0.001$). This study included a diverse age range (i.e. children and adults) with infections being community- and hospital- associated. On the other hand, differences in ciprofloxacin resistance in Europe between children and adult surveillance data (13.4% and 23%, respectively) was found by [65,66]. Among urinary tract infection (UTI) *E. coli*, Fasugba et al. (2016) [67] found the level of ciprofloxacin resistance to be higher in the hospital setting than in the community setting (38% vs. 27%, $P < 0.001$).

Co-trimoxazole is useful in the management of bacterial infections, diarrhoea, HIV-related opportunistic infections, and malaria in sub-Saharan Africa [68]. In the United States (1998–2007), co-trimoxazole resistance increased from 9% to 28% [69]. In earlier years, resistance rates among uropathogenic *E. coli* were around 60% [70]. A review by Ashley et al. (2011) found co-trimoxazole resistance to be higher in Asia than in sub-Saharan Africa (55% vs. 25%). A high *E. coli* co-trimoxazole resistance of 80% was reported from blood cultures in Lahore, Pakistan [71]. Similarly, a multi-center study of 20 yrs from a network of hospitals in the Hubei province of China found co-trimoxazole resistance among bloodstream infections to be 72.1% [72].

There were several limitations in our data extraction process. Firstly, we note that publications on bacteremic antimicrobial resistance are limited in many countries of the WHO African region. Worryingly, Portuguese and French-speaking countries may not have been represented because of language restrictions. Thus, the few reports published in Africa do not provide a comprehensive understanding of the antimicrobial situation in the WHO Africa region. Secondly, the lack of standardization in the formatting of the reports also made comparability difficult (i.e. demographic characteristics [age, sex, and setting of acquisition] of the study population were not always given). This is important, as resistance rates vary within sub-groups and interventions need to be tailored accordingly. Furthermore, resistance data cannot be compared if the reported denominators differ; for example, MRSA rates among patients or cases per 1000 patient days instead of resistance for a given isolate. Thirdly, resistance was reported for larger bacterial groups (e.g. Enterobacteriaceae or Gram-negative), which may obscure species-specific differences [73,74]. Fourthly, resistance data was not periodically (i.e annually) reported; thus, comparing resistance levels within the same time frames or years became difficult. When resistance data is compared in different time frames (i.e. years), this further weakens the reliability of the calculated I^2. Finally, in our review, MRSA resistance was inferred from cloxacillin and oxacillin instead of cefoxitin. Thus, the MRSA rates may not reflect the true situation. The cefoxitin disk test has demonstrated reliability and superiority [75,76] over the historically recommended cloxacillin and oxacillin [77]. Discrepancies between oxacillin and cefoxitin have also been reported across various testing platforms, such as disk diffusion, latex agglutination, and automated commercial systems [78–81].

5. Conclusion

We report medium to high rates of bacteremic MRSA and ESBL-producing *E. coli* in the WHO Africa region, though varied prevalence across countries (i.e. heterogeneity) occurs. Publications covering AMR rates for severe infections were limited. Furthermore, the formats of the reports were non-standardized, making inter-country comparisons difficult. It was impossible to understand the 12-year AMR trend (increases and decreases), as the data between the years was discontinuous. Thus, advocacy for countries in the region to deposit standardized AMR data in public repositories annually needs to be strengthened.

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Competing interests

None declared.

Ethical approval

Not required.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jgar.2022.11.016.

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