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A five-year retrospective study shows increasing rates of antimicrobial drug resistance in Cabo Verde for both *Staphylococcus aureus* and *Escherichia coli*

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Highlights

- First antimicrobial resistance survey in clinical isolates in Cabo Verde
- Increase in methicillin and extended spectrum beta-lactamase resistance
- Generation of base line data for implementation of the national action plan
- Overall susceptibility profile in Cabo Verde comparable to countries of the region

ABSTRACT

Objectives: Data on baseline drug resistance is important in informing future antimicrobial stewardship programs. So far, no data on the antimicrobial drug resistance of clinical isolates was available for the African archipelago of Cabo Verde.

Methods: We have performed a retrospective analysis over five-years (2013-17) of the antimicrombial drug susceptibility profiles of clinical isolates in the two main hospitals of Cabo Verde. For *Escherichia coli* and *Staphylococcus aureus*, representing respectively 47% and 26% of all clinical isolates, the antimicrobial drug resistance profile was reported for six representative drugs.

Results: For *E. coli* we detected an increase in resistance to ampicillin, amoxicillin/clavulanic acid, ceftriaxone, ciprofloxacin, and trimethoprim-sulfamethoxazole and for *S. aureus* to methicillin, erythromycin and trimethoprim-sulfamethoxazole. This increase in both the most commonly isolated bacterial pathogens is of alarm as it might compromise empirical treatment in a setting with limited access to laboratory testing.

Conclusions: When compared to the published low resistance rates in carriage isolates, the more alarming situation in clinical isolates for *S. aureus* might encourage antimicrobial stewardship programs to reduce MRSA in the hospital settings, possibly as part of the Cabo Verdean national plan against antimicrobial drug resistance.

INTRODUCTION

The global burden of antimicrobial-resistant infections is growing at an alarming rate, being responsible for more than half a million deaths worldwide each year [1-3]. In the absence of effective control interventions, annual numbers of deaths related to resistance may rise to 10 million per year by 2050, according to a UK government commissioned review [3], although others have forecast lower numbers, particularly in parts of the world where non-antimicrobial measures can be implemented to prevent infectious disease mortality [4]. These projections emphasize both the international burden and local variation in resistance rates. Several reviews have highlighted the impact of international travel, including immigration, on the worldwide spread of resistant bacteria, including to countries that are effectively controlling their antibiotic use [3,5,6].

The resistance crisis has prompted a rise in antimicrobial stewardship (AMS) programs which aim to reduce inappropriate antibiotic use. Although AMS focuses on antibiotic prescribing practice, it is underpinned by an understanding of local antibiotic susceptibility patterns, which in turn depends on the availability of a reliable medical microbiology laboratory resource. In light of the crisis of antimicrobial drug resistance (AMR), the implementation of clinical bacteriology laboratories in low-resource settings improves patient management, delivering both guidance for individual patient infection management and surveillance for support of antibiotic treatment guideline and policies [6,7].

Cabo Verde (CV) is a sovereign nation composed of 10 islands located in the Atlantic Ocean west of Senegal, with a population in 2016 of 539,560 [8]. In 2017, infectious diseases were the second highest cause of death, reflecting Cabo Verde's economic development [9]. Human antibiotic use is based largely on empirical prescribing and is generally restricted to a small number of relatively narrow spectrum antibiotics [9]. International travel to and from the islands is relatively high; large numbers of the Cabo Verdean population have emigrated, predominantly to the Europe (majority in Portugal, France and Netherlands) and the United States of America and they pay return visits to their homeland, immigrants from mainland Africa, especially other lusophone countries make up 2.9% of the population in 2010 and there are increasing numbers of tourists, including from countries with high rates of antibiotic resistance [10]. Additionally, Cabo Verdean patients may have to travel to Europe for tertiary care, potentially to hospitals with endemic multi-drug resistance problems. Consequently, despite modest antibiotic use in CV, concern about resistance has prompted the implementation of infection control measures [11] and, in 2018, the CV government launched a national plan against antimicrobial drug resistance [9].

Although data on carriage isolates of *S. aureus* in CV were reported to show very low levels of methicillin resistance [12], the overall level of AMR in clinical isolates has not been previously investigated. The aim of the present study was to characterise the antimicrobial drug susceptibility of the most frequently isolated clinical pathogens in the two hospitals in CV, with the more general goal to inform public health planning and antimicrobial stewardship programs.

METHODS

Hospitals

Hospital Agostinho Neto (HAN) and Hospital Baptista de Sousa (HBS), the two main public hospitals in Cabo Verde, participated in the retrospective study (see Supporting information, Table S1). HAN is a 400-bed hospital located in the city of Praia, the capital of Cabo Verde, on the island of Santiago. The hospital has a bed occupancy rate of around 80% and receives patients from Santiago and other islands (often from Fogo, Brava, Maio, Sal, and Boavista, as well as a few cases from São Vicente, São Nicolau, and Santo Antão). HBS is a 220-bed hospital located in the city of Mindelo on the island of São Vicente, and receives patients mainly from Santo Antão and São Nicolau. The clinical laboratories at the two hospitals receive human samples for diagnosis from internal and external patients, living in the islands and from all other islands.

Data collection

Retrospective microbiology laboratory antimicrobial drug susceptibility data for the time period January 2013 to December 2017 were collected in summer 2018. A total of 5669 positive samples from both hospitals were processed (see Supporting information, Table S1). Of the 3577 positive samples processed at HAN, there were 1818 urine samples, 603 pus samples, 154 blood cultures and 1002 other samples. Of the 2092 positive samples processed at HBS there were 1716 urine samples, 88 pus samples, 64 blood cultures and 224 other samples. From these specimens, 1252 *S. aureus* isolates were cultured at HAN and 204 at HBS. The corresponding numbers of *E. coli* isolates were 1753 from HAN and 882 from HBS from all samples and 1539 and 868 from urine respectively (Table S1).

Phenotypic characterization

At both HAN and HBS *S. aureus* was isolated on mannitol salt agar plates (Oxoid) and identified using Pastorex Staph-Plus (Bio-Rad) while *E. coli* was isolated on Eosin Methylene Blue (EMB) agar plates (Oxoid) and in selected cases identity was confirmed using API 20E (Biomerieux). Antimicrobial susceptibility testing discs were from Oxoid and inhibition zones were interpreted using CLSI breakpoints [13].

Statistical analysis

Categorical variables were summarized using the frequency and percentage. The chi-squared test was used to identify differences between susceptibility proportions among islands and regions. The chi-square test for trend in proportions was used to evaluate trends in the *S. aureus* and *E. coli* resistance rates per year. In all cases, p values of ≤0.05 were considered statistically significant and analysis was conducted using R software version 3.5.1.

RESULTS

In the five-year period 2013-17, the microbiology laboratories of the two hospitals HAN and HBS in Cabo Verde reported 5669 positive samples, of which 1456 were positive for *S. aureus* (25.7%), 1252 for HAN and 204 for HBS. The distribution of isolated strains according to the type of sample is given in Supplementary material, Table S1. Susceptibility testing of *S. aureus* for all type of samples from HAN showed resistance to penicillin for 95.1% of isolates, to methicillin (oxacillin) in 15.8%, erythromycin 18.9%, chloramphenicol 4.6%, ciprofloxacin 10.2%, trimethoprim-sulfamethoxazole 17.4% and tetracycline 9.7% (Fig. 1a). Among the *S. aureus* all type of samples from HBS, we noticed resistance to penicillin (87.3%), methicillin (55.1%), erythromycin (48.4%), chloramphenicol (22.4%), ciprofloxacin (27.4%), trimethoprim-sulfamethoxazole (35.7%) and tetracycline (35.1%) (Fig. 1a).

The proportions of resistant bacteria were broken down for the study period (2013 to 2017). A statistically significant trend was found in *S. aureus* isolates in Santiago between 2013 and 2017 for methicillin (oxacillin; p-value <0.0001), penicillin (p-value 0.032), and erythromycin (p-value: 0.022). For the other antibiotics, there was no increase in drug resistance over time (p-value > 0.05) (Fig. 1b). A statistically significant trend was found in *S. aureus* isolates in São Vicente between 2013 and 2017 for four antibiotics: penicillin resistance rate decreased (p-value: 0.0062), chloramphenicol resistance rate decreased (p-value: 0.0031), trimethoprim-sulfamethoxazole resistance rate increased (p-value: 0.018) and methicillin resistance rate increased (p-value: 0.0007). The ciprofloxacin and erythromycin resistance rate decreased in 2013-16 to increase in 2017 (p-value > 0.05) (Fig. 1c). It should be noted that the sample size is low for some antibiotics in certain years due to issues linked to the supply of susceptibility testing discs (Fig. S1, Table S2-S3).

We found significant differences between islands (Fig. 1a): in Santiago we observed higher resistance to penicillin (95.1% vs 87.3%, p-value 0.005); in São Vicente we observed higher resistance to methicillin (55.1% vs 15.8%, p-value <0.0001), erythromycin (48.4% vs 18.9%, p-value <0.0001), chloramphenicol (22.4% vs 4.6%, p-value <0.0001), ciprofloxacin (27.4% vs 10.2%, p-value <0.0001), trimethoprim-sulfamethoxazole (35.7% vs 17.4%, p-value 0.001) and tetracycline (35.1% vs 9.7%, p-value 0.001) (Table S4).

To place the data of antimicrobial drug resistance in clinical samples from CV into an international context, we compared our data to data from two carriage studies from the same two hospitals in CV [14,15] and global resistance surveys in Africa [16,17]. Compared to other countries, we found in Angola higher resistance to trimethoprim-sulfamethoxazole (66.5%) and methicillin (63.0%); in São Tomé and Príncipe higher resistance to trimethoprim-sulfamethoxazole (51.0%) and tetracycline (26.0%).

We used median prevalence of resistance with Interquartile range (IQR) from a systematic review to compare our results to the regions of Africa and we noticed the following (Fig. 1d): in Western Africa for *S. aureus* isolated from patients with a febrile illness, the median prevalence of resistance to tetracycline (58.3%; ranged between 46.0% and 66.7%) and notable resistance to trimethoprim-sulfamethoxazole (45.5%; ranged between 30.8% and 71.4%), chloramphenicol (33.3%; ranged between 12.9% and 56.5%) as well; in Eastern sub-Sahara Africa, the high median prevalence of resistance to tetracycline in *S. aureus* isolated from patients with a febrile illness (69.2%; ranged between 56.5% and 74.9%), as well as to trimethoprim-sulfamethoxazole (39.6%; ranged between 20.0% and 60.6%) and chloramphenicol (36.9%; ranged between 17.7% and 50.7%); in Central/Southern Africa, not only high median prevalence of resistance to trimethoprim-sulfamethoxazole (80.0%; ranged between 51.8% and 92.0%) in *S. aureus* isolated from patients with a febrile illness, but as well as to tetracycline (59.0%; ranged between 38.0% and 80.0%) chloramphenicol (26.0%; ranged between 8.0% and 44.0%) and erythromycin (55.6%; ranged between 24.0% and 82.0%). We noticed the absence of data on resistance to penicillin from around the African region [16].

E. coli was the most frequent bacterium isolated in both hospitals (2635, 46.5%), 1753 for HAN and 882 for HBS. The most common type of samples for *E. coli* were urine (2407, 91.4%) for both hospitals (Table S1). Among the 1539 *E. coli* urine samples from HAN, we documented resistance to ampicillin (78.9%), amoxicillin/clavulanic acid (20.1%), ceftriaxone (28.2%), ciprofloxacin (30.3%), trimethoprim-sulfamethoxazole (60.5%) and gentamicin (21.6%) (Fig. 2a). Among the 868 *E. coli* urine samples from HBS, we found resistance to ampicillin (73.3%), amoxicillin/clavulanic acid (48.6%), ceftriaxone (15.6%), ciprofloxacin (18.7%), trimethoprim-sulfamethoxazole (44.0%) and gentamicin (21.2%) (Fig. 2a).

We found statistically significant increases in resistance in *E. coli* isolates in HAN between 2013 and 2017 for ampicillin (p-value 0.005), amoxicillin/clavulanic acid (p-value 0.016), ceftriaxone (p-value <0.0001), nalidixic acid (p-value <0.0001), ciprofloxacin (p-value 0.004) and trimethoprim-sulfamethoxazole (p-value 0.011) (Fig. 2b) (Fig. S1c, Table S5). For HBS between 2013 and 2017, we found decreased resistance for ampicillin (p-value <0.0001) and increased resistance for ciprofloxacin (p-value 0.029) and ceftriaxone (p-value 0.008) (Fig. 2c) (Fig. S1d, Table S6). At HAN also cefuroxime susceptibility decreased in the same measure as ceftriaxone (data not shown), with both data being compatible with an increase of extended spectrum beta-lactamase (ESBL) positive *E. coli* in Cabo Verde.

We found significant differences between islands (Fig. 2a): in São Vicente we observed high levels of resistance to amoxicillin/clavulanic acid relative to Santiago (48.6% vs 20.1%, p-value <0.0001); in Santiago we noticed statistically significant higher levels of resistance relative to São Vicente for:

ceftriaxone (28.2% vs 15.6%, p-value <0.0001), ciprofloxacin (30.3% vs 18.7%, p-value <0.0001), trimethoprim-sulfamethoxazole (60.5% vs 44.0%, p-value <0.0001). There was no significant difference between islands for ampicillin and gentamicin (Table S7). Carbapenem susceptibility was not tested.

To compare our results with other regions, we used median prevalence of resistance with Interquartile range (IQR) against relevant antimicrobial drugs reported for *E. coli* isolated from patients with a community-acquired febrile illness or urinary tract infection in Western, Central/Southern, and Eastern sub-Sahara Africa [16]. We noticed the following (Fig. 2d): the higher median prevalence of resistance to amoxicillin/clavulanic acid, chloramphenicol and trimethoprim-sulfamethoxazole in all noticed regions of Africa; the lower median prevalence of resistance to ceftriaxone, ciprofloxacin in all noticed regions of Africa; the lower median prevalence of resistance to gentamicin in all regions, besides *E. coli* isolated from patients with a community-acquired febrile illness in Western Africa; for ampicillin resistance, the lower median prevalence of resistance in Western Africa, and the higher in Central/Southern, and Eastern sub-Sahara Africa [16].

DISCUSSION

This report shows an alarming and recent increase in methicillin-resistant *S. aureus* (MRSA) and ESBL positive *E. coli* infections in Cabo Verde by retrospectively analysing the laboratory results of the two main public hospitals of CV located in the capital Praia on the island of Santiago (HAN) and in Mindelo on the island of São Vicente (HBS) for the years 2013 to 2017. This is the first study on the susceptibility profiles of clinical isolates in CV and focusses on the two most common bacterial pathogens isolated in a hospital setting which are *S. aureus* and *E. coli*.

Over the five-year period of review, the most frequent laboratory isolate from clinical samples, *E. coli*, showed for one of the two hospitals (HAN) an increase in resistance to almost all antimicrobial drugs monitored. This is most likely due to the diffusion of clones carrying extended spectrum beta-lactamases (ESBL). This trend was not shared by the second hospital (HBS). Still, the cumulative data show for *E. coli* in CV an increase in resistance to ampicillin, amoxicillin/clavulanic acid, ceftriaxone, cefuroxime (data not shown), nalidixic acid, ciprofloxacin, norfloxacin (data not shown) and trimethoprim-sulfamethoxazole. This is a worrying trend that requires an urgent local antimicrobial stewardship response. Except for a somewhat higher prevalence of ceftriaxone resistance, indicative of extended spectrum beta-lactamase gene circulation, the overall situation is comparable to that of other African studies on antimicrobial drug resistance [16,17].

Analyzing susceptibility profiles of the hospital isolates of *S. aureus* over these five years we noted an increase in methicillin (oxacillin) resistance in both hospitals. At HAN, methicillin resistance increased in parallel to an increase in erythromycin and trimethoprim-sulfamethoxazole resistance, while only the increase in resistance to trimethoprim-sulfamethoxazole was detected at HBS. In the latter case, this may be due to the low number of samples tested for oxacillin susceptibility at HBS. The concomitant increase in resistance to other drugs in methicillin resistant isolates is in line with the multi-drug resistance pattern of some MRSA [18]. When compared to other studies analyzing antimicrobial drug resistance in Africa, the CV data are in line with other reports [12,14-17]. For *S. aureus,* two studies reported the susceptibility profiles of nasal carriage isolates collected from patients and hospital staff at the two hospitals HAN and HBS in Cabo Verde in the years 1997 [12,15] and 2013-14 [14]. For all drugs tested, the clinical isolates showed higher prevalence of resistance than carriage isolates collected in the same locations and in part during the same period. A lower prevalence of MRSA carriage relative to high MRSA prevalence in clinical isolates is well known [18-20], but in this case, the carriage study was performed on nasal isolates of staff and patients, indicating that the striking difference is not only between carriage in the community, but between carriage and disease isolates in the same setting [14,15]. This difference suggests

that an intervention aimed at MRSA in the hospital setting may be sufficient to control this pathogen [21,22].

The strength of our work is that it provides a representative national dataset for AMR infections in Cabo Verde over a 5-year period. The weakness of the study is that the initial analysis of the raw laboratory data indicated a need for a better standardisation of the methodology. For example, the panel of drugs tested against the bacterial isolates frequently changed, and there were extended periods when the susceptibility to key drugs was not tested. In part this was explained by lack of availability of discs for antimicrobial susceptibility testing [7]. In addition, we did not have data on vancomycin resistance in *S. aureus* and carbapenem resistance in *E. coli*, which is another drawback of this study as carbapenem resistance has been reported to increase in the region [23]. In view of the current attention to quality of care and laboratory standardisation in CV [11] and the goals of the national plan to tackle antimicrobial drug resistance [9], it appears that further efforts are needed to guarantee a high standard of laboratory practice relative to antimicrobial drug susceptibility testing.

In summary our work provides the first study of the antimicrobial drug resistance profiles of *S. aureus* and *E. coli* in Cabo Verde. The two bacterial species represent, as in other hospitals world-wide, the majority of clinical isolates (72% of all clinical isolates), and the detection over a five-year period of an increase in antimicrobial drug resistance in both species is of great concern. This is especially worrying as it might jeopardise empirical treatment in a setting where antimicrobial susceptibility testing is not widely available. In addition, these results provide the base line surveillance data to inform the public health planning and antimicrobial resistance master plan in CV. The data are also suitable to support a clinical and health economic study of the impact of developing the existing central clinical microbiology laboratory services on antibiotic prescribing practice and antibiotic resistance, and may have implications for other low and middle income countries with limited medical microbiology laboratory capacity and stewardship systems.

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COMPETING INTEREST

Authors declare no competing interest with respect to the work performed in the manuscript.

ETHICAL APPROVAL

Not applicable.

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FIGURE LEGENDS

Figure 1: Antimicrobial resistance among *S. aureus* isolates. A) in all type of samples between Santiago (HAN) (black) and São Vicente (HBS) (white). Bars represent percentages of resistance. On the bars is the number of tested strains in all type of samples for each island: HAN (black), HBS (white). B) Trends in the proportions of antibiotic resistances from 2013 to 2017 in Santiago (HAN) (B) and 2014 to 2017 in São Vicente (HBS) (C). The chi-squared analysis was applied to test the trends. For details of data see Figure 1S and Table S2-S3. Observed proportions are presented as a solid lines for penicillin (blue), methicillin (light green), erythromycin (orange), chloramphenicol (deep blue), ciprofloxacin (deep green), trimethoprim-sulfamethoxazole (red) and the statistically significant trends are shown as a dotted line (p-value ≤0.05). D) AMR among *S. aureus* for different specimens and region of Africa: Cabo Verde (red-our data, pink[14], yellow[15]), Angola[14] (green), São Tomé and Príncipe[14] (orange), Eastern Africa[16] (grey), Western Africa[16] (cyan), and Central/Southern Africa[16] (blue). Antibiotics are P.PV penicillin, MET methicillin, E erythromycin, C chloramphenicol, CIP ciprofloxacin, SXT trimethoprim-sulfamethoxazole and TE tetracycline. For three of the studies in panel D the median prevalence of resistance against relevant antimicrobial drugs with interquartile range is given.

Figure 1

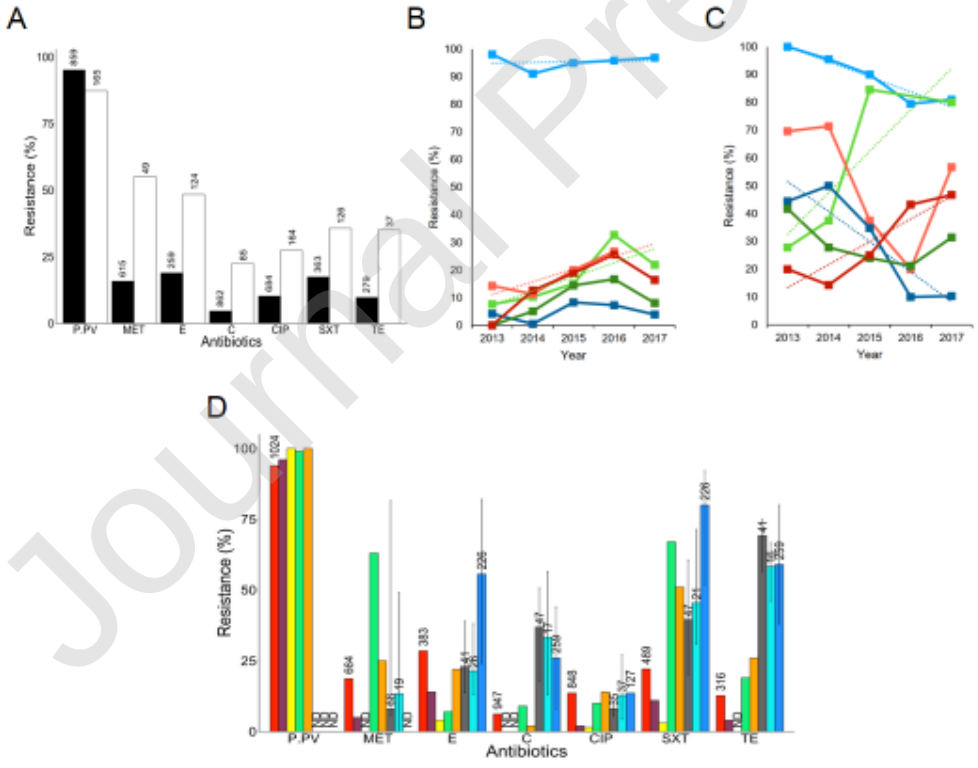

Figure 2: Antimicrobial resistance among *E. coli* isolates. A) in urine type of samples between Santiago (HAN) (black) and São Vicente (HBS) (white). Bars represent percentages of resistance.

On the bars is the number of tested strains in urine type of samples for each island: HAN (black), HBS (white). Antibiotics: AMP ampicillin, AMC amoxicillin/clavulanic acid, CRO ceftriaxone, NA nalidixic acid, CIP ciprofloxacin, SXT trimethoprim-sulfamethoxazole and CN.G gentamicin. B) Trends in the proportions of antibiotic resistances from 2013 to 2017 in Santiago (HAN) (B) and 2014 to 2017 in São Vicente (HBS) (C). The chi-squared analysis was applied to test the trends. For details of data see Figure 1S and Table S5-S6. Observed proportions are presented as a solid lines for ampicillin (blue), amoxicillin/clavulanic acid (light green), ceftriaxone (orange), nalidixic acid (deep blue), ciprofloxacin (deep green), trimethoprim-sulfamethoxazole (red), gentamicin (yellow) and the statistically significant trends are shown as a dotted line (p-value ≤0.05). D) AMR among *E. coli* for different specimens and region of Africa: Cabo Verde (red), Western Africa[16] (WA) (fever (FI) - cyan, urinary tract infection (UTI) - green), Eastern Africa[16] (FI - grey, UTI - pink) and Central/Southern Africa[16] (C/SA) (FI - blue, UTI - yellow). Antibiotics are AMP ampicillin, AMC amoxicillin/clavulanic acid, CRO ceftriaxone, C chloramphenicol, CIP ciprofloxacin, SXT trimethoprim-sulfamethoxazole and CN.G gentamicin. For three of the studies in panel D the median prevalence of resistance against relevant antimicrobial drugs with interquartile range is given.

Figure 2