Five-Year Antimicrobial Susceptibility Trends among Bacterial Isolates from a Tertiary Health-Care Facility in Kigali, Rwanda

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Abstract. Antimicrobial resistance (AMR) is a global public health threat. There is limited information from Rwanda on AMR trends. This longitudinal study aimed to describe temporal trends of antibiotic susceptibility among common bacteria. We collated the antimicrobial susceptibility results of bacteria cultured from clinical specimens collected from inpatients and outpatients and submitted to the microbiology laboratory at King Faisal Hospital, Kigali, Rwanda, from January 1, 2009, to December 31, 2013. Differences in antimicrobial susceptibility between the first and fifth year of the study for each bacterial species was assessed using χ^2 test. Of 5,296 isolates collected, 46.7% were *Escherichia coli*, 18.4% were *Klebsiella* spp., 5.9% were *Acinetobacter* spp., 7.1% were *Pseudomonas* spp., 11.7% were *Staphylococcus aureus*, and 10.3% were *Enterococcus* spp. Colistin and imipenem had greatest activity against gram-negative bacteria. *Acinetobacter* spp. showed the greatest resistance profile to antimicrobials tested, relative to other gram-negative bacteria. Vancomycin retained excellent activity against *S. aureus* and *Enterococcus* species (average susceptibility was 100% and 99.4%, respectively). Trend analysis determined that resistance to imipenem increased significantly among *Klebsiella*, *E. coli*, *Pseudomonas*, and *Acinetobacter* isolates; there was also rising resistance to colistin among *E. coli* and *Pseudomonas* species. Only *E. coli* demonstrated increased resistance to gentamicin. For gram-positive pathogens, vancomycin susceptibility increased over time for *Enterococcus* species, but was unchanged for *S. aureus*. Our data suggest that resistance to imipenem and colistin are rising among gram-negative bacteria in Rwanda. Proper infection control practices and antimicrobial stewardship will be important to address this emerging threat.

INTRODUCTION

Antimicrobial resistance (AMR) is an emerging threat on a global scale,^{1,2} so much so that the issue has appropriately attracted the attention of international health agencies like the World Health Organization (WHO), which have developed ambitious initiatives to combat AMR.^{3–5} Unfortunately, and as emphasized by WHO's global report on surveillance of AMR in 2014, some of the regions of the world with high AMR rates, including sub-Saharan Africa, have generated the least data on prevalence and trends of AMR, which is typically the first step in addressing the problem.^{6–8}

The majority of data published on AMR in east Africa arises from Kenya and Ethiopia, whereas very little emanates from Rwanda or Burundi.⁷ Available data are limited in scope as they are heavily skewed toward rates observed in hospital settings, with a paucity of information on resistance in the community.⁷ National-level data on AMR from the region are almost nonexistent. Even where AMR rates are known, the progress of research is slow relative to the overall global effort.^{6–9}

Data from the late 1980s and 1990s from Rwanda indicate the presence of multidrug resistance among various pathogens including *Streptococcus pneumoniae*, *Neisseria gonorrhea*, *Salmonella typhimurium*, and *Shigella* species.^{10–14} Subsequent reports by Muvunyi and others in 2011, showed higher rates of AMR than previously reported among uropathogenic *Escherichia coli* isolates, suggesting increasing trends for AMR.¹⁵ Quite alarming in that study was the observed high rate of resistance of *E. coli* to commonly used oral antibiotics

to treat urinary tract infections, including amoxicillin (89.3%), ciprofloxacin (41.3%), nitrofurantoin (44.9%), and cotrimoxazole (82.7%).¹⁵

More recently, a study conducted by Ntirenganya and others in 2015, showed that 31.4% and 58.7% of *E. coli* and *Klebsiella* isolates, respectively, were resistant to at least one of the third-generation cephalosporins and 8% of *E. coli* isolates were resistant to imipenem, suggesting extended-spectrum beta-lactamase (ESBL) and carbapenemase-producing strains were present. Furthermore, 82% and 6% of *Staphylococcus aureus* strains were noted to be oxacillin and vancomycin resistant, respectively.¹⁶

Together, these published studies from Rwanda indicate the significant presence of multidrug-resistant (MDR) pathogens, but temporal AMR trends have not been well documented. This study aims to describe 5-year trends of AMR across a broad spectrum of gram-negative and gram-positive pathogens obtained from a large tertiary health-care facility in Rwanda.

MATERIALS AND METHODS

Study design/setting. This was a longitudinal study conducted from January 1, 2009 to December 31, 2013, at King Faisal Hospital (KFH) in Rwanda. This is a large 160-bed capacity multispecialty tertiary health-care facility located in Rwanda's capital city of Kigali. Data were collected on all clinical specimens obtained from both inpatients and outpatients which yielded bacterial growth in culture during the study time frame. No identifying patient information was collected.

Sample collection and processing. Data were collected on all clinical specimens sent to the microbiology laboratory at KFH and included urine, blood, sputum, cerebrospinal fluid, pus swabs, and pleural and ascitic fluid specimens. Samples with improper labeling and those with inadequate patient and specimen identifiers were excluded from the study.

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Similar bacterial species isolated from different samples of the same patient were grouped as a single isolate. Antimicrobial susceptibility patterns of the following organisms were captured during the study time frame: *E. coli*, *Klebsiella* spp., *Acinetobacter* spp., *Pseudomonas* spp., *S. aureus*, and *Enterococcus* spp. A total of 5,296 bacterial isolates were obtained during the study period. Data were aggregated annually, so that the proportion of bacteria susceptible to each antibiotic was provided for each year.

Blood samples were inoculated into blood culture bottles. Urine, wound, pleural and ascitic fluid, as well as sputum cultures were collected in sterile containers. Laboratory materials including sterile containers, antimicrobial disks, and culture media, were manufactured by Becton, Dickinson and Company, Franklin Lakes, NJ.

Blood cultures were incubated in the BD BACTEC 9050 system (Becton, Dickinson and Company) at 37°C for 5 days. Samples with bacterial growth were subcultured on appropriate media guided by gram stain results as follows: gram-positive cocci were plated on mannitol salt agar and blood agar, whereas MacConkey agar and blood agar media were used for isolation of gram-negative bacilli. Additional identification of gram-positive cocci species was performed using catalase and coagulase tests. Identification of species of gram-negative bacilli was done by colony morphology and by using API 20E diagnostic strips (bioMérieux, Hazelwood, MO).

Urine samples, after wet mount examination, were cultured on blood agar and cysteine lactose electrolyte-deficient agar. The number of colonies was counted after 18–24 hours of incubation at 37°C. Specimens with $> 10^5$ colony-forming units/mL urine were considered to show significant growth. Maximum duration of incubation was 48 hours. For wound swabs, pleural fluid, ascites and sputum specimens, the gram stain morphology of principal pathogens dictated the selection of appropriate medium for culture, which was then incubated at 37°C for 24 hours. As with other specimens, identification of bacterial species was done using a combination of colony morphology, growth characteristics on selective media, and by using API 20E diagnostic strips to identify gram-negative bacilli.

Antimicrobial susceptibility testing was performed by the Kirby–Bauer disk diffusion method. The following antibiotic disks were used: ampicillin, 10 µg; cephalixin, 30 µg; ceftazidime, 30 µg; cefotaxime, 30 µg; ceftriaxone, 30 µg; cefalothin, 30 µg; cefuroxime, 30 µg; nalidixic acid, 30 µg; ciprofloxacin, 5 µg; levofloxacin, 5 µg; amikacin, 30 µg; amoxicillin/clavulanic acid (amox/clav), 20/10 µg; erythromycin, 10 µg; gentamicin, 10 µg; amikacin, 30 µg; imipenem, 10 µg; norfloxacin, 10 µg; penicillin, 10 units; oxacillin, 1 µg; piperacillin, 100 µg; cotrimoxazole, 1.25/23.75 µg; nitrofurantoin, 300 µg; chloramphenicol, 30 µg; colistin, 10 µg; and vancomycin, 30 µg.

A suspension from growth on solid media plates was prepared by adding bacterial colonies into sterile distilled water until it approximated the same turbidity as the MacFarland turbidity standard, 0.5. The resulting suspension was inoculated on Mueller–Hinton agar by using a sterile cotton swab. After this procedure, antimicrobial disks were added to the plate with at least 20 mm between each disk and subsequently incubated at 37°C for 18–24 hours. Interpretation of the diameter of bacterial growth inhibition was performed according to 2009 Clinical and Laboratory Standards Institute (CLSI) guidelines and subsequently, the 2012 guidelines,

when they became available. Quality control for the Kirby–Bauer disk diffusion test was performed using three American Type Culture Collection (ATCC) strains: *E. coli* ATCC 25922, *S. aureus* ATCC 25923, and *Pseudomonas* spp. ATCC 27853. Suspensions of the organisms were prepared as described above, and the inhibition diameter obtained was compared with the standard range expected for the ATCC strains.

Statistical analysis. The antimicrobial susceptibility of an organism was expressed as a percentage of the total same species isolates that were sensitive to a particular antimicrobial. This was calculated on an annual basis (calendar year), and trends were assessed from year to year over the entire study period for each bacterial organism. Average annual susceptibility and standard deviation over the entire study period were calculated to provide insight on overall antimicrobial susceptibility patterns. Differences in antimicrobial susceptibility between the first and fifth year of the study for each bacterial species was assessed using χ^2 test. Somers' D statistic (CIR) was used to determine the significance of positive or negative trends in changes in antimicrobial susceptibility over time. Statistical software used was base SAS (R) version 9.2 (SAS institute Inc., Cary, NC).

RESULTS

Description of sample. Overall, 5,296 bacterial isolates were obtained between 2009 and 2013, including *E. coli* (46.7%), *Klebsiella* spp. (18.4%), *S. aureus* (11.7%), and *Enterococcus* spp. (10.3%). *Pseudomonas* spp. and *Acinetobacter* spp. constituted 7.1% and 5.9% of isolates, respectively (Table 1).

Average annual antimicrobial susceptibility profile. *Escherichia coli* was found to be most susceptible to colistin (98.6%), imipenem (92.2%), and nitrofurantoin (84.8%) over the 5-year period (Table 1). It was least susceptible to ampicillin (14.8%), piperacillin (35.4%), and amoxicillin-clavulanate (36.0%). Ciprofloxacin and cefuroxime retained activity against 50.8% and 75.2% of *E. coli* isolates, respectively, whereas ceftriaxone and ceftazidime were active against 67.4% and 66.9% of isolates (only 2-year data available for the latter antimicrobials). *Klebsiella* spp. were found to be most susceptible to colistin (99.8%), imipenem (89.4%), and norfloxacin (69.8%); and least susceptible to piperacillin (18.2%), amoxicillin-clavulanate (24.6%), ceftriaxone (24.8%), and cotrimoxazole (28.4%).

Colistin had activity against 81.5% and 97% of *Acinetobacter* spp. and *Pseudomonas* spp., respectively, whereas for imipenem, susceptibility rate was 45.2% and 84.3%, respectively, for the same organisms. Amikacin and ciprofloxacin were more active against *Pseudomonas* spp. (76.8% and 82.8%) than *Acinetobacter* spp. (59.2% and 18.4%), respectively. Overall, imipenem, colistin, and the aminoglycosides (gentamicin and amikacin) had the most favorable susceptibility profiles for gram-negative pathogens.

Among gram-positive bacteria, susceptibility to vancomycin was 100% for *S. aureus* and 99.4% for *Enterococcus* spp. Oxacillin was active against 97.8% of *S. aureus* isolates, whereas the susceptibility rate for cephalixin, cotrimoxazole, and ciprofloxacin were 86.4%, 72%, and 85%, respectively. *Enterococcus* spp. showed low susceptibility to gentamicin (27.0%) and levofloxacin (54.6%), whereas ampicillin was active against 82.6% of isolates.

TABLE 1
Average annual antimicrobial sensitivity (%) of bacterial isolates from 2009 to 2013

Antimicrobial agent	Bacterial species Antibiotic sensitivity in % (standard deviation)					
	<i>Escherichia coli</i> (N = 2,473)	<i>Klebsiella</i> spp. (N = 975)	<i>Acinetobacter</i> spp. (N = 313)	<i>Pseudomonas</i> spp. (N = 375)	<i>Staphylococcus aureus</i> (N = 617)	<i>Enterococcus</i> spp. (N = 543)
Ampicillin	14.8 (3.7)	—	—	—	20.0 (6.3)	82.6 (1.8)
Penicillin	—	—	—	—	—	26.8 (12.8)†
Oxacillin	—	—	—	—	97.8 (1.1)	—
Piperacillin	35.4 (10.1)	18.2 (4.0)	—	77.0 (6.5)	—	70.4 (32.2)
Amoxicillin–clavulanate	36.0 (21.7)	24.6 (14.3)	—	—	40.6 (23.0)	89.0 (6.2)
Cephalexin	—	—	—	—	86.4 (5.7)	—
Cefuroxime	75.2 (6.0)	48.4 (17.2)	—	—	—	—
Cefotaxime	—	29.0 (8.7)	8.0 (3.3)	—	—	—
Ceftriaxone	—	24.8 (18.9)	7.4 (4.0)	—	—	—
Ceftazidime	—	31.6 (12.5)	15.4 (4.0)	81.0 (11.4)	—	—
Nalidixic acid	51.6 (5.1)	54.6 (12.0)	—	—	—	—
Norfloxacin*	66.4 (2.9)	69.8 (14.3)	—	—	—	—
Ciprofloxacin	50.8 (9.7)	49.6 (5.0)	18.4 (1.8)	82.8 (4.6)	85.0 (9.7)	—
Levofloxacin	—	46.0 (0.0)†	22.6 (12.7)	—	—	54.6 (18.4)
Cotrimoxazole	28.5 (3.4)	28.4 (6.2)	—	—	72.0 (15.8)	—
Nitrofurantoin*	84.8 (3.7)	47.8 (8.6)	—	—	—	—
Chloramphenicol	—	—	—	—	—	59.8 (10.6)
Erythromycin	—	—	—	—	64.0 (10.7)	—
Amikacin	—	64.8 (13.4)	59.2 (22.4)	76.8 (16.3)	—	—
Gentamicin	74.0 (2.6)	51.8 (3.8)	—	77.0 (9.4)	87.2 (6.5)	27.0 (6.0)
Imipenem	92.2 (11.0)	89.4 (10.8)	45.2 (29.5)	84.3 (31.5)†	—	—
Colistin	98.6 (2.0)	99.8 (1.8)	81.5 (20.2)†	97.0 (6.0)†	—	—
Vancomycin	—	—	—	—	100 (0.0)	99.4 (1.3)

*For urine isolates only.

†Less than 5 years of data; only groups with at least 3 years of data were included.

Antimicrobial susceptibility trends. The results of the χ^2 test comparing antimicrobial susceptibility rates for each pathogen in the first (2009) and last year (2013) of the study are shown in Figure 1. The most frequent antimicrobial susceptibility trend pattern over the study period was “no trend” occurring in 29/61 (47.5%) of organism/antimicrobial groups for which susceptibility testing was performed. Of the remaining 32 groups, the majority (22), that is, 68.8% were characterized as “negative trend,” implying significant decreases in antibiotic susceptibility or increasing AMR over time. Only 10 groups were classified as having a “positive trend”: *Acinetobacter* spp. and colistin; *Klebsiella* spp. and nitrofurantoin, cefotaxime, ceftriaxone, and ceftazidime; *S. aureus* and erythromycin, gentamicin, and cephalexin; *Enterococcus* spp. and amoxicillin–clavulanate and vancomycin.

Across all bacterial isolates, *E. coli* had the greatest number of “negative trend” groups ($N = 9$) showing decreasing susceptibility, or increasing resistance, to amoxicillin–clavulanate, gentamicin, nalidixic acid, norfloxacin, ciprofloxacin, cefuroxime, piperacillin, imipenem, and colistin (Figure 2). *Klebsiella* spp. had four “negative trend” groups, including amoxicillin–clavulanate, norfloxacin, cefuroxime, and imipenem (Figure 3), whereas *Acinetobacter* spp. also had two negative trend groups, with decreasing susceptibility to levofloxacin, and imipenem during the study period (Figure 4). Among the group of 23 antimicrobials tested against the different bacterial species, amoxicillin–clavulanate and imipenem registered the greatest frequency of “negative trend” susceptibility profiles.

DISCUSSION

Several published studies have highlighted the growing threat of AMR in sub-Saharan Africa.^{7,8,17,18} It is somewhat

reassuring that there is evidence that AMR is getting more attention than ever before in the region, as in recent decades there has been an increasing number of publications on the subject,⁷ but much more work needs to be done to effectively address the threat. Our study adds to the regional concerns on AMR as it shows that MDR gram-negative pathogens are prevalent in Rwanda and that rates of resistance to important drugs are rising. Three findings in particular are concerning and buttress the point: first is the high resistance rates of gram-negative pathogens to commonly used oral antibiotics like cotrimoxazole, ciprofloxacin, amoxicillin–clavulanate, and cefuroxime; second is the prevalence of resistance to third-generation cephalosporins by Enterobacteriaceae; and third is the significant rising trend of resistance to broad-spectrum antibiotics such as imipenem and colistin which are typically used as “salvage” antibiotics for MDR gram-negative bacterial infections.

Our findings are comparable to other similar studies from the region. Mackay and others, who conducted a 12-month AMR survey from October 2011 to September 2012 at a tertiary facility in Cape Town, South Africa, found that for health-care associated Enterobacteriaceae bloodstream isolates, susceptibility rates were 58.5% to ceftriaxone, 64.6% to gentamicin, and 70% to ciprofloxacin. The study also found that for health-care acquired *Pseudomonas* and *Acinetobacter* strains, they showed less than 80% susceptibility to all antibiotics tested except colistin. A study on AMR performed in Gabon in 2010 covering a wide variety of clinical specimens including urine cytology, blood cultures, and urethral and vaginal swabs, showed that 18% and 3–30% of cultured *Klebsiella* and *E. coli* isolates, respectively, were found to be resistant to third-generation cephalosporins. In addition, 67% of *E. coli* isolates were resistant

	Ampicillin	Penicillin	Oxacillin	Piperacillin	Amoxicillin + clavulanate	Cephalexin	Cefuroxime	Cefotaxime	Ceftriaxone	Ceftazidime	Nalidixic Acid	Norfloxacin	Ciprofloxacin	Levofloxacin	Cotrimoxazole	Nitrofurantoin	Chloramphenicol	Erythromycin	Amikacin	Gentamicin	Imipenem	Colistin	Vancomycin
<i>Escherichia coli</i>																							
<i>Klebsiella</i> spp.																							
<i>Acinetobacter</i> spp.																							
<i>Pseudomonas</i> spp.																							
<i>Staphylococcus aureus</i>																							
<i>Enterococcus</i> spp.																							

Key	
No significant difference	
Significant difference, positive trend*	
Significant difference, negative trend*	
Not tested	

*P value <0.05

FIGURE 1. Trend in bacterial susceptibility to specific antibiotics across the study time period (2009 vs 2013) using χ^2 test.

FIGURE 2. *Escherichia coli* susceptibility to antibiotics showing those with negative trends over time (2009–2013).

FIGURE 3. *Klebsiella* spp. susceptibility to antibiotics showing those with negative trends over time (2009–2013).

to amoxicillin–clavulanate, and the overall resistance rates to quinolones ranged between 58% and 78%.¹⁹

Other studies confirm the emergence of carbapenem-resistant strains in sub-Saharan Africa consistent with our study findings.²⁰ A review of published studies from Africa shows that the prevalence of carbapenemase-producing bacteria isolated in hospitals ranges from 9% to 60% in the sub-Saharan region.²¹ Mushi and others reported on the prevalence of carbapenemase genes among MDR gram-negative bacilli from a tertiary hospital in Mwanza, Tanzania. They found that 35% of 227 isolates had at least one carbapenemase gene with *Klebsiella pneumoniae* (11%), *Pseudomonas aeruginosa* (10%), and *E. coli* (8%) being the most prevalent.²² Poirel and others published a case series in 2011

reporting seven isolates of New Delhi metalloproteinase-1-producing *K. pneumoniae* from patients on different wards of a referral hospital in Nairobi, Kenya, and were found to harbor other resistance determinants including aminoglycoside resistance genes.

One explanation for the rising trends of MDR among gram-negative bacteria could be the emergence and spread of resistant clones. Recent literature have described certain high-risk bacterial clones which harbor resistance mechanisms including plasmids such as *E. coli* ST131 and *K. pneumoniae* ST258 strains which are able to effectively colonize human hosts, have enhanced pathogenicity and may be easily transmitted within health-care settings, all features which explain their rapid spread.^{23,24}

FIGURE 4. *Acinetobacter* spp. susceptibility to antibiotics showing those with negative trends over time (2009–2013).

On the other hand, we did not observe any concerning negative antimicrobial susceptibility trends with *S. aureus*. Rates of susceptibility of the organism to oxacillin were high at 97.8%, and there were no vancomycin-resistant isolates. This is at odds with a recent study from Rwanda which showed that 82% of *S. aureus* strains were oxacillin resistant.¹⁶ This difference may be due to differences in patient populations, the study site—KFH—is a privately owned tertiary health-care facility and samples were obtained from both inpatients and outpatients, whereas the site where the quoted study was performed is a public referral institution and included samples from hospitalized patients alone. One study suggests an interesting explanation for previously reported high rates of oxacillin resistance reported from low-resourced laboratories in Africa, and that is due to misidentification of coagulase-negative staphylococci as *S. aureus*, the former which is typically oxacillin resistant, due to subjective interpretation of manual phenotypic tests, specifically the tube and slide coagulation tests.²⁵ This may be overcome by the use of automated systems.

Our study found that there were reduced susceptibility trends by *Enterococcus* spp. to beta-lactams—penicillin and piperacillin (average annual susceptibility 26.4% and 70.4%, respectively), but 82.6% and 89% of isolates were susceptible to ampicillin and amoxicillin-clavulanate, respectively. As ampicillin has more potent activity against enterococcal species, the disparate susceptibility to the beta-lactam antibiotics was not surprising.^{26,27} However, some studies suggest that the observation of penicillin-resistant and ampicillin-sensitive enterococcal isolates may be related to alterations in its penicillin-binding protein 4 (*pbp4*) gene.²⁸

A myriad of factors are to blame for high and rising AMR in sub-Saharan Africa, including Rwanda, and some are not easily tackled. Kimang'a, in an excellent article on "A situational analysis of antimicrobial resistance in Africa: are we losing the battle?"²⁹ highlights factors contributing to AMR in Africa—including poorly qualified health-care workers who misuse antimicrobials, poor-resourced laboratories with inability to perform full antimicrobial susceptibility testing and/or produce timely results, insufficient dissemination of AMR to antibiotic prescribers, limited antimicrobial formularies, outdated or inappropriate treatment guidelines for infections, and poor infection control practices.^{29,30} High community access to unprescribed antimicrobials probably plays a major role. Probably underrecognized and underappreciated is the contribution of counterfeit or substandard drugs to AMR rates.²⁹ Antimicrobial stewardship programs, supported by an ample evidence as impacting AMR, are lacking in most African health-care settings.³¹ It is very likely that worsening AMR trends in Rwanda reflect and are driven by the overuse of a limited number of antimicrobials which allow for the selection of resistant bacteria, and that nosocomial transmission of these organisms among patients in the setting of suboptimal infection control practices may be playing a role as well.

This study is important as it is the first of its kind in Rwanda showing AMR rates and trends over time for a broad range of bacterial pathogens and provides valuable information for health-care providers and policy makers. However, it has several limitations. The study did not include susceptibility testing for all antibiotics active against the bacteria isolated. This was due to limited resources. However,

the antibiotics tested represent treatment options that are available in Rwanda. We did not perform genotyping of isolates, so could not identify any clonal outbreaks and did not confirm ESBL production by gram-negative bacteria. We did not explore differences in AMR between inpatient and outpatient specimens. As it is well known that hospital-associated pathogens are likely to be more resistant than those that are community acquired, it is plausible that our described AMR rates are lower than would have been observed if we studied only inpatient specimens and higher than that for outpatient samples. Similarly, as we did not define the characteristics of our study population, it will be challenging to compare our reported AMR rates with other facilities within or beyond the country. As a single center study, AMR rates may also not reflect national trends. Lastly, the CLSI interpretation guidelines, changed over the time period of our study and may have negatively impacted AMR trends; however, declining susceptibility trends were already noted before the updated guidelines.

CONCLUSION

This study described prevalence and trends of AMR among common gram-positive and gram-negative bacterial pathogens in the KFH in Kigali, Rwanda. The finding of high rates of resistance by gram-negative bacteria to cephalosporins and rising rates of resistance to valuable drugs like imipenem and colistin are of concern. Institution of AMR surveillance and antimicrobial stewardship programs as well as proper infection control practices are essential to curbing this threat. Antimicrobial guidelines need to be reviewed to address the reality of decreased susceptibility to commonly used drugs.

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