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VANCOMYCIN USE IN PATIENTS DISCHARGED FROM THE EMERGENCY DEPARTMENT: A RETROSPECTIVE OBSERVATIONAL COHORT STUDY

Kristen Mueller, MD,* Craig McCammon, PHARMD,† Lee Skrupky, PHARMD,† and Brian M. Fuller, MD‡

*Division of Emergency Medicine, Washington University School of Medicine and Barnes Jewish Hospital, Saint Louis, Missouri, †Department of Pharmacy, Barnes Jewish Hospital, Saint Louis, Missouri, and ‡Division of Emergency Medicine, Department of Anesthesiology, Division of Critical Care, Washington University School of Medicine, Saint Louis, Missouri

Reprint Address: Kristen Mueller, MD, Division of Emergency Medicine, Washington University School of Medicine, Campus Box 8072, 660 S. Euclid Ave., St. Louis, MO 63110

☐ **Abstract—Background: Infections due to methicillin-resistant *Staphylococcus aureus* (MRSA) are associated with significant morbidity and mortality and are typically treated with intravenous vancomycin. Given vancomycin's time-dependent mechanism of action, it is unlikely that vancomycin administration in the emergency department (ED) prior to disposition home could be beneficial. Study Objectives: To characterize the indications, dosing, and appropriateness of vancomycin use in patients discharged from the ED. Methods: This is a single-center retrospective observational cohort study of patients who received vancomycin in an urban, academic, tertiary care ED. The subjects were consecutive adult patients administered intravenous vancomycin in the ED and then discharged home over an 18-month period. Outcomes were measured 1) to characterize patients receiving vancomycin prior to discharge home from the ED; and 2) to identify patients that did not meet indications for appropriate use based on the 2011 Infectious Diseases Society of America guidelines for treating MRSA infections. Results: There were 526 patients that received vancomycin in the ED prior to discharge during the study period. In this cohort, 368 (70%) patients were diagnosed with skin and soft tissue infections. A MRSA risk factor was present in 396 (75%) patients. Prior to discharge, one dose of vancomycin was administered to 357 (68%) patients. Underdosing of vancomycin occurred in 239 (73%) patients. Conclusions: Vancomycin was given frequently to patients discharged home from the ED, most commonly for conditions where vancomycin was not indicated, such as skin and soft tissue infections. The majority of these patients received a vancomycin dosing strategy that is not only unlikely to lead to clinical improvement, but also has the potential to contribute adversely to the development of antibiotic resistance. Further investigation is needed into the impact of vancomycin use, the emergence of vancomycin resistance, and the role of ED-based antibiotic stewardship.** © **2015 Elsevier Inc.**

☐ **Keywords—antibiotic stewardship; emergency department; methicillin-resistant *Staphylococcus aureus* (MRSA); skin and soft tissue infection (SSTI); vancomycin**

INTRODUCTION

Antibiotic resistance is a major public health concern, and is developing at a rate that outpaces new antimicrobial therapies (1,2). The emergence of multidrug-resistant (MDR) pathogens is frequently related to inappropriate antimicrobial therapy, and is associated with worse outcomes in a variety of infectious conditions (3–9). Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major problem in both community and in-hospital settings, and causes significant morbidity, mortality, and financial burden in the United States (10–15). Additionally, the emergence of vancomycin-intermediate *Staphylococcus*

The protocol was approved by the Human Research Protection Office at the principal investigator's institution.

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aureus (VISA) and vancomycin-resistant *Staphylococcus aureus* (VRSA) is invariably associated with previous vancomycin exposure and threatens the efficacy of vancomycin in the treatment of severe MRSA infections (16–22).

There is an increased interest in the potential role of the emergency department (ED) in antibiotic stewardship (23,24). It is appropriate to administer vancomycin in the setting of a known or suspected MRSA infection, or in the setting of a severe systemic illness with a high risk of mortality (6,22,25). In 2011, the Infectious Diseases Society of America (ISDA) specifically recommended the use of vancomycin in complicated skin and soft tissue infections (SSTI), bacteremia, infective endocarditis, pneumonia, osteomyelitis, septic arthritis, meningitis, and intracranial abscesses (26). Our previous work indicates that vancomycin is commonly administered in the ED, but that the correct weight-based dose was given in the ED only 22% of the time, and that the majority of patients (83.8%) were given an inpatient dose of vancomycin unchanged from the dose administered in the ED (27). Vancomycin use in patients discharged from the ED has not been studied, however. The bactericidal activity of vancomycin utilizes a time-dependent mechanism of action (22,28). Increased mean inhibitory concentration of vancomycin needed to treat MRSA infections is a mechanism of action of VISA (29). For this reason, a single-use dosing scheme is unlikely to yield significant clinical improvement prior to discharge home from the ED, and may be a patient safety issue with respect to the development of MDR pathogens and unnecessary drug exposure. For example, prior in vitro work indicates that any exposure to vancomycin in the previous 30 days increases the mean inhibitory concentration of vancomycin needed to treat MRSA, potentially leading to the development of VISA (19).

We therefore decided to investigate vancomycin use in patients discharged from the ED. This study was designed to achieve the following objectives: 1) to characterize patients receiving vancomycin prior to discharge home from the ED; and 2) to identify patients that did not meet indications for appropriate use based on the 2011 ISDA guidelines for treating MRSA infections (26). Based on the known pharmacokinetic properties of vancomycin, ISDA guidelines, and our previous work on vancomycin dosing in the ED, we hypothesized that vancomycin administration would be common in patients discharged from the ED, and inappropriate based on indication and dosing strategy.

METHODS

This analysis was a single-center, retrospective, observational cohort study conducted in the ED of an urban, academic, tertiary care institution with an annual census of > 90,000 patients. This observational study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies (30). The subjects were consecutive adult patients administered intravenous vancomycin in the ED and then discharged home over an 18-month period (December 2008 to June 2010). The protocol was approved by the Human Research Protection Office at the principal investigator's institution.

Data were collected on patients identified by query of the ED electronic medical record. The medical record was queried for all patients who received intravenous (i.v.) vancomycin in the ED and were subsequently discharged home during the study period. Variables were defined prior to data extraction and placed in a standardized format during the data collection process. All data were collected by the principal investigator and cross-checked for accuracy prior to data analysis.

Data included patient demographics, chief complaint, diagnosis, dose of vancomycin administered in the ED, other antibiotics administered in the ED, antibiotics prescribed on discharge home from the ED, MRSA risk factors, and appropriateness of vancomycin use. In accordance with the 2011 ISDA guidelines for the treatment of MRSA, we defined appropriate use as vancomycin used in complicated SSTIs, bacteremia, infective endocarditis, pneumonia, osteomyelitis, septic arthritis, meningitis, and intracranial abscesses (26). For the purposes of this retrospective study, patients who presented with SSTI and were subsequently discharged home were defined as not having a complicated SSTI, with the assumption that complicated SSTIs would be admitted for further management and treatment. We defined the "correct" dose of vancomycin as 15–20 mg/kg of the actual body weight based on guideline recommendations (22). MRSA risk factors considered appropriate for empiric i.v. vancomycin therapy included the following, as identified in a recent multicenter investigation in the ED setting: diagnosis of abscess, antibiotic use in the last 30 days, reported spider or insect bite, a personal history of MRSA, and close contacts with a similar infection (25). SSTIs were defined as an ED diagnosis of abscess, abscess plus cellulitis, or cellulitis. Outcomes of interest included subsequent return to the ED with the same medical complaint or need for admission for the same medical complaint, and resolution of symptoms by follow-up office or ED visit. All outcomes of interest were assessed for the 12-month period after the initial ED visit.

Descriptive statistics were used to further characterize these data. The data were generated using SAS software, version 9.1of the SAS System for Linux (SAS Institute Inc., Cary, NC). Statistical analysis was completed in consultation with a biostatistician.

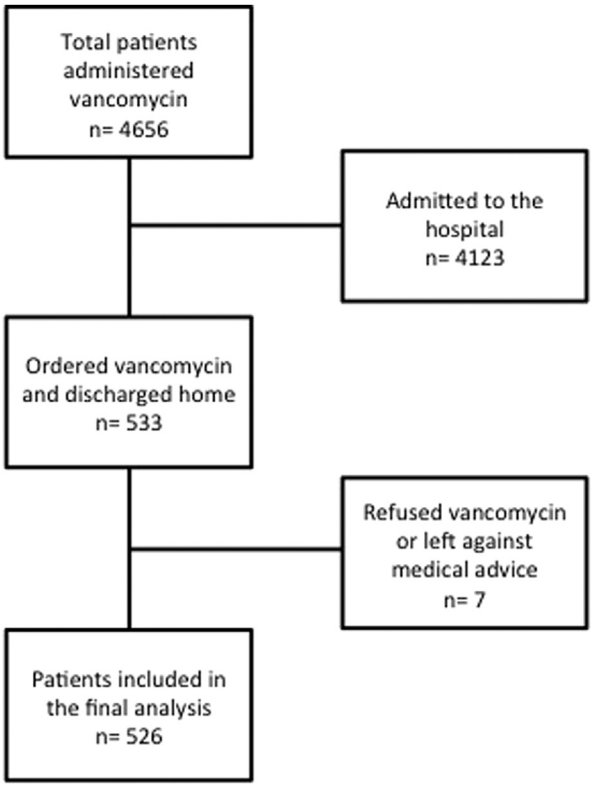

Figure 1. Flow diagram of patients administered vancomycin in the emergency department and subsequently discharged home.

RESULTS

A total of 526 patients were included in the study (Figure 1). Patient characteristics are shown in Table 1. Table 2 shows that the majority of patients had risk factors for MRSA infection; the most common risk factor was ED diagnosis of abscess.

In addition to these data, 368 (70%) patients were diagnosed with an SSTI. Diagnoses in the other 158 (30%) patients in this cohort included fever, urinary tract infection, laceration, altered mental status, headache, device complication, meningitis, hypotension, bacteremia, osteomyelitis, and pneumonia. Culture data were obtained in 289 (55%) patients, with wound cultures performed in 195 (37%) patients; 99 (19%) patients were culture positive for MRSA.

Abscess incision and drainage was performed on 219 (42%) patients. Sixty-two (12%) patients were diagnosed with abscess or abscess plus cellulitis and did not have an incision and drainage preformed.

Figure 2 shows vancomycin exposure in the ED, with respect to dose received and number of doses (27). Underdosing (<15 mg/kg) occurred in 239 (73%) patients, and 357 (68%) patients received only one dose of vancomycin in the ED prior to discharge. In patients that did receive more than one dose of vancomycin in the ED (n = 169), all but one received the same dose on subsequent dosing.

Table 3 shows the co-administration of other antibiotics in the ED. Along with vancomycin, 217 (41%) patients received one additional antibiotic prior to discharge from the ED, and 96 (18%) received two additional antibiotics. The majority of additional antibiotics were given for potential MRSA and Gram-negative bacterial coverage. Two hundred thirteen (41%) patients did not receive any additional antibiotics other than vancomycin in the ED. Outpatient antibiotics were prescribed to 384 (73%) patients. Figure 3 shows the prescribing

Table 1. Characteristics of Patients Given Vancomycin in the ED

Characteristics	n (%)
Subjects, n	526 (100)
Male, n (%)	269 (51)
Age (years), median (IQR)	43 (30-52)
Race, n (%)	
Black	312 (59)
White	190 (36)
Other	24 (5)
Weight (kg), mean (SD)	85.4 (26)
Location prior to ED, n (%)	
Home	484 (92)
Nursing home or extended care facility	25 (5)
Other hospital	17 (3)
ED visit last 3 months, n (%)	200 (38)
Hospitalization last 3 months, n (%)	106 (20)
Allergy, n (%)	
No known drug allergies	400 (76)
Penicillins	64 (12)
Antibiotics in the past 90 days, n (%)	177 (34)
Vancomycin	62 (12)
Comorbidities, n (%)	
Hypertension	165 (31)
Cardiac/congestive heart failure	57 (11)
Diabetes	87 (17)
Chronic obstructive pulmonary disease/asthma	59 (11)
Immunosuppression	19 (4)
End-stage renal disease on hemodialysis	23 (4)
Malignancy	30 (6)
Cirrhosis	20 (4)
Temperature > 38°C	33 (6)
Systolic blood pressure < 90 mm Hg	21 (4)
Heart rate > 100 beats/min	262 (50)

ED = emergency department; IQR = interquartile range.

Table 2. Risk Factors for Methicillin-resistant *Staphylococcus aureus* (MRSA) Based on the Largest Study of MRSA Risk Factors to Date (25).

Risk Factors	n (%)
Diagnosis of abscess	281 (53)
Antibiotics in last 30 days	152 (29)
History of MRSA	102 (19)
Reported insect bite or spider bite	69 (13)
Close contact with a person with a similar infection	16 (3)
No MRSA risk factor	130 (25)

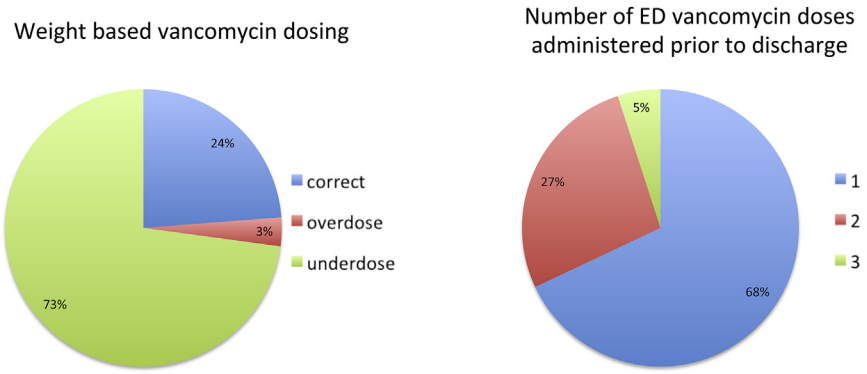

Figure 2. Vancomycin dosing practices for the cohort in which an emergency department (ED) weight was available (n = 328). Correct dose was defined at 15–20 mg/kg actual body weight based on guideline recommendations (31).

patterns of the three most common antibiotics given upon discharge from the ED. The majority of patients treated with outpatient antibiotics were not dosed with these antibiotics in the ED in lieu of intravenous vancomycin.

When 2011 ISDA guidelines for the treatment of MRSA were retrospectively applied to this cohort based on ED diagnosis, 49 (9%) met criteria for vancomycin use in the setting of suspected MRSA infection (Table 4).

There were follow-up data available for 332 (63%) patients. After receiving vancomycin in the ED, 139 (42%) of these patients presented to the ED with the same problem within 1 month, and 42 (12% of n = 332) patients required hospital admission for the same diagnosis within 1 month. Symptom resolution occurred in 197 (60% of n = 332) patients on follow-up within 12 months of the initial ED visit.

DISCUSSION

Although there is increased interest in antibiotic stewardship for ED patients, information regarding current practice patterns is vital before performance improvement initiatives can occur. The findings from this study provide new information regarding vancomycin use in the ED, build on previous work in this area, and provide potential targets for future improvements.

Table 3. Antibiotics Administered in the ED

Antibiotics	n (%)
Vancomycin	526 (100)
Sulfamethoxazole/trimethoprim (SMX/TMP)	122 (23)
Ceftriaxone	54 (10)
Cefepime	36 (7)
Piperacillin/tazobactam	34 (7)
Clindamycin	29 (6)
Cefazolin	22 (4)
Ciprofloxacin	24 (5)
Ampicillin/sulbactam	22 (5)
Cephalexin	13 (3)
Other	41 (8)

ED = emergency department.

Approximately 10% of vancomycin administered in our ED is given to patients subsequently discharged to home (27). Vancomycin exposure such as this, both in terms of dose administered (e.g., under-dosed) and number of doses (e.g., one dose typically), serves little purpose in the eradication of infection. The majority of patients received only one (68%) or two (27%) doses. It is possible that vancomycin is given in this fashion in an effort to get antibiotics "on board," which could theoretically assist in treatment of infection after discharge. However, given vancomycin's time-dependent mechanism of action, this dosing strategy is unlikely to yield clinical improvement (Figure 4). Approximately one-third of patients treated in this fashion re-presented to the ED with the same problem within 1 month. Although outcome data are limited by the retrospective nature of this study, this further supports the low likelihood that ED vancomycin use contributed significantly to resolution of symptoms in this patient cohort.

Inappropriate antibiotic use is the most modifiable cause of MDR pathogen emergence, and the suboptimal dosing strategy seen in this study could contribute to further emergence of VISA and VRSA in

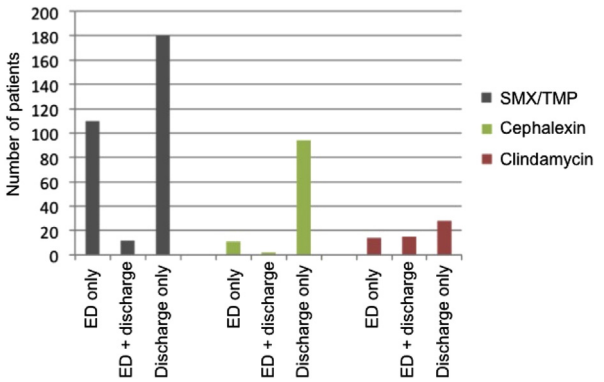

Figure 3. Prescribing practices of the three most common antibiotics prescribed on discharge. ED = emergency department; SMX/TMP = sulfamethoxazole/trimethoprim.

Table 4. Appropriateness of Vancomycin Use According to 2011 ISDA Guidelines for the Treatment of MRSA Infections

Approved uses of Intravenous Vancomycin	n (%)
Complicated skin and soft tissue infection	0 (0)
Bacteremia	1 (<1)
Endocarditis	0 (0)
Pneumonia	4 (<1)
Septic arthritis	0 (0)
Osteomyelitis	7 (1)
Meningitis (including empiric treatment for suspected meningitis)	37 (7)
Other intracranial abscess or infection	0 (0)

ISDA = Infectious Diseases Society of America; MRSA = methicillin-resistant *Staphylococcus aureus*.

the future (19,29,31). Eleven cases of VRSA have been reported in the United States since 2002 (16). The first European case of VRSA was reported in 2014, with no shared epidemiologic link with the U.S. strains, indicating potential independent acquisition of vancomycin resistance in the setting of previous vancomycin exposure (32). Additionally, our investigation into other co-administered antibiotics revealed that a significant minority of this cohort was dosed with antibiotics such as ceftriaxone, cefepime, and piperacillin/tazobactam that may also contribute to the emergence of resistant Gram-negative pathogens (Table 3).

Although a majority of the patients in this cohort had MRSA risk factors, based on a 2006 study investigating MRSA infections in ED patients, of great concern is the fact that, in our cohort, 91% of patients who received vancomycin in the ED prior to discharge did not have an indication for use supported by the 2011 ISDA guidelines for the treatment of MRSA infections (25,26). For example, vancomycin was most commonly administered to treat uncomplicated SSTIs, despite a lack of literature to support this practice (23,26). Based on these recommendations, if an infection is deemed serious enough to merit vancomycin therapy, these patients should be admitted to the hospital for further observation and treatment as opposed to discharged home (23,26).

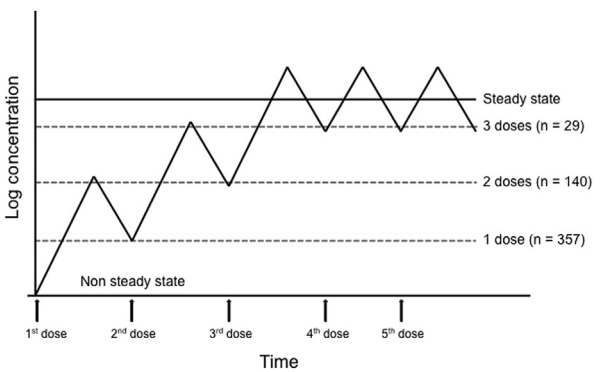

Figure 4. Number of vancomycin doses administered in the emergency department (ED) plotted over a vancomycin steady-state concentration graph. Vancomycin utilizes time-dependent killing, therefore, administration of a limited number of doses in the ED is highly unlikely to achieve a therapeutic killing effect.

Although vancomycin is indicated for serious MRSA infections, it is concerning that nearly 25% of patients in this cohort had no risk factors for MRSA and still received vancomycin prior to discharge from the ED. Equally concerning, of patients in this cohort diagnosed with abscess and abscess plus cellulitis, 12% of patients did not receive a documented incision and drainage of their abscess. Source control is a mainstay of treatment in infectious processes, and there is substantial evidence that indicate adequate incision and drainage alone is sufficient therapy for uncomplicated abscess, without the need for any antibiotics, much less vancomycin (11,26,33–35). Additionally, an important factor in antibiotic stewardship is culture-driven antibiotic dosing. Recent SSTI guidelines recommend culture data on all purulent SSTIs treated with antibiotic therapy (26). In this SSTI-heavy cohort, only 195 (37%) patients had a wound culture obtained. It is vital, both for ED-based antibiograms and de-escalation of therapy, to obtain appropriate culture data to guide future antibiotic use.

Additionally, there is discordance between ED antibiotic dosing and the antibiotics prescribed for outpatient therapy. Only 60% of patients received any antibiotics beyond vancomycin during their ED visit. When patients were discharged with additional antibiotics for SSTIs, they most commonly received sulfamethoxazole/trimethoprim, cephalexin, or clindamycin. However, as shown in Figure 3, only a minority of these patients received oral antibiotics both in ED and on discharge; most patients received these additional antibiotics only on discharge. This dosing strategy not only fails to take into account vancomycin's time-dependent mechanism of action, but also delays the administration of the potentially therapeutic discharge oral antibiotic. As these oral antibiotics utilize different mechanisms of action from vancomycin, delay in administration of the anticipated discharge antibiotic leads to a delay in attaining a clinically effective therapeutic steady-state concentration of the discharge antibiotic. Additionally, when the oral antibiotic is not given in the ED, the opportunity is lost to observe a patient's response to the antibiotic, and to monitor for a potential adverse reaction.

These data further support a need for antibiotic stewardship initiatives in the ED (23). In our previous work on vancomycin, ED vancomycin use strongly influenced inpatient use, both in terms of subsequent dose administered and decision to continue vancomycin therapy (27).

The current work extends those findings, and further suggests that the ED, as the link between the inpatient and outpatient setting, could play a vital role in limiting inappropriate vancomycin exposure.

Limitations

This study is limited by its retrospective design. It is impossible to account for all of the influential factors associated with the decision to administer vancomycin, and this study is limited by a lack of information regarding why vancomycin was given. The fact that all of these patients were discharged home does provide further support and face validity to the supposition that vancomycin was likely not indicated. This is a single-center study in an academic, urban ED. In areas where MRSA risk is low, and vancomycin administration is limited, these results are less significant. The majority of these data are descriptive in nature. Although these data are limited, it is a transparent reflection of how vancomycin is being used in the ED. Finally, although we suspect that vancomycin dosed in this fashion is unlikely to lead to clinical improvement, without a control group of patients that did not receive vancomycin, there remains uncertainty regarding the efficacy of this dosing strategy.

CONCLUSION

Vancomycin is administered with relative frequency in patients discharged from the ED, and typically for conditions where vancomycin is not indicated. As previous work indicates, this practice is unlikely to yield clinical improvement, and has potential to contribute to antimicrobial resistance. The role of ED-based antibiotic stewardship needs to be further investigated, and ED providers must exercise vigilance in the selection and use of antibiotics, especially in the treatment of SSTIs. Through coordinated initiatives that begin in the ED, there is the potential to appropriately tailor antibiotic therapy and promote antimicrobial stewardship practices.

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ARTICLE SUMMARY

1. Why is this topic important?

Antibiotic stewardship is essential to promote the long-term clinical efficacy of antibiotics like vancomycin.

2. What does this study attempt to show?

This study characterizes how vancomycin is used in patients discharged from the emergency department (ED).

3. What are the key findings?

Vancomycin was given relatively frequently to patients discharged home from the ED, and most commonly for conditions where vancomycin was not indicated (e.g., uncomplicated skin and soft tissue infections). The majority of patients in this cohort received only one subtherapeutic dose of vancomycin prior to discharge from the ED.

4. How is patient care impacted?

Patients who receive a subtherapeutic dose of vancomycin coupled with an inadequate number of total vancomycin doses administered are unlikely to benefit clinically from this antibiotic regimen. Inappropriate use of vancomycin has the potential to contribute adversely to the development of antimicrobial resistance.