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Impact of an antimicrobial stewardship programme on reducing broad-spectrum antibiotic use and its effect on carbapenem-resistant *Acinetobacter baumannii* (CRAb) in hospitals in Jordan

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Running title: Impact of an antimicrobial stewardship programme

Objectives: To evaluate the impact of an antimicrobial stewardship programme (ASP) on reducing broad-spectrum antibiotic use and its effect on carbapenem-resistant *Acinetobacter baumannii* (CRAb) in hospitalized patients.

Methods: The study was a retrospective, ecological assessment in a tertiary teaching hospital over 6 years (January 2014 to December 2019). The intervention involved the implementation of an ASP in February 2018 that remains in effect today. This ASP consists of several components, including education, antibiotic guidelines, antibiotic restriction policy with prior approval, audit of compliance to the restriction policy and feedback. Restricted antibiotics were imipenem/cilastatin, ertapenem, meropenem, vancomycin, teicoplanin, tigecycline, colistin, amikacin, piperacillin/tazobactam, levofloxacin and ciprofloxacin. The intervention was evaluated by time-series methods.

Results: Statistically significant decreases in the level of antibiotic use, after the introduction of the ASP, were observed for the following antibiotics: imipenem/cilastatin (P=0.0008), carbapenems (P=0.0001), vancomycin (P=0.0006), colistin (P=0.0016) and third-generation cephalosporins (P=0.0004). A statistically significant decrease in the slope, after the introduction of the ASP, for ertapenem (P=0.0044) and ciprofloxacin (P=0.0117) was observed. For piperacillin/tazobactam, there was a significant increasing trend (P=0.0208) before the introduction of the ASP. However, this increased trend was halted post-introduction of the ASP (P=0.4574). The introduction of the ASP was associated with a significant impact on reducing the levels of CRAb (P=0.0237).

Conclusion: The introduced antimicrobial stewardship interventions contributed to a reduction in the use of several broad-spectrum antibiotics, reversed the trends of increasing use of other antibiotics and were associated with a significant reduction in CRAb.

Introduction

Antimicrobial resistance (AMR) poses a significant threat to public health and global development.[1] Studies suggest that between 25% and 50% of hospitalized patients receive antibiotics, of which up to 50% are considered unwarranted.[2–4] Due to the selective pressure imposed by antibiotic agents over bacterial populations, antibiotic consumption has been linked to the increased prevalence of resistant bacterial infections.[5–10] Carbapenem-resistant *Acinetobacter baumannii* (CRAb) has been recognized as one of the difficult-to-treat pathogens, causing significant morbidity and mortality.[11–13] CRAb is also listed as 'critical priority', for which the development of effective drugs is required.[14] The rate of development of antibiotic non-susceptibility among organisms responsible for human infection is greater than the corresponding rate of antibiotic discovery and development.[15] Thus, conserving the effectiveness of existing antibiotics is a critical issue to be addressed.[15,16] In response to the growing threat of AMR, the World Health Assembly adopted a Global Action Plan (GAP) on AMR in 2015, with one of the key objectives being to optimize the use of antimicrobials in humans.[17]

In February 2018, King Abdullah University Hospital (KAUH) in Jordan implemented an antimicrobial stewardship programme (ASP) consisting of several components, including education, antibiotic guidelines, antibiotic restriction policy with prior approval, audit of compliance to the restriction policy and feedback. The objective of this study was to evaluate the impact of the ASP on reducing broad-spectrum antibiotic use and its effect on the incidence of CRAb in hospitalized patients.

Methods

Study design and population

The study took place at KAUH, Irbid, Jordan. KAUH is a 533 bed tertiary teaching hospital that provides surgical and medical services with ICUs and supports a range of outpatient facilities. The study was retrospective and ecological in nature; it was carried out over the period January 2014 to December 2019. In February 2018, an ASP was implemented in the hospital that remains in effect today. For the purpose of this study, the implementation of this ASP was considered and evaluated as an intervention. This resulted in two study periods, i.e. pre-ASP intervention (January 2014 to January 2018) and post-ASP intervention (i.e. February 2018 to December 2019). The study population included all adult inpatients admitted to KAUH during the study period. The impact of the introduced ASP on reducing the use of broad-spectrum antibiotics and on CRAb was assessed through the evaluation of antibiotic usage and CRAb incidence rates for the period January 2014 to December 2019. An overview of the study characteristics, antimicrobial stewardship interventions, isolation and cleaning policies, and definitions is provided in Figure 1. The approval of the institutional review board (IRB) at Jordan University of Science and Technology and KAUH was obtained for this study (IRB number 354-2020).

Microbiology and pharmacy data

A CRAb case is defined as a patient with an *A. baumannii* isolate from a clinical sample that is resistant to all the carbapenems used in KAUH (i.e. meropenem and imipenem/cilastatin). Identification of isolates and antibiotic susceptibility testing were performed according to standard microbiological procedures, using an automated VITEK 2 Compact system in line

with the CLSI guidelines.[18,19] Duplicated positive CRAb results were excluded and an isolate from the same patient identified within 30 days of a previous isolate with the same identification was considered as the same case. Monthly antibiotic use was converted into the number of DDD, following the classification of antibiotics for systemic use (J01) in the 2019 WHO/ATC index.[20] Data on the monthly incidence of CRAb, antibiotic use and alcohol-based hand rub (ABHR; in L) were extracted from KAUH's health information systems (Enterprise Management Health Information System, version 12.11.1) and were normalized per 100 occupied bed days (OBD).

ASP

Prior to February 2018, hospital policy was to restrict broad-spectrum antibiotics pending approval from the infectious diseases (ID) consultant, but there was no formal enforcement or tracking of prescribers' adherence to this policy. The ASP was launched at KAUH in February 2018 in line with the WHO and CDC guidelines for antimicrobial stewardship,[21,22] and it contained all the core elements recommended by these guidelines. The main aim of the ASP was to improve and measure the use of antimicrobials, mainly those with broad-spectrum activities. The antimicrobial stewardship committee members included ID specialists and representatives from pharmacy (including clinical pharmacists), nursing, information technology (IT), infection control and laboratory personnel. The programme was based on three main interconnected mandates: awareness and education; actions and interventions (antibiotic restriction policy with prior approval); and tracking (audit of compliance to the restriction policy and feedback).

The educational packages were constructed and prepared by the ID specialists and discussed with the ASP team members during regular meetings (mainly infection control personnel and clinical pharmacists). They were mainly based on personal experience and were informed by updated guidelines at other institutions and literature regarding antimicrobial use and bacterial resistance. Learning objectives included increasing prescribers' awareness and knowledge of the most appropriate and rational use of antimicrobials in different clinical situations, and ensuring they had up-to-date information on emerging AMR at local and national levels. We also aimed to inform all prescribers about the ASP activities. Educational activities included lectures to residents and medical staff, grand rounds, workshops, awareness campaigns, specialty-specific lectures on the proper use of antibiotics, brochures and posters distributed throughout the hospital, annual antibiograms and easy access to proper dosing and monitoring of antibiotics that were integrated into the electronic medical system used. Social media and public awareness were also important components of the programme. The educational materials were available on the intranet and the electronic medical system for reuse by the prescribers, but were not available for external review. Hospital residents are physicians who joined different residency programmes (paediatrics, internal medicine, surgery, obstetrics and gynaecology etc.). All residents were involved in the decisions of antimicrobial prescription, with more decision-making given to more senior residents, but the majority of staff entering the prescription into the electronic system would be junior residents. Members of medical staff may prescribe for a patient if no resident is present. Therefore, all prescribers (residents and staff) were included in the training.

The main interventional action in the ASP was the strict antibiotic-approval policy, which required that a prescriber seek approval from an ID consultant before using broad-spectrum antibiotics (i.e. imipenem/cilastatin, ertapenem, meropenem, vancomycin, teicoplanin,

tigecycline, colistin, amikacin, piperacillin/tazobactam, levofloxacin and ciprofloxacin) and antifungals (amphotericin B, caspofungin, anidulafungin and voriconazole). This policy was incorporated into an in-house IT system that connected pharmacy, physicians and the ID consultant via computer and smartphone applications. Prior to introduction of the ASP, a prescriber would write the restricted antibiotic on a paper medication sheet, call the ID consultant for approval and, if approved, they were directed to record 'approved' next to the antibiotic name. However, in most scenarios, this guidance was not followed and restricted antibiotics were given without the necessary approval.

When the new ASP was introduced in February 2018, all antibiotics were required to be ordered electronically. When a physician ordered restricted antibiotics, the physician would record the indication for starting the restricted antibiotics, the name of the ID consultant who approved the prescription and the mobile phone number for the prescriber in the 'clinical comments' section of the medication order. The pharmacist would then have all the approval information available electronically in order to dispense the requested antibiotic. Once the antibiotic was dispensed, a text message was delivered to the on-call ID consultant, with relevant patient and antibiotic details, and with a link for electronic approval.

Effective and continuous tracking (whether or not a prescriber had sought approval before prescribing a restricted antibiotic) was performed alongside the previous two categories. Tracking was performed on a weekly basis initially, then randomly a few times per month after that. According to this policy, there was a penalty for not following the antibiotic-approval process, which comprised written or verbal warnings. Regular committee meetings were held to discuss and report compliance and adherence to different action plans, including the antibiotic-approval policy. Antibiotic consumption and AMR were also reported on a

regular basis, at least every 3 months. Bi-monthly meetings were also carried out in the hospital involving clinical pharmacists and ID specialists to report and discuss compliance of prescribers with antimicrobial stewardship policies, and provide feedback to improve the programme. Antibiograms were produced annually and distributed to all healthcare providers within the hospital. An audit with regard to compliance to the approval policy was performed for 3 months before the ASP started and continued thereafter. The audit measured the percentage of prescribers who called for approval compared with the total number of prescribers who prescribed restricted antibiotics in a specific duration of time. It was performed by the approving ID specialist and the infection control team through the approval software after February 2018.

Other action plans introduced in February 2018 included treatment polices for common infections (e.g. pneumonia and urinary tract infections), antibiotic management algorithms and pathways (e.g. acute otitis media), IV-to-oral antibiotic switching, when appropriate, and culture-based (bacterial or fungal) antibiotic adjustments or de-escalation.

Modelling and statistical analysis

The ASP and CRAb incidence rates were evaluated using segmented regression of interrupted time-series analysis.[23–25] In addition, the potential overall difference in awareness of the issue of antibiotic use and resistance due to the introduced antimicrobial stewardship interventions on the use of third-generation cephalosporins (cefotaxime and ceftriaxone) was evaluated. We also assessed trends in ABHR use prior to the ASP and after the ASP was implemented. This is important since infection control activities and an ASP work together to

control healthcare-acquired infections and this assessment can provide relevant information for infection control quality improvement.[8]

Segmented regression of interrupted time series was employed to assess deviations from the overall level and trend of antimicrobial use and CRAb incidence rates upon implementation of the ASP.

The full interrupted time-series regression model we considered is as follows:

$$Y_t = \beta_0 + \beta_1 T_t + \beta_2 LS_t + \beta_3 TS_t + \phi_1 Y_{t-1} + \sum_{j=1}^{k} \widehat{\omega}_j AO_{jt} + \varepsilon_t \quad (1)$$

where Y_t represents the outcome variable (monthly dispensary volume), β_0 is the intercept representing the baseline dispensary level at time 0, β_1 represents the trend or the average monthly change in the outcome variable prior to the ASP launch, β_2 is the change in level after the ASP implementation and β_3 is the change in trend (slope) after the ASP implementation. T_t is defined as the sequence $\{1,2,3,4,\ldots, n\}$ for the entire study period, LS_t is defined as 0 for the period January 2014 to January 2018 and as 1 for the period February 2018 to December 2019, and TS_t is defined as 0 for the period January 2014 to January 2018 and as sequence $\{1,2,3,4,\ldots\}$ for the period February 2018 to December 2019. To account for potential autocorrelation and outliers in the analysis, we allowed for Y_{t-1} to enter the impact model if significant autocorrelation was detected in the autocorrelation function (ACF) of the residuals. Further, the standardized residuals of the estimated model were evaluated and any $|\varepsilon_t / \text{sd}\ \Sigma\varepsilon_t| > 2.80$ were treated as additive outliers $\sum_{j=1}^{k} \widehat{\omega}_j AO_{jt}$ in the impact model.

In addition to the full interrupted time-series regression model described above, we also presented a reduced (parsimonious) model, which eliminates the model parameters that are

found to be statistically insignificant. In this reduced model algorithm, a backward stepwise approach was applied on the full model that iteratively evaluates the Bayesian Full Information Criteria (BIC) in dropping the statistically insignificant parameters. By dropping these parameters, we can arrive at the most parsimonious interrupted time-series regression model. The BIC is generally defined as

$$BIC = k * ln(n) - 2ln\left(\widehat{LF}_{max}\right) \quad (2)$$

where *k* is the number of estimated parameters in the model, *n* is the number of observations used in model estimation and $\widehat{LF}_{max}$ is the maximized value of the likelihood function from model estimation. Analyses were performed using the SCA Statistical System version 8.1 (Scientific Computing Associates Corp., IL, USA) and R software (R Foundation for Statistical Computing, Vienna, Austria).

Results

Over the 6 year study period (January 2014 to December 2019), a total of 1034 CRAb cases were identified in KAUH. The average monthly CRAb incidence rate was 0.148/100 OBD (range: 0.07–0.27) and the average monthly CRAb incidence rate, normalized per 100 admissions, was 0.541 (range: 0.244–0.897). The average monthly CRAb incidence rate was 0.134/100 OBD in the post-ASP period compared with 0.154/100 OBD in the pre-ASP period.

Changes in antibiotic use and ABHR after the intervention, using segmented regression analysis, are presented in Table 1 (full models) and Table 2 (most parsimonious models). A statistically significant decrease in the level of antibiotic use, after the introduction of the ASP, was observed for the following antibiotics: imipenem/cilastatin (regression coefficient=−1.2877, *P*=0.0008, 95% CI: −2.0025 to −0.5728), carbapenems (regression coefficient=−2.2618, *P*=0.0001, 95% CI: −3.3536 to −1.1699), vancomycin (regression coefficient=−1.2518, *P*=0.0006, 95% CI: −1.9315 to −0.5721), colistin (regression coefficient=−0.5663, *P*=0.0016, 95% CI: −0.9035 to −0.2291) and third-generation cephalosporins (regression coefficient=−1.7234, *P*=0.0004, 95% CI: −2.6244 to −0.8224). There were no significant changes in levels of the remaining targeted antibiotics (Table 2). A statistically significant decrease in the slope after intervention for ertapenem (regression coefficient=−0.0645, *P*=0.0044, 95% CI: −0.1061 to −0.0229) and ciprofloxacin (regression coefficient=−0.0305, *P*=0.0117, 95% CI: −0.0535 to −0.0074) was observed (Table 2). For piperacillin/tazobactam, a significant increase in trend (regression coefficient=0.0417, *P*=0.0208, 95% CI: 0.0072–0.076) was observed before the intervention. However, this trend was halted in the post-intervention period (regression coefficient=−0.0402, *P*=0.4574, 95% CI: −0.1455 to 0.0652) (Table 1). The results of audits for compliance with the approval

policy ranged from 10% to 20% before the ASP and increased to 80% after its implementation. Graphs for monthly antibiotic use are presented in Figures 2 and 3. An increasing trend in the use of ABHR was observed before the intervention period (regression coefficient=0.0392, $P<0.0001$, 95% CI: 0.0323−0.0462). However, a significant decrease in the slope (regression coefficient=−0.0282, $P=0.0120$, 95% CI: −0.0495 to −0.0068) was observed in the post-intervention period (Table 2). Monthly ABHR use is presented in Figure 4. The introduction of the ASP was associated with a significant reduction in CRAb levels (regression coefficient=−0.0259, $P=0.0237$, 95% CI: −0.078 to −0.004). No significant changes in trends (before/after the intervention) were observed (Table 3). Monthly CRAb incidence is presented in Figure 5.

Discussion

The development of AMR can have a catastrophic impact on health systems in low- and middle-income countries (LMICs).[26,27] The findings of this study demonstrated a statistically significant decrease in the level of antibiotic use after the introduction of the antimicrobial stewardship intervention for imipenem/cilastatin, carbapenems, vancomycin, colistin and third-generation cephalosporins. In addition, a statistically significant decrease in the post-intervention slope for ertapenem and ciprofloxacin was observed. Of interest, a significant increase in trend in the pre-intervention period was observed for piperacillin/tazobactam; however, this trend was halted post-intervention. The reduction in use of these antibiotics is of great significance since their use has been linked to the development of resistance in many published studies.[5–10,28–37] The implemented ASP at KAUH is in line with worldwide initiatives to control AMR.[16,37] Antimicrobial stewardship activities have been shown to decrease antibiotic use and incidence rates of pathogens, and to improve the susceptibility of pathogens.[6,10,38–41]

Our non-linear time-series analysis of this study[42] found that the use of third-generation cephalosporins and carbapenems was directly associated with the incidence of CRAb at KAUH. This is consistent with other published findings.[32] The vast majority of CRAb cases were resistant to both meropenem and imipenem/cilastatin (only 0.4% of CRAb cases were resistant to only one of them). Of note, carbapenems were one of the targeted antibiotic groups for this ASP and their restriction was effective in reducing their use in hospitals. This was shown in the present analysis and was reflected in our threshold analysis, where the relative number of times in which the use of carbapenems was observed to be above the identified thresholds was reduced in the post-ASP period.[42] On the other hand, third-

generation cephalosporins were not on the restricted antibiotic list. Nevertheless, the present analysis showed a decrease in their usage level in the post-ASP period, potentially due to the overall impact of the ASP and possibly the increased awareness among prescribers. It is interesting to note that the relative frequency of third-generation cephalosporins use above identified thresholds increased post-intervention.[42] In order that third-generation cephalosporins contribute to a reduction in CRAb incidence rates, there should be a further reduction in the number of times third-generation cephalosporins are allowed to exceed the optimal threshold. This highlights the potential need to optimize the use of third-generation cephalosporins (cefotaxime and ceftriaxone). With respect to ABHR, the present findings showed a reduction in the trend of its use in the post-intervention period. While this reduction requires careful monitoring and further assessment, our threshold analysis study showed more instances of ABHR use above its optimal threshold and showed that ABHR had a significant reducing effect on CRAb, even at its minimum use.[42] Overall, these findings provide evidence that supports the successful implementation of an ASP at KAUH. This was further demonstrated in the observed reduction in the average monthly incidence of CRAb rates for the post-ASP period (0.134/100 OBD) compared with the pre-ASP period (0.154/100 OBD). The reduction in CRAb incidence, as well as being included on the targeted restricted antibiotic list, likely contributed to a reduction in colistin use in the study site hospital. The reduction in colistin use is needed in light of current studies around the world (including South Korea, Italy, Greece and Saudi Arabia) that found increasing rates of resistance to colistin and polymyxin B in Gram-negative organisms.[37,43–46]

Prior-approval programmes limit the supply of antibiotics until after the antibiotic authorization is obtained from the ID specialist. The benefit of this type of intervention on the incidence of nosocomial infections had been shown elsewhere.[47,48] In this study, the

restriction of targeted antibiotics was achieved through the use of a prior-approval system. There were many reasons contributing to the compliance being lower than 100% with the new approval policy, including new or rotating residents who did not know about the policy, miscommunication between residents on whether approval had been obtained for a specific antibiotic or not, and not knowing specific details such as 'approval needs to be renewed weekly if a restricted antibiotic has to be continued for a patient'.

This study has the strength of using robust analysis methods (i.e. time-series analysis).[49] However, the study has some limitations. The study was retrospective and ecological in nature, thus subject to issues that may arise in validating data, controlling for changes in patient population and case mix. Also, it was not possible to actively control other reasons that might have impacted the incidence of CRAb, for example, CRAb focal clusters and CRAb outbreaks arising during the study period. The study could additionally have benefited from evaluation of the impact of the antimicrobial stewardship interventions on patient outcomes (i.e. length of hospital stay and mortality), along with health economics assessment, thus warranting further future work.[50] Finally, this work represented a single-centre assessment and would benefit from being evaluated in other hospitals.

In conclusion, the present study assessed the impact of multifaceted antimicrobial stewardship interventions on reducing the use of certain targeted antibiotics and on CRAb incidence rates in the hospital. Reports on effective and feasible antimicrobial stewardship interventions in LMICs are limited,[51,52] and this study provides evidence supporting successful implementation of an effective ASP. The interventions contributed to a reduction in the use of several broad-spectrum antibiotics, reversed the increasing use trends in other

antibiotics and were associated with a significant reduction in CRAb in the study site hospital.

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Transparency declarations

None to declare.

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Table 1. Changes in antibiotic use and ABHR after the intervention using segmented regression analysis, January 2014 to December 2019

Terms[a]	Intercept	*P* value	Trend	*P* value	Level change after intervention	*P* value	Trend change after intervention	*P* value	ARMA adjustment (coefficient, *P* value)	R^2
All carbapenems	5.0115	<0.0001	0.0730	<0.0001	−2.1979	0.0010	−0.0081	0.8352	AR1 (0.200, *P*=0.01657)	0.6993
Imipenem/cilastatin	3.1125	<0.0001	0.0087	0.5153	−1.5168	0.0313	−0.0087	0.8343	AR1 (0.376, *P*=0.00014)	0.6280
Meropenem	1.1158	0.0106	0.0257	0.0662	−0.3494	0.5841	0.0324	0.4288	AR1 (0.423, *P*=0.00031)	0.6653
Ertapenem	−1.8274	0.0363	0.0624	0.0035	−0.1183	0.5897	−0.0681	0.0046	N/A	0.3102
Piperacillin/tazobactam	6.5337	<0.0001	0.0417	0.0208	−1.0205	0.2184	−0.0402	0.4574	AR1 (0.392, *P*=0.00002)	0.5919
Teicoplanin	1.7311	0.0003	0.0361	0.0043	0.0850	0.8755	0.0033	0.9235	AR1 (0.363, *P*=0.00419)	0.6259
Vancomycin	1.9633	<0.0001	−0.0026	0.7149	−1.1885	0.0033	0.0840	0.0007	AR1 (0.272, *P*=0.01083)	0.4697
Tigecycline	0.2236	0.0548	−0.0021	0.5113	−0.1111	0.4397	0.0021	0.8160	AR1 (0.653, *P*<0.0001)	0.7802
Amikacin	1.1291	<0.0001	−0.0066	0.0742	0.0904	0.6272	−0.0179	0.1375	N/A	0.2587
Ciprofloxacin	1.6756	<0.0001	0.0098	0.0275	−0.0370	0.8679	−0.0292	0.0443	N/A	0.2906
Levofloxacin	3.0179	0.0022	−0.0116	0.5463	−0.9495	0.3122	0.0501	0.4071	AR1 (0.624, *P*<0.0001)	0.5669
Colistin	−0.0036	0.9726	0.0235	<0.0001	−0.5798	0.0042	0.0017	0.8817	AR1 (0.260, *P*=0.03034)	0.6208
Third-generation cephalosporins	6.4027	<0.0001	0.0211	0.0226	−1.7234	0.0004	0.0674	0.0254	N/A	0.4019
ABHR	0.9541	<0.0001	0.0396	<0.0001	−0.0366	0.8588	−0.0269	0.0431	N/A	0.7817

ARMA, autoregressive moving average.

[a]Antibiotic use expressed as DDD/100 OBD; ABHR use expressed as L/100 OBD.

N/A, not applicable

AR1, first-order autocorrelation coefficient

Table 2. Most parsimonious segmented regression models assessing changes in antibiotic use and ABHR after the intervention, January 2014 to December 2019

Terms[a]	Intercept	*P* value	Trend	*P* value	Level change after intervention	*P* value	Trend change after intervention	*P* value	ARMA adjustment (coefficient, *P* value)	R^2
All carbapenems	5.0225	<0.0001	0.0721	<0.0001	−2.2618	0.0001	N/A	N/A	AR1 (0.202, *P*=0.01473)	0.6991
Imipenem/cilastatin	3.2708	<0.0001	N/A	N/A	−1.2877	0.0008	N/A	N/A	AR1 (0.388, *P*=0.00005)	0.6255
Meropenem	1.0530	0.0045	0.0274	0.0026	N/A	N/A	N/A	N/A	AR1 (0.427, *P*=0.00023)	0.6618
Ertapenem	−1.5554	0.0254	0.0555	0.0008	N/A	N/A	−0.0645	0.0044	N/A	0.3041
Piperacillin/tazobactam	6.7991	<0.0001	N/A	N/A	N/A	N/A	N/A	N/A	AR1 (0.457, *P*<0.0001)	0.5564
Teicoplanin	1.6735	<0.0001	0.0383	<0.0001	N/A	N/A	N/A	N/A	AR1 (0.366, *P*=0.00254)	0.6254
Vancomycin	1.9009	<0.0001	N/A	N/A	−1.2518	0.0006	0.0815	0.0006	AR1 (0.271, *P*=0.01052)	0.4686
Tigecycline	0.0838	0.0566	N/A	N/A	N/A	N/A	N/A	N/A	AR1 (0.724, *P*<0.0001)	0.7662
Amikacin	1.1927	<0.0001	−0.0094	<0.0001	N/A	N/A	N/A	N/A	N/A	0.2322
Ciprofloxacin	1.6812	<0.0001	0.0095	0.0156	N/A	N/A	−0.0305	0.0117	N/A	0.2903
Levofloxacin	2.1267	0.0007	N/A	N/A	N/A	N/A	N/A	N/A	AR1 (0.675, *P*<0.0001)	0.5453
Colistin	−0.0081	0.9364	0.0238	<0.0001	−0.5663	0.0016	N/A	N/A	AR1 (0.259, *P*=0.02942)	0.6207
Third-generation cephalosporins	6.4027	<0.0001	0.0211	0.0226	−1.7234	0.0004	0.0674	0.0254	N/A	0.4019
ABHR	0.9599	<0.0001	0.0392	<0.0001	N/A	N/A	−0.0282	0.0120	N/A	0.7816

ARMA, autoregressive moving average.

[a]Antibiotic use expressed as DDD/100 OBD; ABHR use expressed as L/100 OBD.

N/A, not applicable

AR1, first-order autocorrelation coefficient

Table 3. Segmented regression analysis estimates of changes in CRAb (cases/100 OBD) after the antimicrobial stewardship interventions, January 2014 to December 2019

Terms	Coefficient	*P* value
Full segmented regression model (R^2=0.1712)		
Intercept	0.1454	<0.0001
Trend	0.0004	0.4201
Level change after the intervention	−0.0467	0.0438
Trend change after the intervention	0.0006	0.6552
Most parsimonious segmented regression model (R^2=0.1564)		
Intercept	0.1454	<0.0001
Level change after the intervention	−0.0259	0.0237

Figure 1. Overview of the study characteristics, antimicrobial stewardship interventions, isolation and cleaning policies, and definitions

<table>
<tr><td>Setting: The study took place at KAUH, Irbid, Jordan. KAUH is a 533 bed tertiary teaching hospital that provides surgical and medical services with ICUs and supports a range of outpatient facilities, with two paediatric ID doctors, two consultant microbiologists and four infection control nurses, all on a full-time basis.</td><td>Design and dates: The study was interventional, retrospective, ecological in nature and was carried out over the period January 2014 to December 2019. The antimicrobial stewardship intervention took place beginning in February 2018, and its impact on reducing the use of broad-spectrum antibiotics and on CRAb was assessed.</td><td>Population: All adult inpatients admitted to KAUH. Number of OBD and number of admissions were 700 970 (average: 9736; range: 7293–11 400) and 193 218 (average: 2684; range: 1683–3275), respectively.</td></tr>
<tr><td colspan="3">Major relevant changes during the study period: an ASP consisting of several components, including education, antibiotic guidelines for common infections, antibiotic restriction policy (prior approval) and audit of compliance and feedback. Restricted antibiotics: imipenem/cilastatin, ertapenem, meropenem, vancomycin, teicoplanin, tigecycline, colistin, amikacin, piperacillin/tazobactam, levofloxacin and ciprofloxacin.</td></tr>
<tr><td></td><td>Antimicrobial stewardship interventions</td><td>Cleaning policy</td></tr>
<tr><td>Pre-intervention period: 49 months (January 2014 to January 2018)</td><td>• There was a hospital policy to restrict broad-spectrum antibiotics (above) pending approval from the ID specialist, but there was no enforcement or tracking of prescribers' adherence to this approval policy.</td><td>The hospital had been using ready-to-use quaternary ammonium compounds in spray forms as disinfectant with multiply-used towels for cleaning of surfaces. The same product (concentrated) was used for cleaning floors after appropriate dilution until January 2017.</td></tr>
<tr><td>Post-intervention period: 23 months (February 2018 to December 2019)</td><td>• There was a hospital policy to restrict broad-spectrum antibiotics (above) pending approval from an ID specialist, combined with enforcement and tracking of prescribers' adherence to this approval policy.
• Treatment policies for common infections, antibiotic management algorithms and pathways, IV-to-oral antibiotic switching, when appropriate, and culture-based (bacterial or fungal) antibiotic adjustments or de-escalation.</td><td>Since February 2017, hospital cleaning switched to a ready-to-use quaternary ammonium compound wet-wipe disinfectant for cleaning and disinfection of surfaces.</td></tr>
<tr><td colspan="3">Detection of CRAb cases: isolates were referred for microbiology testing if patients had clinical symptoms indicating infection. No change in this strategy occurred over the entire study period.</td></tr>
<tr><td colspan="3">Isolation policy: any patient diagnosed with multiple-resistance microorganisms was subjected to contact precautions until three consecutive negative results obtained with at least 8 h in between.</td></tr>
<tr><td colspan="3">Definition of CRAb: A patient with an A. baumannii isolate from a clinical sample that is resistant to all of the carbapenems used in KAUH (i.e. meropenem and imipenem/cilastatin). Identification of isolates and antibiotic susceptibility performed according to standard microbiological procedures, using an automated VITEK 2 Compact system in line with CLSI guidelines. Duplicated positive CRAb results were excluded and an isolate from the same patient identified within 30 days of a previous isolate with the same identification were considered as the same case.</td></tr>
</table>

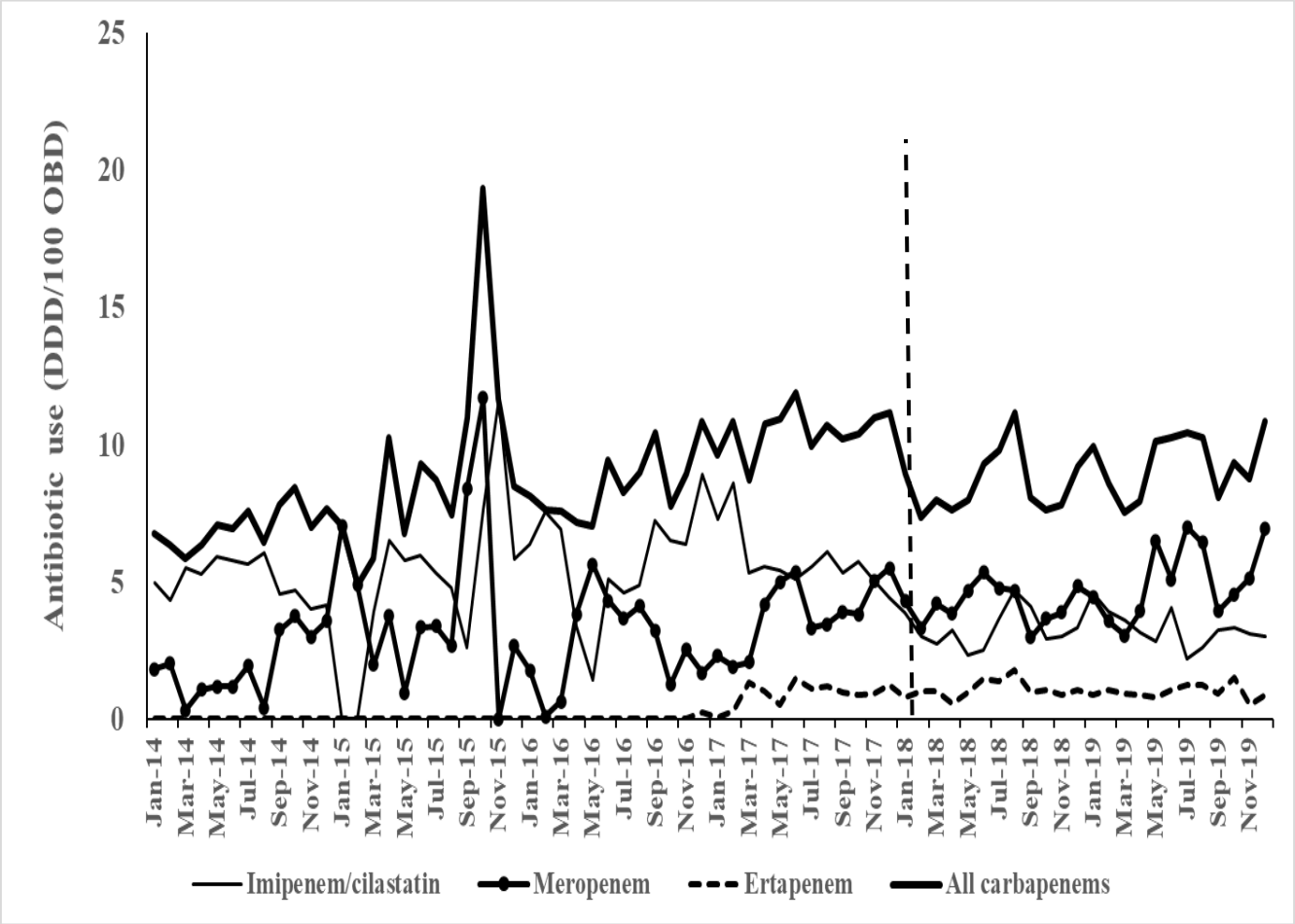

Figure 2. Monthly carbapenem use, January 2014 to December 2019. Vertical dashed line represents the antimicrobial stewardship interventions (February 2018).

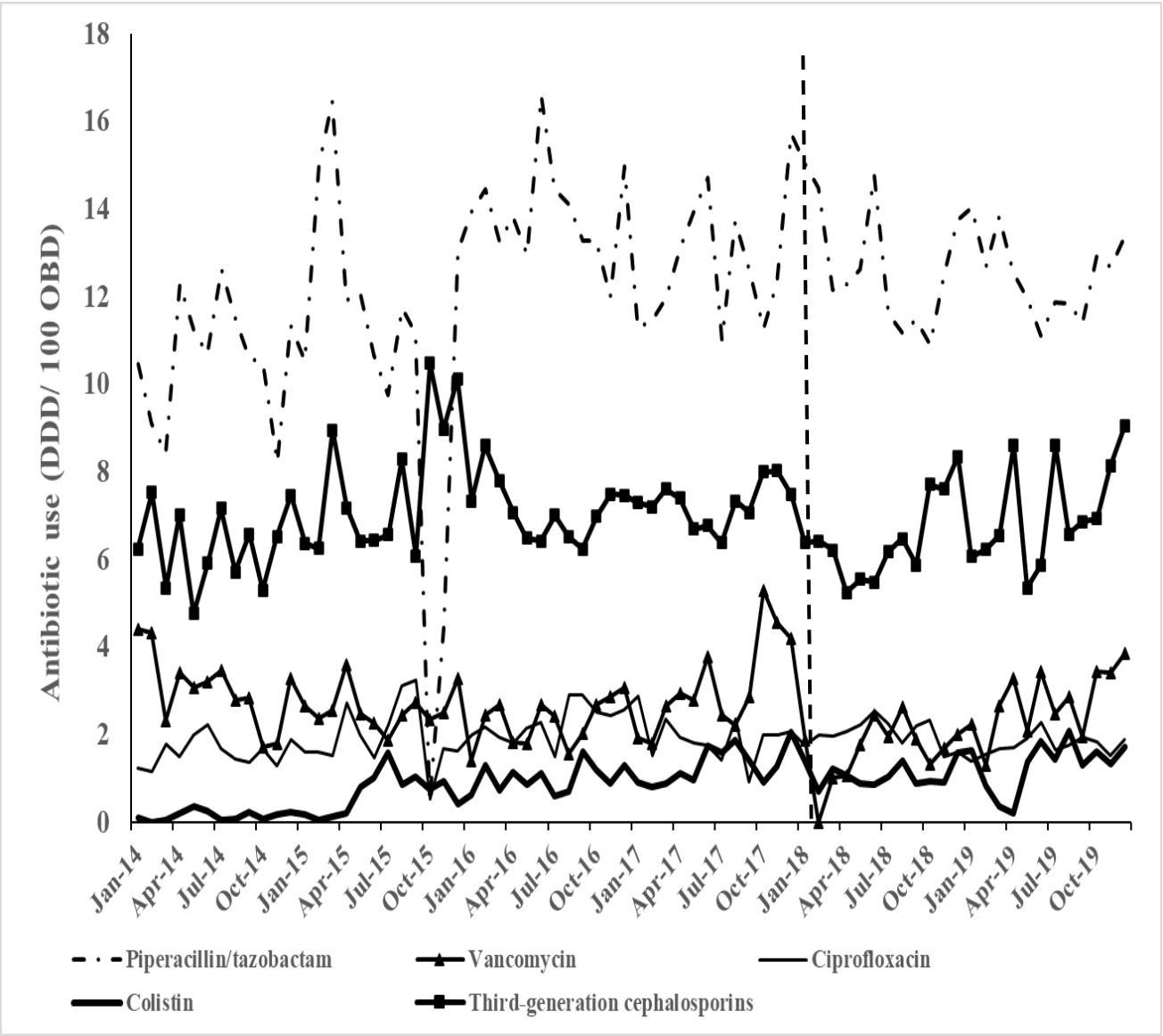

Figure 3. Monthly antibiotic use, January 2014 to December 2019. Vertical dashed line represents the antimicrobial stewardship interventions (February 2018).

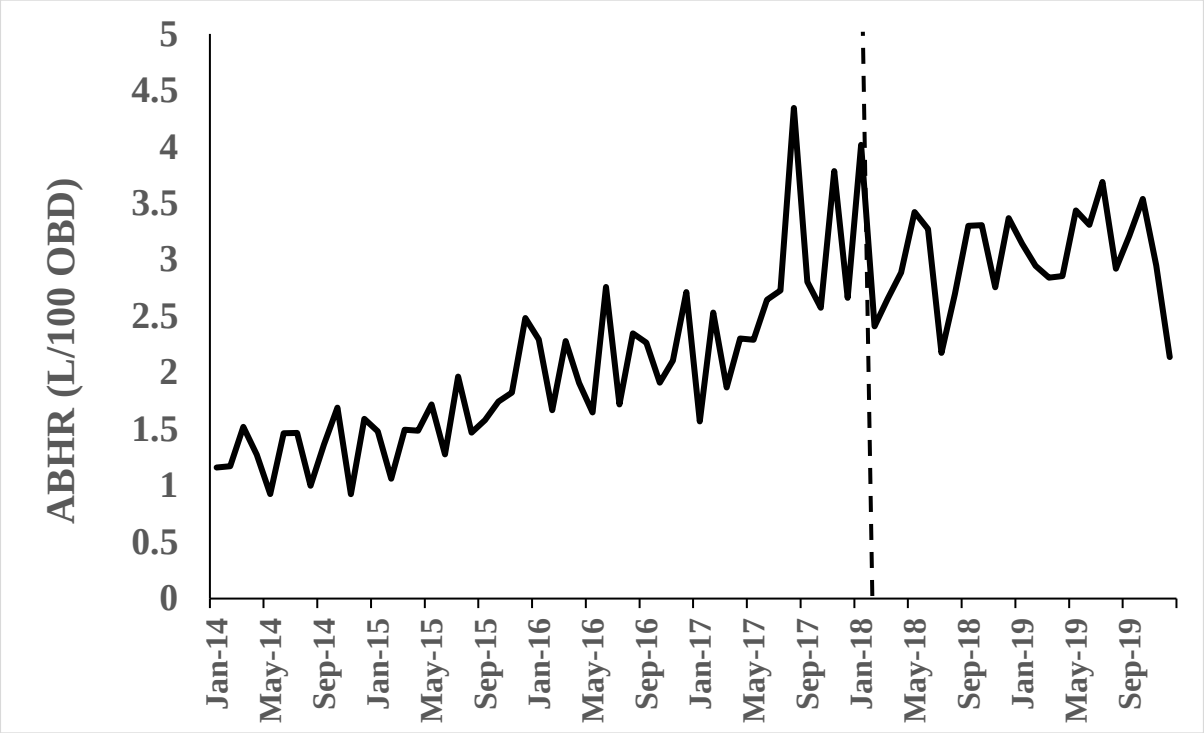

Figure 4. Monthly ABHR use, January 2014 to December 2019. Vertical dashed line represents the antimicrobial stewardship interventions (February 2018).

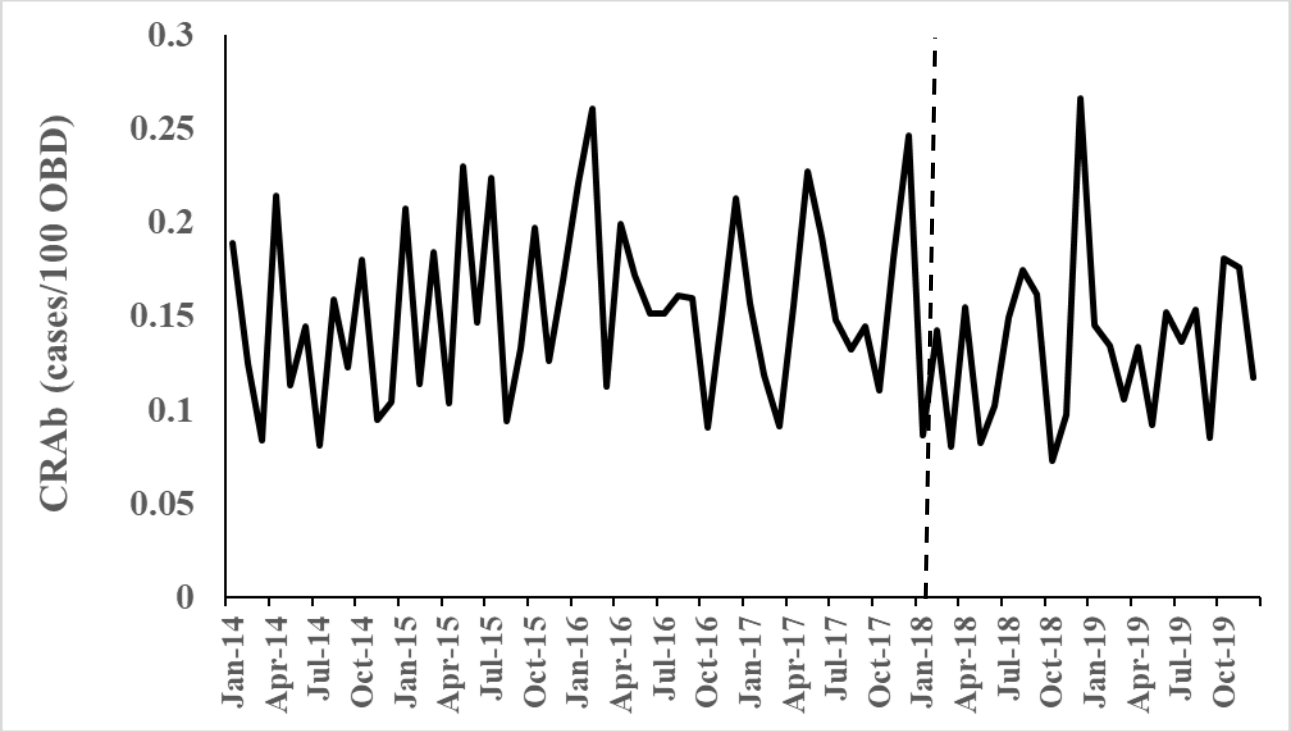

Figure 5. Monthly CRAb, January 2014 to December 2019. Vertical dashed line represents the antimicrobial stewardship interventions (February 2018).