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Identification of thresholds in relationships between specific antibiotic use and carbapenem-resistant *Acinetobacter baumannii* (CRAb) incidence rates in hospitalized patients in Jordan

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Running title: Identification of thresholds in antibiotic use

Background: Antibiotic resistance is a major threat to public health worldwide. The relationship between the intensity of antibiotic use and resistance might not be linear, suggesting that there might be a threshold of antibiotic use, beyond which resistance would be triggered.

Objectives: To identify thresholds in antibiotic use, below which specific antibiotic classes have no significant measurable impact on the incidence of carbapenem-resistant *Acinetobacter baumannii* (CRAb), but above which their use correlates with an increase in the incidence of CRAb.

Methods: The study took place at a tertiary teaching hospital in Jordan. The study was ecological in nature and was carried out retrospectively over the period January 2014 to December 2019. The outcome time series for this study was CRAb cases. The primary explanatory variables were monthly use of antibiotics and the use of alcohol-based hand rub (ABHR). Non-linear time-series methods were used to identify thresholds in antibiotic use.

Results: Non-linear time-series analysis determined a threshold in third-generation cephalosporin and carbapenem use, where the maximum use of third-generation cephalosporins and carbapenems should not exceed 8 DDD/100 occupied bed days (OBD) and 10 DDD/100 OBD, respectively. ABHR had a significant reducing effect on CRAb cases even at lower usage quantities (0.92 L/100 OBD) and had the most significant effect when ABHR exceeded 3.4 L/100 OBD.

Conclusions: The identification of thresholds, utilizing non-linear time-series methods, can provide a valuable tool to inform hospital antibiotic policies through identifying quantitative targets that balance access to effective therapies with control of resistance. Further studies are needed to validate the identified thresholds, through being prospectively adopted as a target

for antimicrobial stewardship programmes, and then to evaluate the impact on reducing CRAb incidence.

Introduction

Antibiotic resistance is a major threat to public health worldwide, causing increasing morbidity and mortality, and incurring significant healthcare costs.[1] *Acinetobacter baumannii* has emerged globally as a significant hospital pathogen, with remarkable ability to up-regulate or acquire resistance determinants and the ability to survive for prolonged periods throughout a hospital environment, thus making it one of the most difficult pathogens to treat and potentiating its ability for nosocomial spread.[2] Carbapenem-resistant *A. baumannii* (CRAb) is listed as an antibiotic-resistant pathogen, with critical priority, for which the development of effective drugs is required.[3] Antimicrobial stewardship aims to inform the appropriateness of antibiotic prescribing practices, while providing access to effective therapy. The challenge for these programmes, however, is to balance the provision of adequate antibiotic treatment with the prevention of the emergence of antibiotic resistance.

In 1994, Stuart Levy hypothesized that the relationship between the intensity of antibiotic use and resistance might not be linear, suggesting that there might be a threshold of antibiotic use, beyond which resistance would be triggered.[4] A threshold is an estimate of the maximum use of any antibiotic in a population that can be used over a specific period without significantly increasing resistance to that antibiotic. This can be converted into a maximum number of patients to be treated with the specific antibiotic in the population.[5] On the basis of Levy's 1994 hypothesis, statistical methods from the field of econometrics, suitable for the identification and estimation of non-linear models, were developed.[5–9] By using the non-linear time-series methods,[8] thresholds of associations between antibiotic use and rates of resistance have been determined.[8,9]

The aim of this work was to identify thresholds in antibiotic use, below which specific antibiotic classes have no measurable impact on the incidence of CRAb, but above which their use correlates with an increase in the incidence of CRAb. In addition, we aimed to measure thresholds in associations between using alcohol-based hand rub (ABHR) and CRAb incidence rates in hospitals.

Methods

Study design and population

The study took place at King Abdullah University Hospital (KAUH), Irbid, Jordan. KAUH is a 533 bed tertiary teaching hospital, which provides surgical and medical services with ICUs and supports a range of outpatient facilities. The study was ecological in nature and was carried out retrospectively over the period January 2014 to December 2019. The study population included all adult inpatients admitted to KAUH during the study period. Minimum data requirements for this analysis were 60 monthly observations (5 years) of antibiotic use and microbiological data.[8] The duration of the time series used in this study was defined by the availability of the longest period of consistent outcome and explanatory variables data, that is a 6 year dataset. The outcome time series for this study was CRAb cases. The primary explanatory variables were monthly use of antibiotics and the use of ABHR. Candidate antibiotics included in the analysis were identified *a priori* on the basis of their resistance profiles and published evidence of their role as risk factors for driving the incidence of CRAb in hospitals.[8] Therefore, we hypothesized that the use of carbapenems, fluoroquinolones, piperacillin/tazobactam, third-generation cephalosporins and aminoglycosides could be important explanatory variables.[8] The approval of the institutional review board (IRB) at Jordan University of Science and Technology and KAUH was obtained for this study (IRB number 122-2019).

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 of the carbapenems used in KAUH (i.e. meropenem and

imipenem/cilastatin). Identification of isolates and antibiotic susceptibility tests were performed according to standard microbiological procedures, using an automated VITEK 2 Compact system in line with the CLSI guidelines.[10,11] 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 quantities of the use of antibiotics were converted into the number of DDD following the classification of antibiotics for systemic use (J01) in the 2019 WHO/ATC index.[12] All required pharmacy and microbiology data were extracted from KAUH's computer systems (Enterprise Management Health Information System, version 12.11.1). Data on the monthly quantities of CRAb, antibiotic use and ABHR (in L) were normalized per 100 occupied bed days (OBD).

Antibiotic policies

KAUH introduced an antimicrobial stewardship programme in February 2018, which has been detailed elsewhere.[13] The antimicrobial stewardship activities introduced included restrictions on broad-spectrum antibiotics (i.e. imipenem/cilastatin, ertapenem, meropenem, vancomycin, teicoplanin, tigecycline, colistin, amikacin, piperacillin/tazobactam, levofloxacin and ciprofloxacin), educational activities for prescribers, antibiotic policies to treat common infections, public awareness campaigns and hand hygiene campaigns.

Modelling and statistical analysis

The foundation of our analysis is to detect significant thresholds in antibiotic use levels that alter trends in CRAb hospital infections. We also consider that thresholds may have a lagged temporal effect where increased antibiotic use levels require one or more periods before causing an effect on the trend of CRAb infections.[8,14,15] There are several methods that can be

used to explore thresholds in explanatory variables. Among the methods are Multivariate Adaptive Regression Splines (MARS),[16] Generalized Additive Models (GAM),[17] Segmented Time-Series Models or Threshold Transfer Function Models,[18] and Segmented Regression or Piecewise Regression Models.[19] The MARS and GAM methods are rather automated algorithms in dealing with threshold non-linearities. The remaining methods require a more hands-on approach to threshold identification and model building.

In this paper, we make use of all the methods and do so in a systematic manner (Supplementary material, available as Supplementary data at *JAC* Online). We began with GAM to explore curvature in the relationships and approximate threshold levels. MARS models were used to further explore thresholds and lagged relationships including lagged relationships in the response variable itself.[20] Furthermore, due to the introduction of the antimicrobial stewardship programme by KAUH starting in February 2018, we examined the potential influence of the established programme on identified thresholds by allowing the MARS models to identify second-order interaction between the threshold values and the periods of pre-intervention and post-intervention (Supplementary material). The MARS model was restated as a Threshold Transfer Function model where autoregressive moving average (ARMA) components can be added to the model to handle complex serial correlation, outlier detection and adjustment can be applied, and the model can be generally refined.[21] In addition, a search algorithm based on Segmented Regression (Piecewise Regression) or Threshold Transfer Function was implemented, screening each variable for potential thresholds.[18] Upon optimizing the threshold breakpoints, a sensitivity analysis was conducted on the lower and upper limit around the optimized threshold value using a one-at-a-time (OAT) approach.

For the purpose of translating the identified thresholds into population-specific antimicrobial stewardship policy suggestions, patient treatments per month were estimated. This was done by multiplying the identified threshold (DDD/100 OBD) by the size of the population (OBD), and then dividing by an average patient treatment (7 DDD). Following this, we presented estimates for population-specific antimicrobial stewardship policy suggestions using two approaches: (i) standard approach, estimated by using the identified threshold; and (ii) conservative approach, estimated by using the lower limit as the threshold. Analysis was 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).[22]

Results

Over the 6 year study period (January 2014 to December 2019), a total of 1034 CRAb cases were identified in KAUH. The number of OBD and the number of admissions were 700970 (average: 9736; range: 7293–11400) and 193218 (average: 2684; range: 1683–3275), respectively. The average monthly CRAb incidence was 0.148/100 OBD (range: 0.07–0.27), and the average monthly CRAb incidence normalized per 100 admissions was 0.541 (range: 0.244–0.897). The average third-generation cephalosporin use was 6.97 DDD/100 OBD (range: 4.76–10.64), the average carbapenem use was 8.86 DDD/100 OBD (range: 4.89–19.32) and the average ABHR use was 2.31 L/100 OBD (range: 0.92–4.34). Analysis of the data showed a positive relationship between third-generation cephalosporin use, carbapenem use and CRAb in KAUH (regression coefficient = 0.006, $P < 0.001$ and regression coefficient = 0.002, $P = 0.0139$, respectively). A negative relationship was demonstrated between ABHR and CRAb (regression coefficient = −0.015, $P = 0.0003$; Table 1). Different lag effects (delay necessary to observe the effect in months) were observed for third-generation cephalosporins, carbapenems and ABHR, that is 2, 4 and 2 months, respectively.

The coefficient of determination (R^2; used to measure the explained variance in the estimated regression model) of the final model was 0.394, that is 39.4% of the variations of the monthly incidence of CRAb over the study period were explained by the factors included in the model.

Charts illustrating the identified thresholds for carbapenems, third-generation cephalosporins and ABHR and their effect on CRAb incidence trends are presented in Figure 1. Contribution charts illustrate the relationship between explanatory variables and CRAb incidence, showing the estimated effect when use levels exceed their respective threshold value, and are presented in Figure S1. Plots for the monthly CRAb incidence versus the use of third-generation cephalosporins, carbapenems and ABHR are presented in Figures S2 and S3. Data on CRAb isolates, obtained from the microbiology department, showed that CRAb isolates were resistant to ceftriaxone, meropenem and imipenem/cilastatin in 96.7%, 97.4% and 97% of the cases, respectively. Non-linear time-series analysis determined a threshold in third-generation cephalosporin and carbapenem use, where the maximum consumption of third-generation cephalosporins and carbapenems should not exceed 8 DDD/100 OBD and 10 DDD/100 OBD, respectively (Table 1). Utilizing the results of the sensitivity analysis for the lower limit (conservative approach), the use of third-generation cephalosporins and carbapenems should not exceed 6 DDD/100 OBD and 10 DDD/100 OBD, respectively (Table 1). ABHR had a significant reducing effect on CRAb even at lower usage quantities (0.92 L/100 OBD) and when ABHR exceeded 3.4 L/100 OBD, it had the most significant effect (Table 1). These findings can then be translated into population-specific antimicrobial stewardship policy proposals (Table 2). Using the standard approach, the findings suggest that the use of both third-generation cephalosporins and carbapenems should be maintained below identified thresholds. Whereas employing a conservative approach suggests that

carbapenems should be maintained below the identified thresholds, third-generation cephalosporins, however, should be reduced by 16% (Table 2).

With respect to the proportion of times the usage volumes exceeded the identified optimal threshold value for a given explanatory variable, further analysis was carried out that compares usage behaviour in the pre-intervention period with that in the post-intervention period (Figure S4). Table 3 reveals that carbapenems exceeded the optimal threshold in 29% of the months in the pre-intervention period, which was reduced to 17% of the months after the antimicrobial stewardship programme was established. ABHR exceeded the optimal threshold in only 6% of the months in the pre-intervention period, which was increased to 17% in the post-intervention period. Third-generation cephalosporins exceeded the optimal threshold in 18% of the months in the pre-intervention period, which increased to 26% after the antimicrobial stewardship programme was established.

Discussion

Controlling rates of CRAb infections in hospitals is vital since options to treat them are limited and these infections are associated with high mortality.[23,24] This study showed temporal relationships between the use of specific antibiotics, ABHR and the incidence of CRAb. The application of non-linear time-series methods to antibiotic use, infection control activities and the development of antibiotic resistance has been utilized recently to measure thresholds for different pathogens in Europe.[8] Nevertheless, to the best of our knowledge, this study is the first attempt to measure thresholds in associations between antibiotic use and the incidence of CRAb in hospitals in the Middle East area.

The use of third-generation cephalosporins and carbapenems was shown to drive the incidence of CRAb at KAUH. 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). The incidence rate of CRAb at KAUH is similar to that in other published studies.[25] The findings were consistent with the resistance patterns obtained from the KAUH microbiology department, which showed that CRAb isolates were resistant to third-generation cephalosporins (ceftriaxone) and carbapenems (meropenem and imipenem/cilastatin). Our findings are in line with recently published data from Hungary, where an association between carbapenems and third-generation cephalosporins was reported.[8] Nevertheless, the identified thresholds in their study are different from our findings. Considering potential changes in molecular epidemiology under sustained antibiotic selection pressure, it is anticipated that thresholds may vary across populations depending on host, environment and organism factors.[8] Different regions have different healthcare systems, different volumes of antibiotic use and different antibiotic resistance patterns.[26] Therefore, tailored thresholds based on modelling local data are needed to reflect context-specific

guidance.[8] Our findings also showed an inverse relationship between the use of ABHR and the incidence of CRAb at KAUH, with an increase in the use of ABHR associated with a decrease in the incidence rates of CRAb. Interestingly, and using the sensitivity analysis of the threshold, ABHR had a significant reducing effect on CRAb, even at its minimum use. However, any usage above the identified threshold accelerated the reduction of CRAb. These findings are important since they confirm the value of ABHR in reducing nosocomial infections in low- to middle-income countries, in addition to those reported elsewhere.[27–30]

The importance of the current findings lies in their ability to set targets for antimicrobial stewardship in the study site hospital and potentially in other similar healthcare settings and populations. Other studies in Jordan and the region found that two of the most frequently prescribed antibiotic groups are third-generation cephalosporins and carbapenems.[31,32] Using standard and conservative approaches, our study provided quantitative targets for hospitals. The uncertainty around estimated thresholds was addressed through conducting sensitivity analysis, which permits estimation of a lower limit for the identified thresholds (conservative approach). When the priority for the antimicrobial management team is strict control of resistance, then the conservative approach should be followed. However, if strict control of antibiotic prescribing may pose a significant challenge and/or concerns, then the standard approach can be followed. The identified thresholds should be used as guidance for balancing the restriction of antibiotics (third-generation cephalosporins and carbapenems) and controlling resistance (CRAb).

The introduction of the antimicrobial stewardship intervention in February 2018 was considered within the threshold modelling. As mentioned previously, we did not find a confounding effect or interaction between the global threshold value and time segment (Supplementary material). We found fewer instances of carbapenem use at a level above the

identified threshold in the post-intervention period, and more instances of ABHR above its optimal threshold, both providing evidence that supports the successful implementation of antimicrobial stewardship interventions at KAUH where the monthly incidence rate of CRAb was reduced to 0.134/100 OBD in the post-antimicrobial stewardship intervention period compared with 0.154/100 OBD in the pre-antimicrobial stewardship intervention period. It is interesting to note that the number of times for carbapenem use above identified thresholds was reduced post-intervention; however, the number of times third-generation cephalosporins were used above identified thresholds was increased post-intervention (Table 3). In theory, based on the threshold analysis, we would like to see a further reduction in the number of times third-generation cephalosporins are allowed to exceed the optimal threshold. However, third-generation cephalosporins were not among the targeted antibiotics for this antimicrobial stewardship programme, highlighting important implications for considering reducing their use through being included within the targeted antibiotics list.

The present study has the strength of using rigorous analysis methods. This work builds upon our previous approach (i.e. linear time-series analysis) for modelling the relationship between antibiotic use and resistance.[33–36] The use of non-linear time-series analysis methods allows for adjustment of the non-independence of serial observations for serial correlations that exist in antibiotic use and resistance time series, to demonstrate temporality in the association between the identified antibiotics and CRAb, along with identifying lagged effects (delays needed to observe an effect) and to consider the non-linear aspects that may exist in modelled series, providing accurate estimates of relationships and thresholds (which will be used to inform antimicrobial stewardship). In addition, this evaluation involved all adult hospitalized patients and the use of routinely collected data, thus selection and information bias are unlikely.

Nevertheless, the study has limitations. As this study is ecological in nature, it was not possible to control for changes in patient population and case mix, which may have impacted CRAb incidence rates in hospitals. The identified thresholds in this study reflect estimates for population third-generation cephalosporin and carbapenem use that do not appear to significantly increase CRAb incidence rates at the population level. Non-linear time-series analysis requires longer time series than linear time series, and the detection of thresholds would better benefit from changes in antibiotic use and resistance. Of note, in our hospital, there were changes in antibiotic use that significantly impacted CRAb incidence rates. With the presented model, 39.4% of the variations in CRAb incidence rates were explained by variables included in the model. The model may be further improved by the inclusion of other potential explanatory factors, for example, data on infection prevention and control activities and proxy measures for changes in patient population and case mix.[37,38] The findings demonstrated thresholds in associations between CRAb cases and the two identified antibiotics. More work is needed to identify thresholds for other high-risk antibiotics that might be associated with other key resistant pathogens. Finally, this work represented a single-centre assessment that was carried out at the hospital-population level. The study would benefit from being replicated in other regional and global centres.

In conclusion, using routinely generated data, we identified minimum thresholds in the relationship between the use of third-generation cephalosporins and carbapenems and the rates of CRAb in hospitals. By identifying a threshold in antibiotic use, hospital guidelines can be informed accordingly, aiming to remove the selection pressure of the identified antibiotic. Complete restrictions of antibiotics pose significant challenges in clinical practice and may induce other resistance due to the need to compensate with other antibiotic agents.[39] Non-linear time-series methods can provide a valuable tool to inform hospital antibiotic

policies through identifying quantitative targets that balance access to effective therapies with control of resistance. Further studies are needed to validate the identified thresholds, through being prospectively adopted as a target for antimicrobial stewardship programmes, and then to evaluate the impact on reducing CRAb incidence.

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Transparency declarations

None to declare.

Supplementary data

Figures S1 to S4, Supplementary material and Supplementary references are available as Supplementary data at *JAC* Online.

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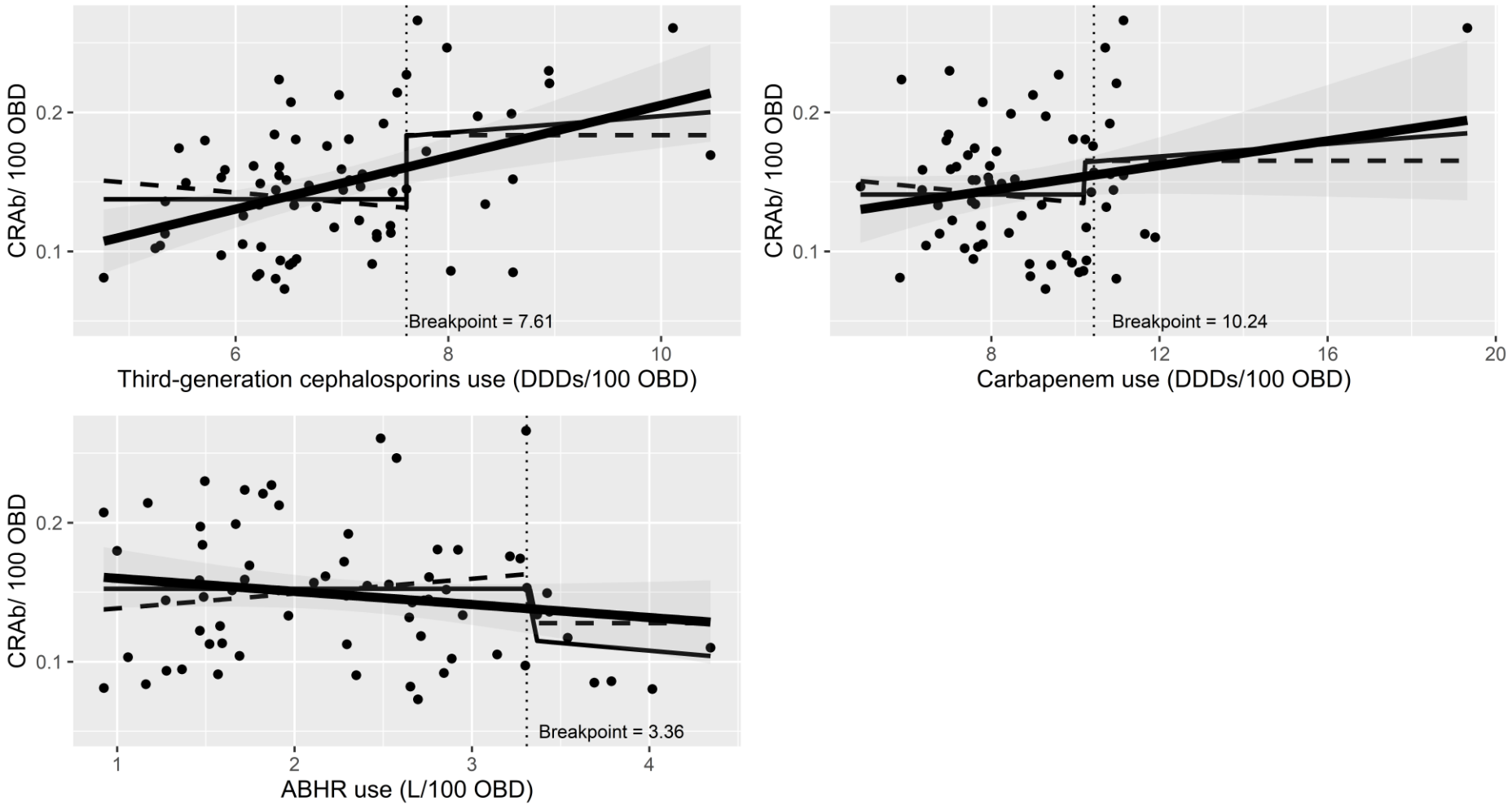

Figure 1. Charts illustrating the identified thresholds for third-generation cephalosporins (lag 2), carbapenems (lag 4) and ABHR (lag 2) and their effect on CRAb incidence trends, January 2014 to December 2019. The thick black line is the fitted linear regression line of the unsegmented data. The thin black line is the fitted linear regression line focusing on x>threshold and the dashed black line focuses on x<threshold.

Table 1. Results of segmented time-series model (Threshold Transfer Function), January 2014 to December 2019

Terms[a]	Lag (months)	Threshold (95% confidence limit [b])	Relationship to threshold	Regression coefficient (95% CI)	*P* value
Constant	N/A	N/A	N/A	0.136 (0.125–0.147)	<0.001
Third-generation cephalosporins	2	7.61 (6.20–8.59)	above	0.006 (0.004–0.009)	<0.001
Carbapenems	4	10.23 (10.08–10.74)	above	0.002 (0.001–0.004)	0.0139
ABHR	2	3.36 (0.92–3.37)	above	−0.015 (−0.022 to −0.007)	0.0003

$R^2 = 0.394$

[a]Third-generation cephalosporin and carbapenem use expressed as DDD/100 OBD; ABHR use expressed as L/100 OBD.

[b]95% confidence limit around the optimised threshold value which was derived using a one-at-a-time (OAT) approach

N/A, not applicable

Table 2. Translation of thresholds identified in non-linear models into population-specific antimicrobial stewardship policy suggestions

Antibiotics	Patient treatments per month[a]			
	maximum suggested by threshold (lower and upper limit)	average use in last 12 months of study	suggested reduction in use (%)	
			standard[b]	conservative[c]
Third-generation cephalosporins	106 (86–120)	102	maintain below threshold	16 (16)
Carbapenems	142 (140–149)	135	maintain below threshold	maintain below threshold

[a]Estimated by multiplying the identified threshold in Table 1 (DDD/100 OBD) by the size of the population (OBD) and then dividing by an average patient treatment (7 DDD).

[b]Estimated by using the identified threshold (106 for third-generation cephalosporins and 142 for carbapenems).

[c]Estimated by using the lower limit as the threshold (86 for third-generation cephalosporins and 140 for carbapenems).

Table 3. Percentage of months, for third-generation cephalosporins, carbapenems and ABHR exceeding identified thresholds

		Percentage of months exceeding threshold		
Policy	Months	third-generation cephalosporins	carbapenems	ABHR
Pre-intervention	49	18%	29%	6%
Intervention	23	26%	17%	17%
Change		8%	−12%	11%