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10.1093/jac/dkab073".

Title: Do specific antimicrobial stewardship interventions have an impact on carbapenem resistance in Gram-negative bacilli? A multicentre quasi-experimental ecological study: time-trend analysis and characterization of ~~the~~ carbapenemases.

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Abstract

Background

Carbapenem-resistant Gram-negative bacilli (CR-GNB) are among the most threatening microorganisms worldwide and carbapenems use facilitates their spread. Antimicrobial stewardship programmes (ASP) can help to optimize the use of antibiotics.

This study evaluates the impact of a multifaceted educational ASP on carbapenem use and on the epidemiology of CR-GNB.

Methods

We conducted a quasi-experimental, time-series study in seven hospitals, from January 2014 to September 2018. The key intervention was composed of educational interviews promoting the appropriate use of carbapenems. The primary endpoints were carbapenems consumption and incidence density (ID) of CR-GNB. All the non-duplicated ~~clinical isolates of~~ CR-GNB clinical isolates were tested using phenotypic assays and PCR for the presence of carbapenemases. Joinpoint regression and interrupted time-series analys~~i~~es were used to determine trends.

Results

A decrease in carbapenems consumption throughout the study period (average quarterly percentage change [AQPC] -1.5%, ~~p-value~~ *P* =<0.001) and a -8.170 (-16.064 to -0.277) level change following the intervention were observed. The ID of CR-*A. baumannii* decreased (AQPC -3.5%, *P* = 0.02) and the overall ID of CR-GNB remained stable (AQPC -0.4%, ~~p-value~~ *P* =0.52). CR-GNB, CR-*P. aeruginosa,* and CR-*A. baumannii*

IDs per hospital correlated with the local consumption of carbapenems. The most prevalent carbapenem resistance mechanisms were OXA-23 for CR-*A. baumannii* (76.1%), OXA-48 for CR-*K. pneumoniae* (66%), and no-carbapenemases for CR-*P. aeruginosa* (91.7%). The epidemiology of carbapenemases was heterogeneous throughout the study, especially for carbapenemase-producing Enterobacteriaceae.

Conclusions

In conclusion, a multifaceted, educational interview-based ASP targeting carbapenem prescribing reduced carbapenem use and CR-*A. baumannii* ID.

Introduction

Carbapenem-resistant Gram-negative bacilli (CR-GNB) stand out among the urgent threats to global public health.[1] Optimizing the use of antibiotics is a key measure to combat resistance[1-3]. The Institutional Programme for the Prevention and Control of Healthcare Associated Infections and Antimicrobial Stewardship (PIRASOA), based on educational face-to-face interviews addressing antimicrobial prescribing, was implemented in 2014 in all the public care centres of Andalusia, Spain (31 hospitals and 27 primary care districts).[4]. This programme led to a reduction of inappropriate antimicrobial treatment rates~~, reduced~~ and ~~the~~ antimicrobial consumption, and had a positive ecologic impact on bacterial resistance ~~at level of~~ in an entire healthcare system[~~6~~5]. Several quarters after the PIRASOA programme's implementation, the carbapenems use and the epidemiology of CR-GNB was heterogeneous across the participating hospitals. We hypothesized that the implementation of a specific antimicrobial-stewardship programme (ASP) in cent~~e~~res with high~~er~~ rates of carbapenem~~s~~ consumption would help to reduce their use and ~~to~~ control the emergence of CR-GNBs.

The objective of the present study was to assess the impact of a multifaceted educational ASP targeting carbapenems use and to describe the prevalence and diversity of the carbapenemases found in CR-GNB in the participating hospitals.

Patients and methods

Study design

Seven hospitals (five university hospitals and two specialty hospitals) from Andalusia, Spain, with carbapenems use above the region's average were included in this quasi-experimental, time-series study. The study was divided into an 11-quarter pre-intervention period (01 January 2014 [start of the PIRASOA programme] to 30 September 2016) and an 8-quarter intervention period (01 October 2016 [start of the intervention on the use of carbapenems] to 30 September 2018).

Ethics

Study approval was granted by the ethics committee of the University Hospital Virgen del Rocío (code RAM-PIR-2016-01) and valid for all the participating centres.

Procedures

The intervention ~~comprised~~ had four components addressing carbapenems prescri~~ptions~~bing: the establishment of local guidelines, the performance of educational interviews, the setting of alerts in the e-prescribing software, and the provision of feedback information to all the staff.

Each local research team established and validated their own guidelines, which included the appropriate indications for initiating carbapenems therapy based on the local epidemiology and the best available evidence. Despite their local adaptation, the main indications for carbapenem prescribing were quite homogeneous across the different guidelines. A common document encouraging de-escalation was also distributed (Supplementary material, Figure S1).

The educational interviews, performed as described elsewhere,[6] were the core activity of the programme. Members of the local teams selected a carbapenem

prescription at their discretion, and then held one-to-one educational interview with the prescribing physician, reviewing key aspects of the antimicrobial therapy and microbiological diagnosis. The interviews followed a structured questionnaire (Supplementary material, Form S2). Prescriptions were classified as "appropriate" when all the items evaluated received an appropriate answer. No changes in the prescription were required.

Two types of alerts were generated by the prescription software: 1) automatic messages after each new carbapenems prescription warning about their strategic relevance and suggesting changes in line with the local guidelines, and 2) customized messages after 48-72 hours, suggesting a de-escalation when indicated based on the review of the case.

A feedback report on carbapenems use and CR-GNB incidence was provided annually by the local team to the different units of their hospital.

All these measures were incorporated into the general components of the PIRASOA programme.

Variables and indicators

Intervention compliance was assessed through the number of educational interviews targeting carbapenems prescriptions, and adherence to the local guidelines was evaluated through the following indicators: proportion of prescriptions rated as appropriate, and proportion of accomplishment of each component of the ASP, by hospital and quarter. To contextualize, we also assessed the total number of educational interviews performed for all antimicrobial prescriptions.

The main dependent variable was the carbapenems (meropenem, imipenem, and ertapenem) use. To control for the "squeezing balloon" phenomenon,[7] the consumption of antipseudomonal cephalosporins (ceftazidime, cefepime) and piperacillin-tazobactam was also monitored. Data were expressed as DDD per 1000 patient-day.

The incidence density (ID) of infections or colonizations caused by MDR-*A. baumannii* (defined as resistant to meropenem and/or imipenem), MDR-*P. aeruginosa* (defined as resistant to meropenem and/or imipenem, and to ceftazidime), and carbapenemase-producing Enterobacteriaceae (CPE) was measured and expressed as number of cases per 1000 patient~~s~~-day. Isolates obtained from clinical samples only, and not from screening samples, were used to estimate infection/colonization ID. The incidence of bloodstream infections (BSI) caused by these organisms and their 14-day~~s~~ crude mortality was recorded. Additionally, the ID of infections or colonizations by ESBL-producing *Escherichia coli* or *Klebsiella pneumoniae* was also assessed, as well as the incidence of BSI caused by them and the 14-day~~s~~ crude mortality resulting from these episodes of bactaeremia.

Most of the information was obtained from the PIRASOA web platform database~~s~~.[4] The incidence and associated mortality of BSI caused by different species were only available for the intervention period.

All the variables were recorded quarterly.

Microbiological procedures

All the non-duplicated clinical isolates of CPE (ertapenem MIC value >0.25 mg/L, according to EUCAST recommendations),~~—~~[8] CR-*A. baumannii*, and CR-*P.*

aeruginosa (both imipenem and/or meropenem resistant according to EUCAST criteria)[8] collected during the ~~post-~~intervention period were analysed for the presence of carbapenemases. In addition to the isolates obtained from the hospitals participating in the quasi-experimental intervention study, we also obtained isolates of the same microorganisms during the same time period of time from an other university hospital in the same region that could not implement the intervention. All isolates were characterized in a central laboratory as follows: a) identification through MALDI-TOF; b) susceptibility testing by agar diffusion with disks, testing ertapenem, imipenem, and meropenem, as well as combination disk test (Rosco, Denmark) ~~which~~ containing meropenem +/- various inhibitors (cloxacilline, dipicolinic acid, and boronic acid); and c) detection by PCR of various carbapenemases with specific primers: OXA-23, OXA-24/40, and OXA-58 for *A. baumannii,*[9] and OXA-48, KPC, NDM, IMP, and VIM for all the isolates.[10]

Statistical analysis

We performed a joinpoint regression analysis[11] to model trend patterns over time and identify significant points of change in the slope of each antibiotic and resistant pathogen time series under study with the Joinpoint Regression Program, version 4.7.0.0.[–12] Trend segments were characterized by the quarterly percentage change (QPC) with the corresponding 95% CI estimated by using log-transformed data and autocorrelated error models of the software in order to account for autocorrelation of data from one quarter to the next. The average QPC (AQPC) was calculated to define each overall time series trend. We used the permutation method to identify the points in time at which trends changed.[11] The maximum number of

joinpoints was set at three, based on the length of the time series. A two-sided *P*-value of <0.05 was considered as statistically significant.

There was an unexpected and global shortage of piperacillin/tazobactam during the third quarter of 2017. We used an interrupted time-series analysis (ITS),[13] to assess the impact of the intervention on carbapenem prescribing and the impact of piperacillin-tazobactam shortage, performing a longitudinal segmented regression with autoregressive moving-average modelling, allowing to estimate changes in levels or trends of antibiotic use related to the intervention, and accounting for detected outliers. We used the Akaike information criterion for model selection.

We also performed a descriptive statistical analysis and used Spearman's correlation coefficient to assess the association between educational interviews and appropriate prescriptionsbing, and between CR-GNB ID and carbapenems consumption per quarter and hospital. ITS, descriptive, and correlation analyses were performed by using R software, version 3.5.1.[14]

Results

Intervention

During the intervention period, a total of 6046 educational interviews on antibiotic prescriptions were carried out, with a range of 406-1828 per hospital. Of these, 1747 involved carbapenems prescriptions (range per hospital: 149-397)–and 61% were classified as appropriate. The rate of appropriate carbapenems prescriptions showed a significant positive correlation with the number of educational interviews per quarters (*rho*=0.89 [95%CI; 0.80 to 0.94] *P* <0.0001).

Antibiotic use

The use of carbapenems decreased throughout the whole study period with a significant AQPC of -1.5%, as shown in Table 1 and Figure 1 (joinpoint regression analysis). The ITS analysis revealed a change of level of -8.170 (-16.064 to -0.277) following the start of the intervention (Figure 2). The overall antimicrobial~~s~~ use also decreased, remaining stable after the second quarter of 2016. Piperacillin-tazobactam use showed a decrease throughout the whole period, parallel to that of carbapenems, while the consumption of the ~~analyzed~~ cephalosporins studied exhibited different trend changes, with a net increase of 9 DDD/1000 patient~~s~~-day between the first and the last quarter of the overall period (Table 1, Figure 1).

There was a global shortage of piperacillin/tazobactam during the third quarter of 2017. An ITS analysis of the impact of this unintended intervention detected significant outliers in this quarter for the use of piperacillin/tazobactam (-21.181 [95%CI -25.976 to -16.386] DDD/1000 patient~~s~~-days, *P* <0.001), for carbapenems (+7.660 [95%CI 2.612 to 12.709] DDD/1000 patient~~s~~-days, *P* =0.01), and for ceftazidime+cefepime (+13.878 [95%CI 4.361 to 23.396] DDD/1000 patients-days, *P* =0.013).

Changes in carbapenems use were heterogeneous when the hospitals were analysed separately (Supplemental material, Figure S3). There was a net decrease in the use of carbapenems in three centres, with an average reduction of -29.6% (range -15.4% to -48.3%) between the pre-intervention and intervention periods and AQPCs of the overall trend ranged from -1.4% to -4.2%. In a further three hospitals, trends fluctuated throughout the study period and the overall trend did not change

significantly. In another hospital, the use of carbapenems was 6.8% higher during the intervention period compared to the pre-intervention period; the overall trend showed an AQPC of +0.9% (*P* =0.028).

The total number of educational interviews per hospital was correlated with a decrease in carbapenems use (*rho*=-0.768, *P* =0.044). However, we could not find a correlation between the number of specific educational interviews on carbapenems prescriptions and carbapenems use (*rho*=-0.559, ~~p~~ *P* =0.192). (Supplementary material, Figure S~~3~~4)

Incidence density and clinical impact of CR-GNB.

The overall CR-GNB ID ~~of CR-GNB~~ remained stable during the study period. When analysed separately, the ID of CR-*A. baumannii* decreased, the ID of CR-*P. aeruginosa* remained stable, and the ID of CPE showed a sustained increase throughout the whole study period (Table 2 and Figure 3). These trends did not change following the start of the intervention. ~~The ID of~~ CR-GNB, CR-*P. aeruginosa* and CR-*A. baumannii* IDs were correlated with carbapenems consumption per hospital and quarter, but not CPE ID (Table 3).

The ID of ESBL-Enterobacteriaceae showed stable trends, without changes during the intervention period. *C. difficile* ID increased initially during the first pre-intervention year-and then remained stable ~~ID~~ until the end of the study period. (Table 2 and Figure 3).

The frequency of BSI caused by CR-GNB and their associated mortality remained stable. There were 43 episodes of CPE bacteraemia, 52 of CR-*P. aeruginosa*

bacteraemia and 23 of CR-*A. baumannii* bacteraemia; their associated mortality was 30.2%, 42.3%, and 39.1%, respectively.

Carbapenems resistance mechanisms

During the intervention period, 1401 GNB isolates were received in the central laboratory (antibiogram results in Supplemetary material, Table S5). Among them, 1244 (88.8%) were carbapenem-non susceptible and were tested for the presence of carbapenemases: 592 (47.6%) were CR-*P. aeruginosa* isolates, 359 (28.8%) CR-*K. pneumoniae,* 222 (17.8%) CR-*A. baumannii,* 65 (5.2%) other species of CR-Enterobacteriaceae, and 4 (0.3%) ~~of~~ other species of CR-*Pseudomonas* spp. Among these isolates, 616 (49.5%) were carbapenemase-producers, with an unequal distribution per species: 212 (95.5%) of the CR-*A. baumannii* isolates carried carbapenemases, 315 (87.7%) of the CR-*K. pneumoniae* isolates, 65 (78.4%) of the other CR-enterobacterales, 49 (8.3%) of the isolates of CR-*P. aeruginosa* and 2 (50%) of the non-*aeruginosa Pseudomonas* spp. isolates.

The most prevalent resistance mechanisms were OXA-23 for CR-*A. baumannii* (76.1%), OXA-48 for CR-*K. pneumoniae* (66%), and VIM for other CR-Enterobacteriaceae (40%) or CR-*Pseudomonas* spp. – non *aeruginosa* (50%); most CR-*P. aeruginosa* did not produce any carbapenemase (91.7%). However, the epidemiology of the CR-GNB and their resistance mechanisms varied between hospitals, as shown in Table 4. There was a clear predominance of specific carbapenemase groups according to the centres: 82% of OXA-48 producers were detected in two hospitals (HVV and HRM) in the same city, 69% of KPC producers in ~~2~~another two hospitals (HPM and HVN), 64% of IMP producers in one centre (HVN),

297 67% of NDM producers in one centre (HT) and 61% of OXA-23 producers in 2two
298 centres (HJ and HVN). In particular, the distribution of carbapenemases among the
299 Enterobacteriaceae showed a significant diversity throughout the study period among
300 hospitals (Supplementary material, Figure S6). Eighty-two percent of OXA-48-
301 producing Enterobacteriaceae were concentrated in two hospitals (HRM and HVV),
302 although they showed different trend lines (Supplementary material, Figure S7): the
303 hospital with more cases (58.2%) showed a sustained upward trend (AQPC=5.2%; *P*
304 <0.05) while the other one, with fewer cases (23.8%),-showed a reduction starting in
305 the third quarter (AQPC=-22.7%; *P* <0.05).
306
307 Discussion
308 A reduction carbapenems use and CR-*A. baumannii* ID was achieved during a
309 multifaceted, education-based ASP targeting carbapenems, implemented in seven
310 Spanish hospitals. Furthermore, CR-*P. aeruginosa* and CR-*A. baumannii* IDs were
311 correlated with the carbapenems consumption.
312
313 Previous ASPs have demonstrated their utility in reducing carbapenem
314 consumption[14-20]. The present study provides additional tools (in particular the
315 targeted educational interview) to achieve this and analyses their impact not only on
316 antibiotic prescribing, but also on CR-GNB ID. The characterization of the resistance
317 mechanisms has enabled us to better define the ecology of the setting where these
318 measures were applied. In addition, the multicentre design of the study and the time-
319 series analysis give robustness to the conclusions.
320 *Carbapenem use reduction: the efficacy of educational interviews*

Educational interview-based ASPs have shown to be effective in reducing the global use of antimicrobials as well as the use of carbapenems at both hospital[6] and whole public health system levels.[5] However, they have always been evaluated as global programmes. The present study included hospitals that continued showing a high use of carbapenems despite the implementation of an underlying general ASP. The addition of a specific programme led to the achievement of the goal of sparing carbapenem usage. Thus, this finding should be interpreted as the result of a synergistic effect of both programmes. This is further supported by the results of the ITS analysis and the correlation found between the local reduction of carbapenems use and the total number of educational interviews, suggesting that holistic educational programmes may help to expand the use of narrower spectrum antibiotics. Such a shift in prescribing behaviour has been previously described in a primary care setting as a benefit of implementing similar educational interview-based ASPs.[21]

Notably, the reduction in carbapenem consumption was achieved without adopting restrictive measures, using educational interventions only. Restriction-based ASPs are a more common option when the target is a specific group of antibiotics because of their faster effect, but their acceptance is lower and their impact is usually shorter-term.[15]

Finally, this result was achieved despite the fact that the unpredicted shortage of piperacillin-tazobactam caused an increase in carbapenem consumption in the third quarter of 2017.

Heterogeneous trends in CR-GNB ID

During the study period, the ID of the different CR-GNB studied showed different trends: an overall decrease ~~of~~ in CR-*A. baumannii* ID was found, CR-*P.*

345 *aeruginosa* ID remained stable, and CPE ID increased. These results are in line with
346 previous studies: although diverse strategies have succeeded in sparing carbapenem
347 usage,[16-22] a secondary reduction of CR-GNB has been found just in a few cases.[19-21,23]

348 Although only the ID of CR-*A. baumannii* decreased during the study period, we
349 found a significant correlation between carbapenem consumption and CR-*A.*
350 *baumannii* and CR-*P. aeruginosa* IDs. Low coefficients indicate that the antibiotic
351 pressure was relevant but not sufficient to predict these microorganisms' IDs.
352 However, the presence of correlation suggests that a higher carbapenem reduction or
353 a longer intervention might have reduced the ID of CR-*P. aeruginosa,* as has occurred
354 in previous studies, such as Abdallah *et al.'s*[19] study where a decrease in CR-*P.*
355 *aeruginosa* ID was described after a 60% drop in carbapenem use.

356 In the case of CPE, carbapenem use predicts their spread in high-prevalence
357 contexts,[24] but this relationship has not been validated in low-prevalence settings.[25,26]
358 We observed an overall low incidence of CPE, even after the rise detected throughout
359 the study period. However, this increase occurred in the context of the global upward
360 trend observed in Spain in recent years, and its growth rate was smaller than the
361 country's overall trend.[27] In this context, an ASP aimed at sparing carbapenems usage
362 may have helped to attenuate the rising trend.

363

364 *Study limitations*

365 Our study has several limitations. Firstly, we analysed aggregated data; this
366 "ecologic bias" prevents extrapolating the results to the patient level.[28] Secondly,
367 certain variables that may have an influence on CR-GNB ID, such as concurrent
368 infection control measures or the use of fluoroquinolones. The latter increases the risk

of dissemination of CR-GNB [29,30] and neither their use nor the number of educational interviews on fluoroquinolones prescriptions were analyzed. In addition, the duration of the study or the reduction in carbapenem use may have been insufficient to achieve the objective of reducing the incidence of CR-GNB. Thirdly, the clonal relationship between the microbial isolates was not investigated and therefore, the presence and extension of outbreaks could not be accurately characterized.

In conclusion, a multifaceted, educational interview-based ASP targeting carbapenem prescribing reduced carbapenem use and CR-*A. baumannii* ID.

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Table 1. Trends in the use of antimicrobials throughout the study period (joinpoint regression analysis).

	Overall trend	Segment 1	Segment 2	Segment 3	Segment 4

DDD per 1000 stays	AQPC (*P* value)	QPC (*P* value)	QPC (*P* value)	QPC (*P* value)	QPC (*P* value)
Overall antimicrobials	-0.5% (0.002)	2014Q1-2016Q2 -1.0% (0.001)	2016Q2-2018Q3 -0.1% (0.86)		
Carbapenems	-1.5% (<0.0001)	2014Q1-2018Q3 -1.5% (<0.0001)			
CFZ + CFP	+1.0% (0.59)	2014Q1-2015Q1 -6.9% (0.04)	2015Q1-2016Q3 +5.6% (0.03)	2016Q3-2017Q2 +18.2% (0.12)	2017Q2-2018Q3 -6.8% (0.003)
Piperacillin-tazobactam	-1.5% (0.007)	2014Q1-2018Q3 -1.5% (0.007)			

Table 2. Trends in the ID of CR-GNB, ESBL-producing Enterobacteriaceae and *C. difficile* (joinpoint regression analysis).

Incidence density	**Overall trend**	**Segment 1**	**Segment 2**
Isolates per 1000 stays	AQPC (*P* value)	QPC (*P* value)	QPC (*P* value)
Carbapenem resistant Gram-negative bacilli	-0.4% (0.52)	2014Q1-2018Q3 -0.4% (0.52)	
Carbapenemase-producing Enterobacteriaceae	+4.0% (0.001)	2014Q1-2018Q3 +4.0% (0.001)	
Carbapenem-resistant *Pseudomonas aeruginosa*	-0.2% (0.864)	2014Q1-2018Q3 -0.2% (0.864)	
Carbapenem-resistant *Acinetobacter baumannii*	-3.5% (0.02)	2014Q1-2018Q3 -3.5% (0.02)	

ESBL-*Escherichia coli*	+0.5% (0.43)	2014Q1-2018Q3 +0.5% (0.43)	
ESBL-*Klebsiella pneumoniae*	+0.6% (0.58)	2014Q1-2018Q3 +0.6% (0.58)	
Clostridioides difficile	+2.8% (0.13)	2014Q1-2015Q1 +15.2% (0.08)	2015Q1-2018Q3 -0.5% (0.56

AQPC, average quarterly percentage change; QPC, quarterly percentage change; ESBL, extended-spectrum β-lactamase producing.

Table 3. Correlation between the incidence density of CR-GNB and the use of carbapenems (Spearman correlation).

Pathogen	**cc**	**~~p~~ *P* value**	**95%CI**
CR-GNB	**0.26**	**0.003**	0.10 to 0.41
CPE	-0.08	0.34	-0.26 to 0.11
CR-*P. aeruginosa*	**0.18**	**0.044**	0.02 to 0.33
CR-*A. baumannii*	**0.18**	**0.042**	0.002 to 0.35

CR-GNB, carbapenem-resistant Gram-negative bacilli; CPE, carbapenemase-producing Enterobacteriaceae.

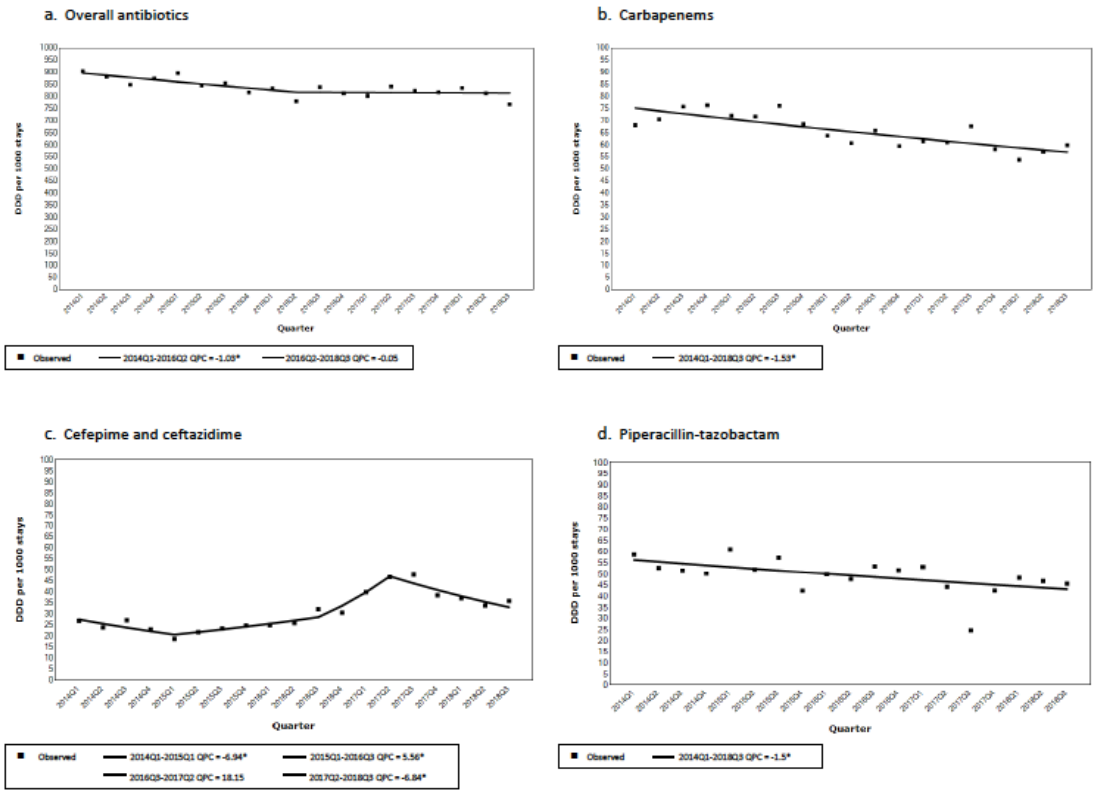
Table 4. Distribution of the main determinants among the different CR-GNB (global and local distribution).

Specie	**Resistance mechanism**	**Total** n (%)	**Hospitals**						
			HJ n	**HPM** n	**HRM** n	**HT** n	**HVV** n	**HVN** n	**HVR** n
A. baumannii n=222	OXA-58	32 (14.4)	1	19	0	1	1	7	3
	OXA-23	169 (76.1)	64	7	18	0	17	40	23
	OXA-24/40	8 (3.6)	0	1	0	0	0	0	7
	NDM	2 (0.9)	0	1	1	0	0	0	0
	VIM	1 (0.5)	0	0	1	0	0	0	0
	No carbapenemase	10 (4.5)	2	1	5	0	0	1	1
	Total	222 (100)	67	29	25	1	18	48	34

P. aeruginosa n=592	KPC	1 (0.2)	0	1	0	0	0	0	0
	IMP	16 (2.7)	0	0	0	2	1	12	1
	VIM	32 (5.4)	5	1	6	14	0	5	1
	No carbapenemase	543 (91.7)	63	33	67	111	45	96	128
	Total	592 (100)	68	35	73	127	46	113	130
K. pneumoniae n=359	KPC	49 (13.6)	4	24	5	1	1	10	4
	NDM	18 (5)	0	0	1	13	1	0	3
	OXA-48	237 (66)	16	15	141	2	54	3	6
	IMP	1 (0.3)	0	0	0	0	0	1	0
	VIM	10 (2.8)	2	1	2	0	0	5	0
	No carbapenemase	46 (12.8)	2	5	9	8	2	2	18
	Total	359 (100)	24	45	157	24	58	21	31
Enterobacterales (non *K. pneumoniae*) n=65	NDM	1 (1.5)	0	0	0	1	0	0	0
	OXA-48	19 (29.2)	1	1	8	1	7	0	1
	IMP	5 (7.7)	0	0	0	4	0	1	0
	VIM	26 (40)	3	7	4	2	1	9	0
	No carbapenemase	15 (23.1)	0	1	6	3	0	2	3

	Total	65 (100)	4	9	18	11	8	12	4
Pseudomonas spp. (non *P. aeruginosa*) n=4	VIM	2 (50)	1	0	0	0	0	1	0
	No carbapenemase	2 (50)	0	0	2	0	0	0	0
	Total	4 (100)	1	0	2	0	0	1	0

Figure 1. Trends in antibiotic use throughout the study period (joinpoint regression analysis).



QPC, quarterly percent change; * Indicates that the QPC is significantly different from zero at the alpha = 0.05 level

574 Figure 2. Interrupted time-series analysis of carbapenems use.

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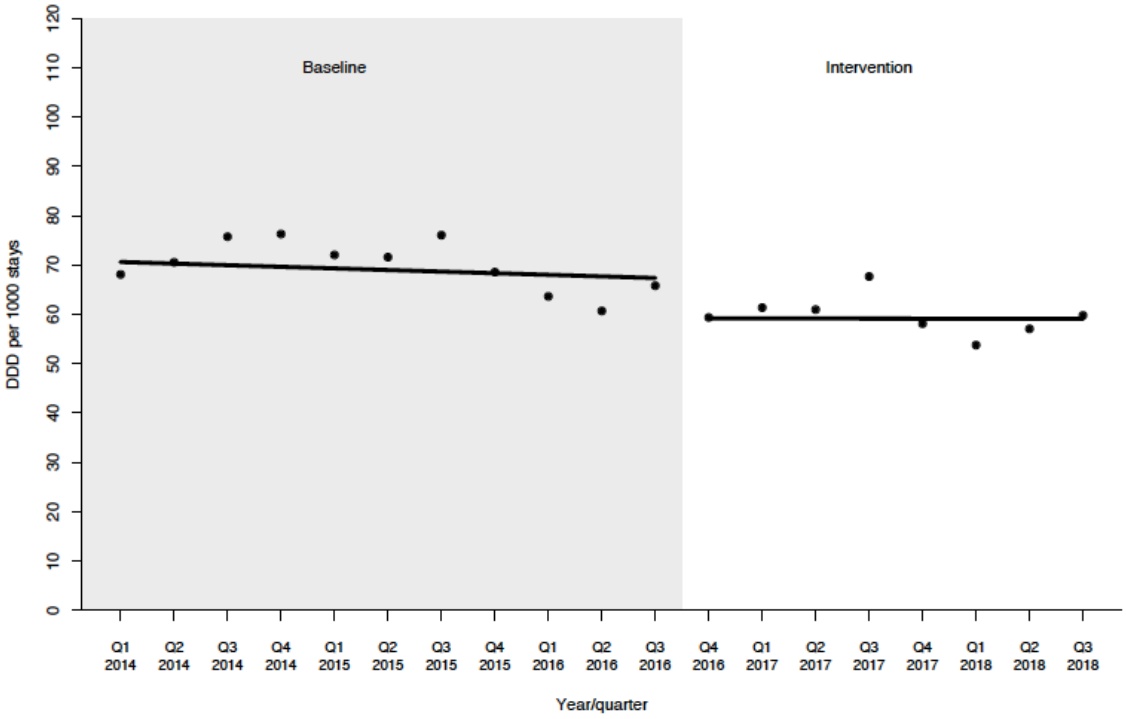

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577 Figures 3. Trends in CR-GNB, ESBL-producing Enterobacteriaceae, and *C. difficile* IDs

578 (joinpoint regression analysis).

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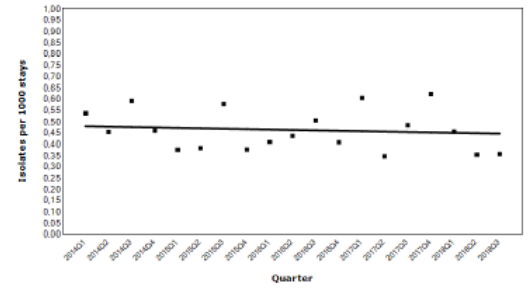
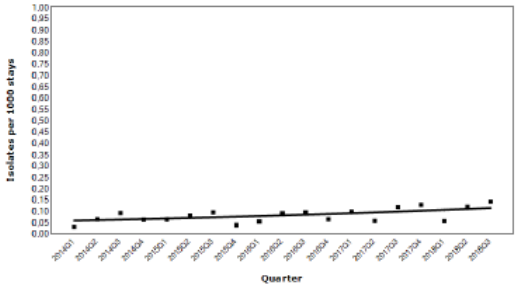
a. Carbapenem-resistant Gram-negative bacilli



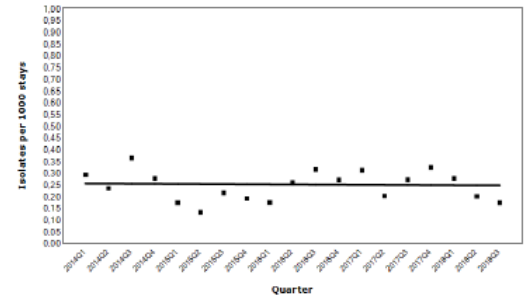
Observed — 2014Q1-2018Q3 QPC = -0.4

b. Carbapenemase-producing Enterobacteriaceae



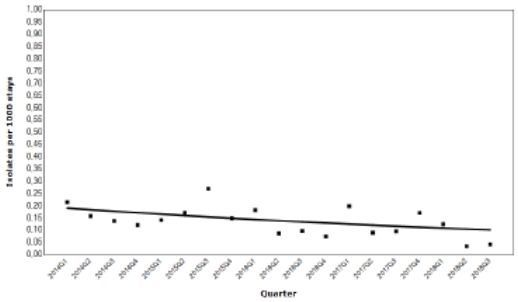
Observed — 2014Q1-2018Q3 QPC = 4.0*

c. Carbapenem-resistant *Pseudomonas aeruginosa*



Observed — 2014Q1-2018Q3 QPC = -0.2

d. Carbapenem-resistant *Acinetobacter baumannii*



Observed — 2014Q1-2018Q3 QPC = -3.46*

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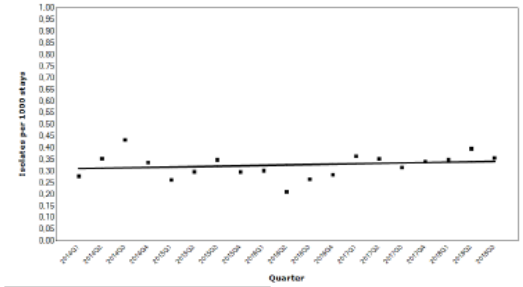
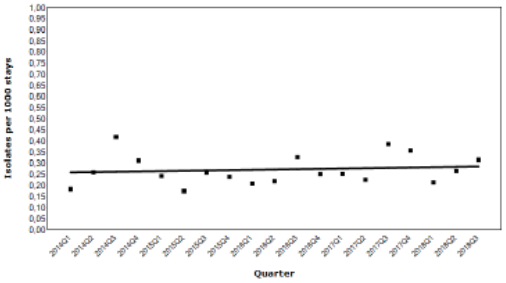
e. ESBL-producing *Escherichia coli*



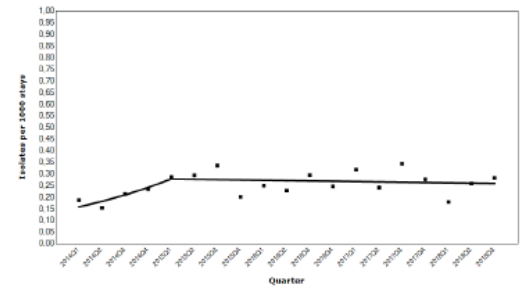
Observed — 2014Q1-2018Q3 QPC = 0.53

f. ESBL-producing *Klebsiella pneumoniae*



Observed — 2014Q1-2018Q3 QPC = 0.6

g. *Clostridioides difficile*



Observed — 2014Q1-2015Q1 QPC = 15.21 — 2015Q1-2018Q3 QPC = -0.50

581 QPC, quarterly percent change; * Indicates that the QPC is significantly different from zero at the alpha = 0.05 level

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