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Meropenem Antimicrobial Stewardship Program: clinical, economic and antibiotic resistance impact.

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Abstract:	Background. There are few prospective studies with sufficient duration in time to evaluate clinical and antibiotic resistance impact of Antibiotic Stewardship Programs (ASP). Methods. Descriptive study between January-2012 to December-2017, pre-post-intervention. An meropenem ASP was initiated in January 2015, in patients who started treatment with meropenem an infectious diseases physician performed treatment recommendations to prescribers. Prospective information was collected to evaluate adequacy of meropenem prescription to local guidelines and to compare results between cases with accepted or rejected intervention. Analysis was performed to verify variables associated with intervention acceptance and with any significant change in meropenem consumption, hospital-acquired multidrug-resistant (MDR) bloodstream infections (BSIs) and 30-day all-cause crude death in MDR BSIs. Results. Adequacy of meropenem prescription and de-escalation from meropenem treatment to narrower-spectrum antibiotic improved progressively over time, after ASP implementation (p <0.001). Interventions on prescription were performed in 330 (38.7%) patients without meropenem justified treatment, in 269 intervention was accepted and in 61 not. Intervention acceptance was associated with shorter duration of treatment, cost and inpatient days (p<0.05); intervention rejection was not associated with severity of patient. During the period 2015-2017, meropenem consumption decreased compared with 2012-2014 [Rate ratio (RR) 0.67; 95%CI: 0.58-0.77, p<0.001]). Likewise decreased, hospital-acquired MDR BSIs rate (RR 0.63; 95%CI: 0.38-1.02, p=0,048) and 30-day all-cause crude death in MDR BSIs (RR 0.45; 95%CI: 0.14-1.24, p=0.09), coinciding in time with ASP start-up. Conclusions. The decrease and better use of meropenem achieved had a sustained

	clinical, economic and ecological impact, reducing costs and mortality of hospital-acquired MDR BSIs.
Response to Reviewers:	Ferrol, October 16th 2018 To the European Journal of Clinical Microbiology and Infection Diseases Editorial Office Dear Editor, We appreciate the valuable reviewers´comments for our manuscript “Meropenem Antimicrobial Stewardship Program: clinical, economic and antibiotic resistance impact” (EJCM-D-18-00706). Please, find hereunder our replies to the reviewers´ comments, in a point-by-point manner. Page 2, line 3: “The authors introduce a five year screening period here but if I read correctly there is only two years of detailed follow up int he end. Two questions: if this is so then correct the timelines and if this is so, then please state whether two years is sufficient follow up or whether a longer term would be needed. Rendering the current paper a bit preliminary ....” Corresponding author´s response: Descriptive study between January-2012 and December-2017, pre-post-intervention. Page 2, Result section: “Somewhere in the text the authors state that the use of handwashing alcohol increased over the study period. So are there other potential confounders here? I am also missing the overall antibiotic use in the hospital during the the study years. How did that evolve? Anything else of relevance that evolved???” Corresponding author´s response in page 10, lines 1-4 The alcohol-based hand-rub consumption increased progressively from 2012 to 2017, about 9.9% per year, without there being a significant change in this annual increase between the pre and post-intervention period. The overall antibiotic use in the hospital during the study years increased from 94.7 DDD/100 OBDs in 2012-2014 to 105.8 DDD/100 OBDs in 2015-2017. Page 3, lines 1-6: “Delete, textbook stuff”. Corresponding author´s response: Despite what is said in this paragraph is evident, we consider this statement describes the rationale to justify our work. Page 5, lines 5-7: “It is OK to exclude double treatments unless it happens very frequently. Can you quantify this a bit??” Corresponding author´s response: Patients who received more than one course of meropenem during their hospitalization (29 patients) were only included once in the study. Page 6, lines 14-19: “So if I understand it correctly the authors used the number of BSIs caused by a restricted set of bacterial species as a proxy for resistance. This seems very strange to me and should be explained in more detail”. Corresponding author´s response: In order to assess the impact on the antibiotic resistance, we analyzed between January 2012 and December 2017 the evolution of incidence density per 1000 OBDs of hospital-acquired BSIs produced by the most frequently isolated microorganisms (coagulase-negative Sthaphylococi excluded): Pseudomonas aeruginosa, Klebsiella spp, E. coli, Enterobacter spp, Staphyloccoccus aureus and Candida spp, between 2012 and 2017. Page 8, lines 6-8: “I do not understand this sentences and it seems to be an important

	one. There seems to be some sort of an omission. Please clarify". Corresponding author´s response: Out of the 852 patients who received treatment with meropenem, in 522 of them the treatment was considered justified because it was adapted to the local empirical treatment guidelines; in 330 (38.7%) the treatment was not considered justified and interventions were performed at the suggestion of appropriate alternative treatment: in 269 (81.5%) of them, the intervention was accepted and in 61 it was not. Page 9, lines 13-15: "Do I understand correctly, again, that the authors state here that the "resistant BSIs" went down and the "susceptible BSIs" went up? So with ASP you prevent a certain category of infections which is then compensated by a set of others? How would then the overall net reduction for BSI on the whole be? And if that does not change then where is the economic and medical benefit??" Corresponding author´s response: The global incidence of bacteraemia adjusted by 1000 OBDs increased by 3.5% during the period 2015-2017 vs 2012-2014. The incidence density of candidemia and MDR BSIs acquired in hospital decreased after ASP start-up in a parallel fashion with the decrease in use of meropenem (Figures 2, 3). In 2015-2017 hospital-acquired MDR BSIs rate was 0.084/1000 OBDs vs 0.133 in 2012-2014 (RR 0.63; 95%CI: 0.38-1.02, p=0.048). Conversely, the incidence density of in-hospital acquired BSIs produced by non-MDR strains of the same microorganisms under study increased 8% during the intervention period (RR 1.08; 95%CI: 0.78-1.51), (Table 4). Page 12, lines 7-8: "Making statements on behaviour is nice but completely out of scope here. Niceness cannot be quantified easily and prior to making statements as you do, data would be needed...." Corresponding author´s response: On page 8, line 12-13 we have included: "the degree of intervention acceptance varied according to prescriber (between 29% to 100%) and infection localization" Our experience and results show that there are some prescribers that are unwilling to accet interventions, but we consider inappropriate to go deeply in detailing to avoid causing discomfort among hospital professionals. Table 1: "There are shiploads of significant differences here that I see hardly explained in the text .... Are all of these negligable with respect to the effect measured in this study????" Corresponding author´s response: We comment in page 12, line 9-11 that "with our intervention we have decreased the incidence of hospital-acquired MDR BSIs and associated mortality despite having increased the total incidence of bacteraemia and global consumption of antibiotics". and in page 12, line 22 "but it does not seem that other variables influenced the results of the study". Thank you very much for your time spent on reevaluating our manuscript. Sincerely yours, Dr. José Francisco García-Rodríguez Infectious Diseases Unit. Department of Internal Medicine. University Hospital of Ferrol, A Coruña, Spain jose.francisco.garcia.rodriguez@sergas.es

Meropenem Antimicrobial Stewardship Program: clinical, economic and antibiotic resistance impact.

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Background. There are few prospective studies with sufficient duration in time to evaluate clinical and antibiotic resistance impact of Antibiotic Stewardship Programs (ASP).

Methods. Descriptive study between January-2012 and December-2017, pre-post-intervention. An meropenem ASP was initiated in January 2015, in patients who started treatment with meropenem an infectious diseases physician performed treatment recommendations to prescribers. Prospective information was collected to evaluate adequacy of meropenem prescription to local guidelines and to compare results between cases with accepted or rejected intervention. Analysis was performed to verify variables associated with intervention acceptance and with any significant change in meropenem consumption, hospital-acquired multidrug-resistant (MDR) bloodstream infections (BSIs) and 30-day all-cause crude death in MDR BSIs.

Results. Adequacy of meropenem prescription and de-escalation from meropenem treatment to narrower-spectrum antibiotic improved progressively over time, after ASP implementation ($p < 0.001$). Interventions on prescription were performed in 330 (38.7%) patients without meropenem justified treatment, in 269 intervention was accepted and in 61 not. Intervention acceptance was associated with shorter duration of treatment, cost and inpatient days ($p<0.05$); intervention rejection was not associated with severity of patient. During the period 2015-2017, meropenem consumption decreased compared with 2012-2014 [Rate ratio (RR) 0.67; 95%CI: 0.58-0.77, $p<0.001$]). Likewise decreased, hospital-acquired MDR BSIs rate (RR 0.63; 95%CI: 0.38-1.02, p=0,048) and 30-day all-cause crude death in MDR BSIs (RR 0.45; 95%CI: 0.14-1.24, p=0.096), coinciding in time with ASP start-up.

Conclusions. The decrease and better use of meropenem achieved had a sustained clinical, economic and ecological impact, reducing costs and mortality of hospital-acquired MDR BSIs.

Keywords. Antimicrobial stewardship; multidrug-resistant; hospital infections; bloodstream infections; carbapenems.

Introduction. Antibiotics are effective drugs in reducing morbidity and mortality of patients, but they have ecological effects such as the appearance and spread of bacterial resistance. Bacterial resistance to antibiotics is a global problem of such magnitude that more than 163 countries committed themselves at the UN General Assembly to put in place measures to deal with it (1). Among the measures proposed are the implementation of antimicrobial stewardship programs (ASP).

ASP are quality improvement programs that include heterogeneous interventions, such as auditing, restriction of specific antibiotics, restriction of treatment duration, and antibiotic cycling or mixing (2). The implementation of these measures has shown to significantly reduce use of antibiotics and hospital costs (3,4), but few studies refer to the impact in clinical outcome (5), antibiotic resistance (6, 7, 8) or incidence of *Clostridium difficile* infection (9,10). The interventions are generally more effective in prospective studies, but there are few studies of this type that cover the entire hospital and with a duration long enough in time to evaluate its effect. In addition, the implementation of ASP should be recommended not only on the basis of well-known cost benefits, but also because of the most relevant clinical advantages for patients (11).

The implementation of ASP requires the provision of resources not always available, and it is necessary to prioritize those interventions that may have greater impact. The aim of our study is to evaluate the impact of ASP implementation on the prescription of meropenem in a 350-bed hospital over 3 years.

Methods.

Study design. Descriptive study between January 2012 and December 2017, pre-post-intervention. We analysed the evolution of adequacy of meropenem prescription and clinical impact, antibiotic consumption and the incidence of bloodstream infections acquired in the hospital.

Setting. The study was conducted in a 350-bed teaching hospital from 2015 to 2017. The hospital has one ICU with 10 beds and does not have transplant programs. The infection prevention and control program was the same throughout the study. From 2012 an infectious diseases (ID) physician performed prospective active surveillance of all episodes of bloodstream infections (BSIs) (12).

Intervention. A multidisciplinary team of professionals was constituted in the University Hospital of Ferrol for ASP implementation, at the end of 2014. Local guidelines for empiric antibiotic treatment were developed and are accessible on our intranet via an icon on every hospital computer desktop. Between January 2015 and December 2017 a prospective follow-up of meropenem use was performed. It was decided to start monitoring meropenem use because it was the broadest spectrum carbapenem in our hospital, in a resource-limited setting for ASP implementation. Ertapenem is available with indication for the treatment of infections caused by extended-spectrum β-lactamases producing enterobacteriaceae (ESBLs) and we do not have other carbapenems.

Patients who started treatment with meropenem were selected every day using a drug dispensation program (all hospital units, except ICU). Prescriber´s counseling measures were performed the first day of prescription and a course on optimization of antibiotics use, targeted at trainee pharmacists and physicians, as well as at primary care physicians, was carried out each year. An annual ASP update was presented at a hospital general clinical session.

An ID physician was released 6 hours a week to perform active surveillance. For each case, the electronic medical record was reviewed by ID physician and antibiotic treatment recommendations to prescribers were given, on a face-to-face or telephone conversation basis, or through an electronic medical record. Additional differential diagnoses, investigations, and adjunctive therapy (for example, removal of urinary or central venous catheters (CVC), drainage of infected collections) were also recommended. Adherence to or rejection of the recommendations were assessed by ID physician 24 and 48 hours post-recommendation as part of the ASP workflow.

Prospective and protocolized information was collected for each case: site of infection, place of acquisition, clinical situation of patient, comorbidity (Charlson index), adequacy of treatment to hospital guideline, acceptance of intervention, treatment de-escalation, days of treatment, clinical evolution, collateral damage, inpatient days, treatment cost and readmission. Patients who received more than one course of meropenem during their hospitalization (29 patients) were only included once in the study. The data was obtained by monitoring the information recorded in the electronic medical record. This study was approved by the Institutional Review Boards and Ethic Committee .

Adequacy of treatment. Cases with meropenem prescription during the last 4 months of 2014 were retrospectively reviewed. This sample of the pre-intervention period was used to compare with patients who started treatment with meropenem during the intervention period, to know if the local guidelines adequacy of meropenem prescription and antibiotic treatment de-escalation improved since ASP implementation. Appropriate treatment with meropenem was considered when it was prescribed in patients with: 1. Severe sepsis (13); 2. history of ESBLs colonization; or 3. hospital-acquired infection in which a broad-spectrum antibiotic treatment was considered necessary. De-escalation antibiotic treatment was defined as the change from meropenem to narrower-spectrum antibiotic over the longer course of the treatment.

Clinical and economic impact. To know the clinical impact of the intervention in cases in whom treatment with meropenem was not justified during 2015-2017, a comparison was made between the cases with accepted intervention (modification of antibiotic treatment) and cases with rejected intervention (they continued with meropenem) in their clinical evolution, days of antibiotic treatment, collateral damage, cost of treatment, inpatient days, and hospital readmission. Death was attributable to infectious process if it occurred within 7 days after starting treatment with meropenem (or days later if the event was directly related to a persistent infection, eg, abscesses, endocarditis) and all-cause crude death was defined over the month follow-up. 30-day infection-

related and all-cause readmission were defined as readmission occurring within 30 days from discharging of current admission.

The impact on antibiotic treatment cost during the 3-year follow-up was estimated based on the difference of the laboratory price between treatment with meropenem and proposed antimicrobial in the intervention, when it was accepted, and assuming the same duration of treatment. The cost savings per inpatient days were made comparing the inpatient days post-intervention between cases with accepted intervention and cases with rejected intervention. The inpatient days potentially avoided in cases with accepted intervention were multiplied by the official cost of one day hospital stay (528 €).

During the study period, antibiotic consumption was assessed as Defined Daily Doses (DDD) per 100 occupied bed days (OBDs) (14). The repercussion on the use of antibiotics was made comparing the DDD/100 OBDs between the years 2012 and 2017.

Impact on resistances. In order to assess the impact on the antibiotic resistance, we analyzed between January 2012 and December 2017 the evolution of incidence density per 1000 OBDs of hospital-acquired BSIs produced by the most frequently isolated microorganisms (coagulase-negative *Sthaphylococi* excluded): *Pseudomonas aeruginosa*, *Klebsiella spp*, *E. coli*, *Enterobacter spp*, *Staphyloccoccus aureus* and *Candida spp*, between 2012 and 2017.

Hospital-acquired BSIs were defined as those diagnosed from blood cultures obtained ≥48 hours after hospital admission or in those cases when, even occurring in the first 48 hours, the patient had been hospitalized during the previous two weeks. Patients with a recurrent isolation of the same microorganisms were considered as a unique episode of BSI unless the sample was obtained one month after the last positive blood culture.

The identification of blood isolates and the determination of resistance to antibiotics were performed according to Clinical Laboratory Standard International (CLSI). The MDR

categorization was applied for extended-spectrum *β*-lactamases or carbapenemase-producing Enterobacteriaceae, all isolates of methicillin-resistant *S. aureus* and *Candida spp*, and all *Pseudomomas aeruginosa* and *A. baumannii* strains fulfilling the German Society for Hygiene and Microbiology criteria for MDR organisms (15).

Colonization was defined as the isolation of the organism from a non sterile site in the absence of symptoms of infection, and infection when patient's doctor prescribed treatment.

Statistical analysis. A descriptive and comparative study of the variables was performed. Quantitative variables are reported as means ± standard deviations, and categorical as frequencies (%). Variables were compared between groups using Chi-square test or Fisher exact test for categorical variables, Student t-test or Mann-Whitney U for continuous variables, as appropriate. Logistic regression was performed to evaluate the predictors of intervention acceptance. Associations between the variables were expressed as odds ratios (ORs) and 95% confidence intervals (CIs). Resistance rates per 1000 OBDs of in-hospital acquired BSIs with a 95%CI and rates of mortality were calculated as Poisson event rates, and compared by testing for homogeneity of rates. Statistical analysis was performed using SPSS software version 19. All tests were 2-tailed, a *P* values < 0.05 was regarded as statistically significant.

Results

Adequacy of treatment. During the last 4 months of 2014, 150 patients received treatment with meropenem and between 2015-2017, 852 patients received it. The indication of justified treatment with meropenem progressively improved over time from 47.3% in 2014 to 76.8% in 2017 ($p < 0.001$), without significant changes in the characteristics of the patients (Figure 1). De-escalation from meropenem treatment to narrower-spectrum antibiotic improved progressively after ASP implementation, from 28% in 2014 to 58.8% in 2017 ($p<0.05$).

Clinical and economic impact. Between 2015 and 2017, 852 patients received treatment with meropenem, of which 565 were male and 287 female; age 68.4 ± 15.9 years (range 1-96 years). The sites of infection were: urinary 334, abdominal 219, pulmonary 187, skin and soft tissue 42, febrile neutropenia 20, intravascular catheter 26, other 24. Place of infection acquisition: hospital onset 363, healthcare-associated 328 and community-associated 161.

Out of the 852 patients who received treatment with meropenem, in 522 of them the treatment was considered justified because it was adapted to the local empirical treatment guidelines; in 330 (38.7%) the treatment was not considered justified and interventions were performed at the suggestion of appropriate alternative treatment: in 269 (81.5%) of them, the intervention was accepted and in 61 it was not.

The clinical characteristics of patients were similar between patients with and without acceptance of ASP recommendations, although the degree of intervention acceptance varied according to prescriber (between 29% to 100%) and infection localization (Table 1). The localizations of infection in urine or abdomen accounted for 61% of accepted interventions. By multivariate analysis, pulmonary infection (OR 0.21; 95%CI: 0.09-0.45) and abdominal infection (OR 0.25; 95%CI: 0.12-0.50) were associated with lower acceptance of the intervention; the patient comorbidity (OR 0.98; 95%CI: 0.88-1.08) or the presence of severe sepsis (OR 0.45; 95%CI: 0.16-1.28) were not associated with the degree of acceptance of the intervention.

There were no significant differences between cases with accepted intervention and cases with rejected intervention in clinical evolution or collateral damage (Table 2). The development of colonization or infection with yeast was lower in cases with accepted intervention. The Charlson index was similar throughout the intervention period and was higher in patients who died: 7.2 ± 2.2 vs 5 ± 2.8, $p<0.001$.

The acceptance of the intervention was associated with shorter duration of antibiotic treatment and inpatient days (Table 3). The duration of antibiotic treatment in the total series did not decrease significantly; in urine infection decreased from 9.4 ± 8.2 days in 2015 to 8.1 ± 6.6 in 2017, and

decrease was significant in treatment of wound infection in abdominal surgery: 22.8 ± 16.3 days in 2015 to 13.6 ± 8.3 in 2017, p<0.05.

The 269 patients in whom the intervention was accepted presented 5.9 inpatient days post-intervention less than cases with rejected intervention, and it was calculated that 1,587 days of hospital stay were saved. The estimated cost savings was 866,915.93 € (28,979.93 € in antimicrobials and 837,936 € in 1,587 days of hospital stay potentially-avoided).

Coinciding in time with the start-up of ASP, there was a 33% decrease in the consumption of meropenem during the intervention period with respect to the years 2012-2014 (RR 0.67; 95%CI: 0.58-0.77, p<0.001), with increase in cefepime consumption (1.2 DDD/100 OBDs in 2012-2014 vs 2.1 in 2015-2017) and stabilisation of ciprofloxacin and piperacillin-tazobactam consumption (Figure 2); ceftazidime consumption decreased by 4.7% and ertapenem decreased by 3.1%.

Impact on resistances. The global incidence of bacteraemia adjusted by 1000 OBDs increased by 3.5% during the period 2015-2017 vs 2012-2014. The incidence density of candidemia and MDR BSIs acquired in hospital decreased after ASP start-up in a parallel fashion with the decrease in use of meropenem (Figures 2, 3). In 2015-2017 hospital-acquired MDR BSIs rate was 0.084/1000 OBDs vs 0.133 in 2012-2014 (RR 0.63; 95%CI: 0.38-1.02, p=0.048). Conversely, the incidence density of in-hospital acquired BSIs produced by non-MDR strains of the same microorganisms under study increased 8% during the intervention period (RR 1.08; 95%CI: 0.78-1.51), (Table 4).

To assess if there were other changes in hospital activity that could have contributed to the decrease in the incidence density of hospital-acquired MDR BSIs we monitored some complexity indicadors (16) (Table 4). In the period 2015-2017 compared to 2012-2014 increased: the number of blood cultures performed per 1000 OBDs (RR 1.14; CI95%: 1.1-1.17, p<0.001), the prevalence of CVC use (4.56% vs 2.29%, p = 0.004), catheter-associated BSIs rate (RR 1.08; 95%CI: 0.85-1.38) and the consumption of parenteral nutrition (RR 1.13; 95%CI: 1.08-1.18, p<0.001); whereas antifungal consumption decreased by 5% (RR 0.95; 95%CI: 0.90-0.99, p=0.04).

The alcohol-based hand-rub consumption increased progressively from 2012 to 2017, about 9.9% per year, without there being a significant change in this annual increase between the pre and post-intervention period. The overall antibiotic use in the hospital during the study years increased from 94.7 DDD/100 OBDs in 2012-2014 to 105.8 DDD/100 OBDs in 2015-2017.

Patients with in-hospital acquired MDR BSIs had higher mortality than patients with non-MDR BSIs: death associated with infection 16.3% vs 6.9% (p=0.008) and all-cause crude death 26.3% vs 18.3% (p=0.09). The incidence density of infection-associated mortality for in-hospital acquired MDR BSIs decreased during the intervention period by 45% (0.012 / 1000 OBDs vs 0.022 in 2012-2014) (RR 0.52; 95%CI: 0.11-1.95) and the incidence density of all-cause crude death decreased by 56.4% (0.017 / 1000 OBDs vs 0.039 in 2012-2014) (RR 0.45; 95%CI: 0.14-1.24, p=0.09), figure 2.

The death rate for hospital acquired bacteraemias produced by non-MDR microorganisms increased over time: infection associated mortality 0.047 / 1000 patients-days in 2012-2014 to 0.058 in 2015-2017 (RR 1.23; 95%CI: 0.64-2.34, p=0.64); all-cause crude mortality 0.12 / 1000 patients-days in 2012-2014 to 0.16 in 2015-2017 (RR 1.28; 95%CI: 0.86-1.91, p=0.26).

Throughout the study period, we did not have bacteraemia due to carbapenemase-producing microorganisms nor vancomycin-resistant *Enterococcus* spp, and the incidence of *Clostridium difficile*-associated diarrhoea remained stable about 0.2/1000 patients-days.

Discussion

The care of patients with suspected infections is complex and metrics to assess ASP impact are poorly defined (17, 18). The implementation of our ASP improved the prescription of meropenem and decreased its use, as well as progressively increased the frequency of de-escalation to narrower-spectrum antibiotic. The acceptance of the intervention made by ID physician decreased days of treatment, cost and inpatient days, without negative impact on patient safety.

Some studies reported shorter length of admission in the intervention group than control group and lower mortality (19). Ng et al (20) reported a significant difference in length of stay between the periods before and after ASP implementation with no difference in mortality, like other studies (21-25). Tedeschi et al. achieved a decrease in meropenem use with no increases in mortality or length of stay, and with a decrease in antimicrobial resistance patterns in a rehabilitation hospital (26).

Only one study assessed incidence of collateral damage following carbapenem de-escalation in a ESBLs endemic setting, and reported fewer adverse reaction in de-escalated group, shorter duration of carbapenem use and less development of resistances (27). There are no prospective studies outside the ICUs that analyze the development of infection caused by yeast during antibiotic treatment, and only one prospective study refers to readmissions after discharging, without differences between patients with or without acceptance of ASP recommendation (28). A study with educational and semi-restrictive measures, carried out in a carbapenem-resistant *Klebsiella pneumoniae* endemic 1200-bed adult care hospital, showed a decrease in antibiotics consumption and incidence of *Klebsiella pneumoniae* bacteremia, without changes in candidemia or consumption of antifungal (29).

In our hospital the incidence of *Clostridium difficile*-associated diarrhoea is low and remained stable and our results show a decrease in the incidence of hospital-acquired candidemia and MDR BSIs; this decrease was parallel to the decrease in meropenem consumption and to decrease in the duration of antibiotic treatment for wound infection in abdominal surgery (30). Candidemia is the fourth cause (4.9%) of hospital-associated BSIs in our hospital and is more frequent in the general surgery department (38.5%). The decrease in the duration of antibiotic treatment, the increase in de-escalation from meropenem to narrower-spectrum antibiotics and the lesser development of colonization caused by yeast in patients in whom the intervention was accepted, all of them have undoubtedly contributed to decrease in candidemia. The decrease in the incidence of yeast infection has occurred despite the increase in the number of surgical interventions, the use of CVC and

parenteral nutrition. This is reflected in decrease of antifungal drugs use during the intervention period (31, 32).

We have observed a decrease in MDR BSIs-associated mortality incidence after starting-up the ASP, as in another study with multifaceted educational intervention (8). The ASPs are underfunded and it is necessary to prioritize for undertaking those interventions that may have a greater impact (33, 34). In a resource-limited setting, we decided to follow the use of carbapenems because they are the antibiotics with the broadest antibacterial spectrum and with a rapid induction of beta-lactamases, and with our intervention we have decreased the incidence of hospital-acquired MDR BSIs and associated mortality despite having increased the total incidence of bacteraemia and global consumption of antibiotics.

The results obtained in our study are undoubtedly due to the good acceptance of the interventions by the prescribers, higher than the median change in antibiotic prescribing (42.3%) for the persuasive interventions described in the literature (35, 36). This should certainly be due to the fact that interventions were performed in a medium-sized hospital and with good interpersonal communication among professionals who also work in infection prevention and control (37, 38). The intervention rejection level was not associated with the severity or comorbidity of the patient and it seemed to be more in relation with clinicians' attitudes in different hospitalization units (39). It is also possible that sensitizacion measures on resistance to antibiotics conveyed through the media and training courses could have played some role over the general population and physicians (40), but it does not seem that other variables influenced the results of the study.

Our achieved cost savings are much higher than ASP cost (an ID physician was released 6 hours a week) warranting the financing of ASPs with more resources to expand the program in the hospital to other antibiotics (26, 35, 36), towards primary care (7, 41) and long-term care settings (42).

The strength of our study is the large number of variables analyzed and prospective data collection over 3 years to evaluate the impact of ASP, and our results prove that ASP is cost-effective. We assessed compliance with local guidelines as the standard for appropriate therapy to reduce the more subjective method of expert opinion-based definitions (18).

Our study has several limitations. The study was restricted to those wards with electronic medication dispensing system (all the hospital except ICU unit), but patients transferred from the ICU to other hospitalization units and who were receiving treatment with meropenem were also followed. The MDR BSIs acquired in ICU between 2012-2017 accounted for 7.8% of hospital bacteraemia, without significant differences between pre and post intervention period, and we believe that the activity of this service has not influenced our results.

The sample size does not allow a regression or time series analysis to provide good stability to the results obtained, but they reflect the changes in consumption of meropenem and in the incidence of in-hospital MDR BSIs and mortality, after starting the ASP; these changes in trend seem to be due to our intervention and not to changes in healthcare during the study period. The single-center design limits the possibility of generalizing our results to other hospitals, and including preferred methods such as control groups or randomization was impractical.

In conclusion, the results of this study show that the decrease and better use of meropenem achieved by our ASP program had a sustained clinical, economic and ecological impact, reducing costs and mortality of hospital-acquired MDR BSIs.

Competing interests

The authors declare that they have no competing interest.

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References:

1. United Nations. General Assembly of the United Nations: President of the 71st Session. 2016. http://www.un.org/pga/71/2016/09/21/press-release-hl-meeting-on-antimicrobial-resistance/ (accesed Nov 21, 2017).

2. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis 2016; 62 (10): e51-e77.

3. Karanika S, Paudel S, Grigoras C, Kalbasi A, Mylonakis E. Systematic review and meta-analysis of clinical and economic outcomes from the implementation of hospital-based antimicrobial stewardship programs. Antimicrob Agents Chemother 2016; 60: 4840-52.

4. ECDC. Summary of the latest data on antibiotic consumption in the European Union: 2017. https://ecdc.europa.eu/sites/portal/files/documents/Final_2017_EAAD_ESAC-Net_Summary-edited%20-%20FINALwith%20erratum.pdf. (accessed Feb 28, 2018).

5. Schuts EC, Hulscher ME, Mouton JW, Verduin CM, Stuart JWTC, Overdiek HWPM et al. Current evidence on hospital antimicrobial stewardship objetives: a systematic review and meta-analysis. Lancet Infect Dis 2016; 16: 847-56.

6. Lawes T, López-Lozano JM, Nebot CA, Macartney G, Subbarao-Sharma R, Dare CRJ, et al. Effects of national antibiotic stewardship and infection control strategies on hospital-associated and community-associated meticillin-resistant Staphylococcus aureus infections across a region of Scotland: a non-linear time-series study. Lancet Infect Dis 2015; 15: 1438-49.

7. Akpan MR, Ahmad R, Shebl NA, Ashiru-Oredope D. A review of Quality Measures for Assessing the Impact of Antimicrobial Stewardship Programs in Hospitals. Antibiotics (Basel) 2016; 5 (1). pii: E5. doi: 10.3390/antibiotics5010005.

8. Molina J, Peñalva G, Gil-Navarro MV, Praena J, Lepe JA, Pérez-Moreno MA, et al. Long-term impact of an educational antimicrobial stewardship program on hospital-acquired candidemia and multidrug-resistant bloodstream infections: a quasi-experimental study of interrupted time-series analysis. Clin Infect Dis 2017; 65 (12): 1992-1999.

9. Feazel LM, Malhotra A, Perencevich EN, Kaboli P, Diekema DJ, Schweizer ML. Effect of antibiotic stewardship programmes on *Clostridium difficile* incidence: a systematic review and meta-analysis. J Antimicrob Chemother 2014; 69: 148-54.

10. Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. 2017 Feb 9; 2: CD003543. doi: 10.1002/14651858.CD003543.pub4.

11. Baur D, Gladstone BP, Burkert F, Carrara E, Foschi F, Döbele S, Tacconelli E. Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and *Clostridium difficile* infection: a systematic review and meta-analysis. Lancet Infect Dis 2017; 17 (9): 990-1001.

12. García-Rodríguez JF, Álvarez-Díaz H, Vilariño-Maneiro L, Lorenzo-García MV, Cantón-Blanco A, Ordoñez-Barrosa P, et al. Epidemiology and impact of a multifaceted approach in controlling central venous catheter associated blood stream infections outside the intensive care unit. BMC Infectious Diseases 2013, 13:445. http://www.biomedcentral.com/1471-2334/13/445. (Accessed Feb 8, 2018).

13. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013; 41 (2): 580-637. .

14. WHO Collaborating Center for Drug Statistics Methodology. DDD definition and general considerations. 2016. Available from: https://www.whocc.no/ddd/definition_and_general_considera/. (Accessed Feb 8, 2018).

15. Mattner F, Bange FC, Meyer E, Seifert H, Wichelhaus TA, Chaberny IF. Preventing the spread of multidrug-resistant gram-negative pathogens: recommendations of an expert panel of the German Society For Hygiene and Microbiology. Dtsch Arztebl Int. 2012; 109 (3): 39-45.

16. Mendez CM, Harrington DW, Christenson P, Spelberg B. Impact of Hospital Variables on Case Mix Index as a Marker of Diseases Severity. Population Health Management 2014; 17: 28-34.

17. Moehring RW, Anderson DJ, Cochran RL, Hicks LA, Srinivasan A, Ashley ESD, for the Structured Taskforce of Experts Working at Reliable Standards for Stewardship (STEWARDS) Panel. Expert Consensus on Metrics to Assess the Impact of Patient-Level Antimicrobial Stewardship Interventions in Acute-Care Settings. Clin Infect Dis 2017; 64 (3): 377-83.

18. Spivak ES, Cosgrove SE, Srinivasan A. Measuring Appropriate Antimicrobial Use: Attempts at Opening the Black Box. Clin Infect Dis 2016; 63 (12): 1639-44.

19. Gums J, Yancey R, Hmilton C, Kubilis PA. A randomized, prospective study measuring outcomes after antibiotic therapy intervention by a multidisciplinary consult team. Pharmacotherapy 1999; 19: 1369-1377.

20. Ng CK, Wu TC, Chan WMJ, Leung YSN, Pli CK, Tsang DNC, Leung GM. Clinical and economic impact of an antibiotics steweardship programme in a regional hospital in Hong Kong. Quality Safety Health Care 2008; 17: 387-392.

21. Chan Y, Lin T, Huang C, Deng S, Wu T, Lue H, Chiu C. Implementation and outcomes of a hospital-wide computerised antimicrobial stewardship program in a large medical centre in Taiwan. J Antimicrob Agents 2011; 38: 486-492.

22. Liew Y, Lee W, Loh J, Cai Y, Tang S, Lim C, et al. Impact of an antimicrobial stewardship program on patient safety in Singapore General Hospital. Int J Antimicrob Agents 2012; 40: 55-60.

23. Díaz-Granados C. Prospective audit for antimicrobial stewardship in intensive care: Impact on resistance and clinical outcomes. Am J Infect Control 2012; 40: 526-529.

24. Lin Y, Lin I, Yen F, Lin P, Shiu Y, Hu H, Yang Y. Impact of an antimicrobial stewardship program with multidisciplinary cooperation in a community public teaching hospital in Taiwan. Am J Infect Control 2013; 41: 1069-1072.

25. Rosa R, Goldani L, dos Santos R. Association between adherence to an antimicrobial stewardship program and mortality among hospitalised cancer patients with febrile neutropaenia: A prospective cohort study. BMC Infect Dis 2014; 14: 286.

26. Tedeschi S, Trapani F, Giannella M, Cristini F, Tumietto F, Bartoletti M, et al. An Antimicrobial Stewardship Program Based on Systematic Infectious Disease Consultation in a Rehabilitation Facility. Infect Control Hosp Epidemiol 2017; 38: 76-82.

27. Lew K, Ng T, Tan M, Tan S, Lew E, Ling L, et al. Safety and Clinical outcomes of carbapenem de-escalation as part of an antimicrobial stewardship program in an ESBL-endemic setting. J Antimicrob Chemother 2015; 70; 1219-1225.

28. Teng CB, Ng TM, Tan MW, Tan SH, Tay M, Lim SF, et al. Safety and effectiveness of improving carbapenem use via prospective review and feedback in a multidisciplinary antimicrobial stewardship programme. Ann Acad Med Singapore. 2015; 44 (1): 19-25.

29. Giacobbe DR, Del Bono V, Mikulska M, Gustinetti G, Marchese A, Mina F, et al. Impact of a mixed educational and semi-restrictive antimicrobial stewardship project in a large teaching hospital in Northern Italy. Infection 2017; 45 (6): 849-856.

30. McCarty TP, Pappas PG. Invasive Candidiasis. Infect Dis Clin North Am. 2016; 30 (1): 103-24.

31. Vena A., Bouza E., Valerio M., Padilla B., Paño-Pardo J.R., Fernández-Ruiz M., et al. Candidemia in non-ICU surgical wards: Comparison with medical wards. PLoS One 2017; 12 (10): e0185339.

32. Lortholary O, Renaudat C, Sitbon K, Desnos-Ollivier M, Bretagne S, Dromer F, French Mycoses Study Group. The risk and clinical outcome of candidemia depending on underlying malignancy. Intensive Care 2017; 43 (5): 652-662.

33. Stenehjem E, Hyun DY, Yu KC, Meyer M, Raj D, Srinivasan A. Antibiotic Stewardship in Small Hospitals: Barriers and Potencial Solutions. Clin Infect Dis 2017; 65 (4): 691-696.

34. Apisarnthanarak A, Bhooanusas N, Yaprasert A, Mundy LM. Carbapenem de-escalation therapy in a resource-limited setting. Infect Control Hosp Epidemiol. 2013; 34 (12): 1310-3.

35. Davey P, Brown E, Charani E, Fenelon L, Gould IM, Holmes A, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database of Systematic Reviews 2013, Issue 4. art. No.: CD003543. DOI: 10.1002/14651858.CD003543.pub3.

36. Cosgrove SE, Hermsen ED, Rybak MJ, File T, Parker SK, Barlam TF. Guidance for the Knowledge and Skills Required for Antimicrobial Stewardship Leaders. Infect Control Hosp Epidemiol 2014; 35 (12): 1444-1451.

37. Burnham JP, Olsen MA, Stwalley D, Kwon JH, Babcock HM, Kollef MH. Infectious Diseases Consultation Reduces 30-Day and 1-Year All-Cause Mortality for Multidrug-Resistant Organism Infections. Open Forum Infect Dis. 2018; 5 (3): ofy026. doi: 10.1093/ofid/ofy026.

38. Seah VXF, Ong RYL, Lim ASY, Chong CY, Tan NWH, Thoon KC. Impact of a Carbapenem Antimicrobial Stewardship Program on Patient Outcomes. Antimicrob Agents Chemother. 2017; 61 (9). pii: e00736-17. doi: 10.1128/AAC.00736-17.

39. Robson SE, Cockburn A, Sneddon J, Mohana A, Bennie M, Mullen AB, et al. Optimizing carbapenem use through a national quality improvement programme. J Antimicrob Chemother 2018; May 24. doi: 10.1093/jac/dky171. [Epub ahead of print]

40. Doron S, Davidson LE, Antimicrobial stewardship. Mayo Clin Proc 2011; 86: 1113-1123.

41. Pulcini C, Morel CM, Tacconelli E, Beovic B, de With K, Goossens H, et al. Human resources estimates and funding for antibiotic stewardship teams are urgently needed. Clin Microbiol Infect. 2017 ; 23 (11): 785-787.

42. Katz MJ, Gurses AP, Tamma PD, Cosgrove SE, Miller MA, Jump RLP. Implementing Antimicrobial Stewardship in Long-term Care Settings: An Integrative Review Using a Human Factors Approach. Clin Infect Dis 2017; 65 (11): 1943-1951.

Table 1. Baseline Demographic and Clinical Characteristics of Patients with and without Acceptance of ASP Recommendations. Years 2015-2017.

Variables	Intervention accepted n=269	Intervention rejected n=61	p
Male gender, n (%)	174 (64.7)	40 (65.6)	1
Median age ± SD, years (range)	66.6 ± 15.7 (10-96)	66.2 ± 19 (6-95)	0.87
Charlson's comorbidity score, Median ± SD, (range)	4.98 ± 3 (0-13.6)	5.06 ± 2.89 (0-12)	0.84
Neutropenia, < 500/mL	5 (1.9)	2 (3.3)	0.62
Severe sepsis	17 (6.3)	6 (9.8)	0.4
Site of infections, n (%)			
Pulmonary	44 (16.4)	19 (31.1)	0.01
Abdominal	74 (27.5)	28 (45.9)	0.009
Skin / soft tissue	15 (5.6)	1 (1.6)	0.32
Urinary	90 (33.4)	10 (16.4)	0.009
Other	46 (17.1)	3 (4.9)	0.016
Acquisition place of infection			
Hospital onset	85 (31.6)	24 (39.3)	0.29
Healthcare-associated	93 (34.6)	24 (39.3)	0.55
Community-associated	91 (33.8)	13 (21.3)	0.07

Table 2. Clinical Results of Patients with and without Acceptance of ASP Recommendations. Years 2015-2017.

Variables	Intervention accepted n=269	Intervention rejected n=61	p
Healing	239 (88.8%)	51 (83.6%)	0.28
Death caused by infection	12 (4.5%)	6 (9.8%)	0.11
All-cause crude death	30 (11.2%)	10 (16.40%)	0.28
Readmission in a month	10# (3.7%)	3* (4.9%)	0.71
Adverse effects	28 (10.4%)	5 (8.2%)	0.81
Phlebitis	44 (16.4%)	8 (13.1%)	0.70
Development of resistance to treatment	6 (2.2%)	0 (0%)	0.60
Diarrhea caused by *C. difficile*	6 (2.2%)	1 (1.6%)	1
Colonization-Infection with *Candida spp*	30 (11.2%)	9 (14.8%)	0.51

[#]4 relapses of the infection, 6 due to other causes.
* No relapse of infection, due to other causes.

Table 3. Economic Results, Patients with and without Acceptance of ASP Recommendations. Years 2015-2017.

Variables	Intervention accepted n=269	Intervention rejected n=61	p
Days of antibiotic treatment	11 ± 10.1	13.8 ± 9	0.05
Cost of antibiotic treatment	108.3 ± 371.2	202.4 ± 504.8	0.09
Total inpatient days, X±SD	17.6 ± 16.8	26.2 ± 23.6	0.001
Inpatient days post-intervention, X±SD	12.6 ± 14.4	18.55 ± 20.5	0.009

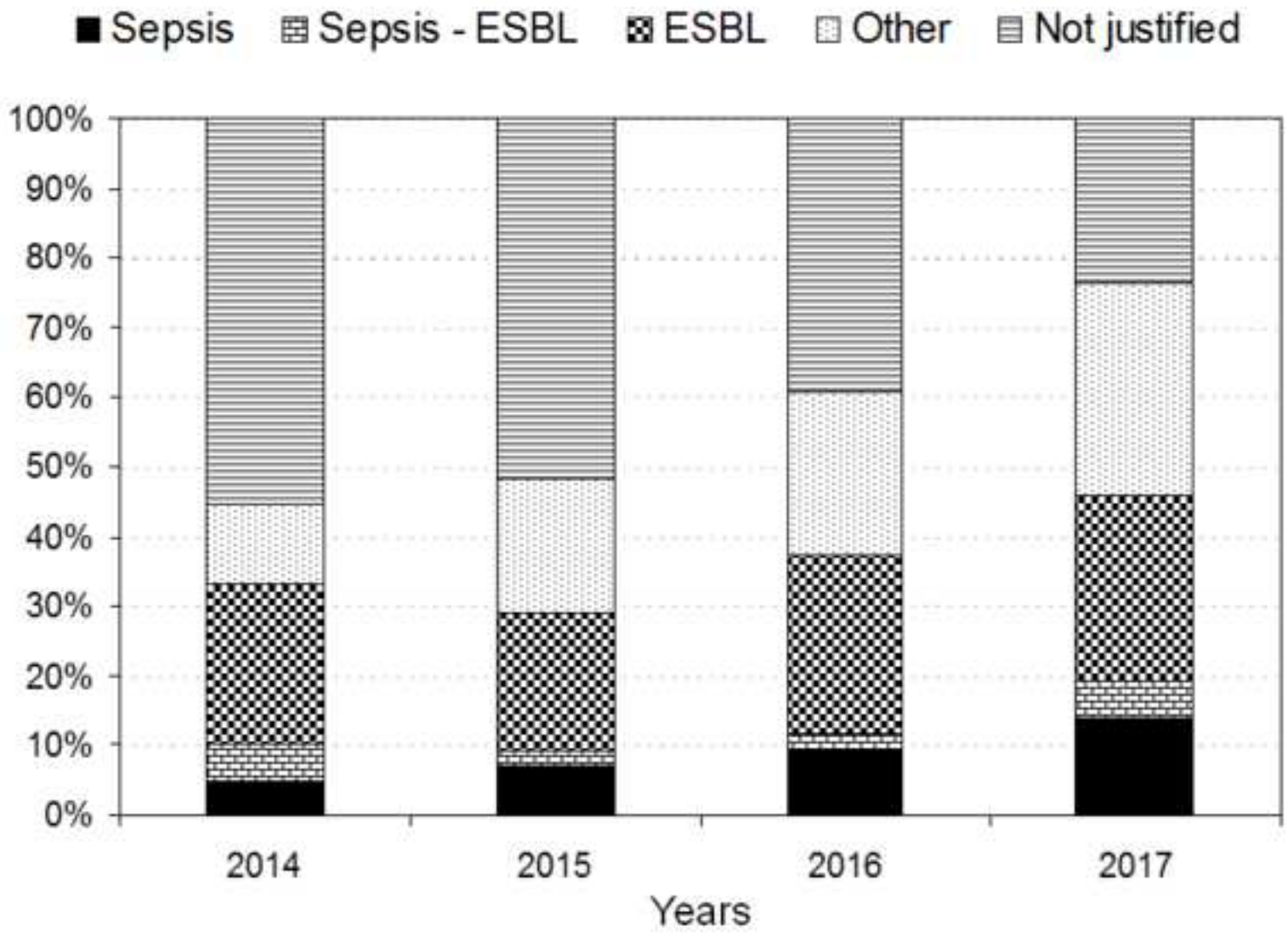
Table

Table 4. Potencial Changes in Healthcare During the Study Period by Year

Healthcare Variable	2012	2013	2014	2015	2016	2017
Nº of patients admitted	14721	14615	14979	14867	14852	15248
Nº of inpatient days	119885	121181	119615	116588	114072	114864
Blood cultures performmed, No.	3242	3340	2985	3003	3419	3074
Nº blood cultures / 1000 OBDs	27.04	27.56	24.95	25.76	29.97	26.76
Hospital-acquired no-MDR BSIs / 1000 OBDs	0.69	0.76	0.71	0.69	0.76	0.88
Intravascular catheter-associated BSIs / 1000 OBDs	0.27	0.39	0.48	0.35	0.42	0.46
Surgical procedures, No.	8848	9285	8836	9148	9352	9151
Case mix index	1.51	1.54	1.56	1.57	1.58	1.59
Parenteral nutrition units, No. / 100 OBDs	2.91	3.87	3.95	4.61	4.13	3.40
Consumption of antifungals, DDD / 100 OBDs	2.91	3.84	3.08	3.49	3.31	2.55

MDR: multidrug-resistant. BSIs: bloodstream infections. OBDs: occupied bed days.

Figure 1. Evolution of the adequacy of treatment with Meropenem Years 2014 (last 4 months), 2015-2017



No. Cases followed	(150)	(281)	(311)	(260)	
Justified treatment	47,3%	57,7%	68,8%	76,8%	P <0,05

Figure 2. Evolution of antibiotic consumption, incidence of MDR bloodstream infections and mortality

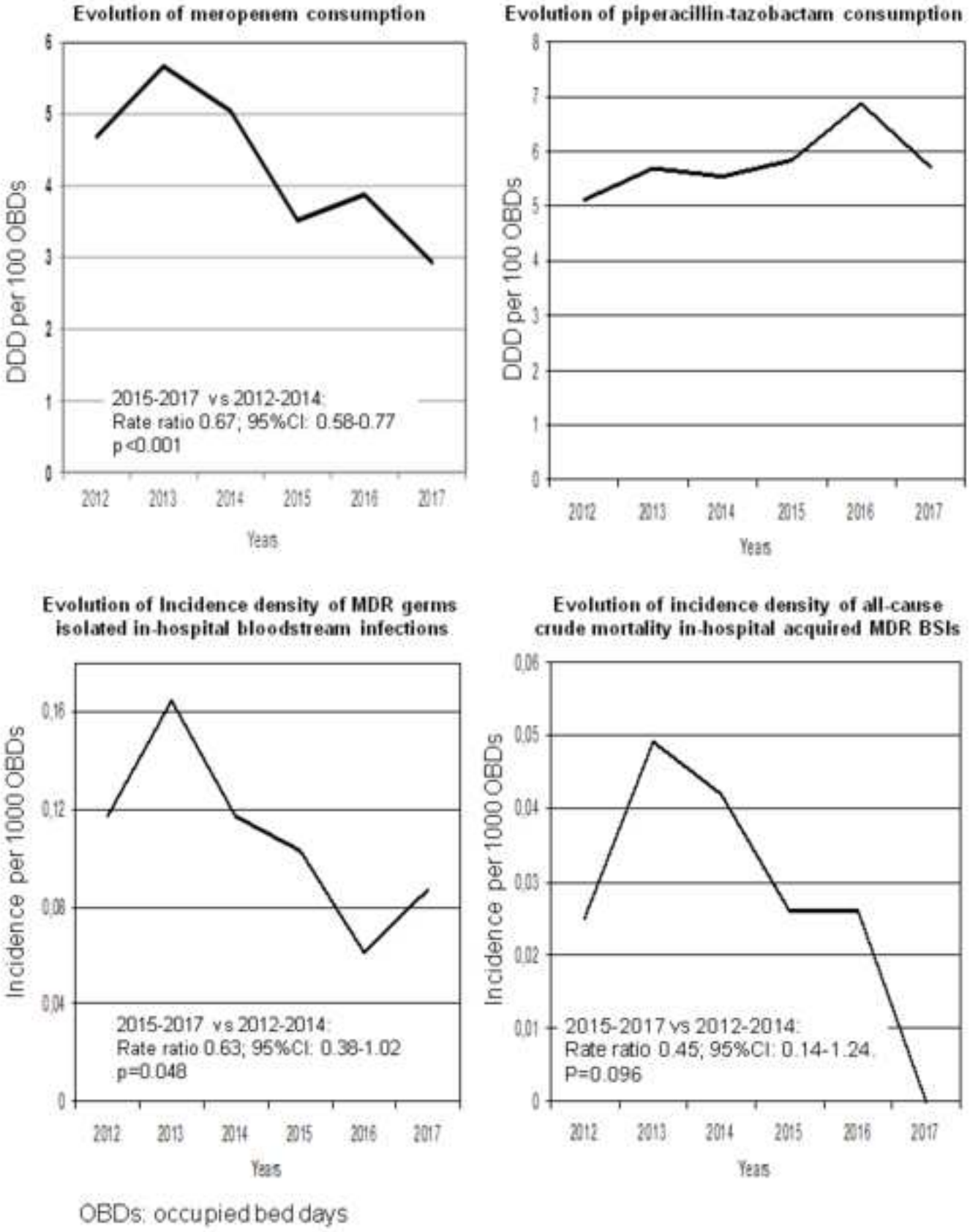


Figure 3. Evolution of the incidence density of MDR microorganisms isolated most frequently in-hospital bloodstream infections