Trends in Antibacterial Drug Consumption in the Intensive Care Unit

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Dedicated to my family and closest friends

Abstract

Adequate use of antibacterials in the ICU is important to help achieve optimum end results. The aim of this study was to present a scenario analysis of the past and current use of antibacterial drugs in the ICU. Special observation was given on respective classes, dosage regimens and indications for administration. The study was carried out at the ICU at Mater Dei Hospital (MDH). Past data was retrieved on an excel database from hospital data, showing annual antibacterial consumption. Present data was collected by manual records taken every 2 weeks for a period of 4 months from the ICU, through a devised 'Antibacterial Collection Sheet'. Critically ill patients over 18 years of age were included. The Anatomical Therapeutic Classification (ATC) / Defined Daily Doses (DDD) methodology as designated by WHO was applied. Administration of antibacterials at MDH ICU between 2009-2017 and in 2019 was analysed.

During the period 2009-2017, an increasing trend in DDD/patient value was observed, with the highest value noted for the year 2015 at, 1872.4. Meropenem and Piperacillin, with a beta-lactamase inhibitor were the two most commonly administered antibacterials during the years, with average yearly DDD values of 3577 and 1362 respectively. The prospective study carried out in 2019, included data of 68 patients, 76% (N=68) of which were male. The age range of these patients was of 21-89 years, with a mean age of 60 years. Fourty-seven% (N=68) were administered an antibacterial for a respiratory infection. The most frequently administered antibacterial was piperacillin/ tazobactam, at 27% (N=68), followed by meropenem, at 19.4% (N=68) of the total number of antibacterials administered. Gentamicin and cefuroxime were among the least frequently prescribed antibacterials, both at less than 1% (N=68). Data presented in this drug utilization study incorporates data from medical and surgical patients in the ICU. Carbapenems and Penicillins with Beta-lactamase inhibitor, were the two most commonly administered antibacterial classes from both the retrospective and prospective study data.

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List of Abbreviations

AUC: Area under curve

BSI: Bloodstream infection

CAI: Community acquired infection

CNS: Central nervous system

CVS: Central vascular system

ESBL: Extended-spectrum beta-lactamases

HAI: Hospital acquired infection

GI: Gastrointestinal

GNB: Gram negative bacteria

GPB: Gram positive bacteria

ICU: Intensive care unit

MDR: Multi drug resistant bacteria

MIC: Minimum inhibitory concentration

MP: Medical Prophylaxis

MRSA: Methicillin-resistant *Staphylococcus aureus*

PK-PD: Pharmacokinetics-Pharmacodynamics

SIRS: Systemic Inflammatory Response Syndrome

SP: Surgical prophylaxis

VAP: Ventilator-associated pneumonia

VRE: Vancomycin-resistant enterococci

Chapter 1: Introduction

1.1 Introduction

> "The intensive care unit (ICU) is an organized system for the provision of care to critically ill patients that provides intensive and specialized medical and nursing care, an enhanced capacity for monitoring and multiple modalities of physiologic organ support to sustain life during a period of acute organ system insufficiency. Although an ICU is based in a defined geographic area of a hospital, its activities often extend beyond the walls of the assigned space to include the emergency department, hospital ward and follow-up clinic" (Marshall et al,2017).

Antibacterial administration can be considered for treatment or as prevention from infection. Adequate usage of antibacterials in the ICU is important to help achieve optimum end results. Conservation of the regulation of emergence of resistance among harmful organisms is important (Malacarne et al, 2004). Good antibacterial management in ICUs incorporates prompt identification of pathogen and optimum therapy of bacterial infections, established on the reported pharmacokinetic-pharmacodynamic characteristics. Unnecessary use of broad-spectrum antibacterials and prolonged use should be prevented (Rosenberger et al, 2012).

1.2 Scenario in the Intensive Care Unit

> "Critical illness is characterized by marked homeostatic disturbance, altered end-organ function, variable pre-existing comorbidity, and anthropometric irregularity'' (Mohr et al, 2005).

Intensive care units are usually located in the main cities of a country. Every year, around 164,000 patients suffering from critical illness are admitted to ICUs in England, Northern Ireland and Wales and 4 million patients in the United States (Marshall et al, 2017).

The aim of therapy provided in an ICU, is to avert additional physiological worsening while the disease is controlled. The ICU team can consist of physicians, pharmacists, physiotherapists, microbiologists, ethicists, social workers, nurses and respiratory therapists, who all form an interprofessional group. In an ideal case scenario, every patient in an ICU should have a single-bedroom, with a sink and arrangement features intended for easy access to devices and monitors used (Marshall et al, 2017).

An ICU should have at least one negative-pressure room, so as to accommodate patients diagnosed with an airborne infection. Electronic medical records are to be easily accessed from the multiple computer stations. The physiologic states of patients who are resident in the ICU is observed more frequently than the state of the person in other wards of the hospital. Monitoring can be done, both in a non-invasive way through a continuous electrocardiogram, or by using an invasive approach, such as monitoring of the intracranial pressure (Marshall et al, 2017).

The progression of infection for patients in the ICU, is correlated with a rise in malaise, fatality and cost. For ICU patients, the rate of nosocomial infections can go up to 25% to 30%. Nosocomial infections could be avertible by operation of infection control programs (Mohr et al, 2005). The ICU carries a substantial antibacterial burden within a hospital, with sepsis being the second noncardiac cause of mortality in ICUs (Trejnowska et al, 2018).

Therapy administration in the intensive care unit is established from patient factors which include the primary and current clinical signs and symptoms, past medical history and any allergic conditions. Problems may arise due to the patient not being able to communicate about reactions to specific drugs and patients not being able to identify specific allergic reactions (Rosenberger et al, 2012).

1.2.1 Antibacterial pharmacotherapy

Typical nosocomial infections that evolve in ICU patients are urinary tract infections, pneumonia, and bloodstream infections. ICU nosocomial infections are related to the use of invasive devices, and preliminary prevention is focused on the removal of the device (Mohr et al, 2005).

In the ICU scenario, patients have critical comorbid illnesses and often need to undergo invasive operations, like surgery, insertion of urinary catheters and insertion of mechanical ventilation. The initial therapeutic approach is to give immediate, combative, yet appropriate empirical therapy for critical infection, and then follow up with de-escalation in accordance to the outcome of antibacterial susceptibility data (Petrosillo et al, 2010).

Relatively narrow-spectrum drugs, such as non-pseudomonal third-generation cephalosporins are to be considered in patients with moderately severe, early-borne infections having no clear-cut risk possibility; like continued hospitalization, immunosuppression or recent extended doses of antibacterials (Luyt et al, 2014).

Broad spectrum therapy refers to antibacterial coverage that includes gram-negative pathogens, including *Pseudomonas* subspecies and resistant pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA).Empiric antibacterial regimens are to be hinged on local resistance trends, the most prevalent microbes linked with an established or suspected infection site and any host factors correlated with the possibility of uncommon or resistant microbes.

Administration of antibacterial against the most probable infecting organism, is more vital than administration of broad spectrum therapy. Patient-specific aspects are to be considered before deciding on an antibacterial regimen (Montravers et al, 2016).

Utilization of 2 antibacterials with variant mechanisms of action aimed at empiric management of infection in cases of higher bacterial resistance is of importance with the increasing worry for gram-negative resistance and the lack of awareness. Two-fold gram-negative protection

usually involves a beta-lactam and an aminoglycoside or fluoroquinolone (Montravers et al, 2016).

In vivo antimicrobial efficacy is determined by pharmacokinetics (PK) and pharmacodynamic (PD) characteristics. PK relates to the serum concentration profile of antibacterial over a period of time and the degree of penetration in the infected site. PD criterions describe serum concentration and its relationship to drug pharmacology and toxicology, bactericidal activity and post-antibacterial effects. Drug dose and antibacterial effectiveness is well understood through the PK/PD relationship. Time-dependent is exhibited in cephalosporins and penicillins. The dosage regimen should maximize the period above the minimum inhibitory concentration (MIC) of antibacterial in opposition to the pathogen. In concentration-dependent killing agents, with extended long-lasting effects, having the proportion of the area under the 24-hour time-concentration curve for the unbound drug to the MIC predicts the result in an accurate way (Jacobs, 2007).

Table 1.1: Pharmacodynamic patterns of antibacterial activity
[Adopted from] Jacobs M. Combating resistance: application of the emerging science of pharmacokinetics and pharmacodynamics. International Journal of Antimicrobial Agents. 2007; 30: 122-126.

Pattern	**Pharmacodynamic correlate**
Time-dependent killing and minimal to moderate persistent effects	Time above MIC>40-50 % of dosing interval*
Time-dependent killing and prolonged persistent effects	AUC/MIC ratio > 30 *
Concentration-dependent killing and prolonged persistent effects	AUC/MIC ratio >30 *

*All correlations are based on nonprotein bound serum levels.

Antimicrobials are discriminated through their mode of action. These are the concentration dependent; aminoglycosides and fluoroquinolones and the time-dependent; Beta-lactams and carbapanems.

Significant PK-PD criteria are peak concentration/ MIC > 8-10 and 24-hour area under concentration curve (AUC)/MIC > 100-120 for aminoglycosides and fluoroquinolones. The latter are more intricate and show both concentration- and time-dependent kill traits based on the efficiency is the AUC/MIC. Other antimicrobials, like carbapenems, have an apparent post-antibacterial result (Luyt et al, 2014).

Table 1.2: Antibacterial therapy depending on the site of infection
[Adopted from] Leekha, S., Terrell, C. and Edson, R., 2011. General Principles of Antimicrobial Therapy. Mayo Clinic Proceedings, 86(2), pp.156-167.

Type	**Bacteria**	**Suggested treatment**
Urinary tract infection	*E.coli*	Ceftriaxone/Ceftazidime and/or aminoglycoside
Severe acute pyelonephritis	*P.aeruginosa* Enterococcus species Staphylococcus species	Ertapenem Piperacillin-Tazobactam 3rd or 4th generation cephalosporin and Metronidazole
Intra- abdominal sepsis	*E.coli* *P.aeruginosa* Enterococcus species Bacteroides species	Ertapenem Piperacillin-Tazobactam 3rd/4th generation cephalosporin and Metronidazole
Nasocomial pneumonia	Enterobacteriaceae *P.aeruginosa* *S.aureus* *S.pneumoniae* *H.influenzae*	Beta-lactam and/or aminoglycoside and/or glycopeptide
Pneumonia without risk factors for MDR pseudomonas	*S.aureus* *S.pneumoniae* *H.influenzae* Other gram-negative bacilli	Third generation cephalosporin and/or macrolide

Skin infections	Streptococcus species Staphylococcus species Gram-negative bacilli	Beta-lactam and beta-lactamase inhibitor Piperacillin-Tazobactam Carbapenem

Shock is the result of the body organs not receiving enough oxygen, leading to a sharp fall in blood pressure. This may be caused by severe dehydration, known as hypovolemic shock, heart failure as a result of cardiogenic shock and septic shock due to a serious infection leading into organ failure. Trauma and conditions like, pancreatitis, result in systemic inflammatory response syndrome. Throughout the patient's period of stay in the ICU, complications of acute respiratory failure may develop. The complications can vary from mild to severe. Pneumonia or chronic obstructive pulmonary disease results from moderate to severe respiratory failure. Patients may require the use of a ventilator to improve comfort and assist in breathing in cases where the patient remains in critical condition. Infection can be the reason why the patient requires intensive care, but also intravenous catheters and other devices which are used for treatment, can cause infections. Pneumonia, can result due to the patient being on the ventilator. Bacteraemia is another type of infection that can occur.

Liver failure or gastric ulcers, formed by sepsis may result in bleeding. Patients in the ICU are at a hazard of forming blood clots, mostly in their lungs and legs. One of the most fatal of the critical illness in the ICU is multiple organ dysfunction syndrome. Sepsis, dehydration, toxic substances and hypertension are a few of the reasons that result in renal failure. Neurological disorders can be detected in the ICU. Stroke, infections, lack of oxygen to the brain tissue occur in critically ill patients which can lead to fatality.

A study conducted in '1999 by Gruppo Italiano per la Valutazione degli Interventi in Terapia Intensiva', showed the use of antibacterials in the ICU, assessed from a pharmaco-epidemiological outlook. Vancomycin and teicoplanin use is associated as first-line treatment for infections caused by the increasing rates of methicillin-resistant *Staphylococcus aureus* in

Italian ICUs. When considering use of antibacterials for prophylaxis management, a distinction is to be made between surgical and non-surgical patients using them. Recommendations for antibacterial use in surgical patients, favour the use for cefazolin, cefoxitin and cefuroxime as first line, or ceftriaxone, glycopeptides and ceftizoxime as second therapy, for not more than 24 hours (Malacarne et al, 2004).

More than one antibacterial can be used in some surgical procedures or patients. Antibacterial combinations include, cephalosporin plus metronidazole for intra-abdominal surgery and ampicillin with gentamicin when endocarditis risk is apparent. For prophylaxis in non-surgical patients, guidelines suggest antibacterial use in, selective digestive decontamination and ventilator-associated pneumonia (VAP) prophylaxis, although limited to specific situations and after the exclusion of mentioned conditions (Malacarne et al, 2004).

There may be cases where antibacterials are used off-label in the ICU, due to the issue of multidrug-resistant pathogens. This is acceptable if enough literature support is provided, which shows an overall plausible risk-benefit ratio for the given context. Tigecycline, was accepted for the remedy of complicated intraabdominal infections, skin structure infections, complicated skin and community-acquired bacterial pneumonia. This was supported by two studies conducted in Argentina which showed that more than 50% of the tigecycline administration was for VAP. The ratio of clinical achievement of more than 200 patients with VAP, cured with tigecycline was higher than 65% (Curcio et al, 2011).

1.2.2 Dosage regimens of antibacterials

Acquiring samples for related cultures before antibacterial prescribing is important to support infection, determine causative pathogens, and set up de-escalation therapy in cases of sensitivity profiles. Regimen choice is to be established on local antibacterial susceptibility design and expected side-effects, while taking into consideration the antibacterials administered within the previous two weeks and attempting not to administer the same classes whenever possible (Luyt et al, 2014).

This is achieved by, understanding the major physicochemical characteristics of the antibacterials, which include; molecular weight, degree of ionization, protein binding, and lipid solubility which will control the way the particular antibacterial is distributed in the body. Fluoroquinolones, which are lipophilic, usually have a large volume of distribution with more tissue penetration. In contrast, hydrophilic antibacterial settle mostly in the extracellular space. Increased volume of distribution is seen with aminoglycosides, beta-lactams, daptomycin, and glycopeptides in critically ill patients (Udy et al, 2013).

Aminoglycoside dosage regimens are to be calculated on adapted body weight. Daptomycin and beta-lactam modifications are to be employed on lean body weight and vancomycin application is to be established on total body weight. In clinically ill and septic patients, it was proposed that clinicians should use higher doses, better known as loading doses of aminoglycosides, beta-lactams, glycopeptides, tigecycline and colistin. The maintenance dose is established based on the drug elimination organ function, since the previously mentioned drugs follow renal elimination. Continuous infusions are to be started after loading dose, no more than halfway through the normal dosing period (Udy et al, 2013).

1.3 Commonly used antibacterials

"Nosocomial infections affect up to 30% of patients in the ICU with a 5 to 10 times higher risk among ICU patients compared to non-ICU patients. Up to 70% of these nosocomial infections are caused by organisms that are frequently resistant to at least one drug" (Volles et al, 2008). Warren et al, carried out a study in an ICU which had previously been applying combative infection control procedures. Four classes of antibacterials having gram-negative activity were cycled throughout 3-to 4-month interludes for 24 months post a 5-month baseline stage of unlimited antibacterial use. The study patients and the rate of acquisition of enteric settlement with a resistant organism to any of the objective drugs remained constant during the cycling period. The approximate amount of *P.aeruginosa* resistant to the chosen drugs increased in all

the hospital throughout the cycling period but decreased when antibacterial cycling was applied in the ICU (Kollef, 2006).

Table 1.3: Categorisation of parenteral antimicrobials established by the most probable for resistance
[Adapted from] Van Seane H, Reilly N, De. Silvestre A, Nardi G. Antibiotic policies in the intensive care unit. Infection Control in the Intensive Care Unit. 2005: 231-246.

Low resistance	High resistance
Piperacillin	Ampicillin
Cephradine	Ceftazidime
Cefotaxime	Gentamicin
Cefepine	Ciprofloxacin
Amikacin	Imipenem
Levofloxacin	

Table 1.3 groups antibacterials into those likely to be highly resistant, meaning that there is a high probability of the pathogen to withstand the effects of the medicine or of low resistance, which infers a decreased probability of the microbe being resistant.

1.3.1 Range of activity of potential pathogens

Table 1.4 describes the respective antibacterial agents used to eradicate the pathogen present.

Table 1.4: Range of antibacterials used against the potential pathogens
[Adapted from] Van Seane H, Reilly N, De. Silvestre A, Nardi G. Antibiotic policies in the intensive care unit. Infection Control in the Intensive Care Unit. 2005: 231-246.

Pathogen	Antibacterials
S.pneumoniae	Penicillin G, Cefotaxime and Ceftazidime
H.Influenzae	Cefotaxime and Ceftazidime
M.catarrhalis	Cefotaxime, Ceftazidime and aminoglycosides
E.coli	Cefotaxime, ceftazidime, aminoglycosides and polymyxins

S.aureus	Cephradine, cefotaxime, ceftazidime, aminoglycosides (e.g. tobramycin) and glycopeptides (vancomycin)
Candida spp	Polyenes (Amphotericin B)
Klebsiella	Cefotaxime, ceftazidime, aminoglycosides and polymyxins (e.g. polymyxin E)
Proteus	Cefotaxime, ceftazidime and aminoglycosides
Morganella	Cefotaxime, ceftazidime and aminoglycosides
Citrobacter	Cefotaxime, ceftazidime, aminoglycosides and polymyxins
Enterobacter	Cefotaxime, ceftazidime, aminoglycosides and polymyxins
Serratia	Cefotaxime, ceftazidime and aminoglycosides
Acinetobacter	Cefotaxime, ceftazidime, aminoglycosides and polymyxins
Pseudomonas	Ceftazidime, aminoglycosides and polymyxins
MRSA	Glycopeptides

1.3.2 Trends in antibacterial use

A study carried out by Alvarez-Lerma, revealed that amid 490 cases of pneumonia acquired from the ICU environment, 214 cases (43.7%) needed a change in the primary antibacterial regimen owing to isolation of a resistant micro-organism (62.1%), or inefficient clinical response to therapy (36.0%). Amidst patients administered an initial unsuitable therapy, mortality from VAP was drastically lower (16.2%) than mortality in patients who received initial inappropriate therapy needing a change in treatment (24.7%). Leibovici et al. stated that mortality related to sepsis is notably increasing in improperly treated patients when evaluated against patients receiving appropriate antibacterial therapy (20% versus 34%) (Esposito et al, 2007).

An investigation was carried out in a 20-bed adult medical-surgical ICU unit of Hospital Santa Luzia in Brasilia-DF, Brazil. Antibacterial drug use was categorised by the ATC/DDD system adopted by WHO. Drugs were stratified into variant clusters based on the organ or system on which they exert their effect and according to their pharmacological and therapeutic traits. DDD presents the mean adult daily maintenance dose of a drug when used for its principal indication. The resultant figure, DDD_{1000} depicted the degree of usage of an antibacterial drug per 1,000 patient-days. The selected drugs were those antibacterial agents of class J01 of the ATC/DDD classification system (Santos et al, 2007).

Pneumonia, often related to the usage of mechanical ventilation, was the most prevelant infection type seen. This was followed by bloodstream infections, related to the use of a central vascular cannulation. Urinary catheters were linked with urinary infection. Penicillin/beta-lactamase inhibitors, third generation cephalosporins, quinolones, carbapenems, glycopeptides and second generation cephalosporins are the most commonly prescribed antibacterial drugs, presented in decreasing order (Santos et al, 2007).

By evaluating the mean utilization of all of the antibacterial drugs for a year, it was noted that there were no drastic changes in the period of 2001-2004. A noticeable rise in the mean use of penicillin/beta-lactamase inhibitors was seen. In contrast, a decrease in glycopeptide use was noticed. This was related to the increasing prescriptions for ampicillin/ sulbactam and amoxicillin/ clavulanic acid. Results show that every patient receives approximately, around two DDDs of antibacterial drugs per day whilst in the ICU. Indications were linked to the occurrence of hospital-acquired infections and drugs administered were those of broad spectrum activity. The mean global rate of nosocomial infection was of 9.8%, which showed reasonable control (Santos et al, 2007).

Overall use of antibacterials in the ICU of Hospital Santa Luzia, in Brazil was higher when compared to other ICUs in Germany and in Sweden. Swedish hospitals mainly used antibacterials with a more narrow spectrum of activity, like cefuroxime and

isoxazolylpenicillin. Regions, such as Sweden see a low frequency of resistant microoganisms when methicillin-sensitive *Staphylococcus aureus* is frequent. In hospital Santa Luzia, no relation between administration of carbapenems and marks of hospital infection was observed. This suggests improper use of such antibacterials.Stricter control of the application of invasive procedures would limit antibacterial agents use. Controlled hand hygiene and application of barrier techniques should also be enforced (Santos et al, 2007).

A surveillance study was conducted in Polish ICUs between April 15, 2014 and June 15, 2015. Survey questions, requesting the number of patient days in the ICU, the average length of ICU stay, and the antibacterial consumption in 2014 were sent to all ICUs. 134 adult ICUs participated and contributed their data for analysis. Antibacterial consumption ranged from 620 to 3960 DDD/1000 patient-days, having a mean of 1520 DDD/ patient days. Carbapenems, quinolones, and cephalosporins are the three antibacterial classes, most administered in Polish ICUs and the average duration of patients' stay in Polish ICUs was between 4.8 days to 35 days, with an average of 11.4 days (Trejnowska et al, 2018).

This study was compared to others based in European countries: in Germany, the SARI Surveillance System and in Sweden, the ICU-STRAMA (Hanberger et al, 2004; Meyer et al, 2013).

The mean annual antibacterial consumption in Poland was 1520 DDD per 1000 patient-days, which is higher when correlated to Germany, having 1305 DDD pd or Sweden, having 1147 DDD pd. In conclusion, the maximal yearly antibacterial usage in Sweden was comparable to Germany; 2134 DDD/1000 pd versus 2216 DDD/1000 pd respectively. Poland showed the highest consumption of the three, with 3960 DDD/1000 pd. The Polish Severe Sepsis Registry, showed that of the 4999 patients admitted to the ICU during the 7 year period, 2003-2009, 89% had a dysfunction of 3 or more organs & the majority of patients were intubated (Kubler et al, 2015).

1.4 Antibacterial resistance

Antibacterial resistance is a factor which affects outcomes for patients in the ICU. This is related to inappropriate prescribing of antibacterial drugs. Resistance impacts health care costs, hospital stays and illness related to antibacterial therapy failures (Kollef et al, 2001).

Antibacterial-use policy is a beneficial tool to cut expenses related to antibacterials and leads to less hospital acquired infections caused by antibacterial resistant micro-organisms. This is demonstrated in a study carried out in the Intensive Care Unit, Font Pré Hospital, Toulon France (Tosi et al, 2018).

A comparative study of before and after antibacterial use policy implementation was applied. This was conducted on an eleven-bed ICU in a general hospital, on patients admitted for a minimum of 48 hours in a five- hour period. Patients' general information, occurrence of nosocomial infections, antibacterial-selective pressure, presence and forms of multi-resistant micro-organisms and charges related to antibacterial use were reported before (1994) and after policy implementation (1995-1998). The results showed that a decline in nosocomial infections caused by antibacterial resistant micro-organisms was recognized: from 37 % (1994) to 15% (1998) of hospital-acquired infections, after 3 years of application of the policy, necessarily because of a decline in methicillin-resistant *Staphylococcus aureus* and ceftazidime-resistant *Enterobacteriaceae.* Hospital-acquired infections by cause of ceftazidime-resistant Pseudomonas species or extended-spectrum Beta-lactamase *Enterobacteriaceae* produced no decline (Geissler et al, 2003).

A DEFINE study carried out in North America on ICU patients with pneumonia published a 14.1% rate of multidrug resistant (MDR) infections, whilst the EUROBACT study on hospital bloodstream infections held in 24 global ICUs , demonstrated a mean of a 47.8% MDR infection rate (Lot et al, 2018).

Amidst gram-negative bacteria, the most common MDR micoorgansims isolated are extended spectrum beta-lactamases producers (ESBL) Enterobacteriaceae and MDR *Pseudomonas aeruginosa*, Acinetobacter spp. and *Stenotrophomonas maltophilia.* Vancomycin resistant

enterococci and Methicillin-resistant *Staphylococcus aureus* are the most commonly identified gram-positive microorganisms (Tosi et al, 2018).

1.4.1 Causes of antibacterial resistance

Antibacterial resistance has shown to be a substantial mortality cause for patients residing in the ICU. The occurrence of both antibacterial-resistant gram-negative bacteria and gram-positive bacteria have been published as being a result of nosocomial infections. Knowledge about the infection present and timing of diagnosis, helps select adequate antibacterial treatment. Duration of antibacterial administration is to be refined so as to limit antibacterial dosage regimens to the shortest possible period; such as eight days for hospital acquired pneumonia (Volles et al,2008).

The risk factors for antibacterial resistance are incorrect use of antibacterials, extended hospitilisation, application of invasive devices like endotracheal tubes and intravascular catheters and inappropriate infection control practice. Prolonged doses of antibacterial regimens, mostly with a single or principal antibacterial or drug class, proves to be the pivoting element leading up to the development of antibacterial resistance.Appropriate dosing, dosage interval and the period of administration need to be mediated for antibacterial efficacy, so as to limit toxicity and prevent new resistance trends from developing (Kollef et al, 2001).

1.4.2 Pathogens likely to be resistant to antibacterials

Organisms which are likely to be resistant to antibacteials include extended-spectrum beta-lactamases (ESBL) producing strains of *Escherichia col*i and *Klebsiella* species, multi-drug resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannnii*, and the resistant gram-positive organisms, MRSA and vancomycin-resistant enterococci (VRE) (Volles et al, 2008).

With regard to gram-positive microbes, vancomycin is the glycopeptide drug of choice. Its spectrum of activity incorporates many of aerobic and anaerobic gram-positive infections. These include MRSA, resistant *Streptococcus* pneumonia, the *Enterococcus* species, and

Clostridium difficile. Linezolid acts against aerobic gram-positive organisms, such as MRSA, *S.epidermidis, Enterococcus* species, and streptococci. The gram-negative aerobes include, *Nocardia* species, and *Mycobacteria* species. Daptomycin, acts mainly on most of the aerobic gram-positive infections, which include MRSA and VRE (Volles et al, 2008).

Colistin has gained importance in fighting strains of *Pseudomonas* and *Acinetobacter.* Tigecycline is used for both resistant gram-negative and gram-positive organisms, like MRSA and VRE, and also, gram-negative bacteria, that include ESBL-producing *Klebsiella* species and *Acinetobacter* species. Other antibacterials include, carbapenems, fluoroquinolones, and fourth generation cephalosporins, which consist of a broad spectrum family of beta- lactam drugs that show a positive pharmacokinetic and safety characteristics (Volles et al, 2008).

GNB infections are major and critical. Delaying therapy, or prescribing inappropriate antibacterial therapy, can lead to a critical effect on the patient's prognosis. Carbapenems produce their bactericidal effect by attaching to penicillin-binding proteins, PLPs, which results in a decreased endotoxin release in destruction of gram-negative bacilli. Resistance to carbapenems is a result of multiple mechanisms, which involve the production of beta-lactamases and flawed porins. Common risk factors for carbapenem resistance is previous of carbapenems administration, previous piperacillin-tazobactam treatment and duration of use, ventilator-acquired pneumonia and intravascular device use (Labaste et al, 2019).

A prospective, observational study was carried out in a 24-bed ICU in Toulouse Rangueil University Hospital, which hosts both surgical and medical patients. Seventy-eight of the 364 patients residing at the ICU were managed with carbapenem therapy for more than 48 hours. Meropenem was the most prescribed antibacterial at 97.5% and imipenem at 2.5%. The median age was 62.5 years, which 74.4% of the patients being male. Carbapenem therapy was administered for ventilator associated pneumonia, community-acquired pneumonia and bacteraemia. More than the majority of cases, 78.2% were prescribed as empirical therapy (Labaste et al, 2019).

In the study population analysed, 20.5% of the patients caught bacterial resistance after starting carbapenem treatment. This highlights the strict control needed for this class of antibacterials when administered in patients having an extended stay in the ICU. It was concluded that the duration of stay in an ICU of more than 29 days, and the existence of *Pseudomonas aeruginosa* in bacteriological samples prior to treatment were the two independent possible risks for acquiring carbapenem resistance (Labaste et al, 2019).

1.4.2.1 MRSA

The European Antimicrobial Resistance Surveillance System in 2007, showed that over 60% of *S. aureus* isolates were found in the ICU. Studies in the recent years, have shown that, in most European countries, decrease in antibacterial resistance was observed in ICUs (Petrosillo et al, 2010).

1.4.2.2 Enterococcus spp.

According to the Canadian National Intensive Care Unit study, vancomycin-resistant enterococci made up 6.7 % of all enterococci, with the *vanA* genotype, mainly *E.faecium* covering 88.2% of all VRE. Resistance is acquired through, overcrowding in wards, contaminated surfaces, patients' own risk factors, prolonged mechanical ventilation and indwelling catheters or invasive devices (Petrosillo et al, 2010).

1.4.2.3 ESBL-producing Enterobacteriaceae

Up to recent years, many of the infections caused by ESBL-producing bacteria were listed as hospital-acquired. Meyer *et al.* stated that there was a continued rise of third-generation cephalosporin-resistant *E.coli* and *Klebsiella pneumonia* from 2001 to 2007 in ICUs (Petrosillo et al, 2010).

1.4.2.4 Non-fermentative organisms: Pseudomonas aeruginosa and Acinetobacter baumannii

Carbapenem resistance rates escalated from 9% in 1995 to 40% in 2004 in *Acinecobacter baumannii* isolates. *A.baumannii* infections, mostly ventilator-associated pneumonia and blood-stream infections, affect severely ill patients in the ICUs. The main risk possibilities include increased age, immune suppression, major trauma or burn victims, use of invasive devices. International ICUs show that, the range of resistance to carbapenems in *P.aeruginosa* ranges from 10 to 48% (Petrosillo et al, 2010).

1.4.3 Antimicrobial susceptibility testing

1.4.3.1 Definitions of the susceptibility categories

Testing categories S, I and R for susceptibility were revised by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and are now correlated to the vulnerability of the infecting organism at the infection site (EUCAST, 2020).

The new definitions are:

Table 1.5: Clinical Breakpoints definitions
[Adopted from] : EUCAST: Clinical breakpoints and dosing of antibiotics [Internet]. Eucast.org. 2020 [cited 24 May 2020]. Available from: https://eucast.org/clinical_breakpoints/

S- Susceptible, standard dosing regimen: A microorganism is categorsied as Susceptible, standard dosing regimen, when there is a high likelihood of therapeutic success using a standard dosing regimen of the agent.
I- Susceptible, increased exposure: A microorganism is categorized as Susceptible, increased exposure, when there is a high likelihood of therapeutic success because exposure to the agent is increased by adjusting the dosing regimen or by its concentration at the site of infection.
R- Resistant: A microorganism is categorized as Resistant when there is a high likelihood of therapeutic failure even when there is increased exposure. *

*Exposure is a function of how the mode of administration, dose, dosing interval, infusion time, as well as distribution and excretion of the antimicrobial agent will influence the infecting organism at the site of infection.

1.4.3.2 Microbial resistance and epidemiological cut-off values (ECOFF)

Table 1.6: Epidemiological cut-off values
[Adopted from]: EUCAST: Clinical breakpoints and dosing of antibiotics [Internet]. Eucast.org. 2020 [cited 24 May 2020]. Available from: https://eucast.org/clinical_breakpoints/

Wild Type (WT)	**Microbiological resistance- Non-Wild Type (NWT)**
Classified as such by the absence of acquired and mutational resistance mechanisms to the drug subject.	Classified as such by the absence of acquired and mutational resistance mechanisms to the particular drug.
By application of the suitable cut-off value in a set phenotypic test organization.	By application of the suitable cut-off value in a set phenotypic test organism.
May or may not clinically be affected by antimicrobial therapy.	May or may not clinically be affected by antimicrobial therapy.

Presented as WT <_ z mg/l	Presented as NWT >z mg/l

Owing to the rise in antimicrobial resistance, rapid antimicrobial susceptibility testing (RAST) has become more valuable, particularly in patients with a BSI. Disc diffusion remains a commonly applied procedure for susceptibility testing, as it is relevant to an extensive spectrum of bacteria and does not require any special equipment. The standardized method established by EUCAST allowed for 16-20 hours of incubation. Based on the previously mentioned disc diffusion method, EUCAST developed a standardized rapid method, to provide susceptibility reports within 4-8 hours of a positive blood culture (BC), with reading times being available at 4, 6 and 8 hours. Past reports showed that inhibition zone size varies with incubation time, and that WT isolates and non WT isolates act divergently. Results show that with the EUCAST RAST method, reliable AST results can be available after 4-8 hours of positivity of BC bottles for seven bloodstream infection pathogens. In conclusion, empirical therapy should be avoided or used for a short time frame until effectual therapy is prescribed to severely-ill patients. Using this method, laboratories can report valid S and R results (Jonasson et al, 2020).

1.4.4 Ways to decrease antibacterial resistance

"Antibiotic resistance is a global and increasing problem that is not counterbalanced by the development of new therapeutic agents" (Plantinga et al, 2015).

Multiple strategies are being implemented to improve antibacterial use. Clinicians should make sure that antibacterial prescribing follows set requirements, that include proper dosages and interval time, optimal treatment period, monitoring of drug levels when required and prevention of undesired drug-drug interactions. The use of antibacterial protocols can avoid unrequired antibacterial prescriptions and increase efficiency of prescribed antibacterials (Kollef, 2006).

Hospital formulary restrictions are employed to counteract methodologic problems. The restrictions include restriction of antibacterials with a broad spectrum activity, like carbapenems or those with a quick onset of resistance, such as cephalosporins and

aminoglycosides, which show an immediate toxification result. The use of an antibacterial protocol, introduced by Rahal et al and based in a community hospital in Queens, New York, limited the clinical usage of cephalosporins. This restriction of cephalosporins served as a way to combat an infection with extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae.* An 80.1 % decrease in hospital administration of the latter microbe, was accompanied with a 44.0% infection decline and colonization with the extended-spectrum beta-lactamase-producing *K. pneumoniae* (Kollef et al, 2001)

Use of narrow-spectrum antibacterials target mainly non-life-threatening infections and also community-acquired pneumonia. Narrow spectrum antibacterials; penicillin, trimethoprim and gentamicin, which in contrast to the broad-spectrum agents, like cephalosporins have been successful in limiting infections with *Clostridium difficile* (Kollef et al, 2001).

As a method to improve treatment, combination therapy seems to be an effective alternative. This is also used as a prevention of developing resistance. Utilization of such technique, is seen in antiretroviral combination therapy which has changed HIV infection management, *Tubercule bacillus*, *Helicobacter* infection, brucellosis and enterococcal endocarditis. The advantage is the synergistic effect, which up to this point is based on *in vitro* studies. Enhanced bactericidal efficiency should contain evolution of resistant subgroups, limiting the development of recently resistant microbes. Combination therapy presents a possibly valuable alternative for MDR Gram-negative microbes, which include *Klebsiella* spp., *P.aeruginosa* and *A.baumannii.* (Petrosillo et al, 2010).

A variable is the insufficiency of random, controlled studies which consist of an appropriate sample proportion. The start of antibacterial therapy, sufficiency of empirical treatment, harmonization infections, negative effects and superinfections are all factors that could influence the end result of the study (Petrosillo et al, 2010).

Antibacterial cycling, where an antibacterial class is retreated from use during a set period of time and reintroduced later on so as to try and restrict bacterial resistance to the re-administered

antibacterial drugs can be used. Gerding et al., evaluated an aminoglycoside cycling over a 10-year period at the Minneapolis Veterans Affairs Medical Center, cycling amikacin and gentamicin. Administration of aminoglycosides has declined over the time frame of this study, effectively resulting in the reduced resistance (Kollef et al, 2001).

Therapeutic drug monitoring (TDM) can be a valuable action towards further accurate dosing in the severely ill. TDM affects measuring drug concentrations in patients to estimate improvement of the pharmacodynamic scope. It is pointed out for drugs which have a narrow therapeutic spectrum & an elevated personal pharmacokinetic variation, such as, aminoglycosides and vancomycin (Economou et al, 2017).

Stewardship teams consist of infectious disease doctors and infectious disease pharmacists, who can help in patient assessment and bestow counsel on amending therapy. Antibiotic time outs (ATO) have been enforced in some centres. ATO is an official measure of re-evaluating antibacterial therapy 48 to 72 hours after commencement. Implementation of ATO, results in a decrease in antibacterial cost due to patients receiving a more restricted therapy course (Lane et al, 2017).

1.4.4.1 Non- antimicrobial prevention strategies

Qushmaq et al, stated that the act of hand-washing contributes to major infection control method, both in acute health care setting and also in controlling the challenge of hospital-acquired infections. Although observational studies highlight the relationship between hand hygiene, hospital acquired infections and antibacterial resistance bacteria, there are no randomized trials designating this. This is applicable in the ICU due to the intimate interaction with patients and health-care workers. Severely-ill patients are more vulnerable to hospital-acquired infection, because of their immune-compromised well-being (Qushmaq et al,2008).

"Hand hygiene guidelines endorsed by the Society for Healthcare Epidemiology of America, the Association for Professionals in Infection Control, and the Infectious Diseases Society of America, recommend that clinicians wash hands with soap and water, or disinfectant, for at

least 15 seconds before and after patient contact and after any contact with a source of micro-organisms" (Qushmaq et al,2008).

An observational study of hand hygiene methods was carried out among clinicians with six multi-disciplinary ICUs at four hospitals in Hamilton, Ontario. The ICU management was blinded to the study objective and study time (Qushmaq et al, 2008).

Table 1.7: Variation in hand hygiene practice in the intensive care units among 4 hospitals
[Adopted from] Qushmaq I, Heels-Ansdell D, Cook D, Loeb M, Meade M. Hand hygiene in the intensive care unit: prospective observations of clinical practice. 2008; 118(10):543-547.

Participating hospitals	**Number of clinicians**	**Proportion of clinicians using hand hygiene (95%)**
Center 1	41	39.0
Center 2	30	66.7
Center 3	27	66.7
Center 4	17	70.6

The method of action planning has demonstrated success in bridging the intention-behaviour gap in other sectors, and should be of use in improving the hand hygiene behaviour field also (Erasmus et al, 2010).

The expenses involved with infection control methods are to be equalized with the expenses resulting from hospital-acquired infections which are targeted at prevention. Innovative approaches, which could affect the progress of resistance, include using vaccines directed against the pili of gram-negative bacteria, like *P.aeruginosa,* thus restricting host colonization with such pathogens (Kollef, 2006).

Innovative utilization of present antibacterials could aid in preserving antibacterial vulnerability. Further studies are required for the concept of antibacterial rotation to be effectual. This would provide a flexible and low cost intervention. Future aims include

restricting prescriptions to those patients that require the respective antibacterials, and minimising the therapy period, which is managed by antibacterial stewardship teams. New antibacterial classes are required. Companies strive to prompt drug discovery, rapid clinical assessment of novel antimicrobial drugs and examine for potential of innovative antibacterial models (Plantiga et al, 2015).

Compelling incentives were put forward with regards to re-examining current dosing regimen to maintain therapeutic adequacy in a scenario where new antibacterials are added to clinical practice. Strategies are to be put forward to achieve appropriate loading doses, correct infusions, and therapeutic drug monitoring, which are supported by the increasing pharmacokinetic/ pharmacodynamics data (Udy et al, 2013).

An accurate drug profile, could lead to individualized patient therapy, where beneficial clinical outcomes can be attained for patients (Roberts et al, 2014).Suitable culture collection and biomarker use, can assist optimal antibacterial therapy and more efficacious, directed infection treatment. Gram stain and culture, molecular diagnostics, and procalcitonin are some factors that could reinforce management of antibacterials. A pedestal of antibacterial stewardship is de-escalation of empiric antibacterials established on culture results and clinical judgement. Longer antibacterial courses of broad-ranging therapy do not certainly boost patient treatment outcome and may result in a higher risk of multidrug resistant organisms (Montravers, 2016).

1.5 Aims of the study

The aims for this study were:

- To conduct a retrospective drug utilization study, by analysing the trend in antibacterials administered in the local ICU for the last 9 years and comparing them to present trends.
- To present a scenario analysis of the current use of antibacterial drugs in the ICU, with focus on respective classes, dosage regimens, indications for use and pharmaceutical formulations.

Chapter 2: Methodology

2.1 Procedure

Authorization was granted by the Faculty University Research Ethics Committee (UREC) and the CEO of Mater Dei Hospital for access to hospital data (Appendix I; III). A scenario analysis of antibacterial use was carried out in the ICU at Mater Dei Hospital. A data collection form was designed and approved by health care professionals (Appendix II). Data was then analyzed using Excel 2013 version.

2.1.1 Preliminary Research

Literature review was carried out on antibacterial use in the ICU; including pharmacotherapy, dosage regimens and trends in administration. Antibacterial resistance was addressed through identifying likely resistant pathogens and discussing ways to decrease the emerging resistance. Online journals, books and guidelines on antibacterial administration were the information sources utilised. Informal meetings were held with healthcare professionals in the ICU at Mater Dei Hospital.

2.1.2 Ethical Approval

The study conducted involved analysis of the consumption of antibacterial data of the past 9 years and viewing the patients' medical records in the ICU at Mater Dei Hospital. Relevant authorities; the data protection officer (Appendix IV), the chief executive officer, the chairman of the Department of Anaesthesia (Appendix V) and the head clinician of the ICU (Appendix VI) at Mater Dei Hospital endorsed the study and it was stressed that the patients' identity was anonymized.

2.1.3 Setting

A scenario analysis of antibacterial use in the Intensive Care Unit at Mater Dei Hospital.

2.1.4 Inclusion and Exclusion Criteria

Patients incorporated in this study were critically ill adult patients who were administered an antibacterial for prophylaxis, empirical or definitive treatment. The inclusion criteria were adults over 18 years and the exclusion criteria were patients under 18 years.

2.1.5 Data collection form

An antibacterial information sheet was developed to facilitate recording of raw data. This was applied for the prospective part of this dissertation, where ICU visits were carried out every two weeks for a duration of 4 months. The data collection form was validated by the different healthcare professionals (one antibacterial pharmacist, ITU head clinician & chairman for the anaesthesia department). Health care professionals were asked to comment on the data collection form content and advise on any variables which should be included or excluded. The layout of the data collection form was clear and easy to use.

The validated antibacterial information sheet (Appendix II) was divided in the following sections. The first part consisted of demographic data which includes gender, male (M) or female (F) respectively and patient's age. The second part of the form related information on antibacterial/s administered, dose, frequency and route of administration, e.g. intravenous, intramuscular, oral or subcutaneously. The third part described the reason for administration, whether it was a community acquired infection, hospital acquired, or given for surgical/medical prophylaxis. The indication for use was categorized under prophylaxis (P), empirical (E) and definitive (D). The primary organ affected by the illness is noted e.g. respiratory, cardiovascular, central nervous system. The fourth and final part lists the treatment start date, whether there was a change from antibacterial, and if yes, which. Any escalation or de-escalation in antibacterial therapy was noted. [1]

[1] Global Point Prevalence Survey of Antimicrobial Consumption and Resistance [Internet]. Global PPS. 2019 [cited 8 December 2019].
Available from: http://www.global- pps.com/documents/

2.1.6 Data collection

Data collection was carried out in the ICU at Mater Dei Hospital. For the prospective part of the study, patients were given a code so as to maintain patients' anonymity. Patients' medical records and drug treatment charts, available at the patients' bedside were reviewed for data including, antibacterial/s administered, dosage & route of administration. Data was recorded in the validated data collection form. For the retrospective part of the study, hospital data was obtained on an excel sheet, showing annual antibacterial consumption from the year 2009 to 2017. Individual antibacterials were labelled according to their ATC code and DDD was used a value to show data consumption. The DDD are extracted from the MDH-Pharmacy database (Access Dimensions) through a dedicated report by (crystal reports) extracting data for antibacterials in DDD. Data was extracted using the 2017 ATC/DDD version. The occupied bed days (OBD) were extracted from the hospital patient administration system (PAS/CPAS) issued internally by the Central Performance Unit of MDH. Information about antibacterial costing for Malta for 2018 was also gathered from the Central Performance Unit of MDH.

2.1.7 Data analysis

Data was inputted in Microsoft Excel 2013 spreadsheet for analysis. A statistician was consulted to inquire about the feasibility of statistical interpretation of the recorded data. Data was presented using bar graphs, clustered columns, pie charts, tables and also described

textually. The ATC/DDD as designated by WHO is applied.[2] This system allows for harmonization of drug groups and constitutes a steady drug utilization tool to permit comparisons of drug use between countries and different health care sectors, allowing for analysis in trends in drug use through the years. "The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults." A single DDD is given for each ATC code and route of administration, e.g. parenteral administration. [2]

The list of ATC classes of antimicrobials encompassed in this study were antibacterials J01(J), presented in Table 2.1, Metronidazole P01AB01 (P), Vancomycin A07AA09 (A). Rifampicin J04AB02 (J04) and Rifabutin J04AB04 (J04).

[2] World Health Organisation (WHO). Purpose of the ATC/DDD system [Internet]. *Whocc*.no.2019 [cited 2020 January 17].
Available from: https://www.whocc.no/atc_ddd_index/

Table 2.1: List of JO1 (J) antibacterials in ATC 4

ATC4 Classification	Antibacterial
J01AA	Tetracyclines
J01BA	Amphenicols
J01CA	Penicillins with extended spectrum
J01CE	Beta-lactamase sensitive penicillins
J01CF	Beta-lactamase resistant penicillins
J01CR	Combinations of penicillins, including beta-lactamase inhibitors
J01DB	1st generation cephalosporins
J01DC	2nd generation cephalosporins
J01DD	3rd generation cephalosporin
J01DF	Monobactams
J01DH	Carbapenems
J01EC	Intermediate-acting sulfonamides
J01EE	Combination of sulfonamides & trimethoprim
J01FA	Macrolides
J01FF	Lincosamides
J01GB	Other Aminoglycosides
J01MA	Fluoroquinolones
J01XA	Glycopeptide antibacterials
J01XB	Polymyxins
J01XC	Steroid antibacterials
J01XD	Imidazole derivatives
J01XE	Nitrofuran derivatives
J01XX	Other antibacterials

Chapter 3: Results

3.1 Retrospective data analysis

Section 3.1 focuses on the retrospective part of the study, referring to data gathered during the period 2009-2017. Trends in use, both annually and per antibacterial class are described.

3.1.1 Trends in quantitative DDD use

Graphs showing the different DDD utilization values, namely; occupied bed days (OBD), defined daily doses per patient (DDD P-T), which is deliberated by dividing the utilization of DDDs with the number of patients, and defined daily doses per 100 bed-days (DDD/100 bed-days), which is a useful value when the drugs administered to inpatients are studied.

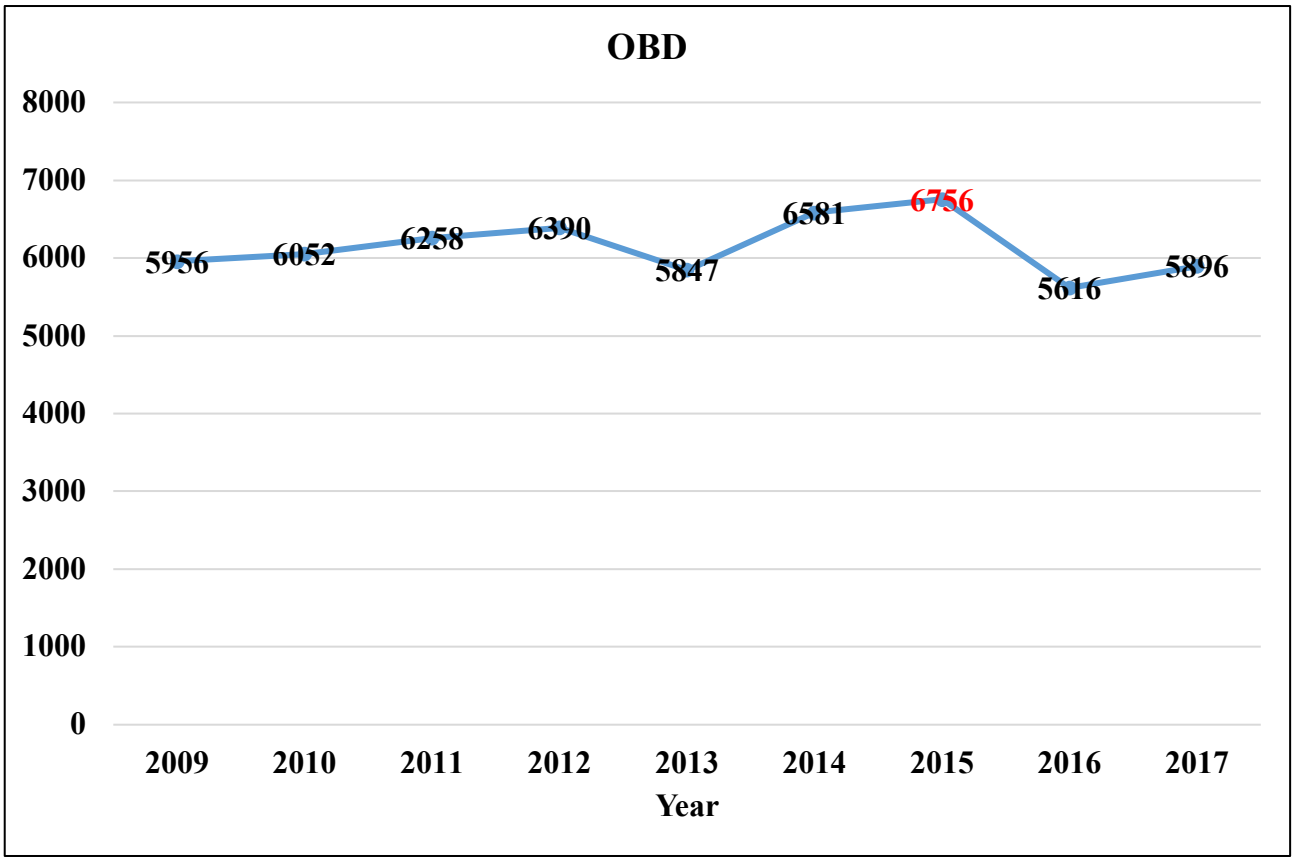

Figure 3.1: Occupied bed days during the years 2009-2017

Figure 3.1 shows the OBD at MDH ICU during the 9-year period analysed. The highest value is seen for the year 2015, at 6756, and the lowest value seen the following year, 2016.

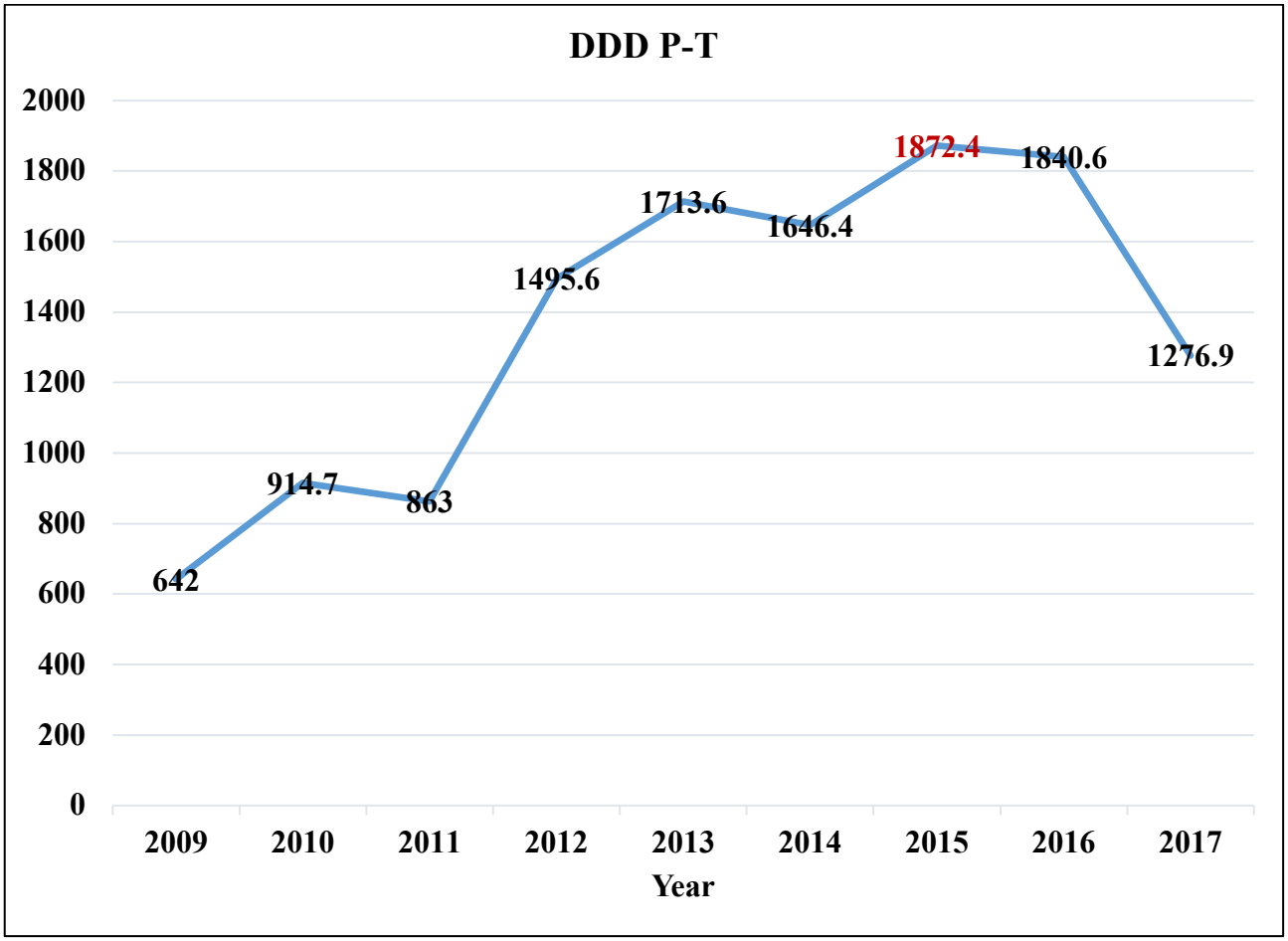

Figure 3.2: Average DDD-PT consumption during the years 2009-2017

Figure 3.2 represents a value for DDD/ patient, which considers the number of patients being medicated, together with the amount of treatment drugs consumed in a specific period of time. The values increase steadily from 2009 to 2013, with the highest values observed for the years 2015 and 2016.

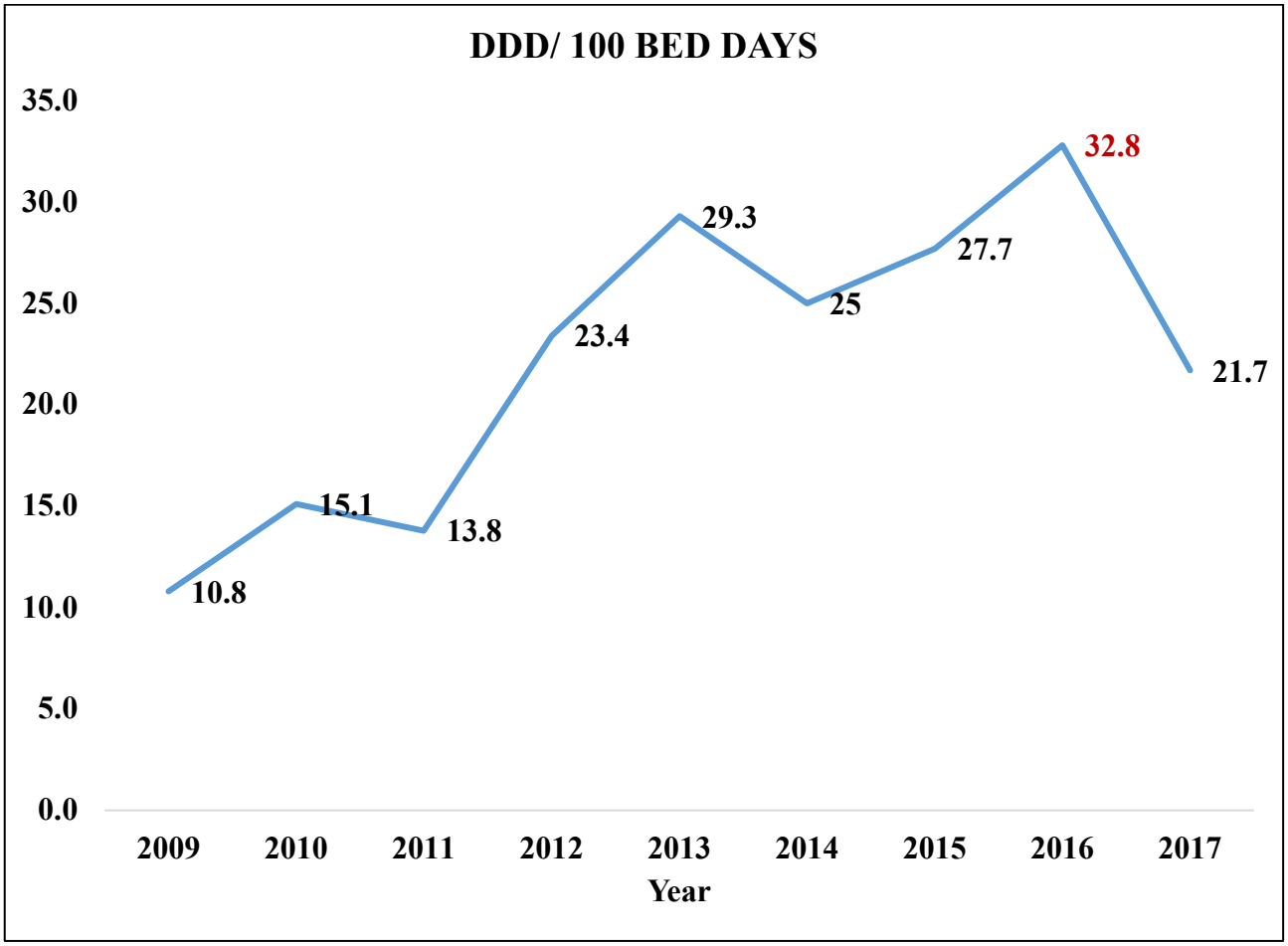

Figure 3.3: DDD/100 bed days during the years 2009-2017

Figure 3.3 incorporates the utilization of DDDs in relation to the OBDs, which results in a value for DDD/ 100 bed days. The highest utilization of DDD can be observed for the year 2016, at 32.8 and the least in 2009, at 10.8. This value is calculated by dividing utilization of DDDs with the number of occupied bed days, multiplied by 100.

3.1.2 Surveillance of antibacterial consumption

The following section describes the trend of use for each year during the period 2009-2017, classified according to class ATC4 as per WHO classification. The highest DDD consumption value is highlighted in dark red, for both sub-section 3.1.2.1 & 3.1.2.2.

3.1.2.1 Data for the period 2009-2017

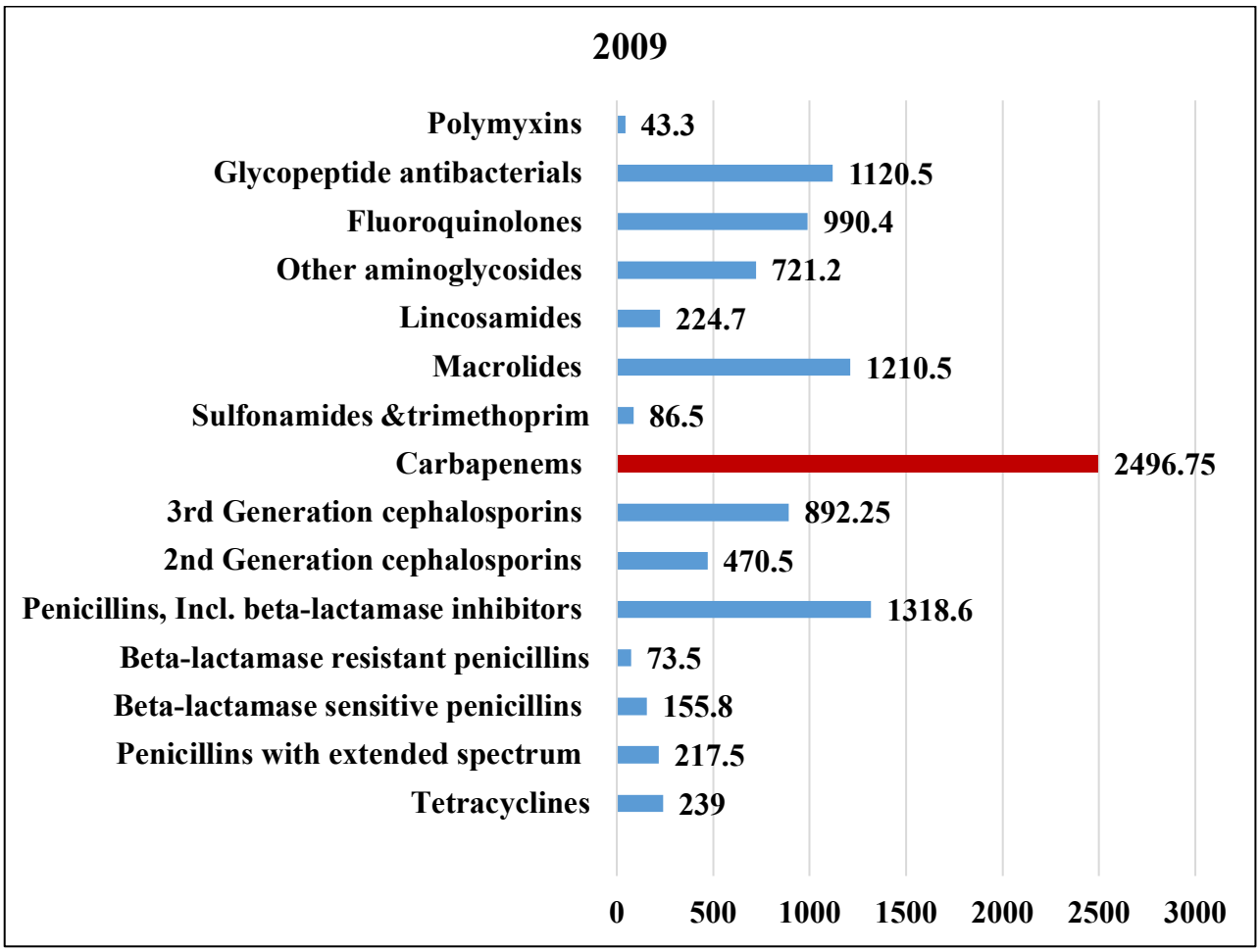

Figure 3.4: Antibacterial use in DDD value for the year 2009

Figure 3.4 highlights the use of the most common antibacterials administered in 2009. The highest DDD consumption value was observed for the antibacterial class carbapenems.

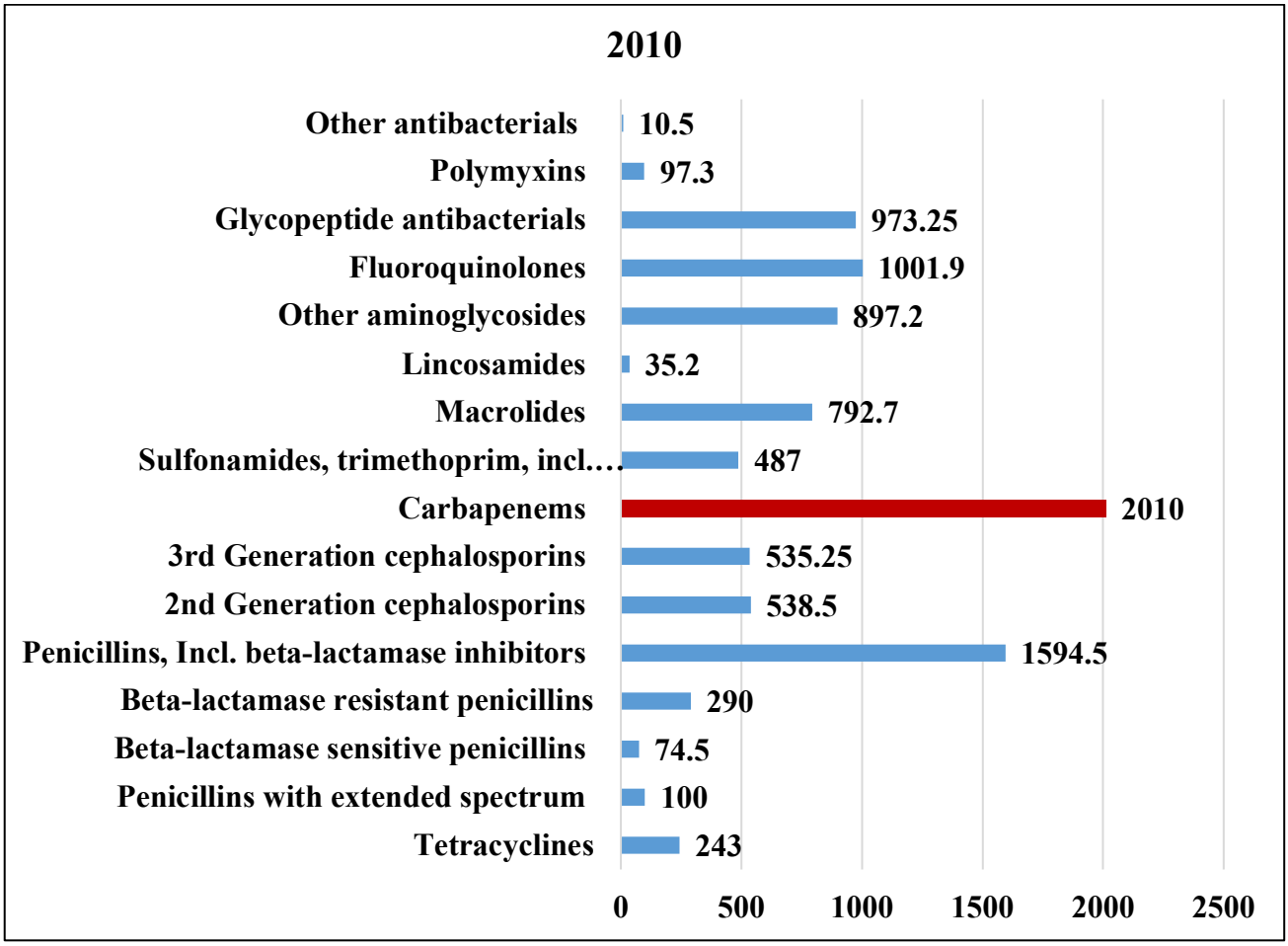

Figure 3.5: Antibacterial use in DDD value for the year 2010

Figure 3.5 highlights the use of the most common antibacterials administered in 2010. Carbapenems are the most administered, followed by the penicillins, including beta-lactamase inhibitors.

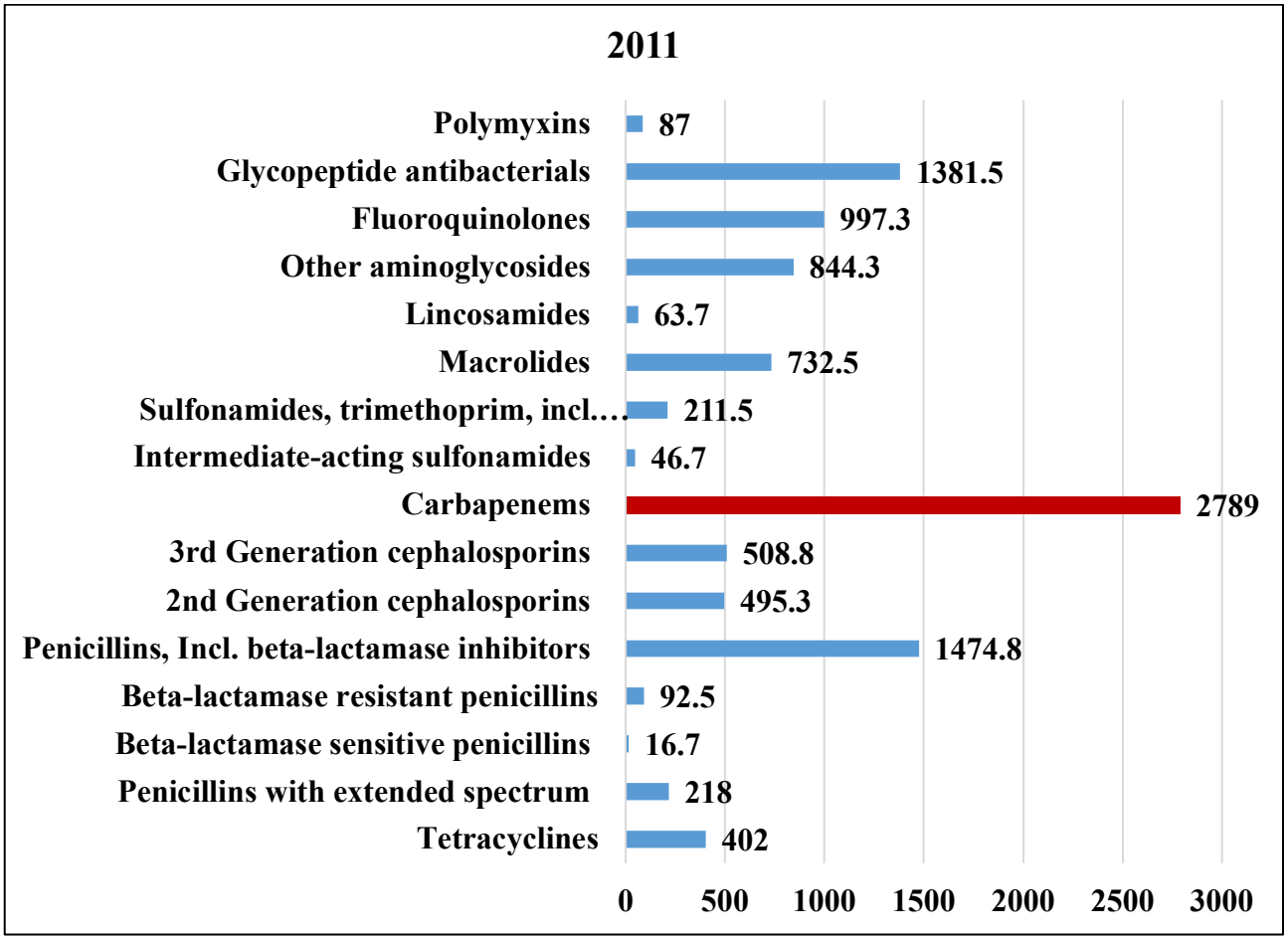

Figure 3.6: Antibacterial use in DDD value for the year 2011

Figure 3.6 highlights the use of the most common antibacterials administered in 2011. Carbapenems and penicillins, including beta-lactamase inhibitors show the highest DDD use.

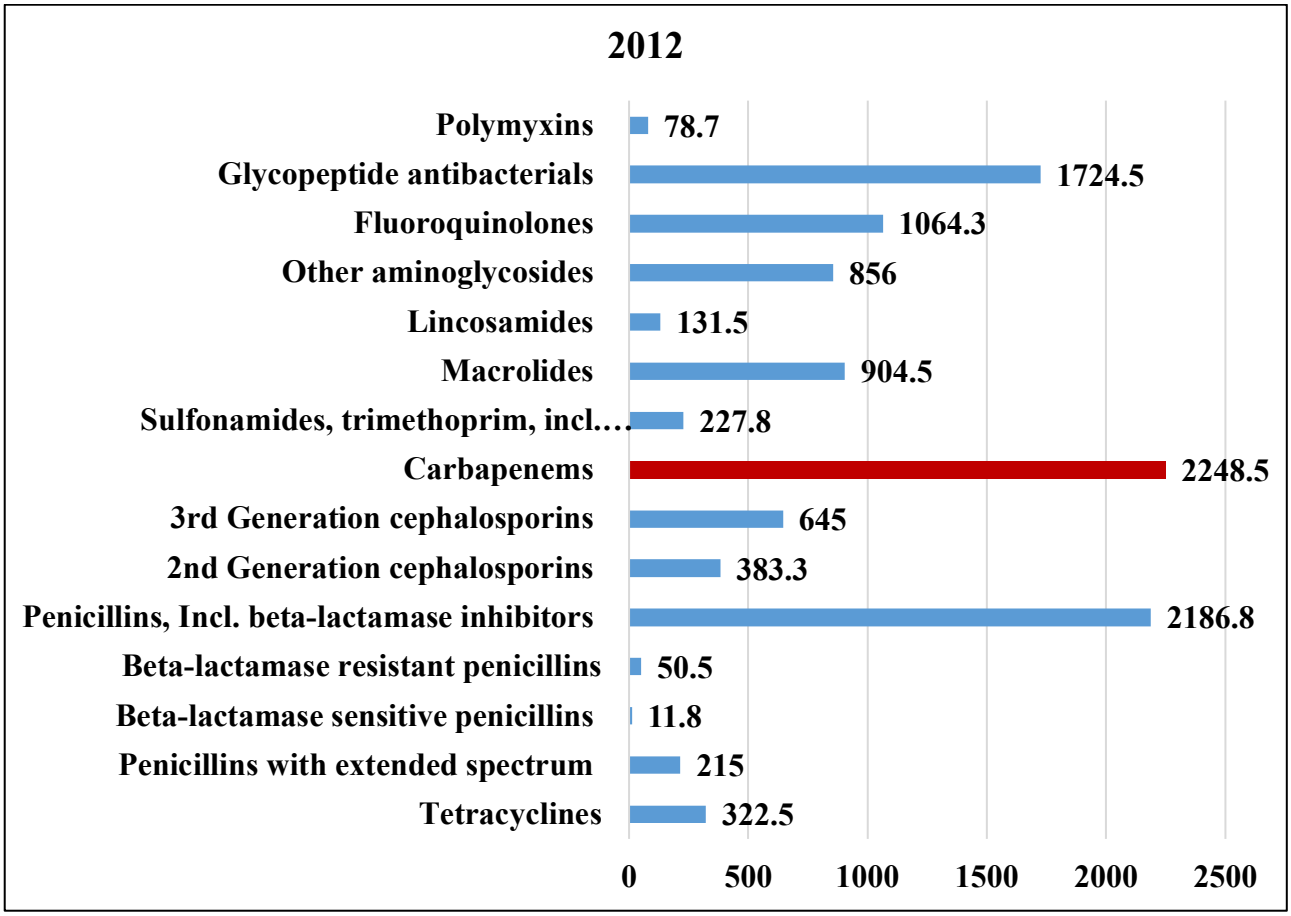

Figure 3.7: Antibacterial use in DDD value for the year 2012

Figure 3.7 highlights the use of the most common antibacterials administered in 2012. Carbapenems and penicillins, including beta-lactamase inhibitors are seen as the two most routinely prescribed antibacterials.

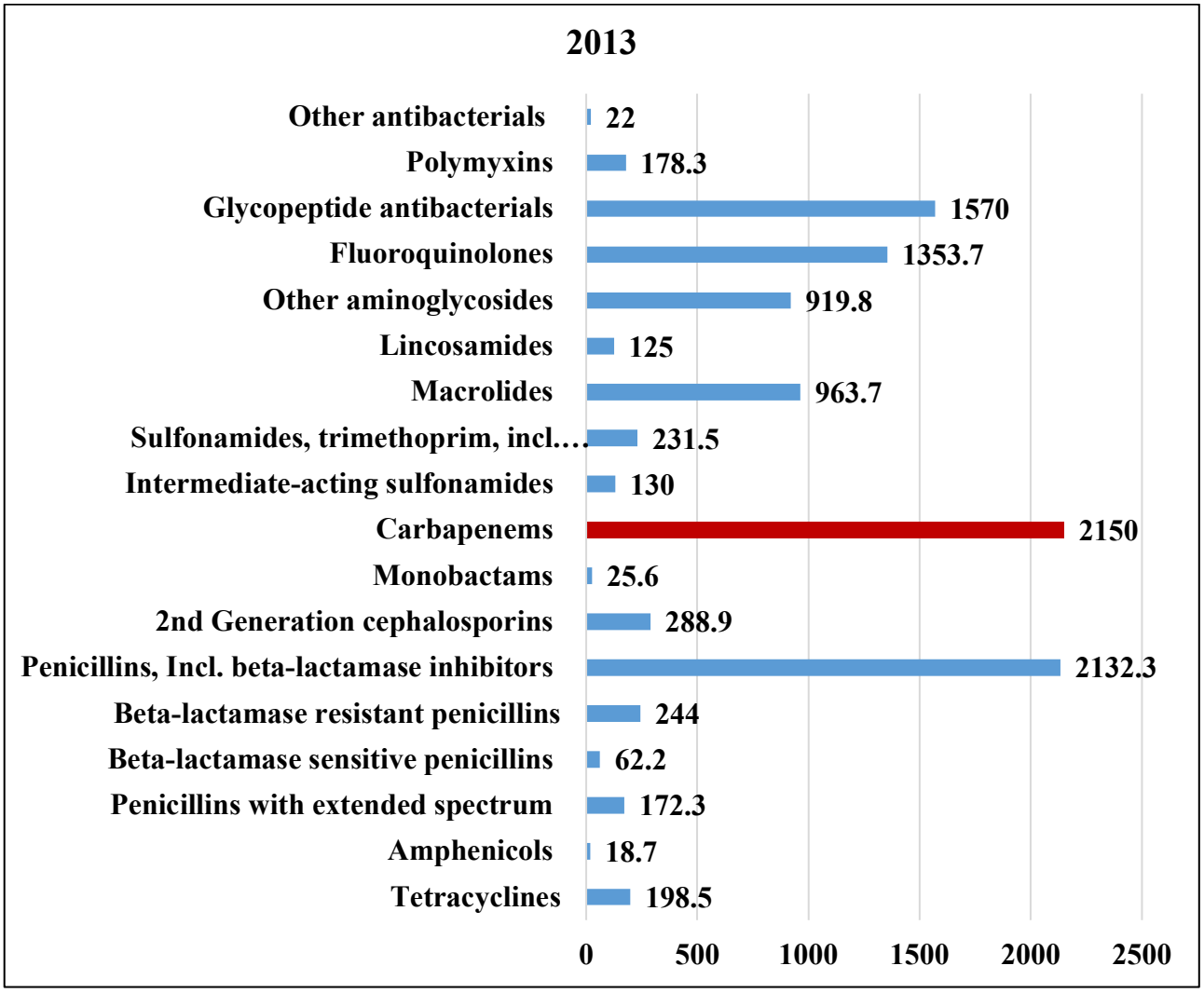

Figure 3.8: Antibacterial use in DDD value for the year 2013

Figure 3.8 highlights the use of the most common antibacterials administered in 2013. Carbapenems and penicillins, including beta-lactamase inhibitors were the two most frequently prescribed antibacterials.

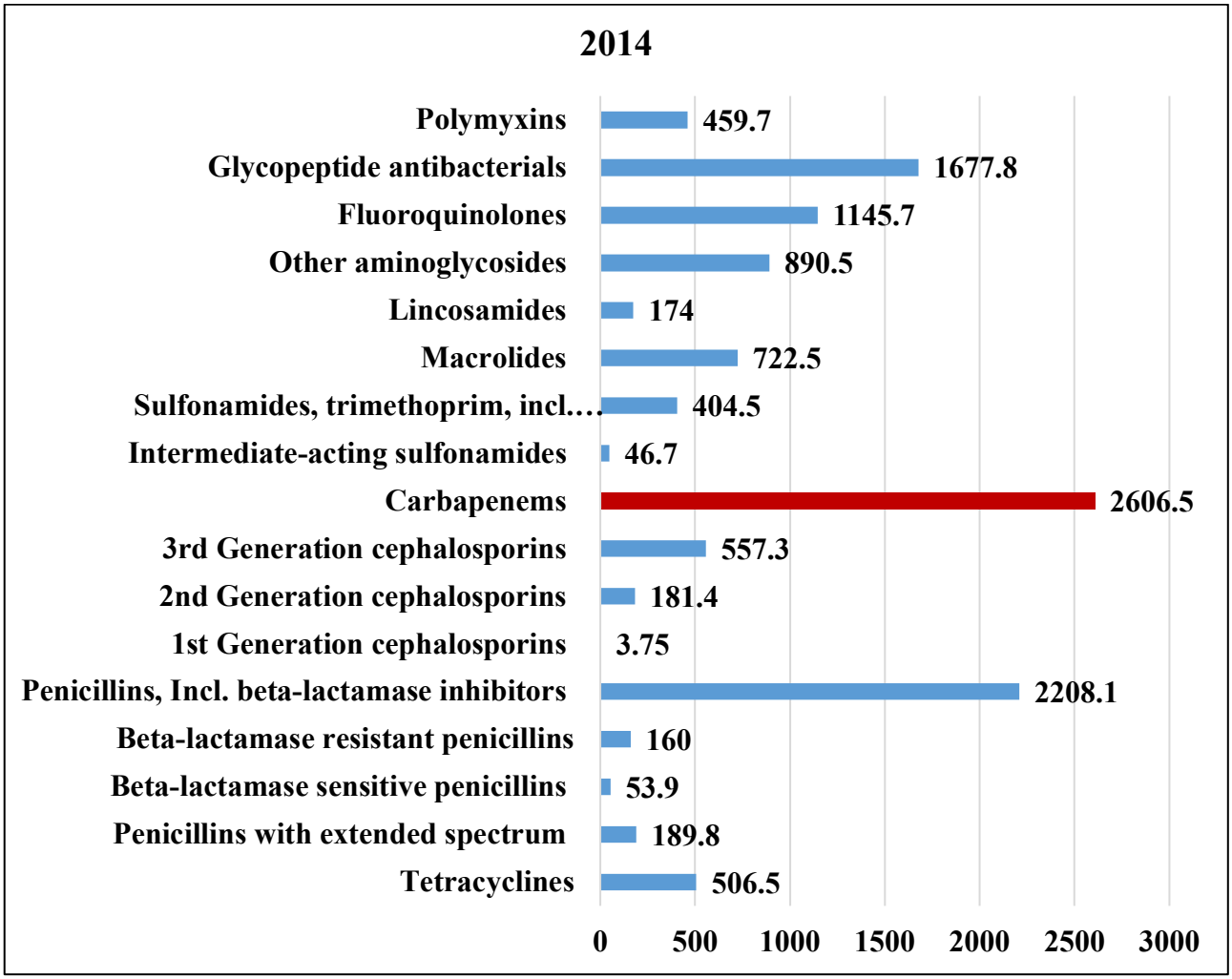

Figure 3.9: Antibacterial use in DDD value for the year 2014

Figure 3.9 highlights the use of the most common antibacterials administered in 2014. Carbapenems and penicillins, including beta-lactamase inhibitors had the two highest DDD consumption values.

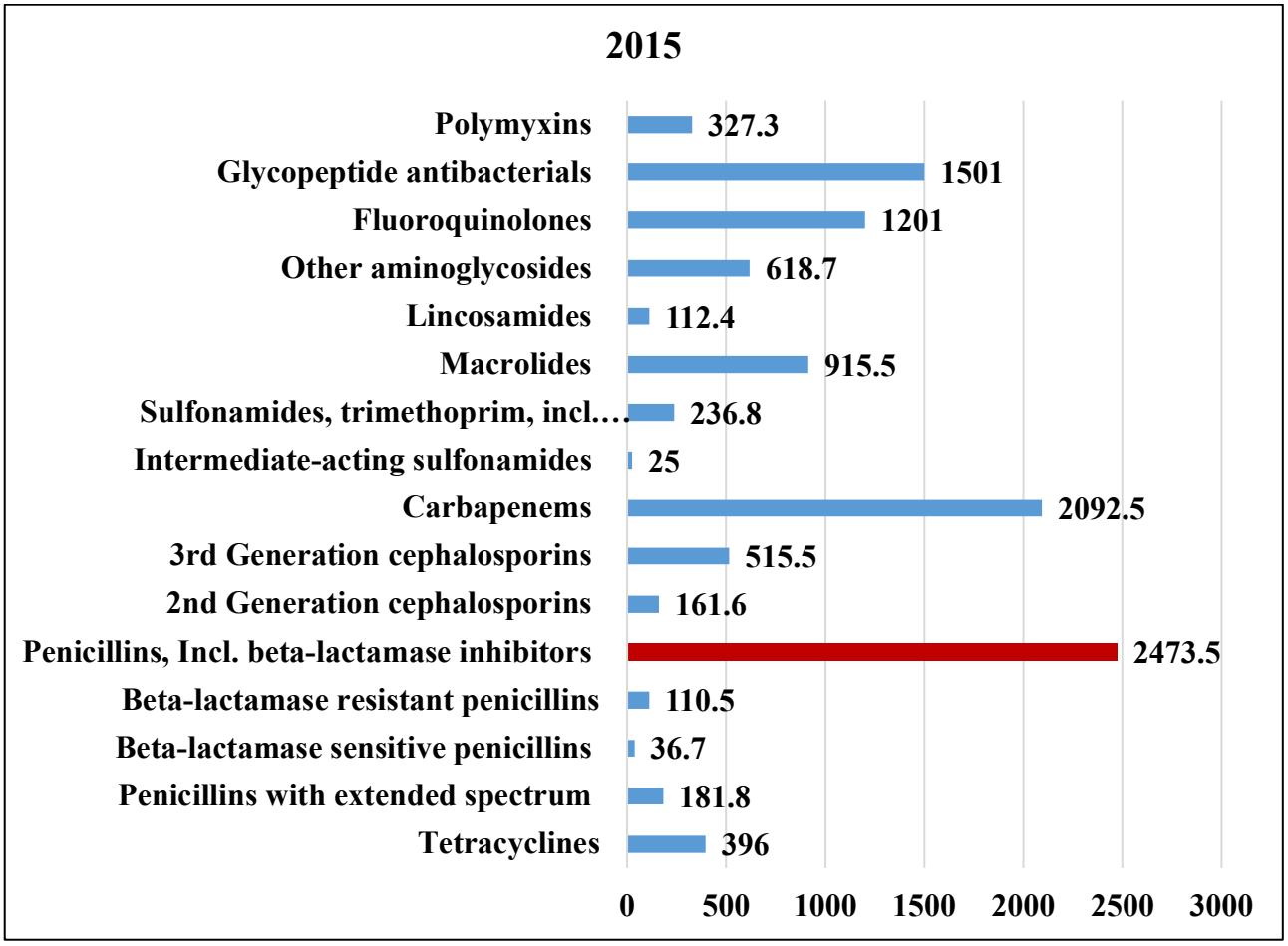

Figure 3.10: Antibacterial use in DDD value for the year 2015

Figure 3.10 highlights the use of the most common antibacterials administered in 2015. The penicillins, including beta-lactamase inhibitors were the most frequently antibacterial class prescribed, followed by carbapenems.

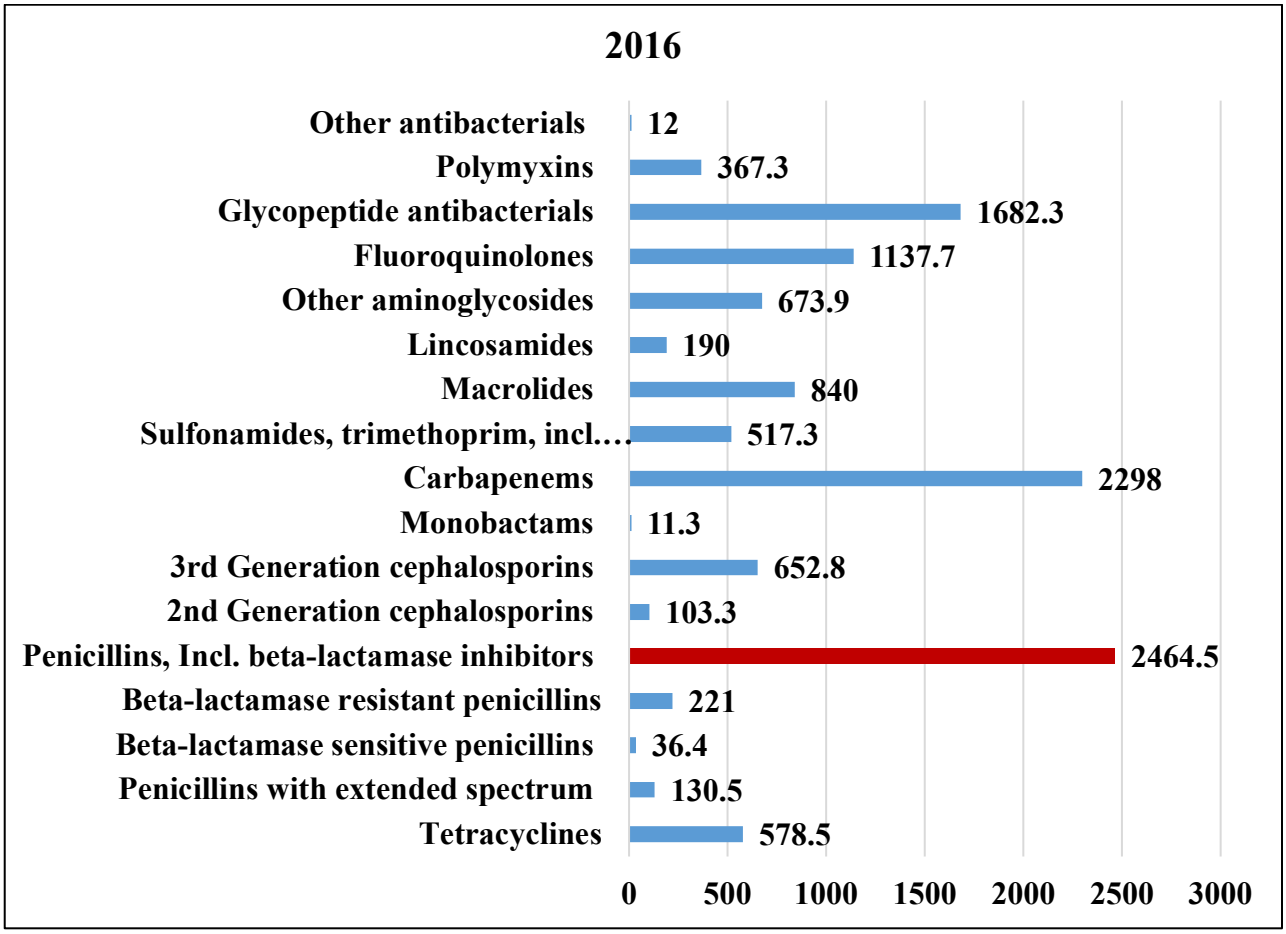

Figure 3.11: Antibacterial use in DDD value for the year 2016

Figure 3.11 highlights the use of the most common antibacterials administered in 2016. Penicillins, including beta-lactamase inhibitors were the most frequently prescribed antibacterial class.

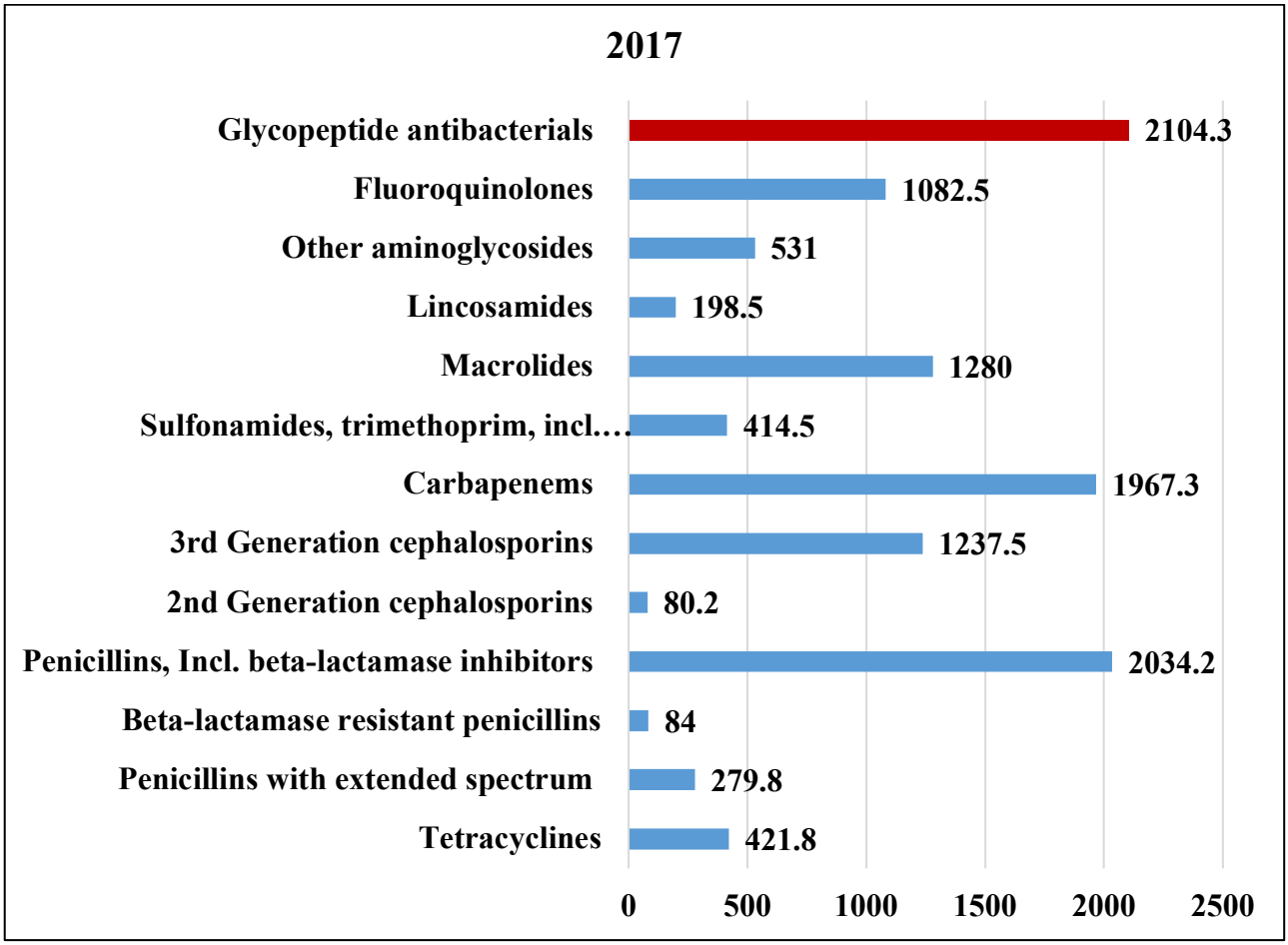

Figure 3.12: Antibacterial use in DDD value for the year 2017

Figure 3.12 highlights the use of the most common antibacterials administered in 2017. The glycopeptide class of antibacterials were observed to have the highest DDD consumption value, followed by the penicillins, including beta-lactamase inhibitors.

3.1.3 Trends in Antibacterial use, classified in ATC4 & ATC5

The following section describes trends of use of each antibacterial class, per year, administered in the ICU during the period 2009-2017. Classifications in DDD value, first grouped under ATC4, and then followed by a more in-depth classification, grouped under ATC5, for the most commonly prescribed antibacterials. The value showing the highest consumption through the years is highlighted in red.

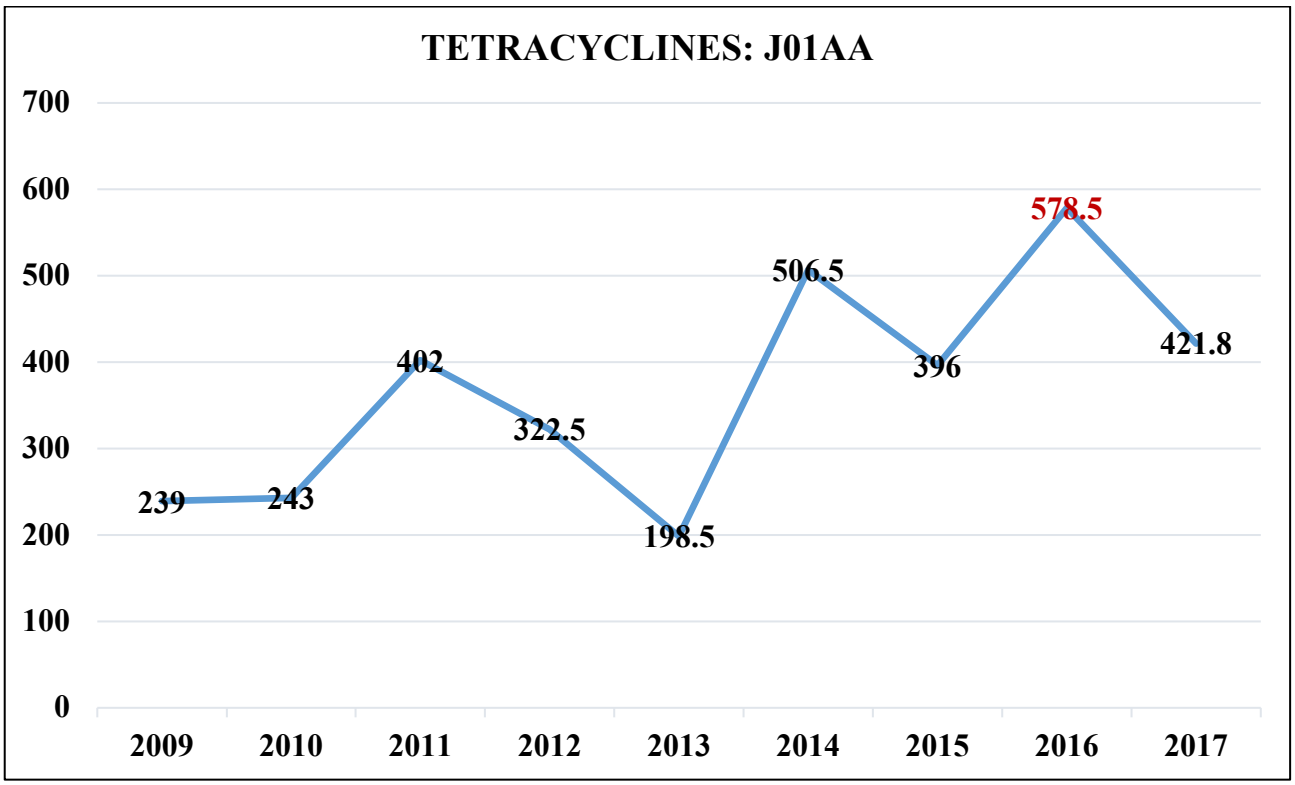

Figure 3.13: ATC class Tetracyclines

Figure 3.13 shows the highest DDD consumption of tetracyclines for the year 2016, and the least for 2009.

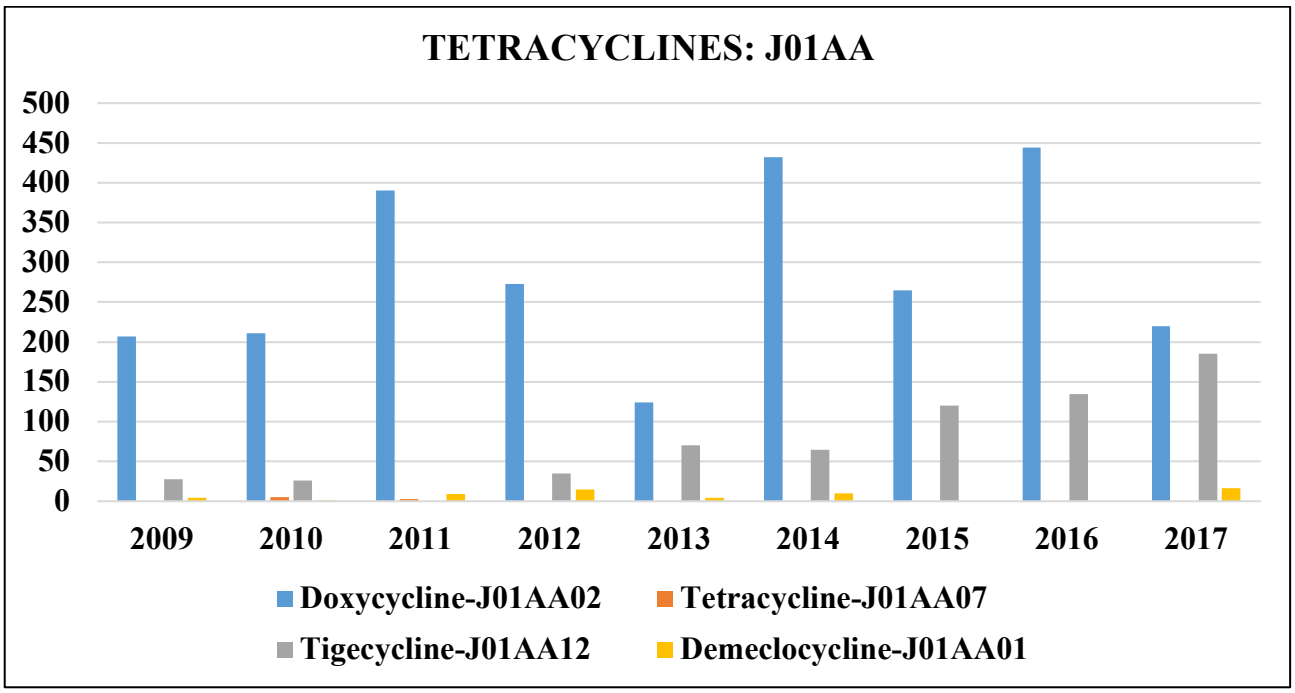

Figure 3.14: Trends in use of Tetracyclines

An increasing trend in DDD administration of tetracyclines was observed, in figure 3.14, from the year 2009 till 2017, with the mostly used tetracycline, being doxycycline.

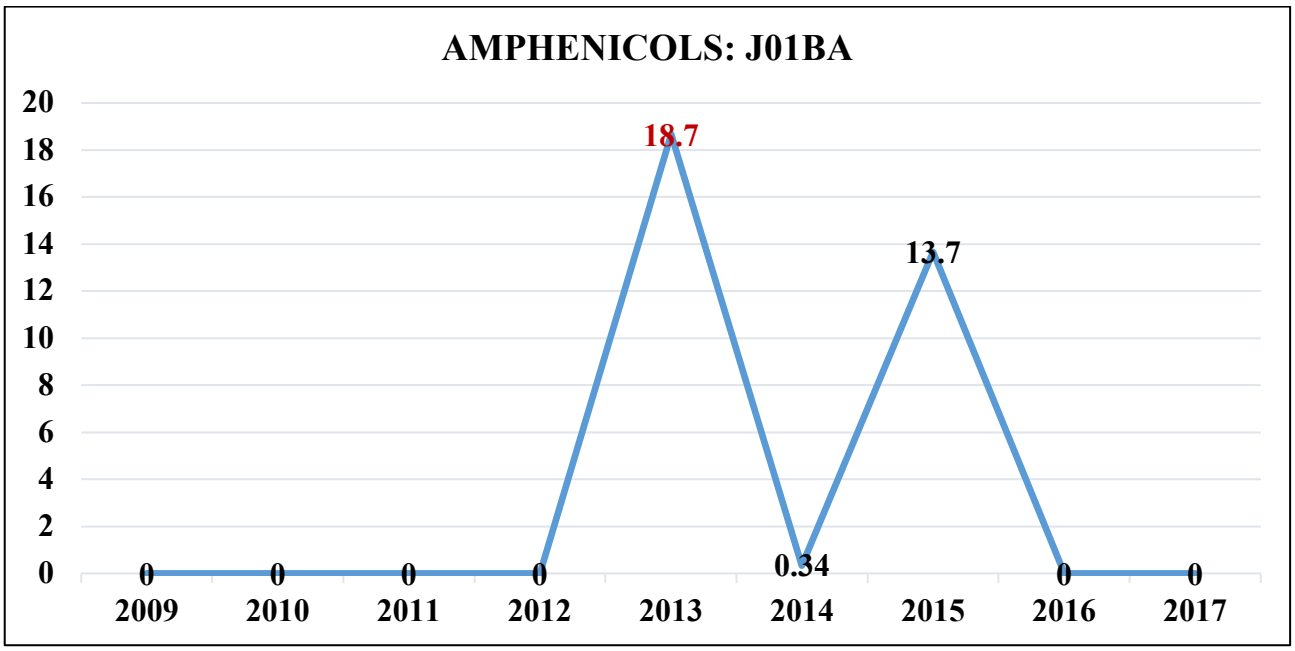

Figure 3.15: ATC class Amphenicols

Figure 3.15 show a peak in amphenicol DDD use for the year 2013 and 2015.

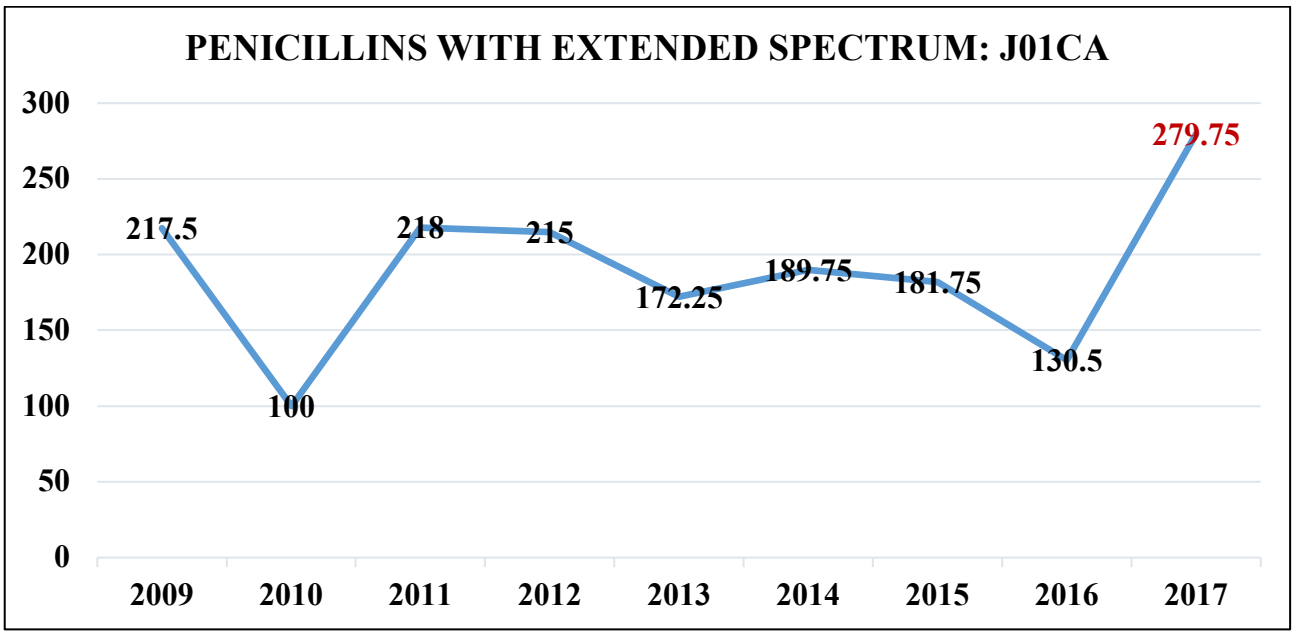

Figure 3.16: ATC class Penicillins with extended spectrum

Figure 3.16 shows a fairly stable DDD use for the penicillins with extended spectrum. The highest DDD consumption value can be observed for the year 2017.

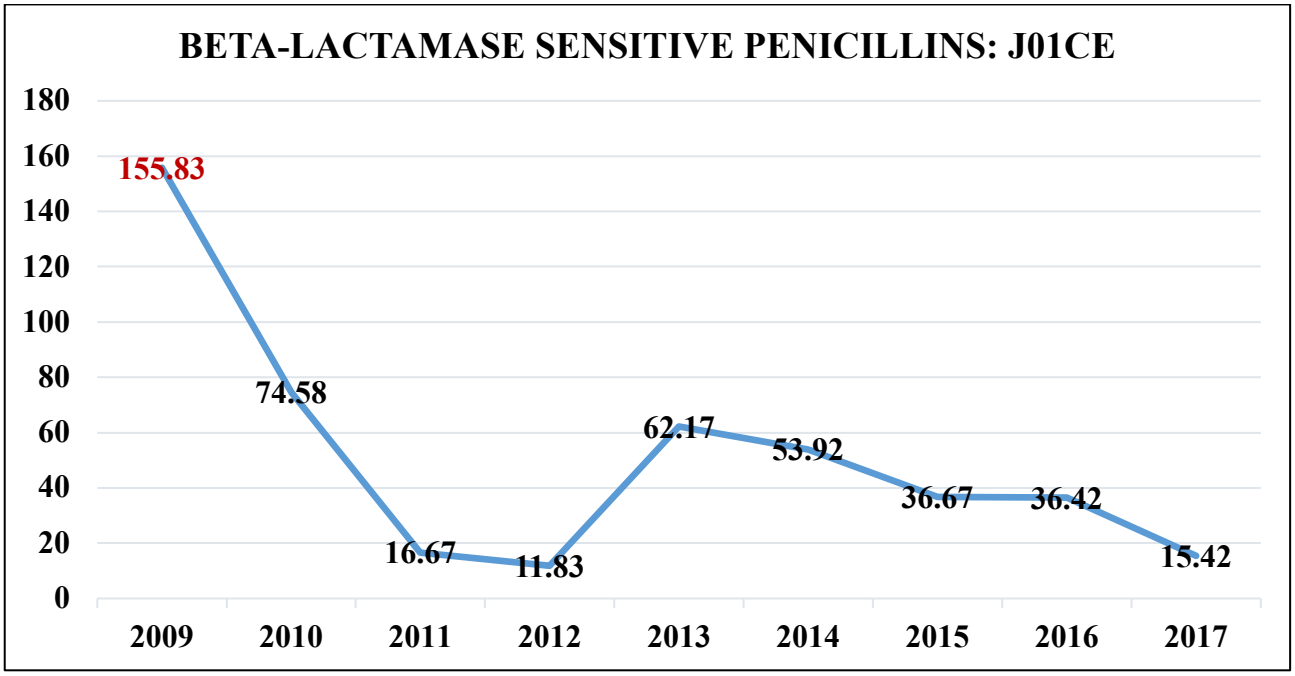

Figure 3.17: ATC class Beta-lactamase sensitive penicillins

The beta-lactamase sensitive penicillins shows a decline in DDD administration through the years, with the peak in use observed for 2009.

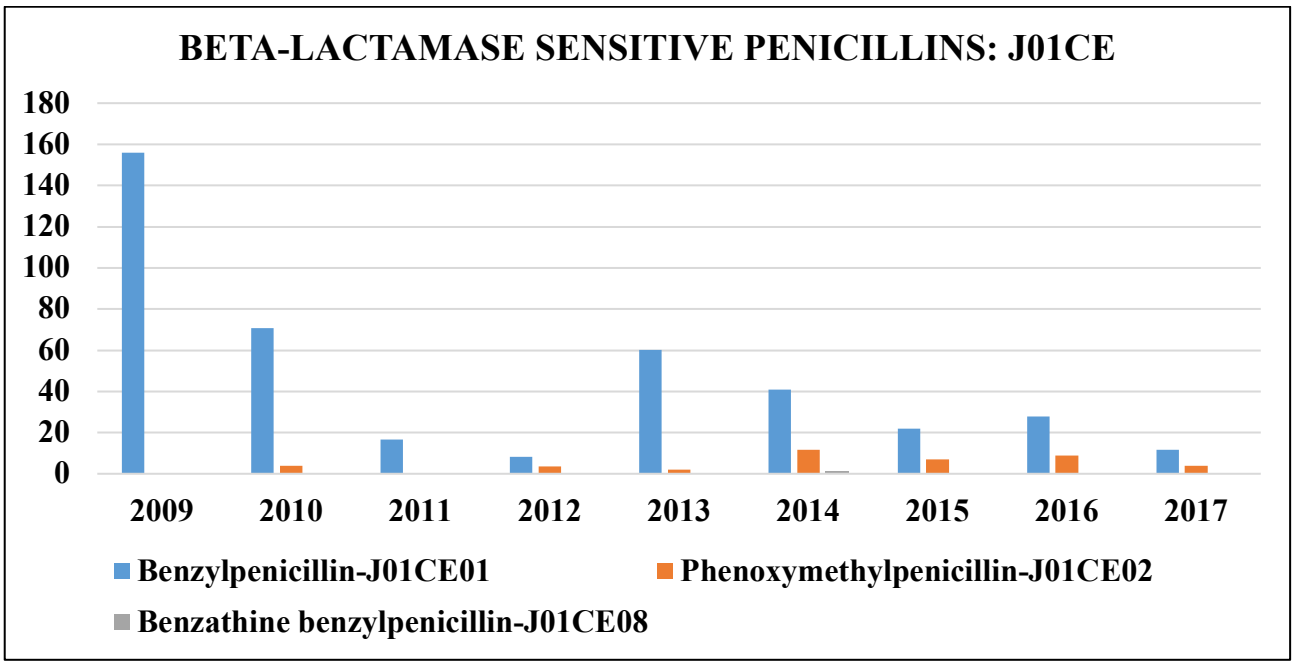

Figure 3.18: Trends in use for the Beta-lactamase Sensitive Penicillins

Figure 3.18 above shows a decreasing trend in use of all three beta-lactamase sensitive penicillins, particularly for benzylpenicillin which was widely used in 2009 , when compared to 2017.

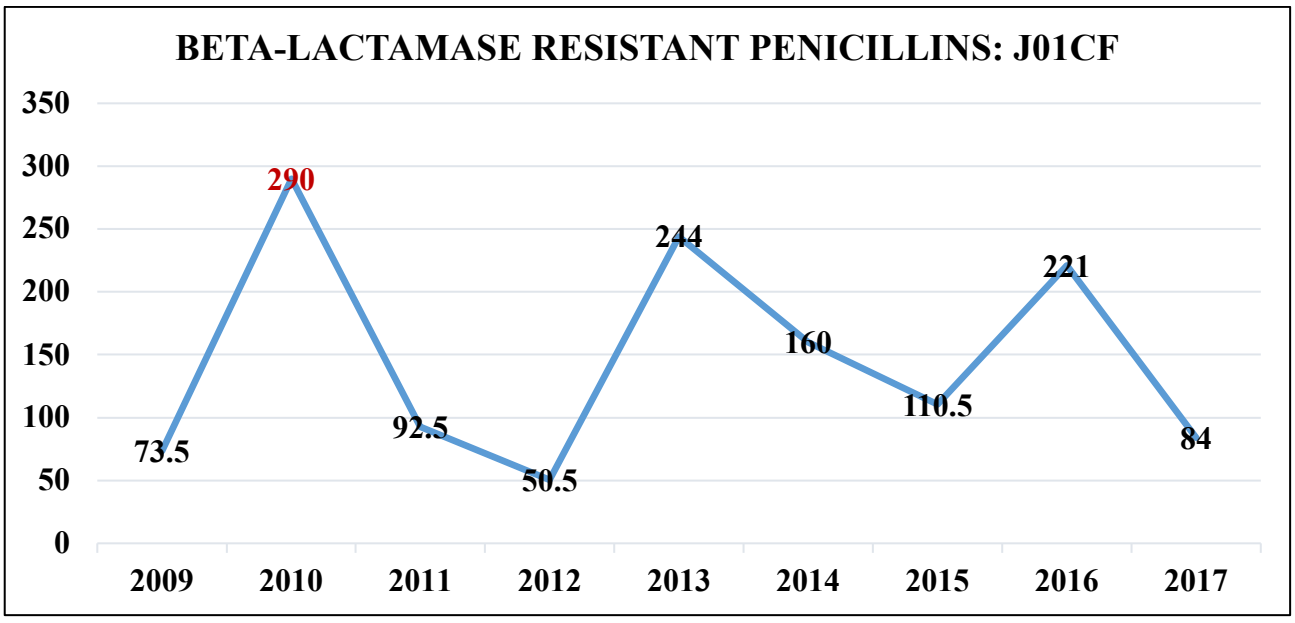

Figure 3.19: ATC class Beta-lactamase resistant penicillins

Figure 3.19 show alternate DDD values for consecutive years. The highest DDD value was observed for the year 2010.

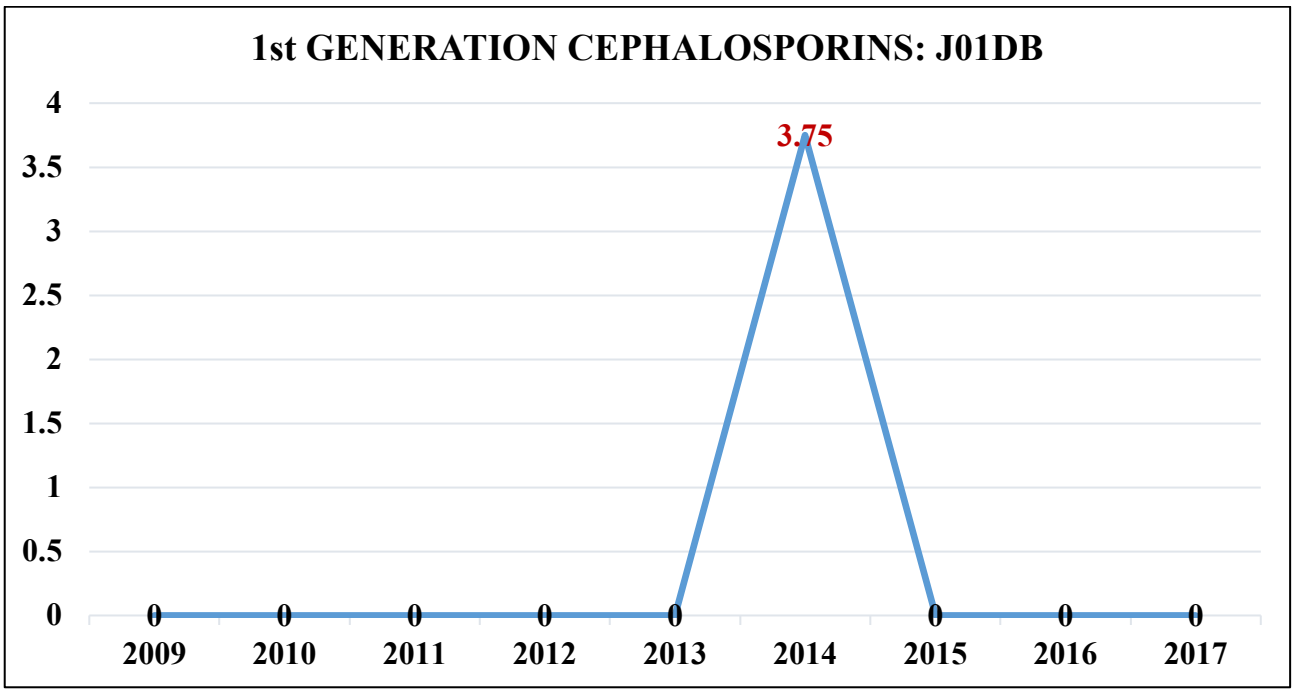

Figure 3.20: ATC class 1st Generation Cephalosporins

Figure 3.20 shows single administration of 1st Generation Cephalosporins for the year 2014.

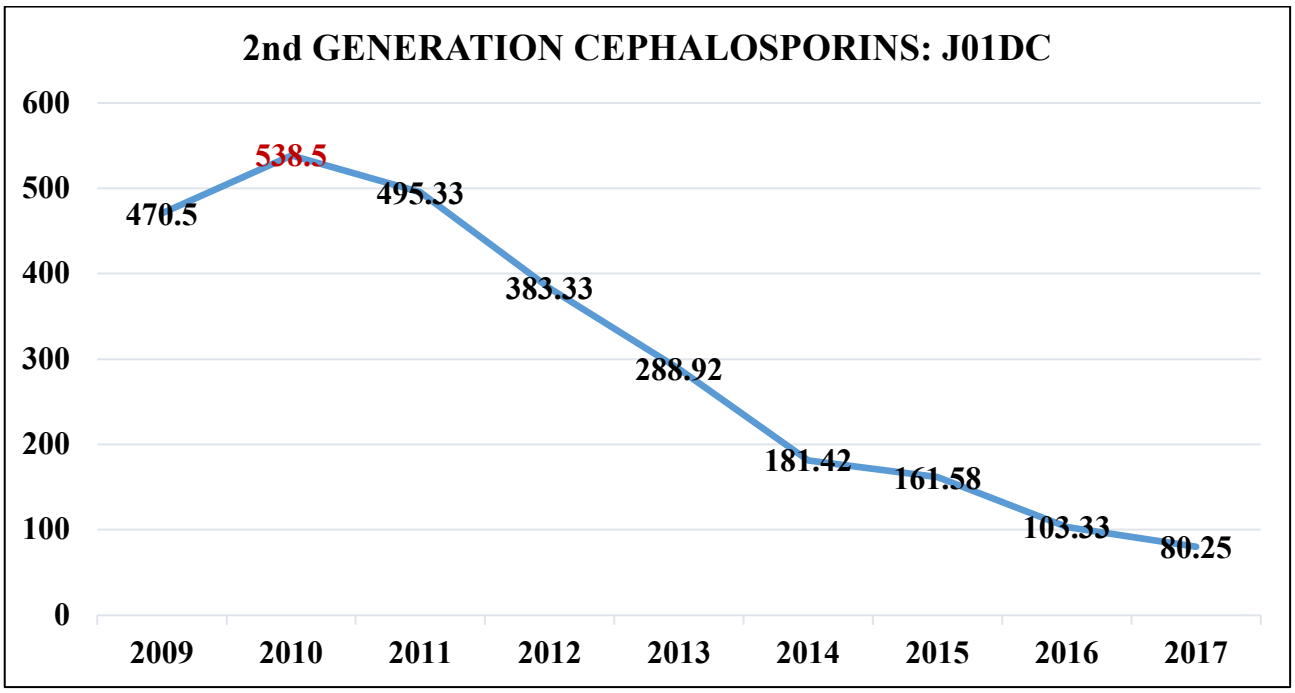

Figure 3.21: ATC class 2nd Generation Cephalosporins

A decreasing trend in DDD use of 2nd Generation Cephalosporins is observed in figure 3.21 above, with the highest consumption for 2010 and the least consumption for 2017.

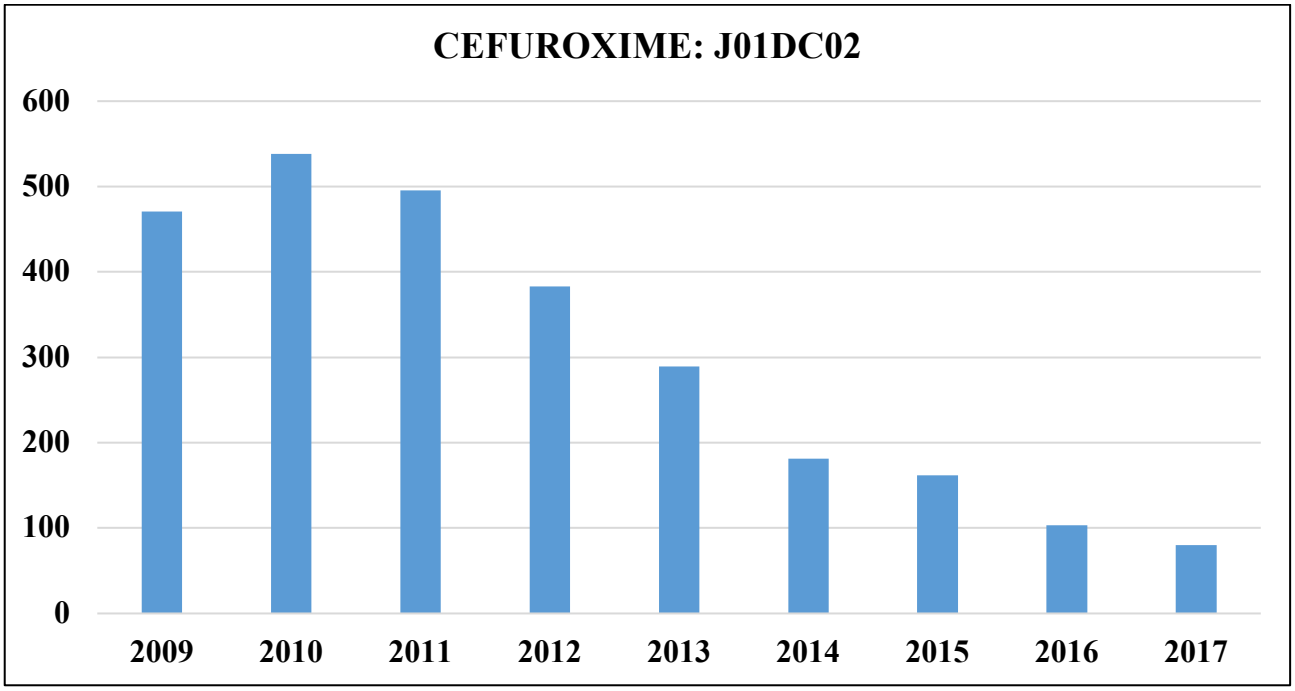

Figure 3.22: Trends in use of 2nd Generation Cephalosporins; Cefuroxime.

Cefuroxime was the only antibacterial administered from the 2nd generation cephalosporins, showing a decreasing trend through the years. Least consumption is observed in the year 2017.

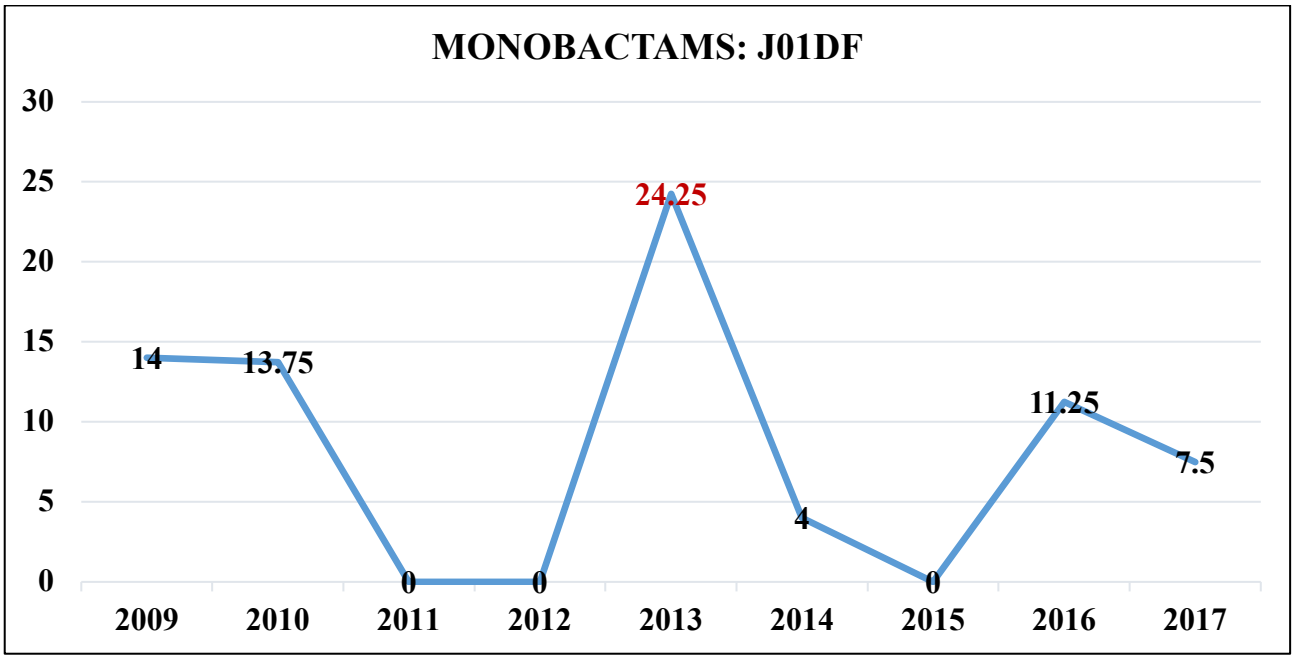

Figure 3.23: ATC class Monobactams

Monobactams shows their highest DDD consumption value for the year 2013, as highlighted in figure 3.23 above.

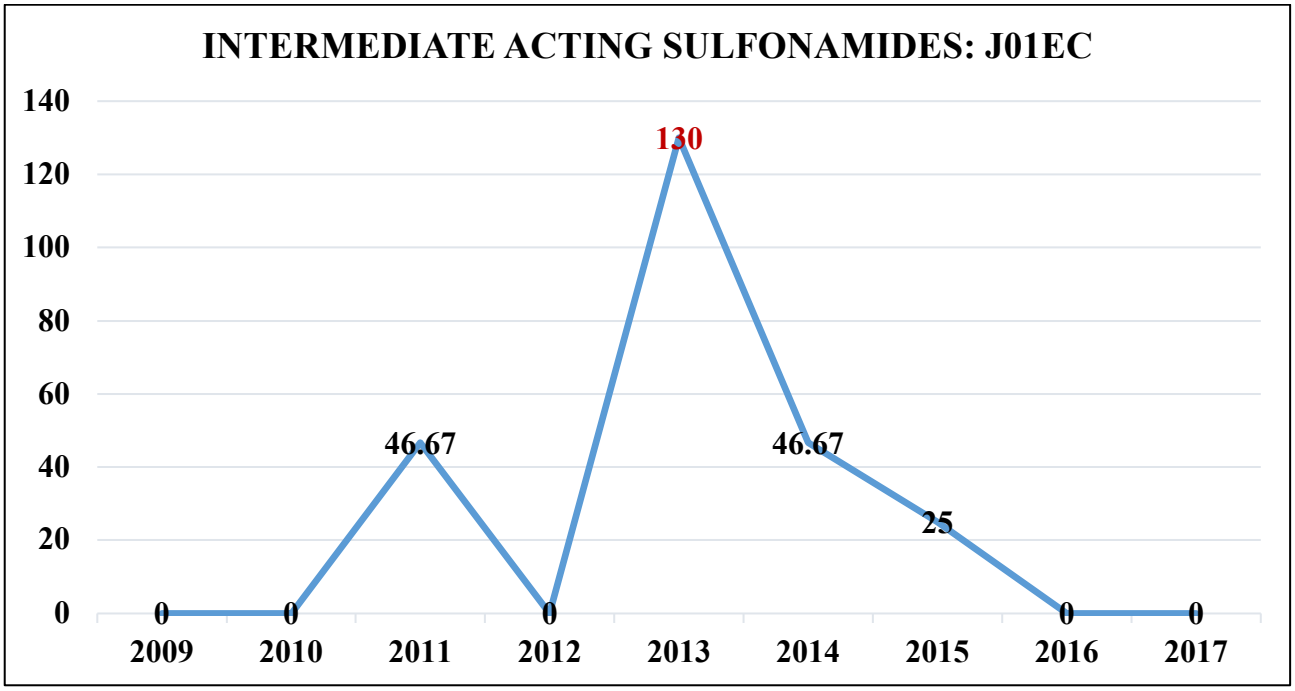

Figure 3.24: ATC class Intermediate-acting Sulfonamides

Figure 3.24 highlights a sharp increase in DDD use for the intermediate acting sulfonamides, for the year 2013.

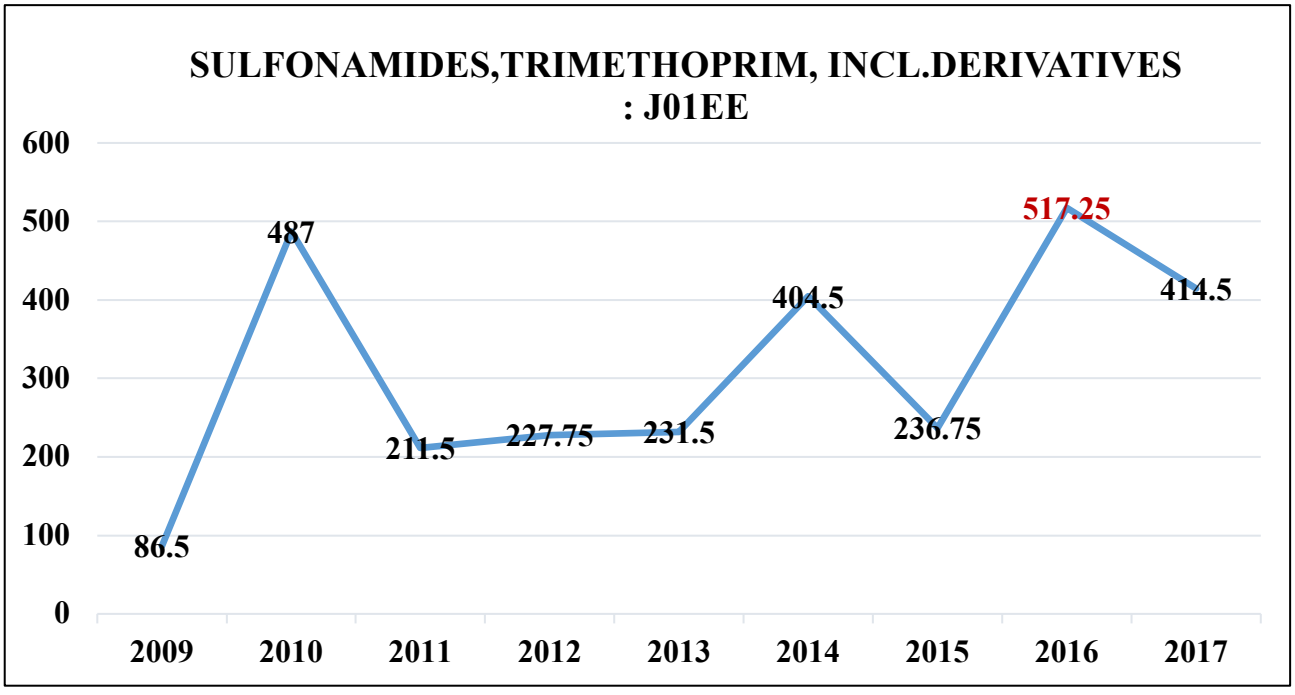

Figure 3.25: ATC class Combination of Sulfonamides & Trimethoprim

Figure 3.25 shows the highest DDD value for 2016, for the antibacterial class sulfonamides & trimethoprim.

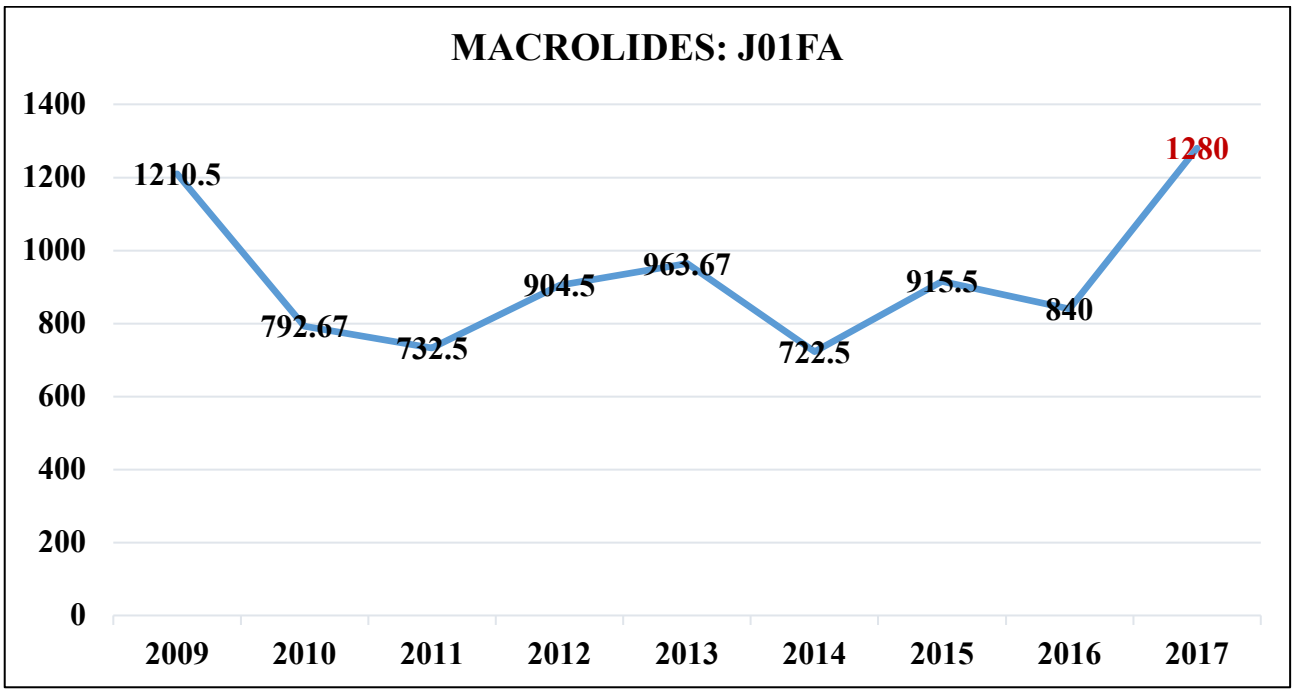

Figure 3.26: ATC class Macrolides

DDD values for macrolide administration remains stable through the years, with a peak in administration observed for 2017, as shown in figure 3.26 above.

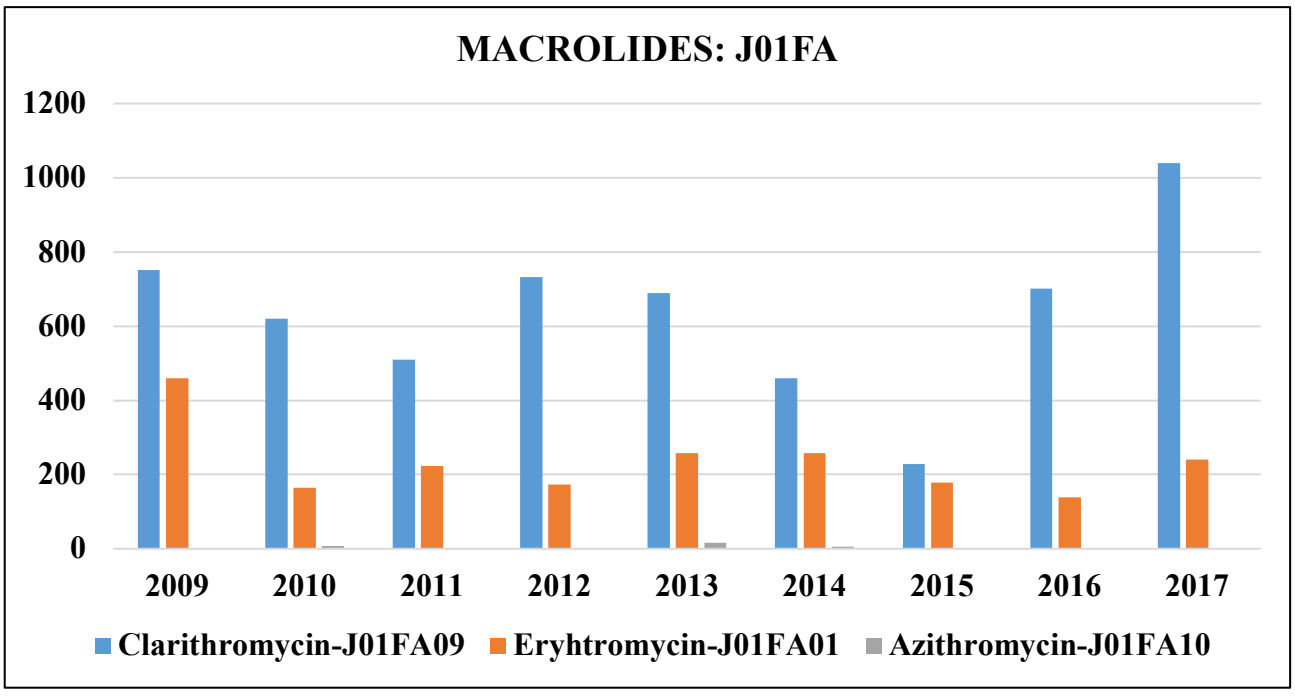

Figure 3.27: Trends in use of Macrolides.

The figure above shows clarithromycin as the mostly administered macrolide through the years, with a peak in administration in 2017.

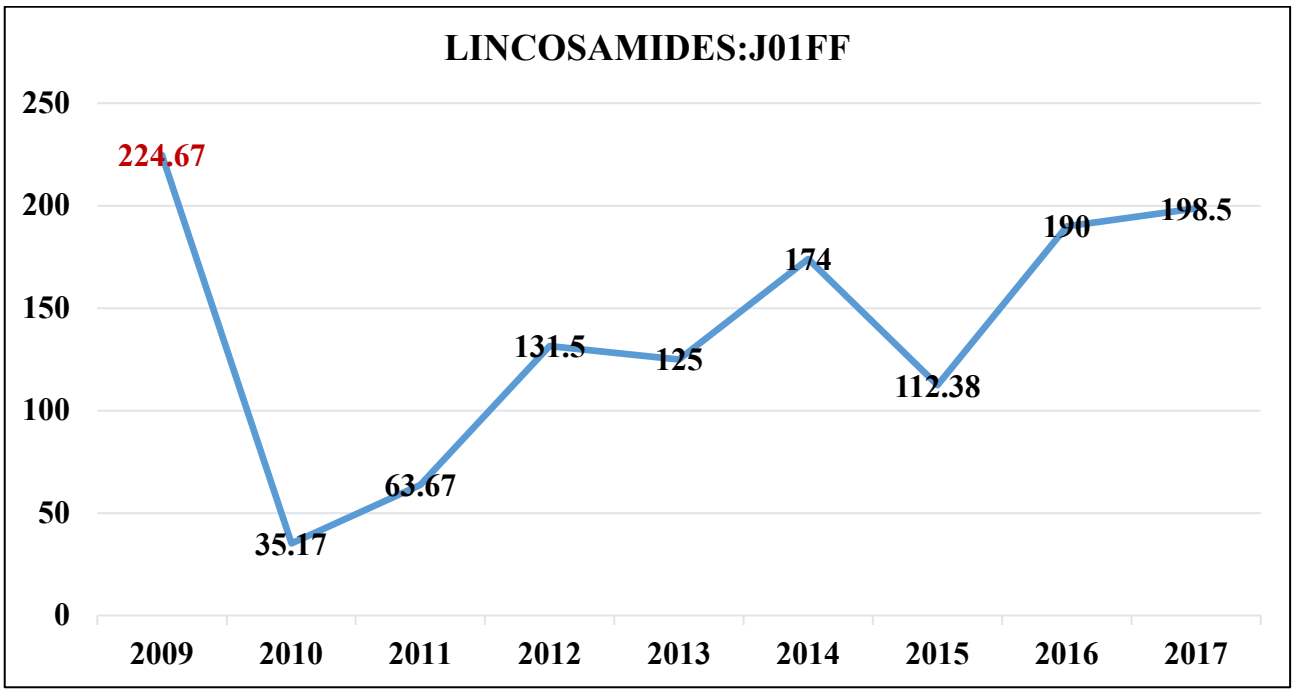

Figure 3.28: ATC class Lincosamides

Figure 3.28 shows the highest value of DDD use for lincosamides for 2009, followed by a sharp decrease in 2010.

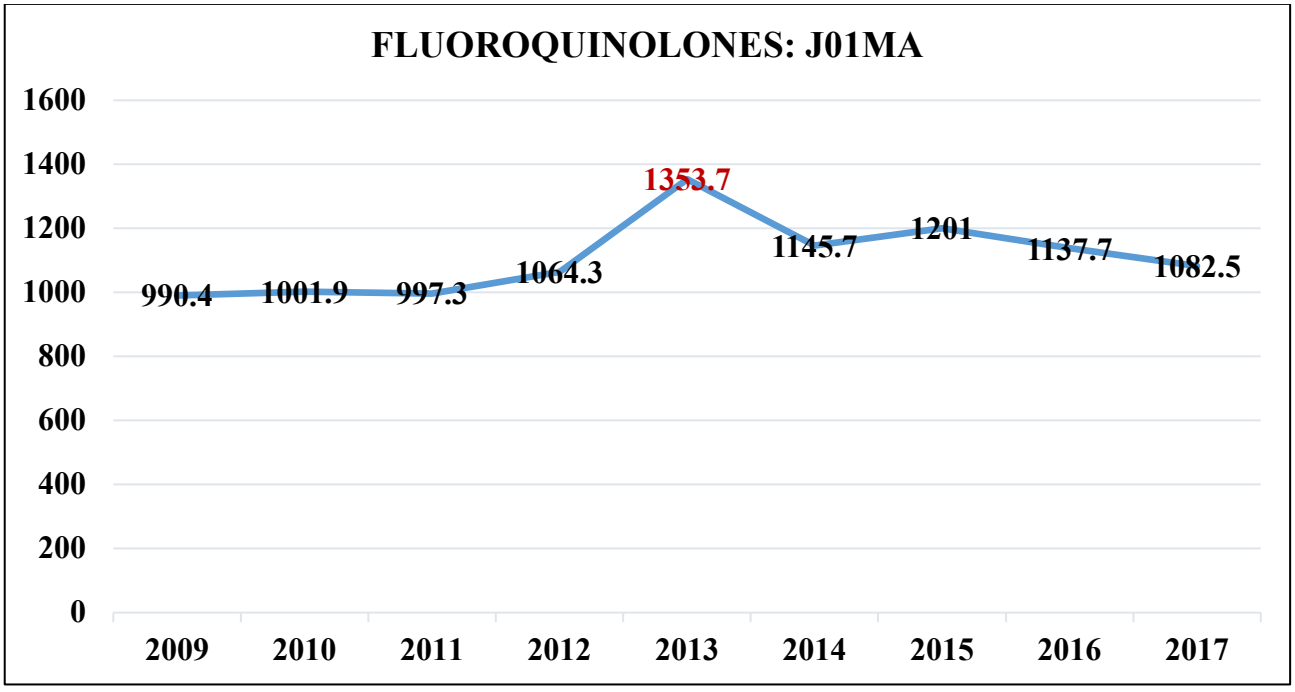

Figure 3.29: ATC class Fluoroquinolones

Figure 3.29 shows a peak in DDD use of fluoroquinolones for the year 2013.

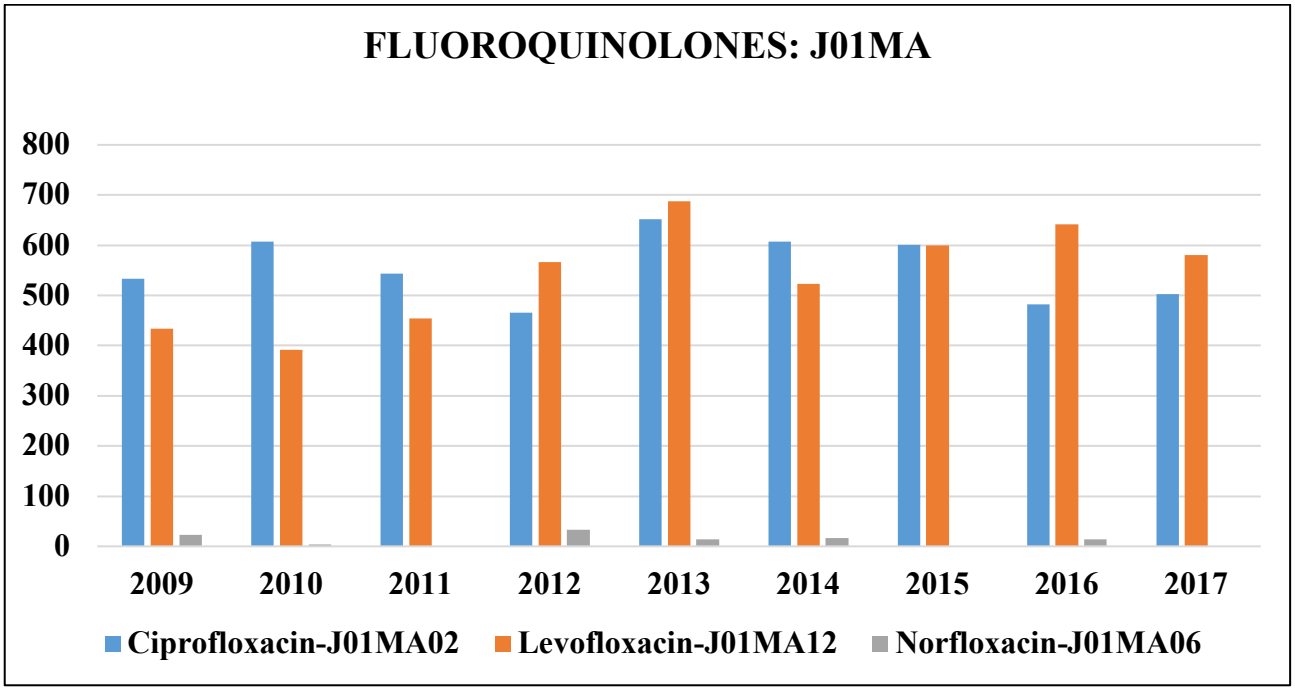

Figure 3.30: Trends in use of Fluoroquinolones.

The figure above shows ciprofloxacin and levofloxacin as the mostly administered fluoroquinolones during the years. A stable trend in use is observed.

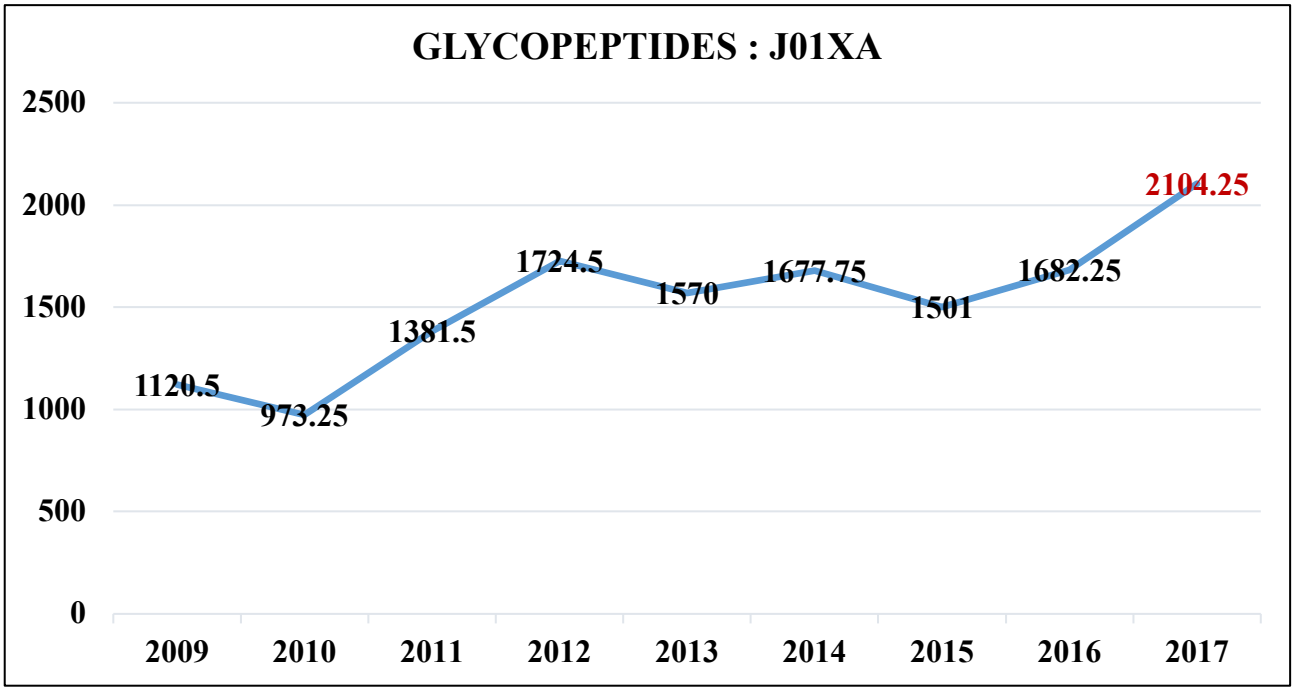

Figure 3.31: ATC class Glycopeptide antibacterials

A stable, increasing trend in DDD use for glycopeptide antibacterials was observed in figure 3.31 above, with the highest DDD use in 2017.

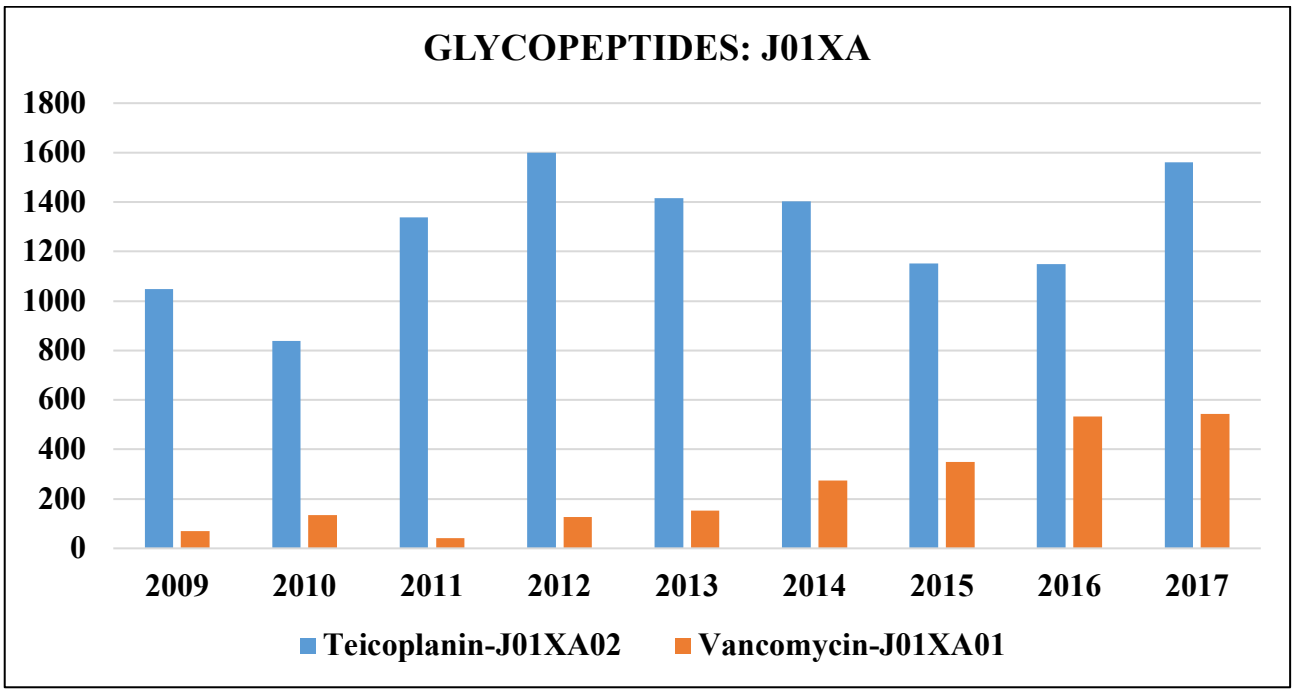

Figure 3.32: Trends in use for Glycopeptides.

The figure above shows teicoplanin as the mostly administered glycopeptide throughout the years, with a high and stable DDD value.

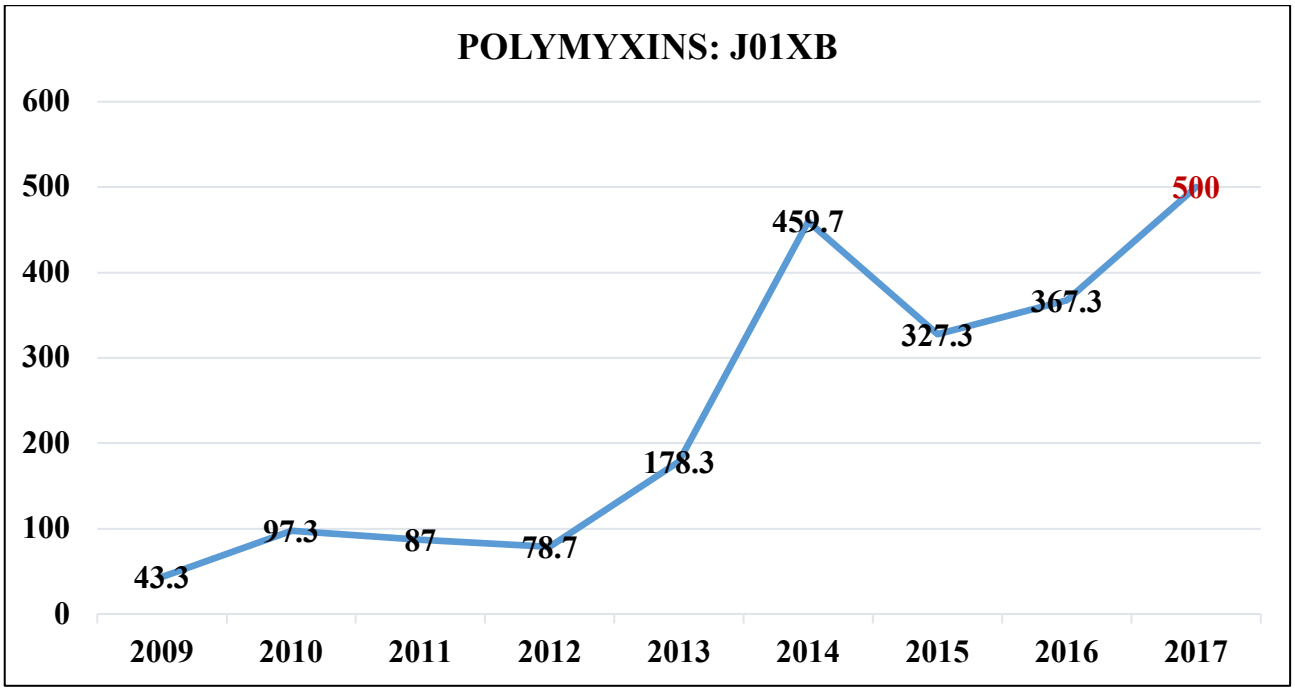

Figure 3.33: ATC class Polymyxins

Figure 3.33 shows as increase in polymyxins DDD administration throughout the years, with the highest DDD value observed for 2017.

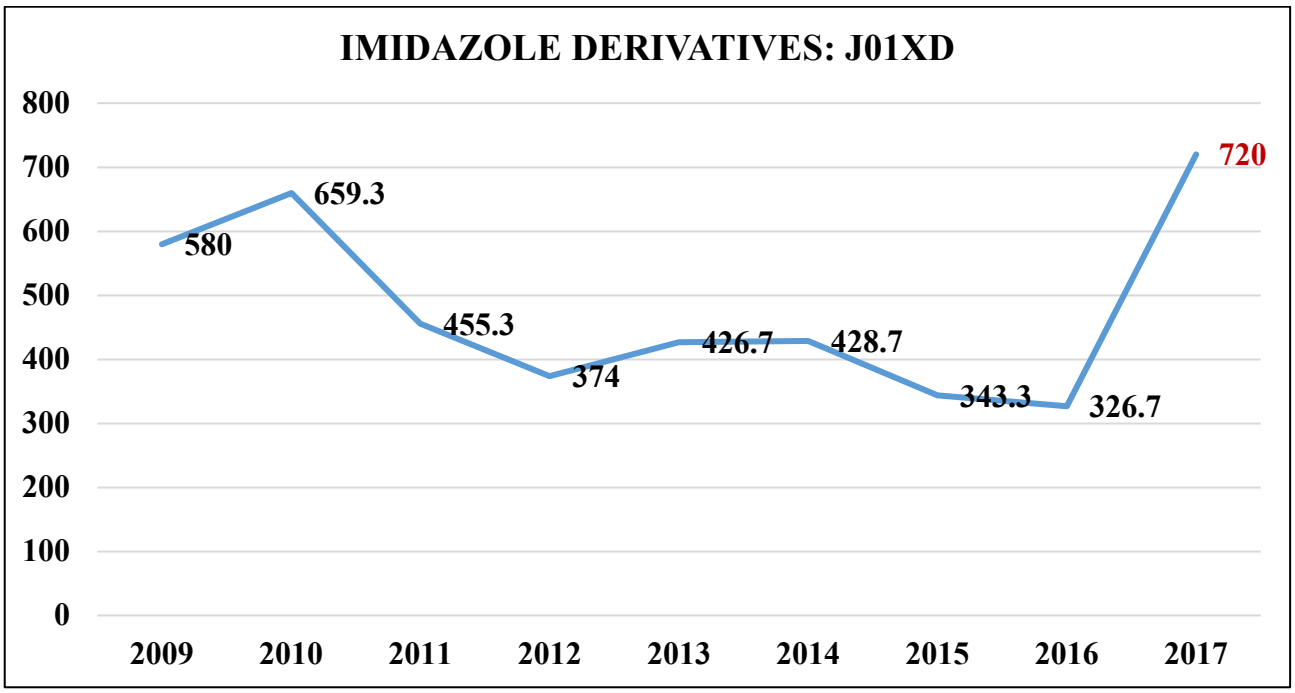

Figure 3.34: ATC class Imidazole derivatives

Figure 3.34 shows a sharp increase in DDD use of Imidazole derivatives, for the year 2017 .

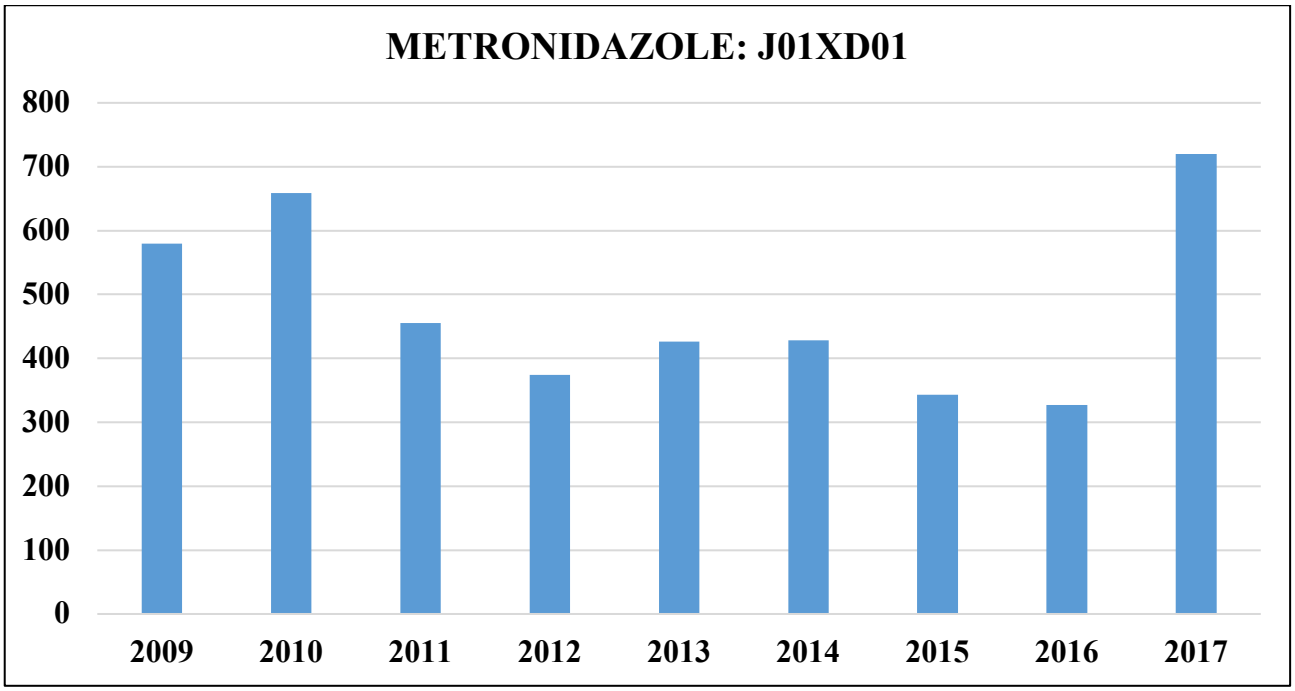

Figure 3.35: Trends in use for Imidazole derivatives; metronidazole.

The figure above shows metronidazole as the only imidazole derivative antibacterial administered. The latter shows a stable trend throughout the years, with a peak in use in the year 2017.

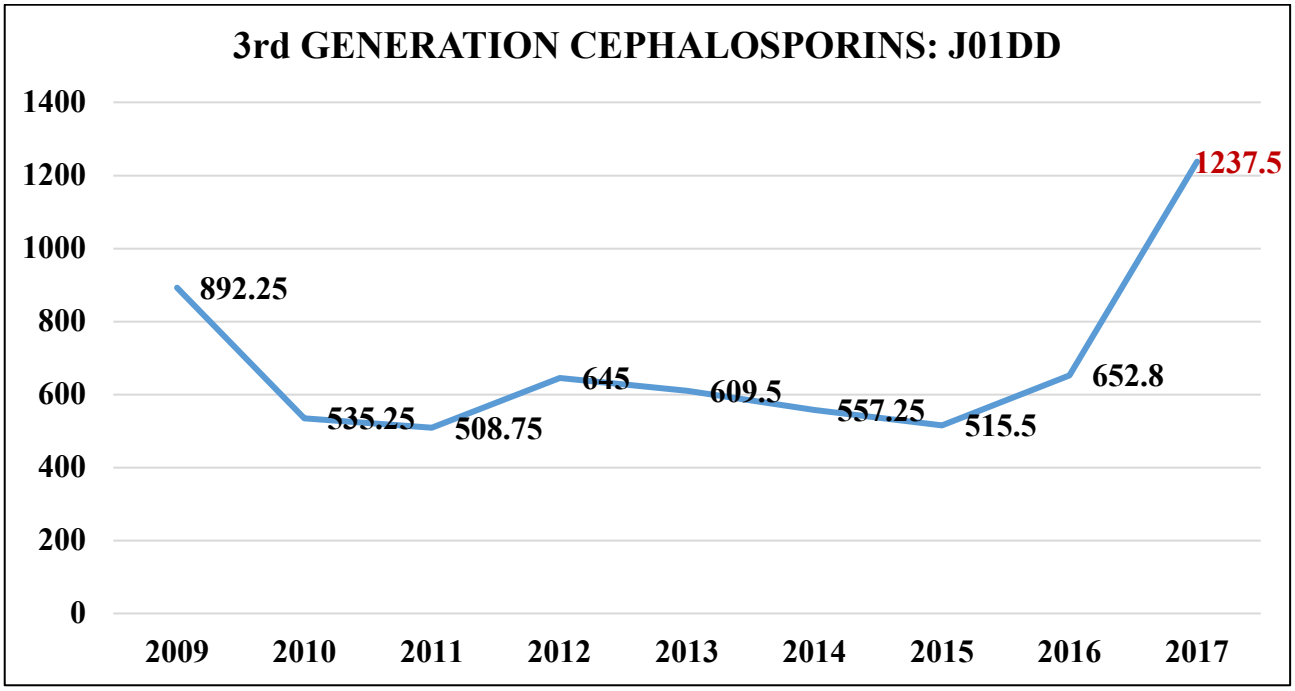

Figure 3.36: ATC class 3rd Generation Cephalosporins (J01DD)

Figure 3.36 shows a sharp increase in DDD use of 3rd generation cephalosporins, for the year 2017.

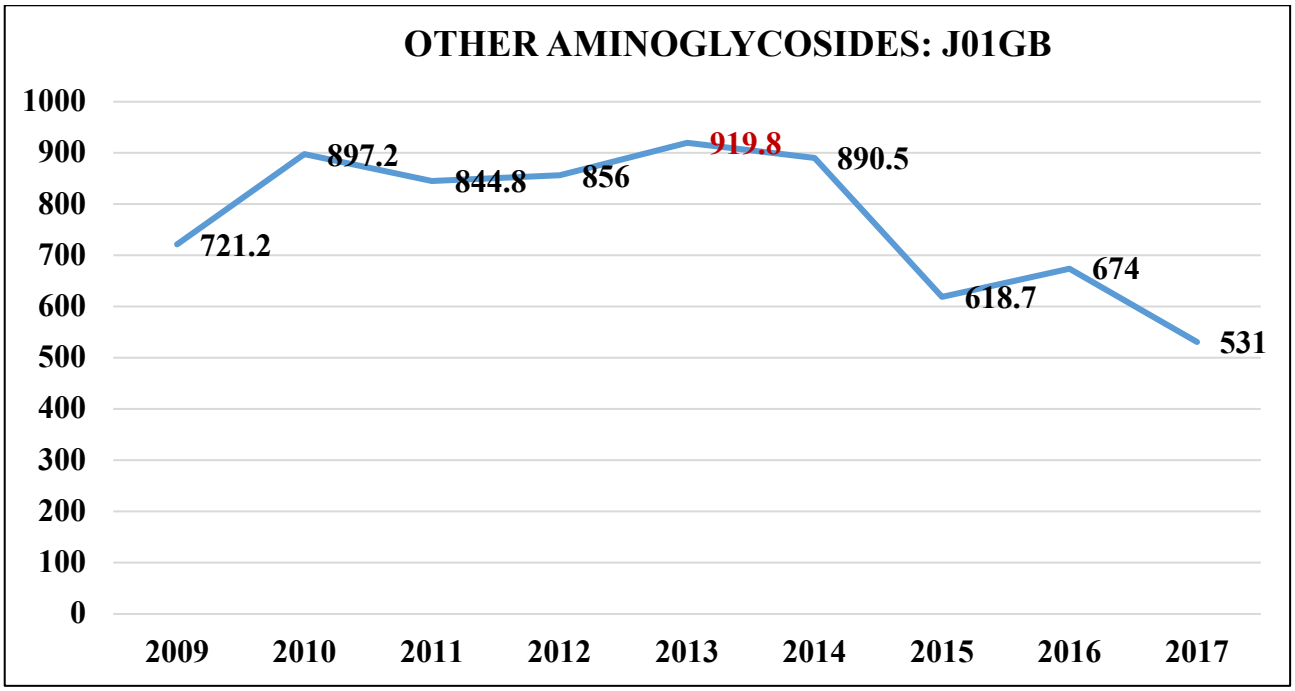

Figure 3.37: ATC class Other Aminoglycosides (J01GB)

Figure 3.37 shows that the highest DDD consumption for other aminoglycosides was observed for the year 2013. A decrease in use was observed from the peak in 2013 till the year 2017.

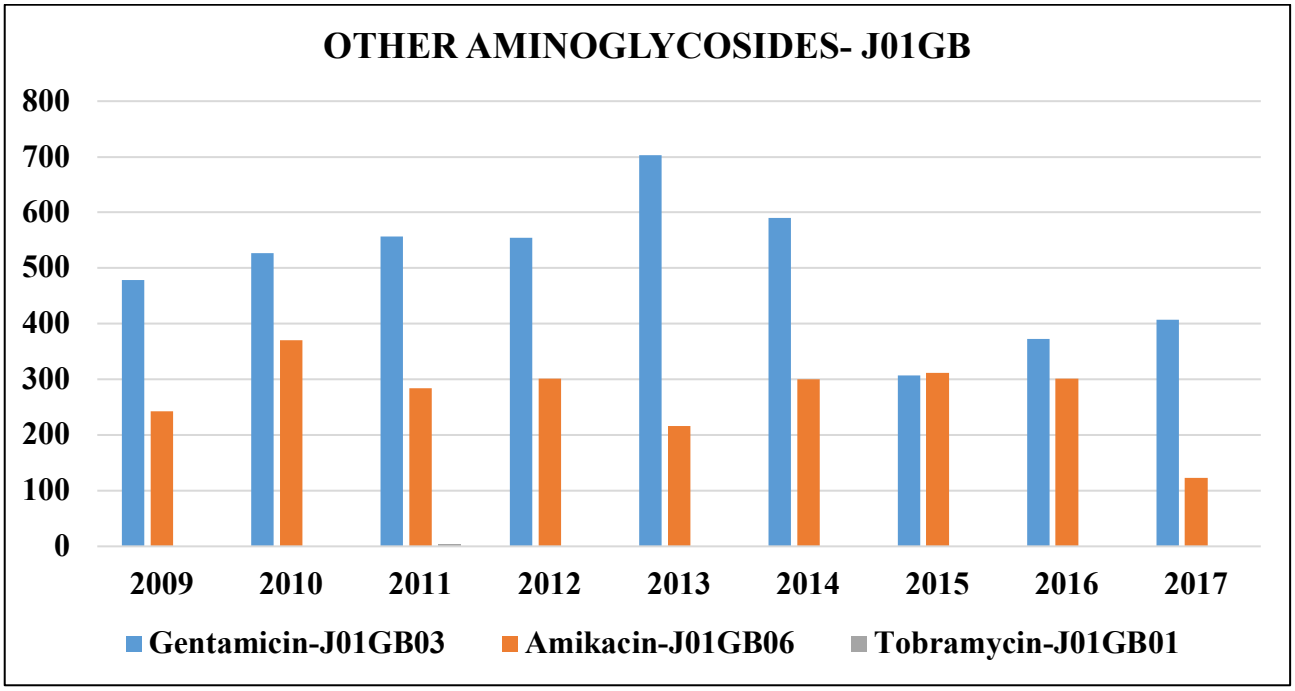

Figure 3.38: Trends in use of Other Aminoglycosides.

Figure 3.38 above shows gentamicin as the mostly administered antibacterial, with a peak in use in 2013, yet keeping a stable trend throughout the remaining years.

3.1.4 Trend in use for Carbapenems and Penicillins and Beta-lactamase Inhibitors

A more in-depth analysis into carbapenems and penicillin and beta-lactamase inhibitors, as these were the two most administered classes of antibacterials, from both the retrospective and prospective part of the study.

Table 3.1: List of Carbapenems (J01DH) administered in the ICU during the period 2009-2017, 2019

Antibacterial	ATC Code	DDD/ U
Meropenem	J01DH02	3 / g
Ertapenem	J01DH03	1 / g
Imipenem with cilastin	J01DH51	2 / g

Table 3.1 above indicates the DDD values and for the carbapenems encountered in this study, all administered through the parenteral route, as indicated by the WHO classification system 2020, used to calculate the total DDD drug use.

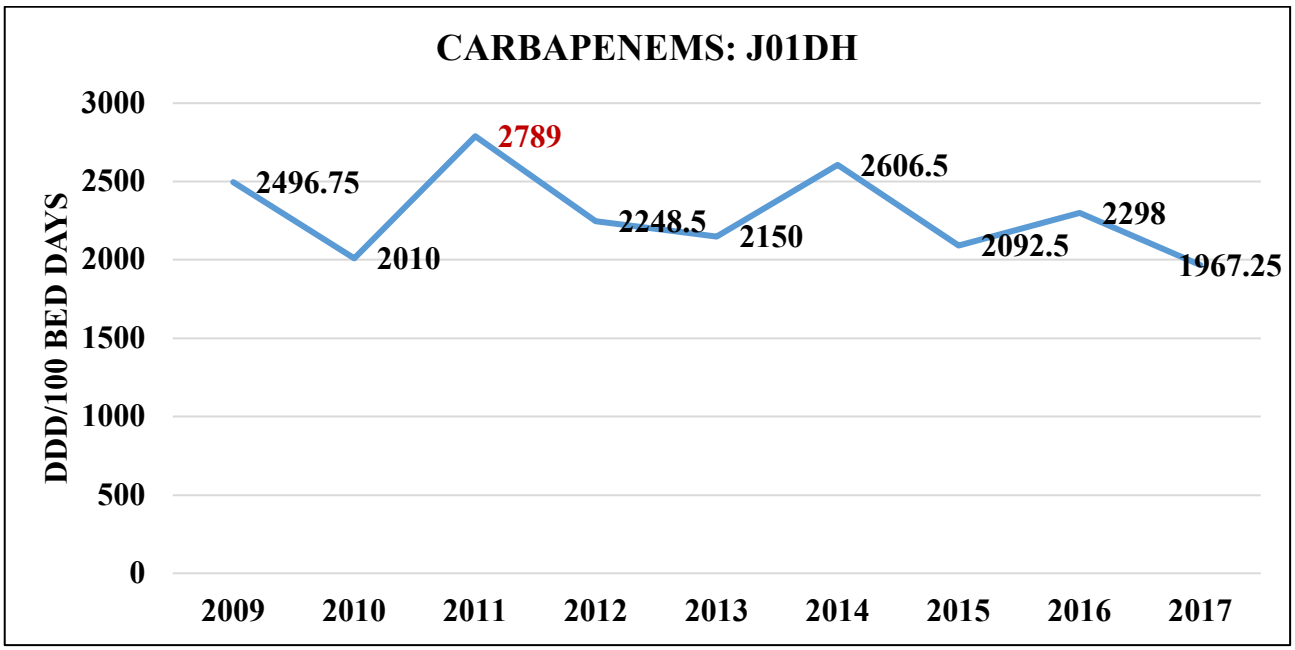

Figure 3.39: Carbapenem use in DDD/100 bed days during the years 2009-2017

The figure above highlights the annual carbapenem (classified in ATC4) use, using the DDD/ 100 bed days unit, through the years 2009-2017. Highest consumption was observed for 2011, at 2789, and the least consumption for 2017, at 1967.3.

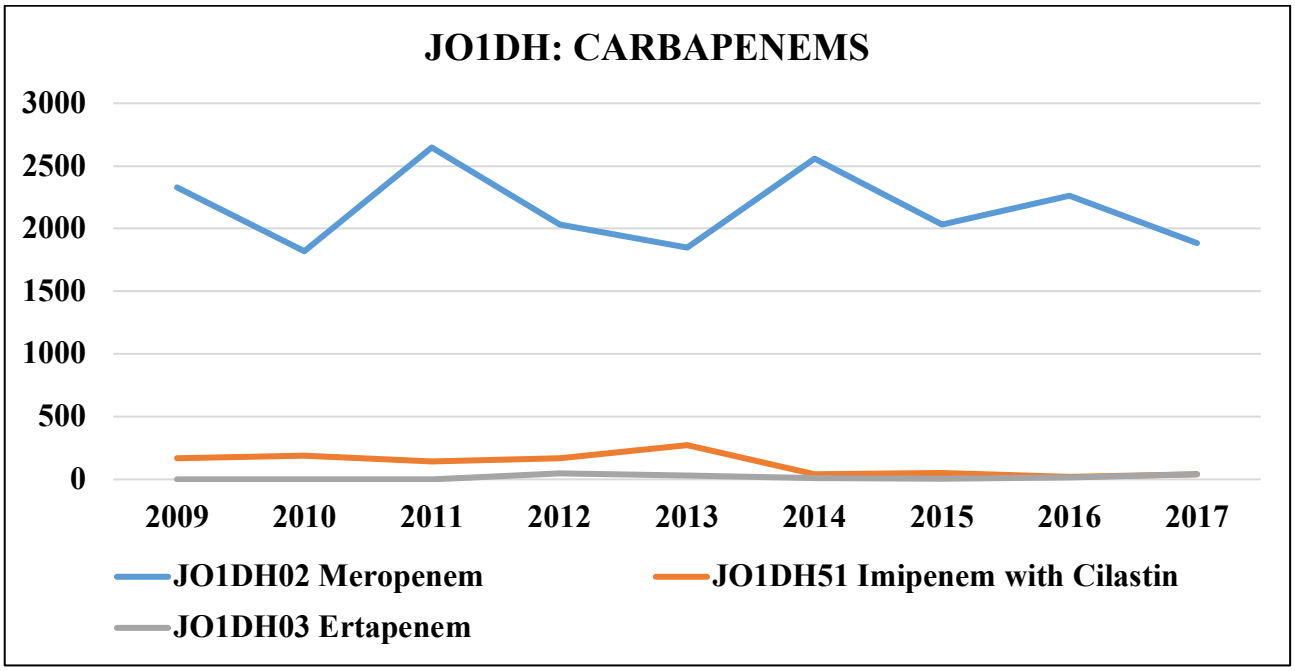

Figure 3.40: Trends of use for Carbapenems (J01DH) during the years 2009-2017

The line graph above shows that meropenem was the most administered carbapenem during the nine-year period, whilst ertapenem was the least carbapenem administered.

Table 3.2: List of Penicillins & Beta-lactamase Inhibitors administered in the ICU during the period 2009-2017, 2019.

Antibacterial	ATC code	DDD / U
Piperacillin & Beta-lactamase inhibitor	J01CR05	14 / g
Amoxicillin & Beta-lactamase inhibitor	J01CR02	3 / g

Table 3.2 above indicates the DDD values and the route of administration for the penicillins & beta-lactamase inhibitors encountered in this study, as indicated by the WHO classification system 2020, used to calculate the total DDD drug use.

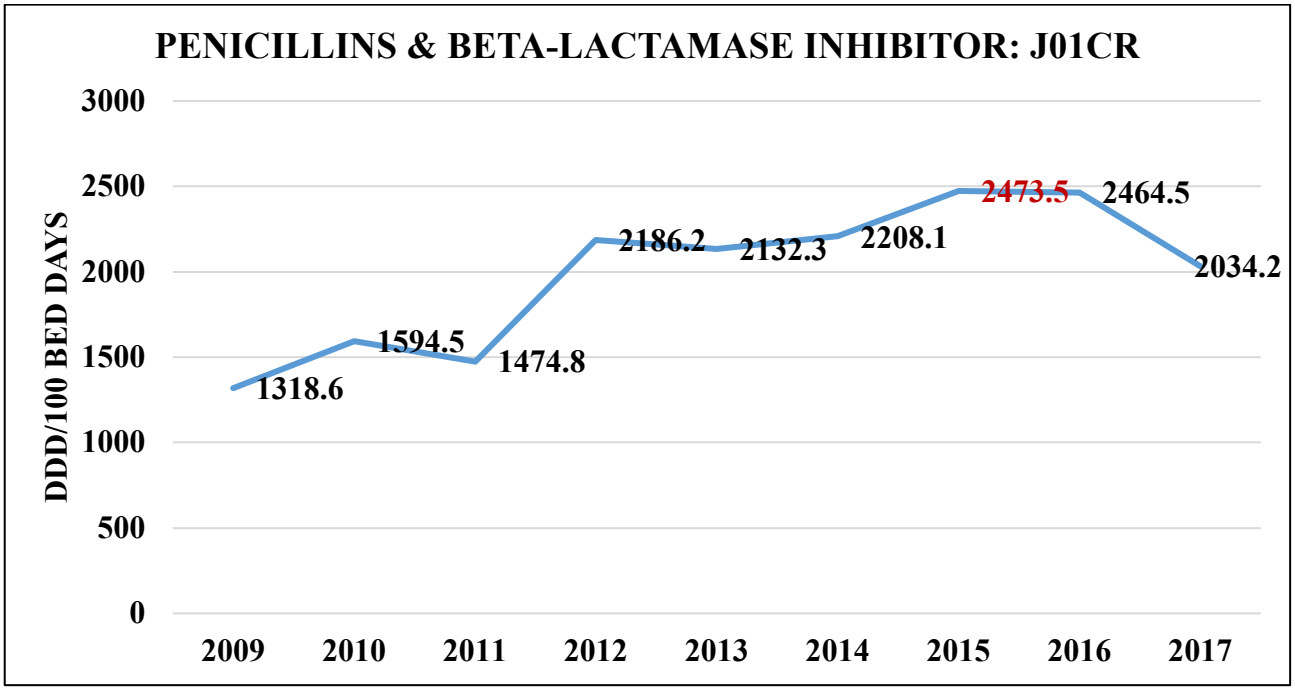

Figure 3.41: Penicillins & Beta-lactamase inhibitor use in DDD/100 bed days during the years 2009-2017

Figure 3.41 highlights the DDD/ 100 bed days value for penicillins & beta-lactamase inhibitor, classified in ATC4 through the years 2009-2017. Highest consumption was observed for 2015, at 2473.5 and the least for 2009, at 1318.6.

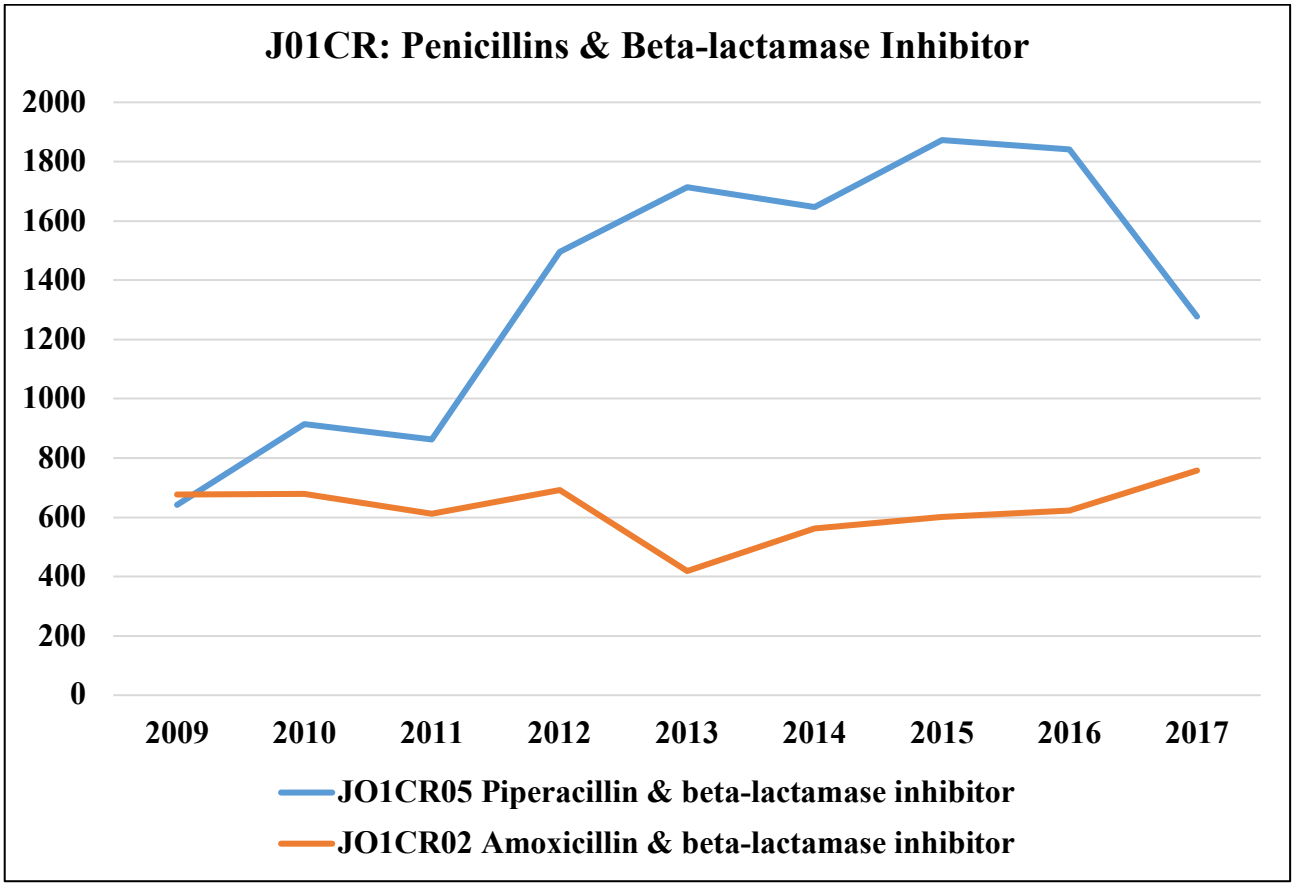

Figure 3.42: Trends of use for Penicillins & Beta-lactamase inhibitors (J01CR) during the period 2009-2017

Figure 3.42 above shows that piperacillin with a beta-lactamase inhibitor was more administered than the other respective penicillin, amoxicillin with a beta-lactamase inhibitor.

Table 3.3: Percentage consumption of Meropenem and Piperacillin & Beta-lactamase inhibitor during 2009-2017

	Year				
Antibacterial	**2009**	**2012**	**2015**	**2017**	**Total (DDD) 2009-2017**
Meropenem	**12%**	**10.5%**	**10.4%**	**9.7%**	**19417**
Total yearly DDD	**2330**	**2033**	**2035**	**1885**	
Piperacillin & Beta-lactamase Inhibitor	**5.2%**	**12.2%**	**15.3%**	**10.4%**	**12265**
Total yearly DDD	**642**	**1495**	**1872**	**1276**	

Table 3.3 above, demonstrates the total yearly DDD values and percentage of use, at intervals, throughout the nine-year retrospective study period. The highest percentage consumption for meropenem, was observed for the year 2009, whilst the highest percentage consumption for piperacillin & beta-lactamase inhibitor was observed for the year 2015.

3.2 Prospective data analysis

A visual representation of the results collected from the devised 'Antibacterial Information Sheet' can be seen in this section. A demographic description of the inpatients present in the ICU throughout the 4-month study period analysed is shown, followed by trends in use of different antibacterial classes.

3.2.1 Demographic data

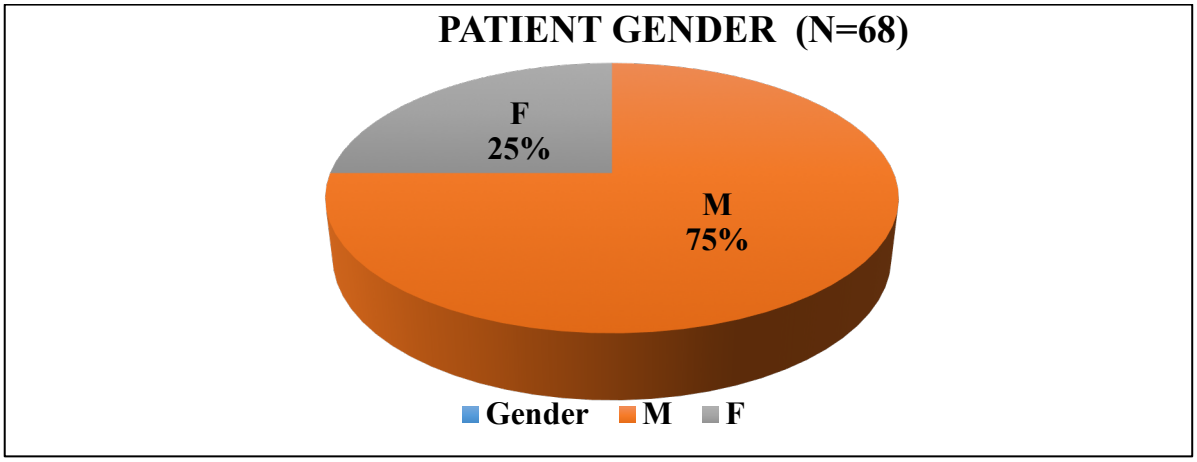

Figure 3.43: Ratio of male : female patients

Figure 3.43 above highlights the sex distribution of patients at the ICU, with the majority being male (n= 68).

Figure 3.44: Patient age group distribution

Figure 3.44 above demonstrates the age distribution among the patients in the ICU (n=68). The youngest at 21 and oldest at 91 years.

3.2.2 Antibacterial consumption

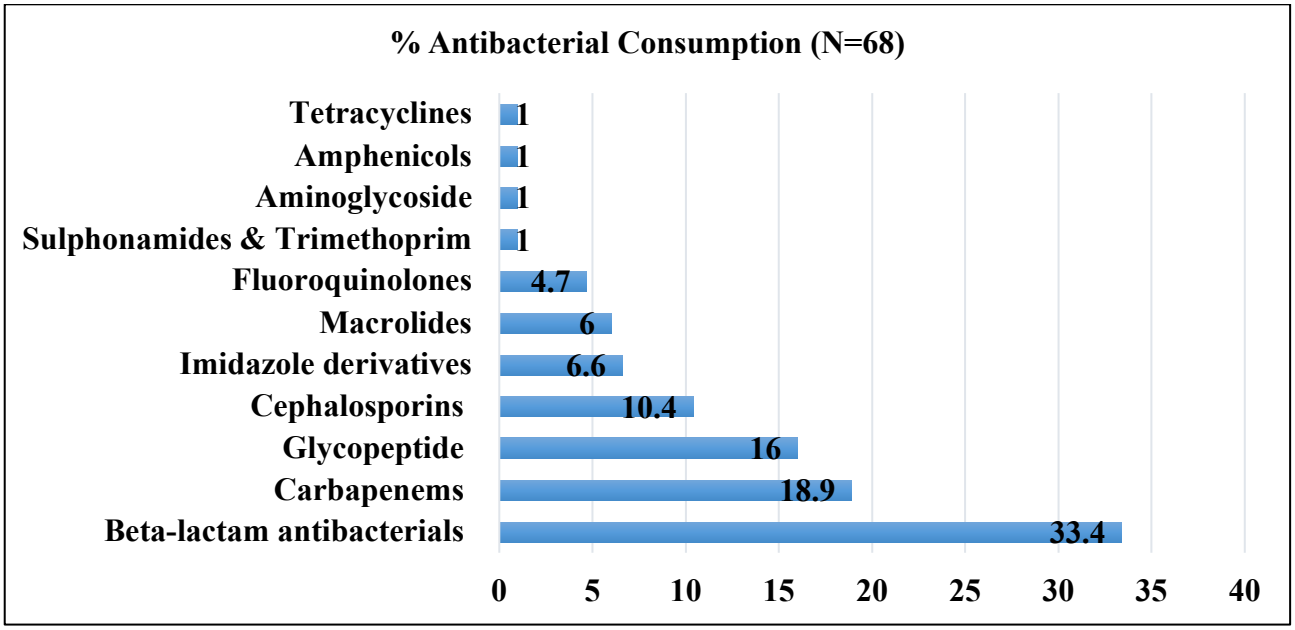

Figure 3.45: Percentage of antibacterial use at MDH ICU during the study period for the year 2019.

Figure 3.45 above shows the percentage of antibacterial use, grouped in ATC4 out of a total of 68 patients. The beta-lactam antibacterials and carbapenems were the 2 most antibacterial groups administered.

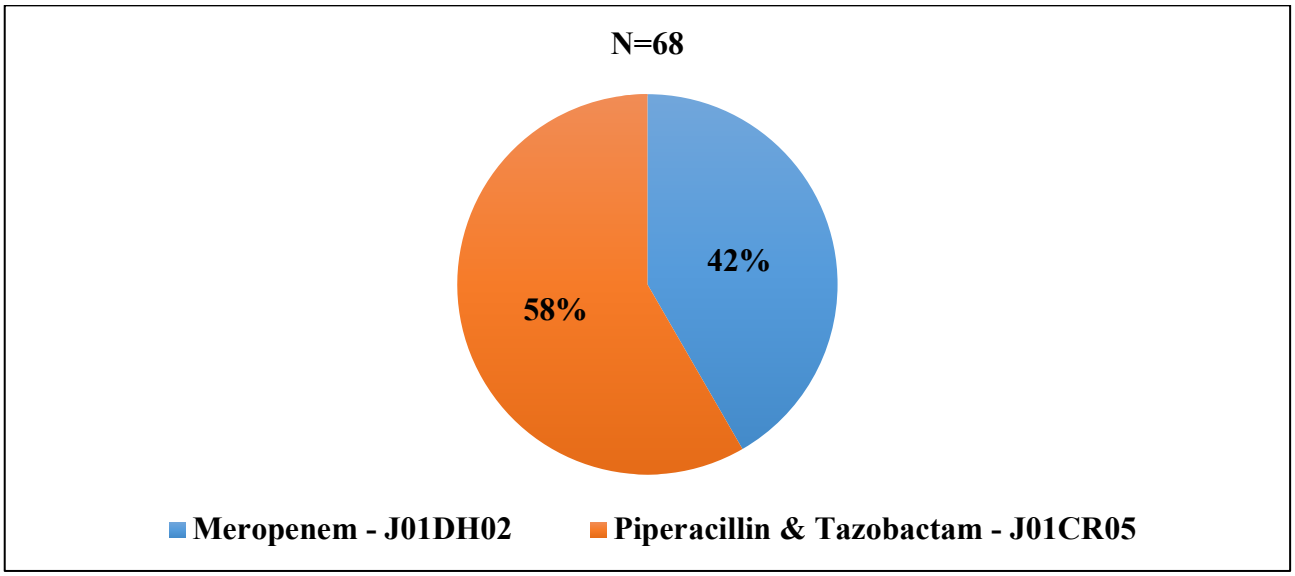

Figure 3.46: Percentage use of the two most administered antibacterials in 2019

3.2.3 Reason for antibacterial therapy administration

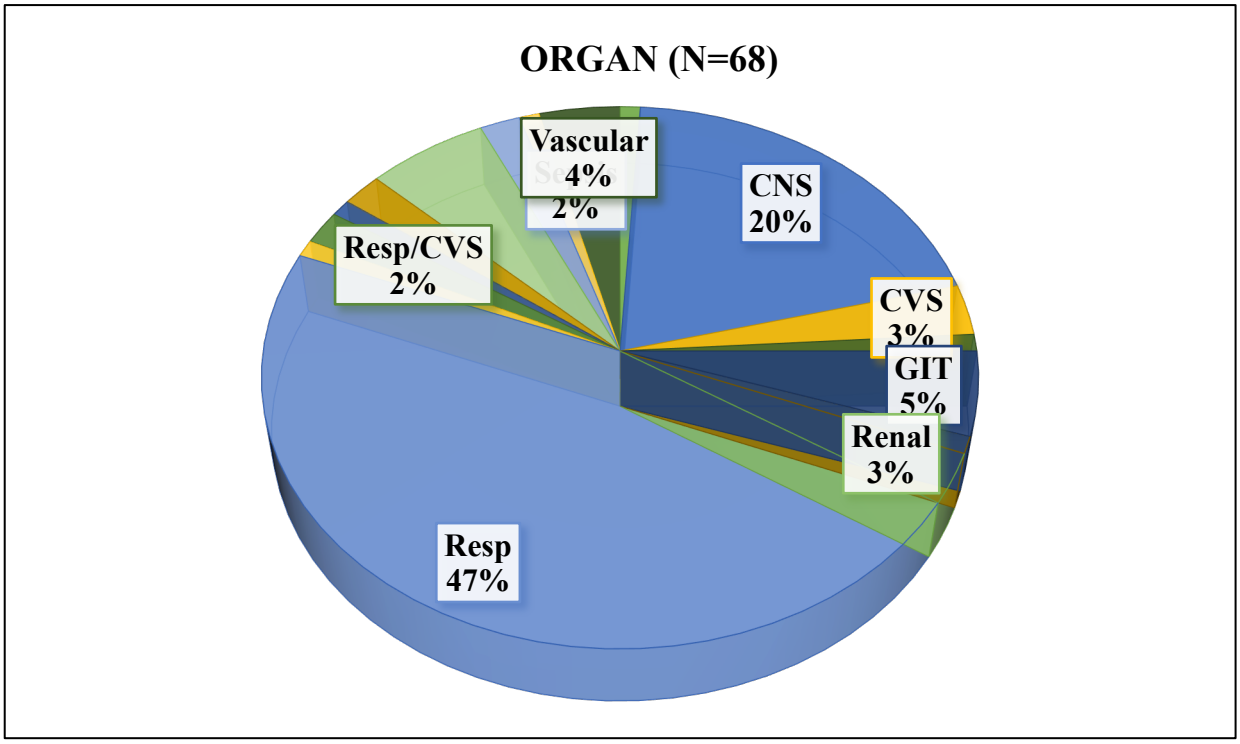

Figure 3.47: Antibacterial targeted at specific organ infection

Figure 3.47 above shows the reason for antibacterial administration. A respiratory infection was the most common cause, at 47% (n=68), with almost half the patients receiving therapy for this specific organ infection.

3.2.3.1 Changes in antibacterial therapy

This sub-section relates to changes in antibacterial therapy noted in the respective patient's bed chart. It highlights trends in use of antibacterial polypharmacy and how therapy for the stated pharmacological reason indicated, can be escalated or de-escalated accordingly.

Table 3.4: Changes in Antibacterial therapy

Initial antibacterial	**Latter Antibacterial**	**Change/Escalation/De-escalation**
Meropenem 1g, 8 hourly, IV for 2 days & Vancomycin 1.25g, 12 hourly IV for 2 days.	Ceftazidime 2g, 8 hourly IV & Ciprofloxacin 500mg, 12 hourly, PO & Metronidazole 500mg, 8 hourly, IV	Escalation
Cefuroxime 1.5g, 8 hourly, IV for 1 day. Meropenem 1g, 8 hourly, IV & phenoxymethylpenicillin 250mg, 12 hourly, PO & Co-trimoxazole 480mg, 12 hourly, PO.	Piperacillin/ tazobactam 4.5g, 24 hourly, IV. Co-trimoxazole 3360mg, 8 hourly, IV for 1 day.	De-escalation
Co-amoxiclav 1.2g, 8 hourly, IV for the 1st 3 days of treatment.	Ceftriaxone 2g, 24 hourly, IV & Metronidazole 500mg 8 hourly, IV	Escalation

It can be noted, that changes in antibacterial therapy are a common practice in an ICU, due to the continuous and rigorous monitoring patient's vitals medical condition and after assessment of the degree of responsiveness to the antibacterial(s) prescribed.

3.3 Antibacterial Costings for Malta in 2018

This section relates to antibacterial costings for Malta for the year 2018. The values shown in the figure 3.48 below, are not representative for antibacterial costings related to the ICU only. Costings data serve as a representative of the trends in administration of the various antibacterial classes and the ultimate financial burden imposed on the healthcare government.

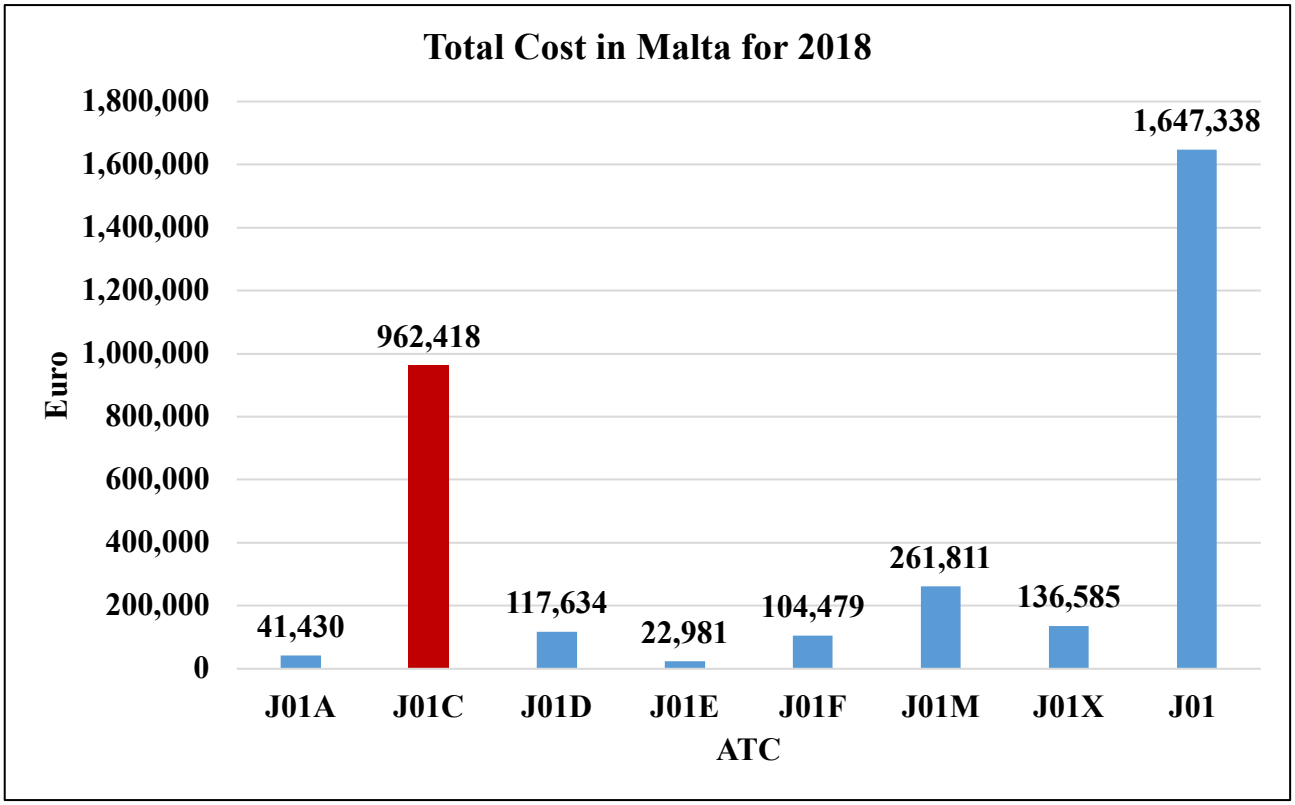

Figure 3.48: Total Cost in Euro for Malta in 2018

Figure 3.48 above shows the antibacterial classes classified in ATC2. ATC class, J01C, representing the beta-lactam antibacterials, penicillins, was the costliest for 2018, at 962.418 Euro, highlighted in red. ATC class J01E, representing sulfonamides and trimethoprim, was the least costly, at 22,981 Euro.

3.4 Data from international reports

The next section relates information gathered for internationally published reports, in particular, the European Centre for Disease Prevention and Control (ECDC), which contains information from different EU/EEA countries, which also includes Malta. Trends in frequency and trends of antibacterial administration throughout the years can be performed and correlated to the data collected in this study.

Table 3.5: Antibacterial consumption for systemic use (ATC group J01) for the hospital sector in 2018 (expressed as DDD per 1000 inhabitants per day)
[Adapted from] European Centre for Disease Prevention and Control. Antimicrobial consumption in EU/EEA, annual epidemiological report for 2018. Stockholm: ECDC; 2019.

ATC	Antibacterial Class	DDD/1000 Inhabitants/ Year
J01A	Tetracyclines	0.12
J01C	Beta-lactams, Penicillins	0.87
J01D	Other Beta-lactam Antibacterials	0.37
J01E	Sulfonamides & Trimethoprim	0.05
J01F	Macrolides, Lincosamides & Streptogramins	0.25
J01M	Quinolones	0.34
J01X	Other Antibacterials	0.31
J01	Total	2.32

Table 3.5 above shows published data for Malta for the year 2018, highlighting use of J01 antibacterials in the hospital sector. DDD per 1000 inhabitants per day was used in the above report as measure for antibacterial consumption for both the community and hospital sector. DDDs per 100 occupied bed-days is the tool proposed when showing antibacterial consumption in the hospital section.

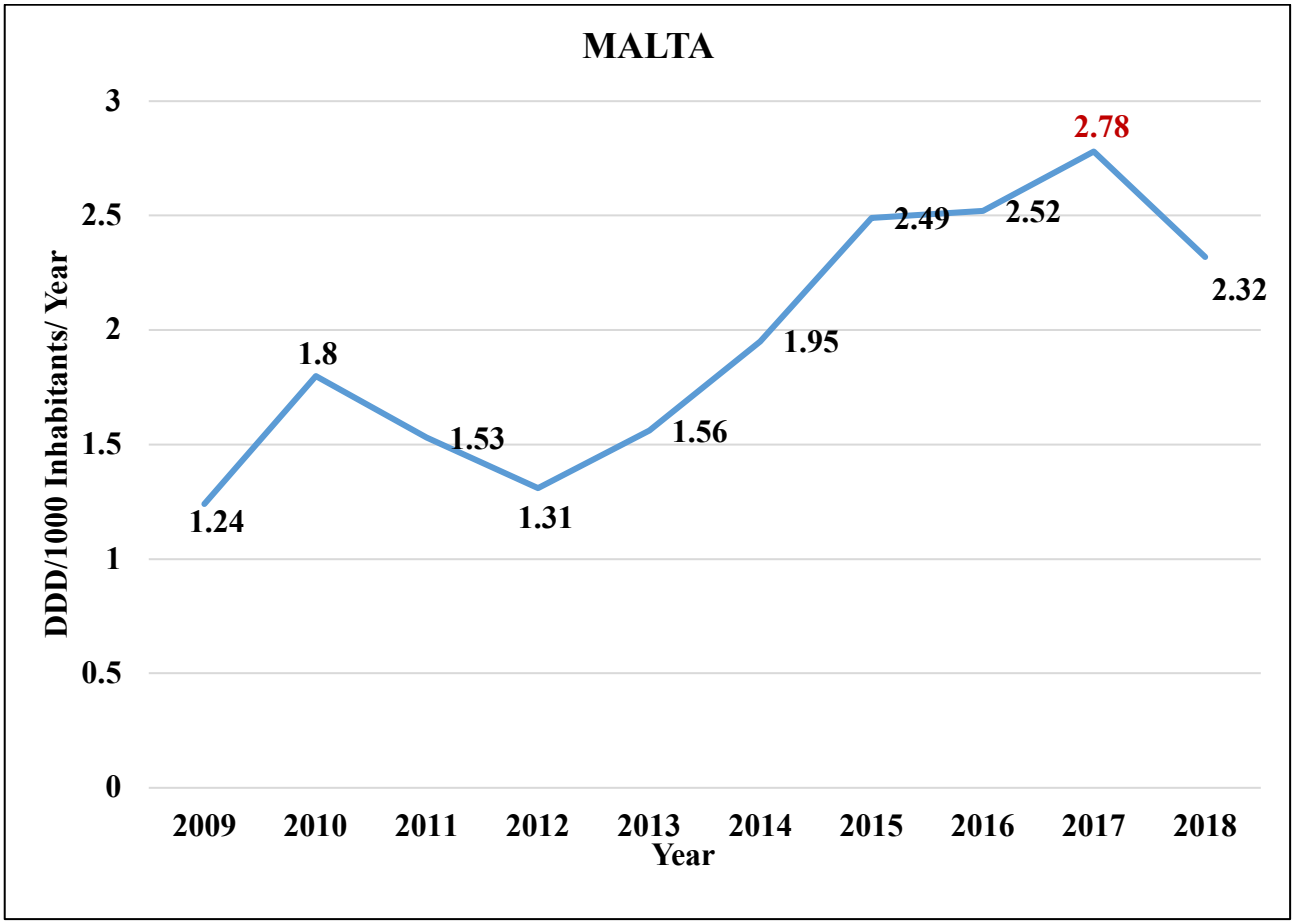

Figure 3.49: Trends in antibacterial consumption (ATC group J01) in the hospital sector, for 2009-2018 (expressed as DDD per 1000 inhabitants per day)
[Adapted from] European Centre for Disease Prevention and Control. Antimicrobial consumption in EU/EEA, annual e epidemiological report for 2018. Stockholm: ECDC; 2019.

Figure 3.49 above shows a moderate increase in DDD/1000 inhabitants per day in the hospital sector during the period 2009-2018. The year 2017, showed the highest DDD/1000 inhabitants per day, at 2.78, followed by the previous year in 2016, at 2.52.

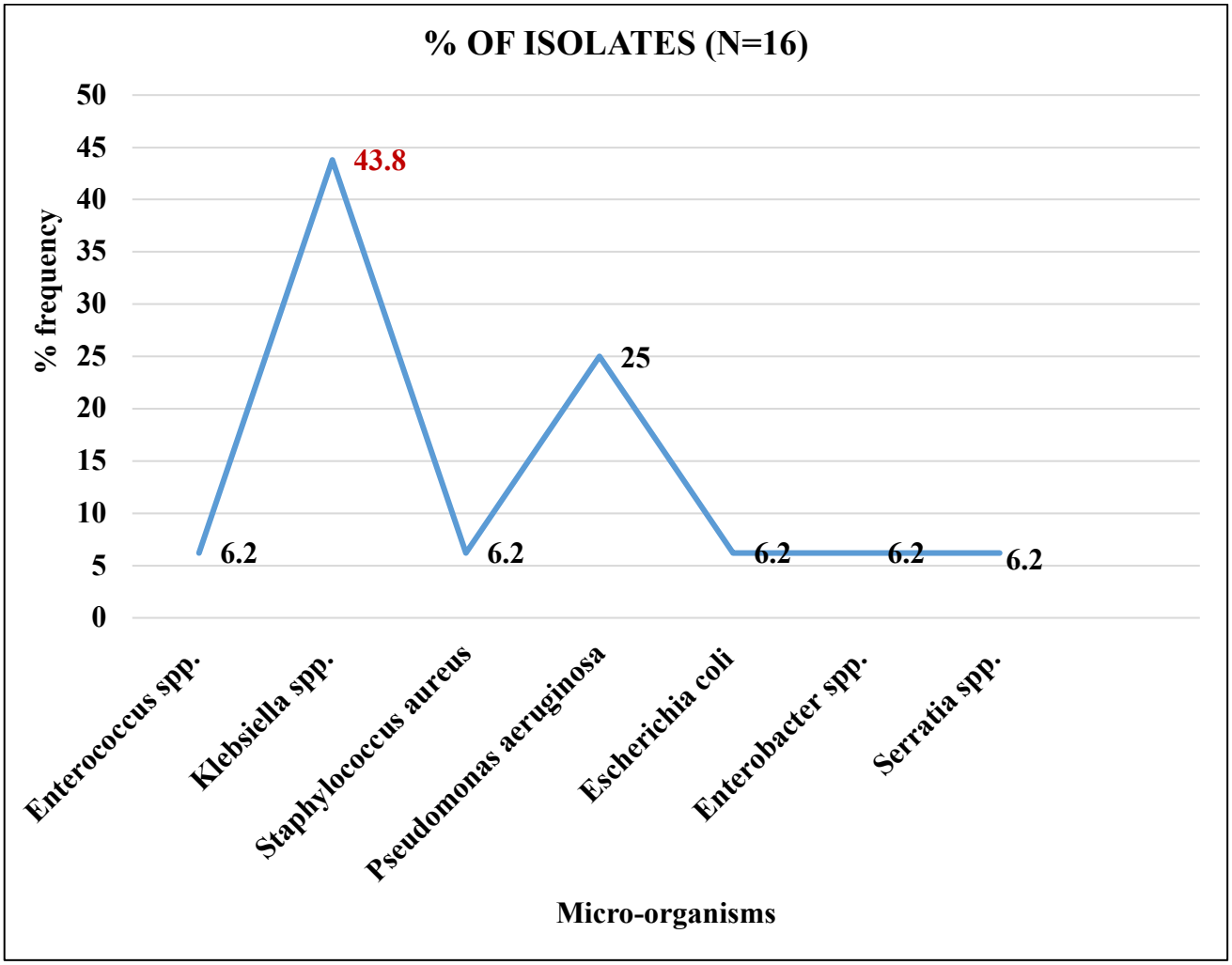

Figure 3.50: Percentage of the ten most frequently isolated micro-organisms in ICU-acquired bloodstream infection episodes for 2017
[Adapted from] European Centre for Disease Prevention and Control. Healthcare-associated infections acquired in intensive care units. In ECDC. Annual epidemiological report for 2017. Stockholm: ECDC; 2019.

Figure 3.50 represents the percentage frequency of the respective isolated micro-organisms in ICU-acquired BSI. 16 isolates were collected for Malta. The highest percentage frequency was attributed to the micro-organism *Klebsiella* spp., followed by the micro-organism *Pseuodomonas aeruginosa*.

Chapter 4: Discussion

4.1 Retrospective study

4.1.1 Interpretation of quantitative data

Patients receiving antibacterial treatment have a greater risk of acquiring multi-drug resistant infections. This increase in antibacterial use, contributes to antibacterial pressure and is a possible factor for acquiring multidrug-resistant bacteria. The DDD-PT value, highlighted in figure 3.2 shows a sharp increase throughout the nine year period, with its highest value for the year 2015 at 1872.4. This value goes in parallel with the OBD value, depicted in figure 3.1 which shows a relatively constant trend in bed days value. This rising trend in antibacterial use goes in agreement with the ESAC-Net surveillance data. The ESAC-Net surveillance data, published in 2017, reported that the population-weighted mean consumption of antibacterials for systemic use in the hospital was 2.9 DDD per 1000 inhabitants/day for Malta in 2017, showing an increasing mean consumption trend during the years 2012-2016.[3]

4.1.2 Trend in antibacterial administration during the period 2009-2017

With reference to figures 3.4-3.12, starting at the year 2009, the highest DDD value was observed for the antibacterial class carbapenems (J01DH), at 2476.8. This is also seen for the years 2010 up until 2014. 2015 shows an increase in use for penicillins, including beta-lactamase inhibitors (J01CR), at a value of 2473.5. This rise in carbapenem administration is also observed for the years 2016 and 2017. The beta-lactamase resistant penicillins (J01CF), monobactams (J01DF) and the 2nd generation cephalosporins (J01DC) were among the antibacterial classes least prescribed, with DDD values ranging from 110.5 DDD to 161.6 DDD. The percentage of prescribing of cephalosporins, other beta-lactams e.g. carbapenems, and other classes of antibacterials were higher in the hospital, rather than in the community.

[3] European Disease Prevention and Control (ECDC). Summary of the latest data on antibiotic consumption in the European Union, ESAC-NET surveillance data [Internet]. Stockholm: *ECDC*; 2017 [cited 2020 May 13]
Available from: https://www.ecdc.europa.eu/en/publications-data/summary-latest-data-antibiotic-consumption-eu-2017

This goes in contrast to penicillins which were not the most administered antibacterials in the hospital section for all countries. Looking into each antibacterial class separately (figure 3.13-3.38), an increase in DDD was observed for the tetracyclines (J01AA), showing its highest consumption in 2016. Tetracycline (J01AA07) was the most administered. Amphenicols (J01BA) show a sharp increase in use for the year 2013. The penicillins with extended spectrum (J01CA) show a relatively stable DDD value throughout the years, with the highest consumption in 2017, at 279.75. This is in contrast to the beta-lactamase sensitive penicillins (J01CE), which show their highest DDD value for the year 2009, at 155.83. The highest consumption for the beta-lactamase resistant penicillins (J01CF) was observed for the year 2010, at 290 DDD. The 1st generation cephalosporins (J01DB) were not reported to be administeted, expect in the year 2014, at just a DDD value of 3.75. Of the 2nd generation cephalosporins (J01DC), cefuroxime was the antibacterial administered. The monobactams (J01DF) and intermediate acting sulfonamides (J01EC) show an increase in use in the year 2013, at 24.25 DDD and 130 DDD respectively. The sulphonamides, trimethoprim, including derivatives (J01EE) show an increase in DDD value from 2009 to 2016. Macrolide (J01FA) antibacterials show their highest consumption for 2017, at 1280 DDD. The lincosamides (J01FF) show their highest consumption for the year 2009, at 224.67 DDD, followed by a sharp decrease for the next year in 2010, at 35.17 DDD. The fluoroquinolones (J01MA) show a fairly stable DDD consumption throughout the nine-year study period. DDD consumption for glycopeptides (J01XA) increases through the years, with the highest value for 2017, 2104.25. Teicoplanin (J01XA02) was the commonly administered glycopeptide. The polymyxins (J01XB) also show a sharp increase in consumption through the years. For the imidazole derivatives (J01XD), metronidazole (J01XD01) was the antibacterial administered, reaching a peak in DDD value in 2017. This peak in use in 2017 was also observed for the 3rd generation cephalosporins (J01DD), at 1237.5. For the other aminoglycosides (J01GB), the highest consumption was reported for 2013, and the least in 2017.

4.1.3 Trends for Carbapenem and Penicillin, with Beta-lactamase inhibitor

With reference to the antimicrobial consumption report for Malta for 2018, it shows a significant increasing trend during the period 2009-2018 for both penicillins and carbapenems. A notable increasing trend was observed for most hospitals in the period 2012-2016 for wide-spectrum antibacterials versus *Pseudomonas aeruginosa* and *Enterobacteriaceae*. From the retrospective study, meropenem and piperacillin, with a beta-lactamase inhibitor were the two most frequently prescribed antibacterial drugs, with an average yearly DDD value of 3577 and 1362 respectively. With reference to figure 3.40, data collected shows that meropenem (J01DH02) was the most administered carbapenem from the retrospective part of the study. Ertapenem (J01DH03) was administered the least. Carbapenem (J01DH) DDD administration per 100 bed-days, showed its highest value for the year 2011, at 2789. The second most prescribed class of antibacterials, is penicillins with a beta-lactamase inhibitor (J01CR), showing a steady rise in DDD/100 bed days from 2009-2017 (figure 3.41). The highest consumption was registered for 2015, at a DDD value of 2473.5.Piperacillin with a beta-lactamase inhibitor; tazobactam (J01CR05), was the preferred penicillin administered (figure 3.42). Penicillins combined with beta-lactamase inhibitors, such as piperacillin – tazobactam, constitute a set of antibacterials prescribed for the management of infections ascribable to ESBL-producing gram negative bacteria, still not potent against carbapenem-resistant gram-negative bacteria.[4]

Results go in tandem with the annual epidemiological report for 2017, which show the beta-lactams, penicillins (J01C) with the highest DDD per 1000 inhabitants per day value, at 1.54, for Malta in the hospital sector. An accumulating trend was noted for piperacillin-tazobactam (J01CR05) during the years 2013-2017. Consumption for carbapenems (J01DH) was at 0.6

[4] European Disease Prevention and Control (ECDC). Antimicrobial consumption in the EU/EEA, annual epidemiological report for 2018 [Internet]. Stockholm: *ECDC*; 2019 [cited 2020 May 5]
Available from: https://www.ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-consumption-europe-2018

DDD per 1000 inhabitants per day for the year 2017. A notable rise in use was seen for Malta, among eight other countries, between 2013-2017. The drug use trends indicate a rise in carbapenem use of 10.86% between the years 2009 and 2011, with a peak in 2014, and use remained fairly stable through to 2017. This finding was identified in the ECDC 2018 report for Malta and the study indicates that the trend has been confirmed for the prospective arm, described further in section 4.2.[5] For 2018 data, carbapenem (J01DH) consumption was 0.04 DDD per 1000 inhabitants per day. The EU/EEA population-weighted mean consumption showed a rigorously sharp rise for Malta, and five other countries, including Bulgaria, Croatia and Hungary. [4]

4.1.3.1 Micro-organisms associated with the respective antibacterials

Penicillins with beta-lactamase inhibitors, e.g. piperacillin/ tazobactam, which is a wide-spectrum antibacterial active against *Pseudomonas aeuruginosa* and *Enterobacteriaceae*, and is used mostly in the hospital setting. Piperacillin/ tazobactam is marketed for first-line use as empiric treatment of serious infections, such as against ESBL- producing microorganisms. This treatment avoids carbapenem overuse. Carbapenems are used in hospitals, as a last reserve, to treat confirmed or suspected serious infections. Its use has led to further infections with carbapenem-resistant bacteria, e.g. CRE, carbapenem-resistant *Acinetobacter baumannii* or carbapenem-resistant *Pseudomonas aeruginosa*. Multidrug-resistant gram negative bacteria can only be treated with a few antibacterials e.g. colistin, which is a polymyxin antibacterial. Patients who were treated previously with the antibacterials have a greater risk of being colonized with MDR bacteria; successive therapy increases the risk, hence contributing to antibacterial pressure. [3]

[5] European Disease Prevention and Control (ECDC). Carbapenem resistant enterobacteriaceae, second update- 26 September 2019 [Internet]. Stockholm: *ECDC*; 2019 [cited 2020 May 5] Available from: https://www.ecdc.europa.eu/sites/default/files/documents/carbapenem-resistant-enterobacteriaceae-risk-assessment-rev-2.pdf

4.2 Prospective study

With reference to figure 3.46, for the prospective arm of the study, beta-lactam antibacterials (J01C) were the most administered antibacterials at 33.4% of a total of 68 patients receiving care at the ICU during the period studied. Carbapenems (J01DH) and Glycopeptide (J01XA) antibacterials followed at 18.9% and 16% respectively. Piperacillin and tazobactam (J01CR05) were the most used (28 patients) followed by meropenem (J01DH02) (20 patients). Among the least administered antibacterials, are the tetracyclines, amphenicols, aminoglycosides and sulfonamides and trimethoprim. These findings go in parallel with the retrospective study findings, described in section 4.1 above.

4.2.1 Modification in antibacterial therapy

Table 3.4, highlights some data on change in antibacterial drug therapy, gathered during the prospective part of the study. Meropenem, class J01DH, was the most antibacterial administered during the study period. This drug is usually administered at a dose of 1g, 8 hourly, IV or 1g, 12 hourly, IV alone or in combination with other antibacterial (s) according to the indication for administration. Additional antibacterial treatment with meropenem included; with vancomycin 1g daily IV for type 1 respiratory failure due to pneumonia; gentamicin 360mg IV for GVHD: type 1 respiratory failure; with teicoplanin 400mg daily IV and clarithromycin 500g BD IV for sepsis infection. Administration in addition to teicoplanin 800mg bd IV for 4 loading doses, then continuing at a maintenance dose of 800mg daily IV for acute spinal cord injury, secondary to trauma. Concomitant administration with clindamycin 600mg qds IV for sepsis. A similar study was carried in an ICU of a tertiary care government hospital in Delhi over a time frame of four months, on 100 patients, reported that all residing patients were being treated with a minimum of two antibacterials. Beta-lactam antibacterials with metronidazole and levofloxacin and metronidazole were common combinations. An aminoglycoside was then added as a tertiary drug. Analysing the prescriptions dispensed, 78% of patients were treated with a beta-lactam antibacterial, aminoglycosides at 56% and carbapenems at 42% (Saxena et al, 2019).

4.2.2 Infections associated with the ICU

Of patients residing in an ICU for longer than 2 days, 6.3% were diagnosed by a minimum of one pneumonia incident. The prevalence of pneumonia was 6.6 episodes per 1000 patient-days. This relates to the prospective data collected, where 47% (n=68) of infections were attributed to a respiratory infection, as highlighted in figure 3.47 above. 3.7 % of ICU patients, with a stay of more than 2 days, acquired an ICU BSI. 36.5% of cases were catheter-related, due to another primary infection. The latter was mostly due to pulmonary infections, gastrointestinal, urinary tract, surgical site and skin infections respectively. Microorganisms in BSI episodes, referring to coagulase-negative staphylococci, followed by *Enterococcus* spp., *Klebsiella* spp. and *S. aureus* are among the most commonly isolated.[4]

4.3 Antibacterial costings

4.3.1 Correlation of costings to antibacterial consumption

With reference to figure 3.48 above, the antibacterial class J01C, beta-lactam antibacterials, proved to be the costliest antibacterial for Malta during the year 2018, at a total of 962,418 Euro per annum. The latter class encompasses, penicillins with extended spectrum (J01CA), the beta-lactamase sensitive penicillins (J01CE), beta-lactamase resistant penicillins (J01CF) and combinations of penicillins, including beta-lactamase inhibitors (J01CR). The highest cost was for the penicillins with extended spectrum, from which amoxicillin 250mg tablet (J01CA04) was issued the most, at 271,400 Euro per annum. Following the beta-lactam antibacterials, are the quinolone antibacterials, J01M, at a total annual cost of 261,811 Euro. The highest quantity issued was attributed to ciprofloxacin 250mg tablet (J01MA02), at an annual cost of 180,160 Euro. The least costly, at 22,981 Euro per annum, was the J01E class, which refer to the sulfonamides and trimethoprim, of which the co-trimoxazole 480mg tablet (J01EE01), at 126,196 Euro per annum was administered the most. With reference to table 3.5, relating the cost data described above, to the annual published antimicrobial consumption report for 2018, the beta-lactams, penicillins, show the highest DDD/1000 inhabitants/ Year value, at 0.87, for Malta, in 2018. This is followed by the other beta-lactam antibacterials, and quinolones, at 0.37 and 0.34 respectively. This shows a parallel relationship with the total cost of J01 antibacterials registered in 2018, as described above. The sulfonamides and trimethoprim, stand at a DDD/1000 inhabitants/ Year value of 0.05, proving to be the least administered. An annual growth rate of 7.2% was observed for Malta, as depicted in figure 3.49, with DDD expressed per 1000 inhabitants per year, starting at 1.24 in 2009, and increasing to 2.32 in 2018. The latter value relates to the total annual cost of 1, 647, 338 Euro, gathered in the local costings data.[4]

4.4 Antibacterial resistance

The ECDC annual epidemiological report for 2017 highlights the 10 most frequently isolated micro-organisms in ICU acquired BSI for Malta (n=16) . The highest percentage of isolates is observed for *Klebsiella* spp., followed by *Pseudomonas aeruginosa* (refer to figure 3.49) No cases for *Acinetobacter* spp. and *Candida* spp. were observed. [4]

With reference to the annual ECDC 2017 report, *Pseudomonas aeruginosa* was the most commonly isolated microorganism in ICU-acquired pneumonia cases. The report also shows increased rates of resistance of *Klebsiella* spp. isolates at 38% for third generation cephalosporins and 11% for carbapenems. Meropenem was the most prescribed carbapenem antibacterial with a sensitivity rate of 55.16%, whilst ertapenem, prescribed less often than the previous carbapenem, at a sensitivity rate of 66.26% of the tested strains. Both drugs are used for the management of pneumonia, complicated urinary tract infections and complicated skin infections. The significant difference in sensitivity rate indicates the underutilization of ertapenem and overutilization of meropenem.[6] This data correlates to the retrospective data collected, as highlighted in figure 3.40.

The increase in resistance of gram-negative species is related to the 3rd generation cephalosporins, fluoroquinolones, carbapenems and aminoglycosides for *Klebsiella pneumoniae*. Resistance for *Pseudomonas aeruginosa* is attributed to ceftazidime, piperacillin tazobactam and fluoroquinolones. Rates of resistance for the year 2017, were 22.5% for carbapenems to *K. pneumoniae* and 64.1% for third generation cephalosporins and fluoroquinolones. [3]

Anti-microbial-resistant isolates in the particular bacteria linked to ICU-acquired HAIs were oxacillin resistance (MRSA) for *S.aureus* isolates, vancomycin resistance for Enterococcus

[6] European Disease Prevention and Control (ECDC). Antimicrobial consumption in: ECDC, Annual epidemiological report for 2017 [Internet]. Stockholm: *ECDC*; 2018 [cited 2020 Jan 6] Available from: https://www.ecdc.europa.eu/en/publications-data/antimicrobial-consumption-annual-epidemiological-report-2017

spp. and ceftazidime resistance for *P.aeruginosa* isolates. *E.coli* isolates, *Klebsiella* spp. isolates and *Enterobacter* spp. isolates were microorganisms indicated for resistance with third-generation cephalosporins. *Klebsiella* spp., *E.coli* isolates, *Enterobacter* spp., *P.aeruginosa* and *A. baumannii* isolates were the microorganisms reported for carbapenem resistance. [7]

For the period 2007-2015, an increase in burden was observed for all antibacterial-resistant bacteria. The percentage increase for carbapenem-resistant bacteria went up from 18% in 2007 to 28% for 2015, with the proportion due to carbapenem-resistant *K. pneumoniae* and *E. coli* doubled from 4.3% in 2007 to 8.79% in 2015. [6]

For 2015, a significant burden due to MRSA infections was observed for Portugal and Malta, along with infections due to carbapenem-resistant and colistin-resistant bacteria. Colistin is an antibacterial reserved as an ultimate resort for multidrug resistant bacteria, which also include carbapenem-resistant micro-organisms. In young adults and adults, the highest infection rates were due to carbapenem-resistant and colistin-resistant bacteria (Cassini et al, 2019; Saxena et al, 2019).

Data reported to EARS-NET for 2018, reports that in the EU/EEA, 32.1% of the *P. aeruginosa* isolates reported were resistant to more than one antibacterial group. The highest EU/EEA population-weighted average resistance proportion was attributed to fluoroquinolones at 19.7%, along with by piperacillin +/ tazobactam, at 18.3%. For Malta, the percentage of resistance to piperacillin +/ tazobactam (%R) to *Pseudomonas aeruginosa*, starts at 16% (N=25) in 2015, and increases to 21.6% (N=37) for 2017. Data for 2018 shows that out of 29 invasive isolates tested, 17.2% proved to be resistant. [8]

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[7] European Disease Prevention and Control (ECDC). Healthcare-associated infections acquired in intensive care units, annual epidemiological report for 2017 [Internet]. Stockholm: *ECDC*; 2019 [cited 2020 May 7]
Available from: https://www.ecdc.europa.eu/en/publications-data/healthcare-associated-infections-intensive-care-units-annual-epidemiological-1

[8] European Disease Prevention and Control (ECDC). Surveillance of antimicrobial resistance in Europe 2018. Stockholm: *ECDC*; 2019 [cited 2020 June 5]
Available from: https://www.ecdc.europa.eu/sites/default/files/documents/surveillance-antimicrobial-resistance-Europe-2018.pdf

CRE can result in carbapenem resistance owing to a variety of means, one of which is seen increasingly is the production of carbapenemase enzymes. ECDC reports on the health impact of AMR evaluated that the amount of deaths related to infections with *K.pneumoniae* resistant to carbapenems increased six times as much during the period 2007-2015. Colistin is increasingly being used to combat CRE infections, but resistance to such drug treatment can develop during treatment. Data reported to EARS-NET for 2018, reports that in the EU/EEA, 37.2% of the *K.pneumoniae* isolates outlined were resistant to more than one antibacterial group. The highest EU/EEA population-weighted average resistance proportion was for third-generation cephalosporins at 19.7%, followed by fluoroquinolones, at 31.6% and carbapenems at 7.5%. For Malta, the percentage of resistance to carbapenems(%R) to *K. pneumoniae*, starts at 4.5% (N=88) in 2015, and 10.3% (N=117) for 2017. Data for 2018 shows that out of 136 invasive isolates tested, 15.4 % proved to be resistant. This shows a significant increasing trend.[8]

Finite antibacterial classes, like polymyxins, mostly colistin, are obtainable for the management of patients with carbapenem-resistant bacteria. Colistin, which is a polymyxin antibacterial, administered in parenteral form and an increase in use was observed in Malta, among eight other countries, for all years during 2012-2016. Ceftazidime-avibactam, which is a recent antibacterial combination with activity versus CRE infections was marketed in 2016 for treatment against complicated intra-abdominal infections, complicated urinary tract infections and infections attributable to aerobic gram-negative bacteria. Meropenem-varobactam is another combination which was authorized for usage in the European union for the same manifestations listed above. [5]

4.5 Limitations

The limitations for this study are as follows:

- Data was gathered from one ICU, in a single hospital and only for a four-month observation period.
- Yearly DDD values about antibacterial consumption were available for the retrospective arm of the study. Monthly values would have made the study more thorough in its analysis.
- Patient demographics were not available for the retrospective arm of the study.
- Relevance of data collected is affected by the small sample size of patients at the ICU at MDH, when compared to other countries. Also, the local ICU hosts both medical and surgical patients, in contrast to other countries which have separate wards respectively.
- This drug utilization study lacked information about the infective micro-organism, both for the retrospective and prospective parts.
- For the prospective part of the study, in particular the devised 'antibacterial information sheet', some data points were not available and hence left out. These include information on the reason for antibacterial administration, referring to HAI, CAI, SP, MP or any other unknown factor. The indication for antibacterial use; prescribed for prophylaxis/ empirical/ definitive treatment was also not available on the patient's treatment chart.

4.6 Recommendations

Recommendations for further study include:

- Looking into the clinical reasoning behind the use of carbapenems and a review of the protocols applied.
- Assembling an antibacterial protocol list on administration for the two most commonly administered antibacterial classes; carbapenems and penicillins, including beta-lactamase inhibitors.
- Gathering pathological information on the isolated micro-organisms from bloodstream infections causing the bacterial infection in the ICU patient.
- Correlating the infective pathogen to the antibacterial(s) prescribed.
- Implementing the methodology applied in this study, to a further study implemented over a longer, continuous time span. This would illustrate a more precise and reliable trend in antibacterial drug use. This would add up to a larger sample, making the study more adequate.
- Analysing the impact of pharmacist antibacterial stewardship in ICU.
- Implementation of regular audits and monitoring of adherence to protocols and pharmacist recommendations.

4.7 Conclusion

This study managed to highlight the trends in the antibacterial administration in the Maltese ICU, through the available information documented. Annual DDD data available, helped highlight a pattern of administration of certain antibacterial classes, which emerged to be the most administered throughout the nine-year period. The four-month study period conducted in 2019, highlighted present use of antibacterial drugs in the ICU and allowed more importance on the reason of administering a particular antibacterial, for a particular infection. Knowledge and analysis of the micro-organism isolated is a subject for future study. The retrospective arm was enhanced by the data obtained from the prospective arm, which showed parallel results. An increase in DDD values was observed through the years 2009-2017, highlighting an increase in infections in the ICU requiring antibacterial drug treatment, irrespective of the reason for administration. Comparison to other European and non-European countries can thus be made, which goes in tandem to published surveillance reports, referred to in the above sections. Both divisions of the study, resulted in the highest DDD consumption for carbapenems and beta-lactam antibacterials, penicillins. Reflection on this rise in carbapenem use is of utmost importance. Their broad-spectrum antibacterial activity with proven effectiveness for infections traceable to beta-lactamase (ESBL) producing bacteria, makes them preferred over other types of antimicrobials in treating life-threatening infections; as encountered in the ICU. This leads to the question of : is this rise going to continue, and if so will it lead to higher rates of resistance?

Interpretations from this study can help guide the healthcare professional team in prudent use of antibacterials, addressing threats posed by multidrug resistant bacteria. Implementation of ways to address antibacterial stewardship, through a clinical surveillance software which integrates all the data necessary, can help to improve management of infections and decrease antibacterial resistance.

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Published Abstracts

Evaluation of antibacterial drug use in an intensive care unit
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Abstract title: Evaluation of antibacterial drug use in an intensive care unit

Rationale use of antibacterial agents in hospitals reduces risk of antimicrobial resistance and ensures adequate anti-infective choices for patients which is particularly relevant for the intensive care unit (ICU).

To evaluate retrospective and prospective antibacterial drug use in the ICU.

This study was carried out at the ICU at an acute care hospital. Past data from hospital from 2009-2017 was retrieved. Present data was collected through patient records from the ICU using a devised 'Antibacterial Collection Sheet' over a period of 4 months, February until May 2019. The Anatomical Therapeutic Classification/ Defined Daily Doses methodology was applied. Data was analysed using Microsoft Excel.

From the retrospective study, meropenem and piperacillin, with a beta-lactamase inhibitor were the most commonly administered antibacterial drugs, with an average yearly DDD value of 3577 and 1362 respectively. From the prospective arm, piperacillin and tazobactam were the most used (28 patients) followed by carbapenems (20 patients).

The drug use trends indicate a rise in carbapenem use of 10.86% between the years 2009 and 2011, with a peak in 2014, and use remained fairly stable through to 2017. This finding was identified in the ECDC 2018 report for Malta [1] and the study indicates that the trend has been confirmed for the prospective arm. Reflection on clinical reasoning behind the use of carbapenems and review of the protocols is suggested.

References:

[1] European Centre for Disease Prevention and Control. Antimicrobial consumption in the EU/EEA, annual epidemiological report for 2018. Stockholm: ECDC; 2019.

Appendices

Appendix I

University Research Ethics Committee approval

L-Università ta' Malta

Faculty of
Medicine & Surgery
University of Malta
Msida MSD 2080, Malta

Tel: +356 2340 1879/1891/1167
umms@um.edu.mt

www.um.edu.mt/ms

Ref No: **FRECMDS_1718_021**

Wednesday 4th April 2017

Ms. Julia Catania
105A, Bliss
Triq Margaret A. Murray
Naxxar NXR4030

Dear Ms. Julia Catania,

Please refer to your application submitted to the Research Ethics Committee in connection with your research entitled:

Use of Antibecterial Drugs in the Intensive Care Unit

The Faculty Research Ethics Committee granted ethical approval for the above mentioned protocol.

Yours sincerely,

Dr. Mario Vassallo
Chairman
Research Ethics Committee

Appendix II

Data Collection Form

ANTIBACTERIAL INFORMATION SHEET

- DATE: _____

Patient number					
Gender (M/F)					
Age					
Antibiotic/s administered					
Dose					
Frequency					
Route of administration					
CAI/ HAI/ SP/ MP/ Other/ Unknown *					
Indication: P, E or D **					
Organ ***					
Treatment Start Date					
Reason Documented (Y/N)					
No change/ Escalation/ De-escalation					
Change from which antibiotic					

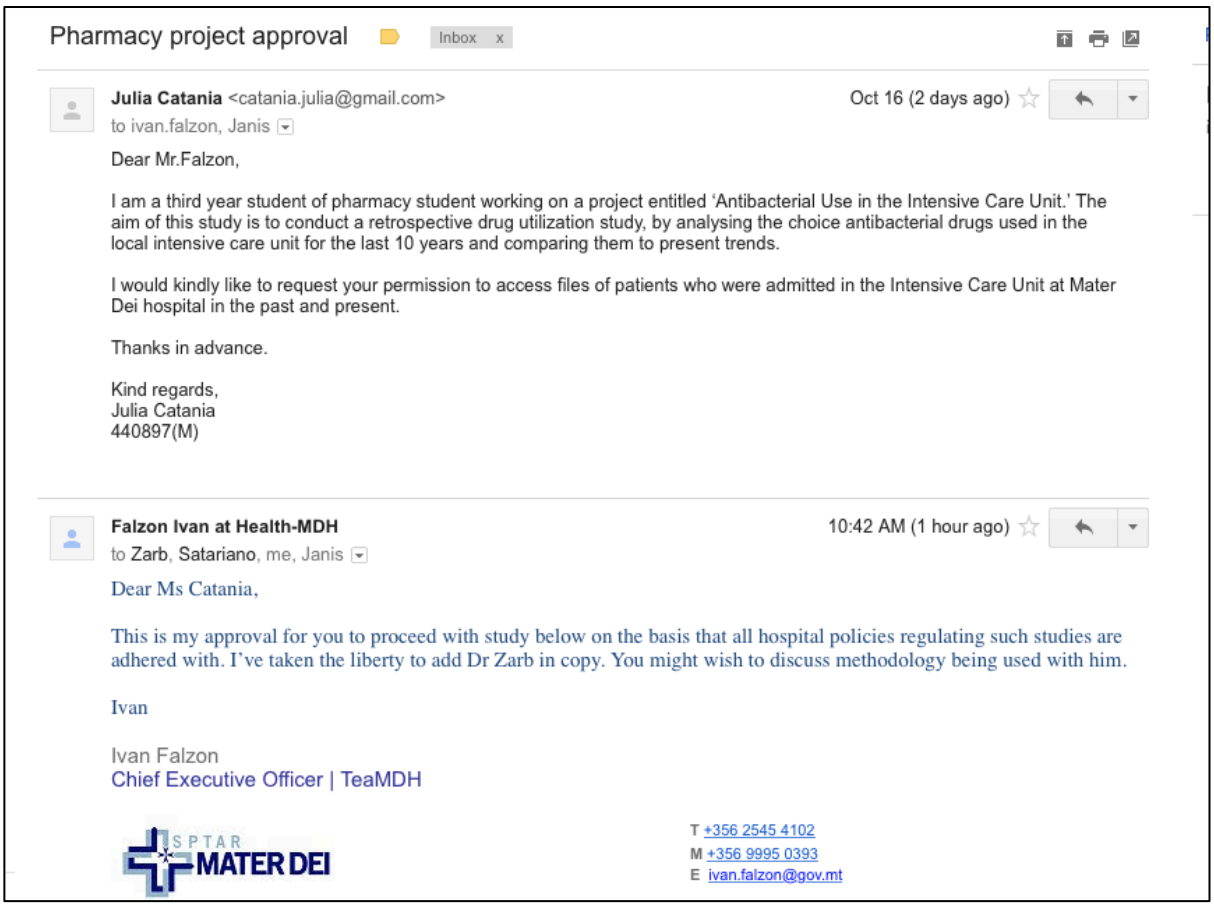
*HAI = Hospital acquired infection; CAI= Community acquired infection; MP = Medical prophylaxis; SP = Surgical prophylaxis

** P=Prophylaxis; E=Empirical & D=Definitive

***Organ: CNS/ EYE/ENT/ RESP/CVS/SST/ BJ/ UT/ GU/OB/ SEPSIS/ BSI (blood stream infection)/ PUO/ UNK

Appendix III

Chief Executive Officer of Mater Dei Hospital



Pharmacy project approval Inbox x

Julia Catania <catania.julia@gmail.com> Oct 16 (2 days ago)
to ivan.falzon, Janis

Dear Mr.Falzon,

I am a third year student of pharmacy student working on a project entitled 'Antibacterial Use in the Intensive Care Unit.' The aim of this study is to conduct a retrospective drug utilization study, by analysing the choice antibacterial drugs used in the local intensive care unit for the last 10 years and comparing them to present trends.

I would kindly like to request your permission to access files of patients who were admitted in the Intensive Care Unit at Mater Dei hospital in the past and present.

Thanks in advance.

Kind regards,
Julia Catania
440897(M)

Falzon Ivan at Health-MDH 10:42 AM (1 hour ago)
to Zarb, Satariano, me, Janis

Dear Ms Catania,

This is my approval for you to proceed with study below on the basis that all hospital policies regulating such studies are adhered with. I've taken the liberty to add Dr Zarb in copy. You might wish to discuss methodology being used with him.

Ivan

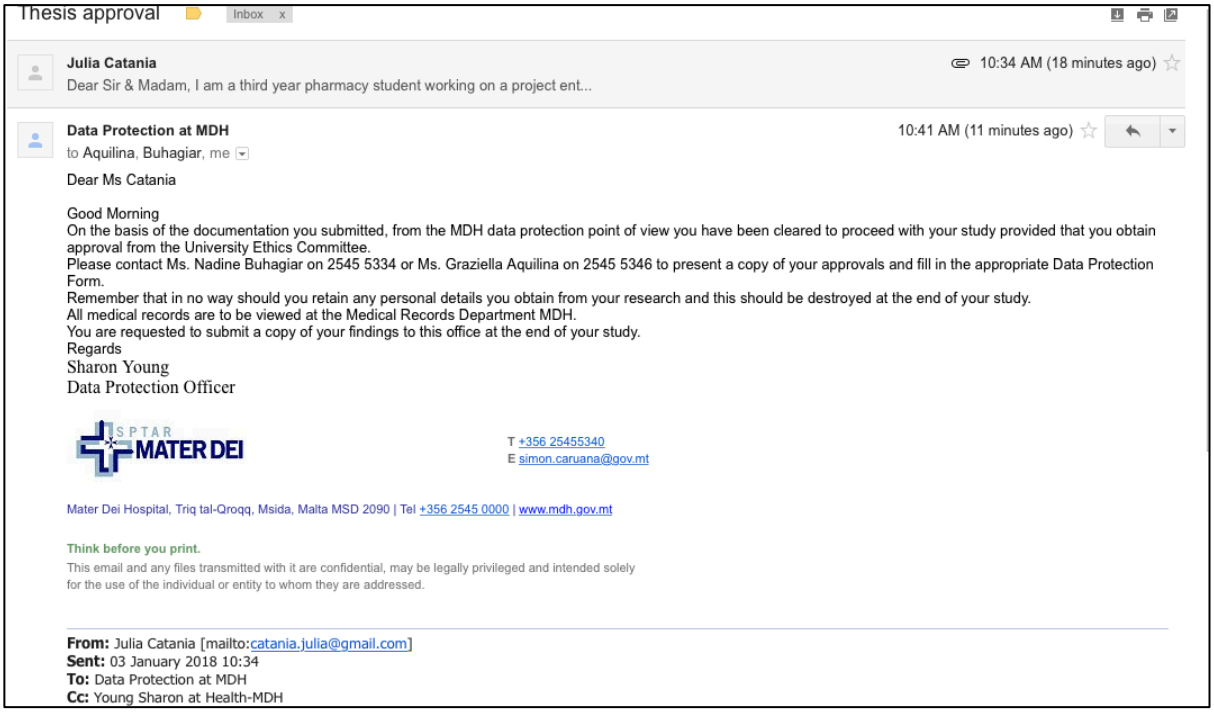
Ivan Falzon
Chief Executive Officer | TeaMDH

SPTAR MATER DEI

T +356 2545 4102
M +356 9995 0393
E ivan.falzon@gov.mt

Appendix IV

Data Protection Officer



Thesis approval Inbox x

Julia Catania 10:34 AM (18 minutes ago)
Dear Sir & Madam, I am a third year pharmacy student working on a project ent...

Data Protection at MDH 10:41 AM (11 minutes ago)
to Aquilina, Buhagiar, me

Dear Ms Catania

Good Morning
On the basis of the documentation you submitted, from the MDH data protection point of view you have been cleared to proceed with your study provided that you obtain approval from the University Ethics Committee.
Please contact Ms. Nadine Buhagiar on 2545 5334 or Ms. Graziella Aquilina on 2545 5346 to present a copy of your approvals and fill in the appropriate Data Protection Form.
Remember that in no way should you retain any personal details you obtain from your research and this should be destroyed at the end of your study.
All medical records are to be viewed at the Medical Records Department MDH.
You are requested to submit a copy of your findings to this office at the end of your study.
Regards
Sharon Young
Data Protection Officer

SPTAR MATER DEI

T +356 25455340
E simon.caruana@gov.mt

Mater Dei Hospital, Triq tal-Qroqq, Msida, Malta MSD 2090 | Tel +356 2545 0000 | www.mdh.gov.mt

Think before you print.
This email and any files transmitted with it are confidential, may be legally privileged and intended solely for the use of the individual or entity to whom they are addressed.

From: Julia Catania [mailto:catania.julia@gmail.com]
Sent: 03 January 2018 10:34
To: Data Protection at MDH
Cc: Young Sharon at Health-MDH

Appendix V

Chairman of the Department of Anaesthesia

SPTAR MATER DEI

Department of Anaesthesia
Level -1
Mater Dei Hospital
Tal-Qroqq, Msida
MSD 2090
Tel: 25457251

27th November, 2017

Ms.Julia Catania
Flat 7, Stella Maris Court,
Triq is- Santwarju,
San Gwann, SGN 1768

To whom it may concern,

Re: *'Use of Antibacterial Drugs in the Intensive Care Unit'*

I acknowledge the study in caption to be carried out within the department of Anaesthesia, Intensive Care and Pain Management.

Yours Sincerely,

Dr. David Gatt MD, MSc, FRCA, FIPP
Chairman - Dept. of Anaesthesia
Mater Dei Hospital

Appendix VI

Head Clinician of the Intensive Care unit

Julia Catania
Flat 7, Stella Maris Court
Triq is-Santwarju
San Gwann, SGN 1768
21-11-2017

Tel 21372911

Dear Dr. Abela

I am a third year Pharmacy student working on a project entitled 'Antibacterial Use in the Intensive Care Unit'. I would kindly like to ask your permission to access files of patients who were admitted in the Intensive Care Unit at Mater Dei Hospital in the past and at present.I assure you that all data regarding patients will be kept confidential in accordance with the Data Protection Act.

Enclosed please find a copy of my proposal.

Thanking you in advance,

Yours truly,

Julia Catania

To be completed by Dr. Abela.

I, Dr Carmel Abela give permission to Julia Catania to access patient profiles at the ICU at MDH as part of her research project.

Signature

- Lead Clinician ITU
- A/Chairman Dept of Anesthesia

Appendix VII

FIP Seville Abstract Poster Submission