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REVIEW

Application of ATC/DDD methodology to analyse antibiotic consumption in internal medicine department: A review

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Abstract

Background: Antibiotic resistance has become a significant problem due to its impact such as higher medical costs, prolonged hospital stays, and increased mortality**.** The Internal Medicine Ward has a high consumption of antibiotics, particularly for gastroenteritis, typhoid, diabetic ulcer, urinary tract infection, and sepsis. The DDD/ATC systems applied in hospitals may provide valid data to evaluate antimicrobial usage as a global standard method. **Objective:** To explore the antibiotic use pattern in the internal medicine department based on the DDD/ATC system. **Method:** The authors explored articles from the database in PMC, Research Gate, and Google Scholar from July 11st, 2020, to July 21st, 2020. The authors included original articles/research, case reports, and meta-analyses from 2006 to 2020, which discussed DDD/100 patient-days or DDD/100 bed-days antibiotics in the internal medicine ward. A major criterion was to ensure all subjects in publications were adults aged above 18. **Result:** Penicillin is the most consumed (127.9 DDD/100 bed-days), followed by Cephalosporin (41.42 DDD/100-bed-days) and Fluoroquinolone (25.87 DDD/100 bed-days). **Conclusion:** The most widespread antibiotic use in Internal Medicine in many countries showed an improvement in rational antibiotic consumption.

Introduction

The ATC (Anatomical Therapeutic Chemical) classifies antibiotics as pharmacologically active ingredients based on the organ or system they act and their therapeutic, pharmacological, and chemical properties (Septa, 2019). The unregulated consumption of antibiotics has contributed largely to the development of bacterial resistance to antibiotics globally (Kuster *et al*., 2008; OECD, 2018; CDC, 2019). Antibiotic resistance is when bacteria develop the ability to defeat drugs designed to kill them; thus, it is not destroyed but continues to grow (CDC, 2021; NIH, 2018). Higher antibiotic resistance triggers higher mortality and hospitalisation costs (Kuster *et al*., 2008; Septa, 2019). Antibiotic resistance has now become a global threat (Nebyu *et al*., 2020). Many publications have shown that antibiotic resistance strongly correlates with the massive usage of antibiotics (Kuster *et al*., 2008; Septa, 2019; Nebyu *et al*., 2020). To evaluate the level of antibiotic consumption, the WHO has suggested the DDD/ATC methodology as a quantitative tool and the Gyssen analysis as a qualitative tool (Kuster *et al*., 2008).

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The DDD has assumed the average maintenance dose per day of antibiotics used for its main indication in adults (Kuster *et al*., 2008). The DDD/ATC systems applied in hospitals may provide valid data in evaluating antimicrobial usage (including antibiotics) and as a global standard method (Kuster *et al*., 2008; Hamdi *et al*., 2013). This study aimed to evaluate antibiotic use in the Internal Medicine Ward, one of the most common words used where antibiotics are largely administered and consumed in hospitals, particularly for gastroenteritis, typhoid, diabetic ulcer, urinary tract infection, and sepsis treatments.

Methods

Design

Several articles were explored from databases including PMC, Research Gate, and Google Scholar from July 11th, 2020, to July 21st, 2020. These included original articles/research, case reports, and meta-analyses from 2006 to 2020. The articles that discussed mainly the DDD/100 patient-days or DDD/100 bed-days antibiotics in the internal medicine ward were included in the search (Figure 1). All subjects in publications were adults aged above 18.

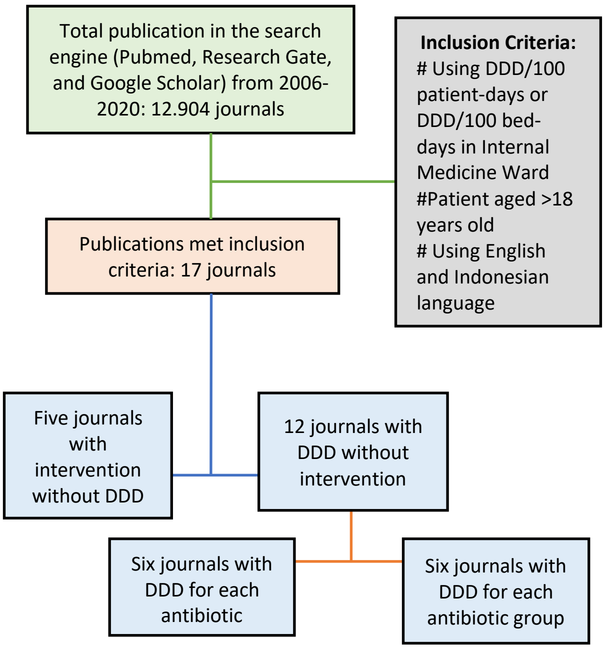

Figure 1: Research method scheme

The search found 12,904 journal articles on PubMed, Research Gate, and Google Scholar. The 12,904 articles were sorted based on inclusion criteria, and 17 focused on antibiotics usage in Internal Medicine, and aligned with the inclusion and exclusion criteria. The 17 journal articles had DDD/100 patient days per antibiotic or antibiotic group.

Results

Exactly 12 of the 17 publications described DDD values. Of the 17 publications, 12 specified the DDD calculation; six articles with DDD per antibiotics groups and six others focused on DDD per active ingredient. Five journals described the improvements in antibiotic consumption after conducting an antimicrobial stewardship program (ASP). Overall, Penicillin was the most popular antibiotic in Internal Medicine, followed by Cephalosporin based on the DDD value (Itamar *et al*., 2008; Aberto *et al*., 2008; Begum *et al*., 2010; Aberto *et al*., 2018; Bolla *et al*., 2019; Nebyu *et al*., 2020;).

The highest penicillin consumption was in Hazhaz Zonal Referral Hospital (HZRH), Eritrea, with 101.48 DDD/100 bed-days for Benzyl-penicillin G. It means in 100 days of the length of stay, 101-102 patients were administered Benzyl-penicillin G (J01CE01). The standard DDD by WHO for Benzyl-penicillin G is 3.6 grams (Nebyu *et al*., 2020) The value of DDD for Benzyl-penicillin G in Hazhaz Zonal Referral Hospital (HZRH) was higher than Orotta National Referral and Teaching Hospital/ONRTH, located in the same area with 22.4 DDD/100 bed-days (Nebyu *et al*., 2020).

A study in Bangladesh presented 31.54 DDD/100 bed-days and 8.58 DDD/100 bed-days for amoxicillin oral and parenteral, respectively (Begum *et al*., 2010). In another study in Nepal, ampicillin was 8.3 DDD/100 bed-days, while amoxicillin was 7.7 DDD/bed-days (Shankar *et al*., 2006; Acharya & Wilson, 2019). Three studies in Europe and Israel reported that Penicillin combined with beta-lactamase inhibitors presented the highest DDD/100 bed-days in four hospitals which were Emilia Romagna-Italy (16.25), Florence-Italy (13.3), Alessandria-Italy (5.42), and Israel (19.2). In Europe and Israel, the most popular Penicillin used was in combination with a beta-lactamase inhibitor, particularly Co-amoxiclav (Itamar *et al*., 2008; Alberto *et al*., 2008; Alberto *et al*., 2018; Bolla *et al*., 2019).

The second highest antibiotic administration in Internal Medicine Ward was the third-generation Cephalosporins. Studies in Jambi, Indonesia showed that Ceftazidime, Cefotaxime, and Ceftriaxone gave 42.11 DDD/100 bed-days (Septa, 2019). The same condition happened in Ethiopia, with 33.1 DDD/100 bed-days for third-generation Cephalosporins (Girma *et al*., 2018). Cephalosporins, such as Cefotaxime and ceftriaxone, are widely used for Pneumococcus infection, which are not sensitive to Penicillin because they can resist beta-lactamase and have low toxicity for patients with renal failure (Deck & Winston, 2012; Siswandono, 2016). The second-generation cephalosporin (cefuroxime) consumption in Palestine and Turkey presented 14.9 and 12.7 DDD/100 bed-days, respectively (Sweileh *et al*., 2007; Hamdi *et al*., 2013). Cefuroxime is active against H. influenzae, N. meningitidis, and S. pneumoniae (Deck & Winston, 2012; MacDougall, 2018; JFC, 2019).

The third antibiotic with high administration in the Internal Medicine Ward was Fluoroquinolone, especially ciprofloxacin, levofloxacin, and norfloxacin. A hospital in Italy showed fluoroquinolones 15.72 DDD/bed-days with ciprofloxacin as the most significant consumption (Alberto *et al*., 2008). Ciprofloxacin is an effective antibiotic against *P. aeruginosa* (MacDougall, 2018).

Figure 2 describes the top eight antibiotics used in internal medicine. They were benzyl-penicillin (127.9 DDD/100 bed-days), amoxicillin (57.12 DDD/100 bed-days), ceftriaxone (41.427 DDD/100 bed-days), gentamycin (26.58 DDD/100 bed-days), ciprofloxacin (25.87 DDD/100 bed-days), ampicillin (22.03 DDD/100 bed-days), Metronidazole (18.59 DDD/100 bed-days), and cloxacillin (5.55 DDD/100 bed-days). Based on six publications without detailed DDD per active ingredient (Figure 3), four groups of antibiotics dominate the usage in Internal Medicine. It was Penicillin, Cephalosporin, Fluoroquinolone, and Glycopeptide.

A study by Vaccheri *et al*. described that antimicrobial consumption in Italy increased from 2004 to 2011 (Alberto *et al*., 2008). It showed 33.01 and 94.49 DDD/100 bed-days in 2004 and 2011, respectively (Alberto *et al*., 2008). The escalation of antibiotic usage especially happened for Penicillin combined with a beta-lactamase inhibitor, Fluoroquinolone, and a third generation of Cephalosporin (Alberto *et al*., 2008; Elena *et al*., 2014). In addition to the eight most widely used antibiotics, some other antibiotics that are also frequently used can be seen in Appendix A.

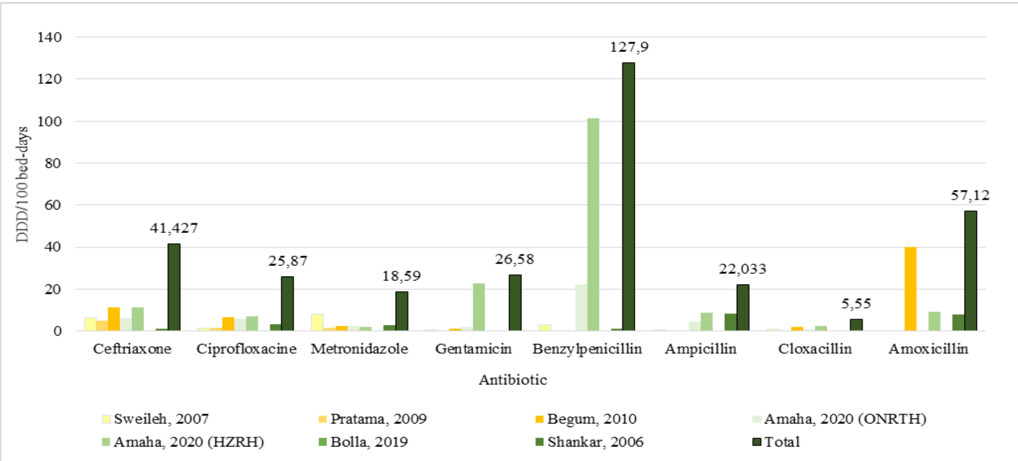

Figure 2: Top eight antibiotics used in internal medicine

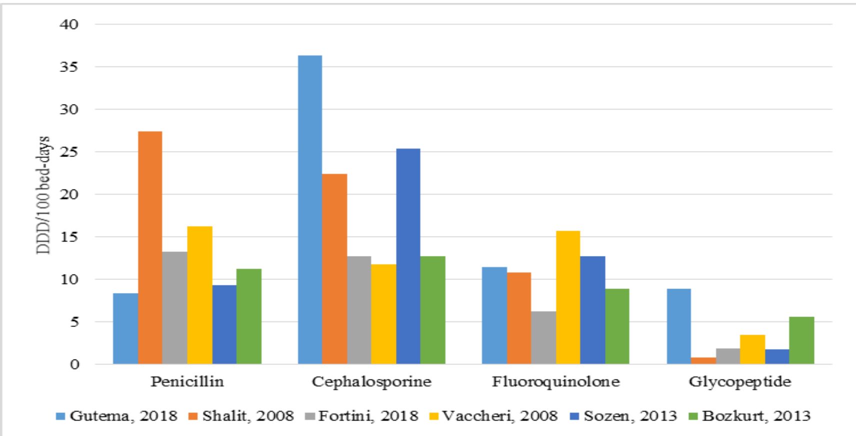

Figure 3: Antibiotic groups in Internal Medicine with the highest consumption

Figure 3 describes the top four groups of antibiotic classes widely used in internal medicine in several studies conducted from 2008 to 2018. The ratio of the use of the penicillin group was highest in the study conducted by Shalit in 2008. While the ratio of cephalosporins and glycopeptides was highest in the study conducted by Gutema in 2018, and the ratio of fluoroquinolones was highest in the study by Vaccheri, (2008).

Three years before ASP implementation, Italy underwent a consistent increase in antibiotic usage each year. Implementing ASP in Italy proved a lower antibiotic consumption (5.3% and 13.86%) in two different hospitals in Italy (Alberto *et al*., 2018). A study in Florence showed a slight decrease in antibiotic administration from 49.5 to 46.9 DDD/100 bed-days (Alberto *et al*., 2018). The implementation of ASP also decreased the use of empirical antibiotics (from 79.81% to 20.19%) and increased the appropriate antibiotic use (from 68% to 75.1%) (Alberto *et al*., 2018; Bolla *et al*., 2019). Another implementation in Turkey also showed the advantage of the program. It reduced the administration from 76.7 DDD/100 bed-days to 51.8 DDD/100 bed-days (Fatma *et al*., 2014). A multifaced implementation in Dr Soetomo Hospital, Indonesia, dramatically decreased antibiotic prescriptions (99.8 to 73 DDD/100 bed-days) (Usman *et al*., 2008).

According to six journals, Figure 4 describes some of the antibiotics used in internal medicine. In the article written by Amaha *et al*. (2020), the use of Benzylpenicillin was the highest (DDD/100 BD = 22.4 and 101.48). In the article written by Bolla *et al*. (2019), the use of Piperacillin + Tazobactam was the highest (DDD/100 BD = 5.42). In Pratama's article, written in 2019, the use of Cefotaxime was the highest (DDD/100 BD = 36.62). In the article written by Begum *et al*. (2010), the use of Amoxycillin (oral) was the highest (DDD/100 BD = 31.54). In the article written by Sweileh *et al*. (2007), the use of Metronidazole was the highest (DDD/100 BD = 7.88). In the article by Shanker *et al*. (2006), the use of ampicillin was the highest (DDD/100 BD = 8.3.

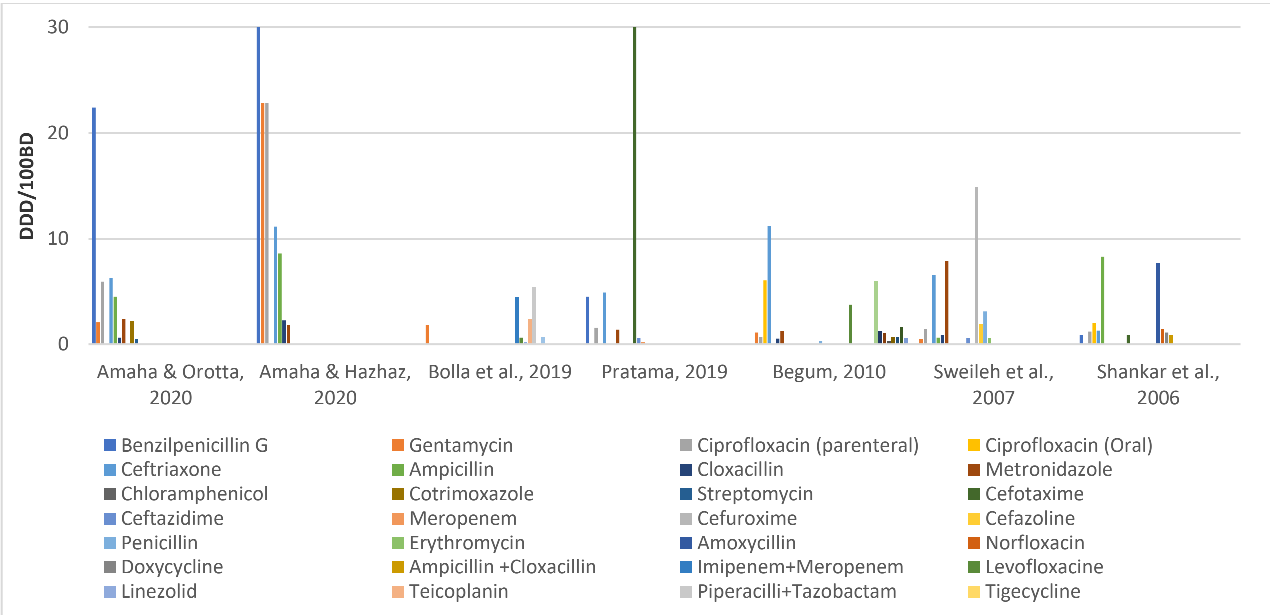

Figure 4: Antibiotic groups in internal medicine with the highest consumption

Discussion

Antibiotic consumption in the Internal Ward varied from one hospital to another. The difference occurs due to patient characteristics, local hospital guidelines and protocol, antibiotic dosage and indication other than first indication, culture and sensitivity test before administration, or overuse of prophylactic antibiotics (Nebyu *et al*., 2020; Sweileh *et al*., 2007). Antibiotics are classified into three groups, "*Access*", "*Watch*", and "*Reserve*", taking into account the impact of different antibiotics and classes on antimicrobial resistance to highlight the importance of appropriate antibiotic use (Kemenkes, 2021). Classification of antibiotics based on the World Health Organisation, the use of the most widely used antibiotics can be seen in Table I.

Table II: Antibiotic classification based on 2021 AWaRe (Access, Watch, Reserve) classification by WHO

Access		Watch	
Drugs	**DDD/100 bed-days**	**Drugs**	**DDD/100 bed-days**
Ampicillin	18.7	Ceftriaxone	60.0
Amoxycillin	15.0	Levofloxacin	21.3
Metronidazole	12.1	Cefixime	13.8
Cefadroxil	3.1	Meropenem	10.4
		Ciprofloxacin	6.9
		Cefoperazone	6.8
		Moxifloxacin	6.4
		Ceftazidime	5.4
		Cefotaxime	3.8
		Cefepime	3.1

Penicillins, particularly Benzyl-penicillin/penicillin G, amoxicillin, and ampicillin, are the "*Access*" group antibiotic in the AwaRe group classification. It was the accessible broad-spectrum antibiotic that may be used as the first line of empirical therapy (WHO, 2019; WHO, 2015). Penicillin is usually used for pneumonia, respiratory infection, endocarditis, and meningitis (Deck & Winston, 2012; Hamdi *et al*., 2013; Brayfield, 2014; Bolla *et al*., 2019; Girma *et al*., 2018; JFC, 2020). Ampicillin and amoxicillin are amino-penicillins which active against gram-positive and gram-negative bacteria. Amino-penicillin was the most potent beta-lactam for *pneumococcus* infection (Deck & Winston, 2012; Kemenkes, 2011). The combination of penicillin and beta-lactamase inhibitors (co-amoxiclav, ampicillin-sulbactam, piperacillin-tazobactam) are essential to prevent hydrolysis of active ingredient by bacteria producing beta-lactamase (Deck & Winston, 2012). In this study, the authors found that Penicillin was the most significantly consumed in Internal Medicine, not only because it has many kinds of active ingredients but also belongs to the "*Access"* group of antibiotics with broad spectrum activity.

The third, Cephalosporin, is a "*Watch" group* antibiotic due to its higher resistance potency than access group antibiotics (WHO, 2015). This study has shown that cephalosporins are the second-highest antibiotics consumed in Internal Medicine. Most of them are available in the parenteral route. Cephalosporins are active against pneumococcus bacteria insensitive to Penicillin, and it is recommended as an empirical therapy for severe infection. Cefotaxime and ceftriaxone resist beta-lactamases and have low toxicity to the kidney compared to other Cephalosporins (Deck & Winston, 2012; Siswandono, 2016). Cephalosporins could enter the blood-brain barrier and actively oppose *H. influenzae, N. meningitidis,* and *S. pneumoniae* (Deck & Winston, 2012; MacDougall, 2018).

Fluoroquinolones are a member of the "*Watch"* group antibiotics. These differ from quinolones because the 7-piperazinyl group and four atoms at the sixth position increase its sensitivity to gram-negative and some gram-positive bacteria (Brayfield, 2014; WHO, 2015; Siswandono, 2016). Ciprofloxacin is the most famous Fluoroquinolone in Internal Medicine Wards since it has the broadest antibacterial activity among the fluoroquinolones, particularly *P. aeruginosa* (Deck & Winston, 2012; Siswandono, 2016).

The high percentage of third-generation Cephalosporins and Fluoroquinolones bring to mind the acceleration of MRSA and ESBL prevalence. In Indonesia, MRSA grew from 18% in 2010 to 24% in 2012 (Usman *et al*., 2013). At the same time, ESBL increased from 22% to 53% in 2010 and 2012 respectively (Usman *et al*., 2013). Fluoroquinolone-resistant *Escherichia coli* (FREC) has also become a threat since 2015, with 51.5 % resistance in 2015 in Indonesia (Usman *et al*., 2013; WHO, 2019).

Antibiotic Stewardship Program (ASP) is a tool for optimising antibiotic usage and decreasing resistance by controlling the overuse or misuse of antibiotic consumption (WHO, 2015). It may apply through guidelines implementation, training and education, surveillance, monitoring, auditing and feedback (WHO, 2015).

This literature review shows that the most popular antibiotics in Internal medicine were penicillin, third and second generation of Cephalosporin and fluoroquinolones. This finding follows a previous publication (Ann *et al*., 2018). Those antibiotics have been used widely and have undergone resistance in several parts of the world.

Conclusion

The most popular antibiotics used in Internal Medicine were Penicillin, especially Benzyl-penicillin with 127.9 DDD/100 bed days, followed by third-generation cephalosporins, ceftriaxone 41.42 DDD/100 bed-days, and fluoroquinolones or ciprofloxacin with 25,87 DDD/100 bed-days. The intervention (Antimicrobial Stewardship Program) in many countries showed an improvement in rational antibiotic consumption.

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Appendix A: The publication described DDD per antibiotic group

No	Author, year	Hospital, country	Antibiotics	DDD/100BD
1	Gutemaa *et al.*, 2018	Tikur Anbessa Specialised Hospital (TASH), Ethiopia	Cephalosporin 3rd gen.	33.1
			Fluoroquinolone	11.4
			Imidazole	11.3
			Glycopeptide	8.9
			Cotrimoxazole	7.8
			Macrolide	5.5
			Penicillin	4.1
			Cephalosporin 4th gen.	3.1
			Penicillin + Beta-lactamase inhibitor	2
			penicilline sensitive betalactamase	1.6
			Aminoglycoside	0.9
			lincosamide	0.6
			Penicillin resistant beta lactamase	0.6
			Tetracycline	0.3
			Carbapenem	0.2
			Cephalosporin 1st gen	0.2
			Streptomycin	0.2
			Amphenicol	0.1
2	Fortini *et al.*, 2018	San Giovanni-Dio Hospital, Italy	Penicillin + beta-lactamase inhibitor	13.3
			Cephalosporin 3rd gen.	12.7
			Macrolide	9.6
			Fluoroquinolone	6.2
			Metronidazole	0.9
			Carbapenem	0.6
			Glycopeptide	1.8
			Aminoglycoside	1.4
			others	0.4
3	Sozen *et al.*, 2013	Isparta State Hospital, Turkey	Penicillin	9.3
			Cephalosporin 1st gen	1.8
			Cephalosporin 2nd gen	12.7
			Cephalosporin 3rd gen	10.9
			Carbapenem	1.2
			Aminoglycoside	0.4
			Glycopeptide	1.7
			Fluoroquinolone	12.7
			Others	5.7
4	Bozkurt *et al.*, 2013	Diyabakir Teaching and Research Hospital, Turkey	Penicilline ± Betalactamase inhibitor	11.2
			Cephalosporin	12.7
			Carbapenem	5.1
			Aminoglycoside	1
			Fluoroquinolone	8.9
			Glycopeptide	5.6
			Linezolid	5.1
			Polymixin	1.2
			Tigecycline	1
5	Vaccheri *et al.*, 2008	Five hospitals in Romagna, Italia	Penicillin + beta-lactamase inhibitor	16.25
			Fluoroquinolone	15.72
			Cephalosporin 3rd gen	11.73
			Glycopeptide	3.44
6	Shalit *et al.*, 2008	Six general hospitals in Israel	Penicillin + Beta-lactamase inhibitor	19.2
			Cephalosporin 2nd gen	14.3
			Fluoroquinolone	10.8
			Penicillin	7.2
			Macrolide	5.9
			Cephalosporin 3rd gen.	5.3
			Aminoglycoside	2
			Cephalosporin 1st gen.	1.5
			Cephalosporin 4th gen.	1.3
			Ureidopenicilline + Beta-lactamase inhibitor	1
			Glycopeptide	0.8
			Carbapenem	0.6
			Others	10.1