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ANTIBIOTIC USE IN SLOVENIAN HOSPITALS

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Abstract

Abstract: Motivation/Background: Antibiotics are commonly overused and misused what increase the emergence of resistant organisms, side- effects and costs. To assess the appropriate use of antibiotics many methods are available. The aim of the present study is to find correlation between antibiotic use and case mix index (CMI) in Slovenian hospitals.
Method: In retrospective study (in the years between 2004 and 2013) we correlated the total consumption of antibiotics for systemic use and CMI. Weighted linear regression test analysis was performed to determine correlation between defined daily dose (DDD) / 100 admissions and DDD / 100 bed-days and CMI.
Results: The total antibiotic consumption in all included hospitals was in mean 317.69 DDD / 100 admissions and 58.88 DDD / 100 bed days, respectively. CMI range were from 1.25 to 3.55. A significant correlation between consumption expressed in DDD / 100 admissions and CMI (p = 0.028) and DDD / 100 bed days and CMI (p =0.008) was found. Conclusions: Thus, detailed analysis of correlations between DDD of antibiotics and CMI may constitutes a proper use of antibiotics.

Keywords: Antibiotics; Case Mix Index; Defined Daily Dose; General Hospitals; University Medical Centres.

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1. Introduction

Antibiotics are commonly used in hospitalized patients (range 19-59%) (1). Large variations in total and pattern of use have been found between countries and between hospitals in the country (2, 3). The most common infection types are respiratory tract (24 %), skin bone, and joint (18 %), intra-abdominal organs (16 %), urinary tract (11 %) (1, 4-6). Antibiotics are commonly overused and misused what increase the emergence of resistant organisms, side- effects and costs. To assess the appropriate use of antibiotics many methods are available. The most accurate is patient-level surveillance what is time consuming and limited to a small number of patients (7). Point prevalence study survey is useful tool to judge the appropriateness of antibiotic use (8). The case mix index

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(CMI) is an economic surrogate marker (i.e. the total cost weights of all inpatients per a defined time period divided by the number of admissions) to describe the average patients' morbidity of individual hospitals (9). In the first study in 2008, Kuster et al. proved methodology and strong significant correlation between defined daily dose (DDD) of antibiotics / 100 admissions and DDD / 100 bed-days and CMI in Canton Zurich, Switzerland hospitals (9). Our study is the first such survey in Slovenia. The aim of the present study is to find correlation between antibiotic use and CMI in 12 Slovenian hospitals including two University hospitals and ten general hospitals.

2. Participants and Methods

2.1. Participants

We performed a retrospective observational study of antibiotic use and CMI in two University Medical Centres, Ljubljana and Maribor and another 10 acute care hospitals, a state in Slovenia, during the study period between 2004 to 2013.

The study included all patients hospitalized in 12 Slovenian hospitals from 2003 to 2014 illnesses by infectious diseases. Patients have been registered in the national statistical collections, which will be presented below, patient information is anonymous.

2.2. Methods

Number of admissions and number of bed-days of infectious diseases were calculated from electronic health information system of hospital care (ZISBO) of the National Institute of Public Health (NIPH) (13) of each patient hospitalized for ≥ 24 hours in the same hospital unit counting the days of admission and discharge together as one bed-day. For the all studied hospitals, aggregate hospital antibiotic consumption data defined daily dose (DDD) were collected from the hospital pharmacies and entered into a Microsoft Office Excel 2010 database. The 2014 version (group J01 (Antibacterial for system use*)) of the ATC Index with DDDs was used. DDD per 100 admissions and DDD per 100 bed-days were calculated for each hospital. CMIs for patient hospitalized in these defined patient care areas were calculated for the studied years (between 2004 and 2013), using data provided by the Database of hospital treatments of the same type based on cost weights for each patient (14, 15). Diagnoses were coded with ICD-10 WHO version 1.3. Table 1 presents the list of infectious diseases that we have included in the analysis. Chosen diagnoses were recommended by the Center for Disease Control and Prevention, Atlanta, USA (16).

The University Medical Centre Ljubljana and University Medical Centre Maribor are tertiary and secondary care hospitals. Other ten hospitals (GH Nova Gorica, GH Brežice, GH Novo mesto, GH Celje, GH Izola, GH Jesenice, GH Ptuj, GH Murska Sobota, GH Trbovlje and GH Slovenj Gradec) are secondary type hospitals

The CMI equals the sum of the total cost weights of all inpatients per a defined time period divided by a number of admissions (9). In Slovenia cost weight are regularly recalculated in the databases Groups of applicable cases (in Slovenian language short (skupine primerljivih primerov SPP).

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IBM SPSS Statistics for Windows, Version 21.0 was used for analysis. Weighted linear regression test analysis was performed to determine correlation between antibiotic use and CMI. A p value ≤ 0.05 was considered statistically significant.

Table 1: Infection Disease Subgroups Definitions and Corresponding International Classification of Diseases, 9th revision, Clinical Modification (ICD – 9-CM) (16), transcoded to ICD 10th revision

Diagnosis	**Code ICD- 10**
Meningitis	A39, G00-G03
Sepsis	A40-A41, O85
Hepatobiliary infections	K83.0, K75.0, K81
Heart infections	I38
Upper respiratory tract infections	A36.0-A36.2, A38, A69.1, J02.0, J32.0-K12.2, K57.8, K85
Lower respiratory tract infections	A22, A37, J10-J18, J86, J90, J85
Intraabdominal infections	A54.6, K35-K37, K61, K65, K63.0, K12.2, K57.8, K85
Urinary tract infections	A54.0, N30.0, N34, N39.0, N13.6, N15.1, N41
Cellulitis	L02 – L08
Infection and inflammatory reaction to prosthetic devices	T82-T89
Postoperative infections	T81.4
Musculoskeletal infections	M86, M90.0 – M 90.2
Infection in pregnancy	O0.80, O23, O98, O41.1, O75.3, O85, O91
Pelvic infections	N70, N73.0-N73.2, N72, N76, N75.1, N96.4

3. Results and Discussions

3.1. Antibiotic Consumption

Antibiotic consumption data are listed in Table 2. From 2004 to 2013 the total antibiotic consumption in all included hospitals was in mean 317.69 DDD / 100 admissions and 58.88 DDD / 100 bed-days. The highest antibiotic consumption with 376.78 DDD / 100 admissions was recorded in GH Nova Gorica and 65.24 DDD / 100 bed-days in GH Celje. In secondary care hospitals antibiotic use ranged from 283.98 to 376.78 DDD / 100 admissions and from 53.47 to 65.24 DDD / 100 bed-days. In University hospitals, Medical Centre Ljubljana and Medical Cetre Maribor, mean antibiotic consumption were 313.10 DDD / 100 admissions and 57.44 DDD / 100 bed-days and 283.98 DDD / 100 admissions and 53.47 DDD / 100 bed-days. From 2004 to 2013 CMI range were from 1.25 to 3.55.

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Table 2: DDD / 100 admissions and DDD / 100 bed-days and CMI in 12 Slovenian hospitals from 2004 to 2013 (mean)

Hospitals	DDD/100 admissions mean	DDD/100 bed-days mean	CMI mean
GH Nova Gorica	376.78	62.37	2.06
GH Brežice	319.85	56.80	2.11
GH Novo mesto	311.75	59.87	2.33
GH Celje	375.06	65.24	2.42
GH Izola	286.83	57.45	2.05
GH Jesenice	298.85	54.60	2.32
UMC Ljubljana	313.32	57.44	2.60
GH Ptuj	325.10	64.32	2.12
UMC Maribor	283.98	53.47	2.54
GH Murska Sobota	288.20	61.52	2.07
GH Trbovlje	309.03	54.16	2.01
GH Slovenj Gradec	302.00	60.37	2.43

Legende: GH – general hospital; UMC-University Medical Centre; DDD – defined daily dose; CMI-case mix index

We calculated DDD / 100 admissions and DDD/100 bed-days for each year from 2004 to 2013. Results are depicted in Table 3. The values were ranged from 296 DDD / 100 admissions in the year 2012 to 336 DDD / 100 admissions in the year 2004 and 56 DDD / 100 bed-days in the years 2012 and 2013 to 61 DDD / 100 bed-days in 2005. The calculated CMI values were ranged from 1.59 in the year 2004 and 2.63 in zhe year 2010.

Table 3: DDD / 100 admissions and DDD / 100 bed-days and CMI for each year from 2004 to 2013

Years	DDD/100 admissions	DDD/100 bed-days	CMI
2004	336	59	1.59
2005	320	61	1.69
2006	311	59	1.72
2007	316	60	1.71
2008	309	57	2.57
2009	323	58	2.62
2010	326	60	2.63
2011	314	59	2.63
2012	296	56	2.61
1013	305	56	2.47

Legende: GH – DDD – defined daily dose; CMI-case mix index

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3.2. Correlation Between CMI and Antibiotic Use at The Hospitals

The correlation between antibiotic use and CMI is shown in Figure 1 and Figure 2. Weighted linear regression test analysis was performed to determine correlation between DDD/ 100 admissions and DDD / 100 bed-days and CMI in 10 GHs and two University hospitals from 2004 to 2013. A significant correlation between consumption expressed in DDD / 100 admissions and CMI (R^2 =0,018, R = 0.135, p = 0.028) and DDD / 100 bed days and CMI (R^2 = 0,027, R = 0.163, p =0.008) was found.

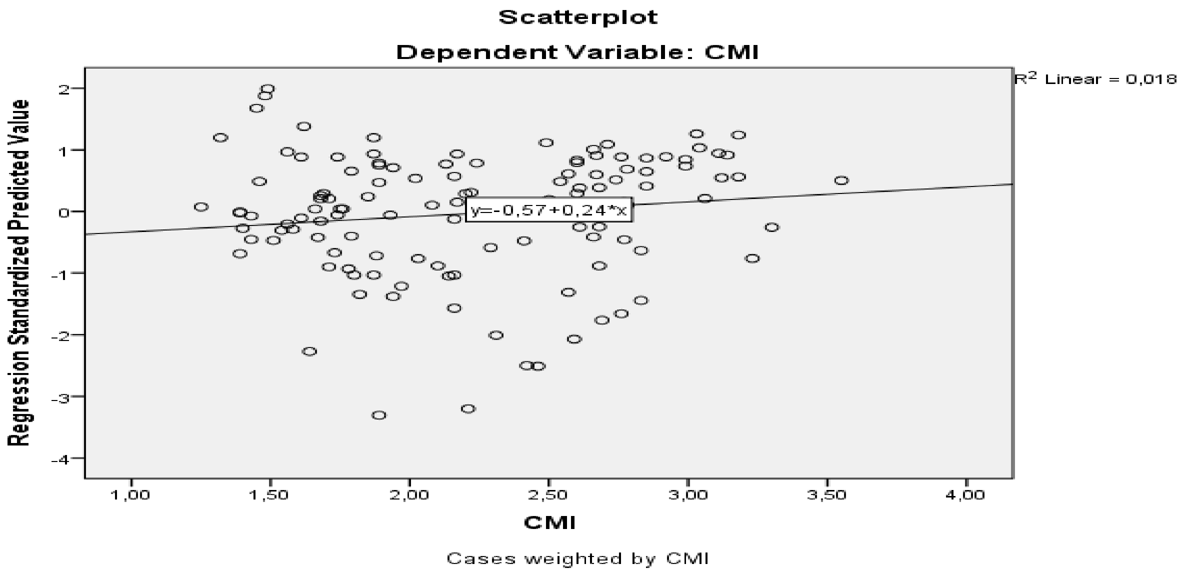

Figure 1: Linear regression between CMI and DDD / 100 admissions in 1O GHs and 2 University hospitals from 2004 to 2013 (R^2 =0,018, R = 0.135, p =0.028)

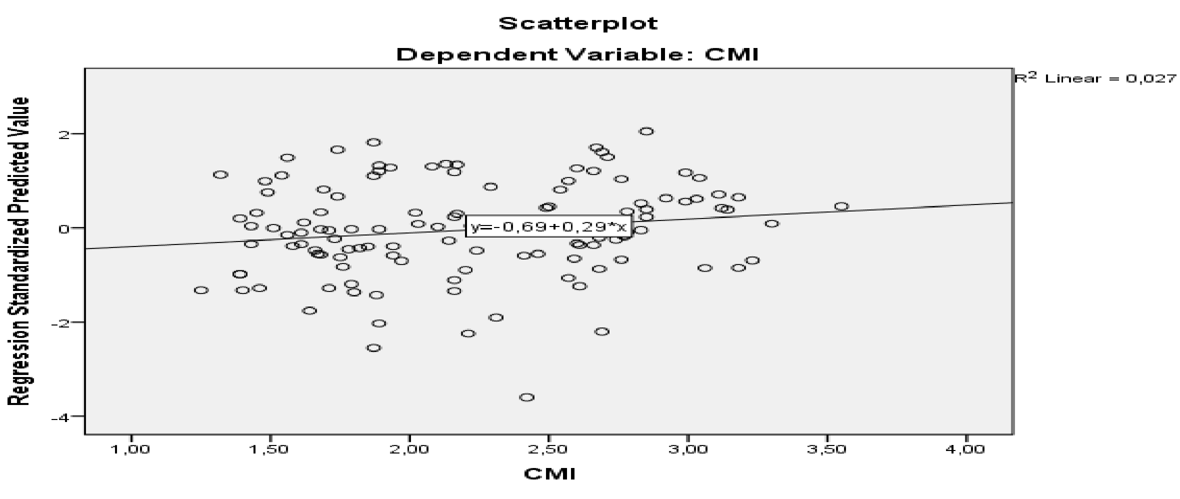

Figure 2: Linear regression between DDD / 100 bed-days and CMI in 10 GHs and 2 University hospitals from 2004 to 2013 (R^2 =0,027, R = 0.163, p = 0.008)

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3.3. DDD / 100 admissions and DDD / 100 bed-days and CMI for certain antibiotics most commonly prescribed in Slovenian hospitals from the years 2004 to 2013

DDD / 100 admissions and DDD / 100 bed days were calculated for certain antibiotics, such as amoxiclav, moxifloxacin, azithromycin, cefuroxim, cefotaxim, antistaphylococcal penicillies, ciprofloxacin, aminoglycoside antibacterials and metronidayole i.v. in mean from 2004 to 2013. Results are shown in Table 4.

Table 4: Mean value of DDD / 100 admissions and CMI calculated from 2004 to 2013 of certain antibiotics

Antibiotics	**DDD / 100 admissions (mean)**	**DDD / 100 bed days (mean)**
J01CR02	84.754	16.802
J01MA14	6.808	1.276
J01FA10	11.696	1.855
J01DC02	9.893	6.692
J01DD01	7.664	4.442
J01CF	13.588	3.043
J01MA02	37.259	6.926
J01G	15.607	2.841
J01XD01	12. 129	2.402

Legende: DDD: defined daily dose
J01CR02 - amoxicillin and enzyme inhibitor / amoksicilin in encimski zaviralec
J01MA14 - moxiflocsacin / moksifloksacin
J01FA10 - azithromycin / azitromicin
J01DC02 - cefuroxime / cefuroksim
JO1DD01 - cefotaxime / cefotaksim
J01CF - antistaphylococcal penicillies / protistafilokokni penicilini
J01MA02 – ciprofloxacin / ciprofloksacin
J01G - / aminoglikozidi
J01XD01 - metronidayole i.v. / metronidazol i.v.

3.4. DDD / 100 Admissions and DDD / 100 Bed-Days and CMI For Certain Antibiotics Most Commonly Prescribed in Slovenian Hospitals for Each Year from The Years 2004 To 2013

DDD / 100 admissions and DDD / 100 bed-days were calculated for certain antibiotics, such as amoxiclav, moxifloxacin, azithromycin, cefuroxim, cefotaxim, antistaphylococcal penicillies, ciprofloxacin, aminoglycoside antibacterials and metronidayole i.v. for each year from 2004 to 2013. Results are shown in Table 5 and 6.

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Table 5: DDD / 100 admissions calculated for each year from 2004 to 2013 for certain antibiotics

Years	J01CR02	J01MA14	J01FA10	J01DC02	JO1DD01	J01CF	J01MA02	J01G	J01XD01
2004	82,09	6,64	13,08	17,19	11,68	18,68	37,52	15,85	11,50
2005	85,19	6,77	13,51	20,69	10,55	20,98	38,93	14,61	12,05
2006	86,98	7,46	14,72	17,83	5,71	22,10	39,59	14,54	13,39
2007	83,38	6,99	13,64	15,63	4,14	23,19	38,08	13,60	13,43
2008	82,68	6,75	12,45	13,70	3,76	24,12	36,59	12,96	12,61
2009	84,69	6,31	11,93	13,89	3,12	23,68	36,06	12,01	12,17
2010	86,13	5,38	9,08	MV	8,78	,73	38,59	18,71	12,73
2011	82,90	6,50	9,38	MV	9,66	,80	36,47	18,10	11,80
2012	84,81	7,52	8,42	MV	9,76	,81	35,53	18,28	11,33
2013	88,69	7,76	10,75	MV	9,48	,79	35,23	17,41	10,28

Legende:
J01CR02 - amoxicillin and enzyme inhibitor / amoksicilin in encimski zaviralec
J01MA14 - moxiflocsacin / moksifloksacin
J01FA10 - azithromycin / azitromicin
J01DC02 - cefuroxime / cefuroksim
JO1DD01 - cefotaxime / cefotaksim
J01CF - antistaphylococcal penicillies / protistafilokokni penicilini
J01MA02 – ciprofloxacin / ciprofloksacin
J01G - aminoglycoside antibacterials / aminoglikozidi
J01XD01 - metronidayole i.v. / metronidazol i.v.
MV / missing value

Table 6: DDD / 100 bed-days calculated for each year from 2004 to 2013 of certain antibiotics

Years	J01CR02	J01MA14	J01FA10	J01DC02	JO1DD01	J01CF	J01MA02	J01G	J01XD01
2004	13,63	1,12	2,17	2,86	1,94	3,10	6,23	2,63	1,91
2005	14,47	1,27	2,29	3,51	1,79	3,56	6,61	2,48	2,05
2006	15,13	1,22	2,56	3,10	,99	3,85	6,89	2,53	2,33
2007	15,55	1,26	2,54	2,92	,77	4,33	7,10	2,54	2,50
2008	15,38	1,17	2,32	2,55	,70	4,49	6,81	2,41	2,35
2009	15,20	1,07	2,14	2,49	,56	4,25	6,47	2,15	2,18
2010	20,39	,84	2,78	13,49	8,78	1,56	7,42	3,34	2,80
2011	17,56	1,38	,60	13,77	9,65	1,78	7,37	3,43	2,69
2012	20,01	1,75	,49	11,66	9,76	1,77	7,24	3,49	2,68
2013	20,70	1,68	,66	10,57	9,48	1,74	7,12	3,41	2,53

Legende:
J01CR02 - amoxicillin and enzyme inhibitor / amoksicilin in encimski zaviralec
J01MA14 - moxiflocsacin / moksifloksacin
J01FA10 - azithromycin / azitromicin
J01DC02 - cefuroxime / cefuroksim
JO1DD01 - cefotaxime / cefotaksim
J01CF - antistaphylococcal penicillies / protistafilokokni penicilini

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J01MA02 – ciprofloxacin / ciprofloksacin
J01G - aminoglycoside antibacterials / aminoglikozidi
J01XD01 - metronidayole i.v. / metronidazol i.v.

Our results shown that from 2004 to 2013 the total antibiotic consumption in all included hospitals were in average 315.63 DDD / 100 admissions and 59.02 DDD / 100 bed days. Kuster et all. described overall antibiotic use in University hospitals in Zurich where it was 491.62 DDD/100 admissions and 68.04 DDD/100 bed-days. The corresponding numbers for the two secondary care hospitals were 39.46 and 50.56 DDD / 100 bed-days and 268.59 and 383.77 DDD / 100 admissions (9). Kern et all. found the overall antibiotic use density in German acute care hospitals 43.5 recommended daily dose (RDD) per 100 patient days (occupied bed days) (median) with the interquartile range of 35-48 RDD / 100 – corresponding to a median of 64.4 DDD / 100 (interquartile range, 53 – 73 DDD / 100) (17). National monitoring of hospital consumption of antimicrobial drugs are indicators of quality, expressed in DDD / 100 admissions and DDD / 100 bed-days (18). In 2007 the national hospital consumption of antibiotics for systemic use was in Denmark DDD / 100 admissions, 288.7in Sweden DDD/ 100 admissions, 278.8 and in the Netherlands DDD/ 100 admissions, 355 (19). Total consumption of antibiotics in Slovenia in GHs in comparison with other countries with more rational prescribing of antibiotics is higher than in Denmark and Sweden and a surprisingly lower than in the Netherlands in 2007 (20). In second Slovenian national healthcare-associated infections (HAIs) prevalence survey (SNHPS) was conducted in acute-care hospitals in 2011. The objective was to assess the sensitivity and specificity of the method used for the ascertainment of six types of HAIs (bloodstream infections, catheter-associated infections, lower respiratory tract infections, and urinary tract infections) in the University Medical Centre Ljubljana. The overall sensitivity of SNPHS collection method for ascertaining HAIs overall was high and the specificity was very high (21). In the second Slovenian national HAIs prevalence survey, conducted within European point prevalence survey of HAIs and antimicrobial use in acute care hospitals, they estimated the prevalence of all types of HAIs and identified risk factors. They found that the prevalence of HAIs in Slovenian acute care hospitals in 2011 was substantial, especially in ICUs. HAIs prevention and control is an important public health priority (22).

Data on the correlation of cost indicators and antibiotic use are limited in the current literature. Our study is the first such survey in Slovenia. We found a statistical significant correlation between antibiotic use and CMI when analysing data of Slovenian hospitals from 2004 to 2013. Correlation was strong significant ($p = 0.028$ and $p = 0.008$, respectively). We demonstrate differences between CMI and antibiotic use in 12 studied hospitals and results are comparable with the studies. Kuster at all. presented the first study to evaluate such a correlation between CMI and antibiotic use within a single institution and across various acute care hospitals. Antibiotic use varied substantially between different departments of the University hospital and between primary and secondary care hospitals. Kunster et all. recommended antibiotic use within and across hospitals, adjustment for CMI as a useful tool in order to take into account the differences in hospital category and patients' morbidities (9). Polk et all. shows of 1 791 180 discharged adults, 63.7% received antibacterial drugs. Mean ± SD hospital-wide use was 839 ± 106 days of therapy's (DOTs) (range, 594–1109) and 536 ± 53.0 length of therapy (LOT) (range, 427–684) per 1000 patient-days. Differences between expected and observed use reflect usage patterns that were benchmarked and are targets for evaluation and intervention (23). In 2008, the Slovenian hospitals most commonly

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prescribed penicillins (39.8%), cephalosporins (22.8%), quinolones (14.6%) macrolides to lincosamides (9.2 %) and other antibacterial agents (5.3%) (19, 20). These groups are often prescribed in other European countries (24). In our study we calculated DDD / 100 admissions and 100 bed-days for amoxiclav, moxifloxacin, azithromycin, cefuroxim, cefotaxim, antistaphylococcal penicillies, ciprofloxacin, aminoglycoside antibacterials and metronidayole i.v. in mean from 2004 to 2013. Results shown high consumption of amoxiclav, azithromycin, cefuroxim, cefotaxim, antistaphylococcal penicillies, ciprofloxacin, aminoglycoside antibacterials and metronidayole i.v. and low consuption of moxifloxacin. On internistic intesive care units (ICU) in Slovenia increased use of penicillins in combination with beta-lactamase inhibitors, cephalosporins 1st and 4th generation, and carbapenems. In surgical ICU it similar to Internistic increased use of penicillins in combination with beta-lactamase inhibitors, the 4th generation cephalosporins, carbapenems (25). In recent ESAC Annual Report published in 2014, in the hospital sector, consumption of antibacterials for systemic use data varied from 1.0 DDD per 1 000 inhabitants and per day in the Netherlands, to 2.8 in Finland. The population-weighted EU/EEA mean consumption was 2.0 DDD per 1000 inhabitants and per day and no significant trends in the mean consumption are apparent for the last five years. The most frequently used subgroup in the hospital sector was penicillins, followed by other beta-lactam antibacterials including cephalosporins and quinolones (26).

4. Conclusions and Recommendations

Thus, detailed analysis of correlations between DDD of antibiotics and CMI may constitutes a proper use of antibiotics. Conclusion. The CMI maybe a valuable tool to facilitate the interpretation of quantitative hospital antibiotics data.

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