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Discrepancies between prescribed daily doses and WHO defined daily doses of antibacterials at a university hospital

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Aims
The defined daily doses (DDD) defined by the WHO are widely used as an indicator to measure antibiotic use in the hospital setting. However, discrepancies exist between countries in terms of antibiotic dosage. The aim of the present study was to compare, for each antibacterial agent available at our university hospital, the prescribed daily doses (PDD) with the DDD.

Methods
Data were extracted from the pharmacy computer system. Antibiotic use was expressed in DDD per 1000 patient days. We also calculated the ratio of number of DDD : number of treatment-days and estimated the average PDD for each antibiotic and route of administration.

Results
The average PDD did not correspond to the DDD for many classes of antibiotics. If fluoroquinolones and cephalosporins were prescribed at a dosage close to the DDD, other antimicrobial classes such as penicillins, aminoglycosides or macrolides were not. Overall, the number of DDD overestimated the number of treatment days by 40%. For the most consumed antibiotic at our hospital, i.e. oral amoxicillin-clavulanic acid, the PDD was three times the DDD.

Conclusions
Our study shows that, except for the fluoroquinolones and the cephalosporins, the number of DDD did not correctly reflect the number of antibiotic treatment days at our hospital. This does not invalidate the systematic approach of the WHO and hospitals should use the DDDs to make national and international comparisons of their antibiotic use. However, each hospital should define and validate its own indicators to describe the local exposures to antibiotics and to study the relationship with resistance.

Introduction

Antibiotic use is being increasingly recognized as the main selective pressure driving resistance to antibiotics [1–3]. In France, national recommendations concerning the organization of the prescription and distribution of antibiotics suggest priority measures that should be implemented in hospitals to control the emergence of antibiotic-resistant bacteria, including control of the overuse and misuse of these drugs [4]. More recently, the French Minister of Health decided that French hos-

pitals should provide authorities with their amount of antibiotic use. The reference method to express antibiotic exposure is the ATC/DDD methodology [5]. For each antimicrobial agent and route of administration, the WHO Collaborating Centre for Drug Statistics and Methodology defines the DDD as the assumed average maintenance adult dose per day for the main indication of this agent and maintains updates [5]. The DDD therefore is an international unit that can be used for international or regional comparisons of antibiotic use in primary care and in hospitals. Recent data on use in primary care in European countries show that the variation in resistance between different European countries can be explained by variation in selection pressure for resistance [6]. However, some authors have underlined the discrepancies existing between countries in terms of antibiotic dosage and have suggested that the classic methods based on the DDDs require further European standardization [7, 8]. Despite these discrepancies and the need for adjustment of a few DDDs, it seems that the number of DDD per 1000 inhabitant-days reflects the number of prescriptions per 1000 inhabitants and therefore is a relevant indicator to compare outpatient antibiotic use between countries or regions [9]. While consensus seems to have been achieved for primary care, there are still questions about which indicator to use to measure antibiotic use in hospitals. Most published data express antibiotic use as a number of WHO-defined DDD per 100 or 1000 patient-days [10–13] or per 100 admissions [14]. The WHO-defined DDD has also been used to demonstrate a quantitative, ecological relationship between antimicrobial use and resistance in hospitals [15–18]. The aim of the present study was to compare, for each antibiotic, the average prescribed daily dose (PDD) at our hospital with the WHO-defined DDD.

Methods

Setting and study period

Besançon Hospital is a university-affiliated, 1228 acute care bed hospital. Specialty services include cardiothoracic surgery, organ transplantation and bone marrow transplantation. For this study, data were collected for the period 1 January to 31 December 2001 for the following wards grouped by specialty: medicine (30 wards), surgery (17 wards) and adult intensive care (two wards). Psychiatry, paediatrics, emergency and gynaecology-obstetrics wards were excluded.

Prescription and dispensing of antibiotics

The standard pharmacy protocol requires that hospital physicians write individual patient prescriptions for antibiotics, but there are no restrictions on antibiotic use. For each antibiotic prescription, the computerized pharmacy dispensing system calculates, from the prescribed dose, the amount of medicines to be dispensed until the next prescription (1, 2 or 3 days). For treatments lasting more than 3 days, the prescription must be renewed. This measure was implemented to limit storage of unused antibiotics on the wards. Since 1998, the pharmacy has maintained a permanent computerized record of each antibiotic dispensed.

For this study, antibiotics were defined as antibacterials for systemic use or group J01 of the WHO Anatomical Therapeutic Chemical (ATC) classification system [5], thus excluding topical antibiotics and antibacterials for tuberculosis. Although, in our hospital, rifampicin was mainly prescribed for bacterial infections other than tuberculosis, its use was not included in the study because it is not part of ATC group J01. For the same reason, oral colistin, oral vancomycin and oral metronidazole were not included in the study.

Demographic data

The annual number of patient-days was provided by the hospital's admission department.

Data analysis

Antimicrobial data were extracted from the pharmacy computer system. The number of grams or international units of antibiotics were further converted into a number of DDD using the 2005 version of the ATC/DDD index [19]. To control for the population size, we determined the antimicrobial use density, expressed as DDD per 1000 patient days, for each antibiotic and route of administration. From the prescription data, we also calculated the number of treatment-days for each antibiotic and route of administration. Finally, for each antibiotic and route of administration, we calculated the ratio of number of DDD : number of treatment-days and estimated the average prescribed daily dose (PDD) in grams as the DDD multiplied by the above-mentioned ratio.

Results

In 2001, the total number of DDD of antibiotics (ATC group J01, antibacterials for systemic use) consumed in our hospital was 200 885. Most of these (184 397 DDDs; 91.8%) were used in the adult hospitalization units selected for the study. In these units, 25 258 patients were admitted to the hospital (re-admissions excluded) and 7153 (28.3%) of these patients received an antibiotic. Table 1 presents antibiotic use for the whole hospital as well as by specialty. The distribution of antibiotic use by class was: β-lactams (ATC group

Table 1
Antibiotic use at Besançon University Hospital, 2001

Type of unit	Number of patient-days	Number of defined daily doses (DDD)	DDD per 1000 patient-days
Medicine	137 675	111 322	808.6
Surgery	109 410	58 584	535.4
Intensive care	9 545	14 487	1517.7
Overall	256 630	184 393	718.5

J01C, 64.3%), fluoroquinolones (J01MA, 18.6%), macrolides, lincosamides and streptogramins (J01F, 5.4%), aminoglycosides (J01G, 4.1%), glycopeptides (J01XA, 3.5%) and other antibiotics (4.1%). The ratio of number of DDD : number of treatment-days for the main antimicrobial classes was: penicillins, 2.25; cephalosporins, 1.00; fluoroquinolones, 1.04; macrolides, lincosamides and streptogramins, 1.23; aminoglycosides, 0.71; and glycopeptides, 0.90. For each individual antibiotic, the number of DDD, the number of treatment-days, as well as the ratio of number of DDD : number of treatment-days and the estimated prescribed daily dose (PDD) are presented in Table 2. Table 3 summarizes the differences in the ratio of number of DDD : number of treatment-days for the main antibiotics and by disciplines. We also observed a large variability of this ratio between wards within disciplines (i.e. medicine and surgery) and these differences were not related to the age of the patients (data not shown).

Discussion

Our study shows that, in our hospital, the average PDD did not correspond to the WHO-defined DDD for many classes of antibacterials. If fluoroquinolones and cephalosporins were prescribed at an average dosage close to the DDD, other antimicrobial classes such as penicillins, aminoglycosides or macrolides were not. Overall, the number of DDD overestimated the number of treatment-days by 40%. This confirms the observation of Kern *et al.* [18]. For the most consumed antibiotic at our hospital, i.e. oral amoxicillin-clavulanic acid, the ratio of number of DDD : number of treatment-days was 2.97. In other words, the PDD was 3 g or three times the DDD, i.e. 1 g, which is consistent with the French national recommendations, which recommend that amoxicillin-clavulanic acid is prescribed at a dosage of 3 g day^{-1} [20]. For parenteral amoxicillin-clavulanic acid, the ratio of number of DDD : number of treatment-days was only 1.29. This is because we applied the latest definition of the DDD for parenteral amoxicillin-clavulanic acid, which increased from 1 to 3 g in 2005. If we had applied the DDD definition prior to 2005, the ratio would have been 3.87. Besides guidelines, perceived toxicity and pharmacodynamics may also explain differences between the DDD and the PDD. For example, amoxicillin, which is regarded as having a low toxicity was prescribed at high doses (ratio of number of DDD : number of treatment-days: oral route = 3.01, parenteral route = 5.98), whereas the aminoglycosides were prescribed at a dose lower than the DDD, i.e. a ratio of number of DDD : number of treatment-days = 0.71. Further investigations, including interviews with prescribers, are needed to confirm this hypothesis.

The distribution of antibacterial classes as a percentage of total use was also strongly influenced by the measurement unit used. Indeed, β-lactams represented 64.3% and 50.1% of total antibiotic use when expressed as number of DDDs and number of treatment-days, respectively. In contrast, the proportion of fluoroquinolones, aminoglycosides and glycopeptides was slightly higher when total use was expressed as number of treatment-days, i.e. 18.6 *vs.* 24.8%, 4.1 *vs.* 7.9% and 3.6 *vs.* 5.5%, respectively.

The ratio of number of DDD : number of treatment-days also showed differences depending on the specialty. It was often the highest in the two intensive care units at our hospital. However, this difference was not observed for vancomycin, ceftriaxone and amikacin (Table 3). Although there was no difference between the DDD and the PDD of parenteral ciprofloxacin for the whole hospital (ratio = 1.01), a difference was observed when the intensive care units were considered separately (ratio = 1.28). Kern et al. have reported even larger differences for fluoroquinolones in haematology-oncology wards [18]. This stresses the need to validate the indicators for each specialty. Additionally, we observed a large variability of the ratio of number of DDD : number of treatment-days between wards. It is likely that this

Table 2
Comparison of the number of defined daily doses (DDD) and the number of treatment-days and estimated prescribed daily dose (PDD) of antibacterials for systemic use (ATC group J01) at Besançon University Hospital, 2001

Antibacterial name	ATC code	Route of administration	Defined daily doses (DDD)		Treatment-days		Ratio of number of DDD : number of treatment-days	Estimated prescribed daily dose (PDD) (g)	WHO defined daily dose (g)
			Number	% Total	Number	% Total			
Amoxicillin-clavulanic acid	J01CR02	Oral	46 675	25.31	15 715	11.88	2.97	3.0	1.0
		Parenteral	14 122	7.66	10 947	8.27	1.29	3.9	3.0
Amoxicillin	J01CA04	Oral	9 583	5.20	3 184	2.41	3.01	3.0	1.0
		Parenteral	10 546	5.72	1 764	1.33	5.98	6.0	1.0
Ciprofloxacin	J01MA02	Oral	12 040	6.53	11 252	8.50	1.07	1.1	1.0
		Parenteral	7 155	3.88	7 084	5.35	1.01	0.5	0.5
Ofloxacin	J01MA01	Oral	8 415	4.56	7 938	6.00	1.06	0.4	0.4
		Parenteral	3 690	2.00	3 514	2.66	1.05	0.4	0.4
Ceftriaxone	J01DD04	Parenteral	9 249	5.02	11 418	8.63	0.81	1.6	2.0
Metronidazole	J01XD01	Parenteral	3 713	2.01	3 789	2.86	0.98	1.5	1.5
Oxacillin	J01CF04	Oral	2 467	1.34	1 656	1.25	1.49	3.0	2.0
		Parenteral	4 313	2.34	1 356	1.02	3.18	6.4	2.0
Pristinamycin	J01FG01	Oral	5 305	2.88	4 050	3.06	1.31	2.6	2.0
Vancomycin	J01XA01	Parenteral	4 902	2.66	5 836	4.41	0.84	1.7	2.0
Imipenem-cilastatin	J01DH51	Parenteral	3 982	2.16	4 105	3.10	0.97	1.9	2.0
Tobramycin	J01GB01	Parenteral	3 441	1.87	4 846	3.66	0.71	0.17	0.24
Ceftazidime	J01DD02	Parenteral	3 339	1.81	2 981	2.25	1.12	4.5	4.0
Piperacillin-tazobactam	J01CR05	Parenteral	3 330	1.81	3 965	3.00	0.84	11.8	14.0
Norfloxacin	J01MA06	Oral	2 995	1.62	3 025	2.29	0.99	0.8	0.8
Amikacin	J01GB06	Parenteral	2 812	1.52	3 605	2.72	0.78	0.8	1.0
Cefotaxime	J01DD01	Parenteral	2 450	1.33	1 521	1.15	1.61	6.4	4.0
Cefepime	J01DE01	Parenteral	2 173	1.18	1 194	0.90	1.82	3.6	2.0
Cefuroxime	J01DC02	Oral	901	0.49	448	0.34	2.01	1.0	0.5
		Parenteral	1 233	0.67	1 713	1.29	0.72	2.2	3.0
Teicoplanin	J01XA02	Parenteral	1 681	0.91	1 500	1.13	1.12	0.45	0.4
Clarithromycin	J01FA09	Oral	1 576	0.85	769	0.58	2.05	1.0	0.5
Spiramycin	J01FA02	Oral	974	0.53	1 249	0.92	0.78	2.3	3.0
		Parenteral	361	0.20	681	0.51	0.53*	1.6	3.0
Ticarcillin-clavulanic acid	J01CR03	Parenteral	1 302	0.71	1 513	1.14	0.86	12.9	15.0
Co-trimoxazole	J01EE01	Oral	908	0.49	1 336	1.01	0.68	1.3	1.92
		Parenteral	340	0.18	210	0.16	1.62	3.1	1.92
Gentamicin	J01GB03	Parenteral	1 240	0.67	2 033	1.54	0.61	0.15	0.24
Phenoxymethylpenicillin	J01CE02	Oral	1 218	0.66	834	0.63	1.46	2.9	2.0
Fosfomycin	J01XX01	Parenteral	1 063	0.58	743	0.56	1.43	11.4	8.0
Piperacillin	J01CA12	Parenteral	940	0.51	1 119	0.85	0.84	11.8	14.0
Roxithromycin	J01FA06	Oral	803	0.44	744	0.56	1.08	0.3	0.3
Cefpodoxime	J01DD13	Oral	769	0.42	801	0.61	0.96	0.4	0.4
Azithromycin	J01FA10	Oral	725	0.39	429	0.32	1.69	0.5	0.3
Colisitin	J01XB01	Parenteral	563	0.31	526	0.40	1.07	3.2**	3.0**
Fusidic acid	J01XC01	Oral	338	0.18	368	0.28	0.92	1.4	1.5
	J01XC01	Parenteral	225	0.12	228	0.17	0.99	1.5	1.5
Doxycycline	J01AA02	Oral	355	0.19	190	0.14	1.87	0.19	0.1
	J01AA02	Parenteral	37	0.02	24	0.02	1.56	0.16	0.1
Clindamycin	J01FF01	Oral	11	0.01	7	0.01	1.43	1.7	1.2
	J01FF01	Parenteral	105	0.06	94	0.07	1.12	2.0	1.8
Aztreonam	J01DF01	Parenteral	32	0.02	27	0.02	1.17	4.7	4.0
Total	J01	–	184 397	100	132 331	100	–	–	

**There is no official DDD for parenteral spiramycin. The DDD given by WHO for oral spiramycin was used. **In million units.*

Table 3
Ratio of number of defined daily doses (DDD) : number of treatment-days for the main antibacterials used at Besançon University Hospital in 2001, by specialty

Antibacterial name	ATC code	Administration route	Ratio of number of DDD : number of treatment-days		
			Medicine	Surgery (*P**)	Intensive care (*P1**, *P2**)
Amoxicillin-clavulanic acid	J01CR02	Oral	3.01	2.91 (<0.001)	ND
		Parenteral	1.27	1.23 (0.006)	1.75 (<0.001; <0.001)
Amoxicillin	J01CA01	Oral	3.10	2.82 (0.005)	ND**
		Parenteral	6.52	3.99 (<0.001)	5.76 (0.03; <0.001)
Ciprofloxacin	J01MA02	Oral	1.08	1.04 (<0.001)	ND
		Parenteral	0.96	1.05 (<0.001)	1.28 (<0.001; <0.001)
Ofloxacin	J01MA01	Oral	1.07	1.04 (0.05)	ND
		Parenteral	0.99	1.04 (0.002)	1.60 (<0.001; <0.001)
Ceftriaxone	J01DA13	Parenteral	0.77	0.93 (<0.001)	0.90 (<0.001; 0.19)
Tobramycin	J01GB01	Parenteral	0.58	0.67 (<0.001)	0.99 (<0.001; <0.001)
Amikacin	J01GB06	Parenteral	0.70	0.83 (<0.001)	0.92 (0.001; 0.18)
Vancomycin	J01XA01	Parenteral	0.80	0.92 (<0.001)	0.82 (0.51; <0.001)

**P: Surgery vs. medicine. P1: Intensive care vs. medicine. P2: Intensive care vs. surgery. **ND: not calculated, less than 30 prescriptions.*

variability reflected prescription habits on the wards rather than differences in patient case-mix that justify dose adjustment. Further investigations are needed to explain why, for example, some non-intensive care wards prescribed oral ciprofloxacin at an average dose of 0.55 g day^{-1} and others at 1.55 g day^{-1}. Such discrepancies suggest that efforts should be made to improve antibiotic prescription in our hospital. The wards considered as outliers should be targeted for investigation and possible intervention.

One limitation of our study is that our computerized pharmacy distribution system does not record information on clinicians' compliance with the dose and length of treatment recommended by the system. Additionally, we do not know if the antibacterials were actually given to the patients. However, a study previously conducted at our hospital showed that the difference between the length of treatment calculated with the computerized pharmacy distribution system was only 5% higher than the length of treatment recorded from patients' charts [21], which strongly suggests that data provided by the pharmacy system are representative of the actual prescriptions. The main aim of the computerized pharmacy dispensing system initially was to reduce storage of medicines in the wards. While fulfilling its original objective, the computerized system has considerably reduced the data management workload and has proven an essential tool for ongoing surveillance of antimicrobial use at our hospital.

Validated antibiotic use data are needed to identify heavy use areas and provide feedback to prescribers [22], to study the relationship between antibiotic use and

resistance, and to design and evaluate interventions, and to decide which intervention is likely to prove successful in a particular setting [23]. Benchmarking is an important initial step to identify problem areas and needs for improvement [24]. Keeping in mind its limitations, an international unit of antibiotic use such as the WHO-defined DDD is an essential tool for comparisons of local, national and international antimicrobial use densities in hospitals. However, the choice between the number of treatment-days, the number of PDD or the number of DDD per 1000 days of hospitalization for use as an indicator of the incidence density of exposure to an antibiotic may, therefore, not be that simple and possibly inappropriate for estimating correlations between 'consumption of' and 'resistance to'. It is likely that the ecological antibiotic pressure of 3 g of amoxicillin-clavulanic acid would have a different effect if it is administered to three patients (3×1 g according to the WHO-defined DDD) or to only one patient (according to the estimated PDD of 3 g at our hospital). Obviously, additional research is needed to determine the value of various indicators of antimicrobial use to study the relationship between antimicrobial resistance and use.

In conclusion, our study shows that, with the exception of the fluoroquinolones and the cephalosporins, the number of DDD does not correctly reflect the number of antibiotic treatment-days at our hospital and patients' exposure to antibiotics would be better reflected by the number of PDD. This does not invalidate the systematic approach of the WHO Collaborating Centre for Drug Statistics Methodology to define and regularly update the DDDs for international comparisons, but should stimulate collaboration with this centre to update the DDDs when needed. Hospitals should use the DDDs to make international comparisons of their antibiotic use; however, each hospital should define and validate its own indicators and find which are the most appropriate to describe the local exposures to antibiotics and to link to resistance data. Finally, the present study would not have been possible without the availability of computerized prescription data. This stresses the importance of implementing computerized dispensing systems in pharmacies and to use these systems to develop and validate indicators of drug utilization in hospitals.

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References

1 Bronzwaer SL, Cars O, Buchholz U, Molstad S, Goettsch W, Veldhuijzen IK, Kool JL, Sprenger MJ, Degener JE. A European study on the relationship between antimicrobial use and antimicrobial resistance. Emerg Infect Dis 2002; 8: 278–82.

2 Goldmann DA, Huskins WC. Control of nosocomial antimicrobial-resistant bacteria: a strategic priority for hospitals worldwide. Clin Infect Dis 1997; 24(Suppl 1): S139–45.

3 Goldmann DA, Weinstein RA, Wenzel RP, Tablan OC, Duma RJ, Gaynes RP, Schlosser J, Martone WJ. Strategies to prevent and control the emergence and spread of antimicrobial-resistant microorganisms in hospitals. A challenge to hospital leadership. JAMA 1996; 275: 234–40.

4 National Agency for the Development of Medical Evaluation. Proper use of antibiotics in hospital. Recommendations for the control of bacterial resistance. Press Med 1998; 27: 1687–8.

5 WHO Collaborating Centre for Drug Statistics and Methodology. Guidelines for ATC Classification and DDD Assignment. Oslo, Norway: WHO, 2003.

6 Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet 2005: 365, 579–87.

7 Baquero F, Baquero-Artigao G, Canton R, Garcia-Rey C. Antibiotic consumption and resistance selection in Streptococcus pneumoniae. J Antimicrob Chemother (50 Suppl), 2002; S2: 27–37.

8 Coenen S, Mölstad S. Preferred antibiotics, dosages and length of treatments in general practice – a comparison between ten European countries. Eur J Gen Pract 2004; 10: 166–8.

9 Monnet DL, Mölstad S, Cars O. Defined daily doses of antimicrobials reflect antimicrobial prescriptions in ambulatory care. J Antimicrob Chemother 2004; 53: 1109–11.

10 Rogues AM, Placet-Thomazeau B, Parneix P, Vincent I, Ploy MC, Marty N, Merillou B, Labadie JC, Gachie JP. Use of antibiotics in hospitals in south-western France. J Hosp Infect 2004; 58: 187–92.

11 Loeffler JM, Garbino J, Lew D, Harbarth S, Rohner P. Antibiotic consumption, bacterial resistance and their correlation in a Swiss University hospital and its adult intensive care units. Scand J Infect Dis 2003; 35: 843–50.

12 Muller-Pebody B, Muscat M, Pelle B, Klein BM, Brandt CT, Monnet DL. Increase and change in pattern of hospital antimicrobial use, Denmark, 1997–2001. J Antimicrob Chemother 2004; 54: 1122–6.

13 Janknegt R, Oude Lashof A, Gould IM, van der Meer JW. Antibiotic use in Dutch hospitals1991–1996. J Antimicrob Chemother 2000; 45: 251–6.

14 Filius PM, Liem TB, van der Linden PD, Janknegt R, Natsch S, Vulto AG, Verbrugh HA. An additional measure for quantifying antibiotic use in hospitals. J Antimicrob Chemother 2005; 55: 805–8.

15 Muller A, Lopez-Lozano JM, Bertrand X, Talon D. Relationship between ceftriaxone use and resistance to third-generation cephalosporins among clinical strains of Enterobacter cloacae. J Antimicrob Chemother 2004; 54: 173–7.

16 Westh H, Zinn CS, Rosdahl VT. An international multicenter study of antimicrobial consumption and resistance in Staphylococcus

aureus isolates from 15 hospitals in 14 countries. Microb Drug Resist 2004; 10: 169–76.

17 Muller A, Mauny F, Bertin M, Cornette C, Lopez-Lozano JM, Viel JF, Talon D, Bertrand X. Relationship between spread of methicillin-resistant Staphylococcus aureus and antimicrobial use in a French University hospital. Clin Infect Dis 2003; 36: 971–8.

18 Kern WV, Steib-Bauert M, de With K, Reuter S, Bertz H, Frank U, von Baum H. Fluoroquinolone consumption and resistance in haematology-oncology patients: ecological analysis in two University hospitals 1999–2002. J Antimicrob Chemother 2005; 55: 57–60.

19 WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD index. Available from: URL. http://www.whocc.no/atcddd/ 2005.

20 AFSSAPS. Guidelines for the antibiotic treatment of lower respiratory track infections. Rev Mal Respir 2003; 20: 462–9.

21 Mandy B, Koutny E, Cornette C, Woronoff-Lemsi MC, Talon D. Methodological validation of monitoring indicators of antibiotics use in hospitals. Pharm World Sci 2004; 26: 90–5.

22 de With K, Bergner J, Buhner R, Dorje F, Gonnermann C, Haber M, Hartmann M, Rothe U, Strehl E, Steib-Bauert M, Kern WV. Antibiotic use in German University hospitals 1998–2000 (Project INTERUNI-II). Int J Antimicrob Agents 2004; 24: 213–8.

23 Weinstein RA. Controlling antimicrobial resistance in hospitals. Infection control and use of antibiotics. Emerg Infect Dis 2001; 7: 188–92.

24 Meyer E, Schwab F, Jonas D, Rueden H, Gastmeier P, Daschner FD. Surveillance of antimicrobial use and antimicrobial resistance in intensive care units (SARI). 1. Antimicrobial use in German intensive care units. Intensive Care Med 2004; 30: 1089–96.