J Antimicrob Chemother 2012; **67**: 2283–2288
doi:10.1093/jac/dks190 Advance Access publication 25 May 2012

Journal of Antimicrobial Chemotherapy

Intensification of antibiotic use within acute care hospitals in the Netherlands

H. M. Kwint[1,2], P. D. van der Linden[3], M. M. B. Roukens[1] and S. Natsch[1]* on behalf of SWAB's Working Group on Surveillance of Antimicrobial Use†

[1]Department of Pharmacy, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; [2]Department of Clinical Pharmacy, Ziekenhuis Gelderse Vallei, Ede, The Netherlands; [3]Department of Clinical Pharmacy, Tergooi Ziekenhuizen, Hilversum, The Netherlands

*Corresponding author. Tel: +31-24-3616405; Fax: +31-24-3616679; E-mail: s.natsch@akf.umcn.nl
†Members of SWAB's Working Group on Surveillance of Antimicrobial Use are listed in the Acknowledgements section.

Received 29 December 2011; returned 10 February 2012; revised 19 March 2012; accepted 14 April 2012

Objectives: To report and analyse trends in antibiotic use in Dutch university hospitals, large teaching hospitals and general hospitals over the period 2003 to 2009.

Methods: Data on the use of antibiotics and hospital resource indicators were obtained by distributing a questionnaire to all Dutch hospital pharmacies. Antibiotic use was expressed as the number of defined daily doses (DDDs) per 100 patient-days, per 100 admissions and per 1000 inhabitants per day. The latter was achieved by extrapolating sample data by means of imputation and up-scaling.

Results: From 2003 to 2009, the mean length of hospital stay decreased from 6.27 to 4.50 days (−28%). Total systemic antibiotic use significantly increased from 52.3 to 69.8 DDDs per 100 patient-days ($P < 0.001$). Despite the overall constant use when expressed in DDDs per 100 admissions, we found a significant increase in the total use of piperacillin/tazobactam, cefazolin, ceftriaxone, meropenem, azithromycin, gentamicin, ciprofloxacin and vancomycin. Mean total systemic use expressed in DDDs per 1000 inhabitants per day gradually increased by 38% from 0.73 in 2003 to 1.01 in 2009.

Conclusions: Total hospital antibiotic consumption is still low in the Netherlands compared with other European countries. Also, between 2003 and 2009 the use of antibiotics in individual hospitalized patients remained stable. However, since they remained in the hospital for a shorter period of time, the number of DDDs per 100 patient-days increased. This results in an intensification of antibiotic treatment per hospital bed, leading to a possible increase in selection pressure towards resistance. This may create a problem for future patients. To limit the emergence and transmission of antimicrobial-resistant bacteria, effective antibiotic stewardship is essential.

Keywords: in-patient use, length of stay, inhabitants, Dutch

Introduction

In 1996 the Working Party on Antibiotic Policy (SWAB) was founded by the Dutch Society for Medical Microbiology, the Society for Infectious Diseases and the Dutch Association of Hospital Pharmacists. SWAB's mission is to manage, limit and prevent the emergence of resistance to antimicrobial agents among medically important species of microorganisms in the Netherlands, thereby contributing to the proper care of patients in this country. The activities of SWAB are supported by a structural grant from the Dutch Ministry of Health, Welfare and Sport. SWAB's Working Group on Surveillance of Antimicrobial Use collects data on national antibiotic use in hospitals.[1] Janknegt *et al.*[2] conducted a study on hospital antibiotic use over the period 1991–96. Liem *et al.*[3] analysed trends in antibiotic use over the period 1997–2002. Since 2003, data on antibiotic use are presented in SWAB's annual report, called NethMap.[4] In the present study, we report on antibiotic use in Dutch hospitals during the period 2003–09. In line with previous reports, we expressed hospital antibiotic use in defined daily doses (DDDs) per 100 patient-days and DDDs per 100 admissions.[2,3,5] Moreover, for the first time, we expressed hospital antibiotic use in DDDs per 1000 inhabitants per day, which is a valuable additional unit of measurement for cross-national comparison.[6]

Methods

All Dutch hospitals—8 university hospitals, 27 large teaching hospitals [providing highly specialized medical care (e.g. heart surgery, neurosurgery, *in vitro* fertilization and high-level intensive care) that lies between that of a

university medical centre and that of a general hospital][7] and 62 general hospitals—were asked to participate in SWAB's national surveillance system. Data on the use of antibiotics in acute care hospitals between 2003 and 2009 were collected by means of a questionnaire distributed to all Dutch hospital pharmacies by SWAB (please see the Supplementary data at *JAC* Online for an example of the questionnaire, in Dutch, as well as an English translation). Data from inpatient wards as well as day care wards were included, whereas outpatient use and dispensing to nursing homes were excluded from the data report. Pharmacies were requested to report on the annual consumption of antibiotics of different (sub)classes of the Anatomical Therapeutic Chemical (ATC) classification system. For this report, only data from the J01 subgroup were used, expressed as DDDs per 100 patient-days, per 100 admissions and per 1000 inhabitants per day. The ATC/DDD classification from the WHO, version 2010, was used to calculate the number of DDDs of the various antibiotics.[8] The DDD is defined as the assumed average maintenance dose per day for a drug used for its main indication in adults.

For each hospital, the annual number of bed-days and admissions was recorded. The number of patient-days was obtained by subtracting the number of admissions from the number of bed-days, as the number of bed-days overestimates actual treatment-days by including both the day of admission and the day of discharge.[3] The mean length of stay was calculated by dividing the number of patient-days by the mean number of admissions.[3] Data on the annual number of inhabitants in the Netherlands were obtained from Statistics Netherlands (CBS).[9]

Statistical analysis

Trend analysis

For the period 2003–09, an overall pooled mean (i.e. weighted mean) was calculated for each year by aggregating data on antibiotic use and patient-days from all the hospitals in our sample. Drug utilization was compared between hospitals and over time by a mixed model for repeated measurements. The response variables were the number of DDDs per 100 patient-days and the number of DDDs per 100 admissions. Changes in the mean number of admissions, mean number of patient-days and mean length of hospital stay between 2003 and 2009 were calculated using the Mann–Whitney *U*-test with continuous variables. *P* values <0.05 were considered statistically significant in all analyses. SAS 9.3 (SAS Institute, NC, USA) or SPSS version 18.0 (SPSS Inc., Chicago, IL, USA) was used for statistical calculations.

DDDs per 1000 inhabitants per day

Hospital consumption data and corresponding hospital statistics were used to estimate total hospital consumption in the Netherlands. First, an algorithm combining linear interpolation, first value carried backward and last value carried forward was used, followed by up-scaling of the dataset to the total number of university hospitals, large teaching hospitals or general hospitals in the Netherlands.[7] Finally, hospital antibiotic consumption was expressed as DDDs per 1000 inhabitants per day. Statistical analyses were performed using R 2.13.1 (R Foundation for Statistical Computing, Vienna, Austria).[10] Because these hospital consumption data were partially observed and partially interpolated, a trend analysis was not performed.

Results

Hospital resource indicators

The number of hospitals that issued data on antibiotic use varied from 39.4% in 2007 to 63.6% in 2003. A total of 86 out of 97 hospitals participated for ≥1 year between 2003 and 2009. Of these 86 hospitals, 48% participated for ≥5 years. Only 13 hospitals participated every year. Most of the hospitals that did not participate in a certain year were small general hospitals.

The mean number of admissions significantly increased from 18194 in 2003 to 22899 in 2009 (+25.9%, $P=0.005$), whereas the mean number of patient-days decreased from 116880 in 2003 to 105375 in 2009 (−9.8%, $P=0.3$). The mean length of stay significantly decreased from 6.27 days in 2003 to 4.50 days in 2009 (−28.2%, $P<0.001$). The largest increase in number of admissions as well as the largest decrease in number of patient-days was seen in the group of large teaching hospitals.

Hospital use of antibiotics

Trend analysis

In 2003, the mean total systemic use expressed in DDDs per 100 patient-days was 52.3, which significantly increased to 69.8 in 2009 ($P<0.001$) (Figure 1a). When expressed in DDDs per 100 admissions, mean total systemic use remained almost constant at 328.2 in 2003 and 314.2 in 2009 (Figure 1b). The same pattern was also seen in university hospitals, large teaching hospitals and general hospitals individually. However, a large variation in quantitative antibiotic use was found between the participating hospitals, in particular in general and large teaching hospitals (Figure 2).

Despite the overall constant use when expressed in DDDs per 100 admissions, we found a significant increase in the total use of piperacillin/tazobactam, cefazolin, ceftriaxone, meropenem, azithromycin, gentamicin, ciprofloxacin and vancomycin (Table 1).

Moreover, the increase in the use of meropenem and vancomycin in each particular type of hospital in both DDDs per 100 patient-days and DDDs per 100 admissions was remarkable. Expressed in DDDs per 100 patient-days, use of meropenem increased from 0.72 in 2003 to 1.70 in 2009 ($P<0.001$) in university hospitals, from 0.16 to 0.58 ($P<0.001$) in large teaching hospitals and from 0.18 to 0.48 ($P<0.001$) in general hospitals. Use of vancomycin increased from 1.36 in 2003 to 2.24 in 2009 ($P<0.001$) in university hospitals, from 0.33 to 1.01 ($P<0.001$) in large teaching hospitals and from 0.19 to 0.44 ($P<0.001$) in general hospitals. Expressed in DDDs per 100 admissions, use of meropenem increased from 5.31 in 2003 to 10.38 in 2009 ($P<0.001$) in university hospitals, from 1.05 to 2.65 ($P<0.001$) in large teaching hospitals and from 1.09 to 1.99 ($P<0.001$) in general hospitals. Use of vancomycin increased from 9.75 in 2003 to 13.52 in 2009 ($P<0.05$) in university hospitals, from 2.10 to 4.75 ($P<0.05$) in large teaching hospitals and from 1.18 to 1.87 ($P<0.001$) in general hospitals.

DDDs per 1000 inhabitants per day

In 2003, national hospital antibiotic consumption expressed in DDDs per 1000 inhabitants per day was 0.73, which gradually increased by 38% to 1.01 in 2009. The increase in the use of meropenem, vancomycin and ceftriaxone was remarkable (308%, 233% and 209%, respectively), as was the increase in the use of colistin (249%), fusidic acid (202%), piperacillin/tazobactam (173%), azithromycin (151%), ceftazidime (90%) and the aminoglycosides tobramycin and gentamicin (110% and 86%, respectively) (Table 2). Almost 50% of all antibiotics used

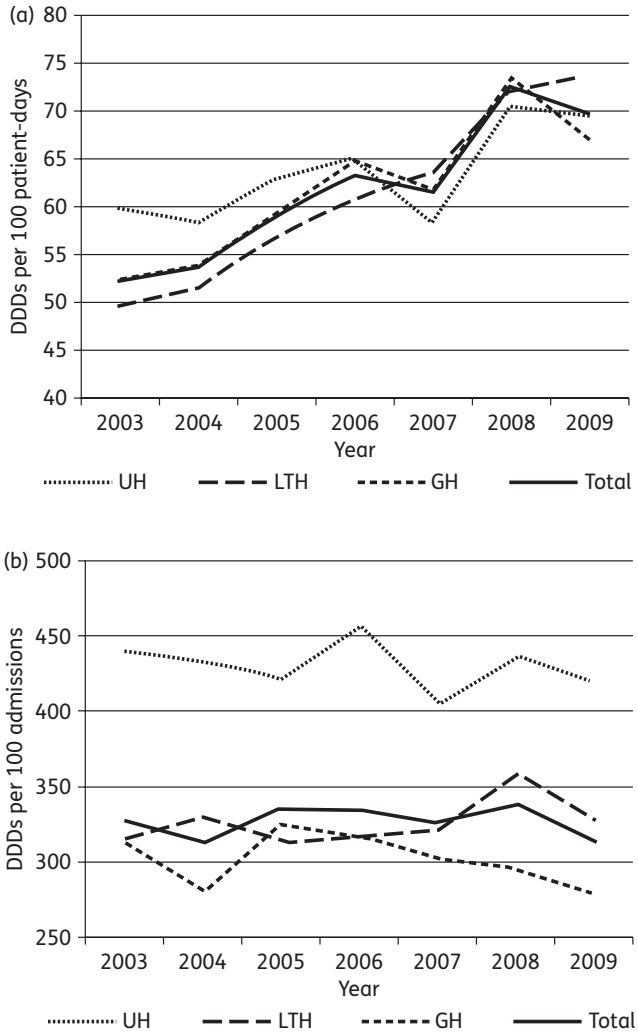

Figure 1. Trend in antibiotic use in Dutch hospitals, 2003–09: university hospitals (UH) versus large teaching hospitals (LTH) versus general hospitals (GH). (a) Use in DDDs per 100 patient-days. (b) Use in DDDs per 100 admissions.

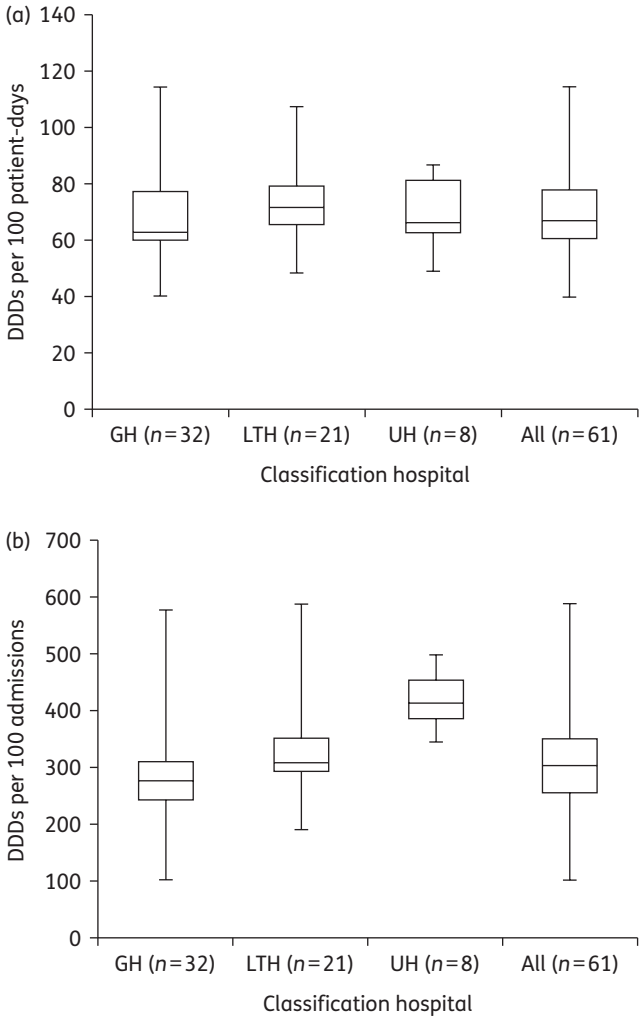

Figure 2. Variance in total use of antibiotics for systemic use (J01) in Dutch hospitals, 2009: university hospitals (UH) versus large teaching hospitals (LTH) versus general hospitals (GH). (a) Use in DDDs per 100 patient-days. (b) Use in DDDs per 100 admissions.

in Dutch hospitals are penicillins (J01C). Other large groups of antibiotics are the cephalosporins, carbapenems and monobactams (J01D), and the quinolones (J01M).

Discussion

Total systemic antibiotic use significantly increased from 52.3 in 2003 to 69.8 in 2009 when expressed in DDDs per 100 patient-days, whereas it remained constant when expressed in DDDs per 100 admissions. Hospital admissions in this period increased by 26% and length of stay decreased by 28%. This means that, on average, individual patients were exposed to the same amount of antibiotics, but because more patients were admitted to the hospital per day, total use of antibiotics per hospital increased. These observations are in line with the study of Liem *et al.*,[3] who described an increase from 47.2 DDDs per 100 patient-days in 1997 to 58.2 DDDs per 100 patient-days in 2002, and a constant use when expressed in DDDs per 100 admissions.

A large variation in quantitative antibiotic use was found between the participating hospitals, in particular in general and large teaching hospitals. Investigation into the determinants that cause this variation—e.g. differences in local antibiotic policy—is warranted.

As stated by Ansari *et al.*[11] and Filius *et al.*,[5] more than one clinical activity variable should be used as the denominator to determine changes in antibiotic use in hospitals for better understanding of the data. In the present study, Dutch hospital antibiotic use is expressed in DDDs per 100 patient-days, DDDs per 100 admissions and, for the first time, DDDs per 1000 inhabitants per day. These data can now be used for cross-national comparison.[6,12] Hospital antibiotic consumption in the Netherlands is still low compared with other European countries, ranging from 0.73 DDDs per 1000 inhabitants per day in 2003 to 1.01 DDDs per 1000 inhabitants per day in 2009. For example, in 2002, Kern *et al.*[13] estimated the hospital antibiotic consumption for Baden-Wurttemberg—a federal state in

Table 1. Trend in antibiotic use in Dutch hospitals (DDDs per 100 patient-days and DDDs per 100 admissions), 2003–09; selected antibiotics, ATC5 level

		DDDs per 100 patient-days			DDDs per 100 admissions		
ATC code	Antibiotic	2003	2009	*P* value	2003	2009	*P* value
J01AA02	doxycycline	1.437	1.523	0.503	8.845	6.698	0.089
J01CA04	amoxicillin	5.829	7.159	<0.001	36.35	32.46	0.302
J01CE01	benzylpenicillin	0.900	1.244	0.048	5.667	5.535	0.624
J01CE05	pheneticillin	0.289	0.286	0.817	1.818	1.318	0.091
J01CF05	flucloxacillin	5.199	6.135	<0.001	32.84	28.02	0.226
J01CR02	amoxicillin/clavulanic acid	12.24	16.68	<0.001	76.17	73.24	0.881
J01CR05	piperacillin/tazobactam	0.284	0.644	<0.001	1.928	2.965	<0.001
J01DB04	cefazolin	1.571	2.746	<0.001	9.756	12.34	0.003
J01DC02	cefuroxime	2.987	3.849	0.292	18.48	16.64	0.964
J01DD01	cefotaxime	0.382	0.524	0.942	2.429	2.537	0.999
J01DD02	ceftazidime	0.631	0.842	<0.001	4.120	3.985	0.316
J01DD04	ceftriaxone	0.744	1.510	<0.001	4.716	7.373	0.017
J01DH02	meropenem	0.235	0.671	<0.001	1.547	3.316	<0.001
J01EA01	trimethoprim	0.530	0.420	0.287	3.296	1.871	0.010
J01EE01	sulfamethoxazole/trimethoprim	2.130	1.858	0.039	13.59	8.598	<0.001
J01FA09	clarithromycin	1.362	1.094	<0.001	8.471	4.868	<0.001
J01FA10	azithromycin	0.256	0.432	<0.001	1.685	2.070	<0.001
J01FF01	clindamycin	1.540	2.308	<0.001	9.757	10.36	0.804
J01GB01	tobramycin	0.626	0.550	0.354	4.189	2.598	0.411
J01GB03	gentamicin	1.672	3.410	<0.001	10.56	15.17	<0.001
J01MA02	ciprofloxacin	4.326	7.818	<0.001	27.45	35.03	<0.001
J01MA06	norfloxacin	0.934	0.555	0.142	5.883	2.358	<0.001
J01XA01	vancomycin	0.368	0.871	<0.001	2.441	4.389	<0.001
J01XB01	colistin	0.076	0.171	0.340	0.535	0.861	0.586
J01XC01	fusidic acid	0.027	0.060	0.848	0.185	0.283	0.894
J01XD01	metronidazole	1.627	1.893	0.049	10.15	8.485	0.527
J01XE01	nitrofurantoin	0.801	1.129	0.034	4.921	4.980	0.281

south-western Germany with 10.6 million inhabitants—to be ~2 DDDs per 1000 inhabitants per day. Also in 2002, median national hospital antibiotic consumption in Europe was 2.1 DDDs per 1000 inhabitants per day, ranging from 1.3 in Norway and Sweden to 3.9 in Finland and France.[6]

The decrease in the duration of hospital stay in the Netherlands has been evident for years and further decreased during our study period. Our data showed that this decrease is most evident in large teaching hospitals. Presuming that the duration of antibiotic therapy for one patient did not change, the most likely consequence of a shortening of the duration of hospital stay is that the antibiotic therapy is continued extramurally. This could be subject to further research.

Another consequence of a reduction in the duration of hospital stay is that more patients with antibiotic treatment can be admitted per bed during a specific period. This results in an intensification of antibiotic treatment per patient-day and per hospital bed, which may cause increased selection pressure towards resistance. Because patients are close to each other in hospitals, increased selection pressure from one bed to the surrounding environment may lead to the transmission of antimicrobial-resistant organisms to other patients within a hospital ward. In particular, the transmission of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci and carbapenem-resistant *Acinetobacter baumannii* to other patients may increase.[14–17] Sites most commonly contaminated in hospitals include bedside rails, bedside tables, blood pressure cuffs, ultrasonic nebulizers, ventilation grills, floors, toilets and call buttons.[14] The contribution of higher antibiotic use in these settings to the spread of resistant microorganisms needs further research. Therefore, closer monitoring of antibiotic consumption and the development of resistance in relation to bed occupancy is warranted.

For meropenem and vancomycin, increases in both DDDs per 100 patient-days and DDDs per 100 admissions were observed in each particular type of hospital between 2003 and 2009, as well as in DDDs per 1000 inhabitants per day. One possible explanation for this increase in the use of meropenem and vancomycin is the increasing emergence of extended-spectrum β-lactamase-producing bacteria and methicillin-resistant staphylococci (particularly coagulase-negative species) in Dutch hospitals.[4] This might be a cause for concern, since this trend towards higher use is more likely to be associated with an increase in selection pressure. For example, in the intensive care

Table 2. Data on the use of antibiotics for systemic use (J01) in Dutch hospitals in DDDs per 1000 inhabitants per day, 2003–09; selected antibiotics, ATC5 level

ATC code	Antibiotic	Year							Percentage change, 2003–09
		2003	2004	2005	2006	2007	2008	2009	
J01AA02	doxycycline	0.021	0.023	0.025	0.025	0.023	0.022	0.023	11
J01CA04	amoxicillin	0.082	0.088	0.101	0.111	0.108	0.099	0.109	33
J01CE01	benzylpenicillin	0.013	0.014	0.016	0.017	0.016	0.015	0.019	46
J01CE05	pheneticillin	0.003	0.004	0.005	0.004	0.004	0.004	0.004	25
J01CF05	flucloxacillin	0.068	0.080	0.089	0.091	0.087	0.086	0.093	37
J01CR02	amoxicillin/clavulanic acid	0.185	0.208	0.225	0.232	0.225	0.220	0.231	25
J01CR05	piperacillin/tazobactam	0.004	0.005	0.006	0.007	0.008	0.009	0.010	173
J01DB04	cefazolin	0.023	0.026	0.032	0.031	0.034	0.033	0.039	67
J01DC02	cefuroxime	0.038	0.045	0.050	0.054	0.049	0.042	0.049	28
J01DD01	cefotaxime	0.008	0.008	0.008	0.008	0.007	0.008	0.008	5
J01DD02	ceftazidime	0.007	0.010	0.012	0.013	0.012	0.012	0.013	90
J01DD04	ceftriaxone	0.008	0.011	0.016	0.019	0.018	0.020	0.025	209
J01DH02	meropenem	0.002	0.004	0.005	0.006	0.007	0.008	0.010	308
J01EA01	trimethoprim	0.008	0.008	0.009	0.009	0.009	0.007	0.006	−18
J01EE01	sulfamethoxazole/trimethoprim	0.030	0.032	0.035	0.034	0.033	0.029	0.030	0
J01FA09	clarithromycin	0.018	0.020	0.022	0.019	0.018	0.015	0.016	−8
J01FA10	azithromycin	0.003	0.003	0.005	0.006	0.008	0.008	0.007	151
J01FF01	clindamycin	0.023	0.027	0.030	0.031	0.031	0.029	0.033	40
J01GB01	tobramycin	0.005	0.007	0.010	0.010	0.009	0.012	0.011	110
J01GB03	gentamicin	0.024	0.024	0.027	0.028	0.031	0.036	0.044	86
J01MA02	ciprofloxacin	0.066	0.077	0.086	0.093	0.101	0.119	0.109	66
J01MA06	norfloxacin	0.012	0.013	0.012	0.012	0.010	0.009	0.009	−24
J01XA01	vancomycin	0.004	0.006	0.009	0.010	0.010	0.011	0.014	233
J01XB01	colistin	0.001	0.001	0.003	0.002	0.002	0.003	0.003	249
J01XC01	fusidic acid	0.000	0.000	0.000	0.000	0.000	0.001	0.001	202
J01XD01	metronidazole	0.023	0.024	0.024	0.027	0.027	0.025	0.026	13
J01XE01	nitrofurantoin	0.012	0.014	0.017	0.016	0.018	0.016	0.017	42

unit, increasing carbapenem use will enhance antibiotic resistance in *Pseudomonas aeruginosa*.[18] Transmission of resistant microorganisms for these types of antibiotics in particular is possible via environmental contamination. In brief, although a single patient may receive an effective antibiotic, the posed antibiotic selection pressure may create a resistance problem for other patients in the near future.

For ciprofloxacin, an increase in total use in DDDs per 100 admissions was observed. This drug is associated with MRSA and *Clostridium difficile*. Since 2005, there has been an increase in *C. difficile* in the Netherlands.[19] There is no notable increase in MRSA due to the very effective 'search and destroy' policy in the Netherlands.[20] However, in 2011 there was an increase in the emergence of MRSA of unknown origin.[21] This could mean a spread through the community. Further research is therefore warranted.

Extrapolation of the Dutch hospital sample data to a national aggregate of hospital antibiotic use was not easy. First, consumption patterns show large variability between hospitals. Second, only 13 hospitals participated every year during our study period, which means that numerous data were interpolated. For this reason, no trend analysis could be performed. Also, we did not test the sample's representativeness of the Netherlands, which is a flaw of this study. However, our interpolated number of patient-days is nearly identical to the number of patient-days reported by CBS (data not shown). A possible limitation is that our data were collected by means of a questionnaire. Finally, a possible source of bias was the variety of methods used by the different Dutch hospital pharmacies to quantify their antibiotic use. Ideally, actual prescription data should be used as a source to measure antibiotic use in hospitals.

Conclusions

Total hospital antibiotic consumption is still low in the Netherlands. Also, the use of antibiotics in individual hospitalized patients remains stable. However, since they remained in the hospital for a shorter period of time, the number of DDDs per 100 patient-days increased. This results in an intensification of antibiotic treatment per hospital bed, leading to a possible increase in selection pressure towards resistance. This may create a problem for future patients. Therefore, everyone should be fully aware of the described situation and take this into consideration when formulating policy around hospital antibiotic use. To limit the emergence and transmission of antimicrobial-resistant bacteria, effective antibiotic stewardship

is essential. Specifically, deliberate use of meropenem and vancomycin is recommended. The emphasis should be on the principle that they should only be used when the correct indication is present. More research is needed to determine the relationship between antibiotic use, environmental contamination, selection pressure and the emergence of resistance.

Acknowledgements

We thank the pharmacists of the participating hospitals for providing data on antibiotic use. We thank Dr R. Donders, PhD, for his contribution to the methodological part of this manuscript.

Members of SWAB's Working Group on Surveillance of Antimicrobial Use

S. Natsch, C. Pellicaan, A. D. Lindemans, T. B. Y. Liem, P. D. van der Linden, A. J. de Neeling, P. N. Panday, H. M. Kwint, A. W. van der Velden, E. M. W. van de Garde, M. Lourens and M. M. B. Roukens.

Funding

This work was supported by a structural grant from the Ministry of Health, Welfare and Sport to the Working Party on Antibiotic Policy (SWAB).

Transparency declarations

None to declare.

Supplementary data

An example of the questionnaire, in Dutch, as well as an English translation are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

References

1 SWAB (Dutch Working Party on Antibiotic Policy). *Stichting Werkgroep Antibiotica Beleid*. http://www.swab.nl (29 December 2011, date last accessed).

2 Janknegt R, Oude LA, Gould IM *et al*. Antibiotic use in Dutch hospitals 1991–1996. *J Antimicrob Chemother* 2000; **45**: 251–6.

3 Liem TB, Filius FM, van der Linden PD *et al*. Changes in antibiotic use in Dutch hospitals over a six-year period: 1997 to 2002. *Neth J Med* 2005; **63**: 354–60.

4 SWAB (Dutch Working Party on Antibiotic Policy). *NethMap 2011—Consumption of Antimicrobial Agents and Antimicrobial Resistance among Medically Important Bacteria in the Netherlands*. http://www.swab.nl/nethmap (29 December 2011, date last accessed).

5 Filius PM, Liem TB, van der Linden PD *et al*. An additional measure for quantifying antibiotic use in hospitals. *J Antimicrob Chemother* 2005; **55**: 805–8.

6 Vander Stichele RH, Elseviers MM, Ferech M *et al*. Hospital consumption of antibiotics in 15 European countries: results of the ESAC Retrospective Data Collection (1997–2002). *J Antimicrob Chemother* 2006; **58**: 159–67.

7 STZ (Association of Tertiary Medical Teaching Hospitals). *Topklinische Ziekenhuizen Nederland*. http://www.stz-ziekenhuizen.nl (29 December 2011, date last accessed).

8 WHO Collaborating Centre for Drug Statistics Methodology. *ATC Index with DDDs 2010*. Oslo, Norway: WHO Collaborating Centre, 2011. www.whocc.no (29 December 2011, date last accessed).

9 CBS (Statistics Netherlands). *Bevolking; Generatie, Geslacht, Leeftijd en Herkomstgroepering, 1 Januari*. http://statline.cbs.nl (29 December 2011, date last accessed).

10 R Development Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing, 2011. http://www.R-project.org/ (29 December 2011, date last accessed).

11 Ansari F, Molana H, Goossens H *et al*. Development of standardized methods for analysis of changes in antibacterial use in hospitals from 18 European countries: the European Surveillance of Antimicrobial Consumption (ESAC) longitudinal survey, 2000–06. *J Antimicrob Chemother* 2010; **65**: 2685–91.

12 Vander Stichele RH, Elseviers MM, Ferech M *et al*. European Surveillance of Antimicrobial Consumption (ESAC): data collection performance and methodological approach. *Br J Clin Pharmacol* 2004; **58**: 419–28.

13 Kern WV, Steib-Bauert M, With K. Comment on: Hospital consumption of antibiotics in 15 European countries: results of the ESAC Retrospective Data Collection (1997–2002). *J Antimicrob Chemother* 2006; **58**: 900–1.

14 Boyce JM. Environmental contamination makes an important contribution to hospital infection. *J Hosp Infect* 2007; **65** Suppl 2: 50–4.

15 Hayden MK, Bonten MJ, Blom DW *et al*. Reduction in acquisition of vancomycin-resistant *Enterococcus* after enforcement of routine environmental cleaning measures. *Clin Infect Dis* 2006; **42**: 1552–60.

16 Kohlenberg A, Brummer S, Higgins PG *et al*. Outbreak of carbapenem-resistant *Acinetobacter baumannii* carrying the carbapenemase OXA-23 in a German university medical centre. *J Med Microbiol* 2009; **58**: 1499–507.

17 Lu PL, Huang LY, Lian ST *et al*. How carbapenem-resistant *Acinetobacter* spp. established in a newly constructed hospital. *Int J Antimicrob Agents* 2008; **31**: 463–6.

18 Ong DS, Jongerden IP, Buiting AG *et al*. Antibiotic exposure and resistance development in *Pseudomonas aeruginosa* and *Enterobacter* species in intensive care units. *Crit Care Med* 2011; **39**: 2458–63.

19 Goorhuis A, Bakker D, Corver J *et al*. Emergence of *Clostridium difficile* infection due to a new hypervirulent strain, polymerase chain reaction ribotype 078. *Clin Infect Dis* 2008; **47**: 1162–70.

20 Wertheim HF, Vos MC, Boelens HA *et al*. Low prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) at hospital admission in the Netherlands: the value of search and destroy and restrictive antibiotic use. *J Hosp Infect* 2004; **56**: 321–5.

21 Lekkerkerk WS, van de Sande-Bruinsma N, van der Sande MA *et al*. Emergence of MRSA of unknown origin in the Netherlands. *Clin Microbiol Infect* 2011; doi:10.1111/j.1469-0691.2011.03662.x.