Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

Changes in antibiotic use in Dutch hospitals over a six-year period: 1997 to 2002

T.B.Y. Liem[1*#], P.M.G. Filius[2#], P.D. van der Linden[3], R. Janknegt[4], S. Natsch[5], A.G. Vulto[1], on behalf of SWAB's working group on the use of antimicrobial agents

Departments of [1]Hospital Pharmacy, [2]Medical Microbiology and Infectious Diseases, Erasmus MC, University Medical Centre Rotterdam, Rotterdam, the Netherlands, tel.: +31 (0)10-463 32 02, fax: +31 (0)10-436 24 00, e-mail: t.liem@erasmusmc.nl, [3]Department of Pharmacy, Apotheek Haagse Ziekenhuizen, The Hague, the Netherlands, [4]Department of Clinical Pharmacy and Toxicology, Maasland Ziekenhuis, Sittard, the Netherlands, [5]Department of Clinical Pharmacy and Nijmegen University Ziekenhuis for Infectious Diseases, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands, [*]corresponding author

ABSTRACT

Objective: To analyse trends in antibiotic use in Dutch hospitals over the period 1997 to 2002.
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 (DDD) per 100 patient-days and as DDD per 100 admissions.
Results: Between 1997 and 2002, the mean length of stay decreased by 18%. The mean number of admissions remained almost constant. Total antibiotic use significantly increased by 24%, from 47.2 in 1997 to 58.5 DDD per 100 patient-days in 2002 ($p<0.001$), whereas expressed as DDD per 100 admissions it remained constant. Antibiotic use varied greatly between the hospitals. Moreover, the mean number of DDD per hospital of amoxicillin with clavulanic acid, clarithromycin, cefazolin, clindamycin and ciprofloxacin increased by 16, 38, 39, 50 and 52%, respectively. Total antibiotic use was higher in university hospitals than in general hospitals.
Conclusion: Between 1997 and 2002, patients hospitalised in the Netherlands did not receive more antibiotics but, since they remained in the hospital for fewer days, the number of DDD per 100 patient-days increased. For macrolides, lincosamides and fluoroquinolones increases in both DDD per 100 patient-days and in DDD per 100 admissions were observed. It is arguable whether these trends result in an increase in selection pressure towards resistance in the hospitals. Continuous surveillance of antibiotic use and resistance is warranted to maintain efficacy and safety of antibiotic treatment.

KEYWORDS

Antibiotics, hospital, surveillance, the Netherlands, utilisation

INTRODUCTION

The increasing prevalence of antibiotic resistant micro-organisms poses a major threat to the health of hospitalised patients.[1,2] Its relationship with antibiotic use and misuse is well recognised. Specific criteria for appropriate use of antibiotics in order to avoid resistance should therefore be developed.[3] Quantitative and qualitative data on the use of antibiotics in hospitals are needed to evaluate strategies that are implemented to contain antimicrobial resistance. Obviously, resistance rates also need to be measured.
In Sweden, Denmark and the Netherlands, annual reports are issued in which resistance rates and antibiotic use data are reported.[4-6] In the Netherlands, Janknegt *et al.* collected data on the use of antibiotics in Dutch hospitals during the period 1991 to 1996.[7] In 1996 the Working Party on Antibiotic Policy (acronym is SWAB; www.swab.nl) was founded by the Dutch Society for Medical Microbiology (NVMM), the Society for Infectious Diseases (VIZ) and the Dutch Association of Hospital Pharmacists (NVZA). The main activities of SWAB are development of guidelines and educational programmes to promote appropriate use of antibiotics and the surveillance of antibiotic use and resistance. These activities are supported by a structural grant from the Dutch Ministry

[#]T.B.Y. Liem and P.M.G. Filius contributed equally to this study and share first authorship.

of Health, Welfare and Sport. In 2000 SWAB's working group on the use of antimicrobial agents started to collect national data on antibiotic use in hospitals. These data are presented in NethMap, the annual report of the SWAB.[6]
In a recent editorial in this journal it was stated that physicians would not directly benefit from these national reports in their daily practice, but that these reports may help to increase their general awareness of the problem of antibiotic resistance.[8] Furthermore these reports may provide a knowledge base for policy decisions, guidelines and research strategies.
The aim of this study was therefore to analyse and report on antibiotic use in Dutch hospitals between 1997 and 2002.

MATERIALS AND METHODS

Population

All Dutch hospitals, 94 general hospitals and 8 university hospitals, were asked to participate in SWAB's national surveillance system. Specialised hospitals, such as psychiatric and orthopaedic hospitals, and rehabilitation centres were excluded. Data on the use of antibiotics in acute care Dutch hospitals between 1997 and 2002 were collected by means of a questionnaire distributed to all Dutch hospital pharmacies by SWAB. Data from inpatient wards as well as day care wards had to be included, whereas outpatient use and dispensing to nursing homes was excluded from the data report.

Antibiotic use

Pharmacies were requested to report on the annual consumption of antibiotics for systemic use, group J01 of the Anatomical Chemical Classification (ATC) system. The use of different (sub)classes of antibiotics was expressed as defined daily doses (DDD) per 100 patient-days and per 100 admissions.[9]
The ATC/DDD classification from the World Health Organisation (WHO), version 2002, was used to calculate the number of DDD of the various antibiotics. The DDD was defined as the assumed average maintenance dose per day for a drug used for its main indication in an adult.[10]

Hospital resource data

For each hospital the annual number of admissions and days spent in the hospital (bed-days) were 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. The mean length of stay was calculated by dividing the mean number of patient-days by the mean number of admissions.

Statistical analysis

Regarding the period 1997 to 2002 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. Drug utilisation was compared between hospitals and over time by a mixed model for repeated measurements. The response variables applied were the number of DDD per 100 patient-days and the number of DDD per 100 admissions. P values less than 5% were considered statistically significant. All statistical analyses were performed by SAS 8.2 (SAS Institute, N.C., USA).

RESULTS

Hospital resource indicators

Between 1997 and 2002 a decrease in the mean length of stay was found in both the total cohort of hospitals and the subgroups of university and general hospitals (*table 1*). The mean number of admissions remained almost constant. As the mean number of patient-days is calculated by multiplying the mean number of admissions by the mean length of stay, a decrease was also found in the mean number of patient-days.

Hospital use

The number of hospitals that issued data on antibiotic use varied from 49 (48%) in 1997 to 59 (58%) in 2002. The reasons given for not participating were other priorities (56%), not being able to generate data on antibiotic use (25%) or no interest (19%).
In 1997 total systemic use in hospitals was 47.2 DDD per 100 patient-days and significantly increased by 24% to 58.5 DDD per 100 patient-days in 2002 ($p<0.001$) (*table 2*). However, total systemic use expressed as DDD per 100 admissions remained almost constant at 385.9 in 1997 and 391.6 in 2002 ($p=0.866$) (*table 3*).
The mean number of total DDD per hospital did not change between 1997 and 2002 (67,176 and 66,714 DDD in 1997 and 2002, respectively).
Regarding trends in antibiotic use over the years, five main categories can be distinguished:

- For macrolides, lincosamides and fluoroquinolones we found a significant increase over the years for both units of measurement;
- For amphenicols and monobactams a significant decrease in both units of measurement was found;
- For tetracyclines, β-lactamase-resistant penicillins, carbapenems, trimethoprim and derivatives, intermediate-acting sulfonamides, aminoglycosides and imidazole derivatives, a constant use in both units of measurement was found;
- For total systemic use, combinations of penicillins including β-lactamase inhibitors, β-lactamase-sensitive

Table 1 *Resource indicators of Dutch hospitals, 1997 to 2002*

	Hospitals		Admissions			Patient-days			Length of stay		
	1997 (n)	2002 (n)	1997 (mean)	2002 (mean)	% change 1997-2002	1997 (mean)	2002 (mean)	% change 1997-2002	1997 (mean)	2002 (mean)	% change 1997-2002
All hospitals	49	59	17,405	17,038	-2.1	142,339	114,038	-19.9	8.2	6.7	-18.3
University hospitals	8	7	25,670	24,441	-4.8	226,264	191,374	-15.4	8.8	7.8	-11.4
General hospitals	41	52	15,793	16,041	+1.6	125,963	103,628	-17.7	8.0	6.5	-18.9

Table 2 *Antibiotic use in Dutch hospitals (DDD per 100 patient-days), 1997 to 2002*

ATC code	Antimicrobial group	Relevant example antibiotic(s)	DDD per 100 patient-days			Average change per year (%)	Trend 1997-2002 (p value)
			1997	2002	Absolute change 1997-2002		
J01AA	Tetracyclines	Doyxcycline	1.6	1.6	0.00	0.071	0.933
J01BA	Amphenicols	Chloramphenicol	0.017	0.0039	0.00	-62.1*	0.007
J01CA	Penicillins with extended spectrum	Amoxicillin	6.5	6.2	-0.34	-1.1	0.212
J01CE	β-lactamase-sensitive penicillins	Benzylpenicillin	1.2	1.2	0.082	1.4	0.004
J01CF	β-lactamase-resistant penicillins	Flucloxacillin	4.1	4.5	0.36	1.7	0.116
J01CR	Combinations of penicillins, incl. β-lactamase inhibitors	Amoxicillin with clavulanic acid, piperacillin with tazobactam	14.4	20.6	6.2	7.4	<0.001
J01DA	Cephalosporins and related substances	Cefazolin, cefuroxim, ceftazidim	5.1	6.3	1.1	4.0	<0.001
J01DF	Monobactams	Aztreonam	0.011	0.0021	-0.009	-27.7*	0.018
J01DH	Carbapenems	Imipenem, meropenem	0.43	0.46	0.034	1.6	0.246
J01EA	Trimethoprim and derivatives	Trimethoprim	0.46	0.48	0.021	0.90	0.353
J01EC	Intermediate-acting sulfonamides	Sulfadiazine	0.061	0.00013	-0.061	-70.8*	0.229
J01EE	Combinations of sulfonamides and trimethoprim	Sulfamethoxazole with trimethoprim	2.6	2.4	-0.22	-1.7	0.0715
J01FA	Macrolides	Clarithromycin	1.9	2.7	0.77	7.1	<0.001
J01FF	Lincosamides	Clindamycin	0.80	1.5	0.67	12.9	<0.001
J01GB	Aminoglycosides	Gentamycin, tobramycin	2.0	2.1	0.13	1.3	0.334
J01MA	Fluoroquinolones	Ciprofloxacin	4.0	5.7	1.7	7.3	<0.001
J01MB	Other quinolones	Pipemidic acid	0.030	0.077	0.046	20.4*	#
J01XA	Glycopeptides	Vancomycin	0.42	0.51	0.092	4.1	<0.001
J01XD	Imidazole derivatives	Metronidazole	1.2	1.4	0.26	4.1	0.622
J01XE	Nitrofuran derivatives	Nitrofurantoin	0.21	0.52	0.31	20.4*	#
J01	Antibiotics for systemic use (total)		47.2	58.5	11.3	4.4	<0.001

P<0.05 = statistically significant; #unable to calculate p value due to too small a number of observations; *due to the low absolute use of these compounds the average change per year bears little practical importance.

Table 3 *Antibiotic use in Dutch hospitals (DDD per 100 admissions), 1997 to 2002*

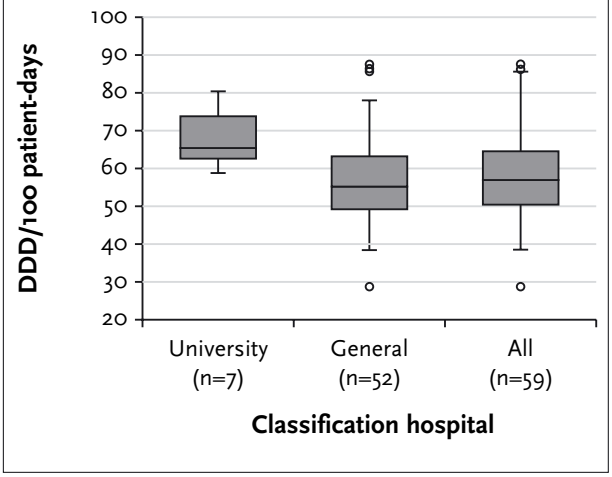
ATC code	Antimicrobial group	Relevant example antibiotic(s)	DDD per 100 admissions			Average change per year (%)	Trend 1997-2002 (p value)
			1997	2002	Absolute change 1997-2002		
J01AA	Tetracyclines	Doyxcycline	13.4	11.0	-2.4	-3.9	0.482
J01BA	Amphenicols	Chloramphenicol	0.14	0.03	-0.1	-28.1*	0.001
J01CA	Penicillins with extended spectrum	Amoxicillin	53.1	40.1	-13.0	-5.4	<0.001
J01CE	β-lactamase-sensitive penicillins	Benzylpenicillin	9.4	8.0	-1.4	-3.2	0.080
J01CF	β-lactamase-resistant penicillins	Flucloxacillin	33.6	28.9	-4.7	-2.9	0.265
J01CR	Combinations of penicillins, incl. β-lactamase inhibitors	Amoxicillin with clavulanic acid, piperacillin with tazobactam	117.6	135.5	17.9	2.9	0.159
J01DA	Cephalosporins and related substances	Cefazolin, cefuroxim, ceftazidim	41.9	41.8	-0.1	-0.05	0.415
J01DF	Monobactams	Aztreonam	0.09	0.01	-0.07	-30.5*	0.007
J01DH	Carbapenems	Imipenem, meropenem	3.5	3.1	-0.4	-2.4	0.754
J01EA	Trimethoprim and derivatives	Trimethoprim	3.7	3.2	-0.5	-3.1	0.902
J01EC	Intermediate-acting sulfonamides	Sulfadiazine	0.5	0.00087	-0.5	-71.9*	0.268
J01EE	Combinations of sulfonamides and trimethoprim	Sulfamethoxazole with trimethoprim	21.1	15.9	-5.3	-5.6	<0.001
J01FA	Macrolides	Clarithromycin	15.4	17.8	2.4	2.9	0.012
J01FF	Lincosamides	Clindamycin	6.6	9.8	3.3	8.5	<0.001
J01GB	Aminoglycosides	Tobramycin	16.0	13.9	-2.0	-2.7	0.458
J01MA	Fluoroquinolones	Ciprofloxacin	32.7	38.0	5.3	3.1	<0.001
J01MB	Other quinolones	Pipemidic acid	0.25	0.51	0.3	15.7*	#
J01XA	Glycopeptides	Vancomycin	3.4	3.4	0.0	-0.01	0.026
J01XD	Imidazole derivatives	Metronidazole	9.6	9.5	-0.01	-0.01	0.458
J01XE	Nitrofuran derivatives	Nitrofurantoin	1.7	3.5	1.8	15.7*	#
J01	Antibiotics for systemic use (total)		385.9	391.6	5.6	0.3	0.866

P<0.05 = statistically significant; #unable to calculate p value due to too small a number of observations; *due to the low absolute use of these compounds the average change per year bears little practical importance.

penicillins, cephalosporins and glycopeptides, a significant increase in DDD per 100 patient-days and a constant use in DDD per 100 admissions was observed;
- For penicillins with extended spectrum and combinations of sulfonamides and trimethoprim we found a constant use when expressed in DDD per 100 patient-days; a significant decrease in the number of DDD per 100 admissions was also found.

The proportion of all penicillins combined represented 55% of total systemic use in both 1997 and 2002. In an in-depth study of the individual antibiotics we found that the mean number of DDD per hospital of amoxicillin with clavulanic acid, clarithromycin, cefazolin, clindamycin and ciprofloxacin increased by 16, 38, 39, 50 and 52%, respectively.
In university hospitals, total systemic antibiotic use increased significantly by 16.5%, from 57.6 in 1997 to 67.1 DDD per 100 patient-days in 2002 (p=0.002), whereas in general hospitals total use increased significantly by 29.4%, from 43.6 in 1997 to 56.4 DDD per 100 patient-days in 2002 (p<0.001). However, total systemic antibiotic use expressed as DDD per 100 admissions in university hospitals remained almost constant at 507.4 in 1997 and 525.2 in 2002. In general hospitals no increase was found either when use was expressed as DDD per 100 admissions: 347.4 in 1997 and 364.2 in 2002. In university hospitals the mean number of DDD per hospital decreased by 1.5%, whereas in general hospitals an increase of 6.5% was observed.
Moreover, a large variation in quantitative antibiotic use was found between the participating hospitals, in particular in general hospitals (*figure 1*).

Figure 1 *Variance in total use of antibiotics for systemic use (J01) in Dutch hospitals, 2002: university vs general hospitals*



DISCUSSION

Our data showed a decrease in the mean length of stay during the study period and a more or less constant mean number of admissions. These trends in hospital resource indicators are consistent with the demographics of all the hospitals as registered by Statistics Netherlands (www.cbs.nl). In addition, we found that trends over time in DDD per 100 patient-days did not consistently correlate with trends in DDD per 100 admissions.
In the present study total antibiotic use significantly increased by 24%, from 47.2 in 1997 to 58.5 DDD per 100 patient-days in 2002. The total number of DDD and admissions remained almost constant between 1997 and 2002. However, length of stay decreased significantly during this period. This means that on average patients used the same number of DDD in a shorter period of time, which might be interpreted in different ways. Firstly, no changes in treatment policies occurred since most patients were already treated with antibiotics during the first days of hospitalisation. Due to intensification of general care, the length of stay decreased. Another explanation might be that antibiotic courses are completed at home with antibiotics supplied by the hospital.
Between 1991 and 1996 total antibiotic use in Dutch hospitals increased by 14% from 37.2 to 42.5 DDD per 100 patient-days in 1996.[7] This might also be the result of a decreasing length of stay over the years (12%) rather than an increase in DDD per admission. The first results of a European surveillance programme demonstrated that the Nordic countries and the Netherlands all show a low total antibiotic use compared with other European countries.[11]
In both university and general hospitals we found a constant use in DDD per 100 admissions and an increase in DDD per 100 patient-days as well. Total systemic antibiotic use was notably higher in university hospitals than in general hospitals. This might be explained by the admission of patients with more complex infections or undergoing complex surgery and transplantations requiring prophylaxis.
In the total cohort of hospitals the mean number of DDD per hospital of amoxicillin with clavulanic acid, clarithromycin, cefazolin, clindamycin and ciprofloxacin increased with 16, 38, 39, 50 and 52%, respectively. As the number of admissions remained almost constant over the years this means an increase in the consumption of these antibiotics per admission. The increase in the use of cefazolin, an agent that is only used for perioperative prophylaxis, may be explained by the publication of a national guideline on perioperative antibiotic prophylaxis in 2000. This guideline strongly recommends the use of cefazolin for surgical prophylaxis.[12] In our cohort of hospitals the percentage of hospitals using cefazolin increased from 37% in 1997 to 69% in 2002 (p=0.001). It is not

clear why the use of the other antibiotics is increasing. Audits on antibiotic prescribing practices at the individual patient level are needed to clarify the increasing use of these antibiotics.

We distinguished five categories concerning trends in antibiotic use over the years. With regard to resistance development it appears that an increase in both the number of DDD per 100 patient-days and the number of DDD per 100 admissions (category 1) is a cause for concern and that no significant change or a significant decrease in both units of measurement (category 2, 3 and 5) is not. The trend in category 4 is less easy to interpret. An increase in the number of DDD per 100 patient-days may be interpreted as an increase in the selection pressure towards resistance. However, this is arguable since the number of admissions and the total number of DDD has remained almost constant over the years. Moreover, an intensification of antibiotic therapy suggests a shortening of duration of antibiotic treatment. Short duration of therapy may lead to less selection of resistant microorganisms.[13,14]

In the present study some methodological problems were encountered. Firstly, one possible source of bias was the variety of methods used by the different Dutch hospital pharmacies to quantify their antibiotic use. The majority of hospitals delivered data based on hospital purchases, while only a few hospitals provided actual dispensing data. Ideally, actual administration data should be used as a source to measure antibiotic use in hospitals, with every dose actually administered to a patient recorded electronically.

Secondly, we aimed to provide census data, covering at least 90% of the acute care hospital population in the Netherlands. The overall response to the enquiry was, however, 58%. In contrast with Denmark, for example, the Dutch government does not make it compulsory for hospitals to deliver their data on the use of antibiotics.[15] Consequently aiming at 90% coverage will be unrealistic. Since the variance in antibiotic use is very large between the hospitals, a representative selection of hospitals is only possible when insight is obtained in the determinants of hospital antibiotic use.

Another possible source of bias may be that as a result of earlier discharge of the less ill patients, patient-days may increasingly originate from sicker patients who more often require antibiotic treatment. However, this is not likely, as the total number of DDD remained constant.

In this survey, data were collected by a questionnaire and processed manually, which is a relatively slow process. In the near future the SWAB wishes to start a national project in order to collect data on hospital drug use in a central data warehouse. This will facilitate the collection of data and the conversion to DDD per 100 patient-days. Data on the use of antibiotics at hospital level might be too crude for identifying subtle trends in antibiotic use of specific patient populations. Therefore, monitoring antibiotic use patterns by specific populations within the hospital (e.g. intensive care and general ward patients; surgical and nonsurgical patients) is warranted. In this way substantial changes can be demonstrated that would be overlooked if hospital-wide data are aggregated into national trends.

In conclusion, patients hospitalised in the Netherlands did not receive more antibiotics but, since they remained in the hospital for fewer days, the number of DDD per 100 patient-days increased. It is arguable whether this results in an increase in selection pressure towards resistance in the hospitals, since the total number of DDD remained almost constant over the years. For macrolides, lincosamides and fluoroquinolones increases in both DDD per 100 patient-days and DDD per 100 admissions were observed between 1997 and 2002. This might be a cause for concern since this trend is more likely to be associated with an increase in the selection pressure. Further research is needed to determine the relationship between antibiotic use, selection pressure and the emergence of resistance. To maintain efficacy and safety of antibiotic treatment, continuous surveillance of antibiotic use and resistance is necessary.

ACKNOWLEDGEMENT

We thank the pharmacists of the participating hospitals for providing data on antibiotic use. This study was supported with a structural grant from the Ministry of Health, Welfare and Sport to the SWAB, no. 366950.01.

REFERENCES

1. Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest 1999;115:462-74.
2. Cosgrove SE, Kaye KS, Eliopoulous GM, Carmeli Y. Health and economic outcomes of the emergence of third-generation cephalosporin resistance in Enterobacter species. Arch Intern Med 2002;162:185-90.
3. Gyssens IC. Quality measures of antimicrobial drug use. Int J Antimicrob Agents 2001;17:9-19.
4. SWEDRES 2004. A report on Swedish Antibiotic Utilisation and Resistance in Human Medicine. ISSN 1400-3473. Swedish Strategic Programme for the Rational Use of Antimicrobial Agents (STRAMA) and the Swedish Institute for Infectious Disease Control. Sweden, Solna, 2004.
5. DANMAP 2003. Use of Antimicrobial Agents and Occurence of Antimicrobial Resistance in Bacteria from Food Animals, Foods and Humans in Denmark. ISSN 1600-2032. Danish Vetrinary Institute. Denmark, Copenhagen, 2003.

6. SWAB. NethMap 2005 - Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands [On-line]. Cited 20 June 2005. http://www.swab.nl.
7. Janknegt R, Oude Lashof A, Gould IM, Van der Meer JWM. Antibiotic use in Dutch hospitals 1991-1996. J Antimicrob Chemother 2000;45:251-6.
8. Cars O. Annual reports of antibiotic use and resistance – for whom? Neth J Med 2004;62:405-6.
9. Filius PMG, Liem TBY, 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.
10. WHO Collaborating Centre for Drug Statistics Methodology. ATC index with DDDs 2002. WHO Collaborating Centre; Oslo, Norway. 2001.
11. Elseviers M, Ferech M, Vander Stichele R, editors. Consumption of antibiotics in hospital care in Europe: first results of the ESAC retrospective data collection [abstract]. 13th European Congress of Clinical Microbiology and Infectious Diseases; Glasgow, UK. 2003.
12. Kasteren MEE van, Gyssens IC, Kullberg BJ et al. Optimising antibiotics policy in the Netherlands. V. SWAB guidelines for perioperative prophylaxis. Ned Tijdschr Geneeskd 2000;144(43):2049-55.
13. Schrag SJ, Pena C, Fernandez J et al. Effect of short-course, high-dose amoxicillin therapy on resistant pneumococcal carriage: a randomized trial. JAMA 2001;286:49-56.
14. Meer JW van der, Natsch S. Completing a course of drug therapy is necessary to combat the infection, not to discourage emergence of resistance. Ned Tijdschr Geneeskd 2004;148(35):1720:2.
15. Müller-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.