NETHMAP 2006



Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands

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Colophon

This report is published under the acronym NethMap by the SWAB, the Dutch Foundation of the Working Party on Antibiotic Policy, in collaboration with the RIVM, the National Institute for Public Health and the Environment of the Netherlands. SWAB is fully supported by a structural grant from the Ministry of Health, Welfare and Sports of the Netherlands.The information presented in NethMap is based on data from ongoing surveillance systems on the use of antimicrobial agents in human medicine and on the prevalence of resistance to relevant antimicrobial agents among medically important bacteria isolated from patients in the community and from patients admitted to hospitals. The document was produced on behalf of the SWAB by the Publishing Department of the RIVM.
NethMap can be ordered from the SWAB secretariat, c/o Academic Medical Centre Afd. Inf.ziekten, Trop. Geneeskunde en AIDS, F4-217, Postbus 22660, 1100 DD AMSTERDAM the Netherlands, Tel. +31 20 566 60 99 Fax +31 20 697 22 86 . NethMap is also available from the website of the SWAB: www.swab.nl. The suggested citation is: SWAB. NethMap 2006 – Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in The Netherlands.

Editors
Prof dr H. A. Verbrugh, Erasmus UMC Rotterdam
Dr A.J. de Neeling, RIVM Bilthoven

The following persons were actively involved in writing parts of this report:
Dr P.M.G. Filius, Erasmus UMC Rotterdam
Prof dr J. Hoogkamp-Korstanje, AMC Maastricht
Drs A.D. Lindemans, Erasmus UMC Rotterdam
Dr E.E. Stobberingh, AMC Maastricht

Board-members of SWAB
Prof dr M. Bonten
Prof dr J.E. Degener
Dr I.C. Gyssens
Drs J.M.R. Hollander
Dr R. Janknegt
Dr B.J. Kullberg (treasurer)
Dr D.J. Mevius
Dr S. Natsch
Dr A.J. de Neeling
Dr J.M. Prins (secretary)
Dr E.E. Stobberingh
Prof dr H.A. Verbrugh (chairman)
Prof dr A.G. Vulto

Members of SWAB's working group on surveillance of antimicrobial resistance
Prof dr J.E. Degener
Prof dr J.A.A. Hoogkamp-Korstanje (chair)
Dr M. van de Laar
Dr M. Leverstein - van Hall
Dr D.J. Mevius
Dr A.J. de Neeling
Dr E.E. Stobberingh
Dr E.W. Tiemersma
Prof dr H.A. Verbrugh

Members of SWAB's working group on surveillance of antimicrobial use
Dr P.M.G. Filius (convener)
Drs A.D. Lindemans (coordinator)
Drs F. Baart
Drs A.J. Freitag- de Koster
Dr R. Janknegt
Drs T.B.Y. Liem
Dr P.D. van der Linden
Dr S. Natsch
Dr A.J. de Neeling
Prof dr A.G. Vulto

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Tabel 1 Centres contributing to the surveillance of antimicrobial resistance

			COM	IUP	PHISIS	Men	Gon
Groningen	Delfzijl	Delfzicht Hospital				0	
	Groningen	Academic Medical Centre				0	0
		Regional Laboratory for Public Health		0		0	0
	Stadskanaal	Refaja Hospital				0	
	Winschoten	St Lucas Hospital				0	
	't Zandt	General practice	0				
Friesland	Leeuwarden	Regional Laboratory for Public Health		0	0	0	0
Drente	Assen	General practice	0				
	Emmen	Scheper Hospital				0	
Overijssel	Deventer	Deventer Hospital					0
		Regional Laboratory for Public Health				0	
	Enschede	Regional Laboratory for Public Health		0	0	0	0
	Hardenberg	Regional Laboratory for Public Health				0	
	Zwolle	Isala Clinics					0
		Hanze laboratory				0	
		Regional Laboratory for Public Health		0			
Gelderland	Apeldoorn	Medical Laboraties ZCA			0	0	
	Arnhem	Regional Laboratory for Public Health			0	0	0
	Barneveld	General practice	0				
	Dieren	General practice	0				
	Doetinchem	Slingeland Hospital				0	
	Ede	Gelderse Vallei Hospital				0	
	Harderwijk	St Jansdal Hospital				0	
	Heerde	General practice	0				
	Nijmegen	University Medical Centre St Radboud		0		0	0
		Regional Laboratory for Public Health			0	0	
	Zelhem	General practice	0				
Utrecht	Amersfoort	Meander Medical Centre				0	0
		General practice	0				
	Bilthoven	National Institute for Public Health and the Environment			0		
	Nieuwegein	Sint Antonius Hospital		0	0	0	0
	Utrecht	Diakonessenhuis				0	
		General practice	0				
		Neth Institute for Health Services Research NIVEL	0				
		Overvecht Hospital				0	
		SALTRO					0
		University Medical Centre				0	0
	Zeist	Lorentz Hospital				0	
Noord Holland	Alkmaar	General practice	0				
		Medical Centre				0	0
	Amsterdam	Academic Medical Centre				0	0
		Academic Hospital VU				0	0
		General practice	0				
		Onze Lieve Vrouwe Gasthuis		0		0	0
		Regional Laboratory for Public Health					0
		Slotervaart Hospital				0	
		St Lucas Hospital				0	
	Baarn	Medical Centre Molendaal				0	
	Haarlem	General practice	0				
		Regional Laboratory for Public Health		0	0		
	Hilversum	Central Bacteriological Laboratory				0	
	Hoorn	Westfries Gasthuis				0	
	Huizen	General practice	0				
	Zaandam	De Heel Hospital				0	0
Zuid Holland	Capelle a/d IJssel	IJsselland Hospital				0	
	Delft	SSDZ laboratories				0	0
	's-Gravenhage	Bronovo Hospital		0		0	
		General practice	0				

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Tabel 1 Continued

			COM	IUP	PH ISIS	Men	Gon
Zuid-Holland		Leyenburg Hospital				0	0
		Regional Laboratory for Public Health				0	
		Rode Kruis / Juliana Children's Hospital				0	
		Westeinde Hospital				0	0
	Dordrecht	Regional Laboratory for Public Health				0	0
	Gorkum	Regional Laboratory for Public Health				0	
	Gouda	Groene Hart Hospital				0	
	Leiden	Diaconessenhuis		0		0	
		KML Laboratory				0	
		University Medical Centre					0
	Leiderdorp	St Elisabeth Hospital				0	
	Rotterdam	General practice	0				
		Erasmus University Medical Centre			0	0	0
		Ikazia Hospital					0
		MCRZ		0	0	0	
		Sophia Children's Hospital				0	
		St Franciscus Gasthuis				0	
	Schiedam	Schieland Hospital				0	
	Spijkenisse	Ruwaard van Putten Hospital			0	0	0
	Voorhout	General practice	0				
	Woerden	Hofpoort Hospital				0	
Noord Brabant	Bergen op Zoom	Lievensberg Hospital				0	
	Breda	Amphia Hospital					0
	's Hertogenbosch	Bosch Medical Centre			0		0
		Regional Laboratory for Public Health				0	
	Ravenstein	General practice	0				
	Roosendaal	St Franciscus Hospital				0	
	Rosmalen	General practice	0				
	Tilburg	Regional Laboratory for Public Health		0	0	0	0
	Uden	General practice	0				
	Veldhoven	Laboratory for Medical Microbiology				0	0
Limburg	Heerlen	Regional Laboratory for Public Health			0	0	0
	Kerkrade	St Jozef Hospital				0	
	Maastricht	General practice	0				
		Academic Medical Centre		0		0	0
	Roermond	St Laurentius Hospital			0	0	0
	Sittard	Maasland Hospital				0	
	Venlo	VieCuri Medisch Centrum voor Noord-Limburg		0		0	0
	Weert	St Jansgasthuis			0	0	0
Zeeland	Goes	Regional Laboratory for Public Health		0	0	0	0
	Middelburg	General practice	0				
	Terneuzen	General practice	0				
		Regional Laboratory for Public Health			0	0	0

(COM=Community, IUP=Intensive Cares/Urology Services/Pulmonology Services, PH ISIS=Public Health Laboratories/ISIS, Men=Meningitis Surveillance, Gon=Gonorrhoea Surveillance)

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Centers contributing to the surveillance of the use of antimicrobial agents

Community usage
Foundation for Pharmaceutical Statistics SFK, The Hague

Hospital usage
We hereby recognise the important contributions of hospital pharmacists of the following hospitals in collecting and providing quantitative data to SWAB on the use of antimicrobial agents in their respective institutions listed hereunder:

Alkmaar, Medisch Centrum Alkmaar; Almelo, Twenteborg Ziekenhuis; Amersfoort, Meander Medisch Centrum; Amstelveen, Ziekenhuis Amstelveen; Amsterdam, Academisch Medisch Centrum; Amsterdam, VU Medisch Centrum; Amsterdam, BovenIJ Ziekenhuis; Amsterdam, O.L. Vrouwe Gasthuis; Apeldoorn, Gelre ziekenhuizen; Arnhem, Rijnstate Ziekenhuis; Assen, Wilhelmina Ziekenhuis; Bergen op Zoom, Ziekenhuis Lievensberg; Blaricum, Ziekenhuis Gooi-Noord; Boxmeer, Maasziekenhuis; Breda, Amphia Ziekenhuis; Capelle aan den IJssel, IJsselland Ziekenhuis; Coevorden/Hardenberg, Streekziekenhuis; Delft, Reinier de Graaf Groep; Den Haag, Bronovo Ziekenhuis; Den Haag, Leyenburg Ziekenhuis, Den Haag, RKZ/JKZ; Den Helder, Gemini Ziekenhuis; Deventer, St. Deventer Ziekenhuizen; Doetichem, Slingeland Ziekenhuis; Dokkum, Streekziekenhuis; Dordrecht, Albert Schweitzer Ziekenhuis; Drachten, Ziekenhuis Nij Smellinghe; Ede, Ziekenhuis Gelderse Vallei; Eindhoven, Catharina Ziekenhuis; Eindhoven, Maxima Medisch Centrum; Enschede, Medisch Spectrum Twente; Geldrop, St. Anna Zorggroep; Goes, St. Oosterschelde Ziekenhuizen; Gorinchem, Rivas Zorggroep; Gouda, Groene Hart Ziekenhuis; Groningen, Groningen Universitair Medisch Centrum; Groningen, Delfzicht Ziekenhuis; Groningen, Martini Ziekenhuis; Groningen, Refaja Ziekenhuis; Haarlem, Kennemer Gasthuis; Haarlem, Spaarne Ziekenhuis; Harderwijk, Ziekenhuis St. Jansdal; Heerlen, Atrium Medisch Centrum; Hengelo, Ziekenhuisgroep Twente; 's Hertogenbosch, Jeroen Bosch Ziekenhuis; Hilversum, Ziekenhuis Hilversum; Hoorn, Westfries Gasthuis; Leeuwarden, Medisch Centrum Leeuwarden; Leiden, Diaconessenhuis; Leiden, Leids Universitair Medisch Centrum; Leiderdorp, Rijnland Ziekenhuis; Leidschendam, Medisch Centrum Haaglanden; Maastricht, Academisch Ziekenhuis Maastricht; Nieuwegein St. Antonius Ziekenhuis; Nijmegen, Canisius Wilhelmina Ziekenhuis; Nijmegen, Universitair Medisch Centrum St. Radboud; Oss, Ziekenhuis Bernhoven; Purmerend, Waterlandziekenhuis; Roermond, Laurentius ziekenhuis; Rotterdam, Erasmus MC; Rotterdam, Ikazia Ziekenhuis; Rotterdam, Medisch Centrum Rijnmond-Zuid; Rotterdam, Sint Franciscus Gasthuis; Sittard, Maaslandziekenhuis; Sneek, Antonius Ziekenhuis; Spijkenisse, Ruwaard van Putten ziekenhuis; Terneuzen, Ziekenhuis Zeeuws-Vlaanderen; Tiel, Ziekenhuis Rivierenland; Tilburg, Elisabeth Ziekenhuis; Tilburg, Tweesteden Ziekenhuis; Utrecht, Diaconessenhuis Utrecht; Utrecht, Mesos Medisch Centrum; Utrecht, Universitair Medisch Centrum Utrecht; Veghel, Ziekenhuis Bernhoven; Veldhoven, Maxima Medisch Centrum; Venlo, VieCuri Medisch Centrum voor Noord-Limburg; Venray, Stichting ZALV; Vlaardingen, Vlietland Ziekenhuis; Vlissingen, Ziekenhuis Walcheren; Weert, St. Jans Gasthuis; Winschoten, Sint Lucas Ziekenhuis; Woerden, Hofpoort Ziekenhuis; Zaandam, Zaans Medisch Centrum; Zeist, Diakonessenhuis Zeist; Zevenaar, Streekziekenhuis; Zoetermeer, 't Lange Land Ziekenhuis; Zutphen, Het Spittaal; Zwolle, Isala Klinieken.

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Preface

On behalf of the Dutch Working Party on Antibiotic Policy we are happy to present the fourth surveillance report, called NethMap 2006, on antimicrobial use and resistance in human medicine in the Netherlands. The Dutch Working Party on Antibiotic Policy was founded in 1996 by three societies of professionals highly involved in the management of infectious diseases in the Netherlands. Thus, the Netherlands Society for Infectious Diseases, the Netherlands Society for Medical Microbiology and the Netherlands Society of Hospital Pharmacists pooled their resources in this Working Party, locally known by its acronym: the SWAB (Stichting Werkgroep Antibiotica Beleid). 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 importance of the SWAB initiative taken by these professsional bodies was immediately clear to the health authorities of the Netherlands and resulted in the decision of the Ministry of Health, Welfare and Sports in 1997 to structurally support the SWAB's activities financially. This recognition and support of SWAB's work by the government continues to this day. SWAB has focused its activities on several major goals, one of which is the development of an integrated surveillancesystem regarding the use of antimicrobial agents and the prevalence of antimicrobial resistance among medically important species of microorganisms. These initiatives corresponded well with the recommendations from the Dutch Council on Health Research (2001) and the European Union (2001). Therefore the Ministry of Health, Welfare and Sports formally invited SWAB in May 2002 to develop such a surveillance system in close collaboration with the Centre for Infectious Disease Control, recently founded in the National Institute of Public Health and the Environment (RIVM).

NethMap 2006 extends and updates the information in the previous three reports. We have added one more years to the trend lines, more species of microbes are monitored and several special analyses have been added that contribute to our insight in the usage data presented and on the combined occurrence of resistance in some species.
Importantly, three surveillance reports called MARAN 2002-2004 have been published regarding the use of antimicrobial agents and the development of antimicrobial resistance in animal husbandry (see www.cidc-lelystad.nl) by the Veterinary Antibiotic Usage and Resistance Surveillance Working Group. The MARAN 2005 report will appear in October 2006.
Taken together the current and future NethMap- and MARAN-reports aim to constitute a comprehensive monitor of the consumption of antimicrobial agents and the prevalence of antimicrobial resistance in the Dutch medical and veterinary arena, respectively. The interaction between these two areas of antibiotic use and resistance is explored in a working group started in 2003 by the ministry of Health, Welfare and Sports and that of Agriculture, Nature and Food Quality. Both SWAB and its veterinary sister group are represented in this working group which discusses the evolution of antibiotic use and resistance in the Netherlands on the basis of our surveillance data.
We hope and trust that NethMap continues to contribute to our knowledge and awareness regarding the use of antibiotics and the resistance problems that may arise from it. We thank all who have contributed to the surveillance efforts of SWAB sofar, and express our hope that they will continue to do so.

The editors:

Prof dr Henri A. Verbrugh dr Han de Neeling

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1 Summary

NethMap 2006 is the fourth annual report of the SWAB containing information regarding the use of antimicrobial agents and the prevalence of resistance to these agents among common human pathogens isolated in the Netherlands. Trends in antibiotic use and resistance are presented in the form of serial annual data collected systematically from 1993 up to 2005.

The overall use of antimicrobial agents in primary health care has remained very stable over the past years at levels just below 10 defined daily dosages (DDD) per 1000 inhabitants per day. However, the consumption level in 2005 rose to 10.5 DDD/1000/day, an increase that was mainly associated with increased use of antibiotics for respiratory infection in the winter months. It remains to be seen whether this signals a change in disease patterns or whether prescribing habits are changing. Also, subtle shifts in the patterns of use of the various classes of antibiotics can be observed. Thus, the use of beta-lactamase sensitive penicillin and of extended spectrum penicillin, primarily amoxicillin, has been declining for some years now, a trend that seems to be counterbalanced by increases in the use of the combination of amoxicillin with clavulanic acid, co-amoxiclav, and in the use of agents belonging to the macrolide class. The use of the fluoroquinolones in primary health care has remained stable, although within this class of agents substitutions seem to occur. Increased use of ciprofloxacin is offset by decreased use of ofloxacin and norfloxacin. These trends may well be relevant in the face of growing rates of resistance against macrolide and fluorquinolone antibiotics among common human pathogens. With regards to urinary tract infection it is interesting to note that nitrofurantoin is now used more often, possibly due to the emergence of resistance to trimethoprim among strains of *Escherichia coli* causing urinary infections.

NethMap 2006 for the first time presents antibiotic consumption data broken down to the level of health care regions. These variations in relative antibiotic consumption are not readily explained. Regions where co-amoxiclav was used most showed relatively low use of amoxicillin, suggesting that substitution has taken place. Also, in a region with lowest use of trimethoprim we observed the highest use of fluoroquinolones, suggesting that again substitution of agents for a similar indication has taken place in this, but not in other regions of the Netherlands. It is currently unknown what determinants are involved, that may explain these regional differences in antibiotic use.

In a separate analysis (Project 1) antibiotic use patterns in primary health care are presented for 31 European countries participating in the European surveillance programme ESAC. The SWAB provided the Dutch data for this project. Clearly significant differences exist in the quantity and quality of antibiotic consumption across Europe, the Netherlands being the country with lowest consumption. For some classes of antibiotics, e.g. the macrolides, penicillins and fluoroquinolones, there is a clear correlation between usage and resistance patterns among common human pathogens across Europe.

In the preceding NethMap report 2005 it was argued that DDD/100 patient-days may not suffice as the sole indicator of antibiotic use in hospitals. It was shown that this indicator is sensitive to changes in the hospital resource data which are used to calculate the denominator, i.e. the number of patients days. NethMap 2005 and NethMap 2006, therefore, present a second indicator of antibiotic use in hospitals, i.e. the number of DDD/100 admissions. Whereas the number of DDD of antibiotics/100 patient-days steadily increased from 43 in 2000 to 54 in 2004, the number of DDD of antibiotics/100 admissions remained relatively constant over this same period of time and was 8% lower in 2004 compared to 2003. The difference in trends between the two indicators could be ascribed to changes in hospital resource data, in this case to the steady decline in the mean length of stay per admission (down from 8.6 days in 2000 to 6.7 days in 2004). Thus, patients hospitalised in the Netherlands on average did not receive more antibiotics but, since they remained in the hospital for fewer days, the number of DDD/100 patient-days increased. Such an increase in DDD/100 patient-days may not necessarily represent an increase in the selection pressure exerted by antibiotic use, i.e. increase the risk of emergence of antibiotic resistance. Although it can be argued that increases in DDD/100 patient days translate in increases in the density of antibiotic use in hospitals, this argument will only hold if the number of beds available and the bed occupancy rate remained stable, and this has not been the case. However, for several classes of antimicrobial agents increases in both DDD/100 patient-days and in DDD/100 admissions were observed, trends that are probably associated with increases in the selection pressure toward antibiotic resistance in hospitals. Such trends were observed for beta-lactamase-resistant penicillins, for co-amoxiclav, the carbapenems, the lincosamides and for nitrofurantoin. The opposite, i.e. trends toward less DDD/100 patient-days and less DDD/100 admissions, was observed for tetracyclines, extended spectrum penicillin (amoxicillin) and for the combination of sulfonamides with trimethoprim.
Although these trends were rather mild and our analysis

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do not show abrupt changes in antibiotic use patterns, subtle shifts may over the years accumulate to represent a significant change in usage and, therefore, have a major impact on the selection pressures present in the hospital setting.
Penicillins are the class of antibiotics most often used in hospitals, they account for almost half of all use. Usage of this class of antibiotics has been increasing over the years relative to that of other classes of antibiotics. Especially the use of broad spectrum combinations, primarily co-amoxiclav, has increased. Within classes of agents shifts are also observed. Thus, ciprofloxacin use has clearly increased at the expense of other fluoroquinolones, as has gentamicin at the expense of other aminoglycosides and vancomycin at the expense of teicoplanin.

The surveillance of antimicrobial resistance continued to include strains of *E. coli* isolated from patients presenting with urinary infection to their primary care physician in general practice, as well as strains of Gram-positive and Gram-negative species isolated in hospital settings. In general practice the resistance of *E. coli* to amoxicillin was higher in 2003/2004 than in previous years (>30% versus approximately 20 %). In addition, the trend toward higher rates of resistance to trimethoprim observed since 1997 continued so that in 2003/2004 23% of all isolates were resistant to this first line agent. Although there were regional differences trimethoprim resistance increased in all. Since trimethoprim was advocated as fist line agent for uncomplicated urinary tract infection in general practice this observation was taken into account when recently the Dutch College of General Practicioners updated their practice guidelines for urinary infection this setting. Combination of trimethoprim with sulphonamide was not an alternative since resistance rates to this combinations run only 2% lower than for trimethoprim alone. However, *E. coli* resistance to nitrofurantoin, another first line agent, remains low as does its resistance toward co-amoxiclav. Both agents are now advocated as first line treatments, nitrofuranoin in adults with uncomplicated urnary tract infection and co-amoxiclav instead of amoxicillin for paediatric patients with (complicated) urinary tract infections. In contrast, resistance toward norfloxacin, often used as second tier agent for urinary infection, has been creeping up to a 3-4% level indicating that use of fluoroquinolones in general practice, even when stable over many years, may ultimately lead to resistance emergence among *E. coli*. Alternatively, resistant *E. coli* may be emerging in hospital settings where the density of fluoroquinolone use is much higher, and subsequently exported from hospitals to the community.

For the first time NethMap presents data on antimicrobial susceptibility of a collection of 446 strains of *Staphylococcus aureus* cultured from 1381 nasal swabs of patients presenting to their primary care physician for non-infectious reasons. Interestingly, resistance to commonly use antistaphylococcal antibiotics remains low, although 4 (1%) strains were methicillin resistant. Since patients visiting their general practitioners are not representative of the population, the true MRSA carriage rate among the Dutch population is probably lower.

In hospitals, the surveillance system covers *Escherichia coli, Klebsiella pneumoniae,Proteus mirabilis, Pseudomonas aeruginosa, Staphylococcus species, Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Helicobacter pylori* and, newly included for the first time, *Enterococcus faecalis* and *Neisseria gonorrhoeae*. In addition, resistance data is presented for *Mycobacterium tuberculosis* and for *Neisseria meningitidis*. The overall impression is that of rather stable rates of resistance for most antibiotics among these pathogens. However, certain trends need to be addressed carefully.

First, the rates of resistance to fluoroquinolones is clearly increasing among clinical isolates of *E. coli, P. aeruginosa, Neisseria gonorrhoeae* and *S. aureus*. In Urology services >10% of *E. coli and S. aureus* are now fluoroquinolone resistant, and in other hospital departments resistance to these agents has reached the 5-10% range. Importantly, fluoroquinolone resistant *E. coli* were observed in <5% of the isolates in the period up to the year 2000. Urology services are also observing vancomycin resistant *E.faecalis* since 2003. Likewise, Intensive Care Units are settings from which resistant micro-organisms, including ciprofloxacin and ceftazidime resistant *E. coli* and *Klebsiella pneumoniae* and ciprofloxacin resistant *S. aureus* routinely emerge. NethMap clearly shows resistance rates to be generally higher among pathogens isolated in such settings. It is good to note that the Working Party on Infection Prevention (WIP) has recently produced guidelines to contain multiple drug resistant organisms in such hospital settings (www.wip.nl) . Another worrisome trend is the steadily increasing rate of resistance to macrolides among clinical isolates of *S. aureus and S. pneumoniae*, both are now approaching the 10% threshhold above which their empiric use may become less reliable and, therefore, limited. However, the first line peniciilin agents for these two important species of Gram-positive pathogens remain effective. Among clinical *S. aureus* isolates the proportion of methicillin resistance was 1-2% in 2003/2004, 2.5 % in 2005, and only 2-3% of *S. pneumoniae* isolates had reduced susceptibility to penicillin. Although still low, these rates may be creeping up and continued vigilance in controlling resistant staphylococci and pneumococci is clearly warranted. These SWAB surveillance data corroborate the

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resistance trends found across Europe as monitored by the European Antimicrobial Resistance Surveillance System (EARSS; www.earss.rivm.nl). This European perspective clearly shows that the worrisome resistance trends noted in the Netherlands can deteriorate further. Thus, fluoroquinolone resistance among invasive strains of *E. coli* reached >20% in nine countries participating in EASS in 2004; likewise amoxicillin resistance rates >50% were reported from 13 countries. In addition, the rates of macrolide resistance and penicillin non-susceptibility among *S. pneumoniae* are much higher in many European countries indicating that the rates we have observed in the Nethelands so far may well increase further.

NethMap 2005 included for the first time data on antibiotic resistance among *Helicobacter pylori* and *Neisseria menigitidis*. The data generally showed stable rates of resistance for *H. pylori* for 1995 until 2004, and this remained so in 2005. For *N. meningitidis* rates of reduced susceptibility to penicillin were approximately 1% in the period 1993-2001. In 2002 and 2003 rates were higher (up to 3%) but it could not be ascertained whether this was the beginning of a trend. The 2004 data showed a 4% level of reduced susceptibility but in 2005 resistance was back at the 1% level arguing against an emerging trend in this case.
In contrast to *N. menigitidis*, the resistance patterns of *N. gonorrhoeae* have worsened considerably over the past years, especially by the emergence of ciprofloxacin resistant strains. This latter phenomenon has prompted the reinstatement of a national resistance surveillance system for this species as well an adjustment of the treatment guidelines for sexually transmitted diseases.
Finally, resistance to antimicrobial agents among isolates of *Mycobacterium tuberculosis* showed them to be susceptible to all four agents tested in >85% of the cases. Resistance to INH was stable at 8-9% and multiple resistance was observed in 2-3% of the strains tested. Resistance to all four agents was rare but occurred in almost 1% of the isolates in 2005. Again, trends of *M. tuberculosis* resistance need to be followed closely to discern the emergence of (multiple) resistance at an early stage.
In conclusion, NethMap aims to present information regarding the use of and resistance to antibiotics in the Netherlands in a manner that is useful for benchmarking and for detecting and following important trends.

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2 Samenvatting

NethMap 2006 is het vierde surveillance jaarrapport van de SWAB en geeft informatie over het gebruik van antibiotica en het voorkomen van antibiotica resistentie in de meest voorkomende, voor de mens pathogene, bacteriesoorten in Nederland.
Op basis van systematisch verzamelde en bewerkte gegevens over het jaarlijkse gebruik aan antibiotica en het voorkomen van antibiotica resistenties kunnen trends worden beschreven.

Over de jaren heen is het gebruik aan antibiotica in de Nederlandse eerstelijns gezondheidszorg zeer stabiel. Het gebruik is tot 2005 steeds onder de 10 DDD per 100 inwoners per dag gebleven. Het gebruik in 2005 was echter 10,51 DDD/1000 inwoners/dag, een toename die vooral veroorzaakt werd door meer gebruik van antibiotica in het winterseizoen. Het valt nog te bezien of hier sprake is van een afwijkend ziektepatroon of dat er sprake is van wijzigingen in het voorschrijfgedrag van huisartsen. Ten opzichte van andere Europese landen blijft Nederland het laagte record houden.
Daarnaast zijn enkele trends waarneembaar. Zo neemt het gebruik van beta-lactamase gevoelige penicilline and van breed spectrum penicilline al enkele jaren langzaam af, terwijl het gebruik van de combinatie amoxicilline met clavulaanzuur (co-amoxiclav) en van antibiotica uit de macroliden groep toeneemt. Het gebruik van fluorochinolones in de eerstelijns gezondeidszorg lijkt stabiel, maar binnen deze groep middelen zijn wel substituties waarneembaar. Er wordt meer ciprofloxacine gebruikt en minder ofloxacine en norfloxacine. Deze trends zijn relevant gezien de toename aan resistentie tegen fluorochinolonen en tegen macrolide antibiotica. Zo lijkt de toename in resistentie tegen trimethoprim onder *E. coli* die urineweginfectie veroorzaken, ervoor te zorgen dat er meer nitrofurantoine wordt voorgeschreven en minder trimethoprim.

In dit rapport wordt voor de eerste keer onderscheid gemaakt in het antibioticagebruik per gezondheidsregio. Indien bepaalde klassen van antibiotica worden geanalyseerd blijken er opmerkelijke verschillen te bestaan tussen regio's. Zo lijken de regio's die relatief veel breedspectrum co-amoxiclav gebruiken relatief weining amoxicilline te gebruiken, hetgeen op substitutie duidt. In een ander geval blijkt er in een regio opmerkelijk veel fluorochinolonen te worden gebruikt terwijl het gebruik aan trimethoprim in dezelfde regio juist uitzonderlijk laag is. Dat zou kunnen betekenen dat in die regio, maar niet in de overige regio's, er substitutie is opgetreden van antibiotica voor hetzelfde indicatiegebied. Ook deze bevindingen geven aanleiding nader onderzoek te doen naar de determinanten van deze regionale verschillen in antibioticum gebruik en bijvoorbeeld na te gaan of er verbanden zijn met het voorkomen van daarbij passende antibioticaresistenties.

In een aparte analyse (Project 1) worden de Nederlandse gebruiksgegevens vergeleken met die van 30 andere landen in Europa in het kader van een Europees surveillance project (ESAC). De SWAB participeerde namens Nederland in ESAC en leverde de gebruiksgegevens aan. Het is duidelijk dat in kwantitieve en kwalitatieve zin er grote verschillen bestaan tussen de diverse Europese landen in het gebruik van antibiotica. Nederland blijft het land waar in de eerste lijnsgezondheidszorg het antibiotiumgebruik het laagst is. Uit het ESAC project komen ook duidelijke aanwijzingen dat er een verband bestaat tussen gebruik en het resistentie probleem van de landen. Hoe meer gebruik van bijvoorbeeld macroliden, penicillines en fluorochinolonen, hoe meer resistentie er tegen deze middelen gevonden wordt onder veel voorkomende pathogene micro-organismen.

In het voorgaand NethMap rapport 2005 werd aannemelijk gemaakt dat het antibioticumgebruik in het ziekenhuis niet alleen weergegeven kan worden door de maat DDD/100 patiënten dagen (ligdagen). Aangetoond werd dat die indicator gevoelig was voor vertekening op grond van verschuivingen in de kengetallen van de ziekenhuiszorg in Nederland, met name voor veranderingen in de gemiddelde opname duur. Deze kengetallen beïnvloeden de grootte van het noemergetal (aantal ligdagen) zeer. In NethMap 2005 werd daarom een extra maat geïntroduceerd, namelijk het aantal DDD/100 opnamen.
Zo is het antibioticumgebruik uitgedrukt in DDD/100 ligdagen gestegen van 43 in 2000 tot 54 in 2004 terwijl het aantal DDD/100 opnamen in dezelfde periode niet is gestegen en in 2004 zelfs 8% lager was dan in voorgaande jaren. Het verschil in deze twee trendlijnen is geheel te verklaren door een afname in de gemiddelde duur per opname; deze was 8,6 dagen in 2000 en 6,7 dagen in 2004. Per opname, d.w.z. per patiënt, werden dus niet meer antibiotica voorgeschreven, maar omdat de patiënt gemiddeld steeds korter in het ziekenhuis verblijft neemt het aantal DDD/100 ligdagen wel toe. Meer DDD/100 ligdagen houdt derhalve niet perse in dat de selectiedruk van antibiotica in de ziekenhuizen is toegenomen. Men zou kunnen stellen dat wél sprake is van toegenomen selectiedruk, immers er worden meer antibiotica per ligdag gebruikt, maar op ziekenhuisniveau neemt daarmee de selectiedruk alleen toe als het aantal bedden en de bedbezetting constant zou zijn gebleven. Dat is echter niet het geval, er zijn tegenwoordig

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minder bedden beschikbaar in ziekenhuizen en de bedbezetting is afgenomen. Voor een aantal groepen antibiotica is zowel het aantal DDD/100 ligdagen als het aantal DDD/100 opnamen gestegen. Voor deze middelen is wel sprake van een toegenomen selectiedruk. Het betreft de beta-lactamase resistente penicillines, co-amoxiclav, de carbapenems, de lincosamiden en nitrofurantoïne. Een tegenstelde trend, minder DDD/100 ligdagen én minder DDD/100 opnamen, werd gevonden voor de tetracyclines, de breedspectrum penicillines (amoxicilline), en voor de combinatie van trimethoprim met een sulfonamide. Hoewel er geen sprake is geweest van een abrupte stijging of daling in het gebruik van de verschillende groepen antibiotica, kunnen minder uitgesproken veranderingen in het gebruik op den duur wel degelijk een belangrijke wijziging in de selectiedruk van antibiotica in de ziekenhuizen opleveren.
Penicillines zijn de klasse antibiotica die het meest worden gebruik in Nederlandse ziekenhuizen, ze beslaan bijna de helft van alle DDD's. Het gebruik van deze groep antibiotica is ten opzichte van andere antibiotica klassen over de jaren heen gestegen, met name het gebruik van het breedspectrum co-amoxiclav. Ook binnen andere groepen antimicrobiële middelen vinden verschuivingen plaats. Zo wordt er meer ciprofloxacine gebruikt ten koste van minder gebruik aan andere fluorochinolonen, en wordt gentamicine steeds vaker verkozen boven andere aminoglycosiden, en vancomycine boven teicoplanine.

De surveillance van antibioticaresistentie in de eerstelijns gezondheidszorg richt zich op *E. coli* geïsoleerd uit de urine van patiënten met een urineweginfectie en in 2005 op *S. aureus* neusdragers. Voor de ziekenhuizen werden zowel Gram-negative soorten en Gram-positieve soorten in de resistentie surveillance betrokken. Het resistentie percentage van *E. coli* voor amoxicilline in de huisartsenpraktijk was in 2003/2004 hoger dan in de voorgaande jaren (>30% versus ongeveer 20%). Daarbij komt dat de al eerder waargenomen trend naar hogere niveaus van resistentie tegen trimethoprim zich heeft doorgezet en nu een niveau van 23% heeft bereikt. Er zijn weliswaar regionale verschillen in dit resistentiepercentage maar in alle regio's van Nederland is onder *E. coli* de resistentie tegen trimethoprim gestegen. Omdat trimethoprim middel van eerste keuze is bij de behandeling van ongecompliceerde urineweg infectie heeft het Nederlands Huisartsen Genootschap haar richtlijn urineweginfectie recent aangepast. Het gebruik van co-trimoxazol levert geen soelaas omdat bij *E. coli* resistentie tegen co-trimoxazol maar 2% lager is dan de resistentie tegen trimethoprim. De resistentie percentages tegen nitrofurantoïne en co-amoxiclav zijn echter laag gebleven zodat deze twee middelen nu worden opgevoerd als middelen van eerste keuze bij de behandeling van urineweginfecties in de huisartsenpraktijk. Daarentegen lijkt het percentage resistentie tegen norfloxacine langzaam op te lopen (tot 3-4%). Dat kan het gevolg zijn van het langdurige gebruik van dit fluorochinolon in de huisartsenpraktijken, of er is sprake van resistentie ontwikkeling bij *E coli* in de ziekenhuizen en export van dergelijke stammen naar de eerstelijns gezondheidszorg.

Voor de eerste keer presenteert NethMap 2005 resistentiegegevens van 1381 *S. aureus* stammen die geïsoleerd zijn uit neuswatten van patiënten uit huisartsenpraktijken. De patiënten waren op het moment van bemonstering niet geïnfecteerd. Het meest opvallend is de bevinding dat 4 van de 446 (1%) van de onderzochte stammen meticilline resistent was. Omdat patiënten die een huisarts bezoeken niet representatief zijn voor de bevolking als geheel, zal het percentage personen dat in Nederland MRSA in de neus draagt waarschijnlijk beduidend lager zijn.

In de Nederlandse ziekenhuizen is het algemene resistentiebeeld redelijk stabiel. Toch zijn er belangrijke trends waar te nemen. Op de eerste plaats stijgen de resistentie percentages voor de fluorochinolonen onder klinische isolaten van *E. coli, Pseudomonas aeruginosa, Neisseria gonorrhoeae* en *Staphylococcus aureus*. In de afdelingen Urologie zijn >10 % van de *E. coli* en *S. aureus* isolaten bijvoorbeeld ciprofloxacine resistent, en in de overige delen van de ziekenhuizen vindt men resistentieniveaus van 5-10%. Dit is belangrijk anders dan in de periode voor de eeuwwisseling, toen het resistentiepeil voor fluorochinolonen onder deze soorten nog lager dan 5 % was. Op dezelfde afdelingen Urologie worden sinds 2003 ook vancomycineresistente *Enterococcus faecalis* stammen geïsoleerd.
Op afdelingen Intensive Care worden in toenemende mate ciprofloxacine resistente en ceftazidime resistente *E. coli* en *Klebsiella pneumoniae* stammen geïsoleerd als ook *S. aureus* stammen die ciprofloxacine resistent zijn. De resistentiepercentages op deze afdelingen liggen duidelijk hoger dan die voor de algemene afdelingen van ziekenhuizen. Recent heeft de Werkgroep Infectie Preventie een richtlijn uitgebracht over het voorkomen van verspreiding van dergelijke (multi)resistente stammen (zie www.wip.nl).
Een andere zorgwekkende trend is de toenemende resistentie tegen de macrolide antibiotica onder klinische isolaten van *S. aureus* en *Streptococcus pneumoniae*. In beide gevallen bereiken ze bijna het niveau van 10% waarboven de bruikbaarheid van deze middelen voor de empirische behandeling van infecties beduidend minder wordt. Daartegenover staat dat het resistentieniveau tegen de middelen van eerste keuze bij de behandeling van infectieziekten met deze Gram-positive bacteriën nog steeds laag is. Zo is het percentage meticilline resistentie onder *S. aureus* 2,1 % van de klinische

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isolaten in 2005. Voor *S. pneumoniae* geldt dat slechts 2-3% verminderd gevoelig was voor penicilline. Hoewel deze resistentie percentages als laag beschouwd moeten worden, zijn zij niet eerder op dit niveau geweest en kan er dus sprake zijn van een beginnende trend naar hogere niveaus. Voortdurende waakzaamheid en controle van resistente isolaten van *S. aureus* en *S. pneumoniae* blijft aangewezen.

De surveillance gegevens van NethMap sluiten goed aan bij de surveillance gegevens van het Europese surveillance project EARSS (European Antimicrobial Resistance Surveilance System, zie www.earss.rivm.nl). EARSS laat zien dat de zorgelijke trends die wij in Nederland waarnemen zich gemakkelijk verder kunnen ontwikkelen naar nog hogere resistentieniveaus. Zo zijn in 2004 de resistentiepercentages tegen fluorochinolonen onder invasieve *E. coli* isolaten tot >20% gestegen in negen andere Europese landen, en 13 landen rapporteerde >50% resistentie tegen amoxicilline. Onder *S. pneumoniae* isolaten zijn de resistentiepercentages tegen macroliden en penicilline in veel Europese landen ook veel hoger dan in Nederland. Zonder tegenmaatregelen kunnen de Nederlandse resistentiepercentages dus gemakkelijk verder oplopen.

NethMap 2005 presenteerde voor het eerst gegevens over de resistentie niveaus bij *Helicobacter pylori* en bij *Neisseria meningitidis*. De gegevens voor *H. pylori* lieten een stabiel beeld zien voor de periode 1995-2004, en dat beeld is in 2005 niet veranderd. Voor *N. meningitidis* was het percentage stammen met een verminderde gevoeligheid voor penicilline ongeveer 1%; ook dit resistentie peil is nagenoeg stabiel in de periode 1993-2001. In 2002 en 2003 werden hogere percentages waargenomen (tot 3%), maar het was niet duidelijk of er sprake is van een beginnende trend naar hogere resistentie niveaus. In 2004 was het percentage nog hoger (4%), maar in 2005 zakte het terug naar het oude niveau van 1%. Het is derhalve niet duidelijk of er sprake is van een trend.
In tegenstelling tot *N. meningitidis* zijn de resistentiepatronen van *N. gonorrhoeae* isolaten in Nederland duidelijk verslechterd. Het belangrijkste fenomeen is het opduiken van steeds meer ciprofloxacine resistente stammen, hetgeen aanleiding is geweest de behandelingsrichtlijnen voor seksueel overdraagbare aandoeningen bij te stellen. Tenslotte worden voor de derde keer resistentiegegevens van *Mycobacterium tuberculosis* gepresenteerd. Van alle geteste isolaten blijkt > 85 % goed gevoelig te zijn voor de vier geteste tuberculostatica. Ook dit percentage is stabiel. INH resistentie wordt gevonden bij 8-9% van de isolaten, en 3-5% van de isolaten is resistent voor twee of meer van de vier middelen. Resistentie tegen alle vier middelen wordt slecht incidenteel waargenomen, hoewel in 2005 bijna 1% van de stammen uniform resistent was.
Een reden om de surveillance van resistentie bij *M. tuberculosis* te handhaven.

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3 Use of antibiotics

This part of the report considers the use of antimicrobial agents in human medicine only. Data on the use of such agents in animal husbandry and veterinary medicine are reported elsewhere.[1]
Human consumption is presented in two parts. One part describes the prescription and use of antibiotics in the community, also termed "Primary Health Care". The second part presents surveillance data on the use of antibiotics in the acute care hospitals in the Netherlands. In the Appendix (Section "surveillance methods and susceptibility testing") details regarding the structural acquisition and analysis of the antibiotic consumption data are presented.
Project 1 describes data from the European Surveillance of Antibiotic Consumption (ESAC) project in which the SWAB participated.

Primary health care

Between 2001 and 2005 the overall use of antibiotics for systemic use in primary health care increased slightly to 10.5 DDD/1000 inhabitant-days (table 1).
The distribution of antibiotics by class in 2005 is presented in figure 1. Tetracyclines (mainly doxycycline) represented 24% of total use in primary health care. Other frequently used antibiotics were penicillins with extended spectrum (mainly amoxicillin), combinations of penicillins with beta-lactamase inhibitors (essentially amoxicillin with clavulanic acid) and macrolides, each representing 18%, 14% and 14% of the total use respectively.
These proportions are very similar to previous years, although some trends might be noticed when the relative use of the different antibiotic classes is followed from 1997 to 2005 (table 2). In 1997, combinations of penicillins with beta-lactamase inhibitors represented 9% of total antibiotic use, whereas in 2005 this proportion was 14%. Similarly the proportion of macrolides increased and the relative use of tetracyclines and penicillins with extended spectrum decreased.

The use of amoxicillin decreased from 2.18 in 1997 to 1.69 DDD/1000 inhabitant-days (-22.5 %) in 2004. In 2005 the use was 1.86 DDD/1000 inhabitant-days. The use of co-amoxiclav increased from 0.92 in 1997 to 1.5 DDD/1000 inhabitant-days in 2005 (figure 2).

The use of macrolides is presented in figure 3. Clarithromycin was the most commonly used macrolide. Its use increased from 0.66 to 0.9 DDD/1000 inhabitant-days in 2005. The use of azithromycin increased as well. The use of erythromycin remained almost constant over the last three years.

Table 1. Use of antibiotics for systemic use (J01) in primary health care (DDD/1000 inhabitant-days), 2001 - 2005 (Source: SFK).

ATC group[a]	Therapeutic group	2001	2002	2003	2004	2005
J01AA	Tetracyclines	2.39	2.33	2.23	2.22	2.41
J01CA	Penicillins with extended spectrum	1.82	1.78	1.77	1.69	1.86
J01CE	Beta-lactamase sensitive penicillins	0.49	0.45	0.44	0.42	0.44
J01CF	Beta-lactamase resistant penicillins	0.25	0.25	0.27	0.28	0.29
J01CR	Penicillins + beta-lactamase-inhibitors	1.25	1.34	1.39	1.38	1.50
J01D	Cephalosporins and related substances	0.07	0.07	0.06	0.05	0.05
J01EA	Trimethoprim and derivatives	0.28	0.27	0.27	0.26	0.25
J01EC	Intermediate-acting sulfonamides	0.00	0.01	0.00	0.00	0.00
J01EE	Sulfonamides + trimethoprim	0.42	0.40	0.39	0.39	0.38
J01FA	Macrolides	1.22	1.24	1.27	1.31	1.42
J01FF	Lincosamides	0.05	0.06	0.06	0.07	0.08
J01GB	Aminoglycosides	0.01	0.01	0.02	0.02	0.02
J01MA	Fluoroquinolones	0.80	0.78	0.78	0.82	0.84
J01MB	Other quinolones	0.04	0.03	0.03	0.02	0.02
J01XB	Polymyxins	0.02	0.02	0.02	0.02	0.02
J01XE	Nitrofuran derivatives (nitrofurantoin)	0.71	0.74	0.78	0.80	0.90
J01XX05	Methenamine	0.06	0.04	0.03	0.02	0.02
J01	Antibiotics for systemic use (total)	9.90	9.81	9.81	9.77	10.51

[a] from the 2006 edition of the Anatomical Therapeutic Chemical (ATC) classification system

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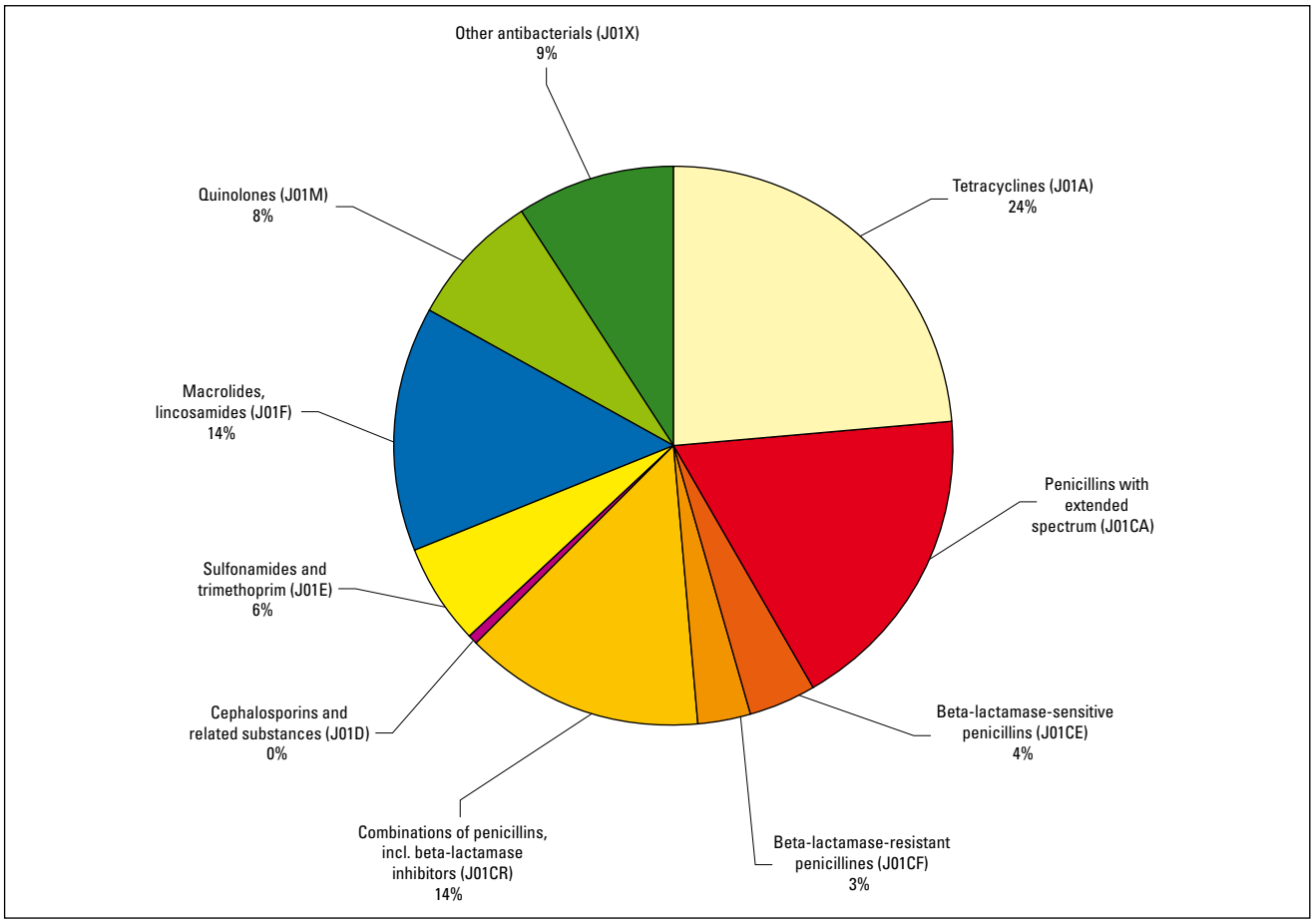


Figure 1. Distribution of the use of antibiotics for systemic use (J01, DDD/1000 inhabitant-days) in primary health care, 2005 (Source: SFK).

Total use of the fluoroquinolones did not change between 1997 and 2005 (table 1). However, between 1997 and 2005, the use of ciprofloxacin almost doubled (figure 4).

Since 2002, ciprofloxacin was the fluoroquinolone used most commonly.
The use of norfloxacin and ofloxacin decreased during

Figure 2. Use of amoxicillin and co-amoxiclav in primary health care, 1997 - 2005 (Source: SFK).

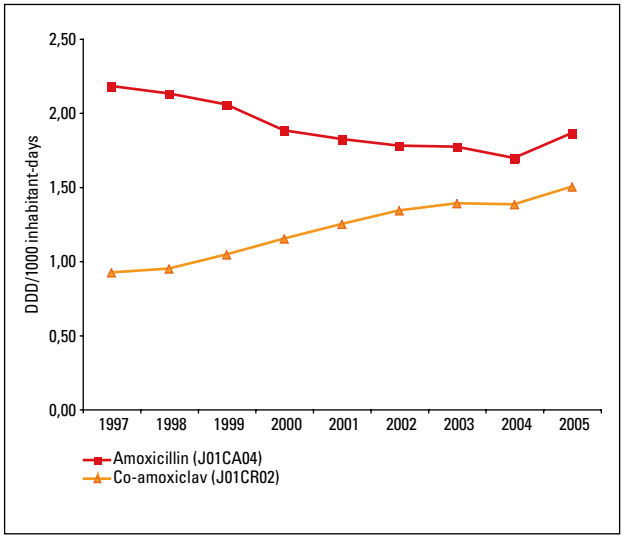
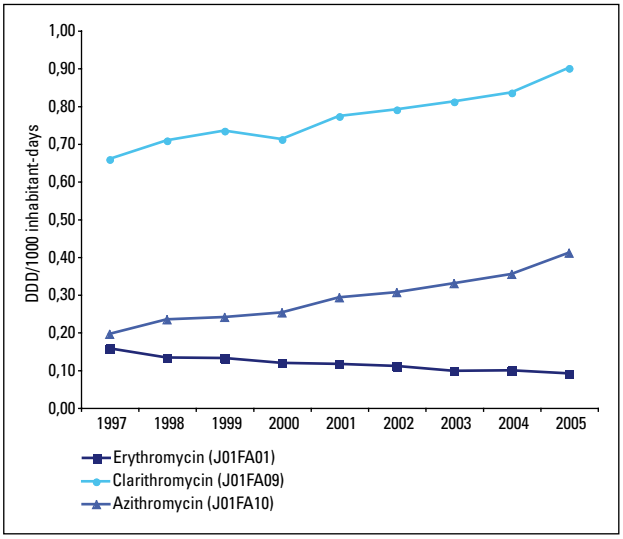


Figure 3. Use of macrolides for systemic use in primary health care, 1997-2005 (Source: SFK).



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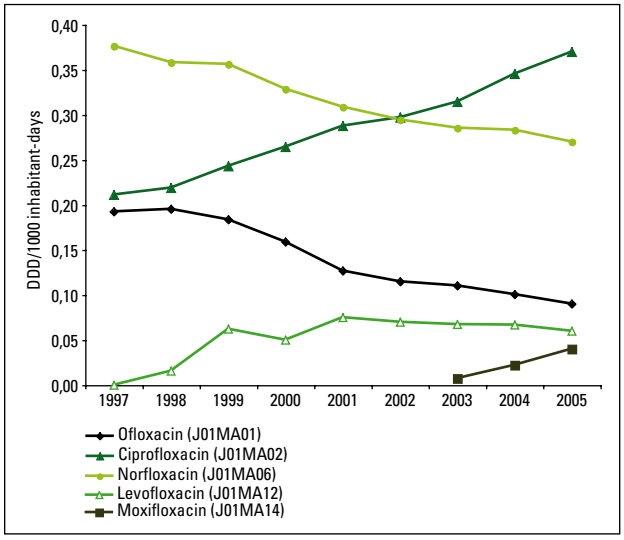


Figure 4. Use of fluoroquinolones for systemic use in primary health care.

these years. The newer fluoroquinolone moxifloxacin has apparently been introduced into primary health care since 2003 and its use has been increasing since.

The use of nitrofurantoin increased from 0.59 in 1997 to 0.90 DDD/1000 inhabitant-days in 2005 whereas the use of trimethoprim remained constant.

Regional differences were observed in relative antibiotic use (figure 5-7). The highest relative use of co-amoxiclav was observed in the regions Zaanstreek-Waterland, Waardenland and Kennemerland, whereas in Stedendriehoek and Noord-Oost-Brabant the use was relatively low (figure 5). In most regions with a relatively high co-amoxiclav use, the use of amoxicillin was relatively low. Vice versa, in regions with a relatively high use of amoxicillin, the use of co-amoxiclav was often lower.
The use of fluoroquinolones did not vary to a large extent (figure 6) apart from the high use in 't Gooi and Nieuwe Waterweg Noord.
Tetracyclines were more often used in the Northern, the Eastern and the Southern regions of the Netherlands, whereas the macrolides were used to a smaller extent in these regions. Conversely, macrolides were more often used in the West and Centre whereas the tetracyclines were less often used in these regions.
In the North of the Netherlands trimethoprim was used more often compared to the other regions (figure 7).
In these northern regions the use of nitrofurantoin was lower. A remarkably low use of nitrofurantoin was observed in 't Gooi, may be complementary to the higher use of fluoroquinolones in that region. In the region Noord Holland Noord trimethoprim had a remarkably high use.
The relative use of trimethoprim with sulfamethoxazole was highest in the region Noord Holland Noord and Midden-Holland.

Discussion

In 2005, total antibiotic consumption was 10.5 DDD/1000 inhabitant-days. It had increased compared to all previous years of surveillance. The increase of total use was due to increased use of tetracyclines, penicillins with extended spectrum, penicillins with beta-lactamase inhibitors and macrolides in the months Februari to April. Most likely there is a relation between this periodically increased use of antibiotics used for respiratory tract infections and an observed epidemic of influenza-like illnesses during these winter months (www.nivel.nl). However the use of antibiotics in primary health care in the Netherlands is still lower than in any other European country (see project 1).
In table 2 we analysed the relative use of the different

Table 2. Distribution of the use of antibiotics for systemic use (J01, % of total DDD/1000 inhabitant-days) in primary health care, 1997 - 2005 (Source: SFK).

ATC group[a]	Therapeutic group	1997	1999	2001	2003	2005
J01A	Tetracyclines	26	25	23	22	24
J01CA	Penicillins with extended spectrum	22	21	19	18	18
J01CE	Beta-lactamase sensitive penicillins	6	5	5	4	4
J01CF	Beta-lactamase resistant penicillins	2	2	3	3	3
J01CR	Penicillins + beta-lactamase-inhibitors	9	10	13	14	14
J01D	Cephalosporins and related substances	1	1	1	1	0
J01E	Sulfonamides and trimethoprim	8	5	7	7	6
J01F	Macrolides and lincosamides	11	12	13	14	14
J01M	Quinolones	8	9	9	8	8
J01X	Other antibacterials	7	10	7	9	9

[a] from the 2006 edition of the Anatomical Therapeutic Chemical (ATC) classification system

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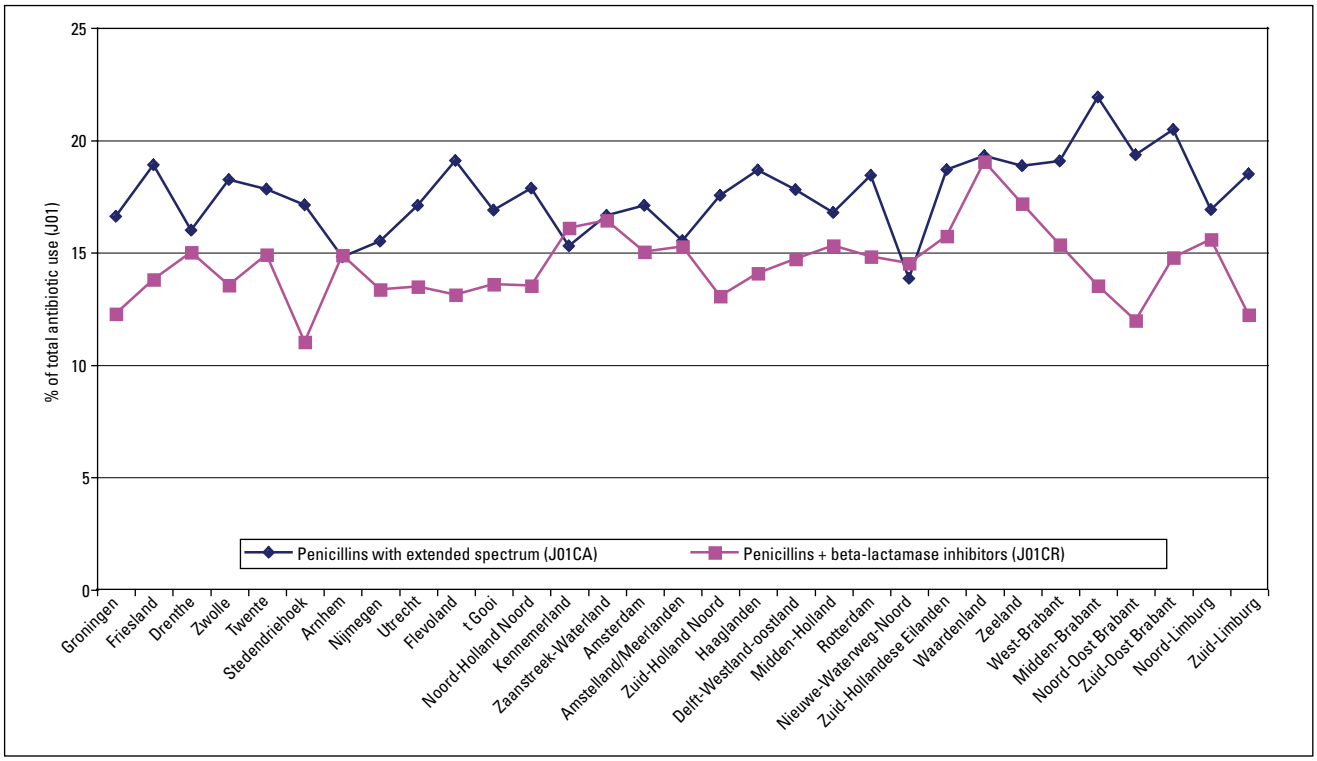
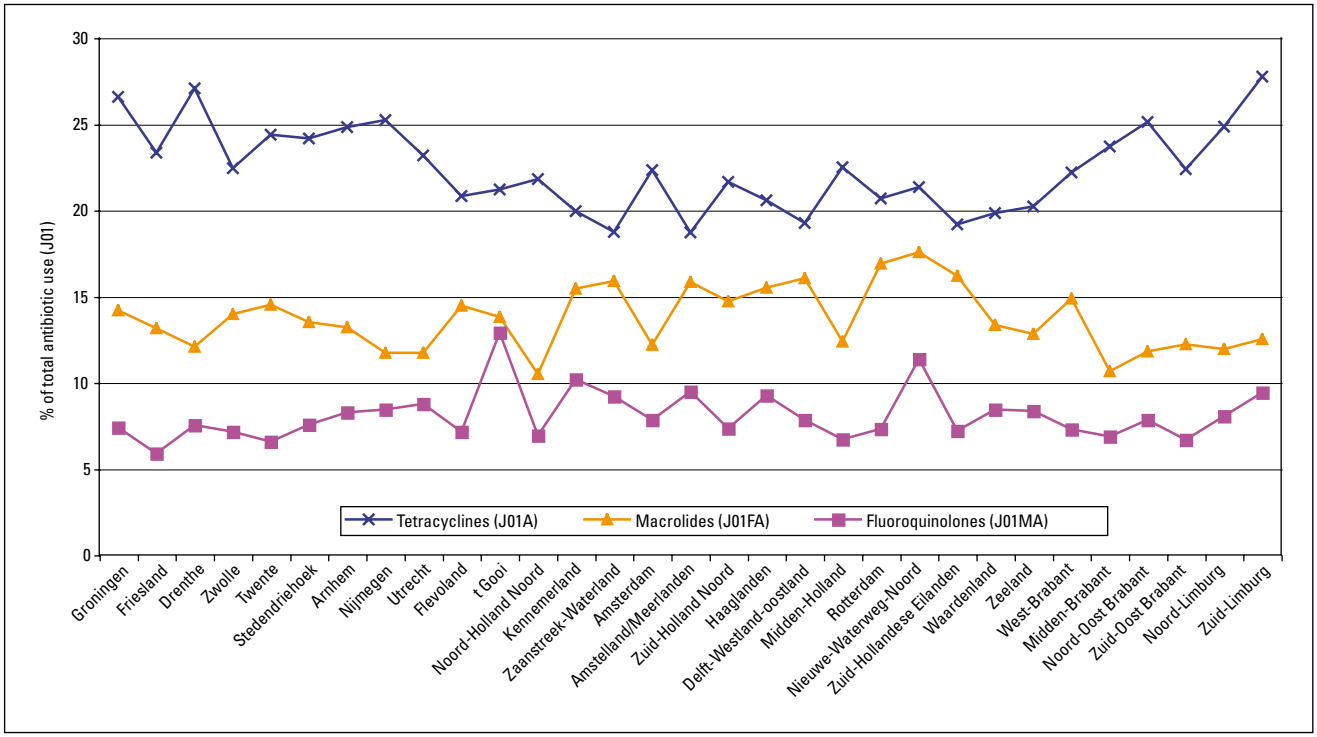


Figure 5. Regional variation in relative use of amoxicillin and of co-amoxiclav in primary health care, 2005 (source SFK).

subclasses over the years. The proportion of penicillins with beta-lactamase inhibitors and macrolides increased and the relative use of tetracyclines and penicillins with extended spectrum decreased. The proportion of use attributed to fluoroquinolones remained almost constant. The use of ciprofloxacin increased whereas the use of

Figure 6. Regional variation in relative use of tetracyclines, macrolides and fluoroquinolones in primary health care, 2005 (Source: SFK).



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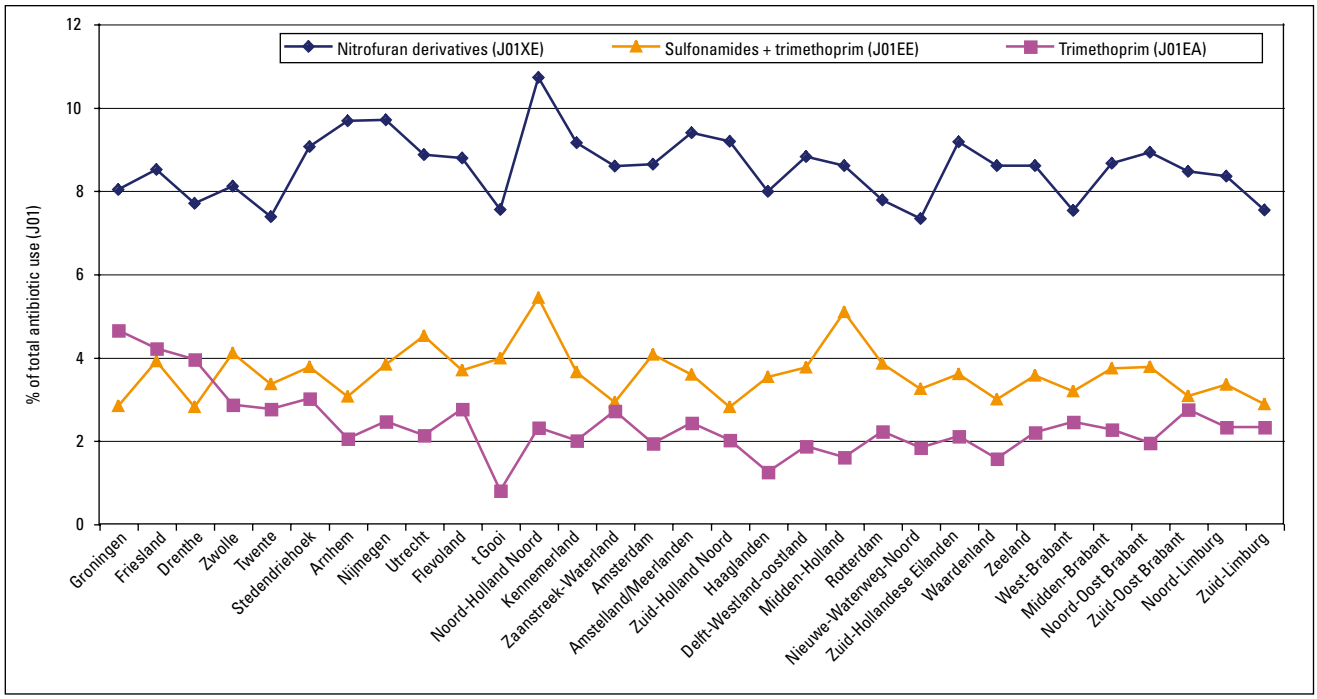


Figure 7. Regional variation in relative use of nitrofuran derivatives, sulfonamides and trimethoprim, and trimethoprim.

norfloxacin and ofloxacin decreased (figure 4). These changes in antibiotic use suggest a change in treatment regimens for respiratory and urinary tract infections over the last decade.
In collaboration with the Foundation for Pharmaceutical Statistics we developed a method to study regional antibiotic use in the Netherlands. In Belgium and Switzerland large differences in antibiotic consumption exist between different geographic parts of those countries. In these first analyses of regional differences by the SWAB, we also observed differences in prescription habits between the different regions of the Netherlands. These differences may be due to different local guidelines or prescription habits.

References

[1] MARAN-2004 – Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in The Netherlands in 2004.

Hospitals

Hospital resource indicators

Between 2000 and 2004 the mean number of admissions per hospital increased from 14849 to 19181 (+ 29%) in our cohort of hospitals. The mean number of bed-days per hospital , however, remained constant at 127816 in 2000 and 128557 in 2004 (+ 0.6%). The average length of stay in these hospitals thus decreased by 22% from 8.6 to 6.7 days.

These trends in hospital resource indicators are more or less consistent with the demographics of all acute care hospitals as registered by Statistics Netherlands (see appendix).

Hospital use

Data on antibiotic use are expressed in DDD per 100 patient-days as well as in DDD per 100 admissions, because trends over time in both units of measurement do not always correlate (tables 3 and 4). The total systemic use of the hospitals in our cohort in 2000 was 43.0 DDD per 100 patient-days, and increased by 25% to 53.8 DDD per 100 patient-days in 2004. In contrast, the total number of DDD/100 admissions slightly decreased from 327.1 to 306.8 DDD per 100 admisssions (- 6%). Differences in trends between the two units of measurement are the result of changes in resource indicators over time. In our cohort more patients (+ 29%) used antibiotics, while the use per patient slightly decreases (- 6%). This indicates that the mean number of total DDD's per hospital still increased. In 2000 the total number of DDD's/hospital was 48565, this increased by 21% to 58841 DDD/hospital in 2004. Since the mean number of patient-days per hospital only slightly decreased (- 3%), the mean number of DDD/100 patient-days has increased 25%.

Four main categories with regard to trends in antibiotic use over the years can be distinguished (tables 3 and 4).

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Table 3. Use of antibiotics for systemic use (J01) in hospitals (DDD/100 patient-days), 2000-2004 (Source: SWAB).

ATC group[a]	Therapeutic group	2000	2001	2002	2003	2004
J01AA	Tetracyclines	1.6	1.6	1.7	1.4	1.5
J01CA	Penicillins with extended spectrum	5.8	6.0	6.1	6.0	6.0
J01CE	Beta-lactamase sensitive penicillins	1.1	1.3	1.2	1.2	1.4
J01CF	Beta-lactamase resistant penicillins	4.3	4.3	4.4	5.4	5.7
J01CR	Combinations of penicillins, incl. beta-lactamase-inhibitors	8.9	9.9	12.2	12.1	12.8
J01DB -DE	Cephalosporins	5.6	6.1	6.3	6.5	7.0
J01DF	Monobactams	0.0	0.0	0.0	0.0	0.0
J01DH	Carbapenems	0.4	0.4	0.5	0.5	0.5
J01EA	Trimethoprim and derivatives	0.3	0.5	0.5	0.5	0.4
J01EC	Intermediate-acting sulfonamides	0.1	0.0	0.0	0.1	0.1
J01EE	Combinations of sulfonamides and trimethoprim, including derivatives	2.3	2.3	2.4	2.3	2.1
J01FA	Macrolides	2.1	2.3	2.7	2.4	2.3
J01FF	Lincosamides	1.2	1.3	1.5	1.6	1.8
J01GB	Aminoglycosides	2.1	2.0	2.1	2.5	2.2
J01MA	Fluoroquinolones	4.7	5.5	5.7	6.4	6.5
J01MB	Other quinolones	0.1	0.1	0.1	0.1	0.1
J01XA	Glycopeptides	0.5	0.5	0.5	0.5	0.6
J01XB	Polymyxins	0.3	0.1	0.1	0.1	0.1
J01XC	Steroid antibacterials (fusidic acid)	0.0	0.0	0.0	0.0	0.0
J01XD	Imidazole derivatives	1.1	1.3	1.5	1.6	1.7
J01XE	Nitrofuran derivatives	0.5	0.5	0.5	0.7	0.9
J01XX05	Methenamine	0.0	0.0	0.0	0.0	0.0
J01XX08	Linezolid	0.0	0.0	0.0	0.0	0.0
J01	Antibiotics for systemic use (total)	43.0	46.5	50.2	51.9	53.8

[a] from the 2006 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Table 4. Use of antibiotics for systemic use (J01) in hospitals (DDD/100 admissions), 2000-2004 (Source: SWAB).

ATC-group[a]	Therapeutic group	2000	2001	2002	2003	2004
J01AA	Tetracyclines	12.1	11.3	11.2	8.8	8.4
J01CA	Penicillins with extended spectrum	44.3	41.5	41.2	38.6	34.3
J01CE	Beta-lactamase sensitive penicillins	8.1	9.2	8.2	7.8	7.8
J01CF	Beta-lactamase resistant penicillins	32.8	31.7	31.5	34.6	33.0
J01CR	Combinations of penicillins, incl. beta-lactamase-inhibitors	68.1	68.0	81.6	77.7	73.1
J01DB-DE	Cephalosporins	42.8	42.3	42.0	42.0	39.4
J01DF	Monobactams	0.1	0.1	0.0	0.0	0.0
J01DH	Carbapenems	3.3	2.4	3.2	3.3	2.8
J01EA	Trimethoprim and derivatives	2.5	3.6	3.3	3.1	2.3
J01EC	Intermediate-acting sulfonamides	0.5	0.1	0.2	0.8	0.3
J01EE	Combinations of sulfonamides and trimethoprim, including derivatives	17.3	15.6	16.0	14.4	12.1
J01FA	Macrolides	15.4	15.7	17.9	15.4	13.4
J01FF	Lincosamides	9.0	9.2	10.0	10.2	10.2
J01GB	Aminoglycosides	16.2	14.0	14.2	15.8	12.5
J01MA	Fluoroquinolones	35.9	38.0	38.2	41.0	37.2
J01MB	Other quinolones	0.4	0.5	0.5	0.6	0.8
J01XA	Glycopeptides	3.8	3.2	3.4	3.4	3.5
J01XB	Polymyxins	2.3	0.8	0.4	0.5	0.6
J01XC	Steroid antibacterials (fusidic acid)	0.1	0.2	0.1	0.2	0.1
J01XD	Imidazole derivatives	8.5	9.0	9.7	10.1	9.6
J01XE	Nitrofuran derivatives	2.8	3.3	3.6	4.7	4.9
J01XX05	Methenamine	0.3	0.1	0.1	0.2	0.4
J01XX08	Linezolid	0.0	0.0	0.1	0.1	0.1
J01	Antibiotics for systemic use (total)	327.1	320.2	336.6	333.2	306.8

[a] from the 2006 edition of the Anatomical Therapeutic Chemical (ATC) classification system

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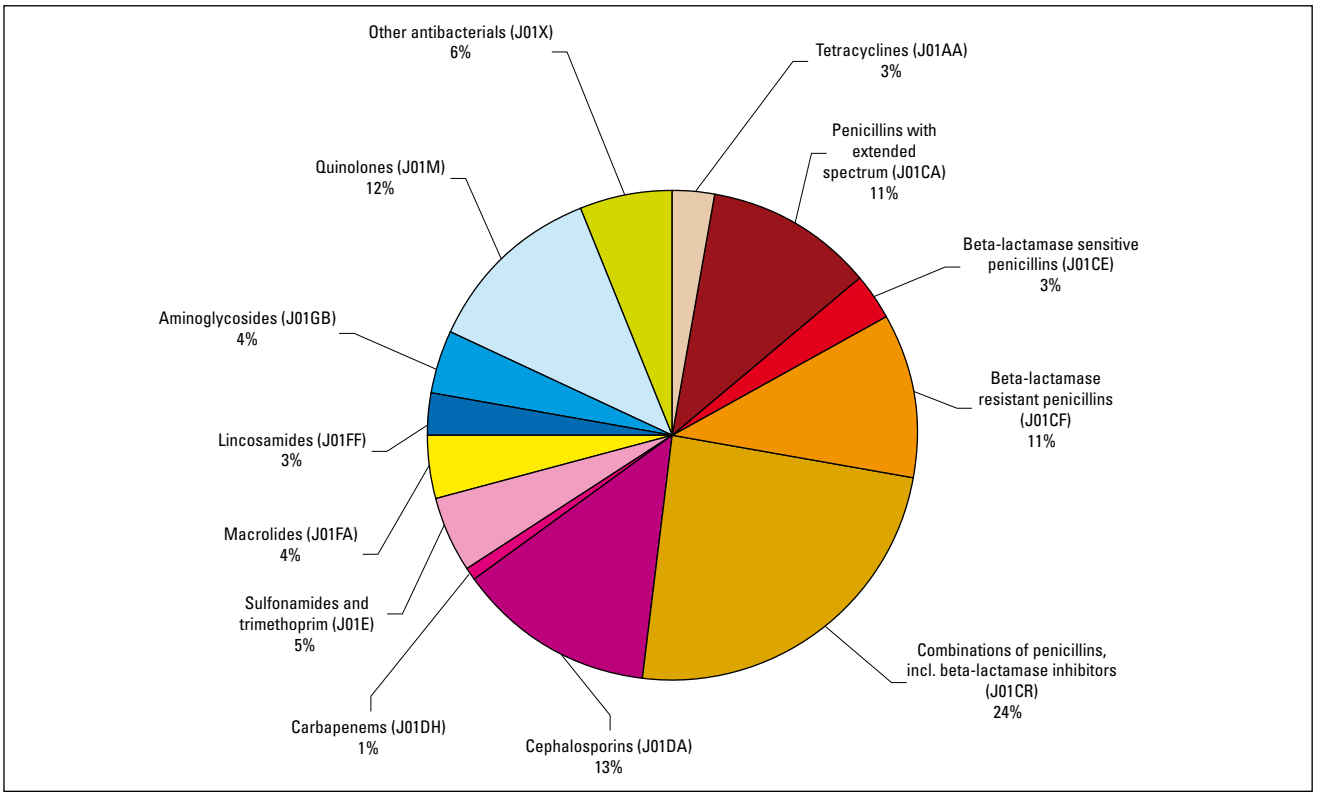


Figure 8. Distribution of the use of antibiotics for systemic use (J01, % of total DDD/100 patient-days) in hospitals, 2004 (Source: SWAB).

1. For lincosamides and nitrofuran derivatives we found an increase in DDD per 100 patient-days as well as DDD per 100 admissions. The average patient used more of these antibiotics than before, even though they were admitted to the hospital for a shorter period of time. Therefore, a truly significant increase in antibiotic use per patient-day is observed.

2. Beta-lactamase resistant penicillins, combinations of penicillins, cephalosporins and fluoroquinolones showed an increase in DDD per 100 patient-days, but the DDD per 100 admissions remained constant. This results in an apparent intensification in antibiotic use per patient-day, because patients used on average the same amount of these antibiotics during average shorter periods of stay in the hospital.

3. For tetracyclines, penicillins with extended spectrum and the combinations of sulfonamides and trimethoprim a decrease in DDD per 100 admissions is seen, while the DDD per 100 patient-days is constant. This means that on average patients used less antibiotics during their (shorter period) stay in the hospital.

4. For the remaining groups of antibiotics no significant changes in both units of measurement were observed.

Figure 9 depicts the distribution of antibiotics per class in 2004. All penicillins combined represent 49% of hospital antibiotic use in the Netherlands. The largest proportion consists of the combination of penicillins (25%), including beta-lactamase inhibitors, mainly co-amoxiclav.

Over the years, we detected a small shift in the relative use of antibiotics (figure 10). First, the relative use of penicillins has increased over the years, with the exception of the subgroup of penicillins with extended spectrum. The relative use of quinolones, and of lincosamines has also increased slightly since 1999. The relative use of penicillins with extended spectrum, tetracyclines, sulphonamides and trimethoprim, macrolides and aminoglycosides has declined since 1999.

The increase in the use of penicillins is mainly due to co-amoxiclav and flucloxacillin. The extended spectrum penicillins (amoxicillin and ampicillin) decreased over the years (figures 10A and B).

Of the cephalosporins, which represented a relatively constant 13% of the total of in-hospital antibiotic use (figures 8 and 9), the second-generation cephalosporins are used the most (figure 11A and B). Of these second-generation cephalosporins, cefuroxime is the most commonly used, with a constant use of 17,3 DDD/100

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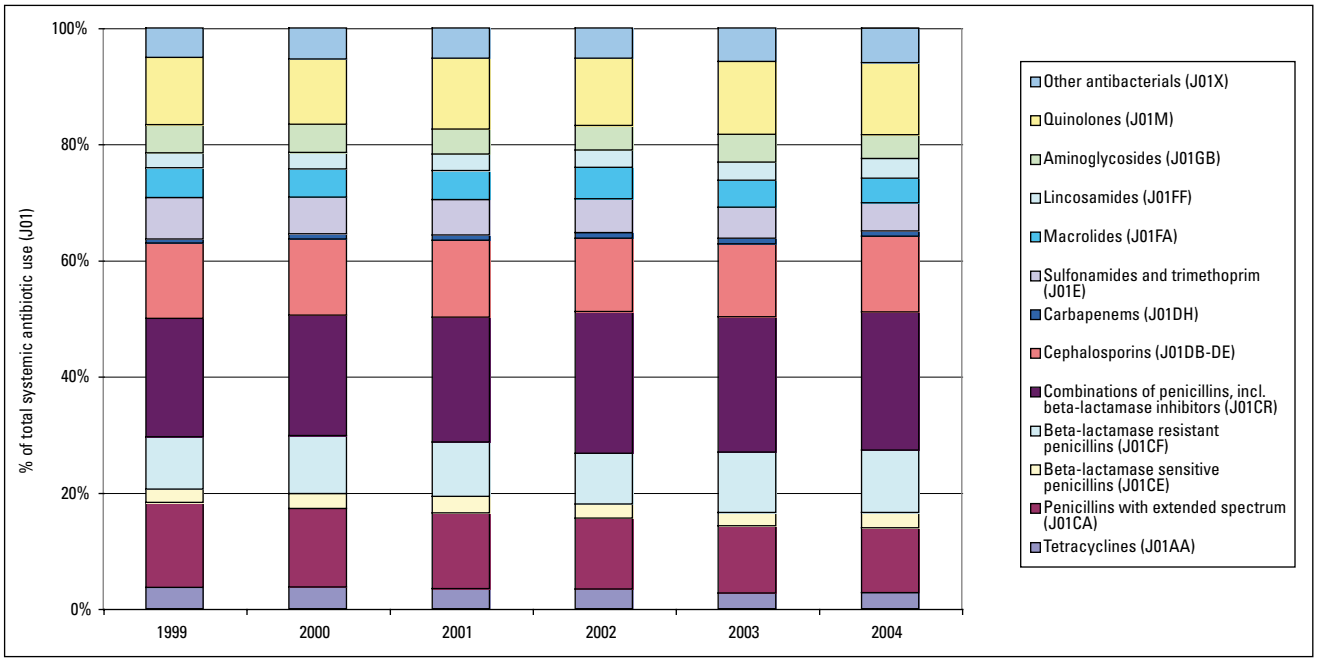


Figure 9. Distribution of the use of antibiotics for systemic use (J01, % of total DDD/100 patient-days) in hospitals, 1999-2004 (Source: SWAB).

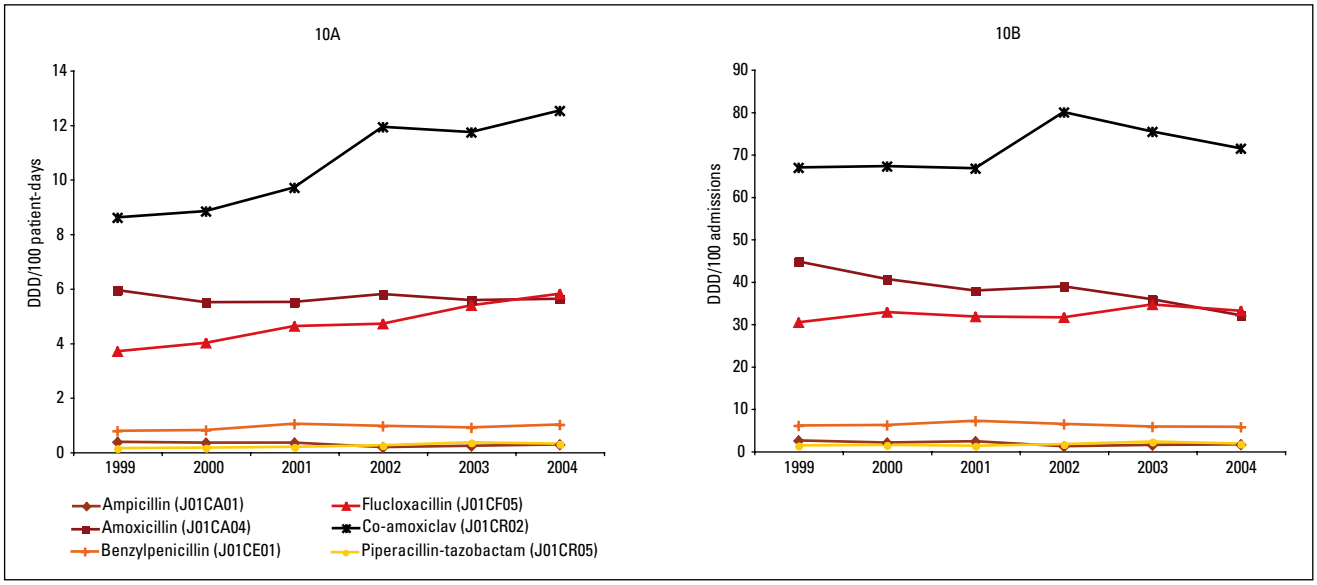
admissions and an increase when expressed in DDD/100 patient-days. First-generation cephalosporines are mainly represented by cefazolin, of which the use increased for both units of measurement from 1999 to 2004.

The relative use of macrolides in hospitals decreased from 5.1% in 1999 to 4.3% in 2004. The most commonly used macrolide is still clarithromycin, as it has been the last few years (figures 12 and B).

The significant increase in the use of aminoglycosides, mainly gentamicin, which was seen in 2003, has leveled off in 2004 (figure 13A and B). The use of gentamicin is still highest, while the other aminoglycosides, tobramycin and amikacin are decreasing further.

The relative use of fluoroquinolones increased between 1999 and 2004 (figure 9). Of the fluoroquinolones, use of ciprofloxacin increased over the years, expressed in both units of measurement (figures 14A and B). Levofloxacin

Figure 10A/B. Use of penicillins in hospitals, 1999-2004 (Source: SWAB).



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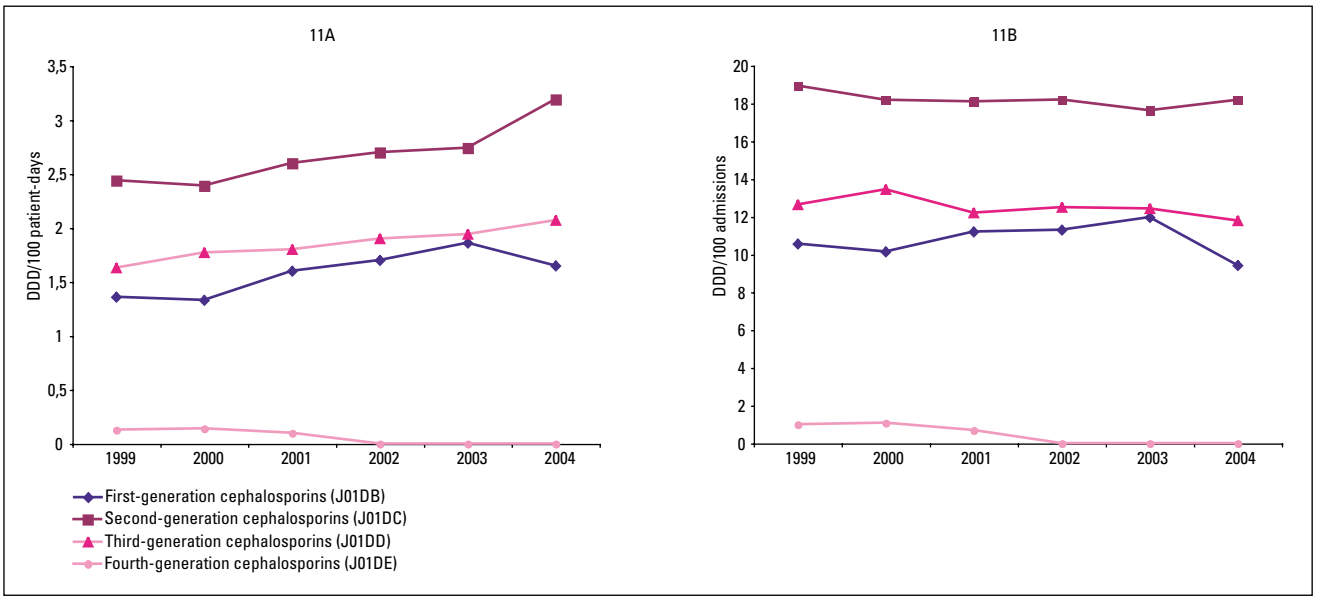


Figure 11A/B. Use of cephalosporins in hospitals, 1999-2004 (Source: SWAB).

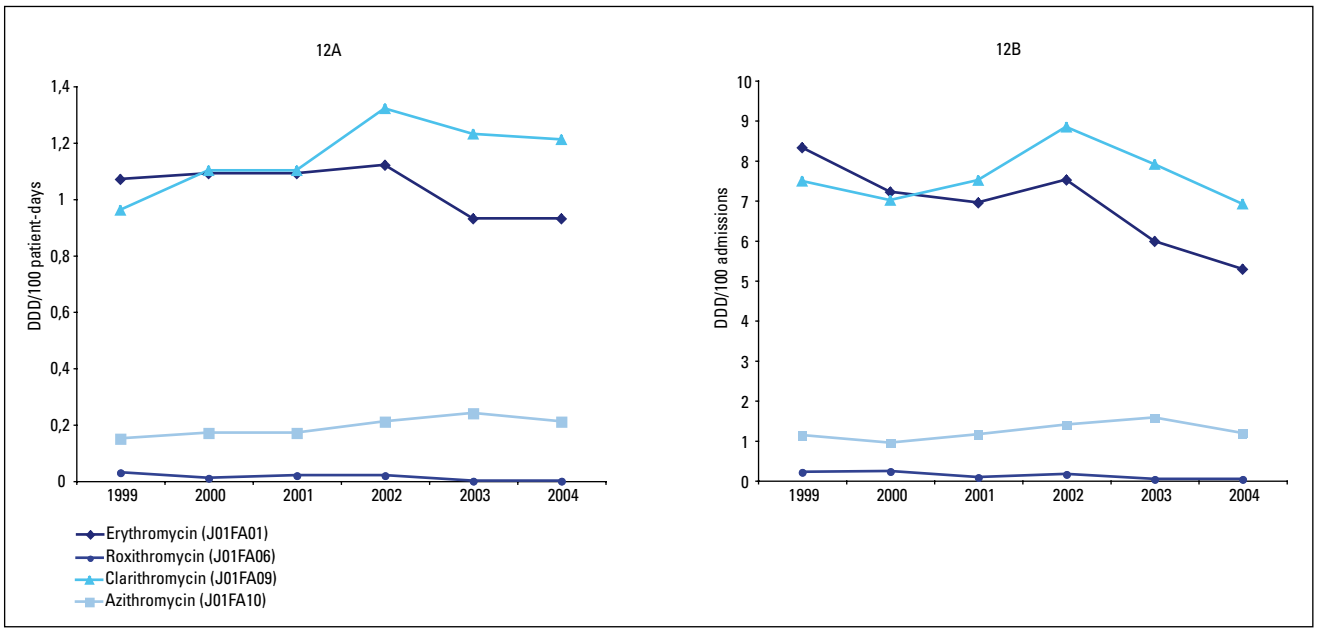
use remained low, but also increased for both units of measurement.
Vancomycin use is still increasing, while the use of teicoplanin remains low (figures 15A and B).

Discussion

The unit in which antibiotic usage is expressed does matter.[1] In relation to antibiotic resistance development the measure of antibiotic use should be a reflection of the antibiotic selection pressure exerted. At the population level the selection pressure is thought to depend on the volume of antibiotics used in a particular geographical area, the number of individuals exposed and the proportion of the population treated with antibiotics.[2] The denominator should thus preferably include information on all these factors. However, there is a lack of studies to determine the correlation between different measures of antibiotic use and the level of antibiotic resistance.

In this edition of NethMap, data on antibiotic use in Dutch hospitals between 2000 and 2004 were expressed

Figure 12A/B. Use of macrolides in hospitals, 1999-2004 (Source: SWAB).



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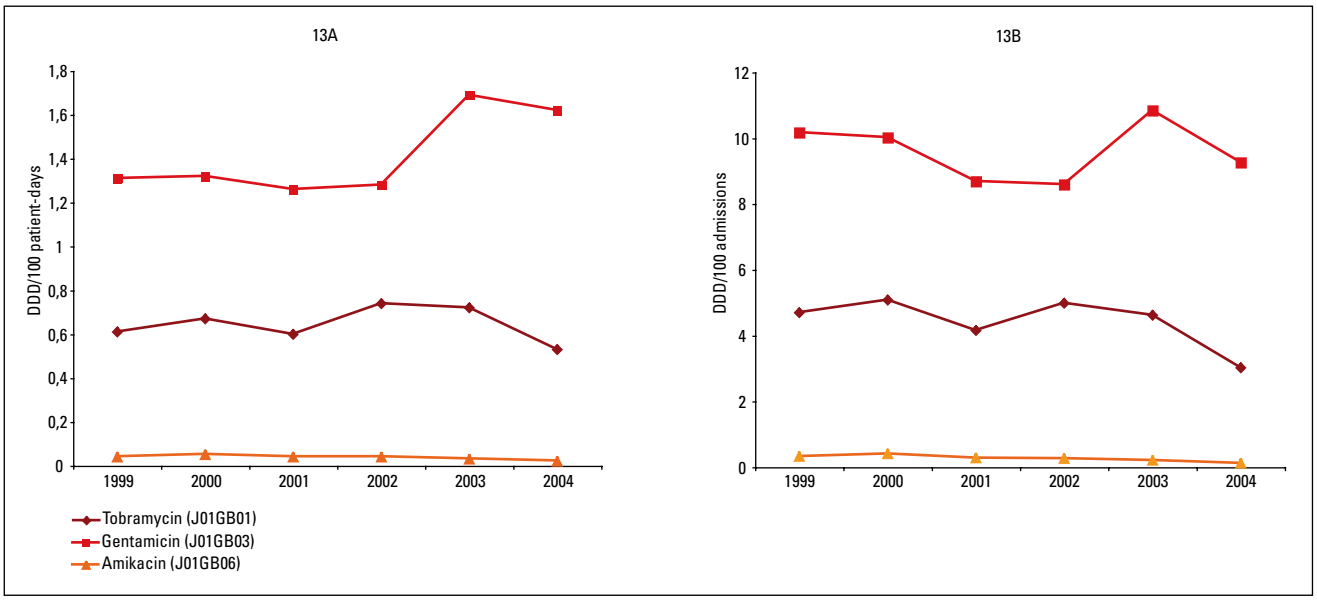
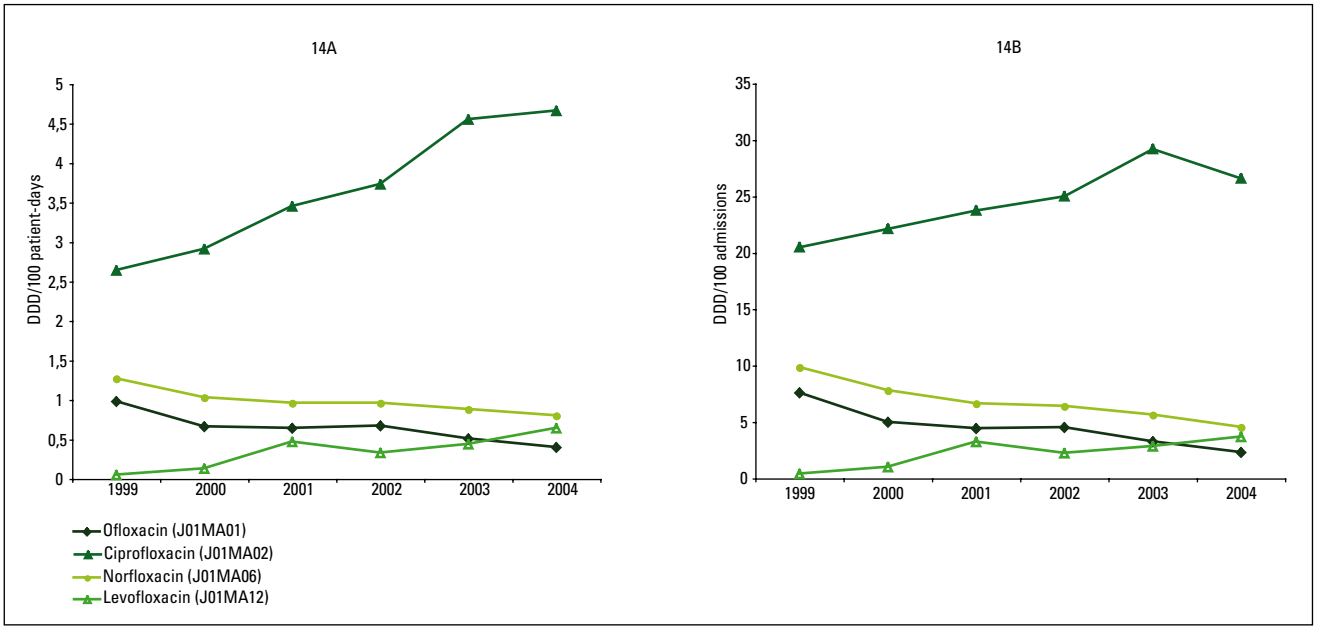


Figure 13A/B. Use of aminoglycosides in hospitals, 1999-2004 (Source: SWAB).

in DDD per 100 patient-days and in DDD per 100 admissions. Until recently an increase in the number of DDD per 100 patient-days has been routinely interpreted as worrisome with regards to the potential for antibiotic resistance development. We have distinguished four main categories with regard to the observed trends in antibiotic use. It is clear that an increase in both the number of DDD per 100 patient-days and the number per 100 admissions (category 1) is worrisome and that no increase in either unit (categories 3 and 4) is not worrisome with regards to resistance development. The trend in category 2 is less easy to interpret.

A constant use per patient combined with an increase in the number of admissions (category 2) is indicative for an increase of the selection pressure exerted by antibiotics in hospitals over the years. However, an intensification of antibiotic therapy per patient-day may in part be due to a shortening of the duration of antibiotic treatments. Such shortening of the duration of therapies may lead to less selection of resistant microorganisms.[3]

Figure 14A/B. Use of fluoroquinolones in hospitals, 1999-2004 (Source: SWAB).



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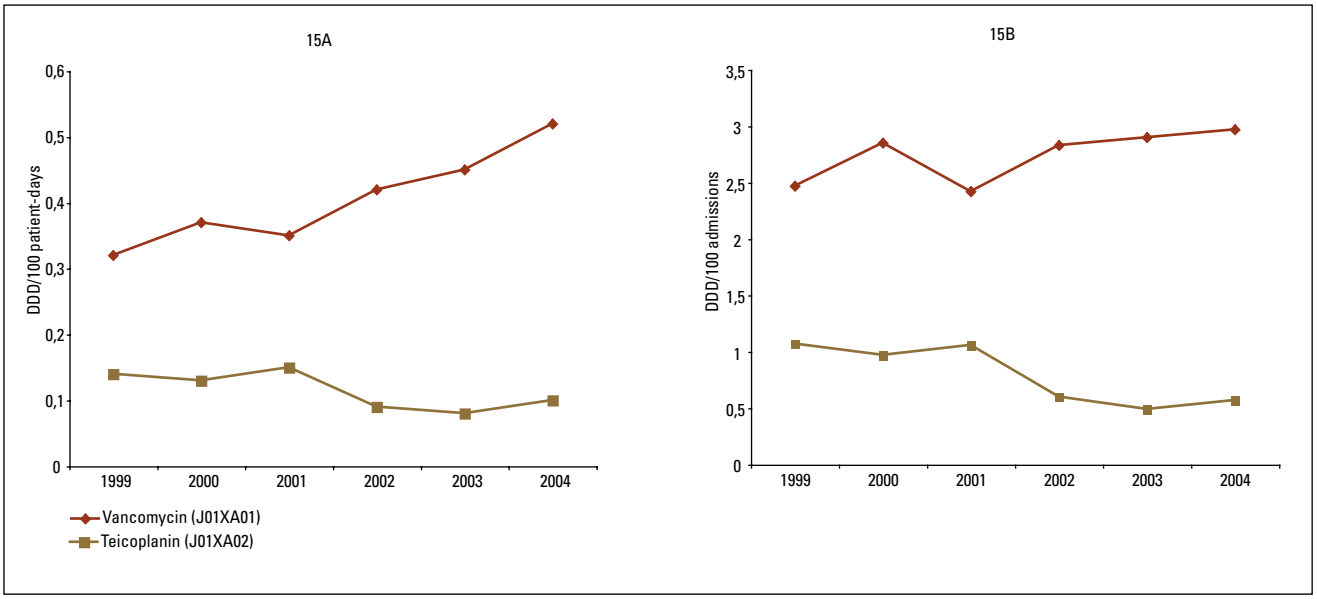


Figure 15A/B. Use of glycopeptides in hospitals, 1999-2004 (Source: SWAB).

In conclusion, over the years 1999-2004 a 25% increase in total use was observed when expressed in DDD/100 patient-days. On average patients did not use more antibiotics. However, the average hospital environment is exposed to 25% more antibiotics in 2004 compared to 1999. With regard to the potential for antibiotic resistance development this higher ecological pressure might result in the selection of resistant strains in individual patients.

The consumption of flucloxacillin and vancomycin continued to increase since 1999. This might be due either to an increased focus on staphylococcal infections or an increased incidence of serious staphylococcal infections in the community and in health care settings.

The analysis of antimicrobial use in Dutch hospitals revealed a significant increase in the use of co-amoxiclav, cefuroxime, ciprofloxacin, clindamycin and nitrofurantoin.
Monitoring and analyzing antibiotic use patterns by specific populations within the hospital (e.g. intensive care and general ward patients, surgical and non-surgical patients) is warranted to assess the rationality of these prescriptions.

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Project 1

European Surveillance of Antimicrobial Consumption (ESAC-project)

PMG Filius, R Janknegt
National representatives of the Netherlands in the ESAC-project on behalf of SWAB

ESAC is an international network of surveillance systems for the collection of data on antibiotic consumption in Europe (http://www.esac.ua.ac.be).The project is granted by DG/SANCO of the European Commission (agreement number 2003211). The principle investigator is professor H Goossens from Antwerpen. Standardized national data on antibiotic consumption in ambulatory as well as hospital care have been assembled in the ESAC database. There were delivered retrospective data for the period 1997-2003 from 31 European countries by the end of 2004. The SWAB is represented by PMG Filius and R Janknegt in the ESAC-project. Data on methodology and ambulatory care data were already published by the ESAC-team.[1-2] To give an impression of the project some results are presented as presented in the Lancet article[1]. Abbreviations of the country names can be found in this article.

Outpatient antibiotic use differed significantly in Europe (figure 1), varying by a factor of 3.2 between the country with the highest rate (32.2 DDD per 1000 inhabitants per day (DID) in France) and the country with the lowest rate (10.0 DID in the Netherlands). In general, countries in southern and eastern Europe consume more antibiotics than countries in northern Europe.

Total outpatient penicillin (J01C) use in 2002 varied by a factor 4.2 between France and the Netherlands. Figure 2 shows the proportion of use of the four different types of penicillins. Total outpatient cephalosporin use was highest in Greece and lowest in Denmark (figure 1)

Total outpatient quinolone use in 2002 varied by a factor of 21.2 between the country with the highest (3.76 DID in Italy) and the country with the lowest (0.17 DID in Denmark) quinolone use (figure 3). Use of quinolones in the Netherlands was 0.81 DID in 2002.

Figure 1

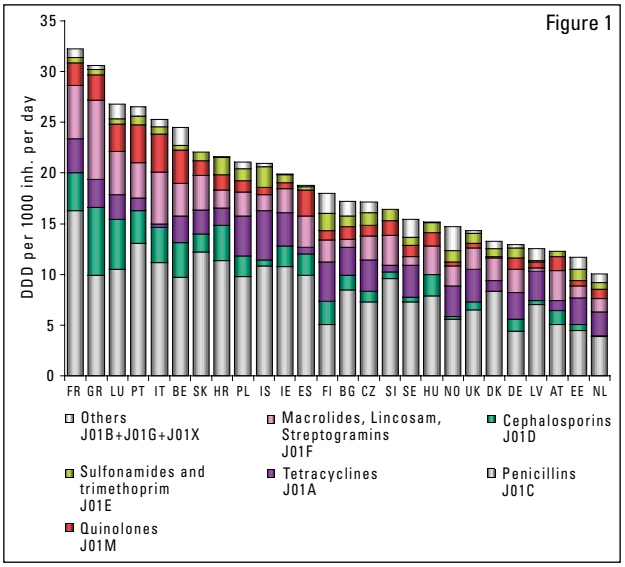


Figure 2

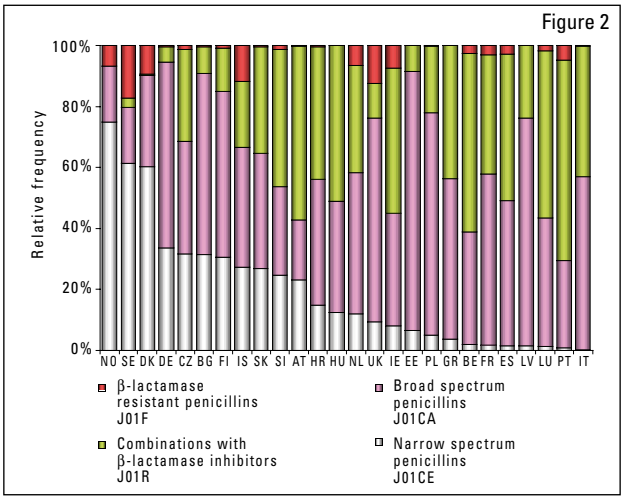
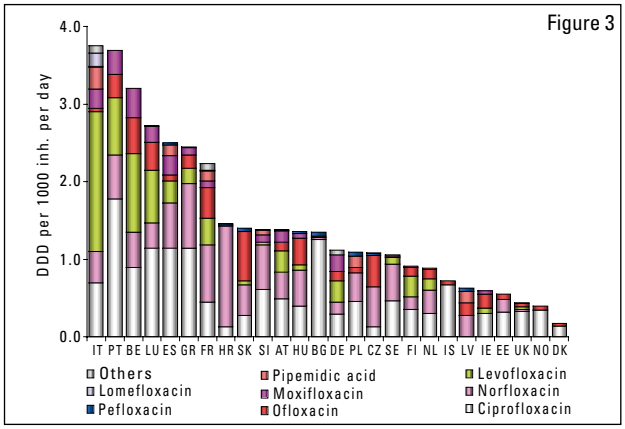


Figure 3



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4 Resistance among common Pathogens

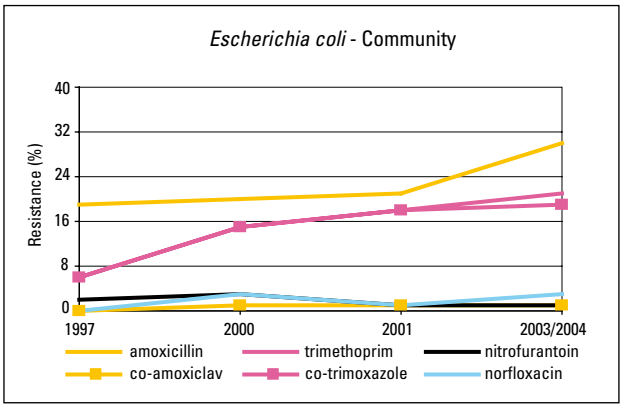
Surveillance of Antimicrobial Resistance in the Community

The prevalence of antibiotic resistance among bacteria causing community acquired infection was determined for strains collected from patients visiting their general practitioner in communities of The Netherlands from 2003-2005. Urine was taken from patients with complaints of an acute uncomplicated urinary tract infection to determine the resistance level in *E. coli* (2003-2004) and nose swabs were taken from patients visiting the doctor for non-infectious complaints to determine the resistance level and carriership in *Staphylococcus aureus* (2005). The materials came from 31 practitioners distributed over the country. See material and methods section for details regarding the acquisition and testing of isolates. The resistance patterns found among 1658 isolates of *Escherichia coli* are compared with the results found for the South in the Southern part of The Netherlands during the years before (1997-2001).

Escherichia coli

Escherichia coli isolates in 2003-2004 came from 3264 females (87%) and 504 males (13%) of whom 47% and 25% revealed positive cultures with *E. coli* (N=1658), respectively. The trends of resistance are presented in figure 1. The antibiotic resistance percentages for both sexes, related to age groups are presented in figure 2. Amoxicillin resistance in the community increased from less than 20% in 1997 to 32% in 2003-2004. The overall prevalence of amoxicillin resistance in 2003-2004 in females was 33% (range 30-35%); the difference between the age groups was not significant. The figures for males differed: the overall percentage resistance was 23 % (range 11-54 %). The resistance rate at the young age (≤ 20 years of age) was the highest, but the number of *E. coli* strains in that age group was very low. The resistance level in the age group 21-50 years of age was significantly lower (11%) than that in the older age groups (p< 0.002). The overall resistance level of amoxicillin in the community was lower than that in Unselected Hospital Departments (40%, see figure 6). Co-amoxiclav resistance varied from 2-5% (mean 2.9%), depending on the age group. The resistance rate was significantly higher in older women than in women under the age of 70 years (p < 0.002), but the level in general was comparable to that in Unselected Hospital Departments during the same study period.
Trimethoprim resistance rates increased over the years, from less than 10% in 1997 in the South to 22% in 2003-2004 for the whole country. The shape of the graph concerning age groups and resistance (figure 2) resembled that of amoxicillin. The difference in resistance rates between females and males in the age groups 21-50 years is significant. The resistance rate of co-trimoxazole for males was equal to that of trimethoprim; the resistance rate of co-trimoxazole among females was 20% for all ages. This was lower than the rate in Unselected Hospital Departments (figure 6). The MIC distribution for both compounds showed a bimodal distribution (figure 3) with a subpopulation of MICs over a broad range from 0.06 – 2 mg/l and one with MICs of 64 mg/l or higher.
Resistance to nitrofurantoin (figure 2) remained at a low level from 1-3% (mean 1.5%) in all age groups during the study period. The MIC distribution showed a unimodal shape over a wide range from 2 to 256 mg/L, with a peak at 16 mg/l (not shown).
Norfloxacin resistance level in the community increased to 3% in 2003-2004 with rates ranging 1-5 % by age class: 1% in the younger age group ≤ 20 years of age and 3-5% in the older age groups (p <0.05), which may reflect more frequent use of this drug in the older ages. There was complete cross-resistance with ciprofloxacin.
It was already indicated in Nethmap 2004 and -2005 that resistance to amoxicillin and trimethoprim among *E. coli* causing community acquired urinary tract infection have reached levels in the community, that make these antibiotics unacceptable as empiric therapy in community acquired urinary tract infections. The Dutch College of General Practitioners (NHG) changed its standard accordingly in 2005 and replaced trimethoprim by nitrofurantoin as the first choice for the empiric treatment of uncomplicated urinary tract infection and replaced amoxicillin by co-amoxiclav for the treatment of paediatric complicated urinary tract infection (i.e. relapsing and recurrent cases) in this setting.
These data also indicate that the rate of resistance in the community resembled that in Unselected Hospital

Figure 1. Trends in resistance to antibiotics among *Escherichia coli* from the Community.



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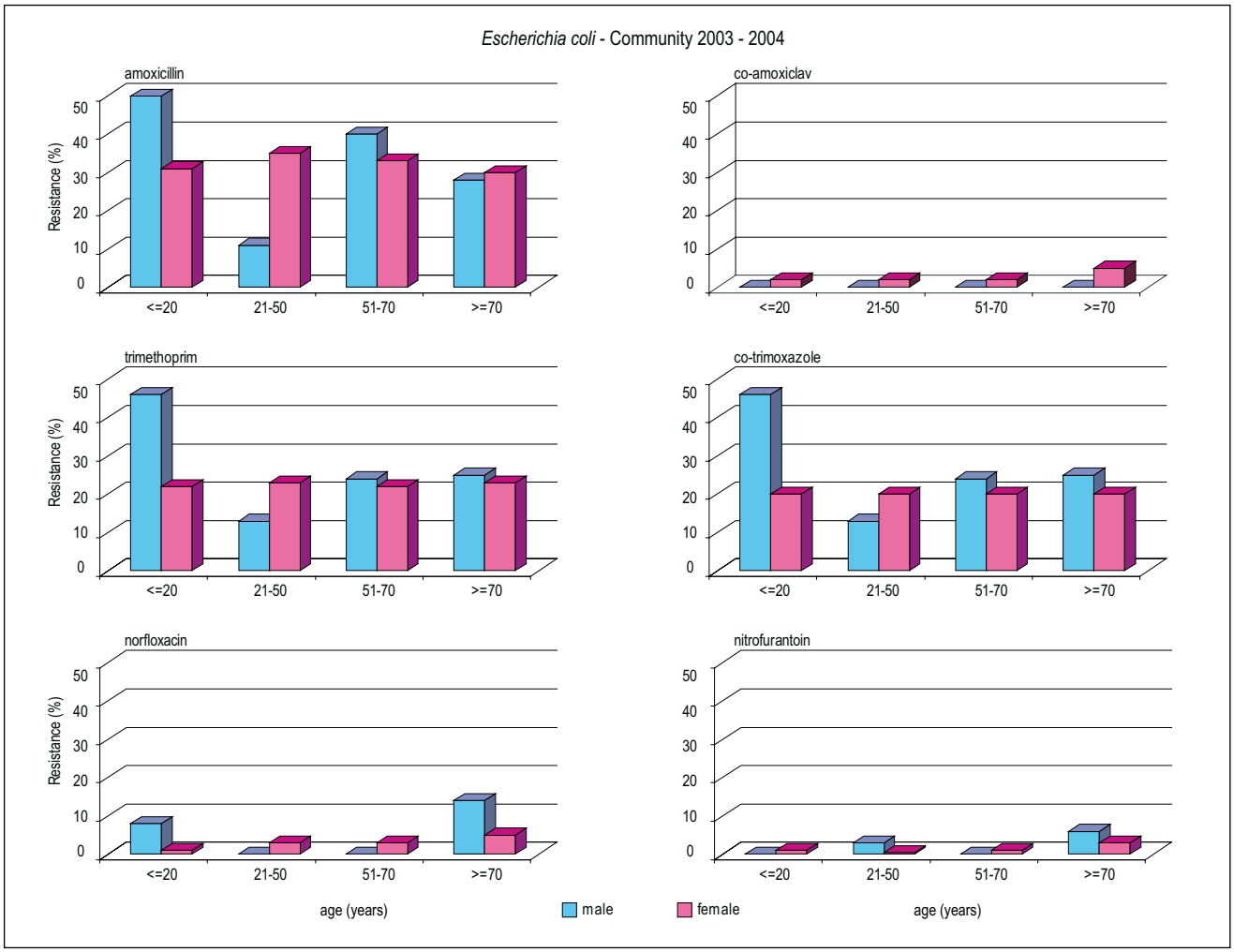


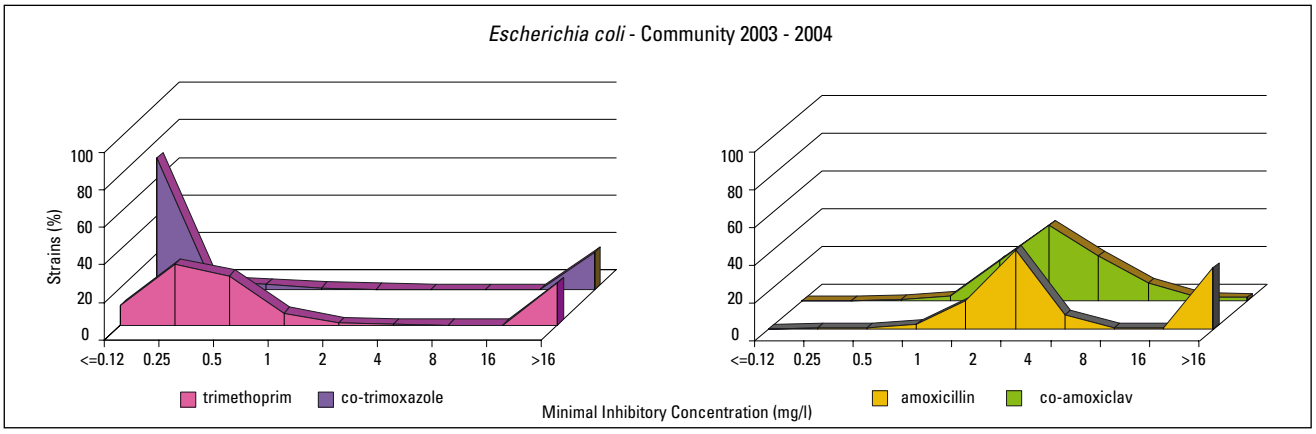
Figure 2. Resistance rates of antibiotics for *Escherichia coli* from the Community – relationship age and gender.

Departments a few years earlier. There is no difference in trends of resistance patterns in the two study populations, only a time delay of two years.

Staphylococcus aureus

A total of 2948 nose swabs were received of which 1381 swabs have been analysed until now. *Staphylococcus aureus* was isolated in 446 of these swabs (32 %). The

Figure 3. MIC distributions for *Escherichia coli* from the Community.



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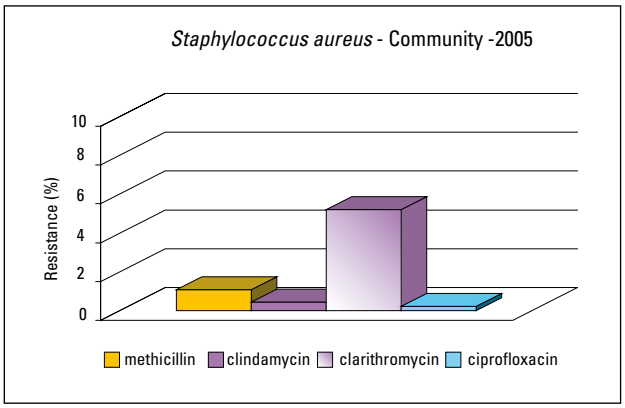
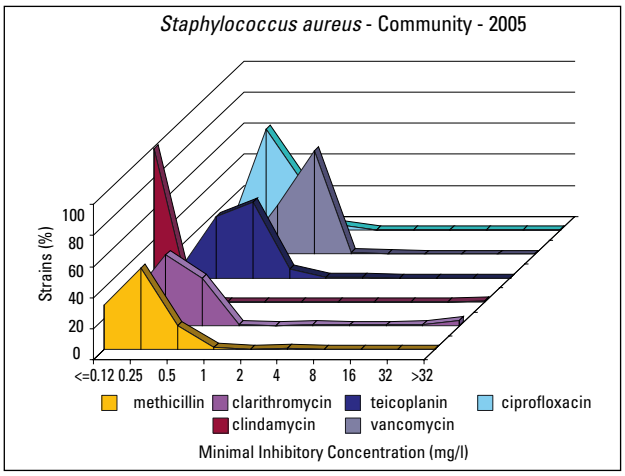


Figure 4. Resistance rates of antibiotics for *Staphylococcus aureus* from the Community.

resistance percentages are given in figure 4. Methicillin resistance was found in 4 isolates.
The MIC distribution (figure 5) showed a unimodal shape over a broad range (0.06 -4 mg/l.
Clarithromycin resistance was found in 5% of the strains, whereas 0.5% was resistant to clindamycin. The MIC distribution of clarithromycin (figure 5) showed the existence of three subpopulations: a large cluster of susceptible strains with MICs of 0.03-0.5 mg/l, some strains with MICs of 1-32 mg/l and a small cluster with MICs >32 mg/l.
Ciprofloxacin resistance was found in 0.2% of the strains. The MIC distribution showed an unimodal curve over a small area (0.25-1 mg/l) with MIC_{90} = 0.5 mg/l. Only two resistant strains were recorded: one with MIC of 2 mg/l and one with MIC of 8 mg/l.
Vancomycin- and teicoplanin resistance were not detected. The MIC distribution of vancomycin (figure 5) showed a unimodal curve over a small area (0.5-4 mg/l), that of teicoplanin was also unimodal, but over a broader

Figure 5. MIC distributions for *Staphylococcus aureus* from the Community.



range (0.06-4 mg/l). The MIC_{90} of vancomycin was 1 mg/l, that of teicoplanin 0.5 mg/l.
Mupirocin resistance was found in 1% of the strains, resistance to fusidic acid was demonstrated in 6% of the isolates. This may may be the consequence of topical use of these drugs in the community practice.

Surveillance of Antimicrobial Resistance in Hospitals

The overall prevalence of antibiotic resistance in hospitals was estimated by using resistance data generated in routine clinical care. Unselected Hospital Departments and outpatients clinics were the sources of strains collected and tested by 11 Regional Public Health Laboratories and four local laboratories covering 30% of the Dutch population (table 1 in appendix). These are designated resistance rates in 'Unselected Hospital Departments'. Resistance rates in Unselected Hospital Departments were compared with the resistance rates among strains isolated from selected departments in 14 large referral hospitals (table 2 in the appendix). These selected departments included the Intensive Care Units, being wards with high use of antibiotics and, consequently, high selective pressure favouring the emergence of resistance. Also included were the Urology Services and the Pulmonology Services, the latter two representing departments with frequent use of specific oral antibiotics. Results were analyzed per species of common nosocomial pathogens and are presented in the accompanying figures.

Escherichia coli

The overall prevalence of amoxicillin resistance in Unselected Hospital Departments Departments increased from 29 % in 1995 to 40% in 2005 (figure 6). Amoxicillin resistance was higher in Intensive Care Units, approximately 42%, without indication of a trend, whereas the resistance in Urology Services increased from 38% in 1996 to 47% in 2004.
The distribution of MICs (figure 7) in Intensive Care Unites showed two subpopulations: a susceptible one with a broad MIC range from 0.5 -8 mg/l and a resistant one with MICs > 32 mg/l.
Co-amoxiclav resistance was at a low level (4%) in Unselected Hospital Departments and in the Urology Services until 2000 (figure 6). Subsequently, an increase in the level of resistance was observed in the Urology Services, which stabilized at 7% in 2004. The level of resistance in Unselected Hospital Departments remained around 4% until 2004, but increased to 6% in 2005, similar to the level found already in 2001 in Urology Services. Co-amoxiclav resistance was much higher in Intensive Care Units, up to 16% in 2004. The MIC distribution of amoxicillin in Intensive Care Units was

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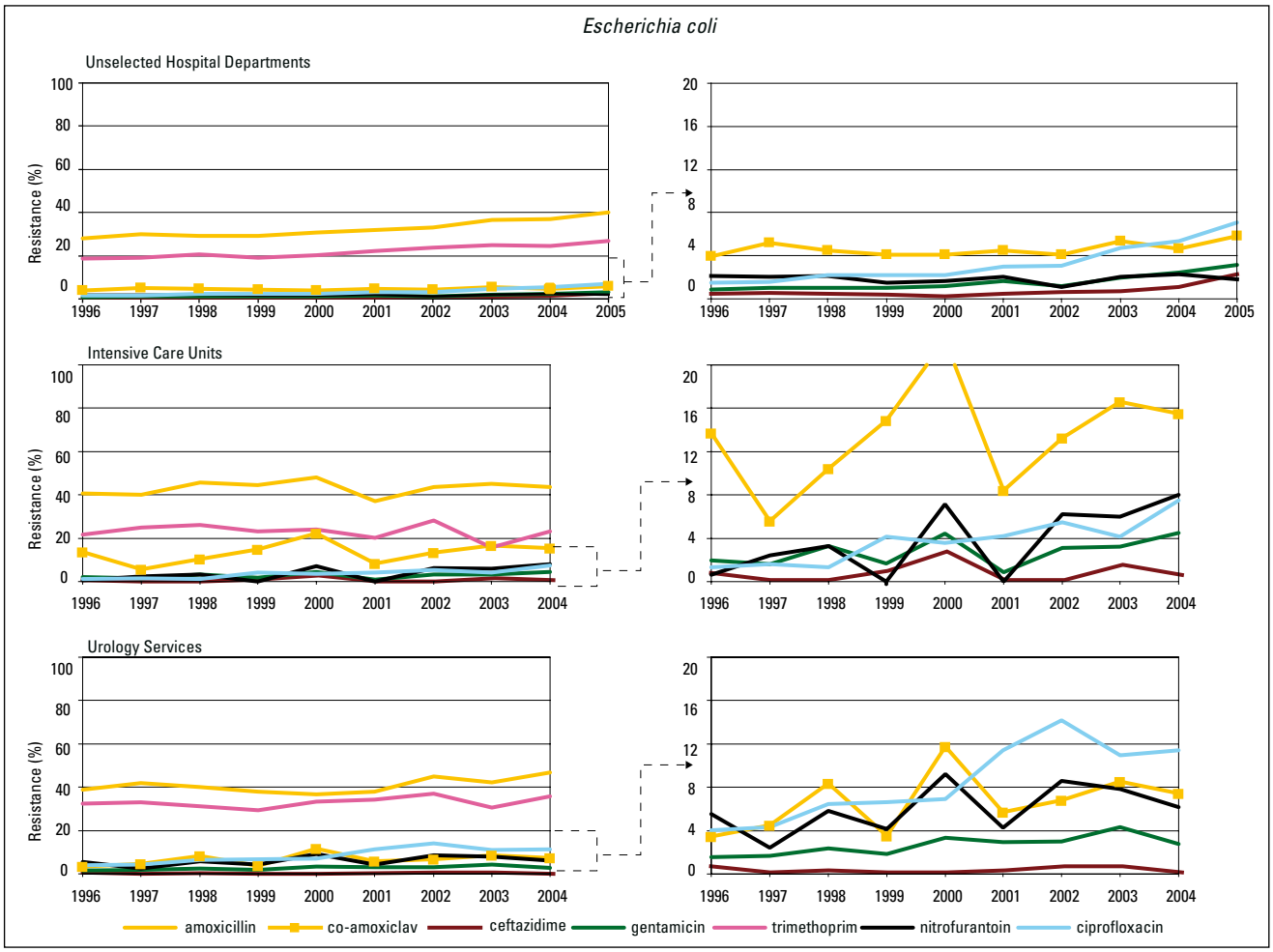


Figure 6. Trends in resistance to antibiotics among *Escherichia coli* from Unselected Hospital Departments, Intensive Care Units and Urology Services.

similar to that found for the community, but the MIC distribution of co-amoxiclav from Intensive Care Units showed a considerable resistant subpopulation (MICs ≥32 mg/l) and a growing number of strains with MICs 16 mg/l. These strains were not found among the community isolates.

Piperacillin resistance varied between the Intensive Care Units, some had high resistance rates (20%), others low (2%), the overall resistance level was 11%. The MIC distribution of piperacillin (figure 7) showed three subpopulations: one susceptible with MICs 0.5-4 mg/l, one intermediately susceptible with MICs 8-64 mg/l and one resistant subpopulation with MICs >64 mg/l. Piperacillin showed higher activity than amoxicillin towards the same subpopulation: the peak of MICs of piperacillin in the susceptible range was at 1 mg/l, that of amoxicillin at 4 mg/l (figure 7). Resistance against piperacillin-tazobactam was rare (range 0.7-4%, overall 3% in 2004). The MIC distribution of piperacillin-tazobactam showed an almost complete disappearance of both resistant and intermediately susceptible populations.

Ceftazidime resistance in Unselected Hospital Departments was very low, but showed an increasing trend, being less than 1% until 2003, but 1.1% in 2004 and 2.3% in 2005 (figure 6). This level was also recorded in the Intensive Care Units and Urology Services. Intensive Care Units had consistently higher resistance rates for 1st and 2nd generation cephalosporins than Urology Services. Overall these increased in Intensive Care Units, whereas that in Urology services remained at the same level since 1996. Cefaclor showed the highest resistance rate: increase from 8% in 1996 to 13% in 2004 in Intensive Care Units vs 3-5% in Urology services (figure 8). The MIC distribution of cefaclor (figure 9) was almost unimodal over a broad range during 1996 and 1997 with a number of susceptible strains with an MIC just below the breakpoint. Thereafter highly resistant strains appeared, resulting in a bimodal shape of the curves with a sharp and increasing peak of resistant strains. The change of the shape of the curve can thus predict development of resistance before it becomes manifest. The MIC distribution of cefuroxime (figure 9) showed the same shape (only shown for 2004), that of cefotaxime and ceftazidime showed a unimodal

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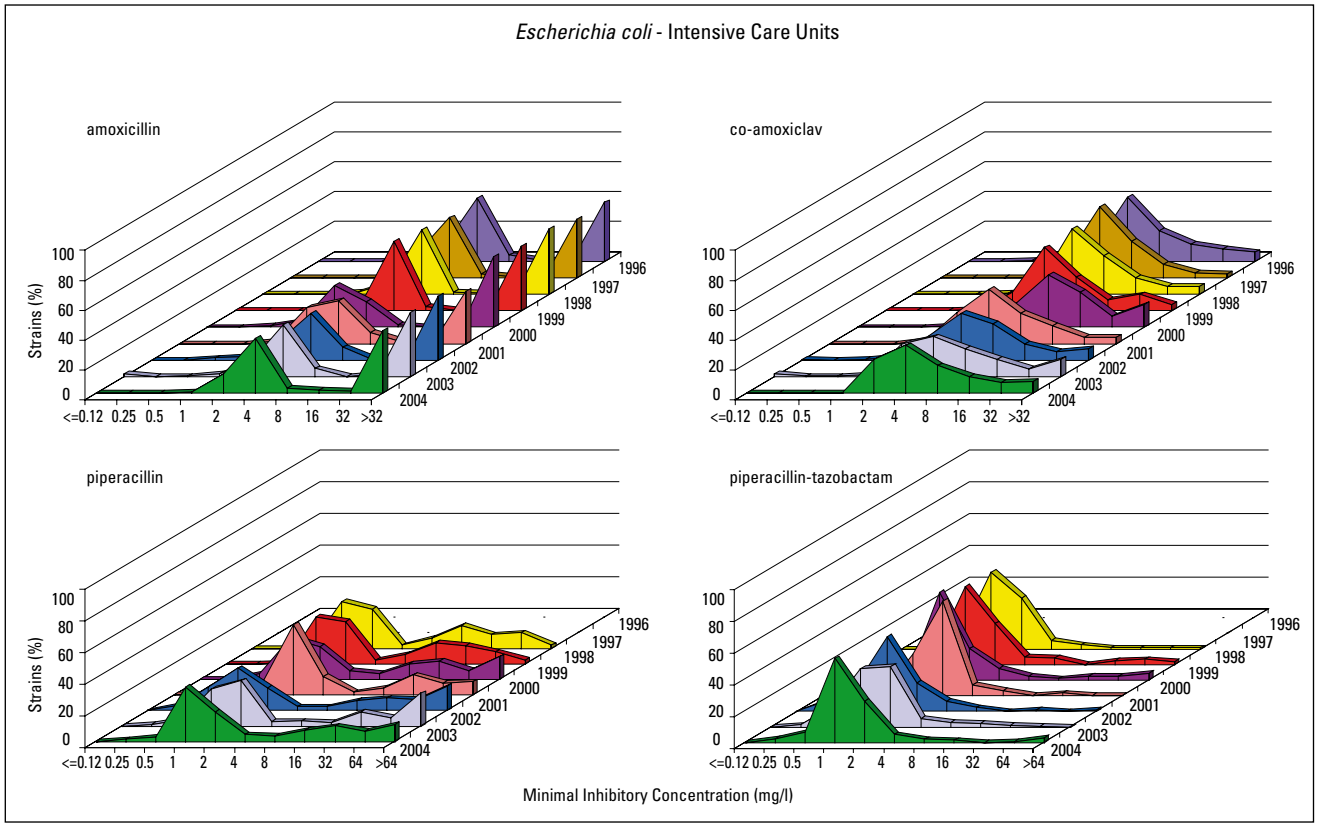
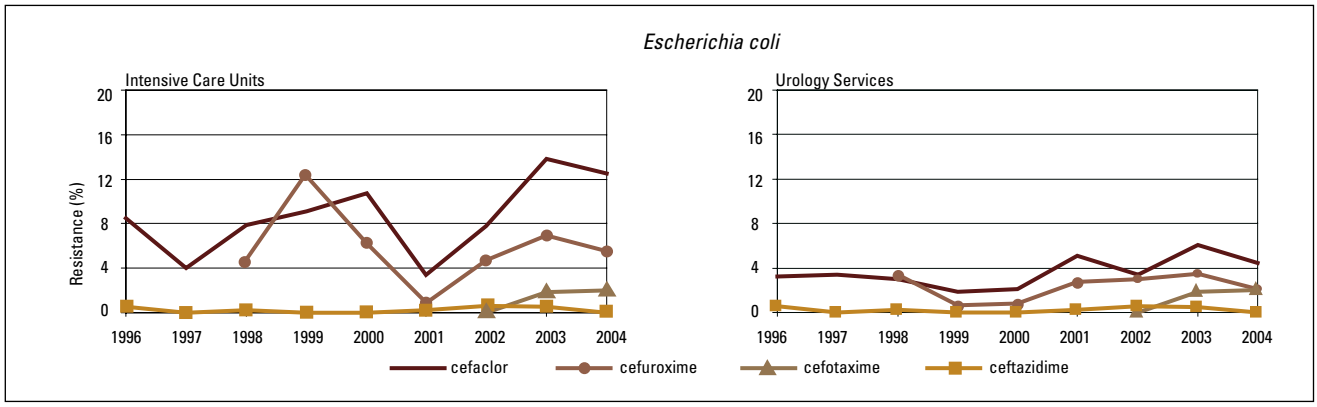


Figure 7. MIC distributions of beta-lactam antibiotics for *Escherichia coli* from Intensive Care Units.

distribution over a very small range (≤0.12-0.5 mg/l). Trimethoprim resistance in Unselected Hospital Departments increased from 18% in 1996 to 27% in 2005 (figure 6). The level of trimethoprim resistance in Intensive Care Units varied around 20-25%. Trimethoprim resistance was significantly higher in the Urology Services and reached 36% in 2004. Co-trimoxazole resistance followed this trend and was only 1-2% lower. The MIC distribution (figure 10) showed that two subpopulations existed: one susceptible and one highly resistant.

Similar differences in resistance rates between Intensive Care Units and the Urology services were observed for nitrofurantoin and the quinolones (figure 6), albeit at a lower prevalence levels. Nitrofurantoin resistance was about 2% in Unselected Hospital Departments, equal to the figures in the community. It was higher in Intensive Care Units (up to 2-8%), and in Urology Services (up to 10%). No clear trend was observed.
Ciprofloxacin resistance increased among *E. coli* from Unselected Hospital Departments to 4% in 2003 and 7% in 2005, thereby equalling the resistance rates

Figure 8. Trends in resistance to cephalosporins among *Escherichia coli* from Intensive Care Units and Urology Services.



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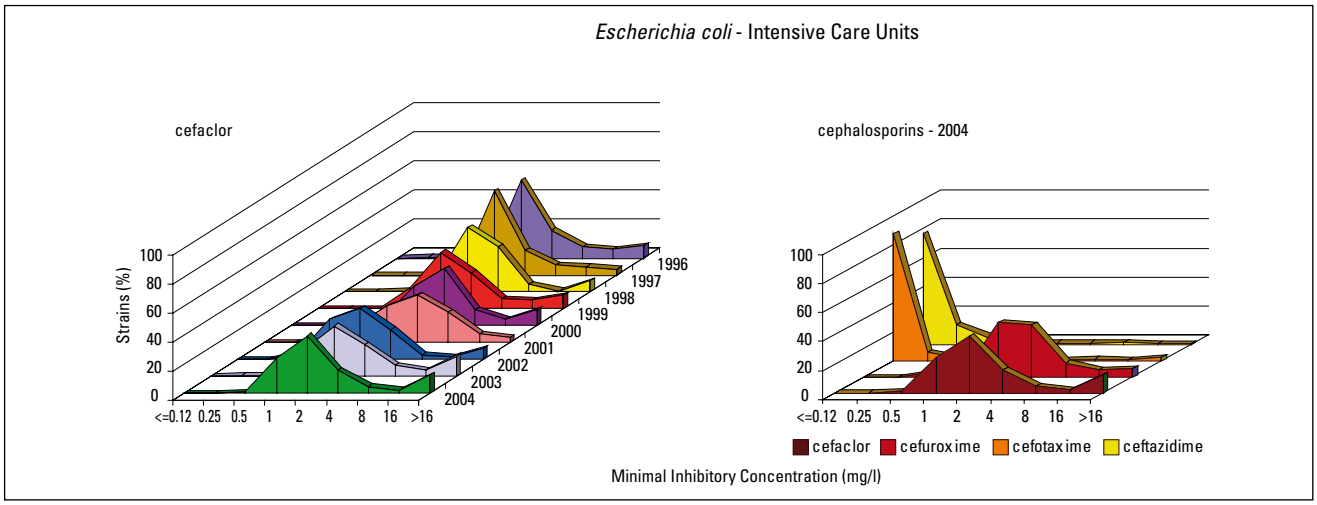
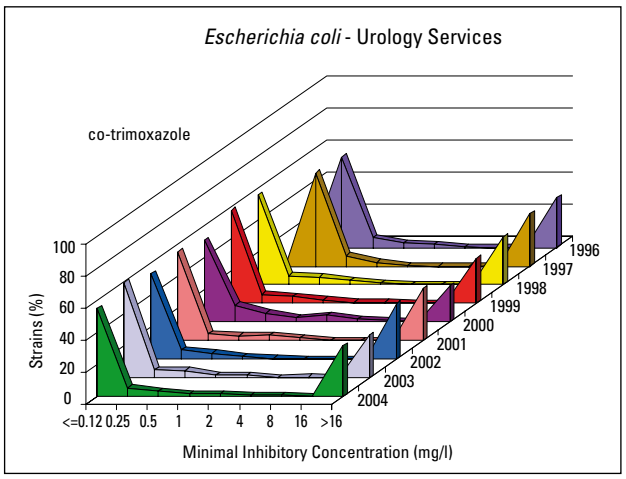


Figure 9. MIC distributions of cephalosporins for *Escherichia coli* from Intensive Care Units.

in Intensive Care Units (figure 6). The resistance in Intensive Care Units increased further to 7% in 2004. The resistance level in Urology Services however increased from 7% in 2000 to 12% in 2004 with a peak of 14% in 2002 (figure 6). The MIC-distributions of norfloxacin and levofloxacin were identical to that of ciprofloxacin (figure 11). The MIC distribution of the quinolones of *E. coli* from Urology Services was bimodal with a large susceptible subpopulation over a very small range and a subpopulation of strains with MIC of >2 mg/l (figure 11). Quinolone resistance spread slowly over the Intensive Care Units: in 1996 only two Units had these strains, compared with five Intensive Care Units in 2002 and 12 in 2004. The percentage of quinolone resistant *E.coli* varied between the centres from 3-25%.
Gentamicin resistance was low in Unselected Hospital Departments, although it seems to increase slightly last years from 1% until 2002 to 3% in 2005, the resistance level in Intensive Care Units and Urology Services varied between 2-4 %, without any visible trend (figure 6). Multiresistance (resistant to ≥ 3 groups of antibiotics) was observed in less than 2% of the strains from Intensive Care Units.

Figure 10. MIC distributions of co-trimoxazole for *Escherichia coli* from Urology Services.



Klebsiella pneumoniae

Co-amoxiclav resistance in *K. pneumoniae* from Unselected Hospital Departments and from Urology Services was as low as that of *E. coli* (3-6%), it varied but did not increase (figure 12). Co-amoxiclav resistance in Intensive Care Units varied at a much higher level (mean 10% until 2000, but showed a steady increase thereafter with a resistance rate of 19% in 2004. Co-amoxiclav resistance in Urology Services was similar to that of Unselected Hospital Departments.
First- and 2nd generation cephalosporin resistance increased slowly in both Intensive Care Units and Urology Services, although that in Urology Services was significantly lower (figure 13). Ceftazidime resistance among *K. pneumoniae* in Unselected Hospital Departments remained lower than 3% over the years, resistance to cefotaxime and ceftazidime had a sporadic character in Intensive Care Units and Urology Services (figure 13). Ceftazidime resistant strains emerged permanently in one Intensive Care Unit and occasionally in another three and in one Urology Service. The rate of 16% resistance observed in 2002 was exclusively due to a high resistance rate in two Intensive Care Units. These strains disappeared in 2003, resulting in an overall resistance rate of less than 2% in 2004.
Trimethoprim resistance increased in Unselected Hospital Departments from 11% in 1996 to 20% in 2005 (figure 12). The level of resistance in Intensive Care Units varied around 17% with large inter-annual variations until 2001. Since 2002 the resistance is 23-30%, equalling the resistance rate in Urology Services

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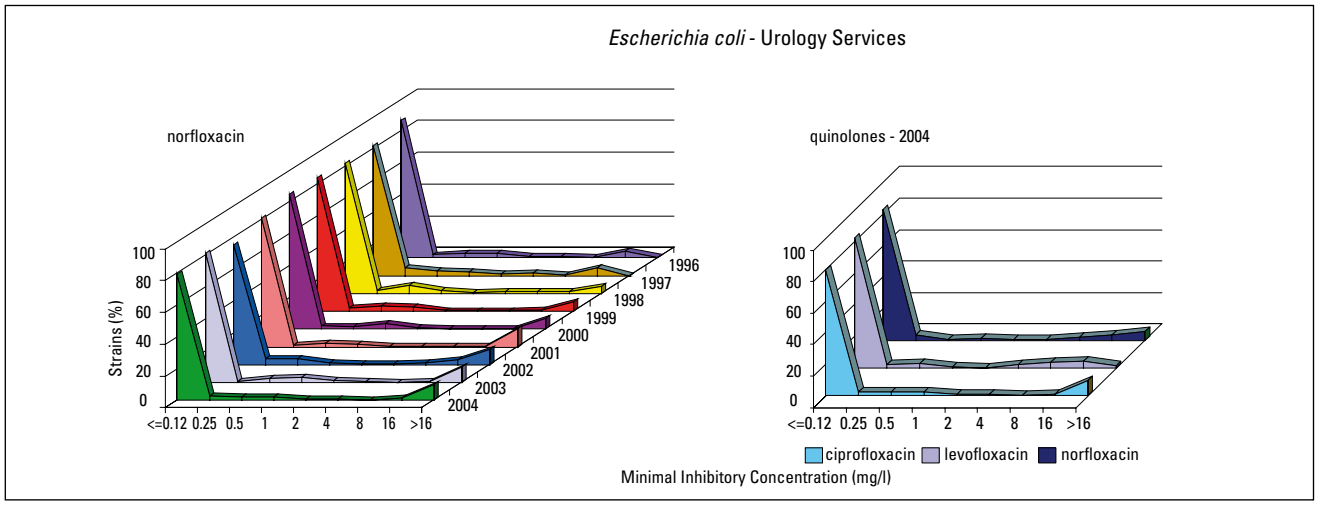
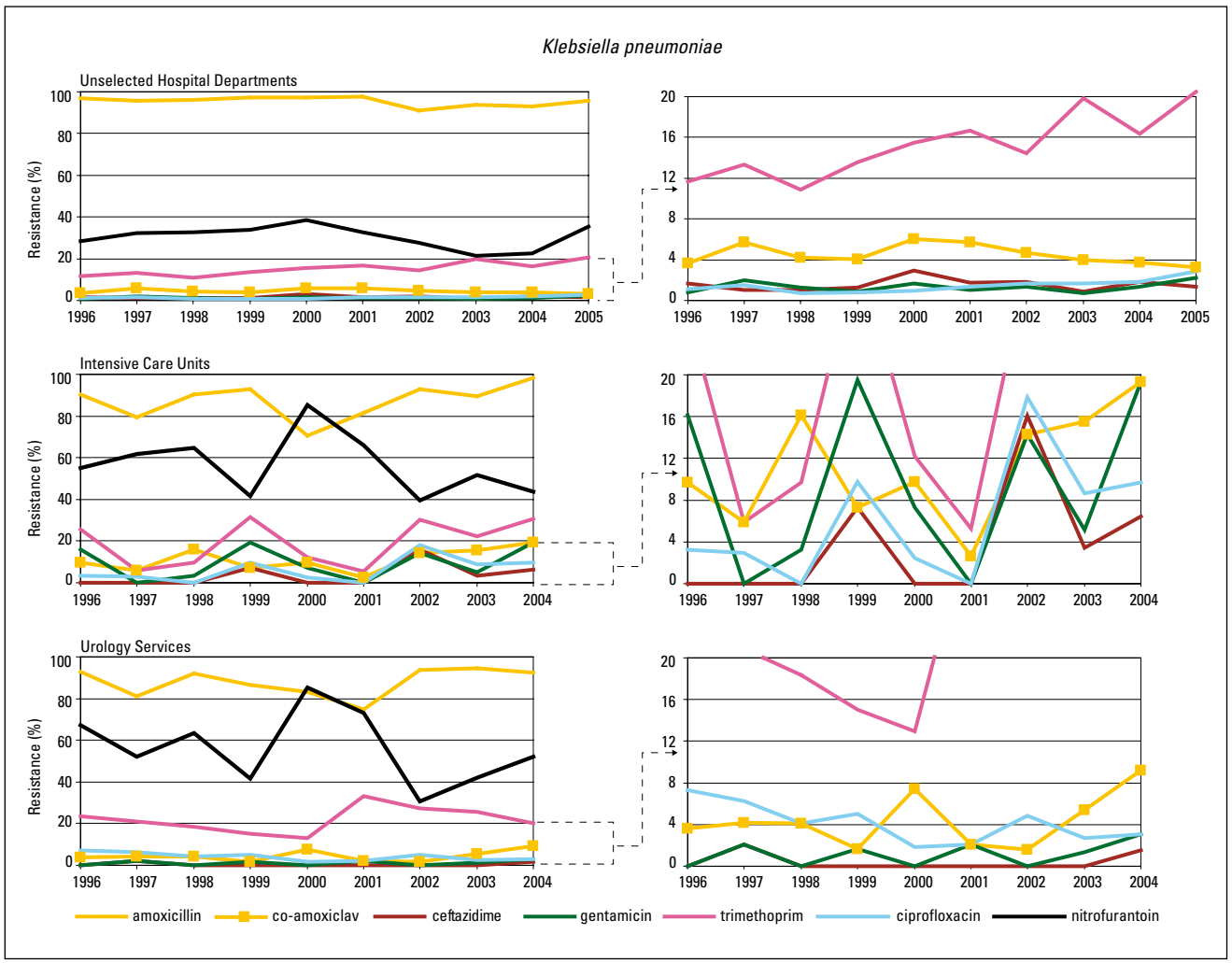


Figure 11. MIC distributions of quinolones for *Escherichia coli* from Urology Services.

Figure 12. Trends in resistance to antibiotics among *Klebsiella pneumoniae* from Unselected Hospital Departments, Intensive Care Units and Urology Services.



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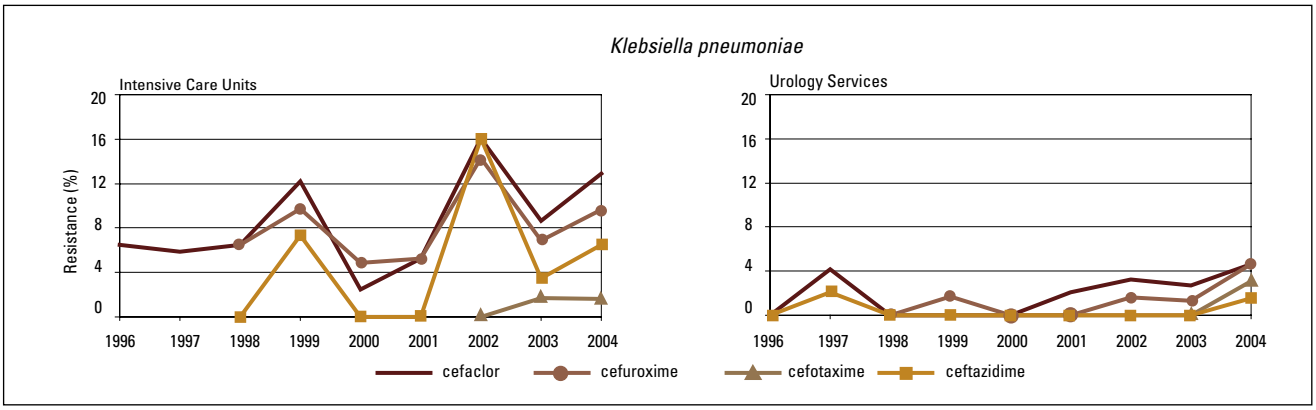


Figure 13. MIC distributions of cephalosporins for *Klebsiella pneumoniae* from Intensive Care Units and Urology Services.

until 2003. In the latter a decrease of resistance to 20% was observed in 2004. Trimethoprim was the drug of first choice in general practice and it is rarely used in Intensive Care Units. The resistance in Unselected Hospital Departments and Intensive Care Units may reflect resistance in the community. The higher resistance rates observed in the Urology Services until 2003 may reflect frequent use of this drug alone or in the combination with sulfamethoxazole by urologists in the years before. Since resistance to trimethoprim increased, many urologists switched to quinolones, which may explain the subsequent decrease of trimethoprim resistance in the last few years. The resistance levels for co-trimoxazole followed the trend of trimethoprim and appeared 29% in Intensive Care Units and 14% in Urology Services in 2004 (not shown).
Nitrofurantoin resistance varied in Unselected Hospital Departments (21-39%) (figure 12). The level of resistance in Intensive Care Units and Urology Services in 2004 was 40% or more.
Gentamicin resistance was low and at a constant level (1-2%) in Unselected Hospital Departments (figure 12). Similar to ceftazidime, *K. pneumoniae* strains resistant to gentamicin were observed permanently in one Intensive Care Unit and sporadically in five others, yielding large overall fluctuations in gentamicin resistance rates over the years of surveillance with an overall rate in 2004 of 4%. Gentamicin resistance in Urology Services was rare.
Ciprofloxacin resistance among *K. pneumoniae* in Unselected Hospital Departments increased slowly, being less than 1% until 2001, 1-2% from 2002-2004 and 3% in 2005 (figure 12). Ciprofloxacin resistance had a sporadic character in Intensive Care Units and Urology Services and did not spread: resistant strains were found in 2-3 Intensive Care Units each year since 2000 (in one permanently) and 2-3 Urology Services each year. The resistance peak in 2002 was exclusively due to resistance problems in two centres. Six Intensive Care Units and eight Urology Services did not have any ciprofloxacin resistant *K. pneumoniae* during the entire study period.
Multiresistance was sporadic except in one Intensive Care Unit where most Klebsiella strains showed combined resistance to co-amoxiclav, ceftazidime, gentamicin and ciprofloxacin from 2002 on.

Proteus mirabilis
Amoxicillin resistance in Unselected Hospital Departments increased from 14% in 1996 to 21% in 2005. Amoxicillin resistance in Intensive Care Units increased to 33% in 2004 (figure 14). Amoxicillin resistance was higher in Urology Services from the beginning (19%), and rose to 35% in 2004, similar to the level in Intensive Care Units. The distribution of MICs showed two subpopulations: a susceptible one and a resistant one (figure 15).
Co-amoxiclav resistance was around 5% in 2004 in Urology Services. Co-amoxiclav resistance in Intensive Care Units was only occasionally observed until 2000. From 2001 on more co-amoxiclav resistant strains emerged (up to 12% in 2004). The MIC distribution of co-amoxiclav showed a considerable number of strains with MICs 4-16 mg/l from 1998 on. These strains have shifted to the right in 2004, resulting in a higher percentage of resistant strains (figure 15).
Trimethoprim resistance in *P. mirabilis* in Unselected Hospital Departments showed a significant increase from 27% in 1996 to 37% in 2005, equalling the levels found in Urology Services since 2001. The resistance level in Intensive Care Units also rose to 40% in 2004 (figure 14).
Cefaclor- and cefuroxime resistance rates varied (2-7%) and were around 5% in Intensive Care Units and 2% in Urology Services respectively. Ceftazidime resistance in *P. mirabilis* was not found.
Gentamicin resistance increased slowly in Unselected Hospital Departments to a 3% level in 2005. It appeared sporadically in some Intensive Care Units and some Urology Services.
Ciprofloxacin resistance among *P. mirabilis* in Unselected Hospital Departments increased from 1-3%

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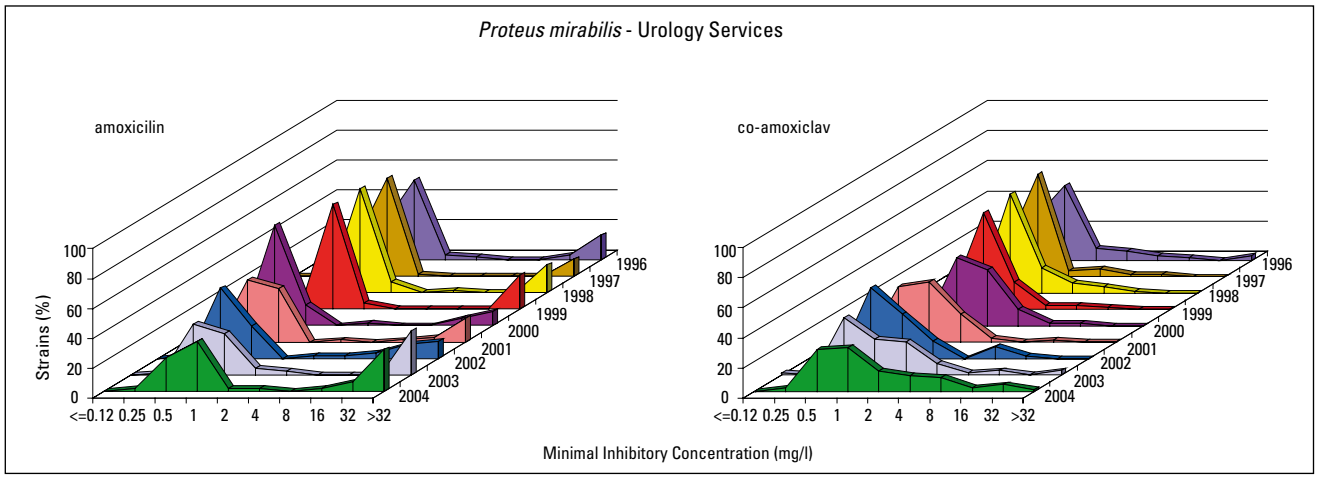
Figure 14. Trends in resistance to antibiotics among *Proteus mirabilis* from Unselected Hospital Departments, Intensive Care Units and Urology Services.

until 2002 to 7% in 2005. This was also found in Urology Services, the resistance level in Intensive Care Units remained low and sporadic.

Pseudomonas aeruginosa

Ceftazidime resistance among *P. aeruginosa* isolated in Unselected Hospital Departments and in Urology Services was consistently low (2-3%). Ceftazidime

Figure 15. MIC distributions of amoxicillin and co-amoxiclav for *Proteus mirabilis* from Urology Services.



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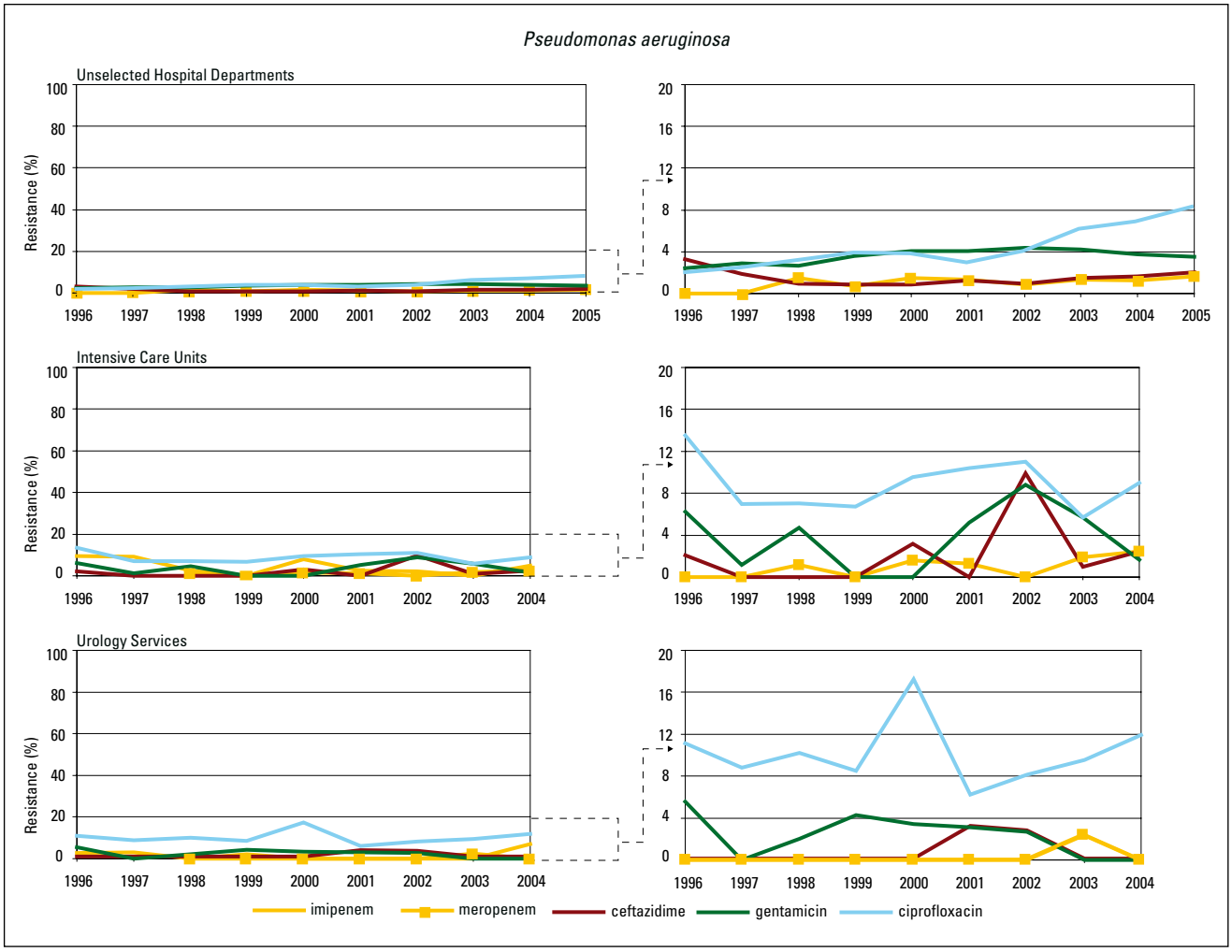


Figure 16. Trends in resistance to antibiotics among *Pseudomonas aeruginosa* from Unselected Hospital Departments, Intensive Care Units and Urology Services.

resistance in Intensive Care Units was an exception. An incidental 10% resistance was recorded in 2002 in five centres (figure 16).
Gentamicin resistance was 2-4% in Unselected Hospital Departments. Gentamicin resistance was found sporadically in some Urology Services. Resistance was found yearly in one to four Intensive Care Units, responsible for the fluctuations in the overall resistance rate from 2-7%. Amikacin- and tobramycin resistance were 1%. The MIC distributions of the three aminoglycosides are presented in figure 17. The distributions were unimodal over a broad range, in general MICs of tobramycin were two times lower than those of gentamicin and four times lower than those of amikacin. Tobramycin-resistant strains were also gentamicin-resistant, but not always amikacin-resistant.
Meropenem resistance among *P. aeruginosa* was less than 2% in Unselected Hospital Departments, Intensive Care Units and Urology Services during the whole study period.

The prevalence of ciprofloxacin resistance increased in Unselected Hospital Departments (from 2% in 1995 to 8% in 2005, figure 16). Ciprofloxacin resistance was higher in Intensive Care Units and Urology Services already in 1996. The resistance rates stabilized since 2000 around 10% in Intensive Care Units and 12% in Urology Services. The peak in resistance in 2000 in Urology Services remained unexplained: strains came from three independent centers and they were not detected anymore during follow up.

Enterococcus faecalis
Before 2002 no amoxicillin resistant *E. faecalis* were found in Intensive Care Units and Urology Services (figure 18). From 2002 on 4% of *E. faecalis* from Intensive Care Units appeared amoxicillin resistant; these strains came from one centre in 2002, from two centres in 2003 and from four centres in 2004. Resistance in Urology Services varied from 1-9% since 2002 and was found in some centres: one in 2002, four in 2003

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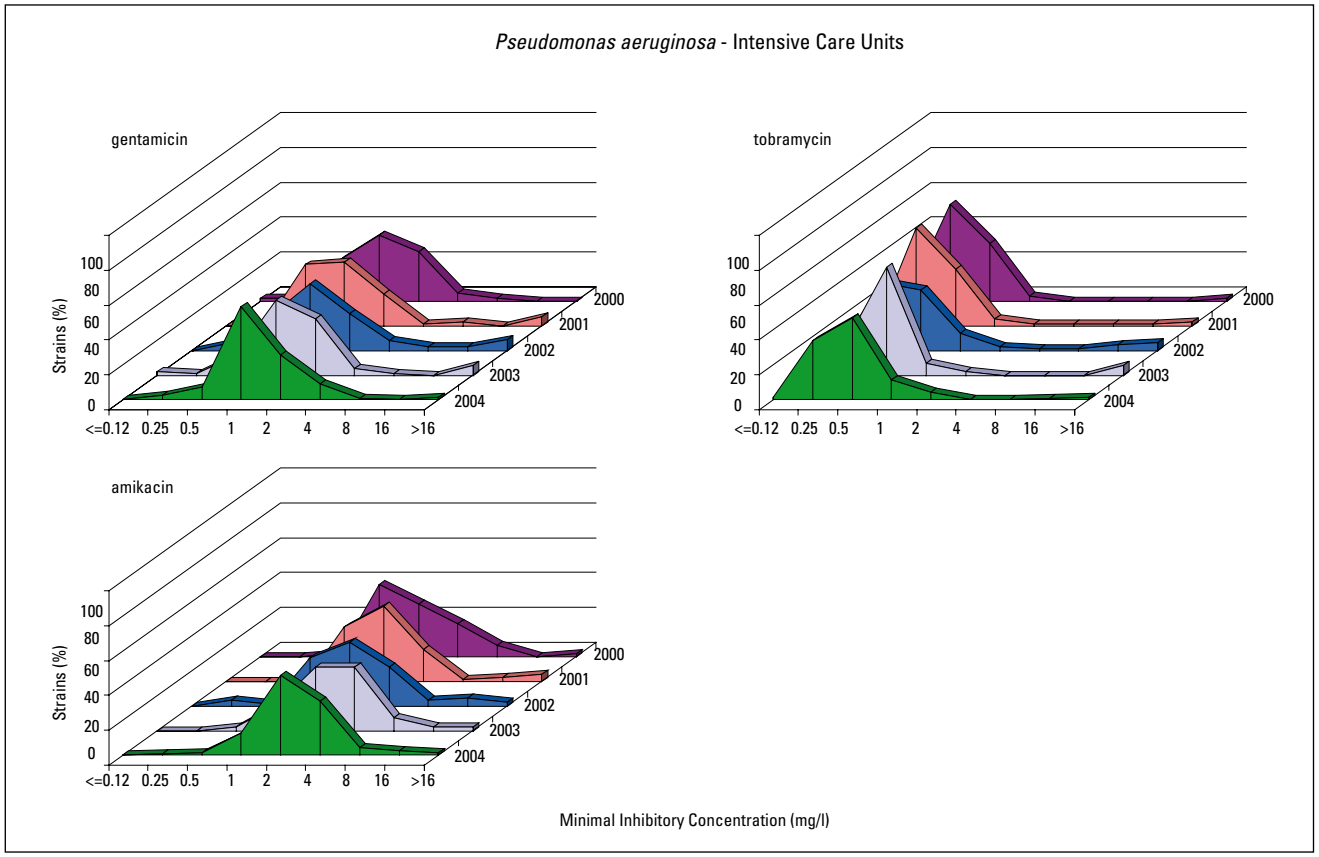
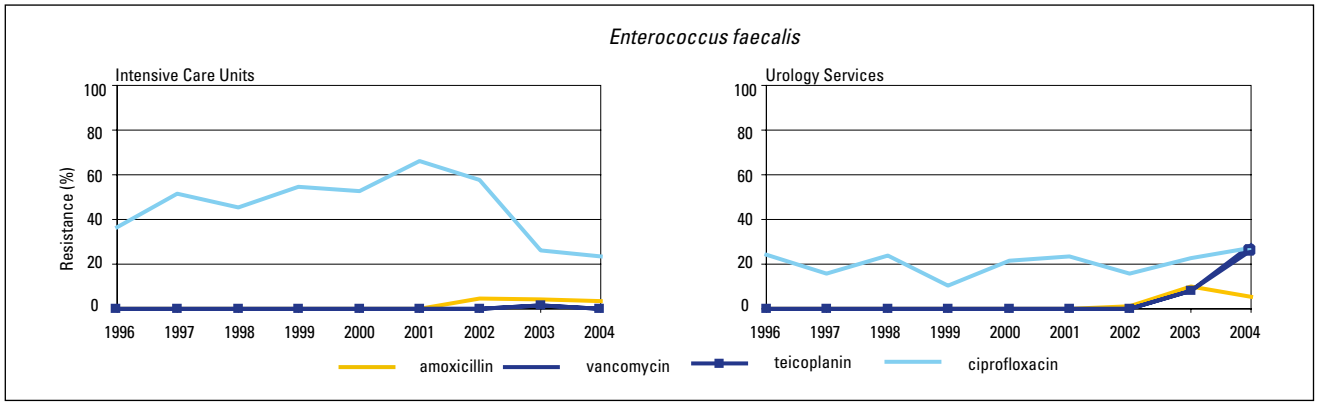


Figure 17. MIC distributions of aminoglycosides for *Pseudomonas aeruginosa* from Intensive Care Units.

and two in 2004. Vancomycin resistance in Intensive Care Units was found in one centre in 2003; two centres had vancomycin resistant strains in Urology Services. All vancomycin-resistant strains (N=12) were also teicoplanin resistant, MICs for both drugs were ≥ 256 mg/l. Eight strains were co-resistant to amoxicillin. Ciprofloxacin resistance in Intensive Care Units was consistently higher than that in Urology Services until 2002 (figure 18). It increased from 1996 to 66% in 2001 and decreased significantly thereafter to 22% in 2004.

The MIC distributions (figure 19) showed a bimodal distribution during the whole study period with a susceptible subpopulation over a range from 0.25-2 mg/l and a resistant subpopulation with MICs of 16 mg/l or more. The resistant subpopulation decreased significantly from 2001 on, whereas the peak of the susceptible cluster moved from 2 mg/l until 2001 to 1 mg/l thereafter. The resistance rate in Urology Services was approximately 20% until 2003 and increased to 28% in 2004 (figure 18). The shape of the MIC distribution of *E. faecalis* in

Figure 18. Trends in resistance to antibiotics among *Enterococcus faecalis* from Intensive Care Units and Urology Services.



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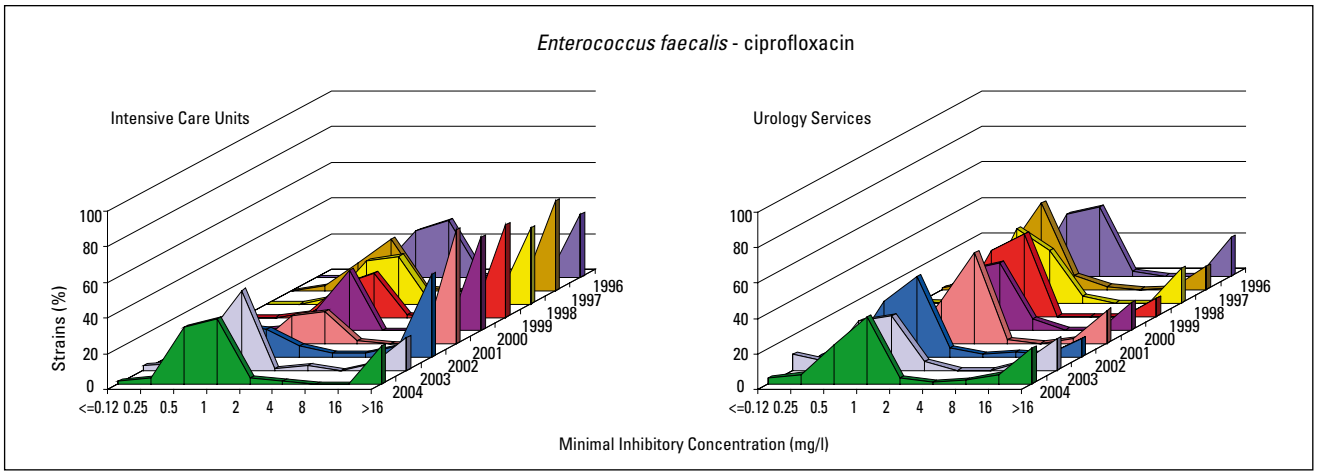


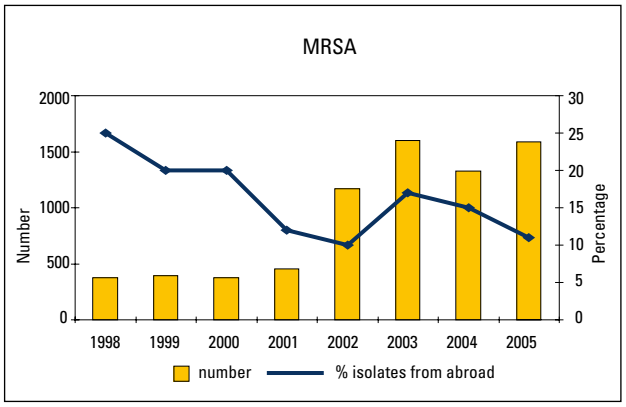
Figure 19. MIC distributions to ciprofloxacin for *Enterococcus faecalis* from Intensive Care Units and Urology Services.

Urology Services did not change over the years, but the top of the susceptible cluster is also moving from 2 mg/l before 2001 to 1 mg/l from 2002 on (figure 19).

Staphylococcus aureus

The prevalence of methicillin resistant *S. aureus* (MRSA) has historically been kept very low in The Netherlands by a stringent 'search-and-destroy' policy and restrictive usage of antibiotics. In 2005 a total of 1589 MRSA isolates were sent to the National Institute of Public Health and the Environment (RIVM), which is similar to the number in 2003 (1601). A detailed questionnaire was received for 1049 (66%) MRSA isolates. Of these, 30% were isolated from wounds/abscesses/furuncles. The proportion of persons who acquired MRSA abroad (through admission or work in a hospital abroad) was 11% (figure 20), mainly from Belgium and Germany. About 76% of the MRSA isolates were found in hospitals (76% in patients, 24% in hospital staff) and 16% of the isolates in nursing homes (64% patients, 36% staff). The remaining isolates (8%) came from patients who acquired MRSA at home (possibly community-acquired MRSA). Most commonly found were MRSA isolates with PFGE type (Dutch classification system) 15 [sequence type (ST) 22; re-emergence of EMRSA-15], 18 [ST8] and 22 [ST5], which all belong to well-known global epidemic MRSA clonal clusters. Of all MRSA isolates, 15% carried the genes for the Panton-Valentine leucocidin genes. The actual incidence of MRSA isolates per province in The Netherlands can be seen online at www.rivm.nl/mrsa.

Figure 20. Numbers and origin of MRSA in The Netherlands.



The overall percentage of MRSA in Unselected Hospital Departments increased to 2.1% in 2005, the percentage of MRSA in Intensive Care Units varied between 0-4% from 1996-2004, it was 3-4% in Urology Services (figure 21). Erythromycin resistance in Unselected Hospital Departments was slowly increasing to 9% in 2005. This was also observed for clarithromycin among isolates from the Intensive Care Units, where the resistance level reached 9% in 2004; the resistance rate in Urology Services varied between 0-4%, which is similar to the level found in the community.

Ciprofloxacin resistance rose among isolates from Unselected Hospital Departments to 5% in 2005 (figure 21). Increasing resistance was observed among Intensive Care isolates to a 14% resistance rate in 2004. Strains from Urology Services showed high resistance rates, but the numbers of strains were very small (30 in 2003, 25 in 2004). None of these quinolone resistant strains were MRSA. Resistance to quinolones in non-infectious patients in the Community is rare (0.2%); the resistance level in Unselected Hospital Departments appeared 7% in the same period. This population was mixed: it consisted of patients visiting the outpatient clinics for the first time after referral by the general practitioner or for repeating visits for treatment by specialists, of patients hospitalized for the first time also after referred by general practitioners and of patients hospitalized for longer time. So the selective pressure for emergence of quinolone resistance may come from various sources:

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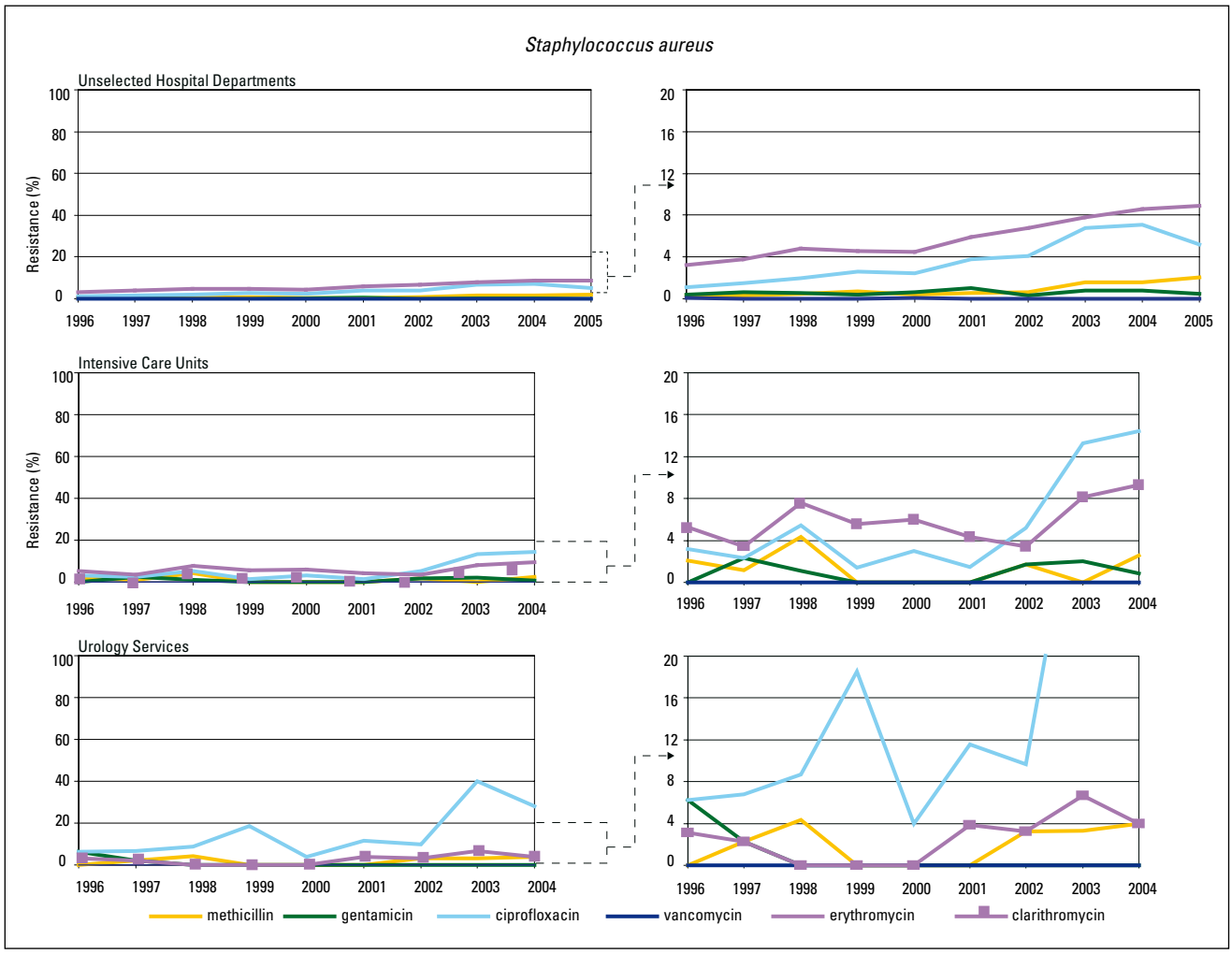
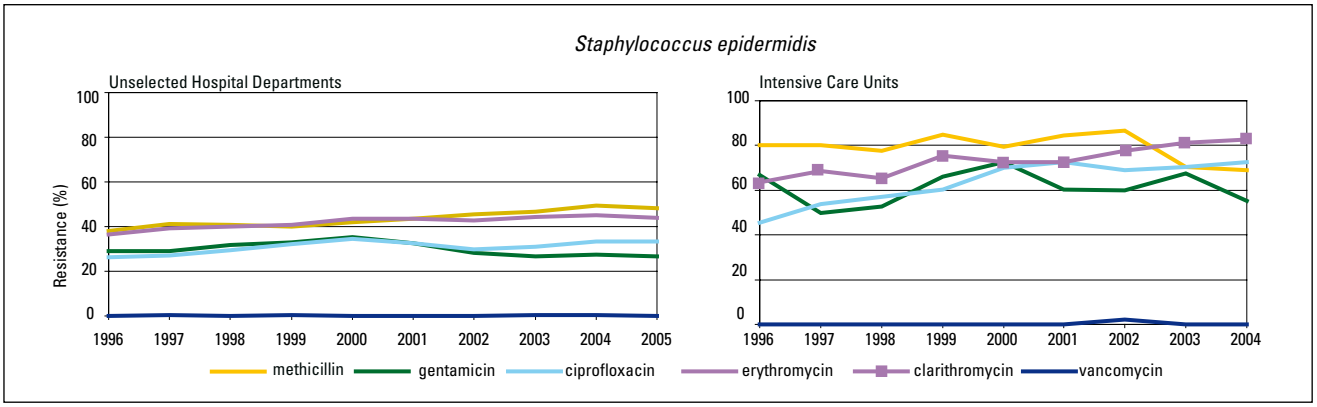


Figure 21. Trends in resistance to antibiotics among *Staphylococcus aureus* from Unselected Hospital Departments, Intensive Care Units and Urology Services.

use of quinolones by general practitioners, by specialists in outpatient clinics and by specialists of hospital departments. It is difficult to indicate which impact is most important.

Intermediate resistance to vancomycin was found in 14 of 80,000 isolates from 1995-2005 in Unselected Hospital Departments. They were not found in the selected departments.

Figure 22. Trends in resistance to antibiotics among *Staphylococcus epidermidis* from Unselected Hospital Departments and Intensive Care Units.



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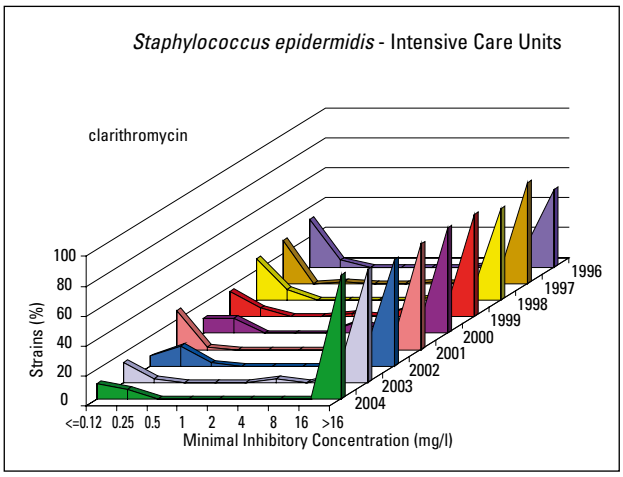


Figure 23. MIC distributions of clarithromycin for *Staphylococcus epidermidis* from Intensive Care Units.

Staphylococcus epidermidis

Methicillin resistance (determined by oxacillin resistance) was frequently found among hospital isolates of *S. epidermidis* (including other coagulase-negative species). Methicillin resistance in Unselected Hospital Departments reached 50% since 2004 (figure 22). Methicillin resistance in Intensive Care Units was 70-80%. Methicillin resistant strains were often co-resistant to erythromycin, clarithromycin, gentamicin and ciprofloxacin.

Erythromycin resistance increased in Unselected Hospital Departments from 37% in 1996 to 43% in 2000 and stabilized thereafter at this level. Clarithromycin resistance in Intensive Care Unites was higher and increased from 64% in 1996 to 83% in 2004. The MIC distribution showed a bimodal distribution with a large cluster with MICs > 16 mg/l and a very small cluster with MICs of 0.5 mg/l or less (figure 23).

Gentamicin resistance remained at a 55-60% level in Intensive Care Units. In contrast, the resistance rate of gentamicin in Unselected Hospital Departments was lower than 30%. This underlines the existence of specific populations circulating in Intensive Care Units, which differ from those found in Unselected Hospital Departments. High resistance levels to many drugs among *S. epidermidis* from Intensive Care Units are usual, apparently as a result of high selective pressure in these wards. Often strains are circulating within these wards, colonizing many patients.

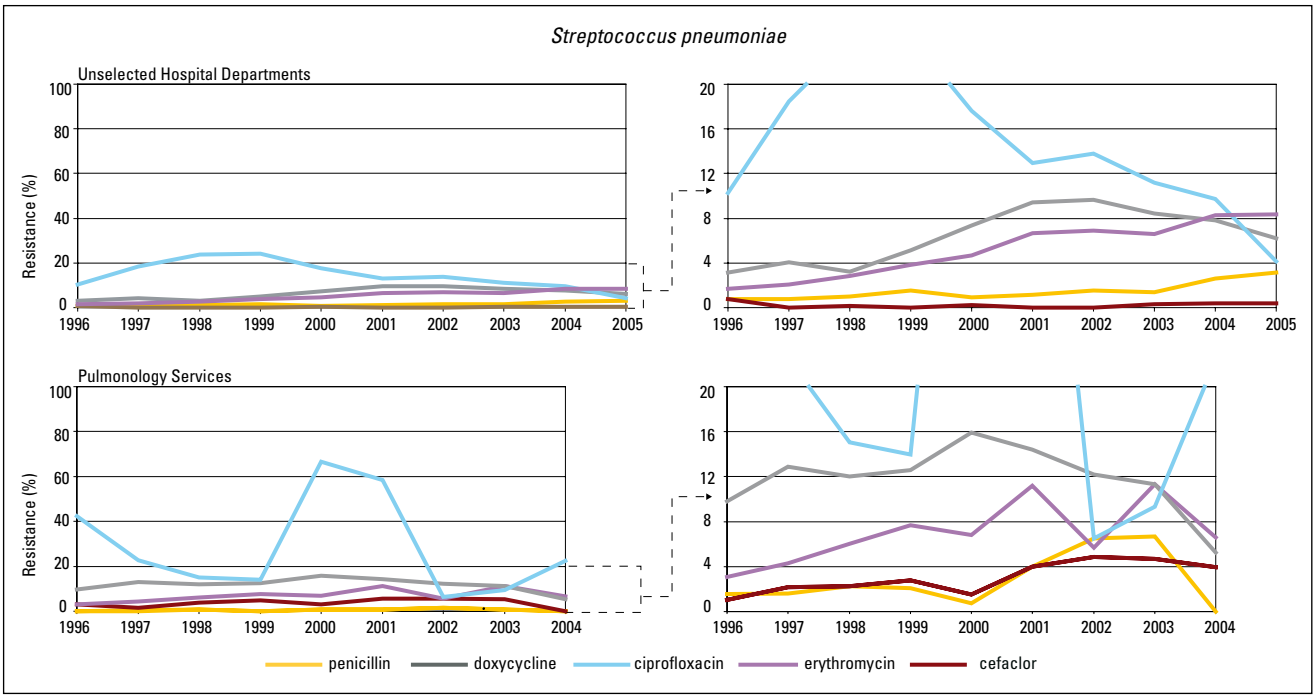
Ciprofloxacin resistance in Intensive Care Units was much higher (60% or more) compared to that in Unselected Hospital Departments (33%).

Vancomycin resistant strains were isolated occasionally in Unselected Hospital Departments; it was rare in Intensive Care Units.

Streptococcus pneumoniae

S. pneumoniae strains less susceptible to penicillin are not often isolated in The Netherlands. Yet the trend is slowly increasing: resistance was less than 1% in Unselected Hospital Departments until 1998, then it varied between 1-2% until 2003 and it increased to 3% in 2005. The resistance rate in Pulmonology Services

Figure 24. Trends in resistance to antibiotics among *Streptococcus pneumoniae* from Unselected Hospital Departments and Pulmonology Services.



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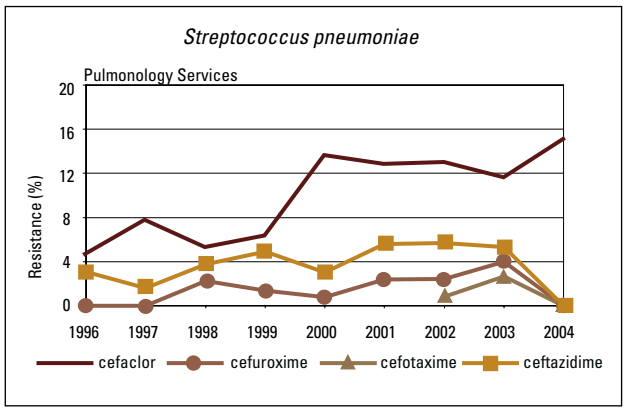
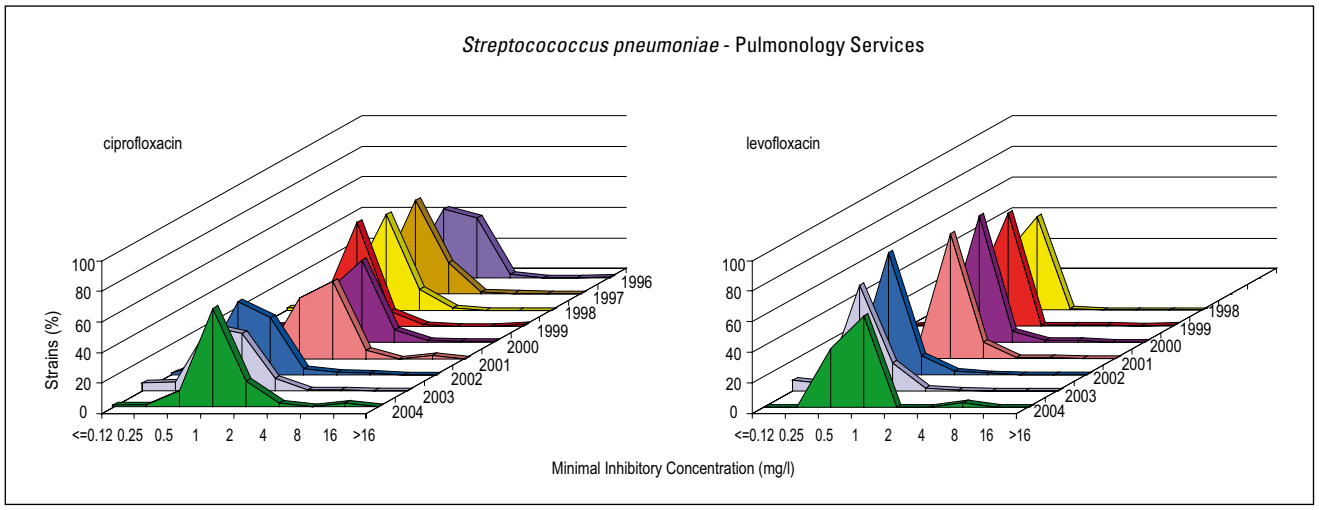


Figure 25. Trends in resistance to cephalosporins among *Streptococcus pneumoniae* from Pulmonology Services.

varied from 3.6% in 2001 and 6.5% in 2002 and 2003 to 1.5% in 2004 (figure 24). Resistance to cefaclor and cefuroxime varied between 2-5% over the years without a clear trend (figure 25). No shifts in MIC distributions or shape of the curves were observed, resistance was due to sporadic emerging strains. Increasing and fluctuating resistance to erythromycin and clarithromycin among clinical isolates of *S. pneumoniae* from all departments was observed until 2003, but it stabilized in 2004 and 2005, being 7% in Pulmonology Services and 8% in Unselected Hospital Departments.
Ciprofloxacin resistance in Unselected Hospital Departments varied until 1999 between 10% and 26%, then decreased to a level of 4% in 2005. The ciprofloxacin resistance rates in Pulmonology Services were initially much higher (in 1995 44%) compared to that in Unselected Hospital Departments, then a decrease was observed over the ensuing years (being 13% in 1999) and again an increase to levels of 60% in 2000 and 2001. Thereafter a significant decrease followed until 6.5% in 2002, which is in the same range as that in Unselected Hospital Departments, but three years later. In 2004 the resistance increased again to 22%. The shape of the graphs in Unselected Hospital Departments and Pulmonology Services is almost similar, but the peaks of resistance in Pulmonology Services were higher and at least one year earlier. Analysis of the distribution of MICs (figure 26) showed that the decrease in the rate of ciprofloxacin resistance from 1999 on was primarily due to a shift from the fully resistant category to the intermediately susceptible category until 1999, whereas a shift to the intermediate and resistant category occurred in 2000 and 2001. In 2002 and 2003 a shift from the resistant and the intermediate category to the full-susceptible category was observed. The shape of the curve in 2004 suggested a slight shift to the intermediately susceptible section. Most strains were inhibited by 1 mg/l and a small number had MICs ≥ 16 mg/l.
Ciprofloxacin is only moderately active against *S. pneumoniae* and most pulmonologists have stopped to prescribe ciprofloxacin for suspected or proven pneumococcal infections. Recently levofloxacin was launched as treatment for respiratory tract infections. Its MIC distribution (figure 26) shows a clear shift to the intermediately susceptible and unsusceptible section in 2004 compared with the years before. Since there is complete cross-resistance between levofloxacin and ciprofloxacin, the increase in ciprofloxacin resistance in 2004 may be explained by increased use and development of resistance to levofloxacin.

Haemophilus influenzae
The prevalence of amoxicillin resistance among *H. influenzae* isolated in Unselected Hospital Departments remained stable (5-8 %) until 2003. In 2004 and 2005 an increase in resistance was observed to 11% (figure

Figure 26. MIC distributions of quinolones for *Streptococcus pneumoniae* from Pulmonology Services.



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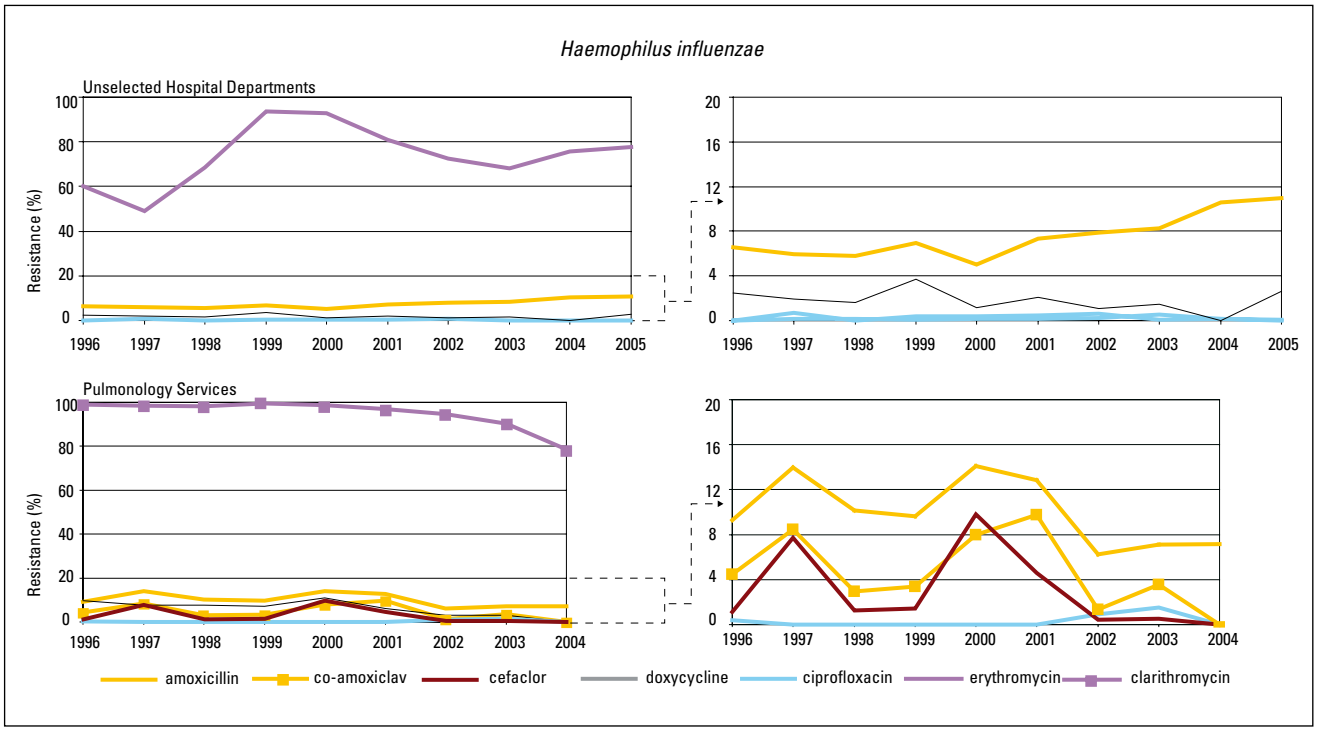


Figure 27. Trends in resistance to antibiotics among *Haemophilus influenzae* from Unselected Hospital Departments and Pulmonology Services .

27). The resistance rate in Pulmonology Services varied somewhat more (8-14%), but no real trend toward increasing rates was discernible (figure 27). Cefaclor resistance varied between 1-9%, cefuroxime resistance was 1% or less during the whole study period. The prevalence of erythromycin resistance among *H. influenzae* from Unselected Hospital Departments was high (70-90%) if all strains with reduced susceptibility (MIC>0.5 mg/l) were counted as resistant. Clarithromycin was tested for isolates from the Pulmonology Services instead of erythromycin. At the same breakpoint of 0.5 mg/l also 70-90% resistance to clarithromycin was recorded (figure 27).
Low prevalence rates (1-2%) with a peak of 4% in 1999 were found for doxycycline resistance among *H. influenzae* isolates from Unselected Hospital Departments. The resistance rates in Pulmonology Services were higher from the beginning (7-9%), but decreased to 3% in 2003.The increased resistance rates for doxycycline among *H. influenzae* isolated until 2001 may reflect doxycycline use in general practice and Pulmonology Services during the preceding years. The knowledge that doxycycline resistance was increasing together with the introduction of antibiotics like clarithromycin and levofloxacin advertised for treatment of respiratory tract infections, might have led to a change in prescription behaviour. Lower use of doxycycline may be an explanation for decreased resistance rates in the last years.

Moraxella catarrhalis
The prevalence of amoxillin resistance among *M. catarrhalis* isolated in Unselected Hospital Departments has been about 80% since 1999 and remained stable until 2002, thereafter a significant decrease to 66% in 2005 was observed (figure 28). The resistance in Pulmonology Services was decreasing from 65 % in 2002 to a level of 20% in 2004. The resistance was due to beta-lactamase since resistance to co-amoxiclav did not occur. The difference with the resistance rate in Unselected Hospital Departments is striking and unexplained.
Resistance to cefaclor and cefuroxime was occasionally found in some years but never exceeded 3%. Resistance to erythromycin showed an overall increase to 10% in 2005 in Unselected Hospital Departments.
Clarithromycin resistance in Pulmonology Services was less than 2% and did not show any trend of development of resistance. The lower resistance rate of clarithromycin compared to erythromycin may be explained by a higher intrinsic activity of clarithromycin towards *M. catarrhalis*: MICs of clarithromycin were 2-4 fold lower than those of erythromycin, which might have resulted in different resistance percentages at the same breakpoint.
Ciprofloxacin resistance was occasionally found in some years, but not recorded anymore in the last two years.
Resistance to doxycycline varied between 2-4 % in Unselected Hospital Departments during the whole study period and it was 4-8% in Pulmonology Services until 2001. Thereafter no resistance was found.

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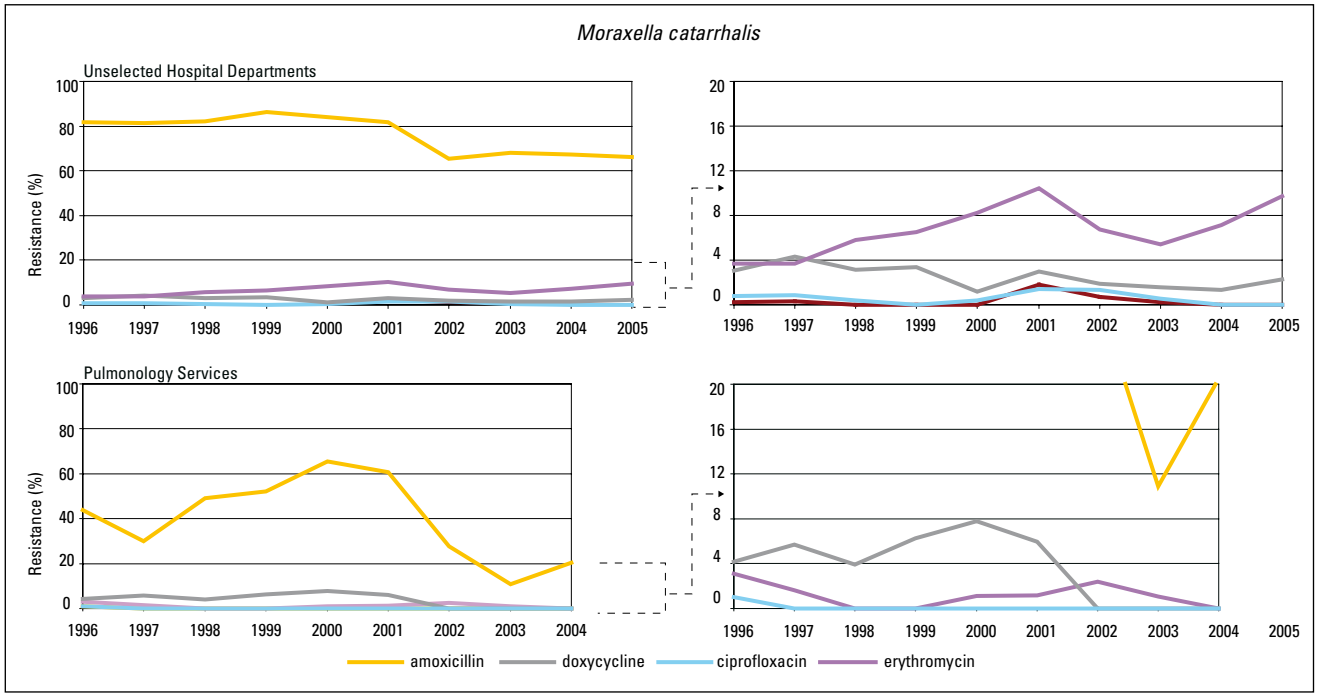


Figure 28. Trends in resistance to antibiotics among *Moraxella catarrhalis* from Unselected Hospital Departments and Pulmonology Services.

Helicobacter pylori

Amoxicillin resistance among *H. pylori* was less than 3% over the years (figure 29). Clarithromycin resistance was 1-6% without a real tendency of increasing resistance, doxycycline resistance was sporadic and metronidazole resistance was stable over the years, 19% in 2005.

Mycobacterium tuberculosis

A total of 10241 strains of *M. tuberculosis* was obtained by RIVM during 1996-2005, in 2005 the number of isolates was 850. INH resistance was fairly stable, 6.5% in 2005 (figure 30). Streptomycin resistance decreased from 10% in 2000 to 5% in 2005. The rifampicin resistance level was stable, 1.4% in 2005. Ethambutol resistance was 0.7%. In 2005 combined resistance was observed in 3% of the isolates (figure 31). Multi Drug Resistance (combined resistance to rifampicin and INH) was recorded in 0.8% of the strains in 2005, similar to earlier years. Resistance to all four tested antimycobacterial drugs was 0.7%.

Neisseria meningitidis

From 1993-2005 a total of 4277 strains from cerebrospinal fluid and 2392 strains from blood were included in the surveillance project of the Netherlands Reference Laboratory for Bacterial Meningitis of the Academic Medical Center, Amsterdam. Penicillin resistance (MIC > 0.5 mg/l) was occasionally found in

Figure 29. Trends in resistance to antibiotics among *Helicobacter pylori* from Unselected Hospital Departments.

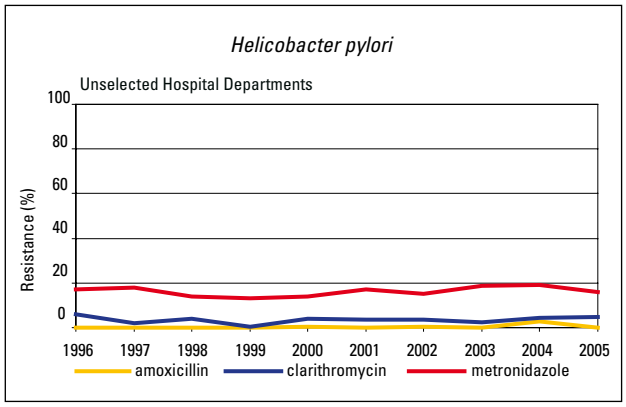
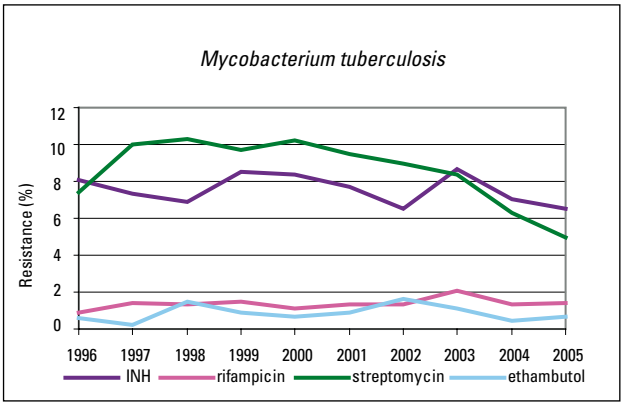


Figure 30. Trends in resistance to antibiotics among *Mycobacterium tuberculosis.*



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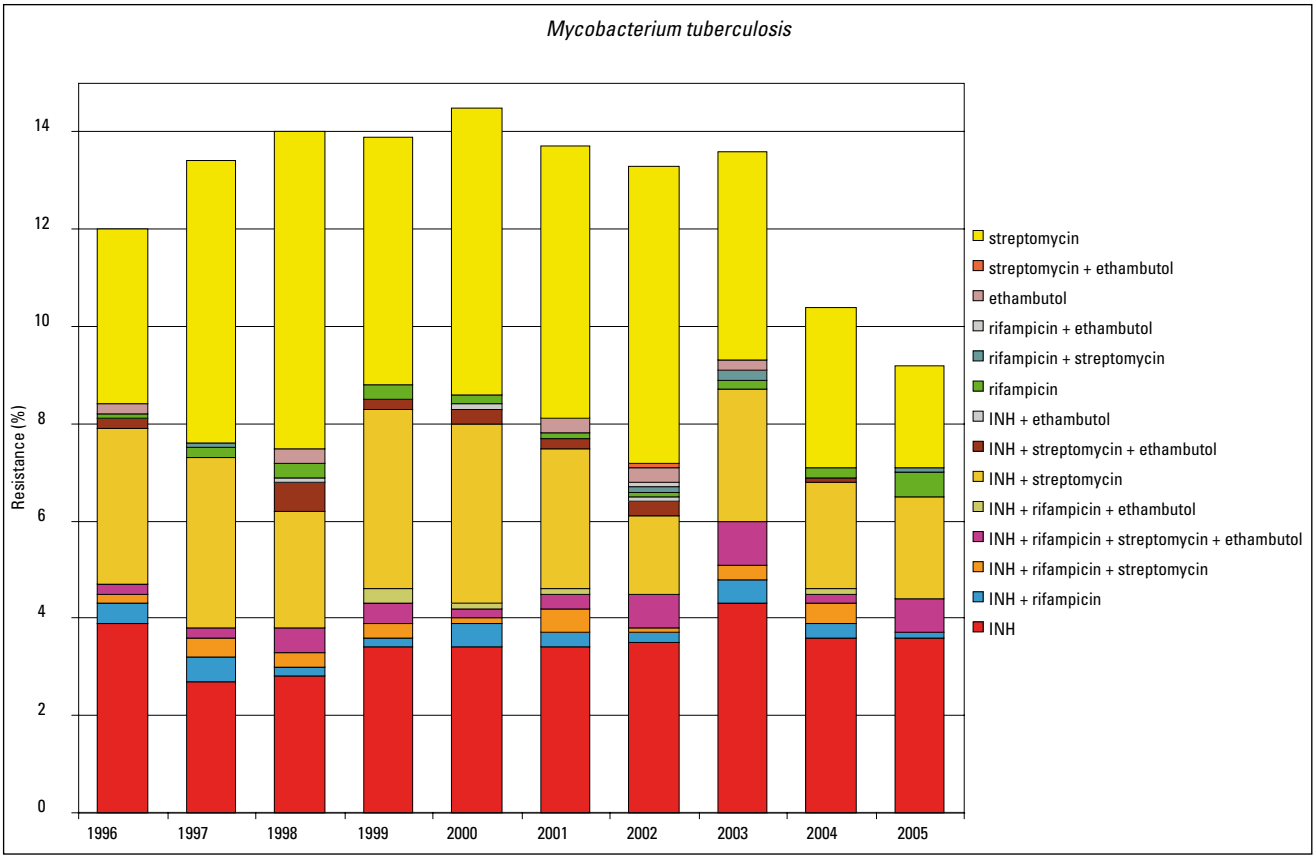


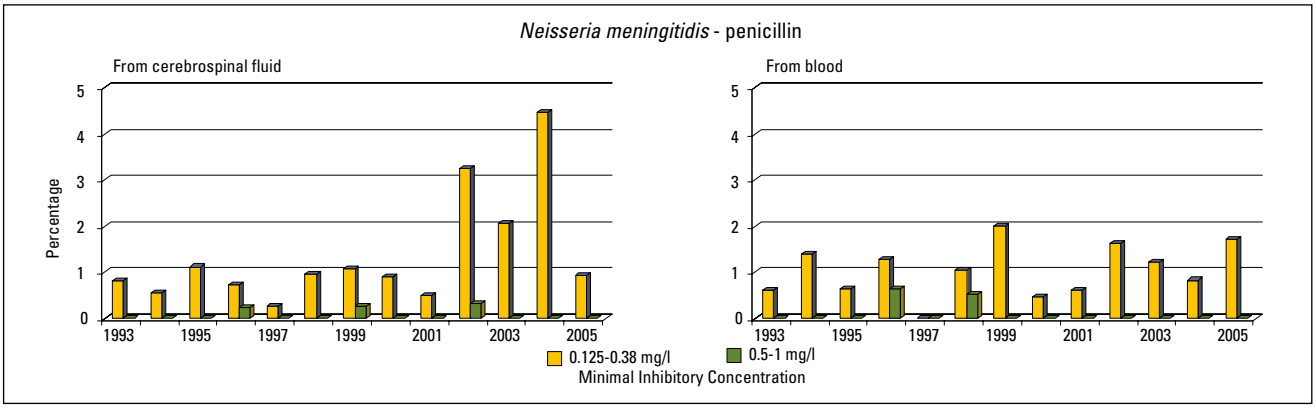
Figure 31. Trends of combined resistance among *Mycobacterium tuberculosis*.

strains both from CSF and blood until 2002 (figure 32). The percentages of strains with moderate susceptibility (MIC 0.125-0.38 mg/l) varied between 0.3 % and 4.4% during the study period, without indication of any trend.

Neisseria gonorrhoeae

The emergence of penicillin-resistance in gonococci prompted the start of a national surveillance in 1976. Until 1990 all penicillin resistant isolates (PPNG) were sent to the RIVM for susceptibility testing. Thereafter the surveillance was limited to all isolates collected in five large laboratories in Amsterdam, Rotterdam and Den Haag. The gonococci surveillance was stopped in 1999. In 2002, 2003 and 2004, the RIVM asked 39 medical microbiological laboratories to describe their methods on gonococci diagnostics and susceptibility testing and to report their results on the incidence and antimicrobial patterns. Data of 5604 strains from 25 laboratories became available. The overall incidence of gonorrhoea was 33/100.000 in 2002 and 27/100.000 in 2003. There

Figure 32.Trends in penicillin susceptibility among clinical strains of *Neisseria meningitidis*.



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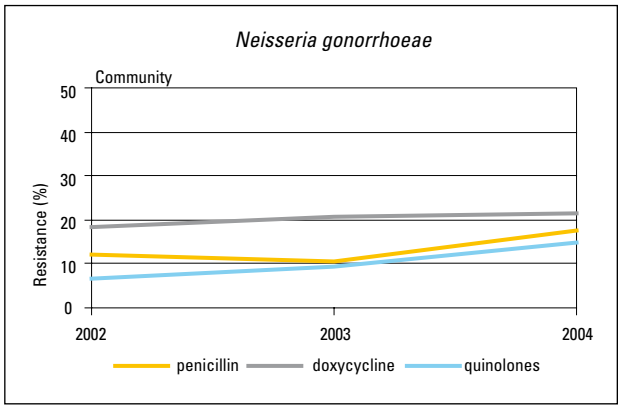


Figure 33. Trends in resistance to antibiotics among *Neisseria gonorrhoeae*.

was a significant difference in geographical distribution: the incidence in the western part of the Netherlands (Randstad) was around 100/100,000 compared to 12/100,000 in the rest of the Netherlands.
The overall penicillin resistance increased significantly from 12% in 2002 to 18% in 2004 (figure 33), doxycycline resistance increased from 18% to 21%. Most impressive was the significant increase in resistance to quinolones from 6.6% in 2002 to almost 15% in 2004. Looking at the geographic distribution, penicillin – and quinolone-resistance was lower in the Randstad compared to other regions, whereas the resistance to doxycycline was higher in the Randstad.
These resistance data are alarming; since it is clear that none of the drugs mentioned above can be relied upon for empiric therapy.
In 2006 a renewed surveillance programme to monitor resistance in gonococci will be implemented, the so called GRAS (Gonococcal Resistance to Antimicrobials Surveillance) programme. The standards for susceptibility testing given by the SWAB will be used and the MICs of penicillin, ciprofloxacin, doxycycline and cefotaxime will be generated. This may give information on the emergence and spread of antibiotic resistance in *N. gonorrhoeae* in the Netherlands and help to develop appropriate treatment regimens.

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Surveillance studies published in the international, peer-reviewed literature containing quantitative susceptibility data of bacterial pathogens isolated in the Netherlands

Apart from the surveillance data presented in NethMap on the basis of the surveillance system developed by SWAB, several individual studies by other authors have reported on the occurrence of antimicrobial resistances among various bacterial species in the Netherlands. These studies were selected for inclusion in NethMap if they met the following criteria: all studies reported on resistance rates based on the measurement of MIC's, i. e. quantitative susceptibility tests were performed on all strains. In addition, strains were collected from patients in multiple centres throughout the Netherlands and the studies were reported in peer-reviewed journals listed in the Medline database. Individually, and taken together, these studies provide further insight into the prevalence and emergence of antimicrobial resistance among medically important micro-organisms in the Netherlands. In addition to the list of studies readers are helped by a crosstable that reveals the combinations of 'bugs & drugs' for which MIC data were reported in each of the listed studies.

1. Endtz HP, Dijk WC van, Verbrugh HA et al. Comparative invitro activity of meropenem against selected pathogens fromhospitalized patients in the Netherlands. MASTIN Study Group. J Antimicrob Chemother 1997;39:149-56.
2. Buirma RJA, Horrevorts AM, Wagenvoort JHT. Incidence of multi-resistant gram-negative isolates in eight Dutch hospitals. Scand J Infect Dis 1991; suppl 78:35-44.
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7. Endtz HP, Mouton JW et al. Comparative in vitro activities of trovafloxacin (CP-99,219) against 445 gram-positive isolates from patients with endocarditis and those with other bloodstream infections. Antimicrob Ag Chemother 1997;41:1146-1149.
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16. Schouten MA, Voss A, Hoogkamp-Korstanje JAA. Antimicrobial susceptibility patterns of enterococci causing infections in Europe. Antimicrob Ag Chemother 1999;37:2542-2546.

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17. Hoogkamp-Korstanje JAA, Roelofs-Willemse J and the Susceptibility Surveillance Study Group. Antimicrobial resistance in Gram-negative bacteria from Intensive Care Units and Urology Services. A nationwide study in the Netherlands 1995-2000. Int J Antimicrob Ag 2003;21:547-556.
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19. Determining incidence of extended spectrum beta-lactamase producing Enterobacteriaceae, vancomycin-resistant *Enterococcus faecium* and methicillin-resistant *Staphylococcus aureus* in 38 centres from 17 countries: the PEARLS study 2001-2002. Int J Antimicrob Agents 2004;24:119-24.
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Table 1. Crosstable of combinations of species of bacteria and antibiotics for which MIC data are presented in the individual studies listed above.

	Staphylo-cocci	Strepto-cocci	Pneumo-cocci	Entero-cocci	Entero-bacte-riaceae	Non-fermenting GNB	*H. influenzae*	*H.pylori*	Meningo-cocci
Penicillin	1,7,10	7,10	1,5,8	1					5,8
Oxacillin	1,18,19,20								
Methicillin	3								
Flucloxacillin	7,10								
Ampicilin				3	2	2	8		
Amoxicillin		7,10	1	1,7,10,16	17			6	
Co-amoxiclav			9		1,2,4,17	1,2	1,9		
Piperacillin	3			3	2,3,4	2,3			
Piperacillin/tazobactam	1,3		1	1,3	1,3,4	1,3	1		
Ticarcillin/clavulanate	3			3	1,2,3	1,2,3	1		
Mezlocillin					2	2			
Cefazolin					2	2			
Cefoxitin					4				
Cefuroxime	10	10			1,2	1,2	1		
Ceftriaxone			5,8		2	2	8		5,8
Cefotaxime		10	22		1,2,4	1,2,19	1		
Ceftazidime					1,2,3,4,17	1,2,3,17,19	1		
Cefpirome				16	4				
Cefepime					4				
Aztreonam					2	2			
Imipenem	1,3,11	11	1,11	1,3,11,16	1,2,3,17	1,2,3,17	1		
Meropenem	1,11	11	1,11	1,11,16	1,4	1	1		
Vancomycin	1,7,10,11	7,10,11	1,11,22	1,7,10,11,16, 19					
Teicoplanin	7,10,11	7,10,11	11	7,10,11,16					
Linezolid	14	14	14,22						
Gentamicin	1,3		1	1,10,16	1,2,3,4,17	1,2,3,17	1		
Tobramycin					2,4	2			
Netilmicin					4				
Amikacin	3				2,3,4	2,3			
Norfloxacin					17	17			
Ciprofloxacin	1,3,7,11,15	7,11,15	1,9,11,15	1,3,7,11,15,16	1,2,3,15,17	1,2,3,15,17	1,9,15		
Ofloxacin	7,15	7,15	15	7,15,16	4,15	15	15		
Trovafloxacin	7	7		7,16				6	
Sparfloxacin	7,11	7,11	9,11	7,11,16			9		
Pefloxacin	7	7		7					
Levofloxacin			22						
Moxifloxacin			22	16					
Clindamycin	1,10,11	10	1,22	1,10					
Erythromycin	1,10,11	10,11	1,11,22	1,10,11,15					
Clarithromycin	10	10,11	9,11,22	10,11			9	6,12,21,23	
Telithromycin			22						
Tetracycline								6	
Minocycline				10					
Chloramphenicol			5,8	16			8		5,8
Quinupristin/dalfopristin	10,11	10,11	11	10,11,15					
Rifampicin	10,11	11	11	11					5,8
Metronidazole								6,12,13, 21,23	
Trimethoprim					17				
Co-trimoxazole					17				
Nitrofurantoin					17				

Numbers correspond with referencenumbers listed above this crosstable.

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Appendix

List of abbreviations

ATC	Anatomical Therapeutic Chemical classification system
ATCC	American Type Culture Collection
CBO	Institute for Quality in Healthcare
CBS	Statistics Netherlands, i.e. the Central Statistical Office of the Netherlands
CFU	Colony Forming Units
CIDC	Central Institute for Animal Disease Control
CLSI	Clinical and Laboratory Standards Institute (formerly NCCLS)
CRG	Dutch Committee on Guidelines for Susceptibility Testing
DDD	Defined Daily Dose
CVZ	College for Health Care Insurance's
EARSS	European Antimicrobial Resistance Surveillance System
ECCMID	European Congress on Clinical Microbiology and Infectious Diseases
ESAC	European Surveillance of Antibiotic Consumption
EU	European Union
GIP	Drug Information Project
ISIS	Infectious Diseases Information System
LINH	Netherlands Information Network in General Practice
MIC	Minimal Inhibitory Concentration
MSSA	Methicillin Sensitive *Staphylococcus aureus*
MRSA	Methicillin Resistant *Staphylococcus aureus*
NCCLS	National Committee for Clinical Laboratory Standards
NHG	Dutch College of General Practitioners
NIVEL	Netherlands Institute of Health Services Research
NVMM	Netherlands Society for Medical Microbiology
PRISMANT	Institute for Health Care Information and Consultancy
RIVM	Netherlands Institute for Public Health and the Environment
SFK	Foundation for Pharmaceutical Statistics
SWAB	Foundation of the Dutch Working Party on Antibiotic Policy
WIP	Working Party on Infection Prevention
WHO	World Health Organisation

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Demographics and denominator data

Table A Trend in the number of inhabitants in the Netherlands (Source: CBS).

Year	Number of inhabitants (1 January)
1997	15 567 107
1998	15 654 192
1999	15 760 225
2000	15 863 950
2001	15 987 075
2002	16 105 285
2003	16 192 572
2004	16 258 032
2005	16 305 526

Table B Resource indicators of acute Hospital care in the Netherlands (Source: CBS).

Year	Hospitals	Discharges (x 1000)	Bed-days (x 1000)	Length of stay (mean in days)
1998	115	1524	13800	9.1
1999	109	1501	12985	8.7
2000	104	1460	12386	8.5
2001	101	1458	11912	8.2
2002	98	1501	12086	8.1
2003	97	1574	11800	7.5
2004	97	1656	11759	7.1

Table C Resource indicators of University Hospital care in the Netherlands (Source: CBS).

Year	Hospitals	Discharges (x 1000)	Bed-days (x 1000)	Length of stay (mean in days)
1998	8	200	2032	10.2
1999	8	201	1914	9.5
2000	8	197	1842	9.4
2001	8	193	1805	9.4
2002	8	193	1820	9.4
2003	8	200	1837	9.2
2004	8	210	1830	8.7

Table D Resource indicators of General Hospital care in the Netherlands (Source: CBS).

Year	Hospitals	Discharges (x 1000)	Bed-days (x 1000)	Length of stay (mean in days)
1998	107	1324	11768	8.9
1999	101	1300	11071	8.5
2000	96	1263	10544	8.3
2001	93	1265	10107	8.0
2002	90	1308	10266	7.8
2003	89	1374	9963	7.3
2004	89	1446	9929	6.9

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Materials and methods

Surveillance of antibiotic use in humans

Data on the consumption of antibiotics were collected by a pre-established protocol, using the ATC/DDD classification that is developed by WHO Collaborating Centre for Drug Statistics Methodology (http://www.whocc.no). The Defined Daily Dose is the assumed average maintenance dose per day for a drug used for its main indication in adults. The DDD is a unit of measurement and does not necessarily reflect the recommended or prescribed daily dose. It enables however comparison of drug consumption statistics at international and other levels.
NethMap 2006 includes data on the use of antibiotics for systemic use, group J01 of the Anatomical Therapeutic Chemical (ATC) classification system. The 2006 update of the ATC/DDD classification system is used to calculate the number of DDDs in this report.

Primary health care

All antibiotics for human use are prescription-only medicines in the Netherlands. The majority of antibiotics are delivered to patients by community pharmacies. Direct delivery of medicines by general practitioners from their own pharmacy reaches approximately 8.4% of the Dutch population, mainly in rural areas.[1]

Data on the use of antibiotics in primary health care were obtained from the Foundation for Pharmaceutical Statistics (SFK; http://www.sfk.nl) and expressed as the number of Defined Daily Doses (DDD) per 1000 inhabitants per day.
Sales data from approximately 90% of all community pharmacies (1585 out of 1732 community pharmacies) are transferred monthly to SFK in an electronic format. The data are subsequently weighted statistically and extrapolated to cover 100% of the deliveries by community pharmacies. The total number of DDDs is divided by the total number of inhabitants that is registered by a community pharmacy (approximately 91.6 of the total number of inhabitants in the Netherlands). Data on the number of inhabitants in the Netherlands are obtained from Statistics Netherlands (CBS; http://www.cbs.nl).
Regional data on the use of antibiotics were also obtained from SFK. The Netherlands is subdivided in 31 AWBZ-regions (figure 1).

SFK data on antibiotic use do not include the use of antibiotics in hospitals. Antibiotics prescribed by hospital based medical specialists to their outpatients are however included. Deliveries from community pharmacies to nursing-homes as an institute are not covered.

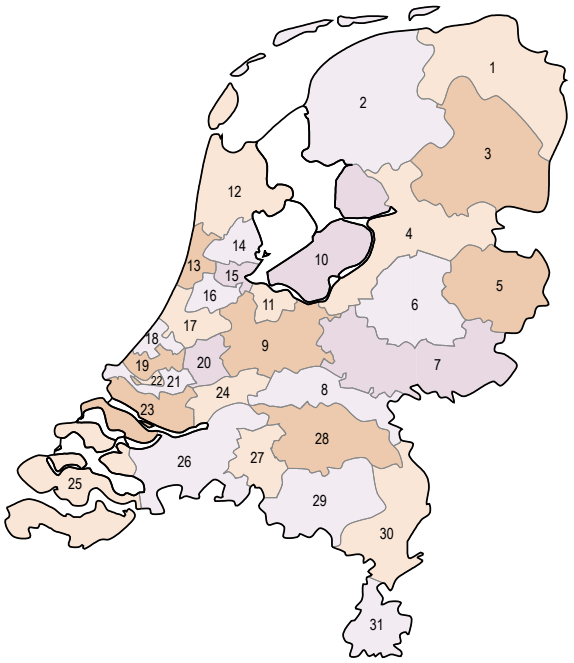


Figure 1. AWBZ-regions.

Hospitals

Data on the use of antibiotics in Dutch hospitals were collected by the SWAB by means of a questionnaire distributed to all Dutch hospital pharmacists. The number of admissions and the number of days spent in the hospital (bed-days) are also registered in the questionnaire. The use of antibiotics is expressed as DDD/100 patient-days and in DDD/100 admissions.[2] The number of patient-days is calculated by subtracting the number of admissions from the number of bed-days to compensate for the fact that in the bed-days statistics both the day of admission and the day of discharge are counted as full days.

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The total number of bed-days and discharged patients (approximates the number of admissions) were obtained from Statistics Netherlands (CBS; http://www.cbs.nl). Data from a sample of 60% of the hospitals are presented in this report.

References

[1] Batenburg-Eddes T van, Berg Jeths A van den, Veen AA van der, Verheij RA, Neeling AJ de. Regional variations in use of pharmaceuticals. National Institute of Public health and the Environment. Bilthoven (the Netherlands), 2002. ISBN 90 6960 099 4. http://www.rivm.nl/bibliotheek/rapporten/270556005.html

[2] 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;55:805-808.

Surveillance of antibiotic resistance and susceptibility testing

Community

Escherichia coli

During 2003 and 2004 strains of *Escherichia coli* were isolated from the urine of consecutive patients consulting their general practitioner in the Netherlands with new complaints compatible with acute uncomplicated urinary tract infection. Thirty-one general practitioners from 21 sentinel stations participating in the sentinel project of the NIVEL joined the study. Patients presenting to their general practitioner with either dysuria, stranguria, urinary frequency or urgency were included irrespective of age and gender and / or presence of indwelling catheter or urinary tract infection in the past three months. Dip slides inoculated with patient's urine (clean voided urine) were sent to the Department for Medical Microbiology of the University Hospital Maastricht for culture and quantitative susceptibility testing of pathogens (according to the SWAB Standard). Bacterial growth was recorded as $< 10^3$,10^3 -10^5 and $> 10^5$ colony forming units per ml. For isolation and identification of the uropathogens isolated standard microbiological methods were used that included API 20E for *Enterobacteriaceae*.

Staphylococcus aureus

During 2005 strains of *Staphylococcus aureus* were isolated from nose swabs taken from patients attending their general practitioner with a non-infectious complaint. Twenty-two general practitioners, most of them participating in the sentinel project of the Netherlands Institute for Health Services research (NIVEL) joined the study. The participating practitioners were located all over the Netherlands, both from cities and rural areas. The nose swabs were taken by the general practitioner and sent to the department of Medical Microbiology of the University Hospital Maastricht for culture and susceptibility testing. For isolation and identification standard microbiological methods were used which include among others the detection of the catalase and coagulase enzymes. The study was approved by the Medical Ethical Committee of the University Hospital Maastricht.
The quantitative antimicrobial susceptibility tests were performed by broth microdilution according to the SWAB standard. *E. coli* ATCC 25922, *E. coli* ATCC 35218 and *S. aureus* ATCC 29213 were used as reference strains. The breakpoints for resistance used were those defined by the NCCLS and the SWAB Standard.

Neisseria meningitidis

From 1993-2005 the Netherlands Reference Laboratory for Bacterial Meningitis received isolates from CSF and / or blood of patients with meningococcal disease. These strains were submitted by 75 bacteriological laboratories distributed over the country. The susceptibility to penicillin was determined by the E-test method. Strains with MIC <= 0.125 mg/l were recorded susceptible, with MIC 0.125-0.38 mg/l moderately susceptible and with MIC > 0.38 mg/l resistant.

Neisseria gonorrhoeae

The National Institute for Public Health and the Environment (RIVM) initiated a study on epidemiology of gonorrhoea and the prevalence of antibiotic resistance in 2002 by contacting 39 microbiological laboratories. A total of 32 laboratories delivered data on origin of the clinical materials, diagnostic methods and susceptibility testing in 2002, 2003 and 2004. Isolates (N=5604) were identified by standard microbiological methods. Susceptibility was determined by agar dilution, agar diffusion and by E-test.

Mycobacterium tuberculosis

The first isolate of *M. tuberculosis* of each patient with tuberculosis in The Netherlands is routinely sent to the RIVM for susceptibility testing and confirmation of identification. Isolates, obtained after more than 6 months from the same patient are judged a new isolate. The susceptibility of the strains is tested quantitatively with a standard agar dilution assay according to the recommendations of the NCCLS. The antibiotics chosen for reporting are INH, rifampicin, streptomycin and ethambutol. Resistance rates represent the proportion of moderately and fully resistant strains
The susceptibility data of 10241 strains, isolated from 1996-2005 are presented in this report.

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Hospitals

Isolates of major pathogenic species were derived from two different sources of hospitals.

Unselected Hospital Departments

The susceptibility data of strains isolated from clinical samples of patients from Unselected Hospital Departments (clinics and out-patient clinics) were forwarded to the National Institute for Public Health and the Environment (RIVM), partly via the online electronic ISIS system, partly on the basis of a longstanding collaborative agreement between the regional public health laboratories and the RIVM. Identification and susceptibility testing was routinely carried out in the regional public health laboratories. Only the first isolate of each species from a patient was used for the study. The species distribution of isolates from various body sites appeared fairly stable during the period. Most isolates came from urine, respiratory tract, pus, wound and blood. The numbers of isolates per species and in each of these clinical materials in 2005 are given in table 1.

The susceptibility of the strains from the Unselected Hospital Departments was routinely determined according to the standard techniques used in the individual laboratories. These methods include standardised agar diffusion assays as well as home-made or commercial broth microdilution assays. The breakpoints defined by the CLSI or by the CRG were used for calculating resistance rates. Resistance rates for *E. coli*, *P. mirabilis*, *K. pneumoniae, P. aeruginosa, S. aureus* and *S. epidermidis* represent the proportion of strains that were considered fully resistant. Resistance

Table 1. First isolates per clinical sample of patients in Unselected Hospital Departments in 2005.

Species (number of isolates)	Clinical material (number)			
	Blood (N=3206)	Pus and Wound (N=17778)	Respiratory tract (N=9737)	Urine (N=18408)
Gram-positive cocci (N=18833)				
Staphylococcus aureus (N=8921)	427	6635	1297	562
Enterococcus sp.(N=4190)	142	1083	70	2895
S.epidermidis incl coag. neg. Staphylococcus (N=2004)	859	658	35	452
Streptococcus pneumoniae (N=1715)	352	298	1055	10
Streptococcus agalactiae (N=1461)	39	655	104	663
Streptococcus pyogenes (N=542)	46	430	52	14
Subtotal	1865	9759	2613	4596
Enterobacteriaceae (N=22145)				
Escherichia coli (N=12166)	735	2488	704	8239
Proteus mirabilis (N=2700)	56	822	225	1597
Klebsiella pneumoniae (N=2327)	174	481	378	1294
Enterobacter cloacae (N=1504)	77	667	350	410
Klebsiella oxytoca (N=1209)	68	389	249	503
Other Enterobacteriaceae (N=2239)	70	779	533	857
Subtotal	1180	5626	2439	12900
Respiratory pathogens (N=4396)				
Haemophilus influenzae (N=2807)	28	453	2325	1
Moraxella catarrhalis (N=979*)*	2	90	887	0
Haemophilus parainfluenzae (N=548)	3	91	452	2
Neisseria meningitidis (N=62)	22	2	38	0
Subtotal	55	636	3702	3
Non-fermenters (N=3537)				
Pseudomonas aeruginosa (N=3409)	99	1459	966	885
Acinetobacter baumannii (N=128)	7	80	17	24
Subtotal	106	1539	983	909
Helicobacter pylori (N=218)	0	218	0	0

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rates for *H. influenzae, M. catarrhalis* and *S. pneumoniae* include strains that showed intermediate susceptibility (I+R, MIC > lower breakpoint).
The results of susceptibility testing of the indicator strains, identified by the SWAB standard and belonging to this collection are presented in this report.

Specific Wards
Unique unrelated consecutive isolates isolated from various clinical materials of patients admitted to Intensive Care Units, from urine of patients admitted to Urology Services and from respiratory specimens of patients admitted to Pulmonology Services were yearly collected from March 1st to October 1st. A maximum of 100 isolates per ward were collected each year. The strains were identified at the local laboratory for medical microbiology, stored at -20^{0}C and then sent to a single laboratory (department of Medical Microbiology of the UMC St Radboud, Nijmegen from 1995-2001, and the department of Medical Microbiology of the University Hospital Maastricht from 2002-2004) for quantitative susceptibility testing. The results of 16,057 indicator strains (table 2) are presented in this report.
The susceptibility of the strains from the specific wards was determined quantitatively, i.e. by MIC determinations by broth microdilution assays using the recommendations of the CLSI for *E. coli*, *P. mirabilis*, *K. pneumoniae*, *P. aeruginosa*, *E. faecalis*, *S. aureus* and *S. epidermidis*. Resistance rates of these organisms likewise represent the proportion of fully resistant strains. For *H. influenzae*, *M. catarrhalis* and *S. pneumoniae* the lower breakpoints (MIC > lower breakpoint) were used to enable comparison with the data of strains from Unselected Hospital Departments. *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *H. influenzae* ATCC 49247 and *S. aureus* ATCC 25923 were used as control strains in the MIC tests performed in the central laboratory.

Table 2. Number of indicator strains (N=16,057) isolated from patients admitted to specified hospital wards and tested for their susceptibility to antibiotics in the period 1996-2004.

Species	Intensive Care Units	Urology Services	Pulmonology Services
E. coli	1329	4498	
K. pneumoniae	392	515	
P. mirabilis	294	623	
P. aeruginosa	799	349	
E. faecalis	590	893	
S. aureus	756	263	
S. epidermidis	476	223	
S. pneumoniae			1316
H. influenzae			1855
M. catarrhalis			886

The antibiotics chosen for reporting were the antibiotics indicated by the Resistance Surveillance Standard of the SWAB published in 1999. This SWAB Resistance Surveillance Standard was also the guideline used for the presentation of these data. The guideline provides criteria for indicator-organisms, indicator-antibiotics, methods and breakpoints to be used.

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