NETHMAP 2007



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

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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 2007 – Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in The Netherlands.

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Table 1 Centres contributing to the surveillance of antimicrobial resistance

			COM	IUP	PH ISIS	Men	Gon
Groningen	Delfzijl	Delfzicht Hospital				0	
	Groningen	Academic Medical Centre				0	0
		Regional Laboratory for Public Health		0	0	0	0
	Hoogeveen	General practice	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	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	
	Arnhem	Regional Laboratory for Public Health			0	0	0
	Barneveld	General practice	0				
	Doetinchem	Slingeland Hospital				0	
	Ede	Gelderse Vallei Hospital				0	
	Harderwijk	St Jansdal Hospital				0	
	Nijmegen	University Medical Centre St Radboud		0		0	0
		Regional Laboratory for Public Health			0	0	
Utrecht	Amersfoort	Meander Medical Centre				0	0
		General practice	0				
	Bilthoven	National Institute for Public Health and the Environment			0		0
	Nieuwegein	Sint Antonius Hospital		0	0	0	0
	Utrecht	Diakonessenhuis				0	
		General practice	0				
		Neth Institute for Health Services Research NIVEL	0				
		Mesos Medical centre				0	
		SALTRO					0
		University Medical Centre				0	0
	Zeist	Diakonessenhuis				0	
Flevoland	Emmeloord	General practice	0				
Noord Holland	Alkmaar	Medical Centre Alkmaar				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 Andreas Hospital				0	
	Baarn	Meander Medical Centre				0	
	Bloemendaal	General practice	0				
	Haarlem	General practice	0				
		Regional Laboratory for Public Health		0	0		
	Hilversum	Central Bacteriological Laboratory				0	
	Hoorn	Westfries Gasthuis				0	
	Zaandam	Zaans Medical Centre				0	0

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Table 1 Continued

			COM	IUP	PH ISIS	Men	Gon
Zuid Holland	Brielle	General practice	0				
	Capelle a/d IJssel	IJsselland Hospital				0	
	Delft	SSDZ laboratories				0	0
	's-Gravenhage	Bronovo Hospital		0		0	
		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	Diakonessenhuis		0		0	
		KML Laboratory				0	
		University Medical Centre					0
	Leiderdorp	Rijnland Hospital				0	
	Rotterdam	General practice	0				
		Erasmus University Medical Centre				0	0
		Ikazia Hospital					0
		Medical Centre Rijnmond Zuid		0	0	0	
		Sophia Children's Hospital				0	
		St Franciscus Gasthuis				0	
	Schiedam	Vlietland Hospital				0	
	Spijkenisse	Ruwaard vd Putten Hospital			0	0	0
	Voorhout	General practice	0				
	Woerden	Zuwe Hofpoort Hospital				0	
Noord Brabant	Bergen op Zoom	Lievensberg Hospital				0	
	Breda	Amphia Hospital					0
	Eindhoven	General practice	0				
	's Hertogenbosch	Bosch Medical Centre			0		0
		Regional Laboratory for Public Health				0	
	Oisterwijk	General practice	0				
	Roosendaal	Franciscus Hospital				0	
	Rosmalen	General practice	0				
	Tilburg	Regional Laboratory for Public Health		0	0	0	0
	Veldhoven	Laboratory for Medical Microbiology				0	0
Limburg	Heerlen	Regional Laboratory for Public Health			0	0	0
	Hoensbroek	General practice	0				
	Kerkrade	Atrium Hospital Kerkrade				0	
	Leudal	General practice	0				
	Maastricht	General practice	0				
		Academic Medical Centre		0		0	0
	Melick	General practice	0				
	Roermond	General practice	0				
		Laurentius Hospital			0	0	0
	Sittard	Maasland Hospital				0	
	Stamproy	General practice	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=Gonorhoea Surveillance)

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Centres 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 Amstelland; Amsterdam, Academisch Medisch Centrum; Amsterdam, VU Medisch Centrum; Amsterdam, BovenIJ Ziekenhuis; Amsterdam, O.L. Vrouwe Gasthuis; Amsterdam, Slotervaart Ziekenhuis, 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, Diakonessenhuis; 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, Diakonessenhuis 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

This is the fifth SWAB/RIVM NethMap report on the use of antibiotics and trends in antimicrobial resistance in the Netherlands in 2006 and before. NethMap is a product of cooperative efforts of members of The Netherlands Society for Infectious Diseases, The Netherlands Society of Hospital Pharmacists and the Netherlands Society for Medical Microbiology. In 1996 the three societies created the Dutch Working Group on Antibiotic Policy, known as 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 micro organisms in the Netherlands, thereby contributing to the quality of care in the Netherlands.

Because of the multidisciplinary composition of SWAB, this foundation can be considered the Dutch equivalent of the Intersectoral Coordinating Mechanisms (ICM's), recommended by the European Union (2001), to control emerging antimicrobial resistance and promote rational antibiotic use.

SWAB has started several major initiatives to achieve its goals. Among these are training programmes for the rational prescribing of antimicrobial drugs, development of evidence based prescription guidelines, the implementation of tailor made hospital guides for antibiotic prophylaxis and therapy and an integrated nationwide surveillance system for antibiotic use and antimicrobial resistance. These initiatives are corresponding well with the recommendations from the Dutch Council of Health Research (2001).

Following these recommendations SWAB's work was and still is made possible by structural funds provided by the Ministry of Health, Welfare and Sports and through the Dutch Centre for Infectious Diseases Control (Centrum voor Infectieziektenbestrijding, CIb) in The National Institute of Public Health and the Environment (RIVM).

NethMap 2007 extends and updates the information of the annual reports since 2001. NethMap parallels the monitoring system of antimicrobial resistance and antibiotic usage in animals in the Netherlands, called MARAN, by the Veterinary Antibiotic Usage and Resistance Surveillance Working Group (VANTURES, see www.cidc-lelystad.nl). Recently MARAN 2005 has been published. Together NethMap and MARAN are aiming at providing a comprehensive overview of antibiotic use in the Netherlands in man and in animal husbandry and therefore are offering insight into the ecological pressure which is associated with emerging resistance trends.

The interaction between the human and veterinarian 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 interdepartmental working group in which the evolution of antibiotic use and resistance in the Netherlands is discussed on the basis of SWAB's and MARAN's surveillance data.

NethMap is thus providing extensive and detailed insight in the Dutch state of medically important antimicrobial resistance, and compares well with the data of the European Antimicrobial Resistance Surveillance System (EARSS, see www.earss.rivm.nl). EARSS collects resistance data of a limited number of invasive bacterial species for the majority of European countries, Israel and Turkey.

We trust that NethMap continues to contribute to our knowledge and awareness regarding the use of antibiotics and the resistance problems which may arise. We thank all who are contributing tot the surveillance efforts of SWAB, and express our hope that they are willing to continue their important clinical and scientific support to SWAB.

The editors:

Prof. dr. John Degener Dr. Han de Neeling

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1 Summary

NethMap 2007 is the fifth annual report of SWAB about 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 from 1993 up to 2006.

The overall use of antimicrobial agents in primary health care had been stable over years at levels just below 10 defined daily dosages (DDD) per 1000 inhabitants per day. However, in 2005 the consumption level rose to 10.5 DDD/1000/day and remained at that higher level in 2006. It remains to be seen whether this signals a change in the incidence of infectious diseases or whether prescribing habits are changing.
Several antibiotics contributed to this increase. One of these, nitrofurantoin, showed a long term increasing trend, probably due to the emergence of resistance to trimethoprim among strains of *Escherichia c*oli causing urinary tract infections and the subsequent recent changes in guidelines. Indeed, new independent data on antibiotic consumption as related to clinical indication, confirmed the increase in the use of nitrofurantoin for cystitis and a corresponding decrease in the use of trimethoprim in the period 1996-2006. This observation is interesting, because it shows that the SWAB surveillance data on drug use can be associated with adherence to recently changed recommendations on the therapy of uncomplicated urinary tract infection in general practice. In contrast, the spectrum of antibiotics prescribed for otitis media, predominantly amoxicillin, did not change in that period. These data were obtained from the Integrated Primary Care Information database (IPCI). NethMap 2007 also presents detailed data on antibiotic prescription as related to gender and age provided by the Foundation for Pharmaceutical Statistics (SFK). The total consumption of antibiotics is much higher in the elderly and in women as compared to men. Trimethoprim and nitrofurantoin are used mainly by women. Children use mostly amoxicillin.

Amoxicillin and other penicillins alone or with beta-lactamase inhibitor (co-amoxiclav) account for almost half of all antibiotics used in Dutch hospitals. Antibiotic use in hospitals was expressed in two units, DDD/100 patient-days and DDD/100 admitted patients. Whereas DDD per 100 patient-days increased from 47 in 2001 to 58 in 2005, DDD per 100 admissions remained constant. This difference was due to the steady decline in the mean length of stay in hospital per admission from 7.9 days in 2001 to 6.3 days in 2005. Thus an average hospitalised patient did not receive more antibiotics but, since he or she stayed in hospital for a shorter period, and the number of admissions increased, the number of DDD/100 patient-days increased. This implies that hospital wards are increasingly exposed to antibiotics. A similar trend is seen for beta-lactamase resistant penicillins, co-amoxiclav, aminoglycosides and fluoroquinolones.
In contrast both DDD/100 patient-days and DDD/100 admissions have increased for carbapenems, lincosamides, glycopeptides and nitrofurantoin. The patients as well as the hospitals are more exposed to antibiotics.
Although these trends were rather modest and our analysis did not show abrupt changes in antibiotic use patterns, subtle shifts may over the years accumulate to represent a significant change in usage and have an impact on the selection pressures in the hospital setting. Indeed hospitals and departments within hospitals differ considerably in antibiotic use pattern. Within antibiotic classes, ciprofloxacin use has increased at the expense of other fluoroquinolones and vancomycin at the expense of teicoplanin.

NethMap 2007 presents detailed data on the prevalence and antimicrobial susceptibility of *Staphylococcus aureus* in 2369 healthy individuals and 2691 patients consulting their primary care physician for non-infectious reasons. *S. aureus* was cultured from 28% of the healthy population and 23% of the patients. Resistance to methicillin (MRSA), confirmed by PCR of the *mec*A gene, was found in only two healthy individuals and in none of the patients. The prevalence of resistance among *S. aureus* strains to other antibiotics except penicillin remained low as well.

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 *Enterococcus faecalis*. In addition, resistance data are presented for *Mycobacterium tuberculosis, Neisseria meningitidis and N. gonorrhoeae*. Certain trends need to be addressed carefully.

First, the rates of resistance to fluoroquinolones are clearly increasing among clinical isolates of *E. coli, P. aeruginosa* and *S. aureus*. In Urology Services more than 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. Indeed fluoroquinolone resistant *E. coli* was observed in less than 5% of the isolates in the period up to the year 2000. Urology Services are also observing

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vancomycin resistant *E. faecalis* since 2003. Likewise, resistant micro-organisms, including ciprofloxacin and ceftazidime resistant *E. coli* and *Klebsiella pneumoniae* and ciprofloxacin resistant *S. aureus* regularly emerge in Intensive Care Units. NethMap clearly shows resistance rates to be generally higher among pathogens isolated in such settings.
The prevalence of multidrug resistance of *E. coli* from Intensive Care units to at least three different antibiotics was less than 2% until 1999 but rose to more than 6% in 2005. Recently the Working Party on Infection Prevention (WIP) has issued guidelines to contain multiple drug resistant organisms (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% threshold above which their empirical use is considered less reliable. However, the first line penicillin agents for these two important species of Gram-positive pathogens remain effective. Among clinical *S. aureus* isolates the proportion of methicillin resistance (MRSA) was 1-2% in 2003/2004, 2.5 % in 2005 and 2.0% in 2006.
Only 2-3% of *S. pneumoniae* isolates had reduced susceptibility to penicillin and resistance to 1 mg/L penicillin in that species is extremely rare in the Netherlands. 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 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 EARSS 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 Netherlands so far may increase further.

NethMap 2007 shows stable rates of resistance for *Helicobacter pylori* in the period 1996-2006. For *N. meningitidis* rates of reduced susceptibility to penicillin were approximately 1% in the period 1993-2001 and a bit higher, around 2% in the period 2002-2006.

Recently the resistance of *N. gonorrhoeae* to ciprofloxacin and other quinolones has worsened considerably. In 2006 the level of resistance to ciprofloxacin rose to far beyond 10%. So quinolones cannot be used for first line treatment anymore. Third generation cephalosporins are still active against all gonococci. This increasing resistance to fluoroquinolones has prompted the reinstatement of a national resistance surveillance system for this species as well as adjustment of the treatment guidelines for sexually transmitted diseases.

Finally, *Mycobacterium tuberculosis* was susceptible to all four tested agents in more than 90% of the cases. Resistance to INH and rifampicin (multiresistance) occurred in only 1% of the isolates in 2006. However, the alarming trends of *M. tuberculosis* resistance in the former Soviet Republics and in Southern Africa urges to closely monitor the emergence of (multiple) resistance at an early stage in the Netherlands.

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2 Samenvatting

NethMap 2007 is het vijfde jaarrapport van de SWAB over het gebruik van antibiotica en het vóórkomen van antibiotica resistentie in de meest voorkomende, voor de mens pathogene, bacteriesoorten in Nederland.
Het rapport beschrijft trends in het jaarlijkse gebruik van antibiotica en het vóórkomen van antibiotica resistentie op basis van systematisch verzamelde en bewerkte gegevens.

Het gebruik van antibiotica in de Nederlandse eerstelijns gezondheidszorg is tot 2005 steeds onder de 10 standaard dagdoseringen (DDDs) per 1000 inwoners per dag gebleven. In 2005 was het gebruik iets hoger, 10,5 DDD/1000 inwoner-dagen, en het bleef op dit nivo in 2006. Het gebruik van nitrofurantoïne was al langere tijd aan het stijgen. Waarschijnlijk kwam dit door de toegenomen resistentie tegen trimethoprim bij urineweginfecties en, als reactie daarop, de aanpassingen in de richtlijnen voor huisartsen. De overgang van trimethoprim naar nitrofurantoïne bij de therapie van cystitis werd ook gezien in een apart onderzoek naar antibiotica gebruik in relatie tot klinische indicatie in de huisartspraktijk (IPCI project).
NethMap 2007 bevat gedetailleerde gegevens over antibioticagebruik in relatie tot leeftijd en geslacht. Oudere mensen gebruiken veel meer antibiotica dan jongeren. Vrouwen gebruiken iets meer antibiotica dan mannen. Vrouwen gebruiken veel meer trimethoprim en nitrofurantoïne dan mannen. Kinderen gebruiken voornamelijk amoxicilline.

Bijna de helft van het antibioticagebruik in ziekenhuizen bestaat uit amoxicilline en andere penicillines, alleen of met een beta-lactamase remmer (co-amoxiclav).
Het antibioticagebruik in ziekenhuizen wordt uitgedrukt in twee maten, DDD per 100 patient-dagen (ligdagen) en DDD per 100 opgenomen patiënten. Het antibioticumgebruik uitgedrukt in DDD/100 ligdagen is gestegen van 47 in 2001 tot 58 in 2005, terwijl het aantal DDD/100 opnamen in dezelfde periode gelijk bleef. Het verschil in deze twee trendlijnen is te verklaren door een afname in de gemiddelde duur per opname. Deze was 7,9 dagen in 2001 en 6,3 dagen in 2005. Per opname, d.w.z. per patiënt, werden dus niet meer antibiotica voorgeschreven, maar omdat de patiënt gemiddeld steeds korter in het ziekenhuis verbleef en het aantal opnames aanzienlijk steeg, nam het aantal DDD/100 ligdagen toe. Dit betekent dat de afdelingen in een ziekenhuis aan meer antibiotica zijn blootgesteld. Een soortgelijke trend wordt gezien voor beta-lactamase resistente penicillines, co-amoxiclav, aminoglycosides en fluorochinolonen.
In tegenstelling tot dit patroon zijn beide maten voor antibioticagebruik gestegen voor de de carbapenems, de lincosamiden, de glycopeptiden en nitrofurantoïne. Dit betekent dat zowel de gemiddelde patiënt als de afdeling aan meer antibiotica zijn blootgesteld.
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.
Binnen groepen antimicrobiële middelen, wordt er meer ciprofloxacine gebruikt ten koste van minder gebruik aan andere fluorochinolonen en het gebruik van vancomycine stijgt, terwijl het gebruik van teicoplanine daalt.

NethMap 2007 toont gedetailleerde gegevens over het de gevoeligheid voor antibiotica van *Staphylococcus aureus* bij 2369 gezonde personen buiten het ziekenhuis en 2691 patiënten die hun huisarts bezochten voor niet-infectieuze aandoeningen. *S. aureus* werd aangetroffen bij 28% van de gezonde populatie en bij 23% van de patiënten. Meticilline resistente *S. aureus* (MRSA), bevestigd met PCR van het *mec*A resistentiegen, werd aangetroffen bij slechts twee gezonde personen en bij geen van de patiënten. Ook de resistentie tegen andere antibiotica, behalve penicilline, bleef laag.

In de Nederlandse ziekenhuizen zijn er enkele belangrijke trends waar te nemen. Op de eerste plaats stijgen de percentages resistentie tegen de fluorochinolonen onder klinische isolaten van *Escherichia coli, Pseudomonas aeruginosa* en *Staphylococcus aureus*. In de afdelingen Urologie is meer dan 10 % van de *E. coli* en *S. aureus* isolaten resistent tegen ciprofloxacine, en in de overige delen van de ziekenhuizen vindt men resistentienivo's van 5-10%. In de periode voor de eeuwwisseling was het resistentiepeil voor fluorochinolonen onder deze soorten nog lager dan 5%. Op 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 aangetroffen 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.
De prevalentie van *E. coli* tegen drie of meer typen antibiotica was minder dan 2% tot 1999 maar steeg tot meer dan 6% in 2005. Onlangs heeft de Werkgroep Infectie Preventie een richtlijn uitgebracht over het voorkomen van verspreiding van dergelijke (multi)resistente stammen (zie www.wip.nl).

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Een andere zorgwekkende trend is de toenemende resistentie tegen de macrolide antibiotica onder klinische isolaten van *S. aureus* en *Streptococcus pneumoniae*. Beide soorten bereiken bijna het niveau van 10% resistentie waarboven deze middelen niet meer geschikt worden geacht voor de empirische behandeling van infecties. 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* (MRSA) 2,0 % van de klinische isolaten in 2006. Slechts 2% van de *S. pneumoniae* was verminderd gevoelig voor penicilline in 2006. Hoewel deze resistentie percentages nog steeds laag zijn, blijft voortdurende waakzaamheid en controle van resistente isolaten van *S. aureus* en *S. pneumoniae* aangewezen.

De surveillance gegevens van NethMap sluiten goed aan bij de surveillance gegevens van het Europese surveillance project EARSS (European Antimicrobial Resistance Surveilance, 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 meer dan 20% gestegen in negen andere Europese landen, en 13 landen rapporteerde meer dan 50% resistentie tegen amoxicilline. Onder *S. pneumoniae* isolaten zijn de resistentiepercentages tegen macroliden en penicilline in de meeste Europese landen ook veel hoger dan in Nederland. Zonder tegenmaatregelen kunnen de Nederlandse resistentiepercentages dus gemakkelijk verder oplopen.

Het nivo van resistentie bij *Helicobacter pylori* is stabiel. Voor *Neisseria meningitidis* was het percentage stammen met een verminderde gevoeligheid voor penicilline ongeveer 1% in de periode 1993-2001 en iets hoger (rond 2%) in de periode 2002- 2006.
De resistentie bij *Neisseria gonorrhoeae* heeft een verontrustend hoog nivo bereikt. In 2006 steeg het percentage ciprofloxacine resistente stammen tot ver boven de 10%. Deze stijging is aanleiding geweest de richtlijnen voor de behandeling van gonorroe bij te stellen. Derde generatie cefalosporines zijn nog wel werkzaam tegen gonokokken.
Tenslotte, 90% van de geteste *Mycobacterium tuberculosis* bleek goed gevoelig voor de vier geteste tuberculostatica. Ook dit percentage is stabiel. INH resistentie werd gevonden bij 8-9% van de isolaten, 3-5% van de isolaten was resistent tegen twee of meer van de vier middelen. Resistentie tegen tegen INH en rifampicine werd in 2006 waargenomen bij slechts 1% van de stammen. Patiënten met dit soort multiresistente stammen zijn echter moeilijk te behandelen en de alarmerende toename van multiresistentie bij *M. tuberculosis* in de vroegere Sovjet republieken en in Zuidelijk Afrika noopt 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 on antibiotic use by indications.

Primary health care

Ten-years trend in antibiotic use: 1997-2006
Over the past 10 years the overall use of antibiotics for systemic use in primary health care remained almost constant at 10 DDD/1000 inhabitant-days (table 1). However, a slight increase in use was observed in 2005 and 2006.

The distribution of antibiotics by class in 2006 is presented in figure 1. Tetracyclines (mainly doxycycline) represented 21% 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%, 15% and 14% of the total use respectively.
These proportions are similar to previous years.

The use of amoxicillin decreased from 2.18 in 1997 to 1.69 DDD/1000 inhabitant-days (-22.5%) in 2004. In 2005 and 2006 it slightly increased to 1.86 DDD/1000 inhabitant-days. The use of co-amoxiclav increased from 0.92 in 1997 to 1.59 DDD/1000 inhabitant-days in 2006 (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 0.84 DDD/1000 inhabitant-days in 2006. The use of azithromycin doubled between

Table 1. 10-years data on use of antibiotics for systemic use (J01) in primary care (DDD/1000 inhabitant-days), 1997-2006 (Source: SFK).

ATC Group*	Therapeutic group	year									
		1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
J01AA	Tetracyclines	2.64	2.55	2.49	2.47	2.39	2.33	2.23	2.22	2.41	2.37
J01CA	Penicillins with extended spectrum	2.18	2.13	2.06	1.88	1.82	1.78	1.77	1.69	1.86	1.87
J01CE	Beta-lactamase sensitive penicilins	0.56	0.52	0.51	0.52	0.49	0.45	0.44	0.42	0.44	0.50
J01CF	Beta-lactamase resistant penicillins	0.23	0.22	0.23	0.24	0.25	0.25	0.27	0.28	0.29	0.31
J01CR	Penicillins + beta-lactamase-inhibitors	0.92	0.95	1.04	1.15	1.25	1.34	1.39	1.38	1.50	1.59
J01D	Cephalosporins	0.13	0.11	0.10	0.08	0.07	0.07	0.06	0.05	0.05	0.04
J01EA	Trimethoprim and derivatives	0.28	0.28	0.30	0.28	0.28	0.27	0.27	0.26	0.25	0.23
J01EC	Intermediate-acting sulfonamides	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00
J01EE	Sulphonamides + trimethoprim	0.48	0.47	0.46	0.43	0.42	0.40	0.39	0.39	0.38	0.37
J01FA	Macrolides	1.12	1.16	1.17	1.13	1.22	1.24	1.27	1.31	1.42	1.39
J01FF	Lincosamides	0.03	0.03	0.03	0.04	0.05	0.06	0.06	0.07	0.08	0.09
J01GB	Aminoglycosides	0.00	0.00	0.00	0.00	0.01	0.01	0.02	0.02	0.02	0.03
J01MA	Fluoroquinolones	0.78	0.78	0.82	0.80	0.80	0.78	0.78	0.82	0.84	0.87
J01MB	Other quinolones	0.06	0.05	0.04	0.04	0.04	0.03	0.03	0.02	0.02	0.02
J01XB	Polymyxins	0.01	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.00
J01XE	Nitrofuran derivatives	0.59	0.59	0.64	0.68	0.71	0.74	0.78	0.80	0.90	1.00
J01XX05	Methanamine	0.07	0.06	0.06	0.06	0.06	0.04	0.03	0.02	0.02	0.03
J01	Antibiotics for systemic use (total)	10.09	9.94	10.02	9.84	9.90	9.81	9.81	9.77	10.51	10.72

* From the 2007 edition of the Anatomical Therapeutic Chemical (ATC) classification system

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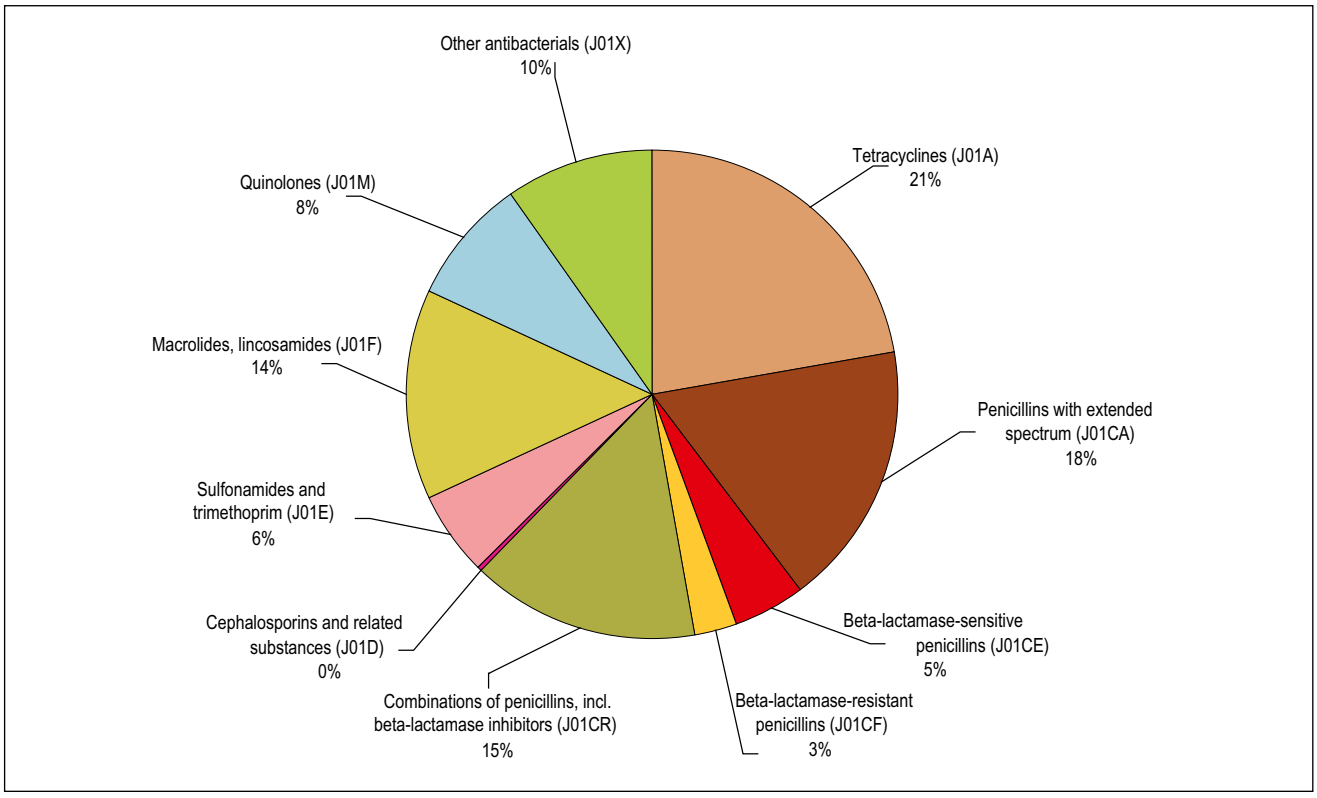


Figure 1. Distribution of the use of antibiotics for systemic use (J01, DDD/1000 inhabitant-days) in primary health care, 2006 (Source: SFK).

1997 and 2006. The use of erythromycin slightly decreased over the past years.

Total use of the fluoroquinolones did not change between 1997 and 2006 (table 1, figure 4). However, between 1997 and 2006, the use of ciprofloxacin almost doubled. Since 2002, ciprofloxacin is the fluoroquinolone used most commonly. Its use is still increasing.
The use of norfloxacin and ofloxacin decreased during these years.

The use of nitrofurantoin increased from 0.59 in 1997 to 1.00 DDD/1000 inhabitant-days in 2006 whereas the use of trimethoprim slightly decreased.

Figure 2. Use of amoxicillin and co-amoxiclav in primary health care, 1997 - 2006 (Source: SFK).

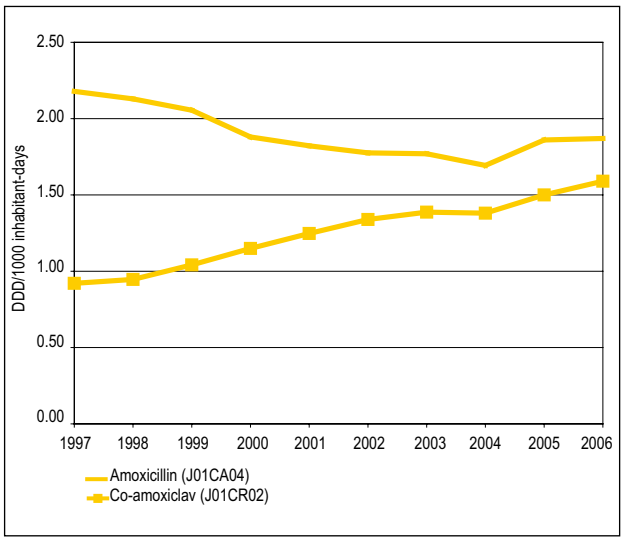
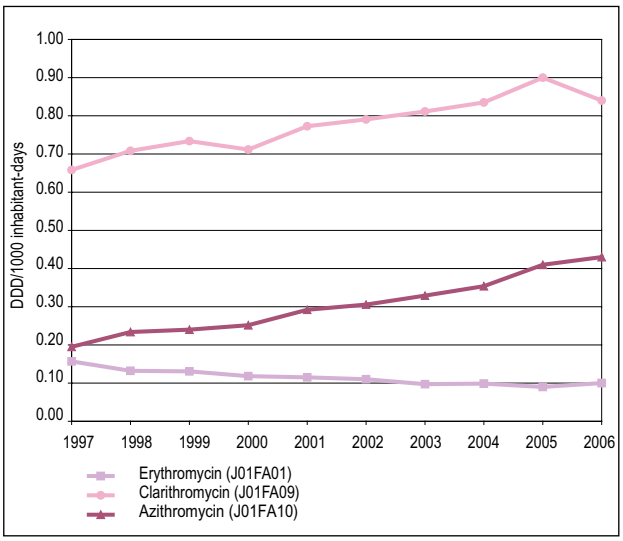


Figure 3. Use of macrolides for systemic use in primary health care, 1997-2006 (Source: SFK).



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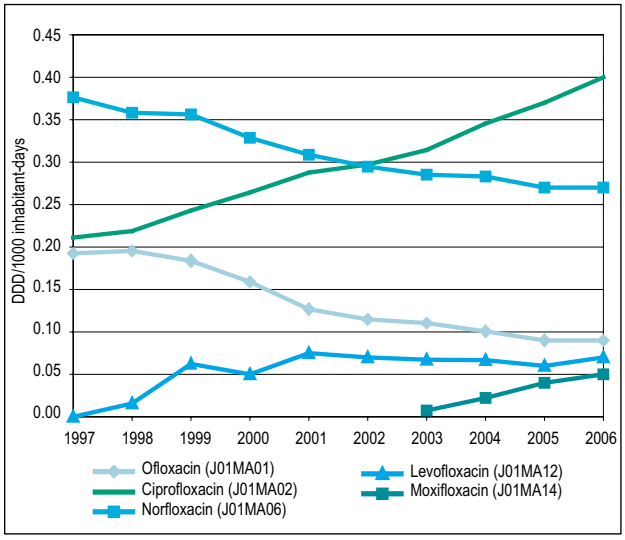


Figure 4. Use of fluoroquinolones for systemic use in primary health care 1997 - 2006 (Source: SFK).

Trends in antibiotic use by age and gender

In 2005 the average use of antibiotics in primary care was 10.5 DDD/1000 inhabitant-days. Figure 5 shows how total use was distributed among all ages, men and women separately. Overall, women used more antibiotics than men, 12.2 versus 8.8 DDD/1000 inhabitant-days. Only at the youngest ages, 0-3 years and above 75 years, men used more antibiotics than women.

Penicillins with extended spectrum, mainly amoxicillin, were used frequently in early childhood. Use decreases during adolescence, but picks up again in adulthood with a peak around 33 years. Generally, from adolescence, the penicillins with extended spectrum were used more by women (figure 6). Macrolides have a similar pattern of use over the ages, but were used less in early childhood (figure 7).

Trimethoprim (J01EA) and nitrofurantoin derivatives (J01XE) were used more by women than by men (0.44 versus 0.06 DDD/1000 inhabitant-days for trimethoprim and 1.62 versus 0.15 DDD/1000 inhabitant-days for nitrofurantoin). These antibiotics had a similar usage pattern, although nitrofurantoin was prescribed far more than trimethoprim. They were both mainly prescribed to women from early adulthood and for women of 60 years and older, and are mostly used for urinary tract infections (figures 8, 9 and project 1).

Fluoroquinolones were more widely used by the elderly. Physicians are advised against prescribing these antibiotics to growing children because of a possible negative effect on growing, weight-bearing joints. Fluoroquinolones were prescribed more evenly in men and women (figure 10).

Discussion

In 2005, total antibiotic consumption was 10.5 DDD/1000 inhabitant-days and was slightly increased compared to previous years. This increased use remained in 2006.

However, the use of antibiotics is still low if compared with other European countries.

In the past 10 years the use of penicillins with beta-lactamase inhibitors, macrolides and nitrofurantoin increased whereas the use of tetracyclines and penicillins with extended spectrum decreased. Moreover, subtle shifts in the patterns of use within the various classes of antibiotics are observed. The overall consumption of the fluoroquinolones remained almost constant whereas the increased use of ciprofloxacin seems to be offset by a decrease in ofloxacin and norfloxacin. Also within the class of the macrolides we see a shift from erythromycin to the newer macrolides as clarithromycin and azithromycin. This trends may be relevant in the face

Figure 5. Total antibiotic use (J01) in DDD/1000 inhabitant-days, by age and gender, 2005.

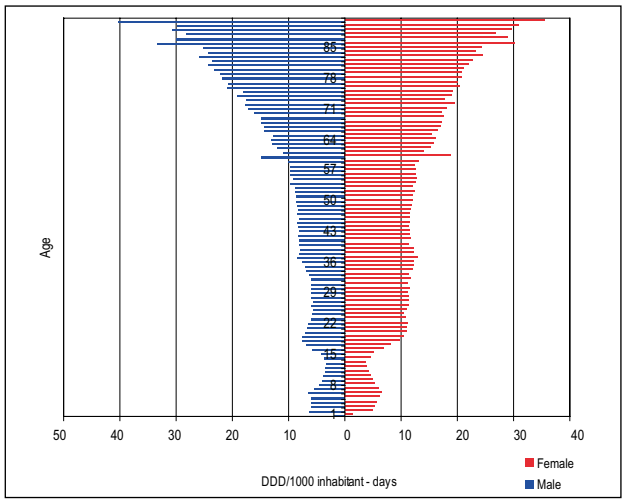
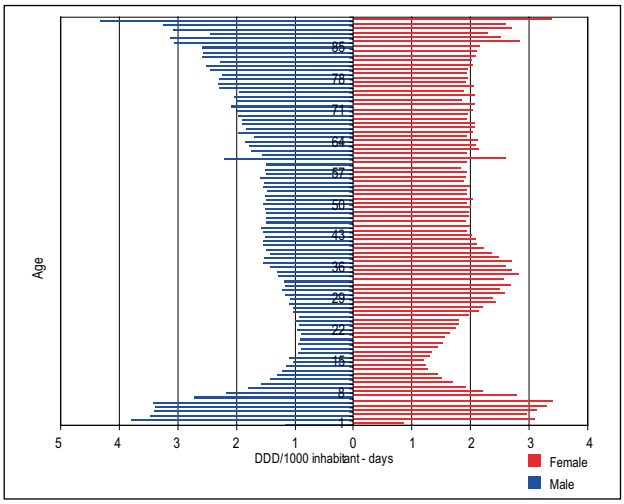


Figure 6. Use of penicillins with extended spectrum (J01CA) in DDD/1000 inhabitant-days by age and gender, 2005.



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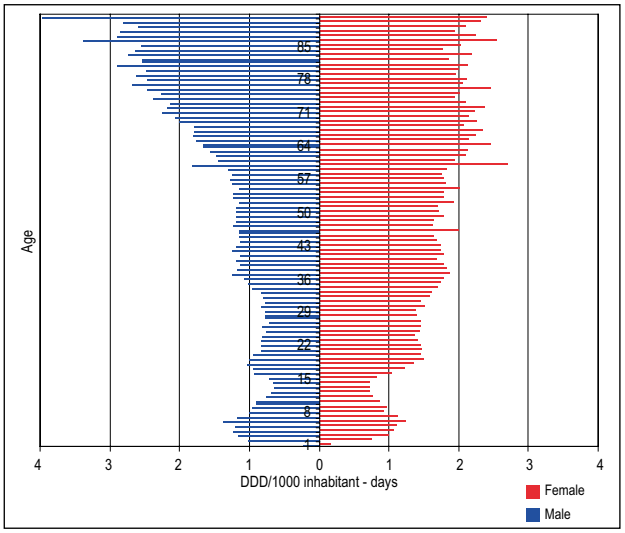


Figure 7. Antibiotic use of macrolides (J01FA) in DDD/1000 inhabitant-days, by age and gender, 2005.

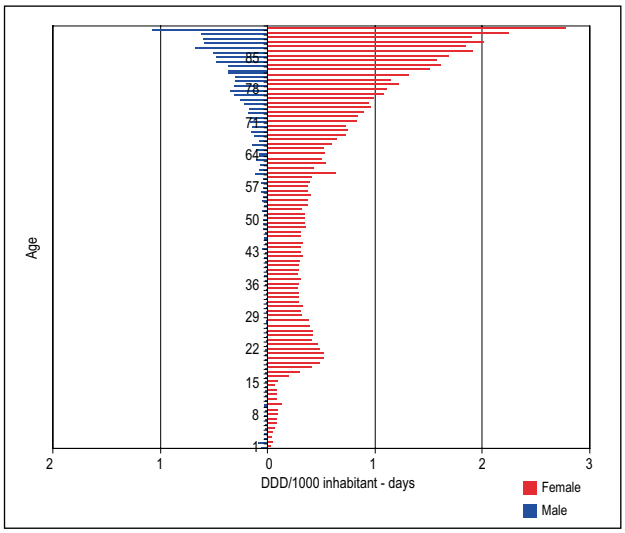


Figure 8. Use of trimethoprim and derivatives (J01EA) in DDD/1000 inhabitant-days by age and gender.

of growing rates of resistance among common pathogens and therewith the rate of treatment failures
The remarkable increase in the use of nitrofurantoin may be explained by the results of project 1. From this project we may conclude that in 1996 only 2% of patients with cystitis were treated with nitrofurantoin and approximately 38% of the cystitis population with trimethoprim. In 2006 more than 40% were treated with nitrofurantoin and 20% with trimethoprim.
This change in treatment may be the result of the national guidelines of the Dutch College of General practitioners (NHG) that have been changed over the years with regard to the pharmacotherapy of urinary tract infections. Before 1999 trimethoprim, nitrofurantoin and short-acting sulphonamides were advised for the treatment of uncomplicated urinary tract infections. In 1999 the NHG guideline has been revised and trimethoprim and nitrofurantoin (3-5 days treatment) were both the drugs of first choice. However, in a footnote it was already stated that the resistance level of *Escherichia coli* towards trimethoprim was higher than towards nitrofurantoin. In 2005 the guidelines were revised again and because of lower resistance levels nitrofurantoin was classified as the drug of first choice (5 days treatment). Trimethoprim is nowadays ranked as a urinary tract infection antibiotic of second choice.

References

[1] MARAN-2005 – Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in The Netherlands In 2005.

Figure 9. Use of nitrofuran derivatives (J01XE) in DDD/1000 inhabitant-days by age and gender.

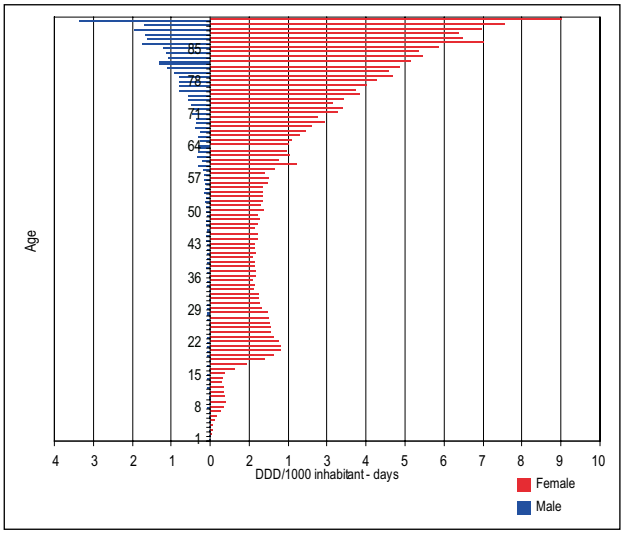
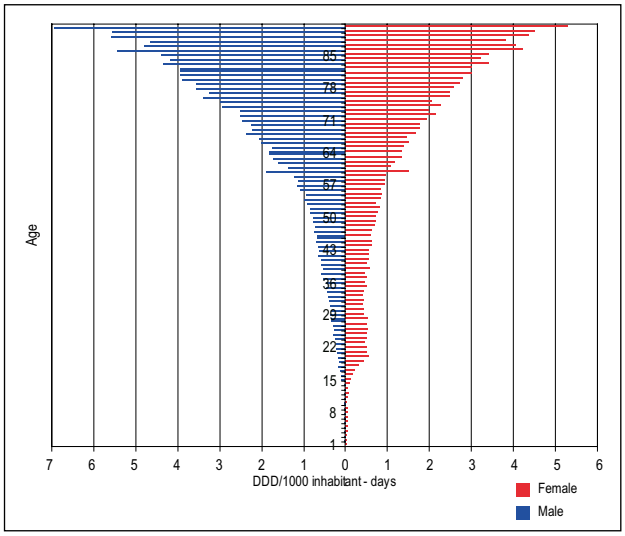


Figure 10. Use of quinolones (J01MA) in DDD/1000 inhabitant-days by age and gender.



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Hospitals

Hospital resource indicators

The average number of bed-days per hospital in our cohort increased slightly from 123056 in 2001 to 130709 (+6.2 %) in 2005. The average number of admissions however, has increased significantly from 15609 in 2001 to 20781 in 2005 (+33%). So the average length of stay in these hospitals has decreased from 7.9 to 6.3 days (-20%).
These trends in the hospital resource indicators are 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 2 and 3).
In 2005, the total systemic use in our cohort of hospitals was 58.3 DDD per 100 patient-days, an increase of 25% compared to the total systemic use in 2001, which was 46.5 DDD per 100 patient-days. However, the total number of DDD per 100 admissions remained constant, 320 in 2001 and 317 in 2005 (-1%). Differences in trends between the two units of measurement are the result of changes in resource indicators over time.
The mean antibiotic use per patient remained constant (-1%), while the number of patients using antibiotics increased (+33%). Thus, the total number of DDDs per hospital increased from 49981 in 2001, to 65859 in 2005 (+32%).
The mean number of patient-days per hospital has decreased by 8% (from 2162 in 2001 to 1981 in 2005), and the total number of DDD per 100 patient-days has increased by 25%.

Five main categories with regard to trends in antibiotic use over the years can be distinguished (tables 2 and 3).

1. Carbapenems, lincosamides, glycopeptides and nitrofuran derivatives showed 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. Since the mean number of admissions per hospital increased, a significant increase in antibiotic use per hospital was observed between 2001 and 2005.

2. For beta-lactamase resistant penicillins, combinations of penicillins, cephalosporins, aminoglycosides and fluoroquinolones DDD per 100 patient-days increased whereas the DDD per 100 admissions remained constant. This implies that the average patient was exposed to the same number of doses. However, since more patients were admitted to the hospital, a significant increase in antibiotic use per hospital was observed.

3. Penicillins with extended spectrum show an increase in DDD/100 patient-days - but a small decrease in DDD/100 admissions. This implies that the average patient was exposed to fewer doses of antibiotics. However, since there were more patients admitted to the hospital, total antibiotic use per ward/hospital increased.

4. For tetracyclines, beta-lactamase sensitive penicillins and the combinations of sulphonamides and trimethoprim the DDD per 100 patient-days remained constant, while a decrease in DDD per 100 admissions was seen. On average, patients used less antibiotics during their shorter stay in the hospital. Since there were more admissions, the relative antibiotic use per ward/hospital remained constant.

5. For the remaining groups of antibiotics no significant change in either unit of measurement was observed.

Figure 11 depicts the distribution of antibiotics per class in 2005. The relative use of the different subclasses of antibiotics remained constant over the past years (data not shown).
The relative use of penicillins was approximately 47%. The largest proportion (24%) consisted of the combination of penicillins, including beta-lactamase inhibitors, mainly co-amoxiclav (figure 12 A and B).

Figures 12 to 17 show the use of the individual antibiotics within the different subclasses.
The use of piperacillin/tazobactam is still low (figure 12A and B). Other penicillins like flucloxacillin and co-amoxiclav gradually increased over the years while amoxicillin remained constant.

The cephalosporins represented 13% of the total of in-hospital antibiotic use (figure 11). The second-generation cephalosporins were most often used (figure 13A and B). However, in 2005 the use of second-generation cephalosporins, mainly cefuroxime, decreased in 2005. The use of first generation cephalosporins (mainly cefazolin) increased for both units of measurement.

The use of macrolides was stable. The use of azithromycin per admission increased from 1.1 DDD/100 admissions in 1999 to 2.0 DDD/100 admissions in 2005 (+78%). However its use was still the lowest of all macrolides (figures 14A and B).

The use of all aminoglycosides has remained constant from 1999 to 2005. The use of gentamicin, the most

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Table 2. Use of antibiotics for systemic use (J01) in hospitals (DDD/100 patientdays), 2001-2005 (Source: SWAB).*

ATC Group*	Therapeutic group	2001	2002	2003	2004	2005
J01AA	Tetracyclines	1.6	1.7	1.4	1.5	1.6
J01CA	Penicillins with extended spectrum	6.0	6.1	6.0	6.0	6.7
J01CE	Beta-lactamase sensitive penicilins	1.3	1.2	1.2	1.4	1.4
J01CF	Beta-lactamase resistant penicillins	4.3	4.4	5.4	5.7	5.8
J01CR	Combinations of penicillins, incl. beta-lactamase-inhibitors	9.9	12.2	12.1	12.8	13.9
J01DB-DE	Cephalosporins	6.1	6.3	6.5	7.0	7.4
J01DF	Monobactams	0.0	0.0	0.0	0.0	0.0
J01DH	Carbapenems	0.4	0.5	0.5	0.5	0.6
J01EA	Trimethoprim and derivatives	0.5	0.5	0.5	0.4	0.6
J01EC	Intermediate-acting sulfonamides	0.0	0.0	0.1	0.1	0.0
J01EE	Combinations of sulfonamides and trimethoprim. including derivatives	2.3	2.4	2.3	2.1	2.3
J01FA	Macrolides	2.3	2.7	2.4	2.3	2.8
J01FF	Lincosamides	1.3	1.5	1.6	1.8	1.9
J01GB	Aminoglycosides	2.0	2.1	2.5	2.2	2.6
J01MA	Fluoroquinolones	5.5	5.7	6.4	6.5	7.3
J01MB	Other quinolones	0.1	0.1	0.1	0.1	0.1
J01XA	Glycopeptides	0.5	0.5	0.5	0.6	0.8
J01XB	Polymyxins	0.1	0.1	0.1	0.1	0.2
J01XC	Steroid antibacterials (fusidic acid)	0.0	0.0	0.0	0.0	0.0
J01XD	Imidazole derivatives	1.3	1.5	1.6	1.7	1.5
J01XE	Nitrofuran derivatives	0.5	0.5	0.7	0.9	1.0
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)	46.5	50.2	51.9	53.8	58.3

* From the 2007 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Table 3. Use of antibiotics for systemic use (J01) in hospitals (DDD/100 admissions), 2001-2005 (Source: SWAB).*

ATC Group*	Therapeutic group	2001	2002	2003	2004	2005
J01AA	Tetracyclines	11.3	11.2	8.8	8.4	8.8
J01CA	Penicillins with extended spectrum	41.5	41.2	38.6	34.3	36.4
J01CE	Beta-lactamase sensitive penicilins	9.2	8.2	7.8	7.8	7.5
J01CF	Beta-lactamase resistant penicillins	29.4	29.5	34.6	33.0	31.4
J01CR	Combinations of penicillins, incl. beta-lactamase-inhibitors	68.0	81.6	77.7	73.1	75.4
J01DB-DE	Cephalosporins	42.3	42.0	42.0	39.4	39.8
J01DF	Monobactams	0.1	0.0	0.0	0.0	0.0
J01DH	Carbapenems	2.4	3.2	3.3	2.8	3.2
J01EA	Trimethoprim and derivatives	3.6	3.3	3.1	2.3	3.0
J01EC	Intermediate-acting sulfonamides	0.1	0.2	0.8	0.3	0.3
J01EE	Combinations of sulfonamides and trimethoprim, including derivatives	15.6	16.0	14.4	12.1	12.2
J01FA	Macrolides	15.7	17.9	15.4	13.4	15.1
J01FF	Lincosamides	9.2	10.0	10.2	10.2	10.5
J01GB	Aminoglycosides	14.0	14.2	15.8	12.5	13.9
J01MA	Fluoroquinolones	38.0	38.2	41.0	37.2	39.7
J01MB	Other quinolones	0.5	0.5	0.6	0.8	0.5
J01XA	Glycopeptides	3.2	3.4	3.4	3.5	4.1
J01XB	Polymyxins	0.8	0.4	0.5	0.6	1.1
J01XC	Steroid antibacterials (fusidic acid)	0.2	0.1	0.2	0.1	0.2
J01XD	Imidazole derivatives	9.0	9.7	10.1	9.6	7.9
J01XE	Nitrofuran derivatives	3.3	3.6	4.7	4.9	5.6
J01XX05	Methenamine	0.1	0.1	0.2	0.4	0.1
J01XX08	Linezolid	0.0	0.1	0.1	0.1	0.2
J01	Antibiotics for systemic use (total)	320.2	336.5	333.2	306.8	316.9

* From the 2007 edition of the Anatomical Therapeutic Chemical (ATC) classification system

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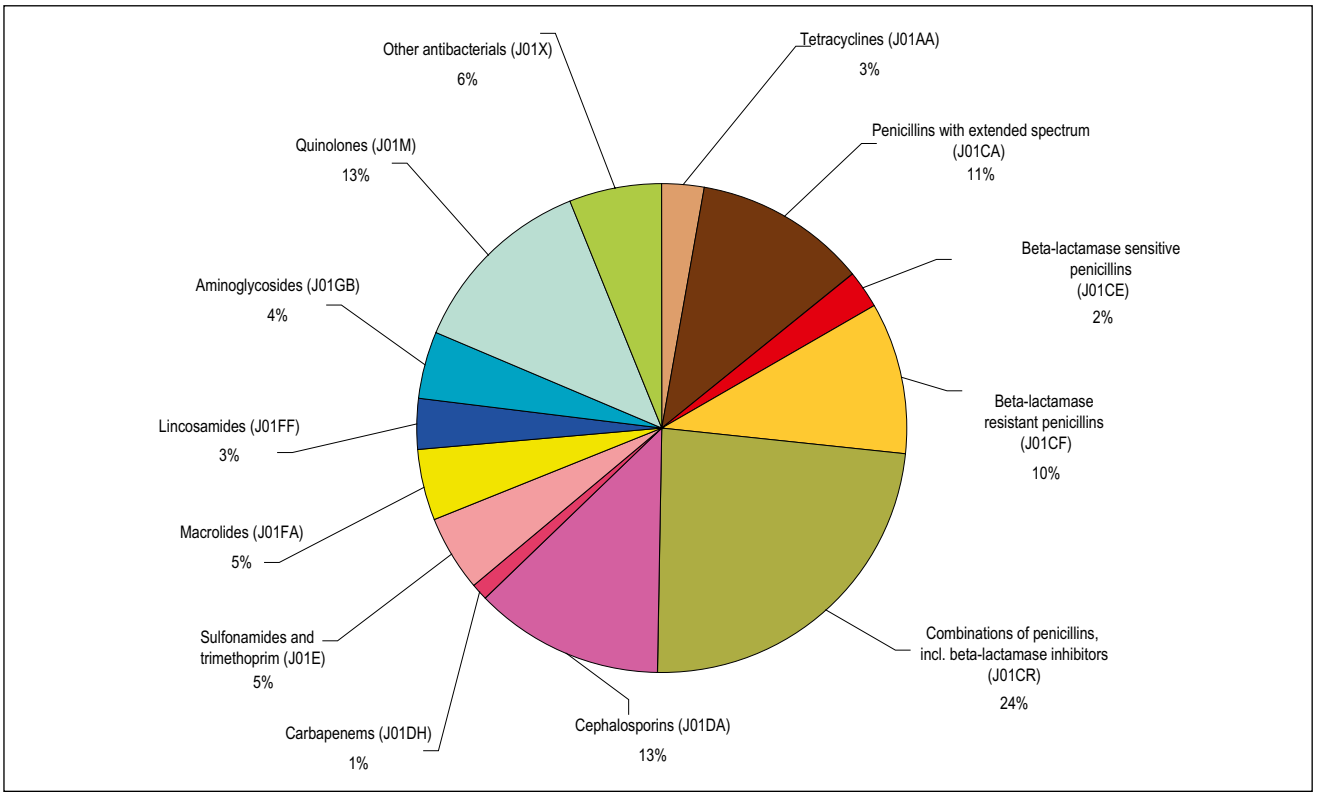


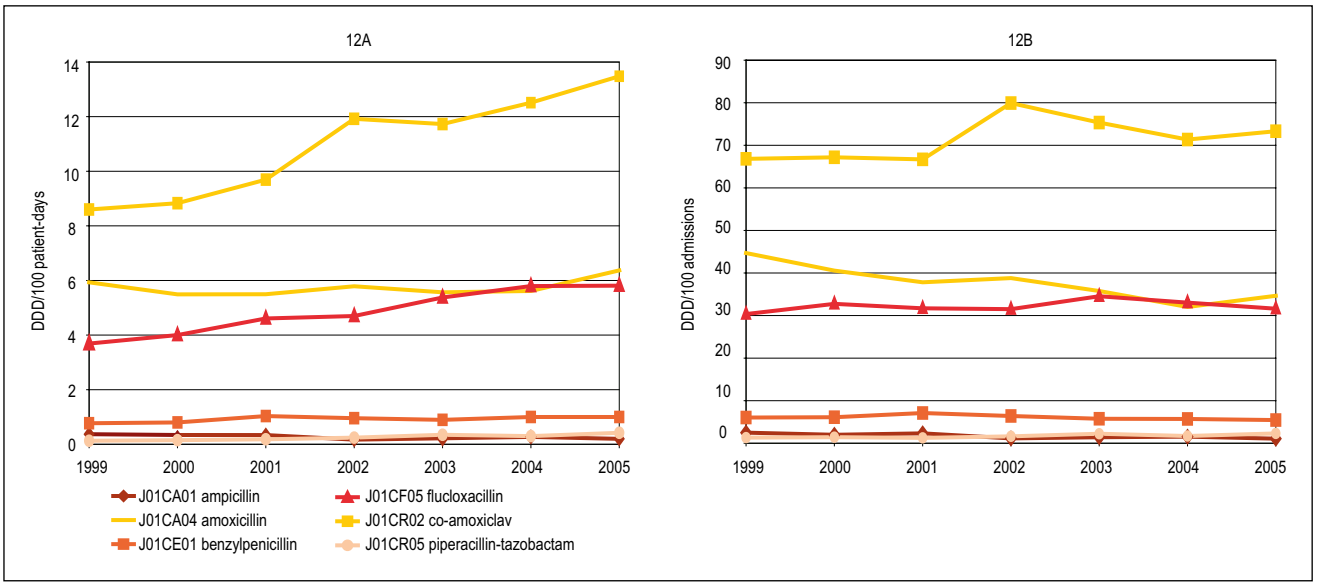
Figure 11. Distribution of the use of antibiotics for systemic use (J01, DDD/100 patient-days) in hospitals, 2005 (Source: SWAB).

commonly used aminoglycoside, increased slightly per 100 admissions, but the number of DDD/100 patient-days increased markedly from 1.3 in 2001 to 1.8 in 2005. Tobramycin use also increased in 2005 (figure 15A and B). This seems to be a result of the increase in admissions per year.

Use of ciprofloxacin per year increased, expressed in both units of measurement (figures 16A and B).

Vancomycin use is increasing in both units of measurement. The use of teicoplanin remained low (figures 17A and B).

Figure 12. Use of penicillins in hospitals, 1999-2005 (Source: SWAB).



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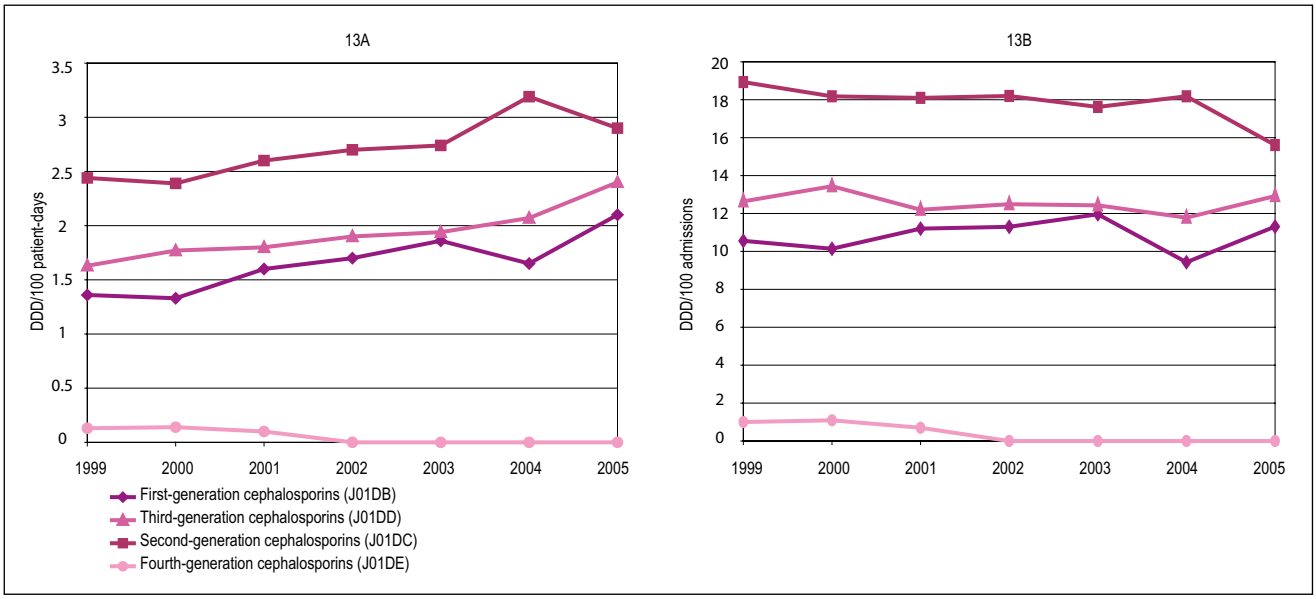


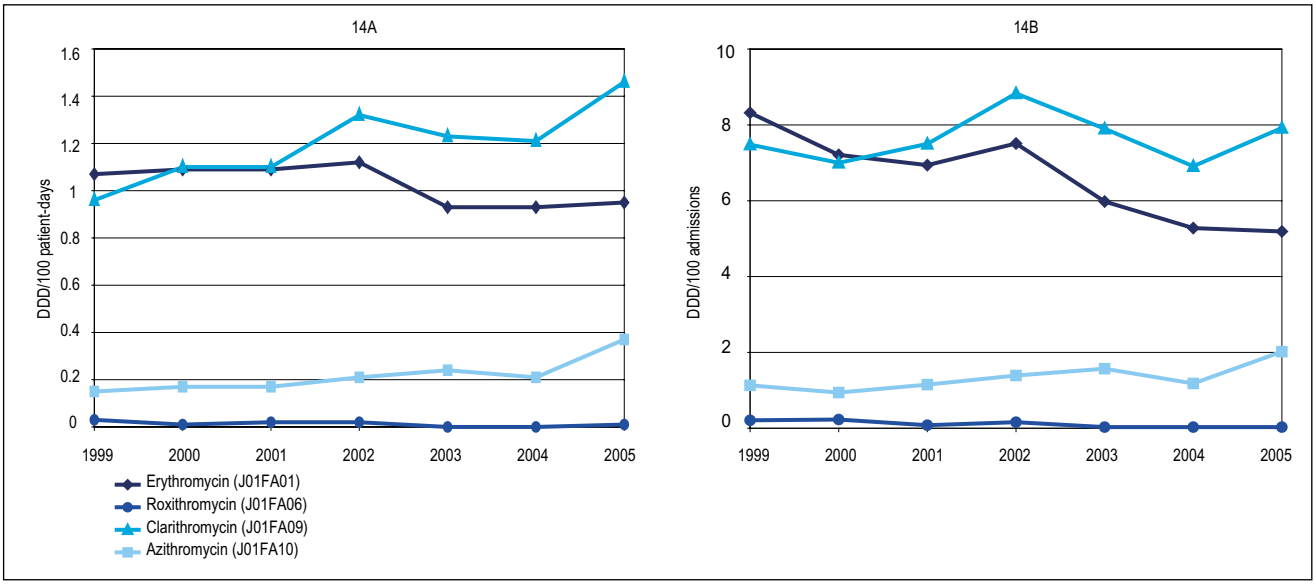
Figure 13. Use of cephalosporins in hospitals, 1999-2005 (Source: SWAB).

Discussion

The unit in which antibiotic usage is expressed matters.[1] This is important when hospital resource indicators change over a study period. 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.

Since NethMap 2004, data on antibiotic use in Dutch hospitals have been expressed in DDD per 100 patient-days and in DDD per 100 admissions. An increase in the number of DDD per 100 patient-days has previously been routinely interpreted as worrisome concerning the potential for antibiotic resistance development.

Figure 14. Use of macrolides in hospitals, 1999-2005 (Source: SWAB).



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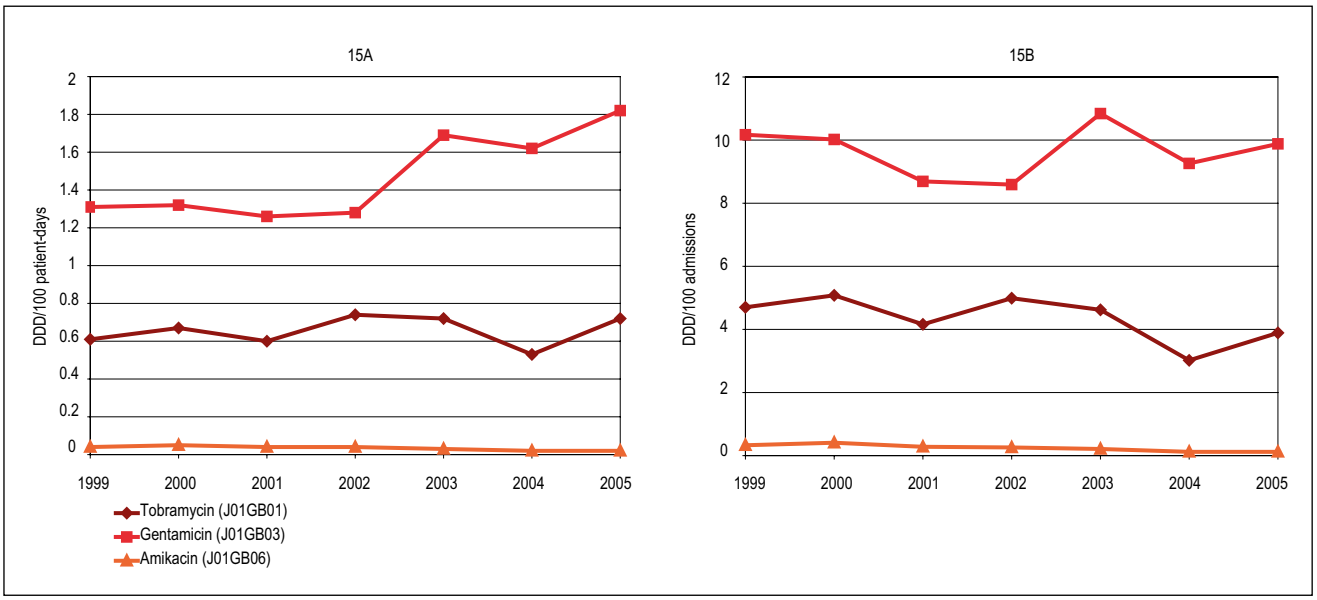
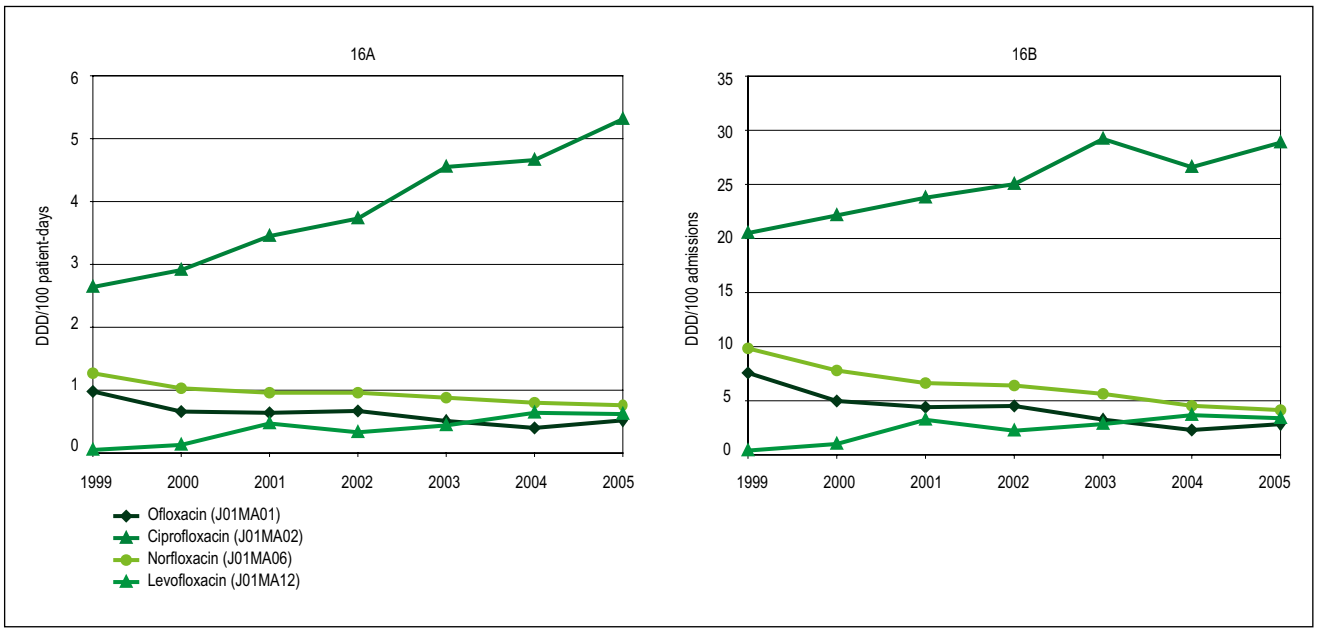


Figure 15. Use of aminoglycosides in hospitals, 1999-2005 (Source: SWAB).

We have distinguished five 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 4 and 5) is not worrisome with regards to resistance development. The trends in category 2 and 3 are less easy to interpret.
A constant (category 2) or slightly decreased (category 3) use per patient combined with an increase in the number of admissions is indicative for an increase of the selection pressure exerted by antibiotics in hospitals over the years. However, an intensification of antibiotic therapy per 100 patient-days may in part be due to an increase in the number of admitted patients, and possibly a shortening of the duration of antibiotic treatment. Such shortening of the duration of therapy may lead to less selection of resistant microorganisms.[3]

Figure 16. Use of fluoroquinolones in hospitals, 1999-2005 (Source: SWAB).



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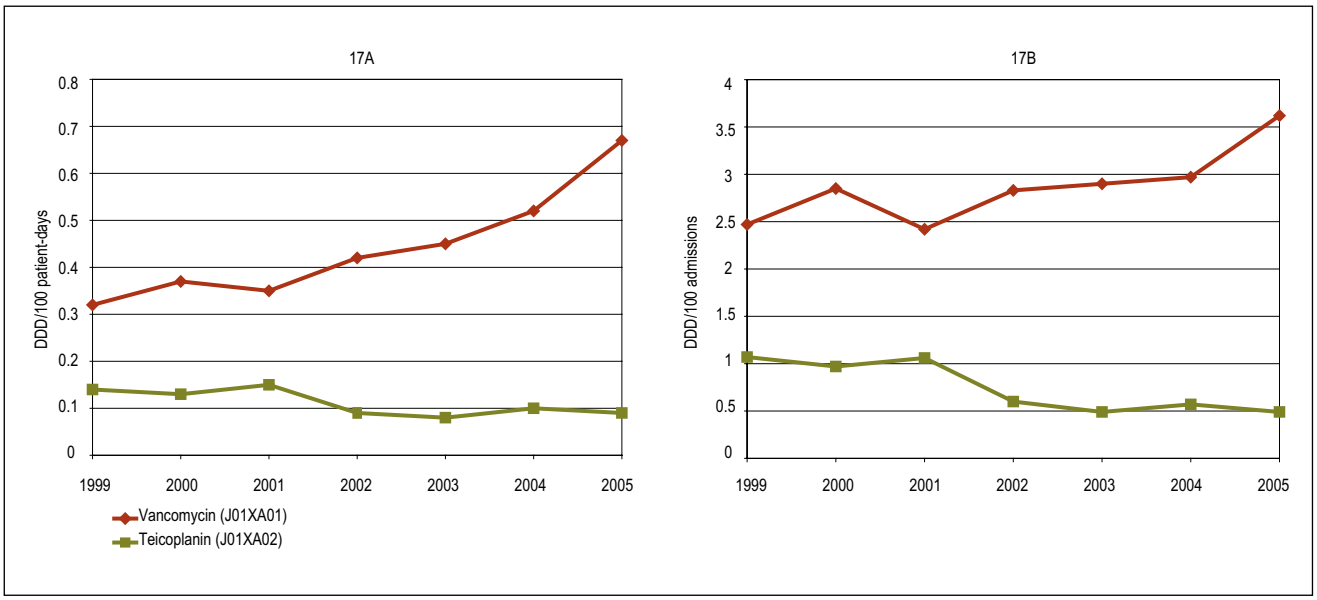


Figure 17. Use of glycopeptides in hospitals, 1999-2005 (Source: SWAB).

In conclusion, over the years 2001-2005 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 2005 compared to 2001. 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 has been increasing 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, ciprofloxacin, clindamycin and nitrofurantoin.

Monitoring and analyzing patterns in antibiotic use by specific populations within hospitals (e.g. patients in intensive care units and in general wards, surgical and non-surgical patients) is warranted to assess the rationality of these prescriptions.

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1 Filius, PMG, Liem TBY, van der Linden PD, Janknegt R, Natsch S, Vulto AG and Verbrugh HA. An additional measure for quantifying antibiotic use in hospitals. J Antimicrob Chemother. 2005; 55:805-8.

2 Levy, SB. Antibiotic resistance: Consequences of inaction. Clinical Infectious Diseases 2001;33, Suppl.3, S124-9.

3 Schrag, SJ, Pena C, Fernandez, J et al. Effect of short-course, high-dose amoxicillin therapy on resistant pneumococcal carriage: a randomized trial. JAMA 2001;286:49-56.

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Project 1

Antibiotic Use By Indication

P vd Linden, A Lindemans and PMG Filius
on behalf of SWAB's working group on surveillance of antimicrobial use

Recently, SWAB's working group on the surveillance of antibiotic use started a project to get insight into the indications for antibiotics prescribed in ambulatory care. Data were obtained from the Integrated Primary Care Information database (IPCI; http://www.ipci.nl). This database is located at the Erasmus University Medical Centre Rotterdam (see section Materials and Methods). To give an impression of the project some results are presented. The project will be submitted for publication.

From our quantitative surveillance data on antibiotic use in the past ten years we conclude that the use of nitrofurantoin almost doubled whereas the use of norfloxacin and trimethoprim decreased. When considering the top-5 of antibiotics used for cystitis in the past ten years a shift in the use of antibiotics is observed (Figure 1). In 1996 nitrofurantoin represented 2% of the prescriptions whereas in 2005 this was 40%. This increase was accompanied by a decrease in the use of trimethoprim and norfloxacin. These observed trends can probably be explained by revisions made in the guidelines of the Dutch College of Dutch Practitioners (NHG) for urinary tract infections in the past ten years (see discussion chapter 3, ambulatory care).[1]

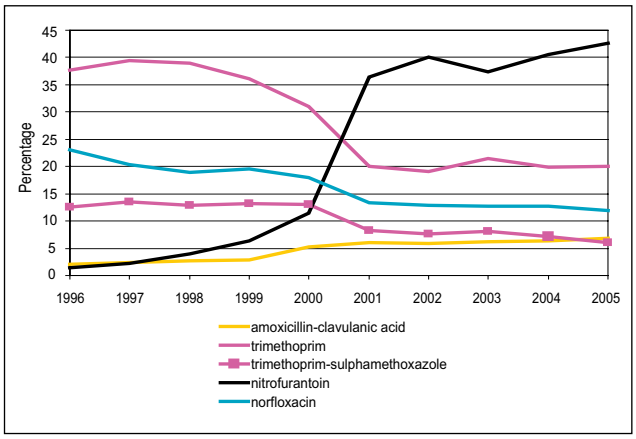


Figure 1. Prescribed antibiotics (%) for cystitis.

Amoxicillin is the most often used antibiotic for otitis media acuta in children at the age of 0-1 year (Figure 2).[2] Over the past ten years prescribing habits for otitis media acuta in this age category did not change. About 12% of the prescriptions concerned amoxicillin with clavulanic acid. The rationality of these amoxicillin with clavulanic acid prescriptions needs further analysis.

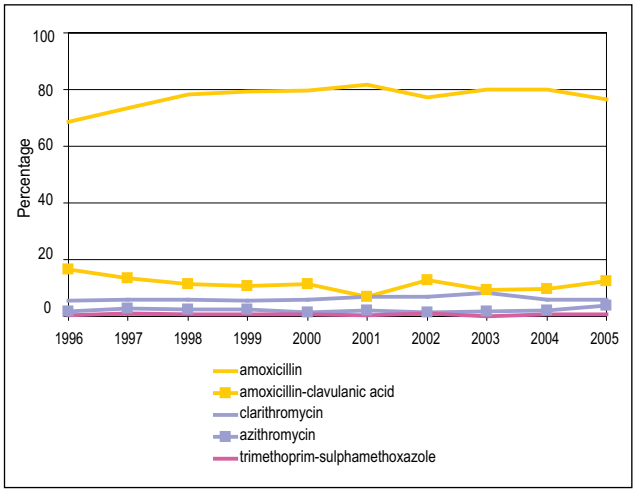


Figure 2. Prescribed antibiotics (%) for otitis media acuta.

From these preliminary results it may be clear that insight into the indications of antibiotics as is presented in this project may help to interpret observed trends in antibiotic use which is worthwhile when developing antibiotic policies to contain the resistance problem.

References

[1] NHG-standaard Urineweginfecties (tweede herziening). Huisarts Wet 2005;48:341-52.

[2] NHG-standaard Otitis Media Acuta (eerste herziening). Huisarts Wet 1999;42:362-6.

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4 Resistance among common Pathogens

Surveillance of Antimicrobial Resistance in the Community

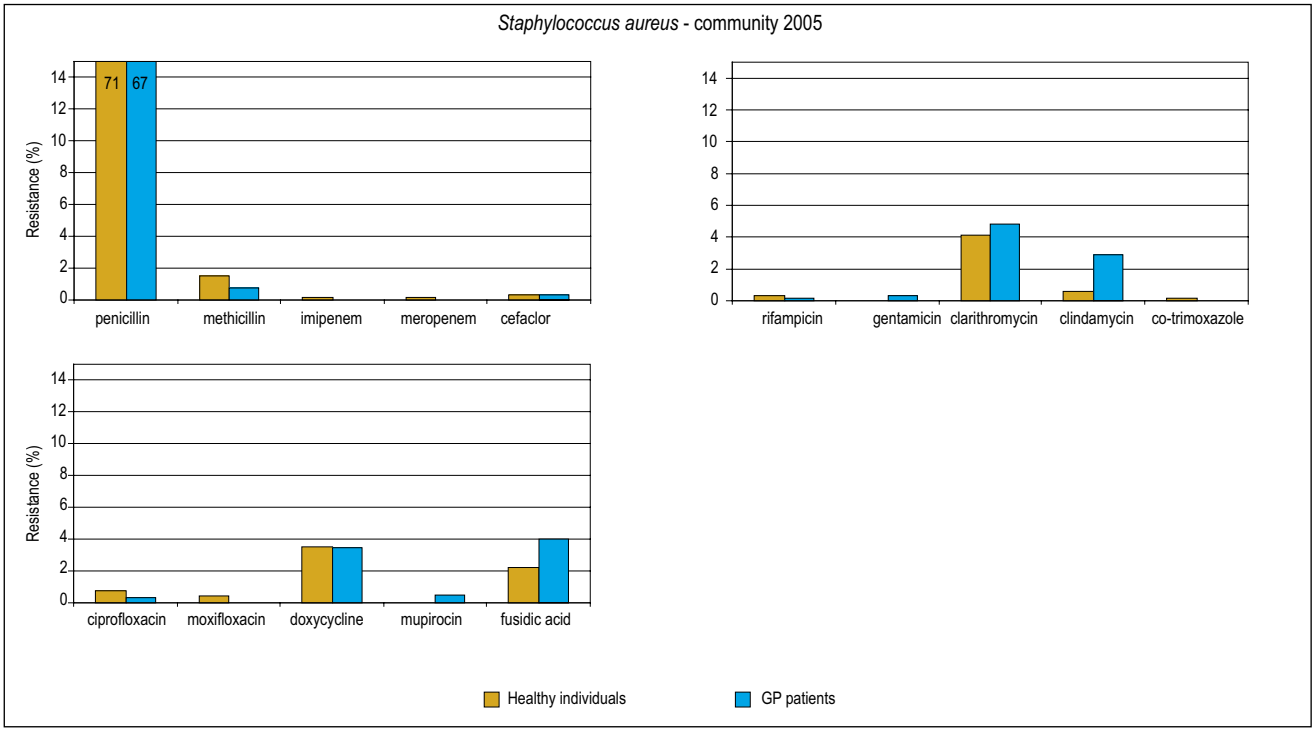
The prevalence of antibiotic resistance among *Staphylococcus aureus* as part of the indigenous flora of healthy persons was determined to get insight in the carrier state and the basic level of resistance in this reservoir in the community. Further the carrier rate and resistance level in patients visiting their general practitioner (GP) was determined. The study started in 2005.

Carrier state and resistance level in healthy individuals

To determine the carrier state in healthy individuals, a random sample of 4000 individuals between 18 and 75 years of age was taken from the municipal administration in Heerlen, a city in the Southern part of the Netherlands. Each person received an envelope by mail with the request to deliver a nasal swab for research (see appendix for detailed information on methods). A total of 2369 nasal swabs were obtained; *S. aureus* was isolated in 656 samples, resulting in a carrier rate of 28%.
Penicillin resistance was found in 71% of the strains (figure 1). The distribution of MICs (figure 2) showed a bimodal shape with one population (27%) having MICs ≤ 0.06 mg/l and a second population (73%) with MICs over a large area (0.25-16 mg/l) with MIC_{90} 8 mg/l.

Methicillin resistance was seen in 11 strains (1.5%); two strains harboured the *mec*A gene and were classified as MRSA. So 0.3% of the *S. aureus* carriers had an MRSA, which is 0.1% of the total healthy population.
Cefaclor resistance was very low (0.3%) and cefuroxime resistance was not found. This in contrast with imipenem– and meropenem resistance rates which were 0.2%. Resistance to linezolid, vancomycin or teicoplanin was not found. According to the MIC distributions of linezolid (figure 2) 12% of the strains had an MIC 4 mg/l, which is just below the new breakpoint given by the CLSI and therefore the strains were recorded susceptible. However this breakpoint was originally 2 mg/l. Taking this criterion the strains with MIC 4 mg/l would be judged resistant. The breakpoint was increased by the CLSI to include some wild type strains (6% of around 60.000 strains in a random study) which showed discrepancy in outcome by using different susceptibility tests. The number of 12% with MIC 4 mg/l found by us in the community is high and is reason for concern. Linezolid is a drug never used so far in the community. Further surveillance may elucidate this finding. Calculating MIC_{90} we found vancomycin MIC_{90} 1 mg/l, teicoplanin MIC_{90} 0.5 mg/l and linezolid MIC_{90} 4 mg/l. Clarithromycin resistance was found in 4% of carriers compared to 0.6% resistance to clindamycin.
Ciprofloxacin resistance was 0.8% in carriers; the MIC distribution (figure 2) showed a unimodal shape over

Figure 1. Resistance to antibiotics among *Staphylococcus aureus* from healthy individuals and GP patients in the community.



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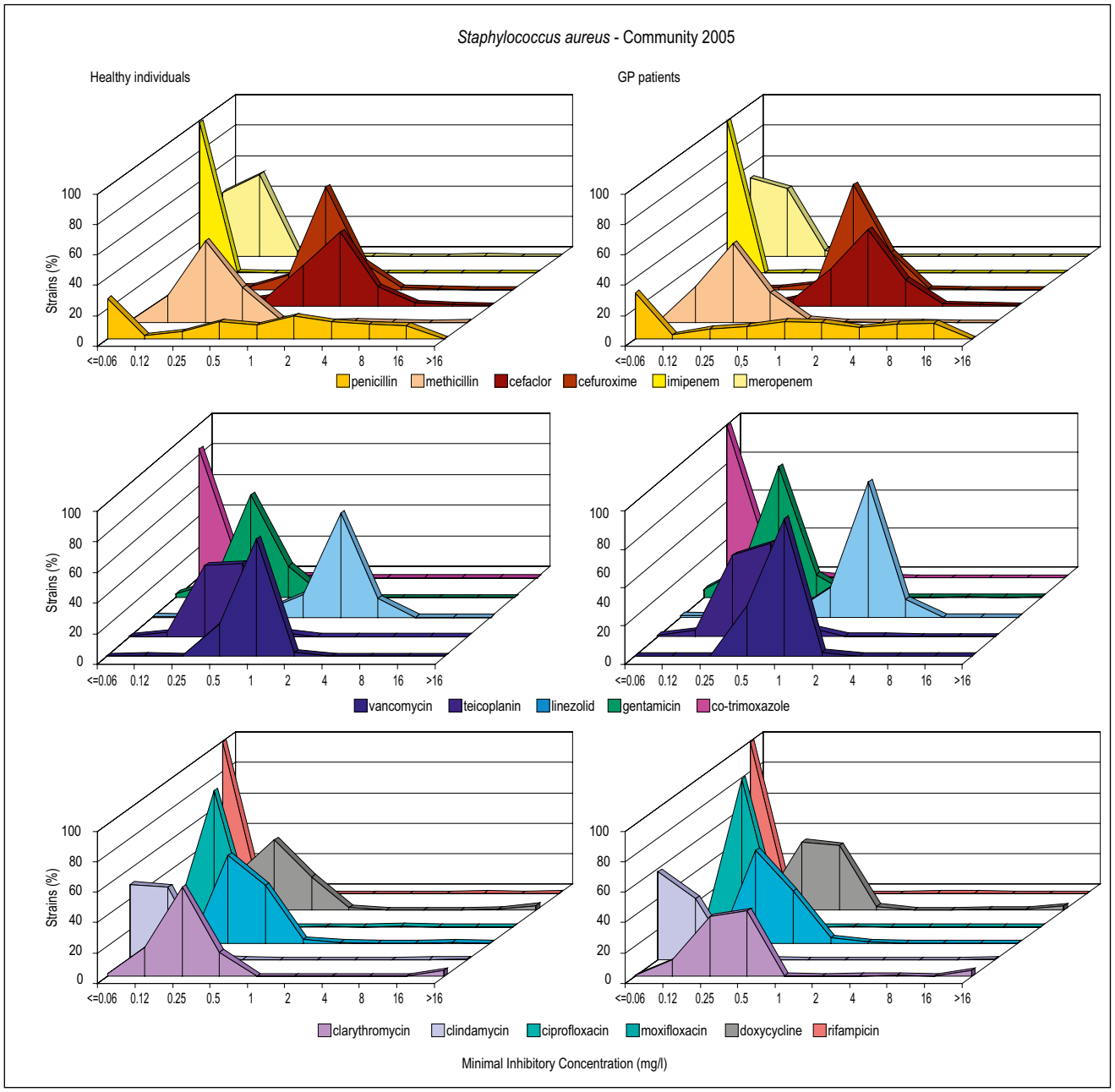


Figure 2. MIC distributions of antibiotics tested for *Staphylococcus aureus* from the community.

a small range (0.25-1 mg/l) with five strains with MIC > 1 mg/l. The MIC_{90} was 0.5 mg/l, which is normal.
Moxifloxacin resistance was observed in 0.5% of the strains; in general the MICs for moxifloxacin were 4-fold lower than for ciprofloxacin with MIC_{90} 0.12 mg/l. One strain was resistant to ciprofloxacin, moxifloxacin, penicillin, methicillin, cefaclor and clarithromycin. Two other ciprofloxacin-resistant strains were also resistant to moxifloxacin.
Doxycycline resistance was determined in 3.5% of the strains (figure 1). Fusidic acid resistance was found in 14 isolates (2.2%). Resistance to gentamicin and mupirocin was not observed.

Carrier state and resistance level in GP patients
Thirty practitioners from all over the country participated in the study. Patients visiting the GP for a non-infectious complaint were asked to allow taking a nose swab for research on *S. aureus* carrier state. See appendix for methods.
A total of 2691 patients participated in the study. They came from the Northern and Eastern part of the country (mostly rural area, N=482), Central part (urban area, N=901) and Southern part (mixed industry and urban area, N=1308). Overall *S. aureus* was isolated in 617 nose swabs, resulting in an overall carrier rate of 23% which is significantly lower than the 28% carrier rate in

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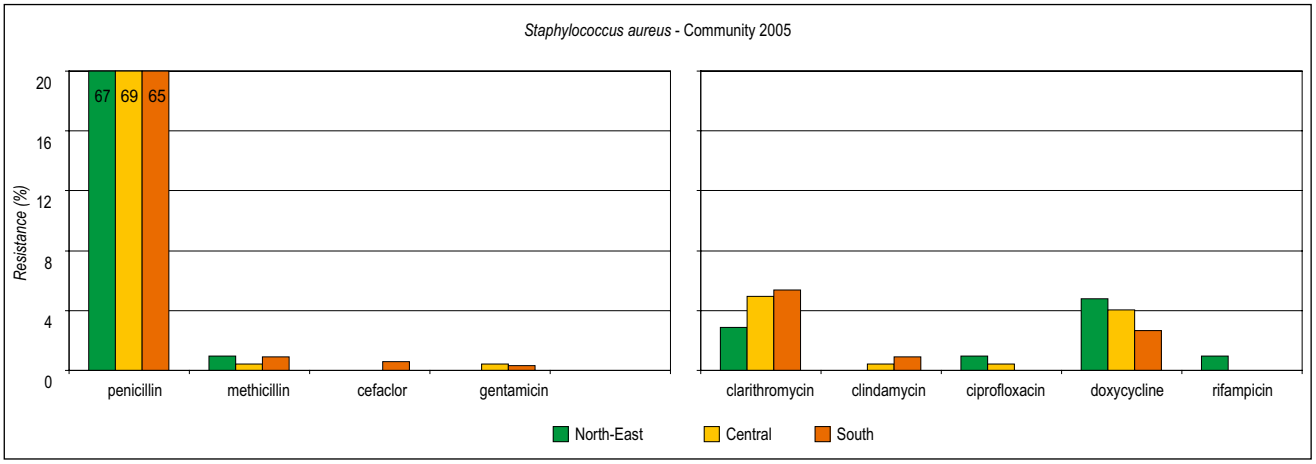


Figure 3. Resistance to antibiotics among *Staphylococcus aureus* in North/East-, Central- and South Netherlands.

healthy individuals (p< 0.005). The carrier rate was 22% in the North/East region, 25% in the Central region and 26% in the Southern region. The carrier rate in the North/East rural area was lower than in the other areas possibly due to a lower degree of urbanization.
Resistance to penicillin was found in 67% of the patients (figure 3), which is similar to the carrier rate in healthy individuals. The MIC distribution (figure 2) had the same bimodal shape as that of healthy individuals, but the highly susceptible population was larger (31%) and the MIC_{90} appeared 16 mg/l. The resistance rate differed not between the three regions (figure 3). Resistance to methicillin was found in five strains, but none of them harboured the *Mec*A gene and therefore the strains could not be classified as MRSA.
Cefaclor resistance was as low as that in healthy individuals; it was only found in the Southern region (figure 3), where also the group of healthy individuals came from. Imipenem- or meropenem resistance was not found. The MIC distributions in patients and healthy and individuals were identical. Resistance to linezolid, vancomycin and teicoplanin was not demonstrated in either population, but the MIC distribution of linezolid in GP patients (figure 2) showed the same pattern as that for strains from healthy individuals: 10% of the strains had an MIC 4mg/l, which is also high and reason for further surveillance.
Clarithromycin resistance was observed in 5% of the isolates from patients, which is slightly more than in healthy individuals. The prevalence of resistance in the South (5.5%) and 5% in the central region were higher than the prevalence of 3% in the North. The MIC distribution in patients was slightly different from that in healthy individuals with a larger population with MICs 1 mg/l, whereas the peak in healthy individuals was sharp and at 0.5 mg/l. This may predict a shift to higher MICs in the future. Striking was the finding of cross-resistance with clindamycin in 19 clarithromycin-resistant strains (2.9%). Such cross-resistance was only 0.6% in healthy individuals (p< 0.002).
Ciprofloxacin resistance was low in patients (two strains, 0.3%) and moxifloxacin resistance was not demonstrated (figure 3). The two resistant strains were also resistant to penicillin, one to doxycycline as well.
The percentage of resistance to fusidic acid was 4%, significantly higher than in healthy individuals (p< 0.05). Resistance to mupirocin was found in three strains, one of these was also resistant to fusidic acid. Previous treatment with these drugs must have led to resistance in these strains. Doxycycline resistance was similar in GP patients and healthy individuals, but differed from region to region (figure 3), 5% in the North/East, 4% in the Central area and 2.5% in the South. The MIC distributions of doxycycline and clarithromycin were similar. In patients the distributions were broader than in healthy individuals. Gentamicin resistance was found in two strains, one of these strains was co-resistant to clarithromycin.

Multi Drug Resistance in the community
Combined resistance to two or more systemic antibiotics was found in 6% of the strains, both from healthy individuals and GP patients. Combined resistance to penicillin/doxycycline and penicillin/clarithromycin predominated in each population (figure 4). Resistance to three or more antibiotics of different classes was demonstrated in 1.2% of strains from healthy individuals and GP patients, so 0.35% of the investigated healthy population carried a multi drug resistant *Staphylococcus aureus*..

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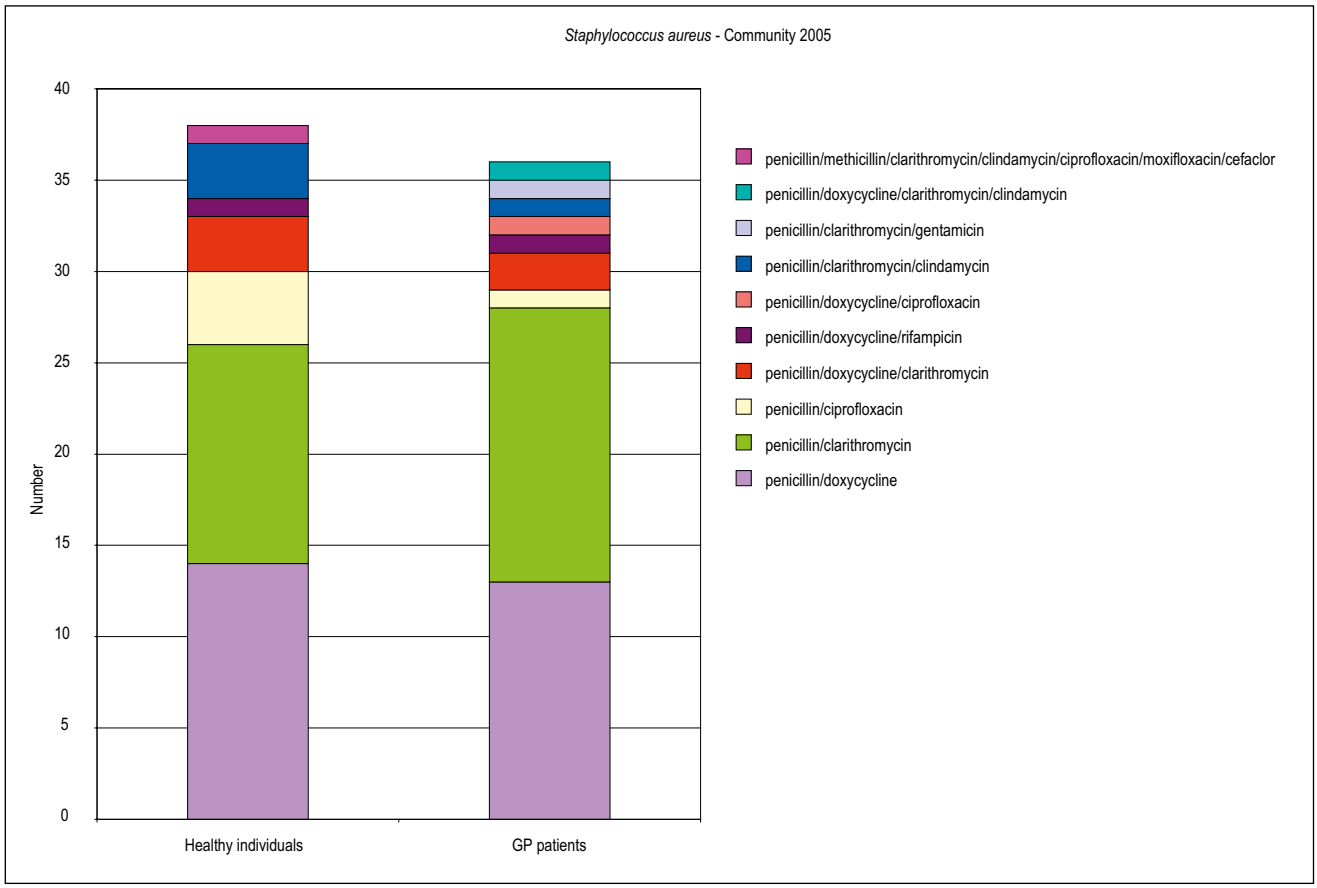


Figure 4. Multidrug resistance among *Staphylococcus aureus* from the community.

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 outpatient 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 13 large referral hospitals (table 2 in the appendix). These selected departments included the Intensive Care Units, being wards with a 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 analysed 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 increased from 28 % in 1996 to 41% in 2006 (figure 5). Amoxicillin resistance was higher in Intensive Care Units, fluctuating around 42% until 2004 and showed a sharp increase to 56% in 2005, whereas the resistance in Urology Services increased steadily, but slower from 38% in 1996 to 41% in 2005.

The distribution of MICs (figure 6) in Intensive Care Units showed two subpopulations: a susceptible one with a broad MIC range from 0.5-8 mg/l (peak at 4 mg/l) and a resistant one with MICs > 32 mg/l. The resistant subpopulation was steadily growing during the years.

Co-amoxiclav resistance was at a low level (4%) in Unselected Hospital Departments and in the Urology Services until 2000 (figure 5). Subsequently, an increase in the level of resistance was observed in the Urology Services, which stabilized at 8.5% in 2005. The level of resistance in Unselected Hospital Departments increased to 6% in 2006, similar to the level found already in 2001 in Urology Services. Co-amoxiclav resistance was much higher in Intensive Care Units, with fluctuations to 22% in 2004. The MIC distribution of amoxicillin in Intensive Care Units was similar to that found for the community,

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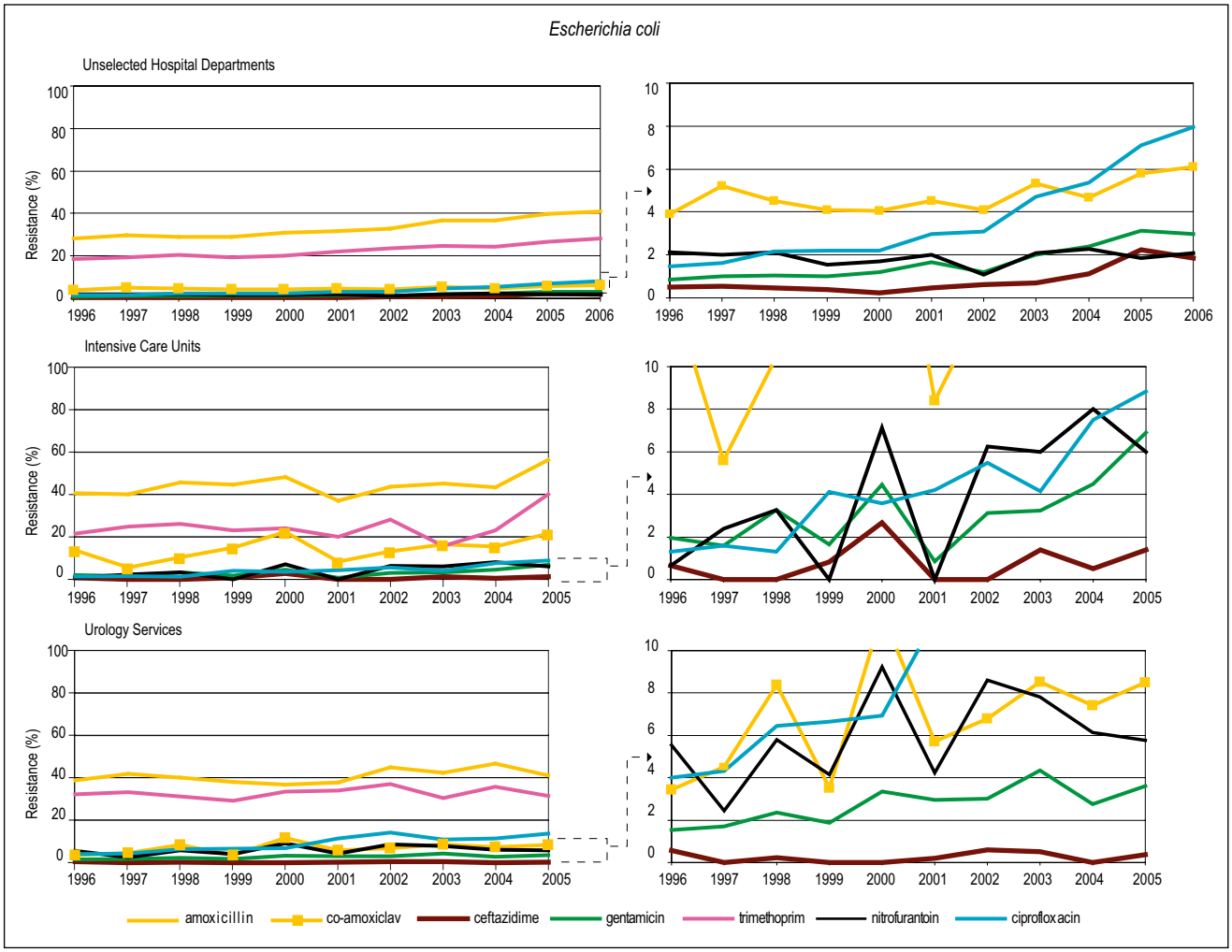


Figure 5. Trends in resistance to antibiotics among *Escherichia coli* from Unselected Hospitals, Intensive Care Units and Urology Services.

but the MIC distribution of co-amoxiclav from Intensive Care Units showed a considerable resistant subpopulation (MICs > 16 mg/l) and a growing number of moderate susceptible strains with MICs 16 mg/l. Such an intermediate population may predict upcoming resistance. 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%) until 2004; in 2005 a sharp increase in resistance was recorded in all Intensive Care Units with an overall percentage of 38%. The MIC distribution of piperacillin (figure 7) showed three subpopulations: one susceptible with MICs 0.5-4 mg/l, one intermediate with MICs 8-64 mg/l and one resistant subpopulation with MICs > 64 mg/l. This pattern existed since 2000; from that time on a shift could be observed from moderate susceptible to resistant. Piperacillin showed higher activity than amoxicillin towards the same subpopulation: the peak of MICs of piperacillin in the susceptible range was at 2 mg/l, that of amoxicillin at 4 mg/l (figure 6). Resistance to piperacillin-tazobactam was still exceptional (range 0.7-4.5%, overall 1.5% in 2005). The MIC distribution of piperacillin-tazobactam showed an almost complete disappearance of populations resistant or intermediate to piperacillin alone.

Ceftazidime resistance in Unselected Hospital Departments was very low, but showed an increasing trend, being less than 1% until 2003, but 1% in 2004 and 2% in 2006. 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 18% in 2005 in Intensive Care Units versus 3-5% in Urology services (figure 7). The MIC distribution of cefaclor (figure 8) was almost unimodal over a broad range during 1996 and 1997 with a number of strains with an MIC just below the breakpoint of susceptibility and the MIC_{90} being 8-16 mg/l until 2000. From 2000 on highly resistant strains appeared, resulting in a bimodal shape of the curves with

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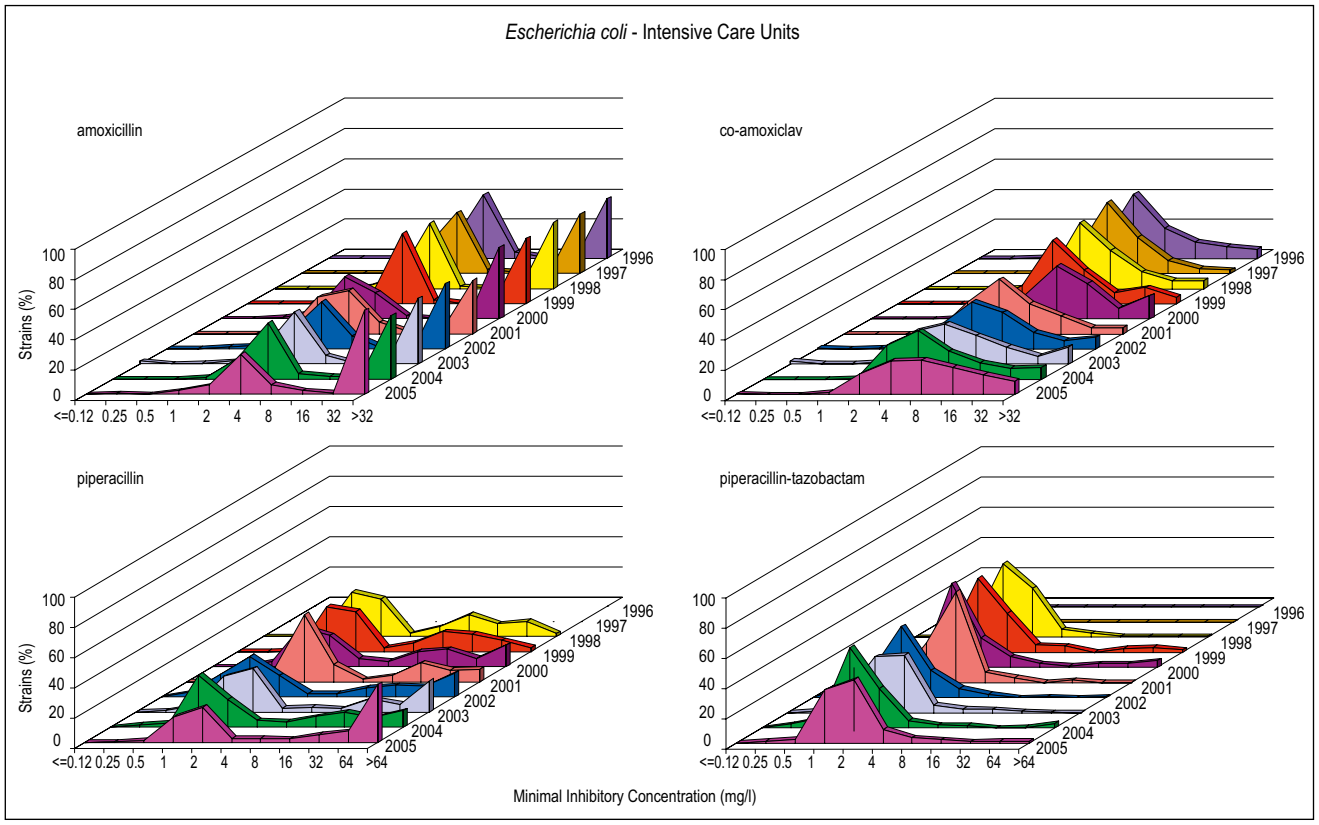
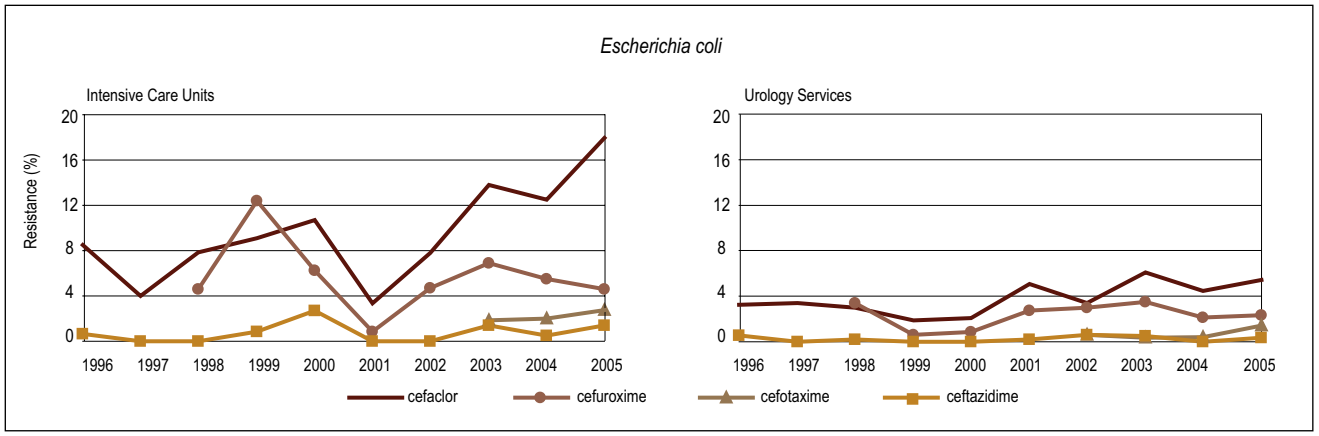


Figure 6. MIC distributions of beta-lactam antibiotics for *Escherichia coli* from Intensive Care Units.

a sharp and increasing peak with resistant strains and an increase of the MIC_{90} to 64 mg/l. The change of the shape of the curve can thus predict development of resistance before it becomes manifest. The MIC distribution of cefuroxime (figure 8) showed a unimodal shape over a broad range (only shown for 2005), both cefotaxime and ceftazidime showed a unimodal distribution over a very small range (<= 0.12-0.5 mg/l).
Trimethoprim resistance increased steadily in Unselected Hospital Departments over the years from 18% to 28% (figure 5). The level of trimethoprim resistance in Intensive Care Units fluctuated around 20-25% until 2004, but in 2005 a high resistance rate of 40% was found, thereby exceeding the trimethoprim resistance in the Urology Services which fluctuated from 32-37% during the last 10 years. Co-trimoxazole resistance followed this trend and was only 1-2% lower. The MIC distribution (figure 9) showed that two subpopulations existed: one susceptible and one highly resistant. Nitrofurantoin resistance was about 2% in Unselected Hospital Departments, equal to the figures in the community. This was also observed for Intensive Care

Figure 7. Trends in resistance to cephalosporins among *Escherichia coli* from Intensive Care Units and Urology Services.



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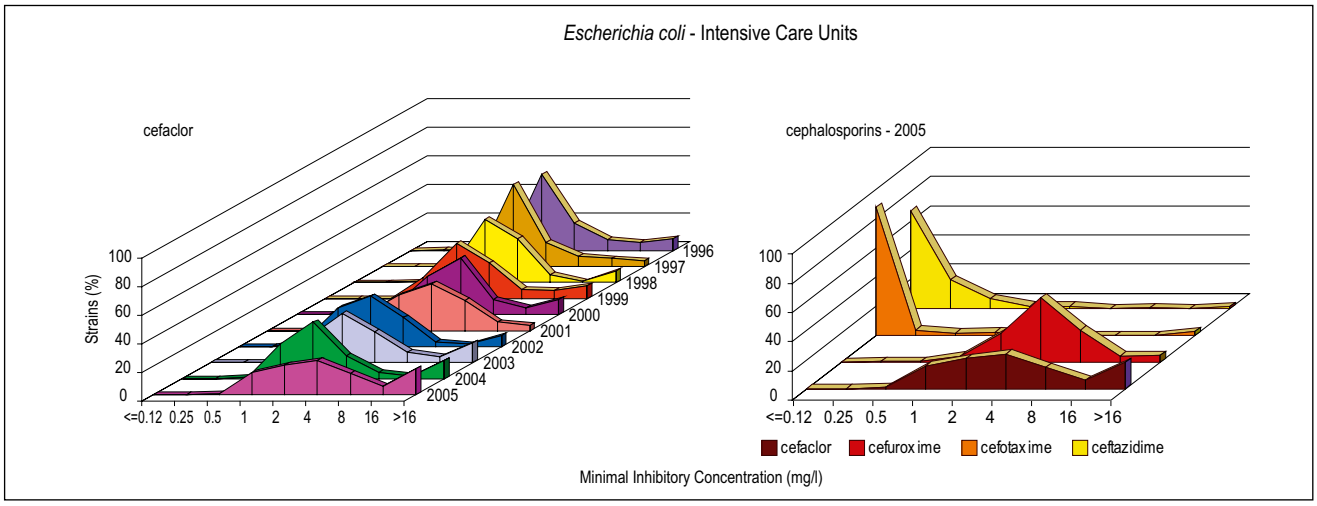
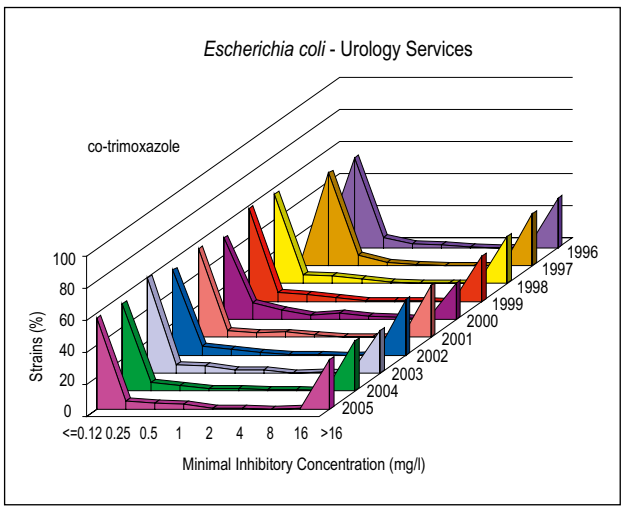


Figure 8. MIC distributions of cephalosporins for *Escherichia coli* from Intensive Care Units.

Units until 2000. Then it increased slowly to a mean of 6% during the last five years, thereby equalling the resistance level among strains from Urology Services, which fluctuated around 6% from the beginning. Ciprofloxacin resistance increased slowly but steadily among *E. coli* from Unselected Hospital Departments to 4% in 2003 and 8% in 2006, thereby equaling the resistance rates in the Intensive Care Units. The resistance in Intensive Care Units increased further to 9% in 2005. The resistance level in Urology Services however increased rapidly from 7% in 2000 to 14% in 2005 (figure 5). The resistance percentages and the MIC distributions of norfloxacin, levofloxacin and ciprofloxacin were similar (figure 10). The MIC distribution of the quinolones for *E. coli* from Urology Services was bimodal with a large susceptible subpopulation over a small range (MICs 0.008-0.03 mg/l, not shown in the figure) and a small subpopulation

Figure 9. MIC distributions of co-trimoxazole for *Escherichia coli* from Urology Services.



of strains with MIC > 2 mg/l (figure 10). 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 14 in 2005. The percentage of quinolone resistant *E. coli* varied between the centres from 3-25%.
Gentamicin resistance was low in Unselected Hospital Departments, although it seemed to increase slightly last years from 1% until 2002 to 3% in 2006, the resistance level in Intensive Care Units and Urology Services fluctuated between 2-4 % until 2004; it was overall 7% in 2005 (figure 5). Analysing this figure, it appeared that resistance was found in seven centres with resistance levels varying from 7-12 %, six centres had no gentamicin resistance.

Multi Drug Resistance in Intensive Care Units
Resistance to ≥ 3 groups of antibiotics in Intensive Care Units was recorded for various combinations, mostly at low levels. Yet some trends could be observed: The number of combinations to which resistance was found, increased significantly during the years and the number of antibiotics within the combinations increased over the years (figure 11). Until 1999 only resistance to a combination of three antibiotics was found, thereafter resistance to four antibiotics (from 2000 on) or five antibiotics (from 2003 on) were recorded. This comprised roughly 2% of the strains yearly. Resistance rate to three antibiotics seemed to increase from 2% in 1996 to 4% in 2004 and 2005. Resistance to the combination co-amoxiclav + co-trimoxazole + another drug was prevalent. The other drugs were cefuroxime, ciprofloxacin or gentamicin or a combination of these. Multiresistance to the combination co-amoxiclav / co-trimoxazole / ciprofloxacin was found yearly from 1996 on (0.5 – 1.5% of the *E. coli* strains collected each year). Resistance to the combination co-amoxiclav / co-trimoxazole / cefuroxime emerged in 1998 and was demonstrated in

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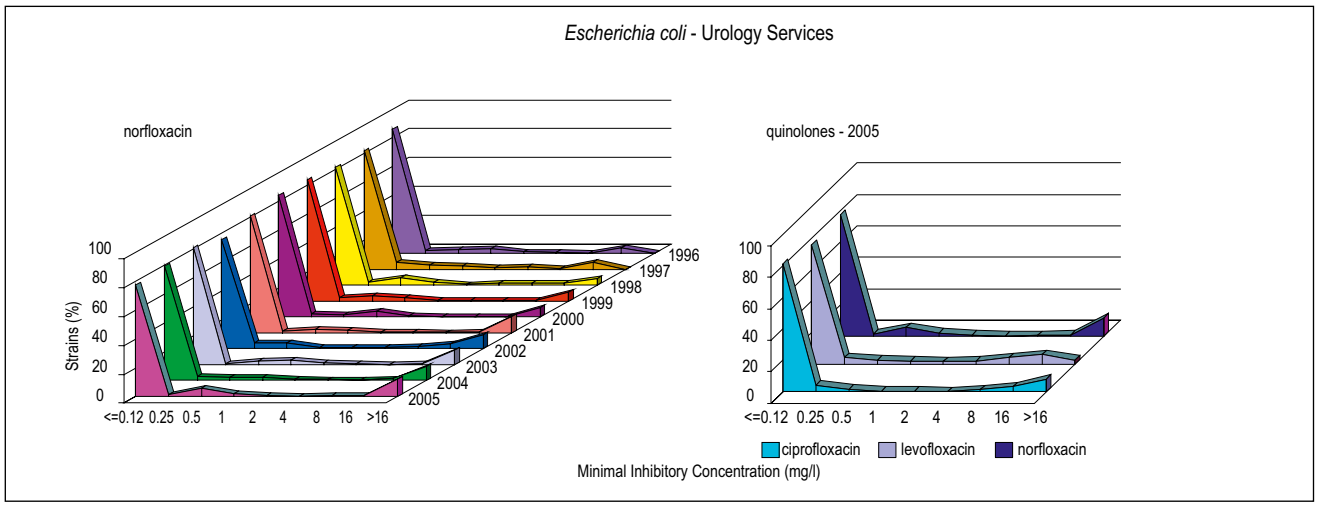
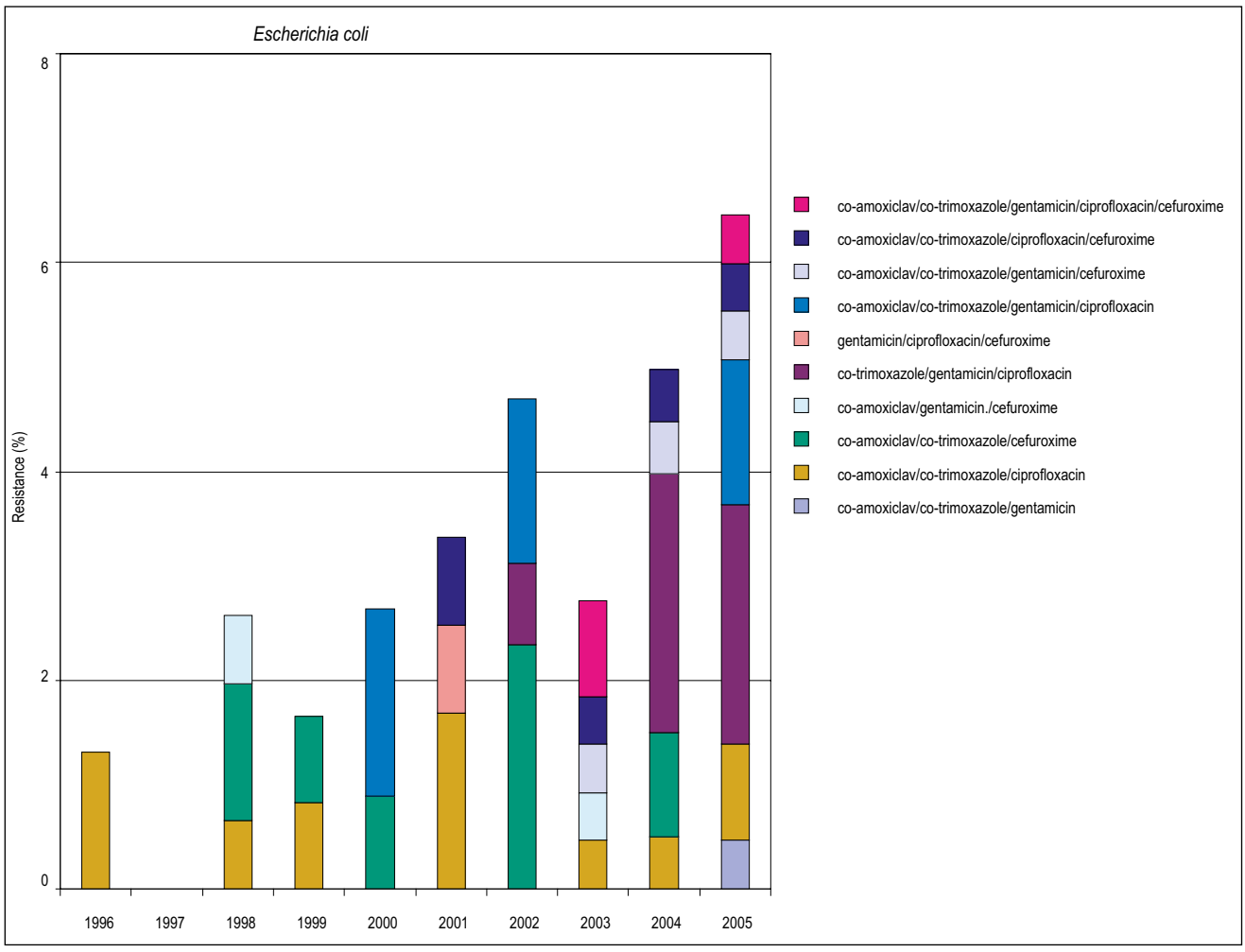


Figure 10. MIC distributions of quinolones for *Escherichia coli* from Urology Services.

1-2% of the strains yearly thereafter, except in 2000, but from 2001 the resistance to this combination was expanded with resistance to ciprofloxacin as well.

Resistance to the combination co-trimoxazole / gentamicin / ciprofloxacin emerged in 2000 in 1% of the isolates and increased to 2.5% in 2004 and 2005.

Figure 11. Trends in multidrug resistance among *Escherichia coli* from Intensive Care Units



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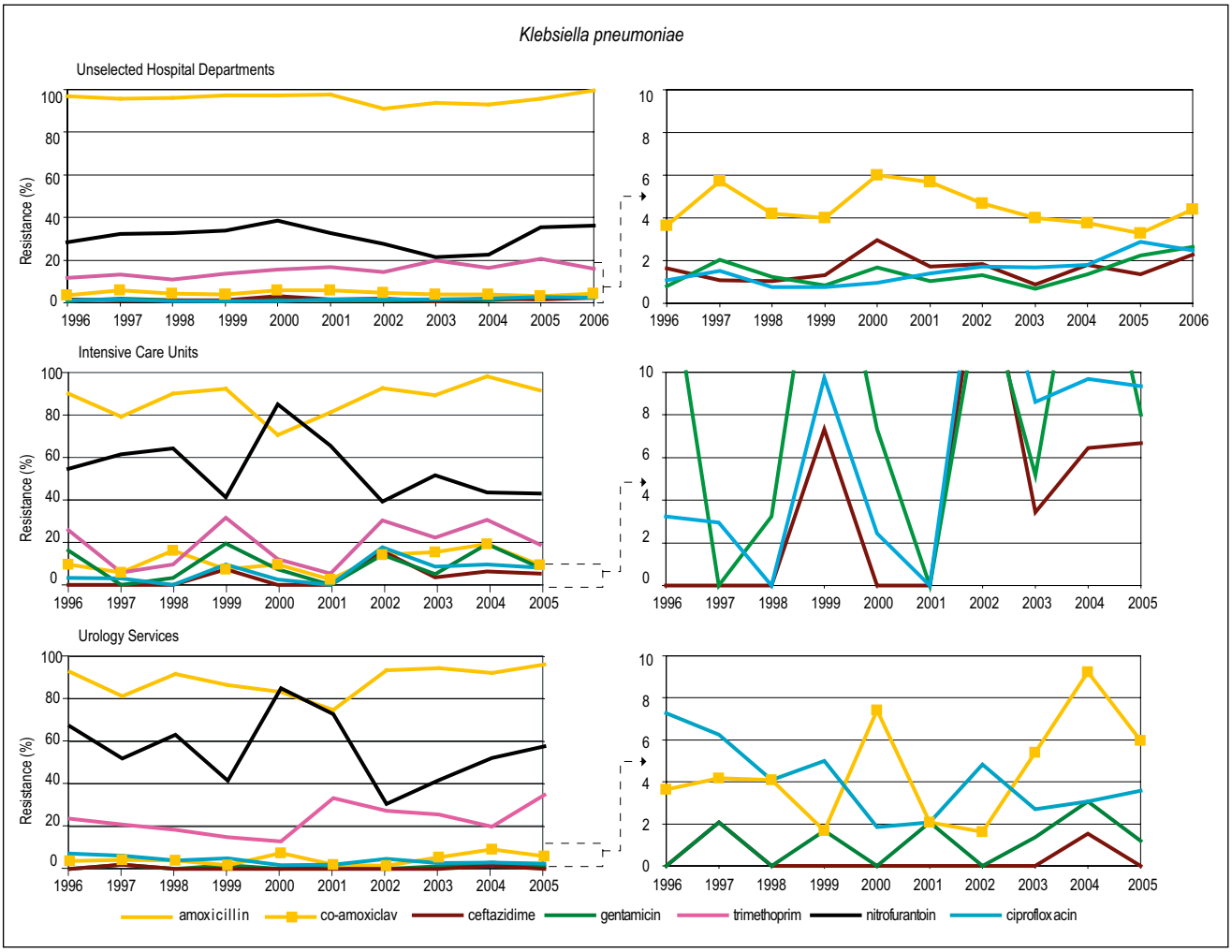
Klebsiella pneumoniae

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 fluctuated but did not increase (figure 12). Co-amoxiclav resistance in Intensive Care Units fluctuated at a much higher level (4-19%). Co-amoxiclav resistance in Urology Services was similar to that in Unselected Hospital Departments. Resistance to first- and 2nd generation cephalosporin 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 was sporadic 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 3% in 2003 and 6% in 2004 and 2005. Overall cefotaxime resistance was less common than ceftazidime resistance.

Trimethoprim resistance increased with some fluctuations in Unselected Hospital Departments from 11% in 1996 to 16% in 2006 (figure 12). The level of resistance in Intensive Care Units fluctuated around 20%. In Urology Services an increase of resistance to 36% was observed in 2005. 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 by urologists in the years before. The resistance to 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 fluctuated in Unselected Hospital Departments (21-39%) (figure 12). The level of resistance in Intensive Care Units and Urology Services

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



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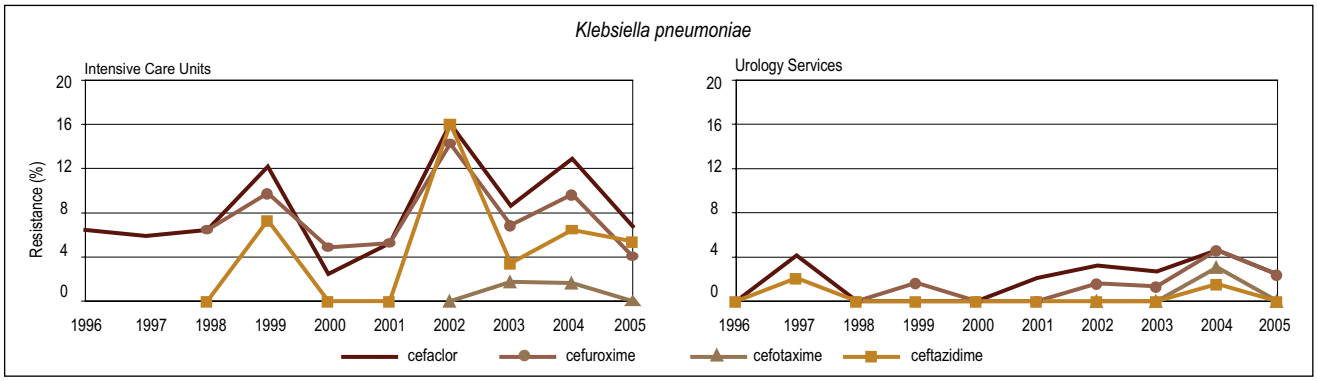
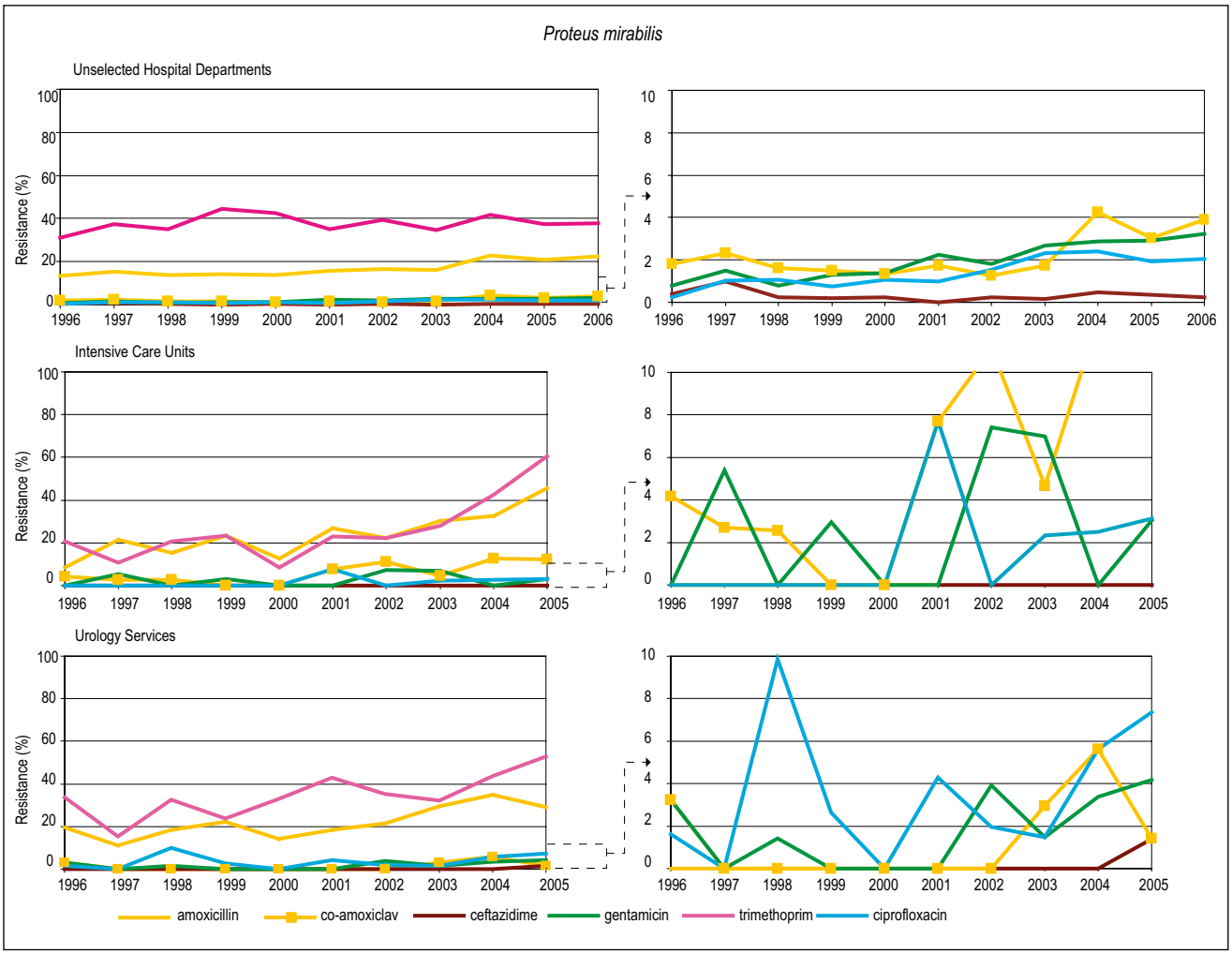


Figure 13. Trends in resistance to cephalosporins for *Klebsiella pneumoniae* from Intensive Care Units and Urology Services.

in 2004 was 40% or more.
Gentamicin resistance was low and at a constant level (1-3%) 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 2005 of 8%. 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 2.5% in 2006 (figure 12). Ciprofloxacin resistance had a sporadic character in Intensive Care Units and Urology

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



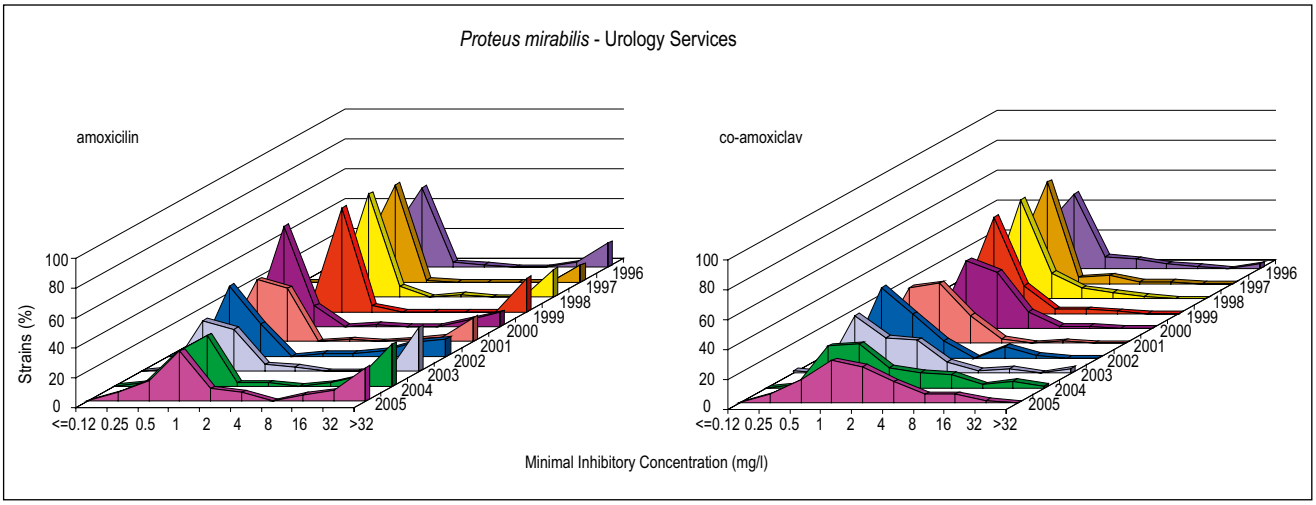
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Services and did not spread: resistant strains were found in 2-4 Intensive Care Units each year since 2000 (in one permanently) and 2-3 Urology Services each year. Four Intensive Care Units had problems with ciprofloxacin-resistant *K. pneumoniae* in 2005: the resistance level varied from 12-36% in these four wards, resulting in a mean of 9% in all investigated wards. This figure is therefore not representative for the resistance rate of ciprofloxacin among *K. pneumoniae* in Intensive Care Units in the Netherlands.
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 showed a steady increase, from 14% in 1996 to 23% in 2006. Amoxicillin resistance in Intensive Care Units increased to 46% in 2005 (figure 14). Amoxicillin resistance was higher in Urology Services from the beginning (19%), and increased to 30% from 2003 until 2005. The distribution of MICs of strains from the Urology Services showed two subpopulations: a susceptible one and a resistant one with MICs > 16 mg/l (figure 15). In 2005 the range for the susceptible population broadened (0.2-8 mg/l versus 0.2-2 mg/l in the years before) and intermediate strains with MIC 16 mg/l emerged. This may predict a shift to resistance in the next years.
Co-amoxiclav resistance was around 4% in Unselected Hospital Departments and 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 and 2005). 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 and 2005, 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 38% in 2006, equaling the levels found in Urology Services in 2004; in 2005 the level in Urology Services rose to 53%. The resistance level in Intensive Care Units increased rapidly from 28% in 2002 to 61% in 2005 (figure 14).
Ceftazidime resistance in *P. mirabilis* was less than 1%.
Gentamicin resistance increased slowly in Unselected Hospital Departments to 3% in 2006. This was also found for Intensive Care Units and some Urology Services.
Ciprofloxacin resistance among *P. mirabilis* in Unselected Hospital Departments increased from 1-2% during the study period. The resistance level in Intensive Care Units remained low and sporadic, but the resistance in Urology Services increased to 7% in 2005.

Pseudomonas aeruginosa
Ceftazidime resistance among *P. aeruginosa* isolated in Unselected Hospital Departments and in Urology Services was consistently low (2-3%). Ceftazidime resistance in Intensive Care Units remained below 1.5%. An incidental 10% resistance was recorded in 2002 (figure 16) in five centres.
Piperacillin resistance among *P. aeruginosa* isolated in Intensive Care Units was not found until 2001; then an increasing number of Intensive Care Units delivered resistant strains: two centres in 2001, five in 2002 and seven in 2005. The proportion of resistant *P. aeruginosa* strains in these centres fluctuated between 20-30%. The overall percentage for all centres was calculated 4-14% from 2001 on (figure 16). Piperacillin resistance in Urology Services was accidental, fluctuating between 2-4%, affecting 2-3 centres. The resistance to piperacillin/tazobactam followed that of piperacillin:

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



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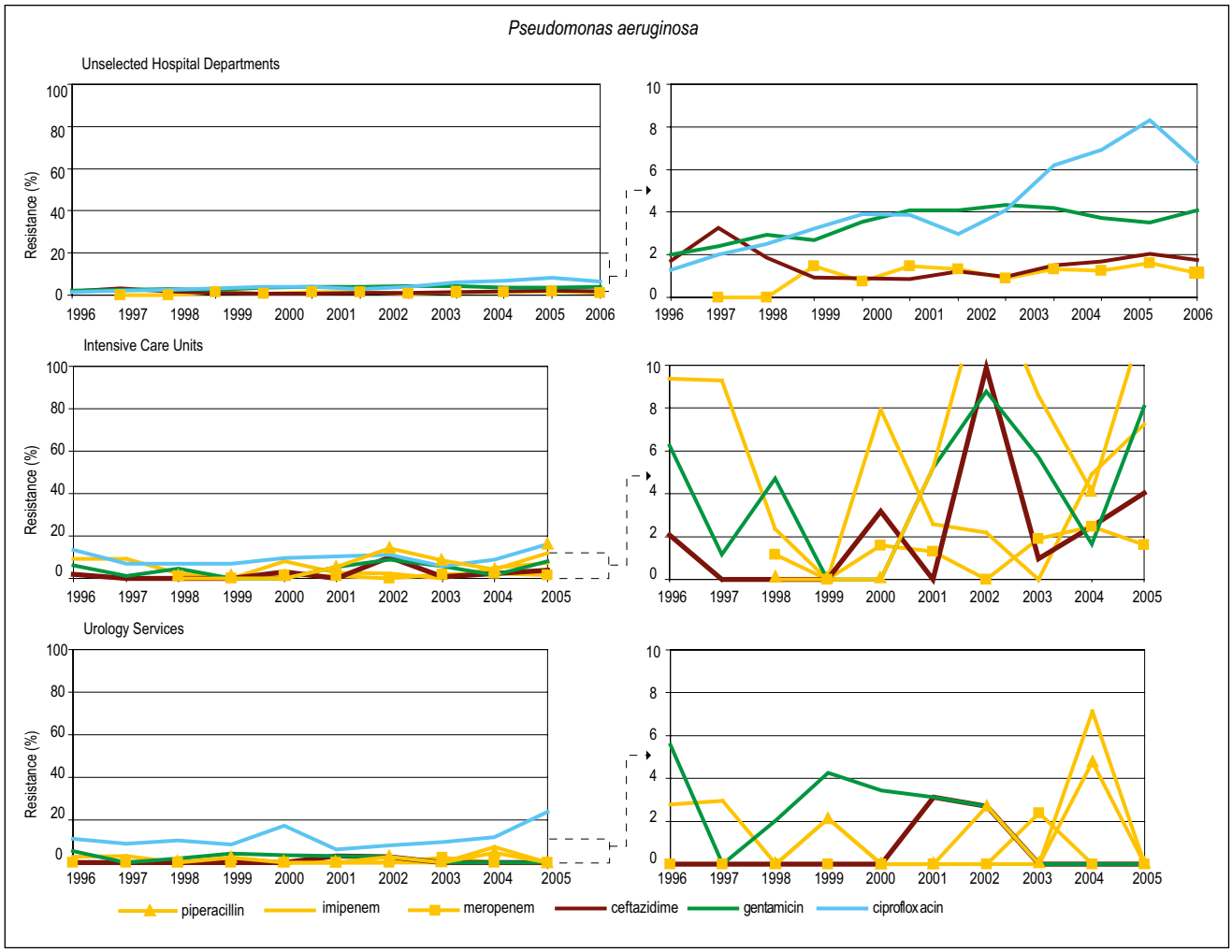
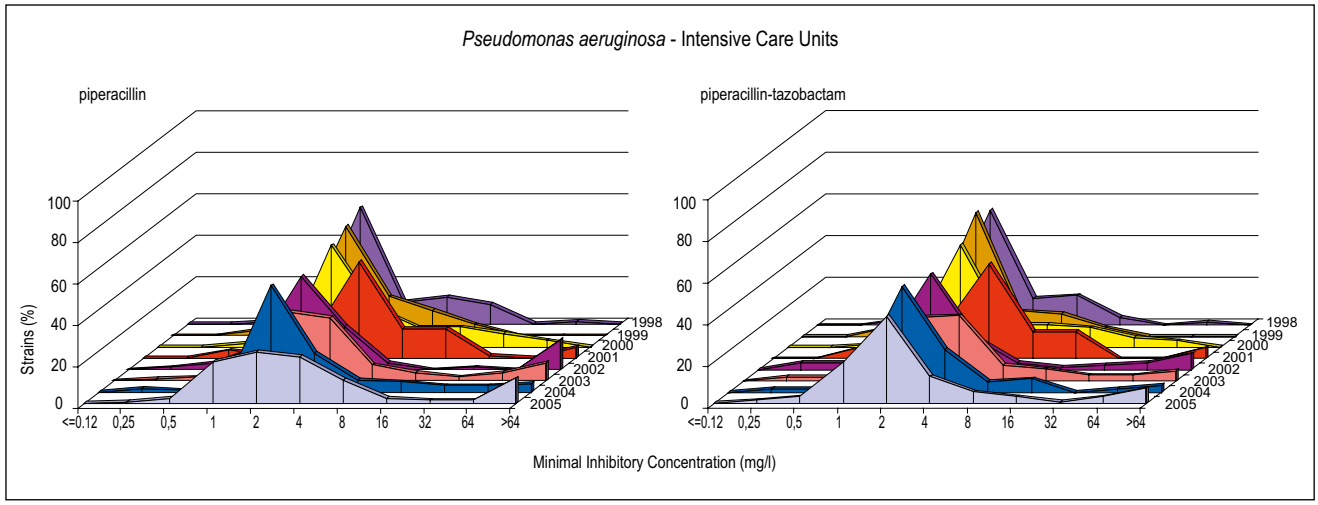


Figure 16. Trends in resistance to antibiotics among *Pseudomonas aeruginosa* from Unselected Hospitals, Intensive Care Units and Urology Services.

it was found in two centres in 2001 and six in 2005 (not shown). The MIC distributions of piperacillin and piperacillin/tazobactam are given in figure 17. They were unimodal from 1998 to 2000 over a broad range (0.5-32 mg/l) with a shoulder in the area MIC 8-32 mg/l; from 2001 the MIC distributions became bimodal,

Figure 17. MIC distributions of piperacillin and piperacillin/tazobactam for *Pseudomonas aeruginosa* from Intensive Care Units.



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showing a subpopulation with MICs 0.5-16 mg/l, a very small number of strains in the intermediate area and a subpopulation with MICs > 64 mg/l. The latter is growing, together with a shift of the median in 2005 to higher MICs and disappearance of the "shoulder". The same phenomenon was observed for piperacillin/tazobactam.

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 five Intensive Care Units, responsible for the fluctuations in the overall resistance rate from 2-8%. Amikacin- and tobramycin resistance rates were 2% and 6% respectively in 2005. The MIC distributions of the three aminoglycosides are presented in figure 18. 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.

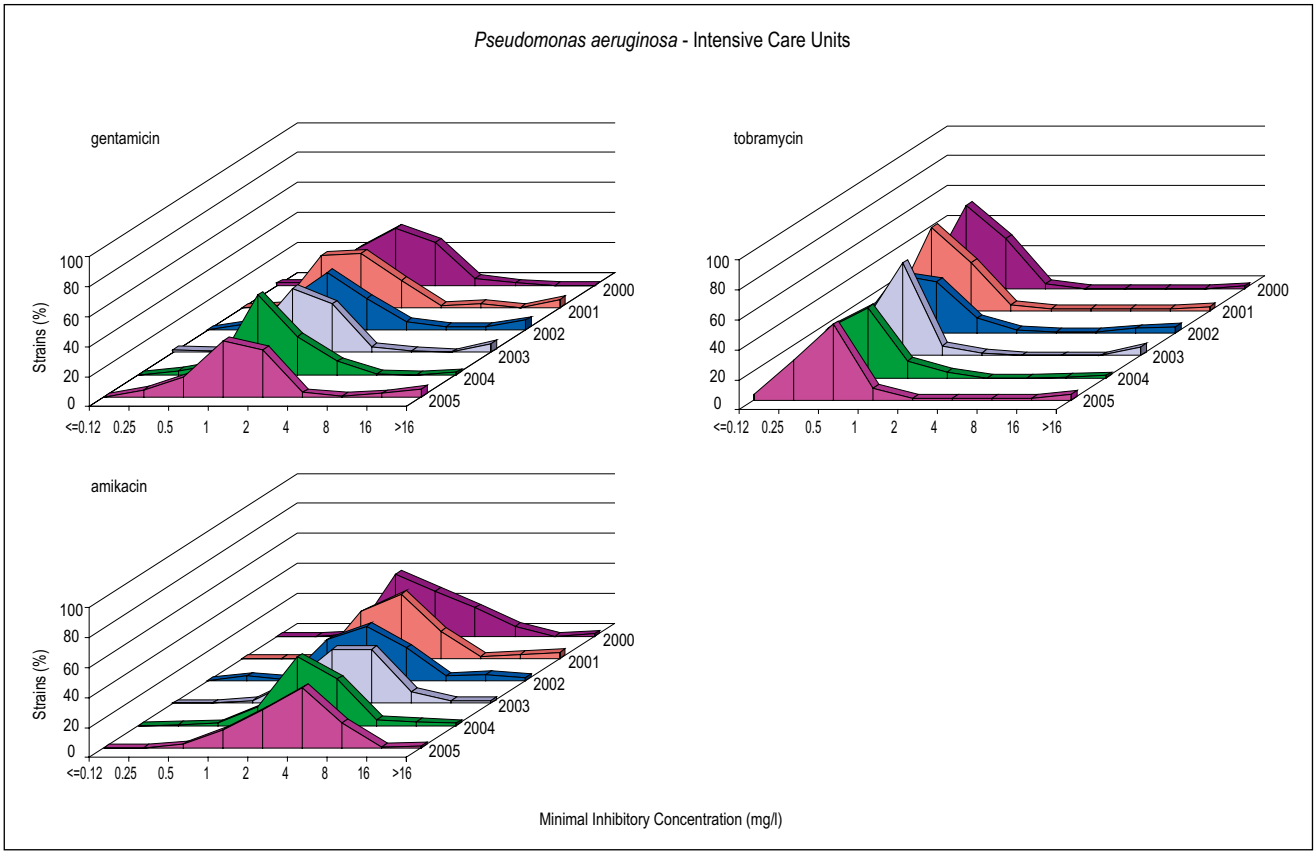
Meropenem resistance among *P. aeruginosa* was less than 2% in Unselected Hospital Departments, Intensive Care Units and Urology Services during the whole study period.

The prevalence of ciprofloxacin resistance increased slowly in Unselected Hospital Departments (2% in 1996 to 6% in 2006, figure 16). Ciprofloxacin resistance was higher in Intensive Care Units and Urology Services already in 1996. The resistance rates in Intensive Care Units decreased from 13 % in 1996 to 7-10% until 2004, but increased in 2005 to 16%. Also the trend in Urology Services was increasing, to 23% in 2005. Resistant strains were found in all centres in 2005. The levels of resistance to levofloxacin paralleled those of ciprofloxacin, but were higher: 20% in Intensive Care Units and 32% in Urology Services in 2005.

Enterococcus faecalis

Before 2002 no amoxicillin resistant *E. faecalis* were found in Intensive Care Units and Urology Services (figure 19). From 2002-2004 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 in 2004; no amoxicillin-resistant strains were found in 2005. The resistance to amoxicillin in Urology Services fluctuated from 1-9% since 2002 and was found in some centres: one in 2002, four in 2003 and two in 2004; thereafter they disappeared. 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 which is evidence for clonal spread of a *Van*A gene positive strain.

Figure 18. MIC distributions of aminoglycosides for *Pseudomonas aeruginosa* from Intensive Care Units.



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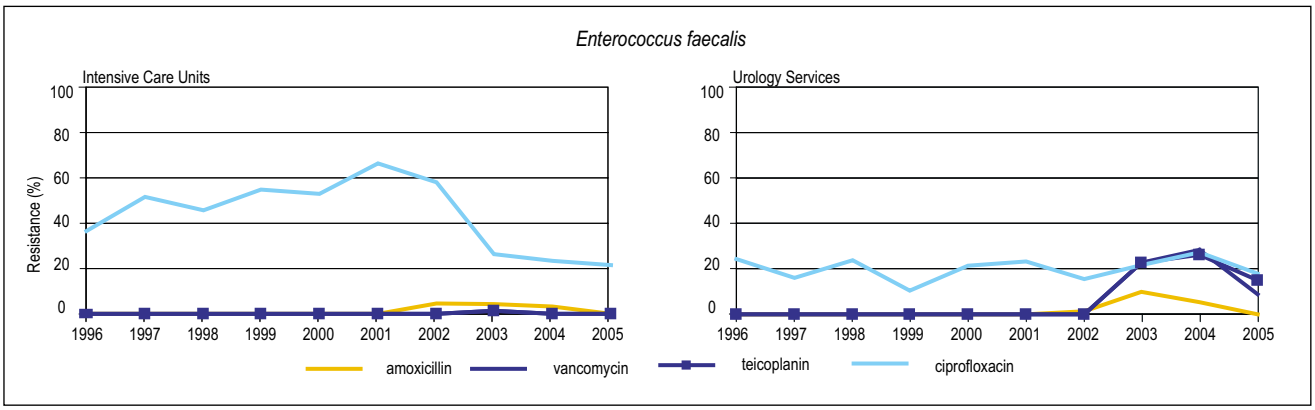


Figure 19. Trends in resistance to antibiotics among *Enterococcus faecalis* from Intensive Care Units and Urology Services.

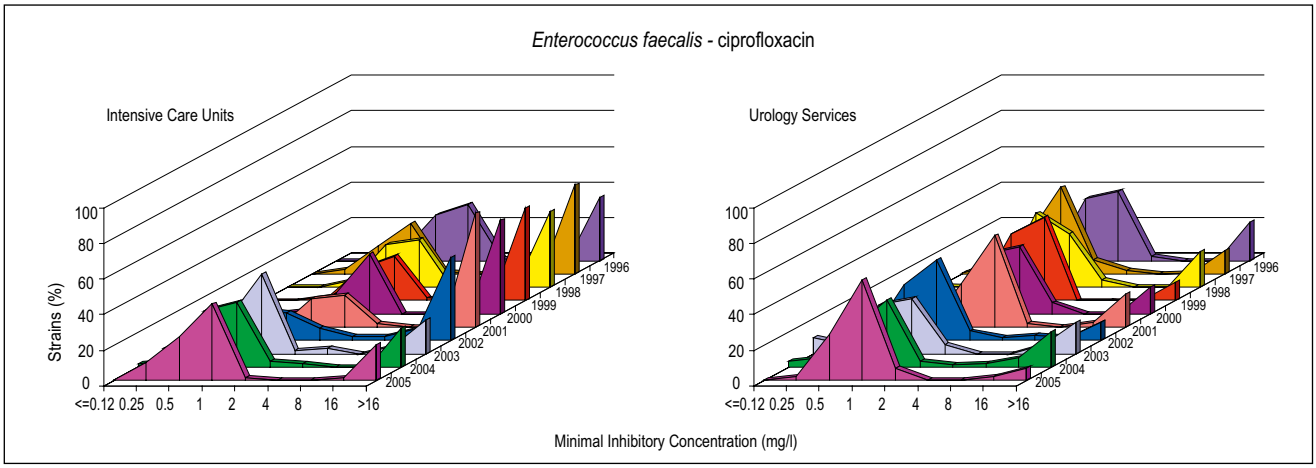
MICs for both drugs were > 128 mg/l. Eight strains were co-resistant to amoxicillin. Resistance to amoxicillin is more frequent in *E. faecium*, but this species was not investigated.

Ciprofloxacin resistance in Intensive Care Units was consistently higher than in Urology Services until 2002 (figure 19). It increased from 36% in 1996 to 66% in 2001 and decreased significantly thereafter to 24% in 2004 and 21% in 2005 at levels found consistently for Urology Services during the last ten years. The MIC distributions (figure 20) were bimodal 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. So the move within the population was already visible in 2002, when the resistance was still high calculated by breakpoint. The resistance rate in Urology Services was approximately 20% until 2003, it increased to 28% in 2004, but decreased to 18% in 2005 (figure 19). The shape of the MIC distribution of *E. faecalis* in Urology Services did not change over the years, but the top of the susceptible cluster was also moving from 2 mg/l before 2001 to 1 mg/l from 2002 on (figure 20).

Staphylococcus aureus

The prevalence of methicillin resistant *Staphylococcus aureus* (MRSA) has historically been very low in the Netherlands due to the stringent 'search-and-destroy' policy and the restrictive usage of antibiotics. In 2006 a total of 2012 MRSA isolates (one per patient) were sent to the National Institute of Public Health and the Environment (RIVM), which is an increase of 16% compared to 2005 (figure 21). A detailed questionnaire was received for 1426 (71%) MRSA isolates. Of these, 21% 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 21), mainly from Belgium and Germany. About 75% of the MRSA isolates were found in hospitals and 15% in nursing homes. The remaining isolates (10%) came from patients who acquired MRSA at home

Figure 20. MIC distributions of ciprofloxacin for *Enterococcus faecalis* from Intensive Care Units and Urology Services.



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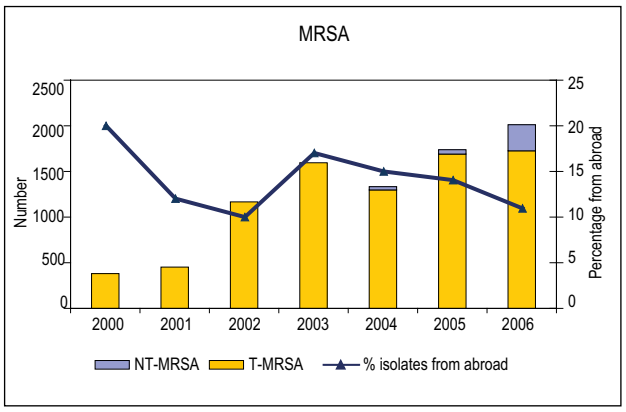


Figure 21. Numbers and origin of MRSA in The Netherlands.

(possibly community-acquired MRSA). A significant proportion (14%) of all MRSA isolates in 2006 was non-typeable by Pulsed Field Gel Electrophoresis (NT). The NT isolates showed ST398 and were related to animal husbandry. Most commonly found PFGE clusters among other MRSA isolates (Dutch classification system) were cluster 15 [sequence type (ST) 5; re-emergence of EMRSA-15], cluster 18 [ST8] and cluster 22 [ST5], which all belong to well-known global epidemic MRSA clonal clusters. Fifteen percent of all MRSA isolates carried the genes for Panton-Valentine leucocidin. The actual incidence of MRSA isolates per province in the Netherlands is being monitored online at http://www.rivm.nl/mrsa.

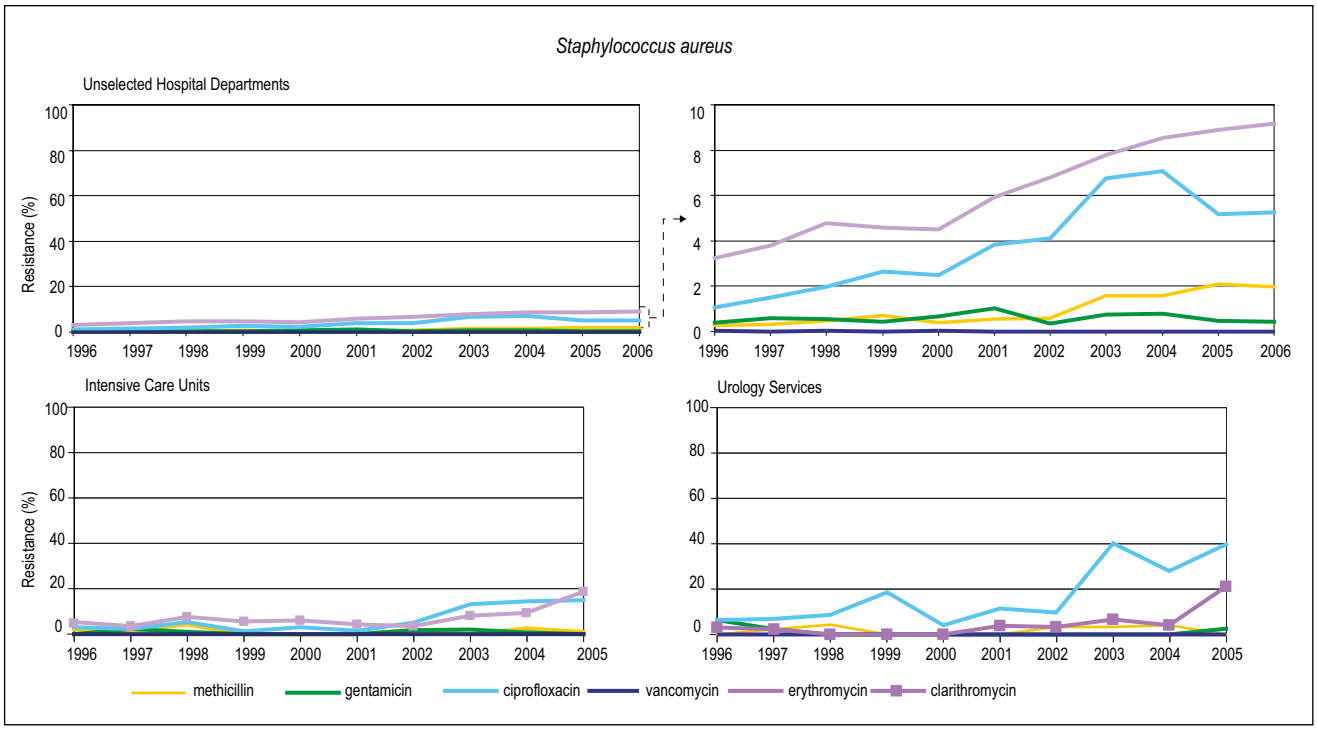
The overall percentage of MRSA in Unselected Hospital Departments increased to 2% in 2006, the percentage of MRSA in Intensive Care Units and Urology Services fluctuated between 0-4% from 1996-2005 without any trend (figure 22).

Erythromycin resistance in Unselected Hospital Departments was slowly increasing to 9% in 2006. Clarithromycin resistance among strains from Intensive Care Units increased from 9% in 2004 to 19% in 2005; the resistance rate in Urology Services paralleled that of the Intensive Care Units. The resistant strains came from nine centres; four centres had no resistant strains. Ciprofloxacin resistance rose among isolates from Unselected Hospital Departments to 5% in 2006 (figure 22). Resistance in Intensive Care isolates increased to 15% in 2005. Strains from Urology Services showed high resistance rates, but the numbers of strains were very small (30 to 40 per year). None of these quinolone resistant strains were MRSA. Resistance to quinolones in non-infectious patients in the Community was rare (0.2). Vancomycin resistance was reported in 14 of 80,000 isolates from 1995-2006 in Unselected Hospital Departments (not confirmed). Vancomycin resistant isolates were not found in the selected departments.

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 23). The number of *S. epidermidis* from Intensive Care Units in

Figure 22. Trends in resistance to antibiotics among *Staphylococcus aureus* from Unselected Hospitals, Intensive Care Units and Urology Services.



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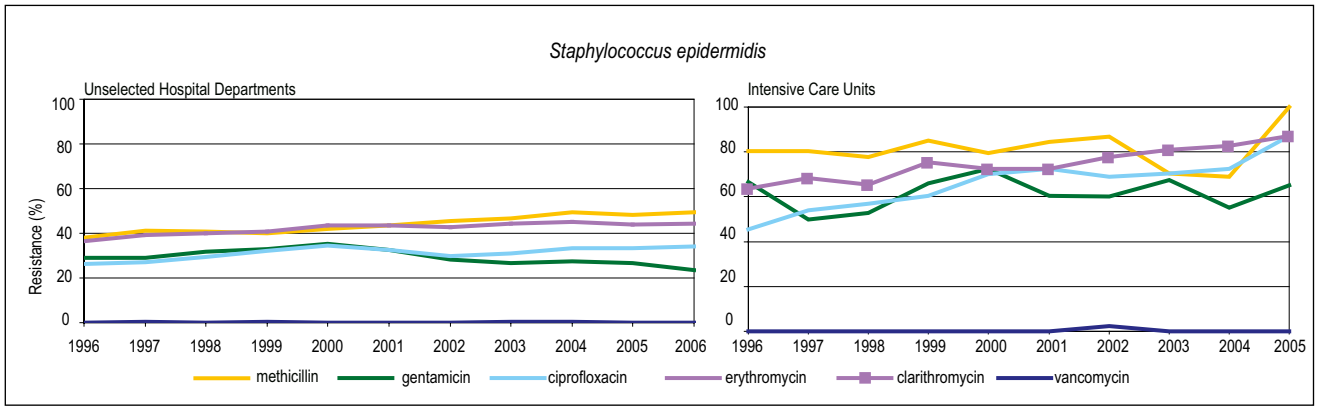
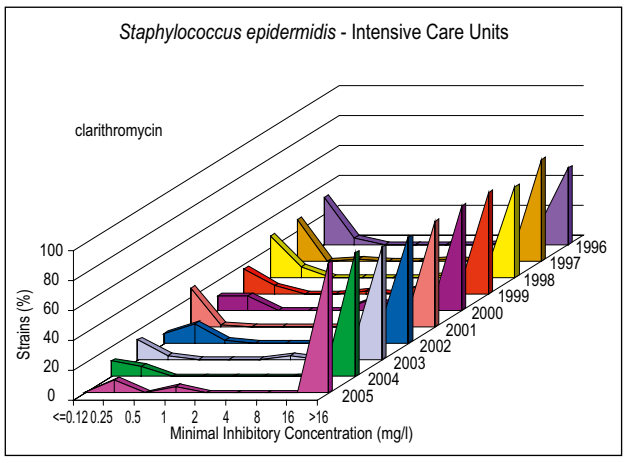


Figure 23. Trends in resistance to antibiotics among *Staphylococcus epidermidis* from Unselected Hospitals and Intensive Care Units.

2005 was low (23 strains). All strains were methicillin resistant. Methicillin resistant strains were often co-resistant to erythromycin, clarithromycin, gentamicin, ciprofloxacin and meropenem. The emergence of resistance to meropenem in Intensive Care Units was impressive. Being less than 20% until 2001, it rose to 46% in 2002 and stabilized at that level thereafter. Erythromycin resistance increased steadily in Unselected Hospital Departments from 37% in 1996 to 43% in 2000 and stabilized thereafter at this level. Clarithromycin resistance in Intensive Care Units was much higher and increased from 64% in 1996 to 87% in 2005. 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 24). Gentamicin resistance remained at a 55-65% level in Intensive Care Units. In contrast, the resistance rate of gentamicin in Unselected Hospital Departments was less 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 common, apparently as a result of a 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 (34%). Vancomycin resistant strains were reported occasionally in Unselected Hospital Departments.

Figure 24. MIC distributions of clarithromycin for *Staphylococcus epidermidis* from Intensive Care Units.



Streptococcus pneumoniae

S. pneumoniae strains non-susceptible to penicillin (intermediate plus resistant) are not often isolated in the Netherlands. Yet the trend was slowly increasing. The percentage resistance was less than 1% in Unselected Hospital Departments until 1998, then it fluctuated between 1-2% until 2003, and increased to 2% in 2006 (figure 25). The resistance rate in Pulmonology Services fluctuated at a higher level than that in the Unselected Hospital Departments until 2003 (6.5%), then it decreased to 3.5% in 2005. Resistance to cefaclor increased since 1999 from 4% to more than 20% in 2005, making cefaclor therefore not useful anymore for empiric therapy in bacterial respiratory tract infections (figure 26). Resistance to 2nd and 3rd generation cephalosporins remained at 4% or less during the study period. The MIC distributions for cefuroxime showed a unimodal shape over a small range (0.03-0.25 mg/l with MIC_{90} 0.12 mg/l); from 1998 on small resistant subpopulations with MICs 4 mg/l emerged, whereas in 2005 a highly resistant (MIC > 16 mg/l) subpopulation was observed, resulting in a real bimodal shape of the distribution.
Increasing and fluctuating resistance to erythromycin and clarithromycin among clinical isolates of *S. pneumoniae* from all departments was observed until 2003, but it stabilized from 2004 on, being 8% both in Pulmonology Services and Unselected Hospital Departments in 2005 and 2006 respectively.
Ciprofloxacin resistance in Unselected Hospital Departments fluctuated until 1999 between 10% and 26%; then a steady decrease was observed to a level

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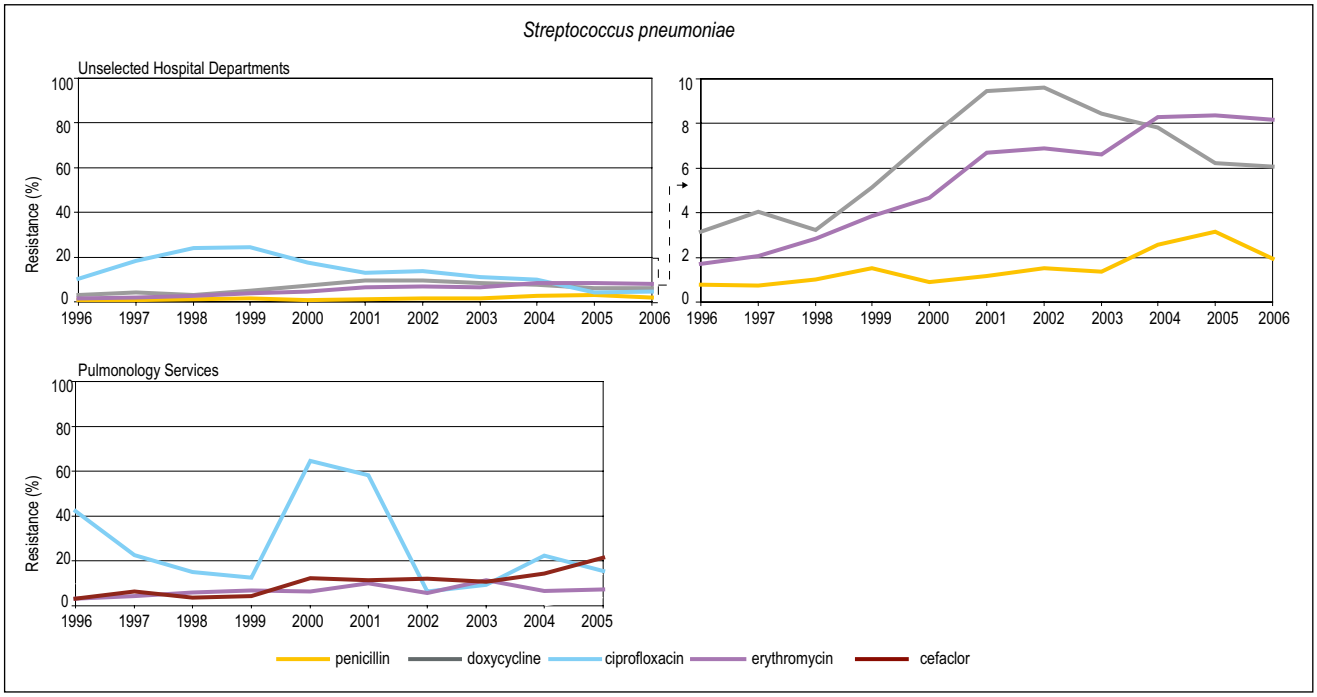


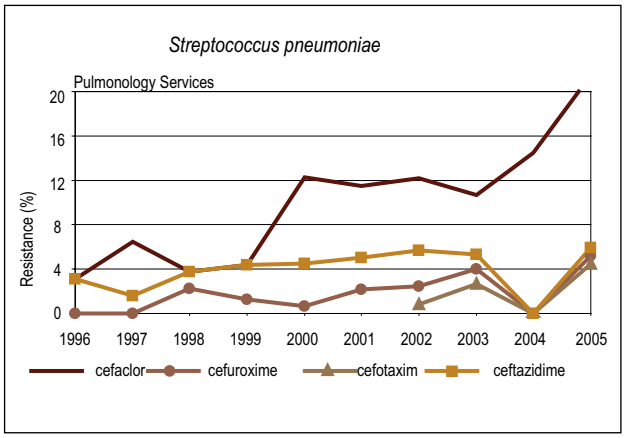
Figure 25. Trends in resistance to antibiotics among *Streptococcus pneumoniae* from Unselected Hospitals and Pulmonology Services.

of 4% in 2005. The ciprofloxacin resistance rates in Pulmonology Services also showed a high degree of variability which may be due to breakpoints which cut the wild type distribution of MICs. In the last few years levofloxacin and moxifloxacin were launched for treatment of respiratory tract infections. The MIC distribution of levofloxacin (figure 27) showed a clear shift to intermediate and resistant categories in 2004 compared with the years before.

Haemophilus influenzae

The prevalence of amoxicillin resistance among *H. influenzae* isolated in Unselected Hospital Departments remained stable (5-8%) until 2003. In 2004-2006 the resistance increased to 11% (figure 28). The resistance rate in Pulmonology Services fluctuated somewhat more (8-14%), but no real trend toward increasing rates was discernible (figure 28). 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) are counted as resistant. Clarithromycin was tested for isolates from the Pulmonology Services instead of erythromycin. Taking also the low breakpoint of 0.5 mg/l a 90-100% resistance to clarithromycin was recorded (figure 28).
Low prevalence resistance rates (1-2%) with a peak of 4% in 1999 were found for doxycycline among *H. influenzae* isolates from Unselected Hospital Departments. The resistance rates in Pulmonology Services were higher from the beginning (7-9%), but decreased to 3-4% in 2003 and thereafter.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. Lower use of doxycycline may be an explanation for decreased resistance rates in the last few years. Co-trimoxazole is one of the drugs used for COPD. The resistance to this combination was 10-20% until 2003, 55% in 2004, and 25% in 2005. The possible explanations for the peak in 2004 are the difficulty with susceptibility testing by microbroth dilution and the low number of strains collected. The testing method was replaced in 2005 by E-test and then 25% resistance was recorded, which is higher compared to the years until 2003, and a matter of concern.

Figure 26. Trends in resistance to cephalosporins among *Streptococcus pneumoniae* from Pulmonology Services.



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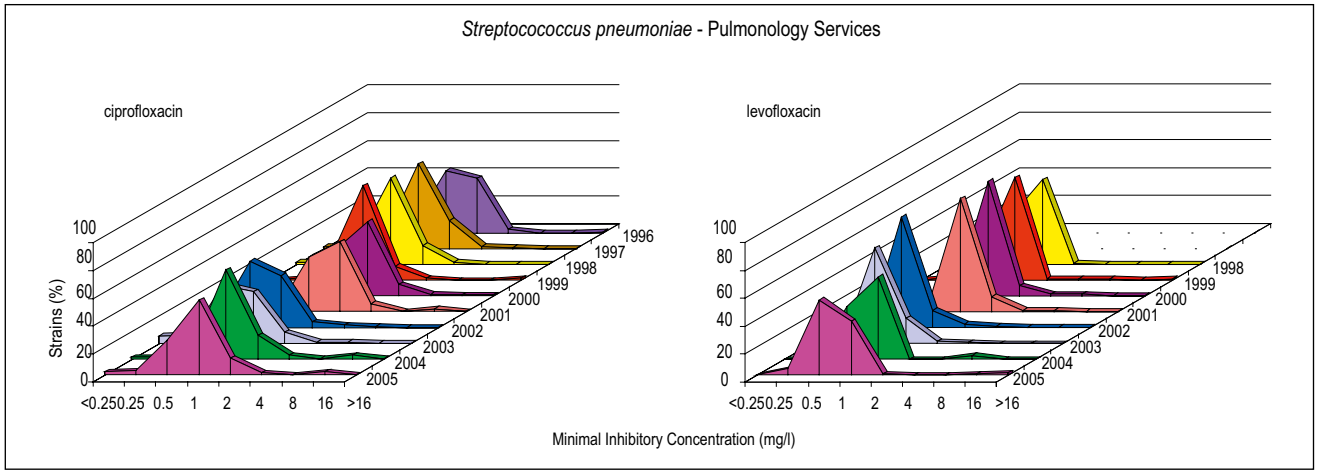


Figure 27. MIC distributions of quinolones for *Streptococcus pneumoniae* from Pulmonology Services.

Moraxella catarrhalis

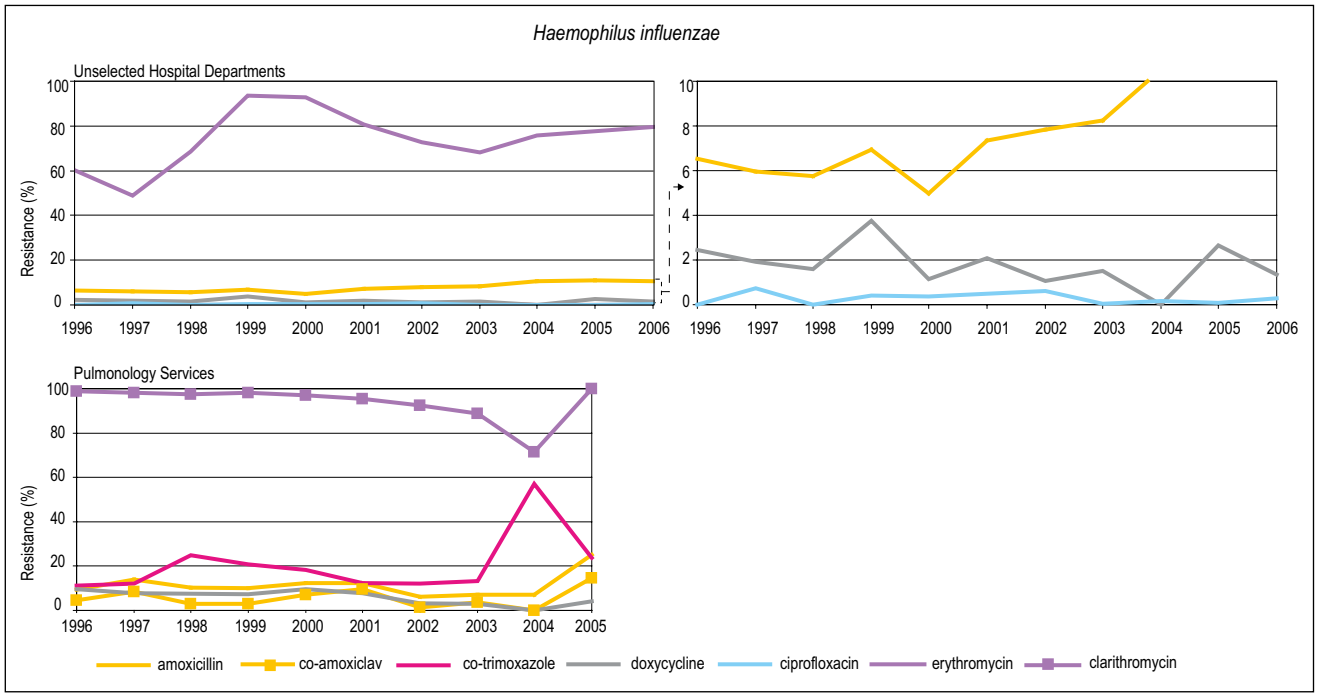
The prevalence of amoxicillin resistance among *M. catarrhalis* isolated in Unselected Hospital Departments has been about 80% since 1999 and remained stable until 2002, thereafter a significant decrease to 66% in 2005 and again an increase in 2006 were observed (figure 29). The resistance in Pulmonology Services was decreasing from 65 % in 2002 to a level of 20% in 2004, but increased to 49% in 2005. The resistance was completely due to beta-lactamase since resistance to co-amoxiclav did not occur.

Resistance to cefaclor and cefuroxime was occasionally found in some years but never exceeded 5%. Resistance to erythromycin in Unselected Hospital Departments almost doubled from 4% in 1996 to 7% in 2006. 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 may have resulted in different resistance percentages at the same breakpoint.

Ciprofloxacin resistance was occasionally found, but not in the last two years.

Resistance to doxycycline fluctuated between 2-4 % in Unselected Hospital Departments during the whole study period and was 4-8% in Pulmonology Services until

Figure 28. Trends in resistance to antibiotics among *Haemophilus influenzae* from Unselected Hospitals and Pulmonology Services.



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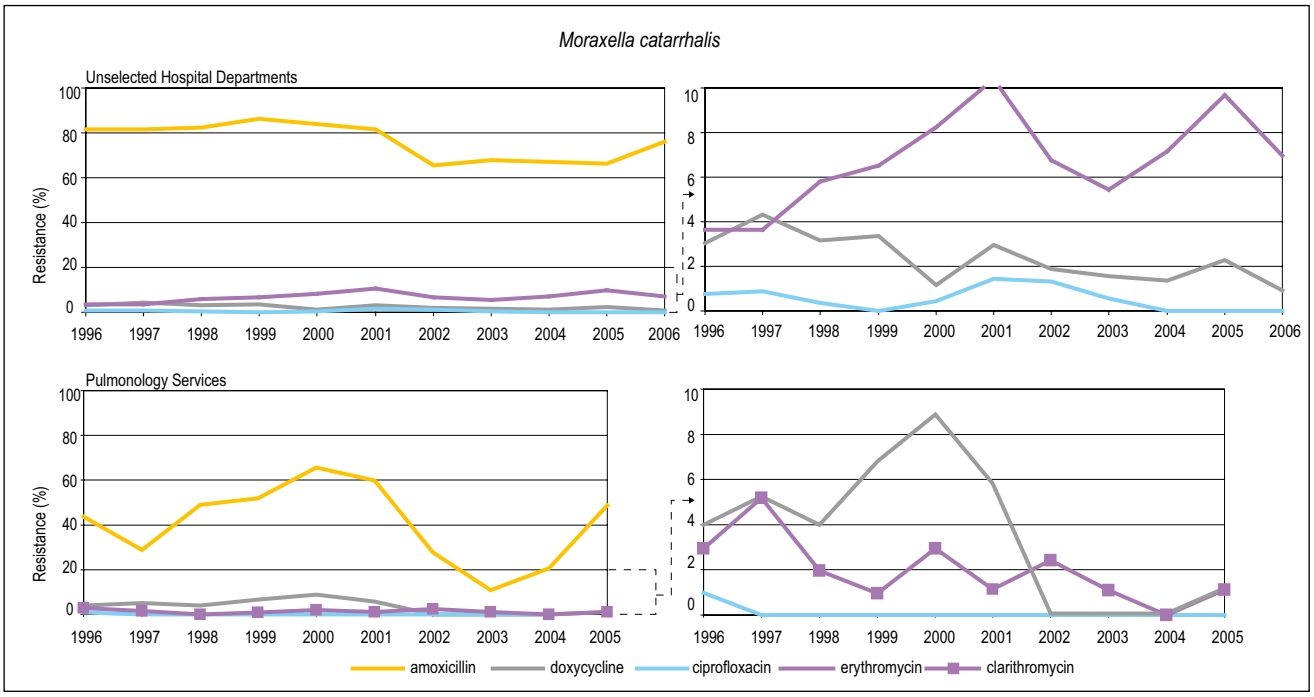


Figure 29. Trends in resistance to antibiotics among *Moraxella catarrhalis* from Unselected Hospitals and Pulmonology Services.

2001. Thereafter no resistance was found until 2005, when 1% resistance was recorded.

Helicobacter pylori

Amoxicillin resistance among *H. pylori* was less than 3% over the years (figure 30). Clarithromycin resistance was 1-6% without a real tendency of increasing resistance, doxycycline resistance was sporadic and metronidazole resistance was stable over the years, 17% in 2006.

Mycobacterium tuberculosis

A total of 10968 strains of *M. tuberculosis* were investigated at the RIVM during 1996-2006. In 2006 the number of isolates was 727. INH resistance remained stable, 6% (figure 31). Streptomycin decreased from 10% in 2000 to 6% in 2006. The rifampicin resistance level remained stable, 1% (figure 31). Ethambutol resistance was 0.8% in 2006. Combined resistance to more than one drug was observed in 3% of all isolates (figure 32). Multi Drug Resistance (combined resistance to rifampicin and INH) was recorded in 1% of the strains and resistance to all four antimycobacterial drugs was 0.6% in 2006.

Neisseria meningitidis

From 1993-2006 a total of 4366 strains for cerebrospinal fluid and 2471 strains from blood were included in the surveillance project of the Netherlands Reference Laboratory for Bacterial Meningitis of the Academic Medical Center, Amsterdam. Strains moderately susceptible (MIC 0.125-0.38 mg/l) occurred in less than 1% of the strains before 2002. Thereafter 2-4%, both from CSF and blood, appeared moderately susceptible.

Figure 30. Trends in resistance to antibiotics among *Helicobacter pylori* from Unselected Hospitals.

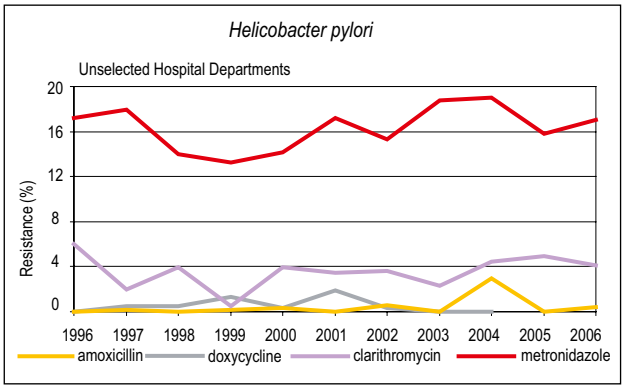
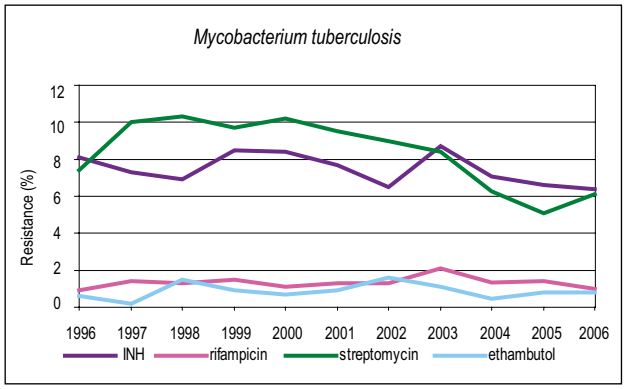


Figure 31. Trends in resistance to antibiotics among *Mycobacterium tuberculosis*.



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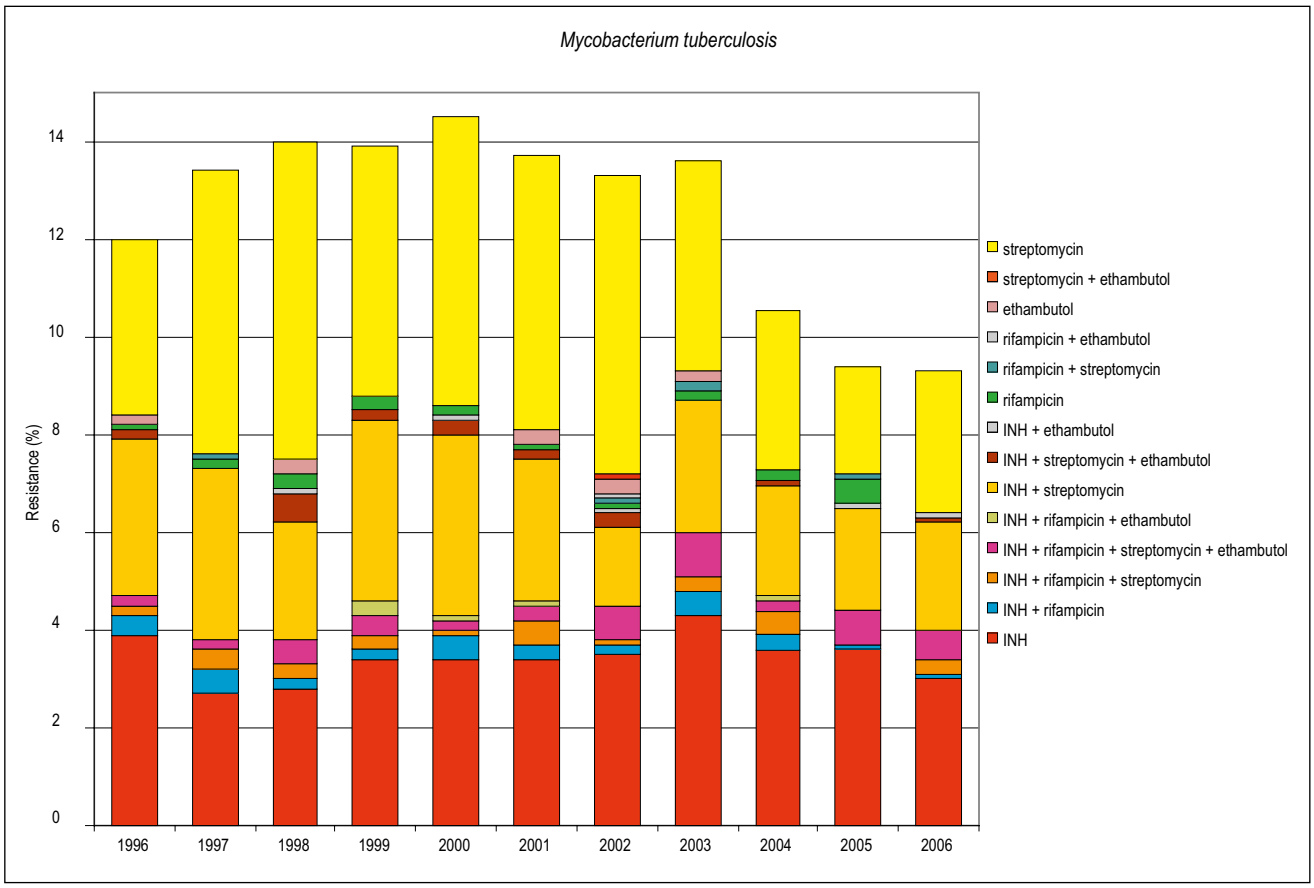


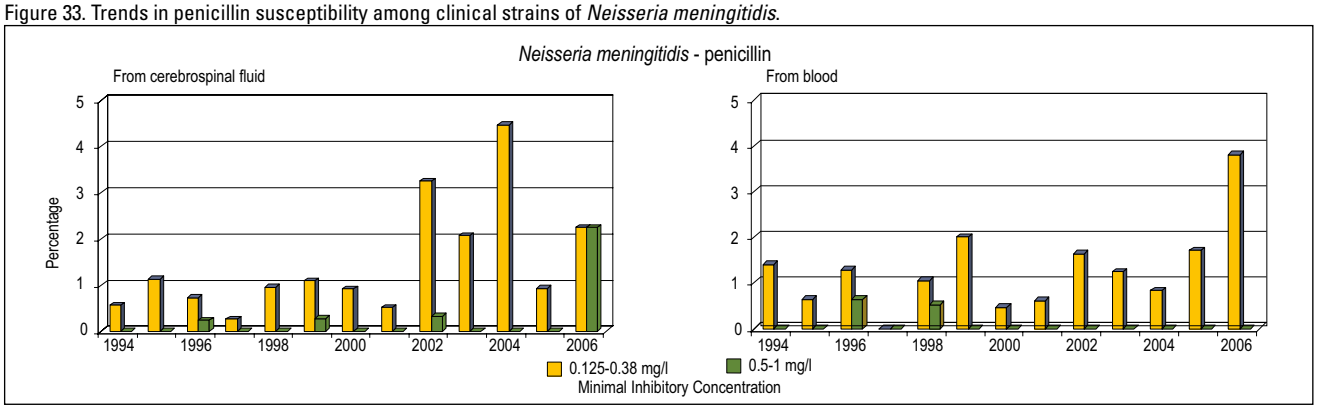
Figure 32. Trends of combined resistance among *Mycobacterium tuberculosis*.

Penicillin resistance (MIC ≥ 0.5 mg/l) was occasionally found in strains both from CSF and blood until 2002 (figure 33), but in 2006 2% of the CSF strains were resistant.

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. From 1990–1999 the surveillance was limited to all isolates collected in five large laboratories in Amsterdam, Rotterdam and Den Haag. In 2002, 2003 and 2004, the RIVM asked Medical Microbiology Laboratories to report their results on the incidence and antimicrobial patterns. Data of5604 strains from 25 laboratories became available. The overall incidence of gonorrhoea was 33.5/100,000 in 2002 and 27.0/100,000 in 2003. There 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. In 2006 a renewed surveillance programme to monitor resistance in gonococci was implemented, the so called GRAS (Gonococcal

Figure 33. Trends in penicillin susceptibility among clinical strains of *Neisseria meningitidis*.



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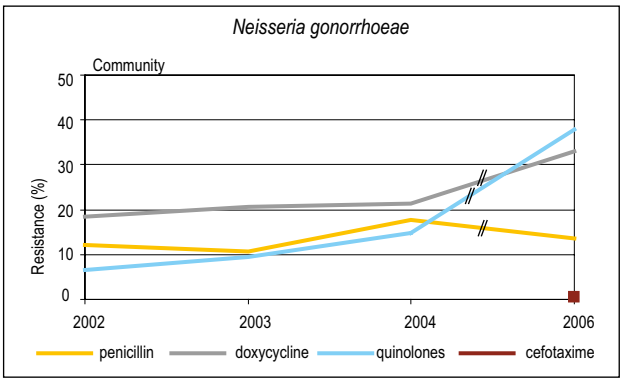


Figure 34. Trends in resistance to antibiotics among *Neisseria gonorrhoeae.*

Resistance to Antimicrobials Surveillance) programme. Participating centres are the 14 clinics for STD in the Netherlands and their public health laboratories. In 2006 a total of 177 strains were included in the study. MICs were determined for penicillin, doxycycline, ciprofloxacin and cefotaxime. The results of this study, which is still ongoing, are compared with the results generated during the surveillance studies of the RIVM before.

The overall penicillin resistance increased significantly from 12% in 2002 to 18% in 2004 and decreased to 14% in 2006 (figure 34). Doxycycline resistance increased from 18% to 21% in 2004 and 33% in 2006; most impressive was the significant increase in resistance to quinolones from 6.6% in 2002 to 38% 2006. The percentage resistance to penicillin and quinolones was lower in the Randstad compared to other regions, whereas doxycycline resistance was higher in the Randstad. Cefotaxime was first tested in 2006 and 0.6% resistance was found.

The number of strains obtained in 2006 was much lower than the number from the former surveillance projects and may not be representative for the Netherlands as a whole. However the increase in resistance is alarming. A 5% resistance level is acceptable for any empiric therapy, it is clear that none of the drugs mentioned above except cefotaxime or ceftriaxone can be used anymore for empiric therapy.

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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.
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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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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		1,2,4,24	1,2,19,24	1		
Ceftazidime					1,2,3,4,17,24	1,2,3,17,19,24	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
IPCI	Integrated Primary Care Information
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
2006	16 334 210

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
2005	96	1681	11515	6.9

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
2005	8	214	1825	8.5

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
2005	88	1467	9690	6.6

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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 2007 includes data on the use of group J01 (antibiotics for systemic use) of the Anatomical Therapeutic Chemical (ATC) classification system. The 2007 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 (1615 out of 1800 community pharmacies) are transferred monthly to SFK in an electronically 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).
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.

Data on antibiotic use by indications were obtained from the Integrated Primary Care Information (IPCI) database (IPCI; http://www.ipci.nl). This database is located at the Erasmus University Medical Centre Rotterdam and is operated by the department of Medical Informatics in close collaboration with the Unit of Pharmaco-epidemiology.
At present there are 82 practices belonging to 150 general practitioners, who are providing data to the database at on ongoing basis. The database contains information on more than 500.000 patients. This is the cumulative number of patients who have ever been part of the dynamic cohort of registered patients. IPCI has implemented a research specific module into the regular software program used by the general practitioners, which requests the linkage of an indication to each prescription. The International Classification of Primary Care (ICPC) is the coding system used for the coding of patient symptoms, diagnoses and indications, in addition to the available free text. The National Database of drugs enables the coding of prescriptions according to the Anatomical Therapeutic Chemical (ATC) classification scheme applied by the WHO. Data from the GP computer system are anonymised and downloaded on a monthly basis.

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.
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.

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Surveillance of antibiotic resistance and susceptibility testing

Community

Staphylococcus aureus
The prevalence of antibiotic resistance among *Staphylococcus aureus* in the indigenous flora of non-hospitalised patients i.e. patients visiting their general practitioner and of healthy volunteers was determined. General practitioners (GPs) (n=30) from all over the Netherlands, most of them participating in the Sentinel project of the Netherlands institute for Health Services research (NIVEL), participated in the study. The distribution of the GPs included per region was as follows: two from the north, three from the eastern part, eleven from the central region and thirteen from the southern part. From patients visiting their GP with a non-infectious complaint a nose swab was taken from the anterior nostrils and sent to the microbiological laboratory of the University Hospital Maastricht. A total of 2691 patients were included in the study.
In addition 4,000 healthy individuals between the age of 18 and 75 years old, living in Heerlen, a city of 92,000 inhabitants in the southern part of the Netherlands, was taken from the municipal administration. Each person received an envelope by mail containing information about the study, instructions for taking a nasal swab from the anterior nostrils and material for returning the swab to the laboratory of Medical Microbiology in Maastricht. A total of 2369 swabs were received from this group. Swabs were analysed for the presence of S. *aureus* using standard microbiological methods which included enrichment broth and the detection of catalase and coagulase enzymes. In addition, the susceptibility to the following antimicrobial agents was determined using a broth dilution method in micro-titre trays: penicillin, methicillin, erythromycin, tetracycline, clindamycin, cefaclor, rifampicin, ciprofloxacin, imipenem, meropenem, cefuroxime, linezolid and co-trimoxazole (MCS diagnostics, Swalmen, The Netherlands). The resistance against fusidic acid and mupirocin was determined by the disc-diffusion method. *Staphylococcus aureus* ATCC 29213 was used as reference strain. The breakpoints for resistance were according to CLSI guidelines. Strains resistant to erythromycin were tested for the presence of inducible resistance to clindamycin by the double disc method. The study was approved by the Ethical Committee of the University Hospital Maastricht.

Neisseria meningitidis
From 1993-2006 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 intermediate and with MIC ≥ 0.5 mg/l resistant.

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 CLSI. The antibiotics chosen for reporting are INH, rifampicin, streptomycin and ethambutol. Resistance rates represent the proportion of moderate and fully resistant strains.
The susceptibility data of 10968 strains, isolated from 1996-2006 are presented in this report.

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 2006 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 local laboratory (mainly CLSI) were used for calculating resistance rates (R = fully resistant) for *E. coli*, *P. mirabilis*, *K. pneumoniae, P. aeruginosa, S. aureus* and *S. epidermidis*. Resistance rates for *H. influenzae, M. catarrhalis* and *S. pneumoniae* included 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.

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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 on) for quantitative susceptibility testing. A total of 22500 strains were collected from 1996-2005, the results of 18120 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 NCCLS 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.

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

Table 1. First isolates per clinical sample of patients in Unselected Hospital Departments in 2006.

Species (number of isolates)	Clinical material (number)			
	Blood (4721)	Pus and wound (22495)	Respiratory tract (12697)	Urine (27332)
Gram-positive cocci (24954)				
Staphylococcus aureus (11343)	652	8226	1543	922
Enterococcus spp.(5543)	286	1207	121	3929
S. epidermidis incl coag. neg. Staphylococcus (2276)	938	672	52	614
Streptococcus pneumoniae (2552)	554	444	1544	9
Streptococcus agalactiae (2383)	81	1209	103	990
Streptococcus pyogenes (858)	113	638	80	27
Subtotal	2624	12396	3443	6491
Enterobacteriaceae (31349)				
Escherichia coli (17738)	1165	2985	939	12649
Proteus mirabilis (3737)	112	1001	285	2339
Klebsiella pneumoniae (3193)	230	602	456	1905
Enterobacter cloacae (1997)	119	774	479	625
Klebsiella oxytoca (1632)	89	455	333	755
Other Enterobacteriaceae (3052)	166	951	752	1183
Subtotal	1881	6768	3244	19456
Respiratory pathogens (5533)				
Haemophilus influenzae (3530)	38	547	2944	1
Moraxella catarrhalis (1313)	2	114	1197	0
Haemophilus parainfluenzae (625)	5	100	519	1
Neisseria meningitidis (65)	20	5	40	0
Subtotal	65	766	4700	2
Non-fermentors (4844)				
Pseudomonas aeruginosa (4616)	144	1898	1258	1316
Acinetobacter calcoaceticus (228)	7	102	52	67
Subtotal	151	2000	1310	1383
Helicobacter pylori (565)	0	565	0	0

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presentation of these data. The guideline provides criteria for indicator-organisms, indicator-antibiotics, methods and breakpoints to be used.

Table 2. Number of indicator strains (N=18120) isolated from patients admitted to specified hospital wards and tested for their susceptibility to antibiotics in the period 1996-2005.

Species	Intensive Care Units	Urology Services	Pulmonology Services
E. coli	1546	5052	
K. pneumoniae	467	599	
P. mirabilis	327	695	
P. aeruginosa	923	387	
E. faecalis	660	994	
S. aureus	863	301	
S. epidermidis	499	233	
S. pneumoniae			1451
H. influenzae			2147
M. catarrhalis			976

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