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

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2008

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 Studio 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 2008 – 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
		Municipal Health Service Groningen					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
		Municipal Health Service Fryslan					0
Drente	Assen	General practice	0				
		Municipal Health Service Drenthe					0
	Emmen	Scheper Hospital				0	
Overijssel	Deventer	Deventer Hospital					0
		Regional Laboratory for Public Health				0	
	Enschede	Regional Laboratory for Public Health		0	0	0	0
		Municipal Health Service Twente					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
		Alysis Centre					0
		Hulpverlening Gelderland Midden					0
	Barneveld	General practice	0				
	Dieren	General practice	0				
	Doetinchem	Slingeland Hospital				0	
	Ede	Gelderse Vallei Hospital				0	
	Harderwijk	St Jansdal Hospital				0	
	Heerde	General practice	0				
	Nijmegen	University Medical Centre St Radboud		0		0	0
		Regional Laboratory for Public Health CWZ			0	0	0
		Municipal Health Service Nijmegen					0
	Zelhem	General practice	0				
Utrecht	Amersfoort	Meander Medical Centre				0	0
		General practice	0				
	Bilthoven	National Institute for Public Health and the Environment			0		
	Nieuwegein	Sint Antonius Hospital		0	0	0	0
	Utrecht	Diakonessenhuis				0	
		General practice	0				
		Neth Institute for Health Services Research NIVEL	0				
		Mesos Medical centre				0	
		SALTRO					0
		University Medical Centre				0	0
		Municipal Health Service Utrecht					0
	Zeist	Diakonessenhuis				0	
Noord Holland	Alkmaar	General practice	0				
		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	
		Municipal Health Service Amsterdam					0
	Baarn	Medical Centre I				0	
	Haarlem	General practice	0				
		Regional Laboratory for Public Health		0	0		
	Hilversum	Central Bacteriological Laboratory				0	
	Hoorn	Westfries Gasthuis				0	
	Huizen	General practice	0				
	Zaandam	Zaans Medical Centre				0	0

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Table 1 Continued

			COM	IUP	PH/ISIS	Men	Gon
Zuid Holland	Capelle a/d IJssel	IJsselland Hospital				0	
	Delft	SSDZ laboratories				0	0
	's-Gravenhage	Bronovo Hospital		0		0	
		General practice	0				
		Leyenburg Hospital				0	0
		Regional Laboratory for Public Health				0	
		Rode Kruis / Juliana Children's Hospital				0	
		Medical Centre Haaglanden				0	0
		Municipal Health Service Den Haag					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	
		Municipal Health Service Rotterdam					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
		Municipal Health Service West-Brabant					0
	Eindhoven	Municipal Health Service Eindhoven					0
	Helmond	Municipal Health Service Zuidoost Brabant					0
	's Hertogenbosch	Jeroen Bosch Medical Centre			0		0
		Regional Laboratory for Public Health				0	
	Ravenstein	General practice	0				
	Roosendaal	Franciscus Hospital				0	
	Rosmalen	General practice	0				
	Tilburg	Regional Laboratory for Public Health		0	0	0	0
		Municipal Health Service Hart voor Brabant					0
	Uden	General practice	0				
	Veldhoven	Laboratory for Medical Microbiology				0	0
Limburg	Heerlen	Regional Laboratory for Public Health			0	0	0
		Atrium Medical Centre				0	0
	Maastricht	General practice	0				
		Nursing home Vivre location KLevarie	0				
		Nursing home De Zeven Bronnen	0				
		Academic Medical Centre		0		0	0
		Municipal Health Service Zuid-Limburg					0
	Roermond	Laurentius Hospital			0	0	0
	Sittard	Maasland Hospital				0	
	Venlo	VieCuri Medical Centre		0		0	0
		Municipal Health Service Noord- en Midden Limburg					0
	Weert	St Jansgasthuis			0	0	0
Zeeland	Goes	Regional Laboratory for Public Health		0	0	0	0
		Municipal Health Service Zeeland					0
	Middelburg	General practice	0				
	Terneuzen	General practice	0				
		Regional Laboratory for Public Health			0	0	0

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

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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; peldoorn, Gelre ziekenhuizen; Arnhem, Rijnstate Ziekenhuis; Assen, Wilhelmina Ziekenhuis; Bergen op Zoom, Ziekenhuis Lievensberg; Blaricum, Tergooi ziekenhuizen; 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; en Haag, RKZ/JKZ; Den Helder, Gemini Ziekenhuis; Deventer, St. Deventer Ziekenhuizen; Doetinchem, 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, Tergooiziekenhuis; 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, ZorgSaam 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 sixth SWAB/RIVM NethMap report on the use of antibiotics and trends in antimicrobial resistance in the Netherlands in 2007 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 2008 extends and updates the information of the annual reports since 2003. 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 2008 is the sixth 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 1996 to 2007.

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. Since 2005 the consumption level has increased to 11.1 DDD/1000 inhabitant-days in 2007. 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 coli* causing urinary tract infections and the subsequent changes in guidelines. Amoxicillin is being substituted by amoxicillin plus clavulanic acid (co-amoxiclav).

Amoxicillin, co-amoxiclav and other penicillins account for almost half of all antibiotics used in Dutch hospitals. Use of tetracyclines was much lower in hospitals than outside hospitals. Antibiotic use in hospitals was expressed in two units, DDD/100 patient-days and DDD/100 admitted patients. Whereas DDD/100 patient-days increased from 47 in 2001 to 62 in 2006, DDD/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 2006. Thus an average hospitalised patient did not receive more antibiotics but, since he or she stayed in hospital for a shorter period, the number of admissions and the number of DDD/100 patient-days increased.

Within antibiotic classes, ciprofloxacin use has increased at the expense of other fluoroquinolones and vancomycin at the expense of teicoplanin.
The use of antibiotics in Intensive Care Units was two times as high as the average antibiotic use in hospitals (132 versus 58 DDD/100 patient-days). Particularly the use of benzylpenicillin, piperacillin plus tazobactam, second and third generation cephalosporins, carbapenems and erythromycin was higher in Intensive Care Units as compared to the hospital as a whole, whereas first generation cephalosporins were used predominantly outside IC's.
In 2006 SWAB collected data on the use of antimycotics in Dutch hospitals. The total use of antifungals amounted 3.2 DDD/100 patient-days. Patients in academic hospitals used eight times as much antifungals as compared to patients in general hospitals. Use of polyenes, mainly liposomal amphotericin, was 30% of the total antimycotic use. Triazoles, mainly fluconazol, contributed 70%.

NethMap 2008 presents data on the prevalence and antimicrobial resistance of *Staphylococcus aureus* in three categories of people outside hospitals. Resistance to methicillin (MRSA), confirmed by PCR of the *mec*A gene, was found in the nose of 2 of 2369 healthy individuals, in none of 2691 patients visiting their general practitioner (GP) and in 2 of 37 nursing home residents (6%). Similarly, the prevalence of resistance to ciprofloxacin was much higher in nursing home residents (28%) as compared to healthy individuals (0.8%) and patients in general practices (0.3%).
The resistance to other antibiotics was low (less than 5%) in the commensal flora of healthy persons and GP patients, but the level of resistance in nursing home residents was significantly higher. Nursing homes also harboured multiresistant strains: 15% of the strains were resistant to three or more classes of antibiotics, most often combinations of penicillin, clarithromycin, doxycycline and ciprofloxacin. This may be explained by frequent use of these drugs, which may induce the circulation of resistant strains in nursing homes.

In 2007 a survey was started on the prevalence and the resistance of *Streptococcus pneumoniae* outside hospitals. Carriership of *S. pneumoniae* in healthy children (4%) was significantly higher than in healthy adults (2%). In both groups resistance to clarithromycin (9-16%), co-trimoxazole (5-9%) and doxycycline (11-18%) was found.

Escherichia coli from the urine of patients visiting their general practitioner was still susceptible to a first generation cephalosporin, cefaclor. In contrast patients in Intensive Care Units showed a high frequency of resistance.

Recently *Neisseria gonorrhoeae* has become frequently resistant to ciprofloxacin (44%), tetracycline (28%) and penicillin (14%). So quinolones cannot be used for first line treatment anymore and the treatment guidelines for sexually transmitted diseases have been adapted accordingly. Third generation cephalosporins are still active against all gonococci.
The National Reference Centre for Bacterial Meningitis occasionally found strains of *Neisseria meningitidis* which were intermediate to penicillin, 1% in the period 1993-2001 and 2-4% in the period 2002-2007.
Mycobacterium tuberculosis remained susceptible to all four tested antimycobacterial agents (INH, rifampicin, streptomycin and ethambutol) as found in 90.7% of the isolates received at the RIVM. Resistance to INH was found in 6% of the isolates. Resistance to INH and rifampicin (multiresistance) occurred in only 1%.

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In hospitals the resistance of clinical isolates of *Escherichia coli* to penicillins, first generation cephalosporins, trimethoprim/co-trimoxazole and fluoroquinolones has gradually increased. In Intensive Care Units in 2006 more than 40% of the strains were resistant to amoxicillin and trimethoprim, 18% to cefaclor and 9% to ciprofloxacin. In Urology Services more than 15% of *E. coli* are now resistant to fluoroquinolones, and in other hospital departments resistance to these agents has reached the 5-10% range. The resistance to second and third generation cephalosporins and gentamicin in clinical isolates of *E. coli* remained low in all hospital departments taken together. Resistance to gentamicin was observed in some hospitals but was not a general problem. Likewise, ciprofloxacin- and ceftazidime-resistant *Klebsiella pneumoniae* and gentamicin- and ciprofloxacin-resistant *Pseudomonas aeruginosa* were isolated in some IC's but not in all. So local surveillance of resistance is essential for a good antibiotic policy.

The prevalence of multiresistance of *E. coli* from Intensive Care Units to at least three different antibiotics was less than 2% until 1999 but rose to 5-6% in 2005 and 2006. Production of extended spectrum beta-lactamase (ESBL) was detected in 0.8% of 1267 isolates of *E. coli* and in 6% of 402 isolates of *K. pneumoniae* sampled in the period 1998-2005.

The resistance to amoxicillin of *Enterococcus faecalis* has increased significantly since 2002 in Intensive Care Units. These departments also harbour *Staphylococcus epidermidis* strains which are frequently resistant to a broad range of antibiotics.

Only 2% of the *Streptococcus pneumoniae* isolates from Unselected Hospital Departments and Pulmonology Departments showed reduced susceptibility to penicillin in 2007. 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.

A worrisome trend is the steadily increasing rate of resistance to macrolides among clinical isolates of *Staphylococcus aureus* and *Streptococcus pneumoniae*. Both are now approaching the 10% threshold above which their empirical use is considered unreliable. Among clinical *S. aureus* isolates the proportion of methicillin resistance (MRSA) rose to 2.8% in 2007, according to the ISIS electronic surveillance system. In 2007 the RIVM received 36% more MRSA isolates for molecular typing, mainly strains from persons in contact with pigs or calves, the so-called NT MRSA, which is non-typeable by standard Pulsed Field Gel Electrophoresis.

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2 Samenvatting

NethMap 2008 is het zesde jaarrapport van de Stichting Werkgroep Antibioticabeleid (SWAB) over het gebruik van antibiotica en het vóórkomen van resistentie tegen antibiotica bij de meest voorkomende, voor de mens pathogene, bacteriesoorten in Nederland. Het rapport beschrijft trends op basis van systematisch verzamelde en bewerkte gegevens.

Het gebruik van antibiotica in de Nederlandse eerstelijns gezondheidszorg bleef tot 2005 onder de 10 standaard dagdoseringen (DDD) per 1000 inwoners per dag. In 2005 was het gebruik iets hoger, 10,5 DDD/1000 inwonerdagen, en het is sindsdien licht verder gestegen tot 11,1 DDD/1000 inwonerdagen in 2007. Het gebruik van nitrofurantoïne was al langere tijd aan het stijgen. Waarschijnlijk kwam dit door de toegenomen resistentie tegen trimethoprim bij de verwekkers van urineweginfecties en, als reactie daarop, de aanpassingen in de richtlijnen voor huisartsen. Bij de penicillines zien we een geleidelijke vervanging van amoxicilline alleen door de combinatie co-amoxiclav.

De penicillines, voornamelijk amoxicilline en co-amoxiclav, besloegen bijna 50% van het antibioticagebruik in ziekenhuizen. Het gebruik van tetracyclines was veel lager in het ziekenhuis dan in de open bevolking. Het antibioticumgebruik uitgedrukt in DDD/100 ligdagen is gestegen van 47 in 2001 naar 62 in 2006, terwijl het aantal DDD/100 opgenomen patiënten in dezelfde periode gelijk bleef. Het verschil in deze twee trendlijnen is te verklaren door een afname in de gemiddelde duur per opname. Deze daalde van 7,9 dagen in 2001 naar 6,3 dagen in 2006. Per opname, d.w.z. per patiënt, werden dus niet meer antibiotica voorgeschreven, maar het aantal DDD/100 ligdagen nam toe omdat de patiënt gemiddeld steeds korter in het ziekenhuis verbleef. Het gebruik van ciprofloxacine steeg ten koste van het gebruik van andere fluorochinolonen en het gebruik van vancomycine steeg, terwijl het gebruik van teicoplanine daalde.
Het antibioticagebruik in Intensive Care units bleek in 2006 meer dan twee maal zo hoog als het gebruik in het gehele ziekenhuis (132 versus 58 DDD/100 ligdagen). Vooral het gebruik van benzylpenicilline, piperacilline met tazobactam, tweede en derde generatie cefalosporines, carbapenems en erytromycine lag veel hoger in Intensive Care afdelingen dan gemiddeld in het hele ziekenhuis, terwijl eerste generatie cefalosporines voornamelijk buiten de IC gebruikt werden.
In 2006 verzamelde SWAB voor het eerst gegevens over het gebruik van antischimmel middelen in het ziekenhuis. Het totale gebruik bedroeg 3,2 DDD/100 ligdagen. Het gebruik in academische ziekenhuizen lag acht maal zo hoog als het gebruik in de algemene ziekenhuizen. Het gebruik van polyenen, voornamelijk liposomaal amphotericine, was 30% van het totale antimycotica gebruik, de rest kwam voor rekening van de tri-azolen, voornamelijk fluconazol.

Gegevens over de prevalentie en resistentie tegen antibiotica in de bevolking kwamen uit (1) de surveillance onder gezonde personen, huisartspatiënten en verpleeghuisbewoners die op de afdeling Medische Microbiologie in Maastricht wordt uitgevoerd in samenwerking met huisartspraktijken in het hele land, het Nederlands Instituut voor Onderzoek in de Gezondheidszorg (NIVEL) en regionale afdelingen van de GGD, (2) het Nederlands Referentielaboratorium voor Bacteriële Meningitis en (3) het RIVM.
NethMap 2008 toont gegevens over de gevoeligheid voor antibiotica van *Staphylococcus aureus* in drie categorieën van personen buiten het ziekenhuis. Meticilline-resistente *S. aureus* (MRSA), bevestigd met PCR van het *mec*A resistentiegen, werd aangetroffen in slechts 2 van 2369 neusswabs van gezonde personen, bij geen van 2691 huisartspatiënten en bij 2 van 37 bewoners van twee verpleeghuizen (6%). Ook de resistentie tegen ciprofloxacine lag veel hoger bij de *S. aureus* stammen van verpleeghuisbewoners (28%), dan bij gezonde personen (0,8%) en bij huisartspatiënten (0,3%).
De resistentie tegen andere antibiotica was laag (minder dan 5%) in de commensale flora van gezonde personen en huisartspatiënten. Maar het resistentieniveau bij inwoners van verpleeghuizen bleek aanmerkelijk hoger, terwijl bij hen ook multiresistente stammen werden aangetroffen: 15% van de stammen was resistent tegen drie of meer antibiotica. Meestal betrof het combinaties van penicilline, claritromycine, doxycycline en ciprofloxacine. Kennelijk worden deze middelen vaak gebruikt in verpleeghuizen, waarbij het risico van circulatie van resistente stammen binnen het verpleeghuis reëel is.
In 2007 werd een begin gemaakt met het onderzoek naar de prevalentie van en resistentie bij *Streptococcus pneumoniae* in de commensale flora van verschillende bevolkingsgroepen. Het dragerschap bij gezonde kinderen (4%) was significant hoger dan bij gezonde volwassenen (2%). Bij beide groepen werd resistentie tegen claritromycine (9-16%), co-trimoxazol (5-9%) en doxycycline (11-18%) gemeten.
Escherichia coli, geïsoleerd uit urine van huisartspatiënten met klachten van een urineweginfectie, waren goed gevoelig voor een eerste generatie cepfalosporine, cefaclor. De resistentie tegen eerste generatie cefalosporines was hoog onder patiënten op Intensive Care afdelingen.

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Onder *Neisseria gonorrhoeae* hebben de resistenties tegen ciprofloxacine (44%), tetracycline (28%) en penicilline (14%) verontrustend hoge niveaus bereikt. Deze gegevens zijn aanleiding geweest de richtlijnen voor de behandeling van gonorroe bij te stellen. Resistentie tegen derde generatie cefalosporines werd niet waargenomen.
Van *Neisseria meningitidis* werden incidenteel stammen gevonden met een verminderde gevoeligheid voor penicilline, ongeveer 1% in de periode 1993-2001 en iets vaker (2-4%) in de periode 2002-2007.
Van de in 2007 geteste *Mycobacterium tuberculosis* bleek 90,7% goed gevoelig voor de vier meest gebruikte tuberculostatica. Dit percentage is stabiel. INH-resistentie werd gevonden bij 6% van de isolaten, 3% was resistent tegen twee of meer van de vier middelen. Resistentie tegen INH en rifampicine werd waargenomen bij 1% van de stammen.

Gegevens over de resistentie tegen antibiotica in ziekenhuizen kwamen (1) uit de geautomatiseerde registratie door het RIVM van bacteriestammen uit klinieken en poliklinieken die werden onderzocht in 11 streeklaboratoria en vier andere grote laboratoria en (2) uit de surveillance naar resistentie op Intensive Care Afdelingen, Urologie- en Longafdelingen van 14 grote ziekenhuizen.
In de Nederlandse ziekenhuizen zijn de resistentiepercentages onder klinische isolaten van *Escherichia coli* tegen de penicillines (amoxicilline, co-amoxiclav, piperacilline), eerste generatie cefalosporine, trimethoprim/co-trimoxazol en fluorochinolonen, geleidelijk gestegen. Op de Intensive Care afdelingen was in 2006 meer dan 40% van de stammen resistent tegen amoxicilline en trimethoprim, 18% tegen cefaclor en 9% tegen ciprofloxacine. Op de afdelingen Urologie was de resistentie tegen ciprofloxacine het hoogst (15%), in de overige afdelingen werden resistentieniveaus van 5 tot 10% waargenomen. De resistentie tegen tweede en derde generatie cefalosporines en gentamicine bij klinische isolaten van *E. coli* bleef laag op alle ziekenhuisafdelingen, wanneer zij samen werden genomen. Gentamicine-resistentie bleek vooral een locaal probleem. In sommige ziekenhuizen werden resistentiepercentages tot 15% gevonden, in andere ziekenhuizen werd gedurende de hele studieperiode geen resistentie waargenomen. Evenzo bleek de resistentie tegen ciprofloxacine bij *Klebsiella pneumoniae* en de resistentie tegen gentamicine en piperacilline bij *Pseudomonas aeruginosa* op Intensive Care afdelingen, vooral een lokaal en geen algemeen landelijk probleem. Lokale resistentiesurveillance is daarom essentieel voor een goed antibioticumbeleid.
De resistentiepercentages in Intensive Care afdelingen lagen voor de meeste antibiotica hoger dan in algemene en urologische afdelingen behalve voor trimethoprim en ciprofloxacine want deze twee middelen worden veel toegepast bij patiënten met urinewegproblemen. De hogere resistentiepercentages voor sommige antibiotica op de Intensive Care afdelingen zullen het gevolg zijn van selectie door het hoge antibioticumgebruik op de IC.
Multirersistentie (resistentie tegen drie of meer klassen van antibiotica) onder *E. coli* nam toe, van minder dan 2% tot 1999 naar 5-6% in 2005 en 2006.
Opvallend is de toename van de amoxicilline-resistentie onder *Enterococcus faecalis*, die vóór 2002 niet werd waargenomen en nu op diverse Intensive Care afdelingen wordt gezien. Op alle Intensive Care afdelingen worden hoge percentages multiresistente *Staphylococcus epidermidis* aangetroffen, blijkbaar als gevolg van hoge selectiedruk. Vaak circuleren deze stammen binnen afdelingen en koloniseren de opgenomen patiënten.

Slechts 2% van de *Streptococcus pneumoniae* isolaten afkomstig van algemene afdelingen en longafdelingen was verminderd gevoelig voor penicilline in 2006 en 2007. Een zorgwekkende trend is de toenemende resistentie tegen macroliden onder klinische isolaten van *S. pneumoniae* en *Staphylococcus aureus.* Beide species hebben bijna het niveau van 10% resistentie bereikt, de grens waarboven middelen niet meer geschikt worden geacht voor de empirische behandeling van infecties.

Het percentage meticilline-resistentie onder klinische isolaten van *S. aureus* (MRSA) steeg van 2,0 % in 2006 naar 2,8% in 2007 (elektronische surveillance via het ISIS systeem). De grootte van deze stijging, 40%, komt overeen met de 36% stijging van het aantal isolaten van MRSA dat in 2007 naar het RIVM werd gestuurd voor typering. Laatstgenoemde stijging kwam grotendeels voor rekening van de vee-gerelateerde zogenaamde NT-MRSA.

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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 total hospital consumption in acute care hospitals in the Netherlands. In addition data on use in Dutch intensive care units are presented as well as data on the use of antimycotics in acute care hospitals. In the Appendix (Section "surveillance methods and susceptibility testing") details regarding the structural acquisition and analysis of these consumption data are presented.

Primary health care

Ten-years trend in antibiotic use: 1998-2007
Over the past 10 years the overall use of antibiotics for systemic use in primary health care remained almost constant. From 1998-2004 use was 10 DDD/1000 inhabitant-days (table 1). Over the past three years use increased gradually to 11 DDD/1000 inhabitant-days. The distribution of antibiotics by class in 2007 is presented in figure 1. Tetracyclines (mainly doxycycline) represented 24% of total use in primary health care. Other frequently used antibiotics were penicillins with extended spectrum (mainly amoxicillin), combinations of penicillins with beta-lactamase inhibitors (essentially amoxicillin with clavulanic acid) and macrolides, each representing 17%, 15% and 14% of the total use respectively. These proportions are similar to the proportions in previous years.

The use of amoxicillin decreased from 2.13 in 1998 to 1.69 DDD/1000 inhabitant-days (-20.5 %) in 2004. Between 2005 and 2007 it slightly increased to 1.91 DDD/1000 inhabitant-days. The use of co-amoxiclav increased from 1.04 in 1998 to 1.66 DDD/1000 inhabitant-days in 2007 (figure 2).

The use of macrolides is presented in figure 3. Clarithromycin was the most commonly used macrolide. Its use slightly increased from 0.71 to 0.80 DDD/1000 inhab-

Table 1. 10-years data on use of antibiotics for systemic use (J01) in outpatient care (DDD/1000 inhabitant-days), 1998-2007 (Source: SFK).

ATC Group*	Therapeutic group	year									
		1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
J01AA	Tetracyclines	2.55	2.49	2.47	2.39	2.33	2.23	2.22	2.41	2.37	2.58
J01CA	Penicillins with extended spectrum	2.13	2.06	1.88	1.82	1.78	1.77	1.69	1.86	1.87	1.91
J01CE	Beta-lactamase sensitive penicilins	0.52	0.51	0.52	0.49	0.45	0.44	0.42	0.44	0.50	0.46
J01CF	Beta-lactamase resistant penicillins	0.22	0.23	0.24	0.25	0.25	0.27	0.28	0.29	0.31	0.32
J01CR	Penicillins + beta-lactamase-inhibitors	0.95	1.04	1.15	1.25	1.34	1.39	1.38	1.50	1.59	1.66
J01D	Cephalosporins	0.11	0.10	0.08	0.07	0.07	0.06	0.05	0.05	0.04	0.05
J01EA	Trimethoprim and derivatives	0.28	0.30	0.28	0.28	0.27	0.27	0.26	0.25	0.23	0.22
J01EC	Intermediate-acting sulfonamides	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.00
J01EE	Sulphonamides + trimethoprim	0.47	0.46	0.43	0.42	0.40	0.39	0.39	0.38	0.37	0.36
J01FA	Macrolides	1.16	1.17	1.13	1.22	1.24	1.27	1.31	1.42	1.39	1.39
J01FF	Lincosamides	0.03	0.03	0.04	0.05	0.06	0.06	0.07	0.08	0.09	0.10
J01GB	Aminoglycosides	0.00	0.00	0.00	0.01	0.01	0.02	0.02	0.02	0.03	0.03
J01MA	Fluoroquinolones	0.78	0.82	0.80	0.80	0.78	0.78	0.82	0.84	0.87	0.91
J01MB	Other quinolones	0.05	0.04	0.04	0.04	0.03	0.03	0.02	0.02	0.02	0.02
J01XB	Polymyxins	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.01	0.00
J01XE	Nitrofuran derivatives	0.59	0.64	0.68	0.71	0.74	0.78	0.80	0.90	1.00	1.07
J01XX05	Methanamine	0.06	0.06	0.06	0.06	0.04	0.03	0.02	0.02	0.03	0.03
J01	Antibiotics for systemic use (total)	9.94	10.02	9.84	9.90	9.81	9.81	9.77	10.51	10.72	11.11

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

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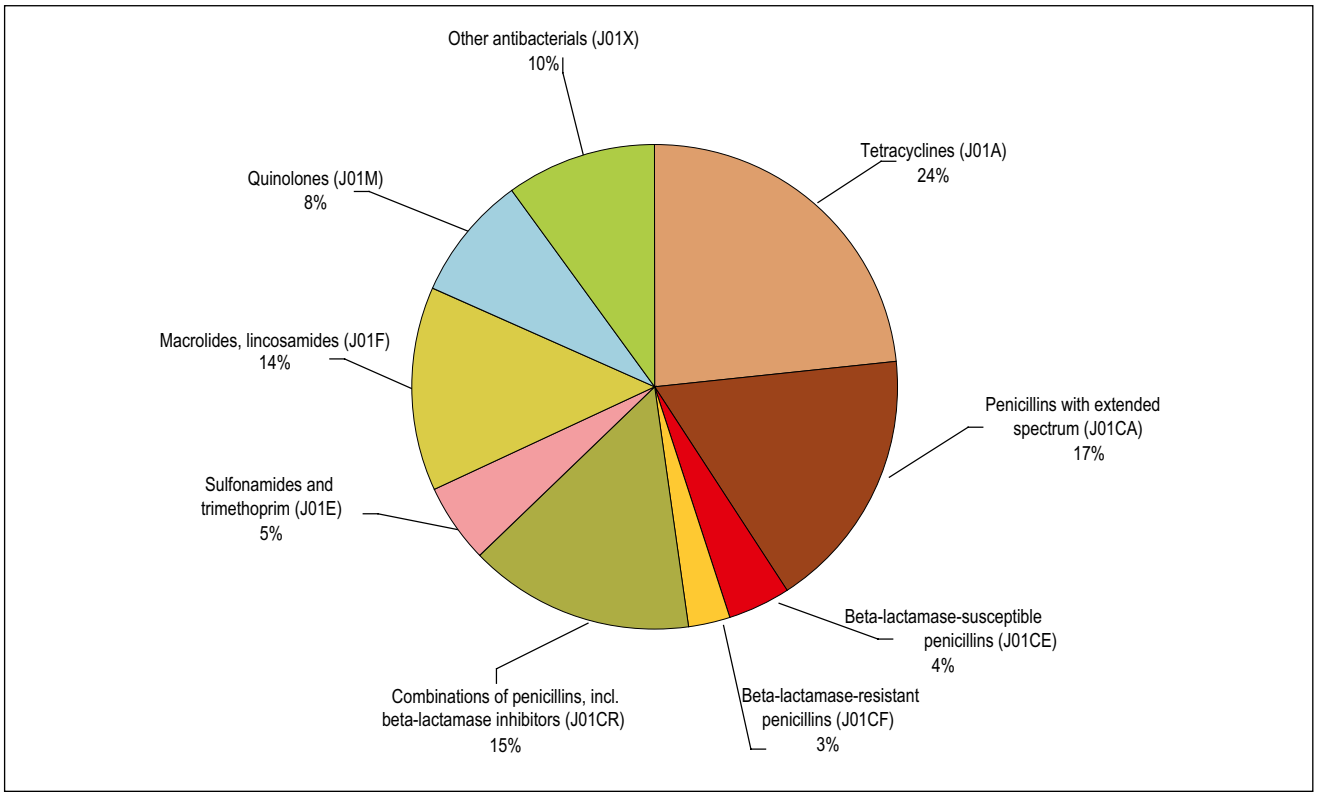


Figure 1. Distribution of the use of antibiotics for systemic use (J01, DDD/1000 inhabitant-days) in primary health care, 2007 (Source: SFK).

itant-days in 2007. The use of azithromycin doubled between 1998 and 2007. The use of erythromycin slightly decreased over the past years.

Total use of the fluoroquinolones did not change between 1998 and 2007 (table 1, figure 4). However, between 1998 and 2007, 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 moxifloxacin almost equals the use of levofloxacin in 2007.

The use of nitrofurantoin increased from 0.59 in 1998 to 1.07 DDD/1000 inhabitant-days in 2007 whereas the use of trimethoprim slightly decreased.

Figure 2. Use of amoxicillin and co-amoxiclav in primary health care, 1998 - 2007 (Source: SFK).

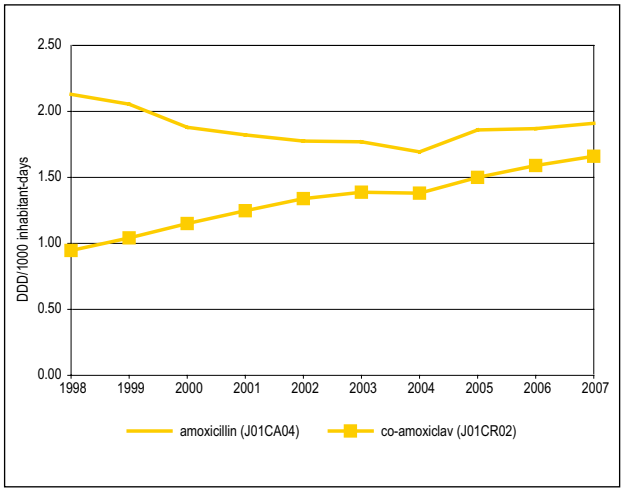
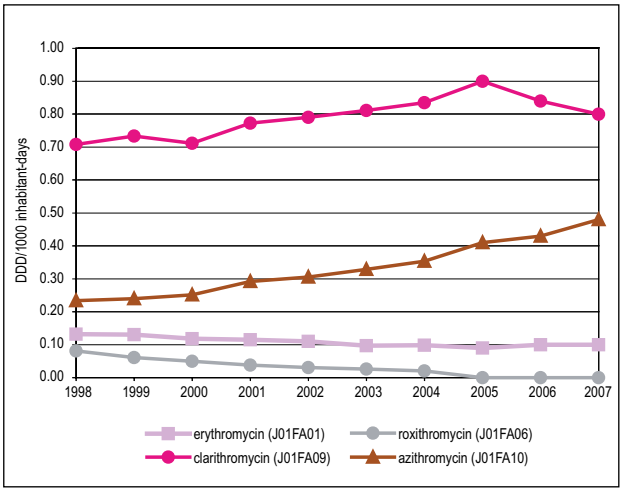


Figure 3. Use of macrolides for systemic use in primary health care, 1998-2007 (Source: SFK).



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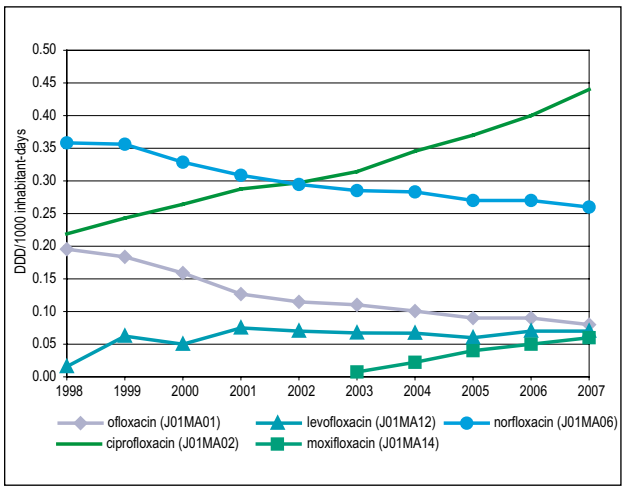


Figure 4. Use of fluoroquinolones for systemic use in primary health care 1998 - 2007 (Source: SFK).

Discussion

In 2005, total antibiotic consumption was 10.5 DDD/1000 inhabitant-days and was slightly increased compared to previous years. In 2006 and 2007 total use in primary care increased to 11.1 DDD/1000 inhabitant-days.

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. These trends may be relevant in the face 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 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. In 2005 these guidelines were revised 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.

Hospitals

Hospital resource indicators

Over the past years the average number of beddays in our cohort of hospitals has remained more or less constant (+0.9%);131570 beddays in 2002 and 132799 beddays in 2006. The average number of admissions however, has increased from 17075 in 2002 to 20978 in 2006 (+23%). The average length of stay in these hospitals has therefore decreased from 7.7 to 6.3 days (-18%).

The 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 of antibiotics

Total hospital use

Data on antibiotic use are expressed in DDD/100 patient-days as well as in DDD/100 admissions, because trends over time in both units of measurement do not always correlate (tables 2 and 3).

Total systemic use of antibiotics in our cohort of hospitals was 62.2 DDD/100 patient-days in 2006, an increase of 24% compared tot the total systemic use in 2002, which was 50.2 DDD/100 patient-days. The number of patient-days remained more or less constant, while the average number of DDD per hospital increased from 57464 in 2002 to 70447 in 2006 (+23%).

The number of DDD/100 admissions has remained practically the same, 336.5 DDD/100 admissions in 2002 and 335.8 DDD/100 admissions in 2006.

Both the number of patients and the DDD per hospital increased with 23%, therefore the mean antibiotic use per patient remained constant.

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

1. Increase in both units of measurement.

For combinations of penicillins (incl. beta-lactamase-inhibitors), trimethoprim, lincosamides, fluoroquinolones, glycopeptides and nitrofurantoin an increase in DDD/100 patient-days as well as in DDD/100 admissions was seen. Even though the average patient was admitted to the hospital for a shorter period of time, they used more antibiotics than before.

2. Increase in DDD/100 patient-days, constant DDD/100 admissions.

Penicillins with extended spectrum, beta-lactamase resistant penicillins beta-lactamase sensitive penicillins, cephalosporins , carbapenems and aminoglycosides showed an increase in DDD/100 patient-days, while the DDD/100 admissions remained more or less 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.

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Table 2. Use of antibiotics for systemic use (J01) in hospitals (DDD/100 patient-days), 2002-2006 (Source: SWAB).*

ATC Group*	Therapeutic group	2002	2003	2004	2005	2006
J01AA	Tetracyclines	1.7	1.4	1.5	1.6	1.6
J01CA	Penicillins with extended spectrum	6.1	6.0	6.0	6.7	7.6
J01CE	Beta-lactamase sensitive penicilins	1.2	1.2	1.4	1.4	1.4
J01CF	Beta-lactamase resistant penicillins	4.4	5.4	5.7	5.8	5.9
J01CR	Combinations of penicillins, incl. beta-lactamase-inhibitors	12.2	12.1	12.8	13.9	15.1
J01DB-DE	Cephalosporins	6.3	6.5	7.0	7.4	8.4
J01DF	Monobactams	0.0	0.0	0.0	0.0	0.0
J01DH	Carbapenems	0.5	0.5	0.5	0.6	0.6
J01EA	Trimethoprim and derivatives	0.5	0.5	0.4	0.6	0.8
J01EC	Intermediate-acting sulfonamides	0.0	0.1	0.1	0.0	0.0
J01EE	Combinations of sulfonamides and trimethoprim. including derivatives	2.4	2.3	2.1	2.3	2.1
J01FA	Macrolides	2.7	2.4	2.3	2.8	2.5
J01FF	Lincosamides	1.5	1.6	1.8	1.9	2.0
J01GB	Aminoglycosides	2.1	2.5	2.2	2.6	2.5
J01MA	Fluoroquinolones	5.7	6.4	6.5	7.3	8.0
J01MB	Other quinolones	0.1	0.1	0.1	0.1	0.1
J01XA	Glycopeptides	0.5	0.5	0.6	0.8	0.7
J01XB	Polymyxins	0.1	0.1	0.1	0.2	0.2
J01XC	Steroid antibacterials (fusidic acid)	0.0	0.0	0.0	0.0	0.0
J01XD	Imidazole derivatives	1.5	1.6	1.7	1.5	1.7
J01XE	Nitrofuran derivatives	0.5	0.7	0.9	1.0	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)	50.2	51.9	53.8	58.3	62.2

* 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), 2002-2006 (Source: SWAB).*

ATC Group*	Therapeutic group	2002	2003	2004	2005	2006
J01AA	Tetracyclines	11.2	8.8	8.4	8.8	8.7
J01CA	Penicillins with extended spectrum	41.2	38.6	34.3	36.4	41.0
J01CE	Beta-lactamase sensitive penicilins	8.2	7.8	7.8	7.5	7.7
J01CF	Beta-lactamase resistant penicillins	29.5	34.6	33.0	31.4	31.8
J01CR	Combinations of penicillins, incl. beta-lactamase-inhibitors	81.6	77.7	73.1	75.4	81.7
J01DB-DE	Cephalosporins	42.0	42.0	39.4	39.8	45.3
J01DF	Monobactams	0.0	0.0	0.0	0.0	0.0
J01DH	Carbapenems	3.2	3.3	2.8	3.2	3.0
J01EA	Trimethoprim and derivatives	3.3	3.1	2.3	3.0	4.2
J01EC	Intermediate-acting sulfonamides	0.2	0.8	0.3	0.3	0.1
J01EE	Combinations of sulfonamides and trimethoprim, including derivatives	16.0	14.4	12.1	12.2	11.5
J01FA	Macrolides	17.9	15.4	13.4	15.1	13.4
J01FF	Lincosamides	10.0	10.2	10.2	10.5	10.8
J01GB	Aminoglycosides	14.2	15.8	12.5	13.9	13.7
J01MA	Fluoroquinolones	38.2	41.0	37.2	39.7	43.3
J01MB	Other quinolones	0.5	0.6	0.8	0.5	0.3
J01XA	Glycopeptides	3.4	3.4	3.5	4.1	3.9
J01XB	Polymyxins	0.4	0.5	0.6	1.1	0.9
J01XC	Steroid antibacterials (fusidic acid)	0.1	0.2	0.1	0.2	0.1
J01XD	Imidazole derivatives	9.7	10.1	9.6	7.9	9.0
J01XE	Nitrofuran derivatives	3.6	4.7	4.9	5.6	5.2
J01XX05	Methenamine	0.1	0.2	0.4	0.1	0.1
J01XX08	Linezolid	0.1	0.1	0.1	0.2	0.2
J01	Antibiotics for systemic use (total)	336.5	333.2	306.8	316.9	335.9

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

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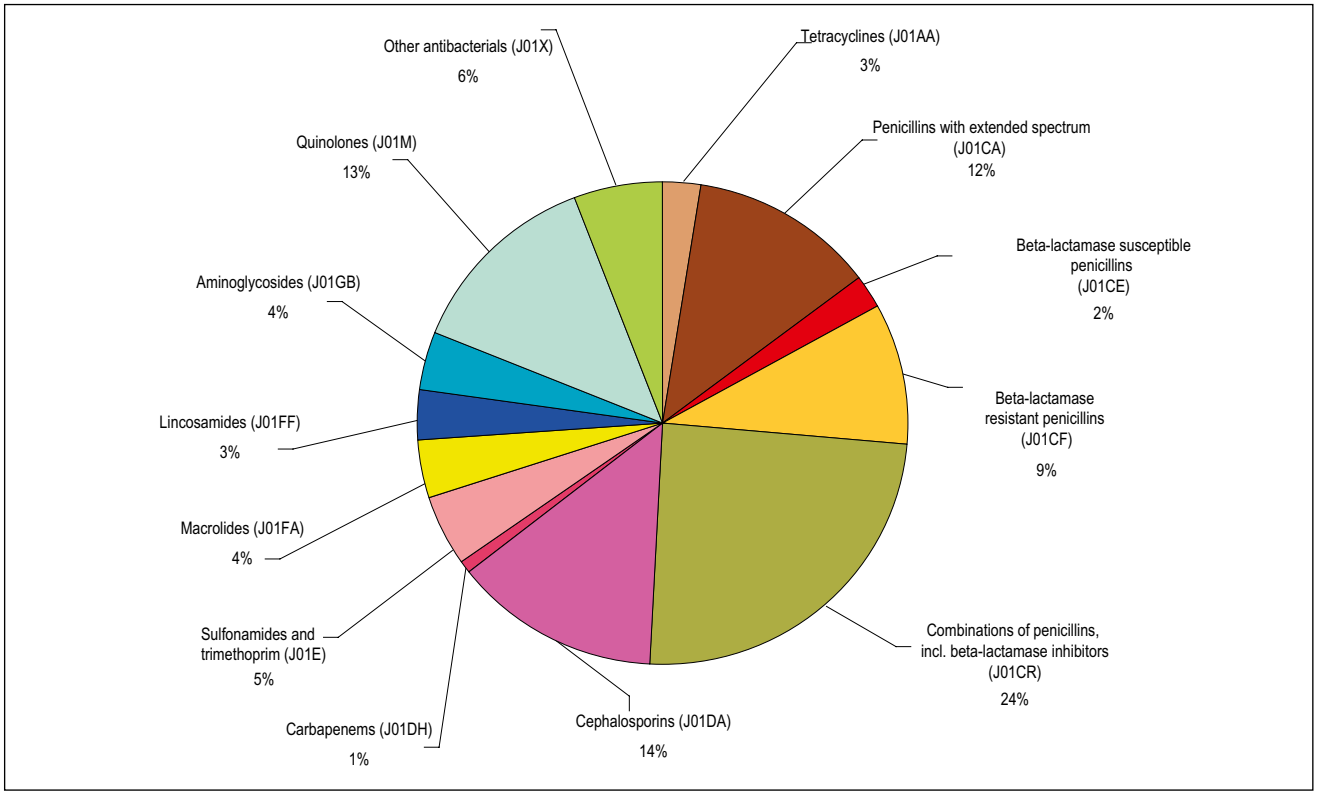
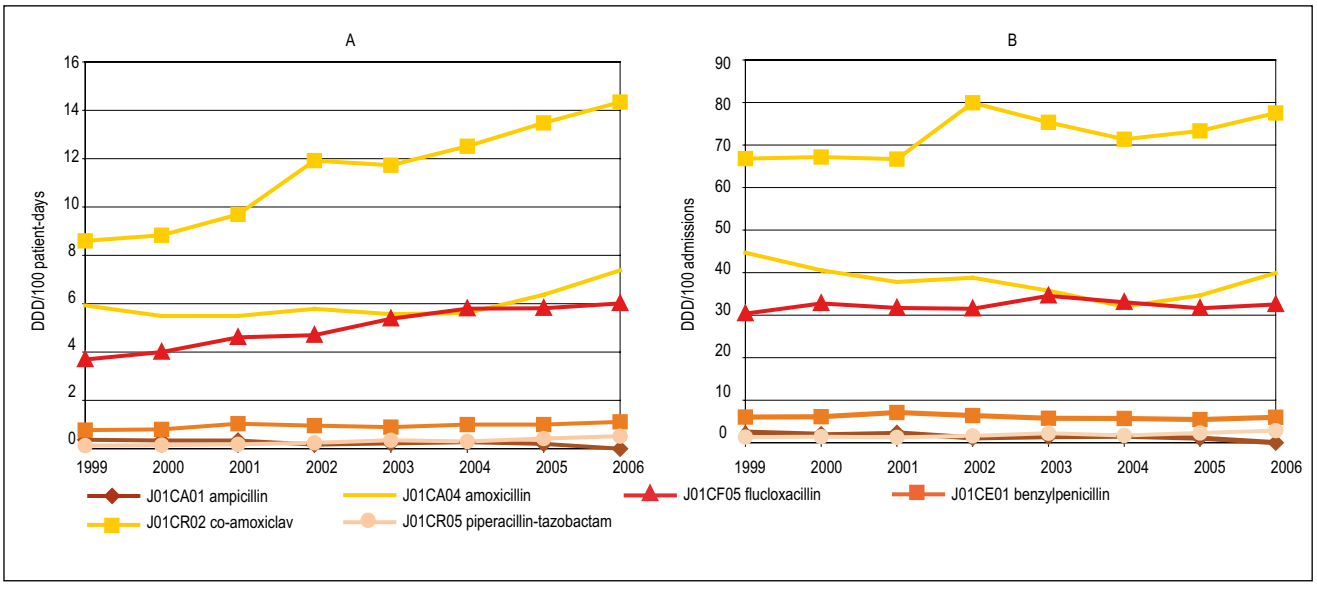


Figure 5. Distribution of the use of antibiotics for systemic use (J01, DDD/100 patient-days) in hospitals, 2006 (Source: SWAB).

3. Constant number of DDD/100 patient-days, decrease in DDD/100 admissions.
For tetracyclines and macrolides, the DDD/100 patient-days remained constant, but the DDD/100 admissions decreased. The average patient used less antibiotics, during a shorter stay in the hospital. Due to the increase in admissions, the relative use per ward/hospital remained constant.

4. Decrease in both units of measurement.
Combinations of sulfonamides and trimethoprim showed a decrease in DDD/100 patient-days as well as DDD/100

Figure 6. Use of penicillins in hospitals, 1999-2006 (Source: SWAB).



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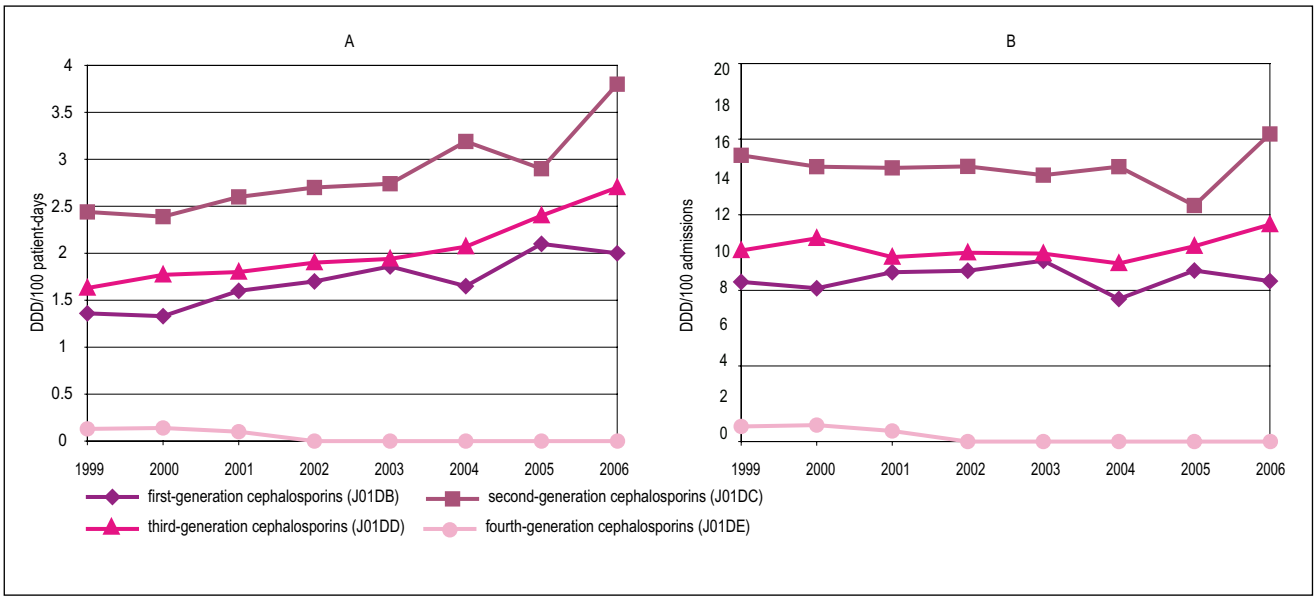


Figure 7. Use of cephalosporins in hospitals, 1999-2006 (Source: SWAB).

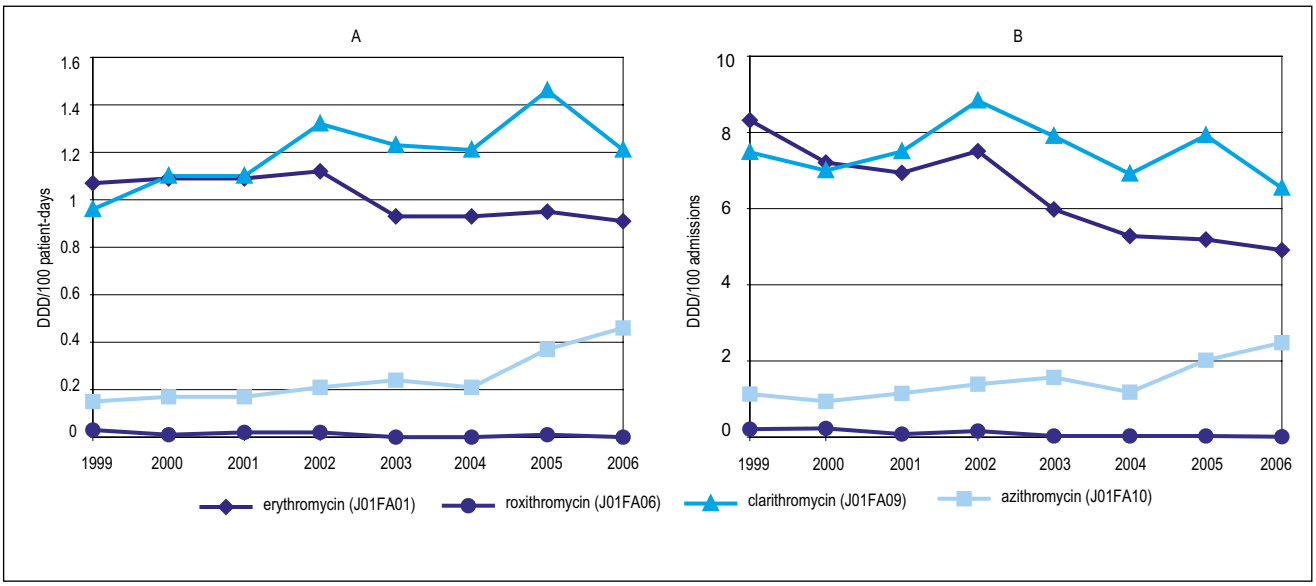
admissions. This implies that the use of these antibiotics decreased significantly in the average patient. This might be due to a reduction of the number of doses per patient as well as a reduction in the exposed number of patients, or a combination of both.

Figure 5 depicts the distribution of antibiotics per class in 2006. The relative use of the different subclasses of antibiotics remained constant over the past years (data not shown).
The relative use of of penicillins was approximately 47%. The largest proportion (23%) consisted of the combination of penicillins including beta-lactamase inhibitors, mainly co-amoxiclav (figure 6A and B).

Figures 6 to 11 show the use of the individual antibiotics within the different subclasses.
Co-amoxiclav, the most commonly used penicillin, shows an increase in both units of measurement since 1999 (figure 6A & B).

The cephalosporins represented 14% of the total of in-hospital antibiotic use (figure 5). The second and third-generation cephalosporins were most often used and their use is increasing (figure 7A and B).
It seems that over the past years the average patient used

Figure 8. Use of macrolides in hospitals, 1999-2006 (Source: SWAB).



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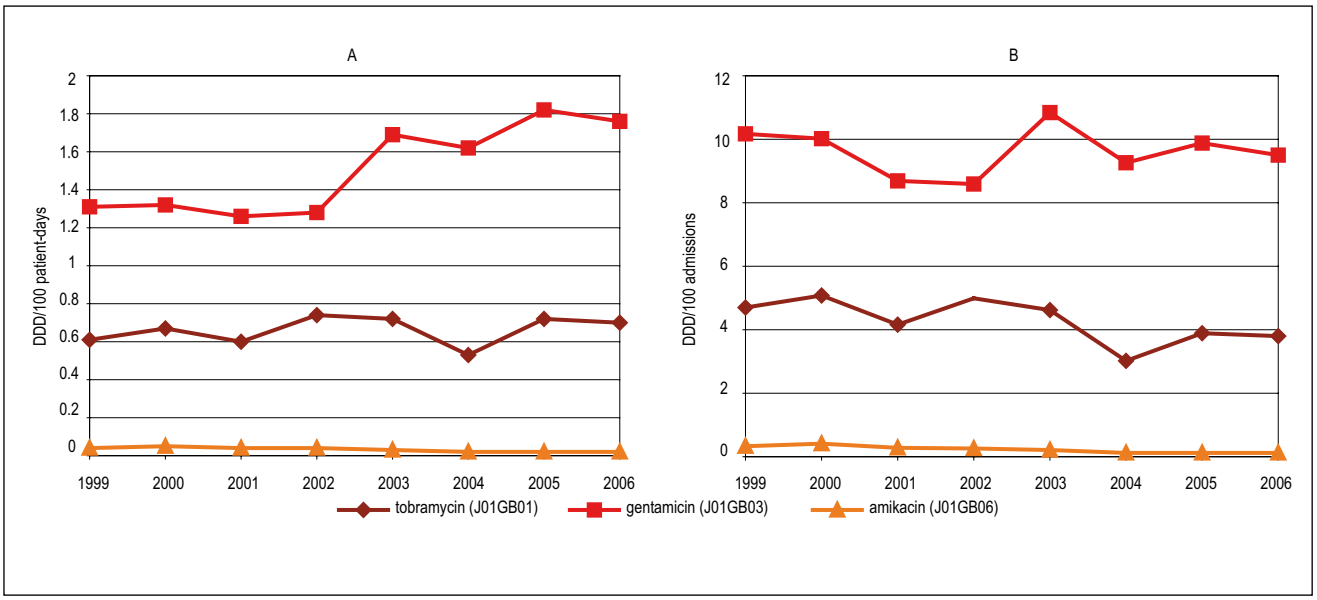


Figure 9. Use of aminoglycosides in hospitals, 1999-2006 (Source: SWAB).

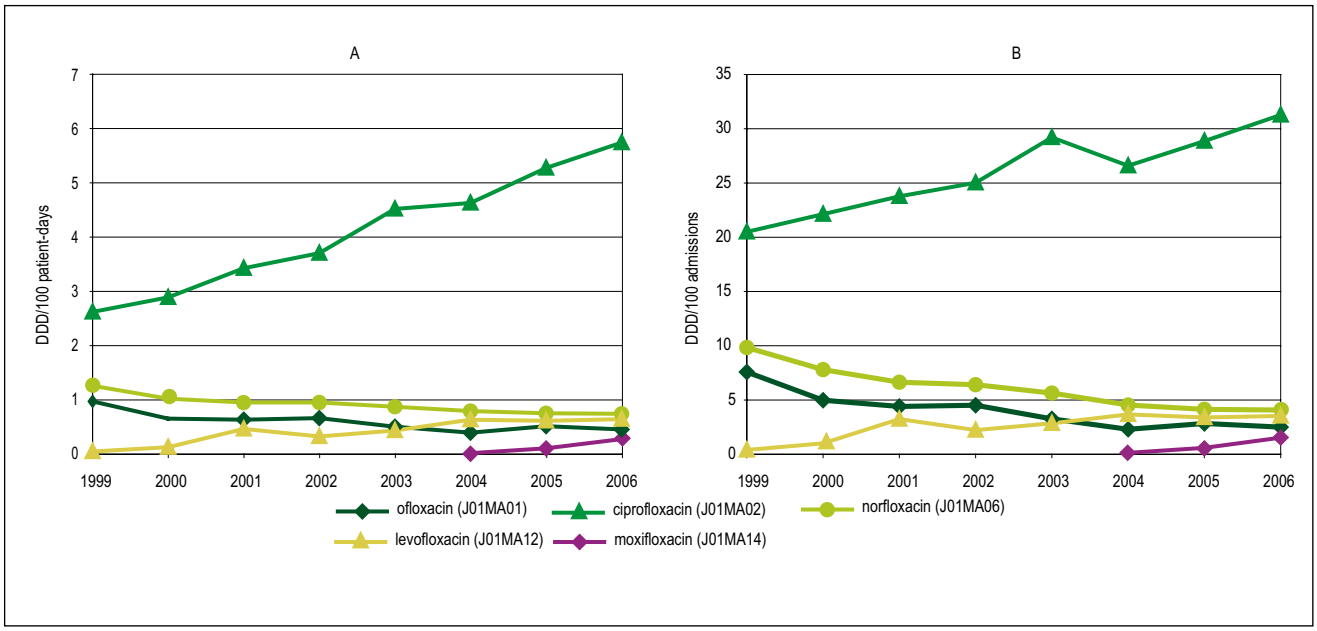
less macrolides. The use of erythromycin is still decreasing over the years The use of azithromycine has more than doubled from 1999 (1.1 DDD/100 admissions) to 2006 (2.5 DDD/100 admissions in 2006). However, azithromycin was still used the lowest of all macrolides (figures 8A and B).

The use of all aminoglycosides has remained constant from 1999 through 2006. Gentamicin is the most commonly used aminoglycoside. It's use increased slightly per 100 admissions, but the number of DDD/100 patient-days increased markedly from 1.3 in 2002 to 1.8 in 2006.

The past 2 to 3 years it's use seems to stabilise (figure 9A and B).
Use of ciprofloxacin is continuously increasing, expressed in both units of measurement, while the use of the other quinolones remain relatively low (figures 10A and B).

Vancomycin use is increasing markedly in both units of measurement. The use of teicoplanin remained low and decreased further (figures 11A and B).

Figure 10. Use of fluoroquinolones in hospitals, 1999-2006 (Source: SWAB).



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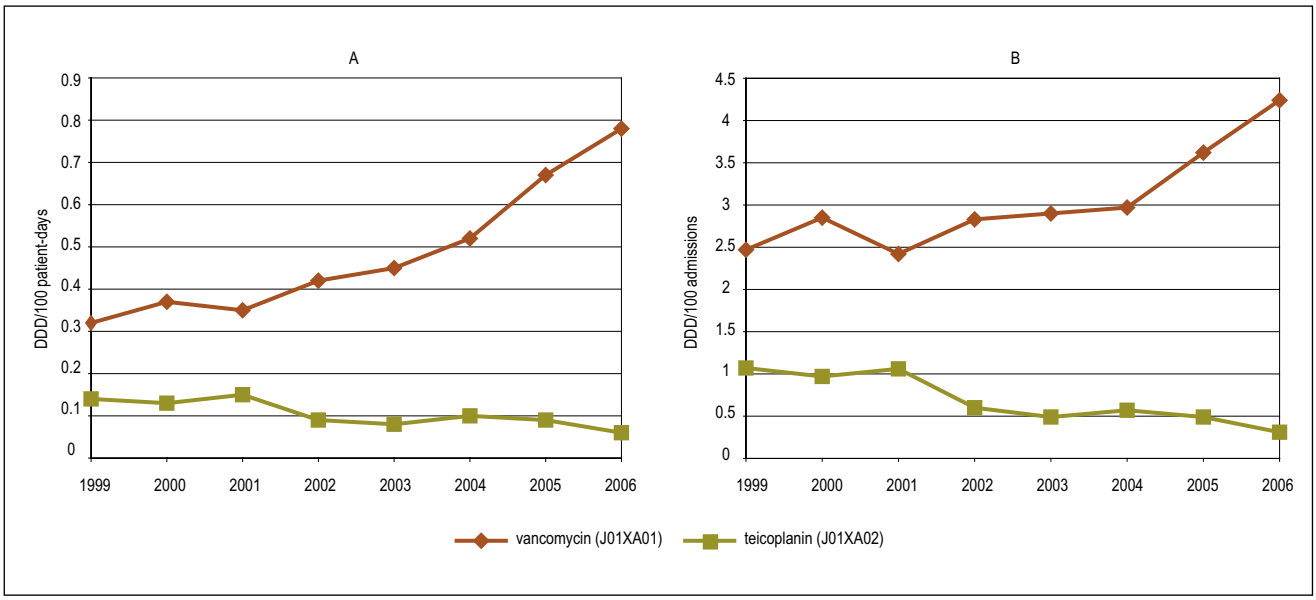


Figure 11. Use of glycopeptides in hospitals, 1999-2006 (Source: SWAB).

Antibiotic use at intensive care units

In 2006 data on antibiotic use in intensive care units was collected in 13 hospitals.

In these 13 hospitals, the overall average use of systemic antibiotics was 58.7 DDD/100 patient-days. In the intensive care units of these hospitals, the total average use was 132 DDD/100 patient-days, more than twice as much (table 4).

Except for the tetracyclines, the use of all therapeutic groups of antibiotics per 100 beddays is higher in the intensive care departments compared to the entire hospital. The use of benzylpenicillin and piperacillin with tazobactam appears to be especially concentrated in the intensive care units (figure 12). Carbapenems are also much more frequently prescribed in the intensive care population (table 4). First-generation cephalosporins are hardly used in the intensive care units whereas the use of second and third generation is markedly increased when compared with total hospital use (figure 13). From table 4 and figure 14 and 15 it might be concluded that the relative use of erythromycin, ciprofloxacin and other antibacterials (mainly vancomycine) is also high among intensive care patients.

Hospital use of systemic antimycotics

Total use of antimycotics for systemic use is 3.21 DDD/100 patient-days (table 5). In university hospitals, the use of systemic antimycotics is almost eight times higher compared to general hospitals. This is mainly the result of use of the polyenes (amphotericin B formula-

Table 4. Total hospital use of antibiotics for systemic use (J01) compared to use in intensive care, 2006 (Source: SWAB).

ATC group*	Therapeutic group	Intensive care use (n =13)	Total hospital use (n= 13)
J01AA	Tetracyclines	0.9	1.2
J01CA	Penicillins with extended spectrum	10.6	6.1
J01CE	Beta-lactamase sensitive penicillins	5.1	1.5
J01CF	Beta-lactamase resistant penicillins	9.8	5.8
J01CR	Combinations of penicillins. incl. beta-lactamase-inhibitors	21.5	14.8
J01DB -DE	Cephalosporins	25.8	10.6
J01DH	Carbapenems	4.6	0.5
J01E	Sulfonamides and trimethoprim	4.2	2.7
J01FA	Macrolides	10.1	2.6
J01FF	Lincosamides	3.0	1.9
J01GB	Aminoglycosides	6.0	1.8
J01M	Quinolones	18.4	6.6
J01X	Other antibacterials	12.0	2.6
J01	Antibiotics for systemic use (total)	132.0	58.7

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

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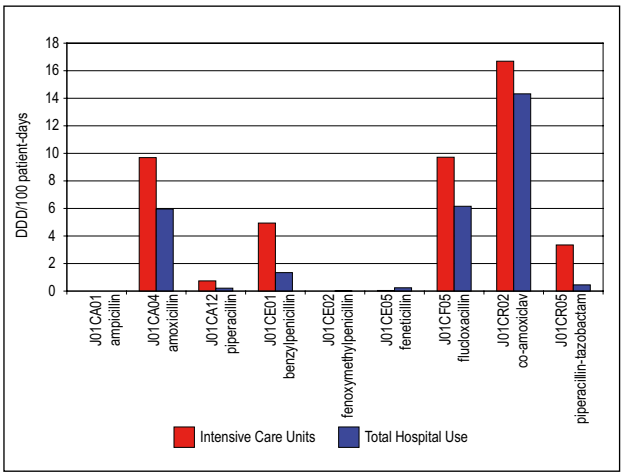


Figure 12. Use of penicillins in Intensive Care Units compared with total hospital use, 2006 (source: SWAB).

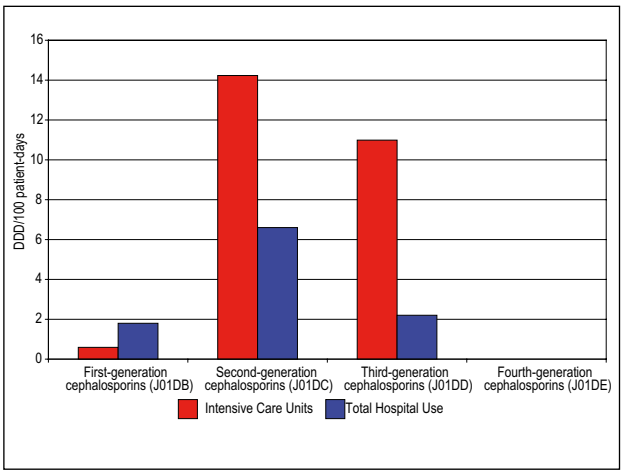


Figure 13. Use of cephalosporins in Intensive Care Units compared with total hospital use, 2006 (source: SWAB).

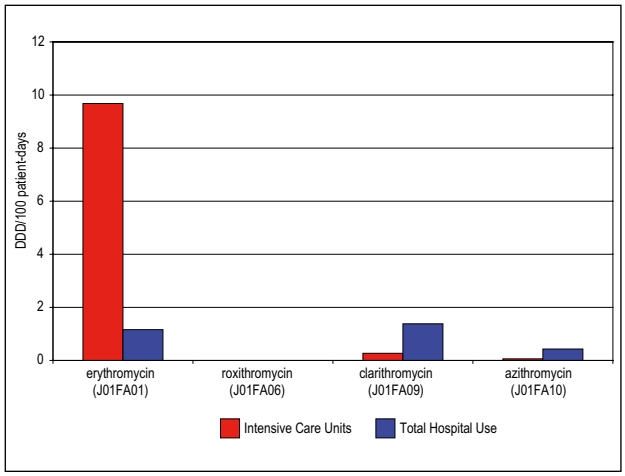


Figure 14. Use of macrolides in Intensive Care Units compared with total hospital use, 2006 (source: SWAB).

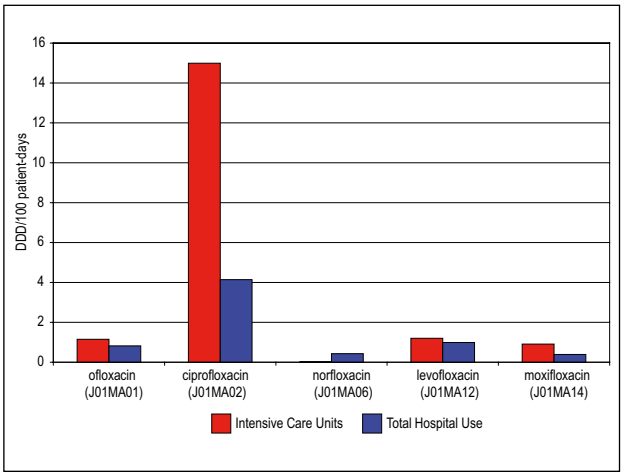


Figure 15. Use of fluoroquinolones in Intensive Care Units compared with total hospital use, 2006 (source: SWAB).

tions) and triazole derivatives.
The distribution of the use of antimycotics for systemic use in the different types of hospitals is illustrated in figures 16A, B, C.

In our cohort of 44 hospitals that participate in the surveillance of antimycotic drugs, the use of the polyenes represented 30% of the total in-hospital systemic antimycotic use (figure 16A). Of the three different products within this group, liposomal amphotericin B is used most frequently with 79% (figure 17).

Table 5. Use of antimycotics for systemic use (J02) in hospitals (DDD/100 patient-days), 2006 (Source: SWAB).*

ATC group*	Therapeutic group	Total 2006 (n=44)	General hospitals (n=39)	University hospitals (n=5)
J02AA01	Polyenes (Amfotericin B formulations)	0.97	0.12	5.61
J02AB02	Ketoconazole	0.03	0.03	0.03
J02AC	Triazole derivatives	2.16	1.38	6.41
J02AX01	Flucytocin	0.01	0.01	0.02
J02AX04	Caspofungin	0.04	0.02	0.16
J02	Antimycotics for systemic use (total)	3.21	1.56	12.23

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

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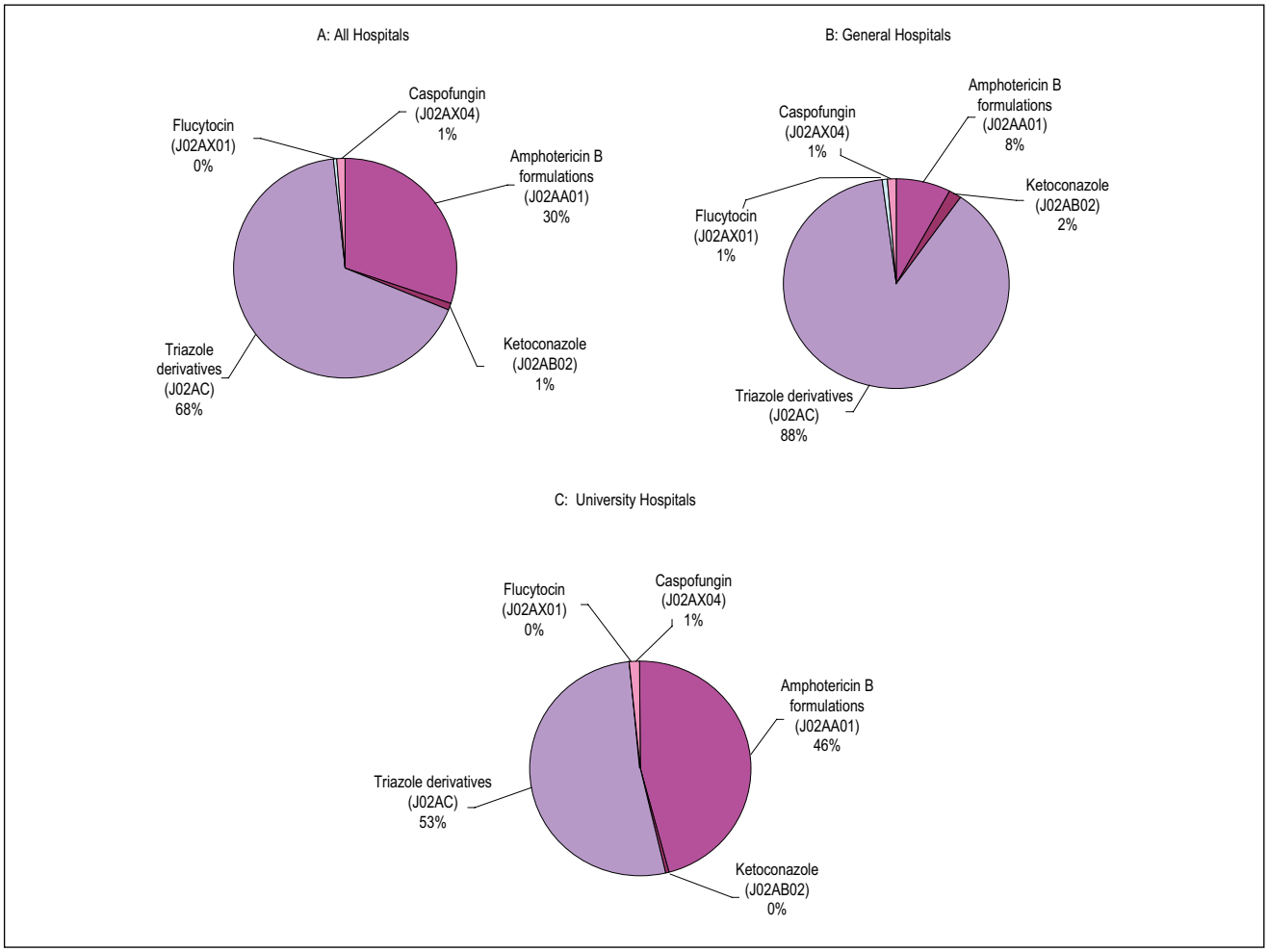


Figure 16. Distribution of the use of antimycotics in All Hospitals (A), General Hospitals (B) and University Hospitals (C), 2006 (source: SWAB).

The triazole derivatives represented 68% of the total in-hospital systemic antimycotic use (figure 16A). Fluconazole was the most commonly used antimycotic in general hospitals as well as in university hospitals (figure 18)

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/100 patient-days and in DDD/100 admissions.

We have distinguished four main categories with regard to the observed trends in antibiotic use. An increase in both the number of DDD/100 patient-days and the number per 100 admissions (category 1) is worrisome. It will be also obvious that no increase in either unit (categories 3, 4) is not worrisome with regards to resistance development. The trends in category 2 are less easy to interpret.

When a constant use per patient (category 2) is seen, and this is combined with an increase in the number of admissions, this is indicative for an increase of the selection pressure exerted by antibiotics in hospitals over the years.

An intensification of antibiotic therapy per 100 patient-days, however, 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]

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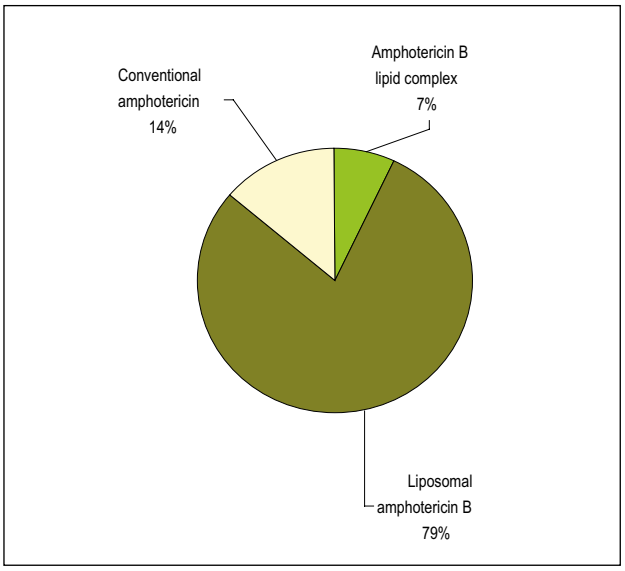


Figure 17. Distribution of the use of amphotericin B formulations in hospitals.

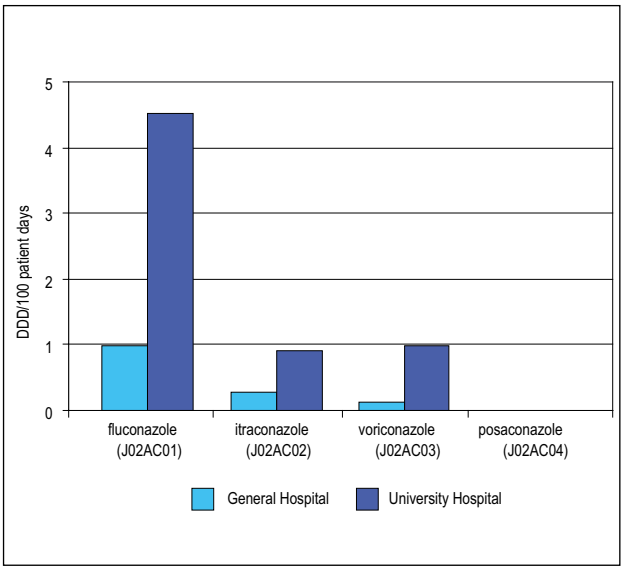


Figure 18. Distribution of the use of triazole derivatives in General- and University Hospitals, 2006 (source: SWAB).

Over the years 2002-2006, a 24% increase in total antibiotic use was observed when expressed in DDD/100 patient-days. The average patient did not use more antibiotics.
Nonetheless, the average hospital environment is exposed to 24% more antibiotics in 2006 compared to 2002. This higher ecological pressure may result in the selection of resistant strains.

The consumption of vancomycin and ciprofloxacin has increased significantly since 1999. The increase in vancomycin use 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 increase in ciprofloxacin use may be explained by an increase in the incidence of gram-negative resistant micro-organisms.

Data on the use of antibiotics in the intensive care departments of 13 Dutch hospitals are presented in this report for the first time. Total hospital use in these 13 hospitals per 100 patient-days was similar to the total hospital use in our entire cohort of hospitals (49 hospitals). Therefore, this sample appears to be representative for the average use in Dutch intensive care units.
Since we have no data on intensive care use over the past years it is not possible to conclude that the trends observed in total hospital use are mainly caused by changes in intensive care use. The relative higher use of broad-spectrum antibiotics like the third generation cephalosporins, carbapenems and ciprofloxacin in intensive care departments might be explained by the more complex infection problems in intensive care patients and the higher incidence of resistant micro- organisms. Erythromycin is used as a prokineticum in many Dutch intensive care departments. First generation cephalosporins are restricted to surgical prophylaxis in most Dutch hospitals and therefore hardly used in the intensive care units.

We cannot compare antimycotic use data over the years because SWAB collected these data for the first time in 2006. In university hospitals, the use of systemic antimycotics is almost eight times higher compared to general hospitals. This is explained by the high concentration of haematology- and oncology-patients in university hospitals who are at risk, or have clinical features of invasive fungal infections. In our dataset it is not possible to distinguish between prophylaxis and therapy.
For many years, conventional amphotericin B was the only fungal agent available for the empirical treatment of patients with prolonged and profound neutropenia that is unresponsive to broad-spectrum antibiotics and for the treatment of invasive aspergillosis and candidiasis. It's excessive nefrotoxicity has meant that it is now largely superseded by safer antifungal agents like the lipid formulations of amphotericin B, caspofungin and voriconazole.

With the presented data in NethMap we cannot assess the rationality and quality of prescriptions in Dutch hospitals. However, in general terms we may conclude that in comparison with other European countries total hospital use and the relative use of broad spectrum antibiotics is low.[4]
Point prevalence surveys may be useful to determine the appropriateness of antibiotic therapy and to gather insight into the demographics, infections and antibiotics used within specific hospital populations.[5]

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4 Resistance among common Pathogens

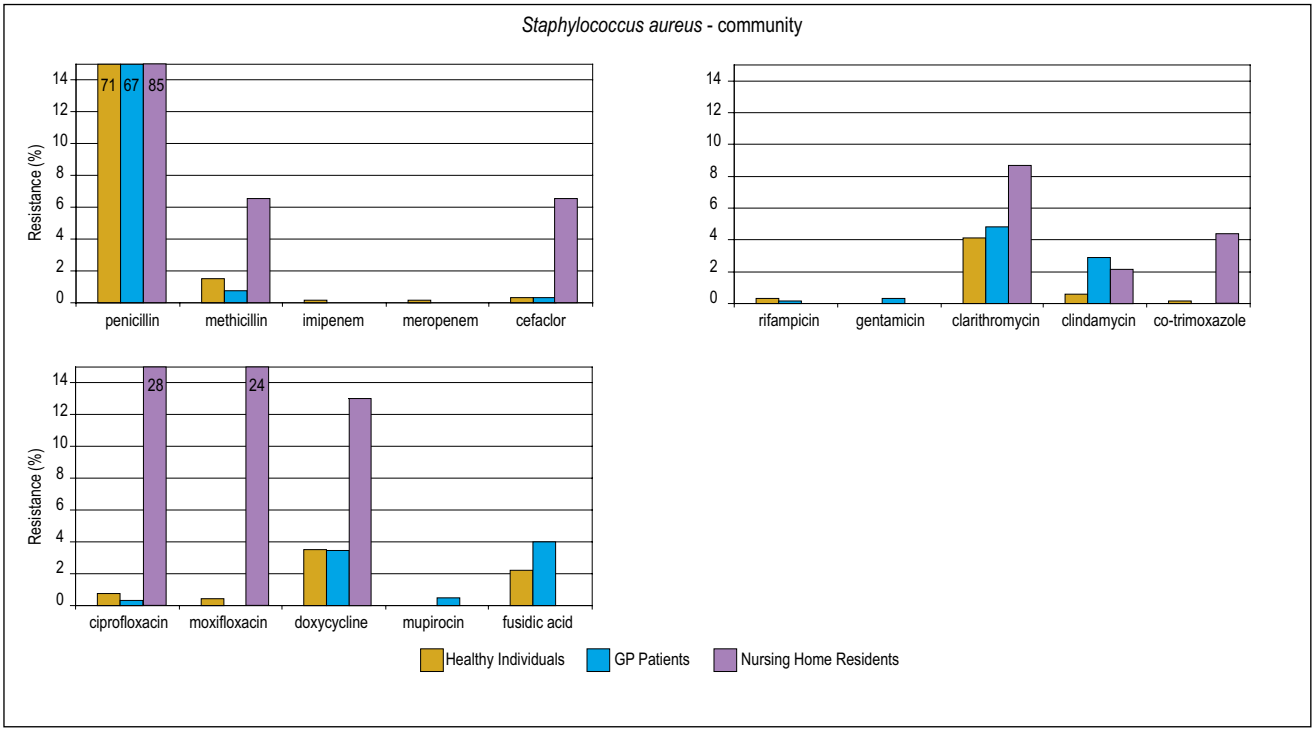
Surveillance of Antimicrobial Resistance in the Community

The studies on resistance level in the community focus on three different goals: (1) estimation of resistance in the indigenous flora of healthy persons in various circumstances and of various ages, giving information about the basic level of resistance in human reservoirs and
(2) estimation of resistance in patients visiting their general practitioner (GP) and out-patients clinics for complaints of urinary tract infections and respiratory tract infections and
(3) estimation of resistance in special pathogens like meningococci and gonococci.
Several longitudinal multicentre studies within the national project Surveillance of Extramural Resistance in the Netherlands (SERIN) were carried out or are ongoing in various parts of the Netherlands in cooperation with the Department for Medical Microbiology, University Hospital Maastricht, the Netherlands Institute for Healthy Services research (NIVEL) and the regional Institutes for Public Health Services (GGDs).
Resistance data were obtained for *Staphylococcus aureus* as part of the indigenous flora of healthy persons to determine the basic level of resistance in the human reservoir. This study was expanded with estimation of carrier state and resistance level of *S. aureus* in residents of nursing homes. Further, the resistance rate of indicator organisms *(S. aureus* and *Escherichia coli*) in patients visiting their general practitioner was studied. Another surveillance project was started to determine the carrier state and level of resistance of *Streptococcus pneumoniae* in healthy children and healthy adults.
In 2006 the RIVM started a surveillance of resistance of *Neisseria gonorrhoeae* among patients from outpatient-STI clinics, the GRAS project.
Since 1993 the Netherlands Reference Laboratory for Bacterial Meningitis has been determining the resistance level of *Neisseria meningitidis* from patients admitted to hospital for meningococcal disease.
The first isolate of *Mycobacterium tuberculosis* of each patient with tuberculosis in the Netherlands is routinely sent to the RIVM for susceptibility testing and confirmation of identification.
Results of all these studies are presented here.

Staphylococcus aureus

The prevalence of antibiotic resistance among *S. aureus* as part of the indigenous flora of residents of nursing homes was determined to get insight in the carrier state and the basic level of resistance in this reservoir in the community. This study is started in 2007 and will continue in 2008 in various parts of the Netherlands. The first results obtained in the South of the Netherlands are published here. The carrier state in these nursing homes was compared with the carrier state and resistance levels

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



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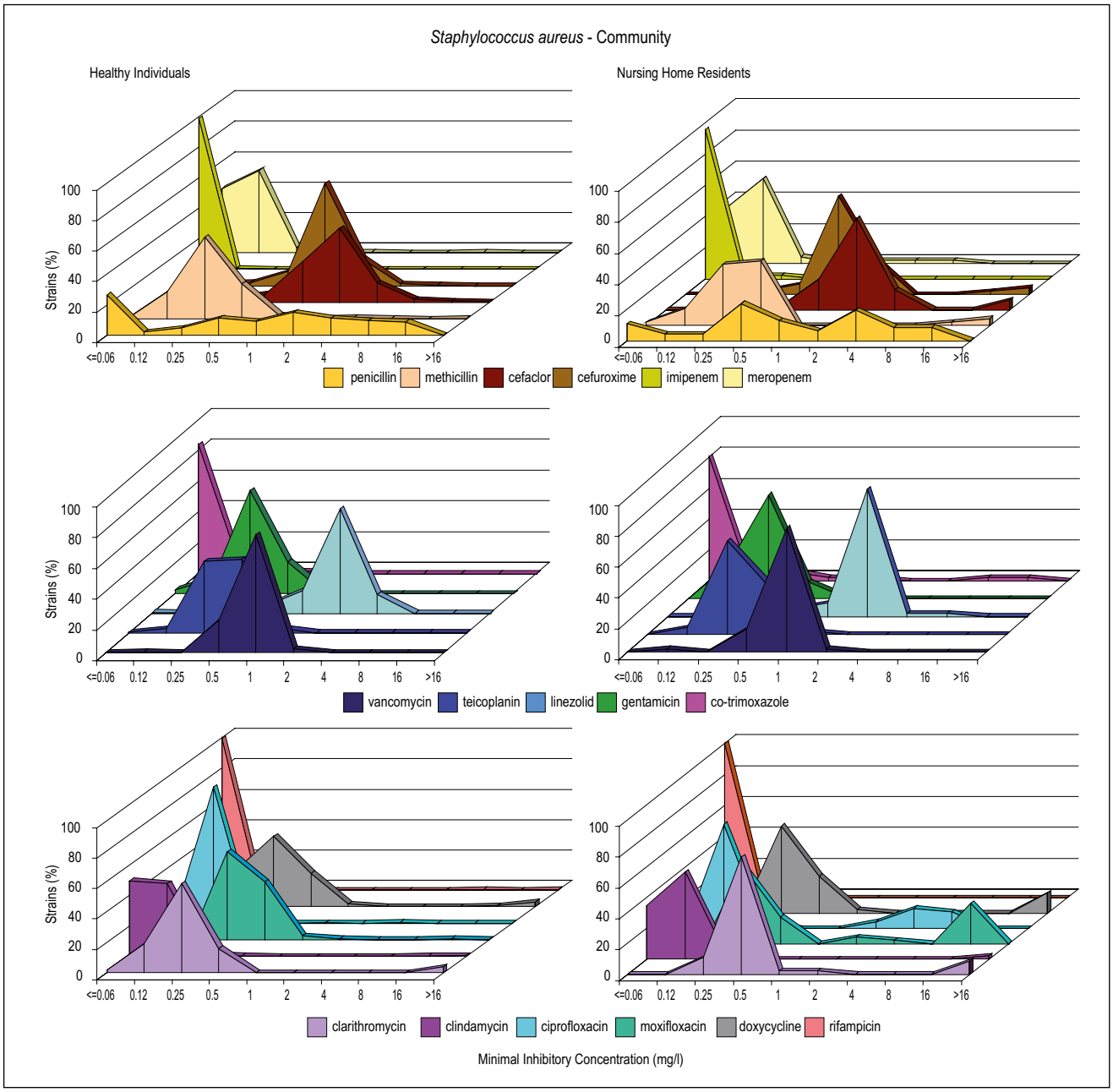


Figure 2. MIC distributions of antibiotics tested for *Staphylococcus aureus* from healthy individuals in the community and nursing home residents.

in healthy persons and patients visiting their general practitioner for non-infectious complaints, not treated in the recent past, but having contact with medical practice.

Carrier state and resistance level of *Staphylococcus aureus* 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 (see Appendix for detailed information on methods). A total of 2369 nasal swabs were obtained and *S. aureus* was isolated in 656 samples (carrier rate 28%). Penicillin-resistance was found in 71% of the strains (figure 1). The distribution of MICs (figure 2) was bimodal 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 absent. Clarithromycin-resistance was found in 4%

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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 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 of *Staphylococcus aureus* in GP patients without infections
A total of 2691 patients visiting their GP participated in the study. Overall *S. aureus* was isolated from 617 nose swabs, a carrier state of 23% which is significantly lower than the carrier state in healthy individuals ($p< 0.005$). Penicillin-resistance (67%) and MIC distributions were almost similar to those found in healthy individuals. MRSA strains were not isolated.
Cefaclor-resistance was similar to that in healthy individuals. Imipenem-, meropenem-, linezolid-, vancomycin- and teicoplanin-resistance were not found. Ciprofloxacin-resistance was low in patients (two strains, 0.3%) and moxifloxacin-resistance was not demonstrated (figure 1). The two ciprofloxacin-resistant strains were also resistant to penicillin, one to doxycycline as well.
The fusidic acid resistance rate was 4%, being significantly higher than that in healthy individuals ($p< 0.05$). Resistance to mupirocin was found in three strains, one of them was also resistant to fusidic acid. Previous treatment with these drugs could have led to resistance in these isolates. Doxycycline-resistance was similar in both study groups. Two strains were gentamicin-resistant (0.3%), one of these strains showed co-resistance to clarithromycin.

Carrier state and resistance level of *Staphylococcus aureus* in nursing home residents
Nasal swabs were taken after informed consent from nursing home residents in Maastricht, a city in the Southern part of the Netherlands. One hundred eleven residents having somatic disabilities without infections from two nursing homes were screened. Forty six *S. aureus* isolates were obtained from 37 residents, resulting in a carrier rate of 33%, which is not significantly different from the carrier rate in healthy individuals.
Penicillin-resistance was found in 85% of the strains, which is higher than in GP patients ($p<0.05$) and in healthy individuals (figure 1). The MIC distribution showed three subpopulations: one with MIC <0.12 mg/l, one with MIC 0.5-2 mg/l and one with MIC 4-16 mg/l (figure 2). Methicillin-resistance was found in three strains (6.5%) from two individuals. Both had the *MecA* gene and were classified as MRSA. This is significantly higher than the carrier state found in healthy individuals and GP patients. Both the resistance to cefaclor (6.5%) and the resistance to cefuroxime (4%) were higher than in the other study groups. The MIC distributions of cefaclor and cefuroxime were bimodal with a large susceptible population and a small resistant population. The resistant subpopulation was not observed in healthy individuals. Clarithromycin-resistance was observed in four strains (9%). One of them was also resistant to clindamycin. Co-trimoxazole-resistance was found in 4% of the strains.
Ciprofloxacin-resistance was recorded in 28% of the strains, which is significantly higher than in healthy individuals and GP patients ($p<0.02$) (figure 1). Moxifloxacin-resistance was high as well (24%). These resistance rates may reflect selection by frequent use of quinolones for various indications in nursing homes. Resistance to doxycycline was 13%, which is also significantly higher than that in healthy carriers and GP patients. All isolates were susceptible to vancomycin, teicoplanin, gentamicin, imipenem, meropenem, rifampicin, mupirocin and fusidic acid. Two isolates (4%) were resistant to linezolid.

Multiresistance of *Staphylococcus aureus* in the community
Combined resistance to two or more antibiotics for systemic use was found in 6% of the strains from healthy individuals and GP patients and in 46% of the strains from nursing home residents (figure 3). The combinations penicillin/doxycycline and penicillin/clarithromycin predominated in healthy individuals and in GP patients, the combination penicillin/ciprofloxacin predominated in strains from nursing home residents. Combined resistance to three or more antibiotics of different classes was demonstrated in 1.2% of the strains from healthy individuals and GP patients. When extrapolated to the community as a whole: 0.35% of the healthy Dutch population is carrier of multiresistant *S. aureus*. Resistance to three or more antibiotics of different classes was demonstrated in 15% of the strains from nursing home residents. This high frequency of multiresistance in residents of nursing homes is a matter of concern. It may reflect selection by frequent use of antibiotics in a closed community and poses a serious problem for the treatment of infections in patients of nursing homes.

Streptococcus pneumoniae
The carrier state and prevalence of antibiotic resistance among *S. pneumoniae* as part of the indigenous throat flora of healthy persons was determined to assess the basic level of antibiotic resistance in the community. Furthermore the carrier state and resistance of this micro-organism in patients with complaints of a lower respiratory

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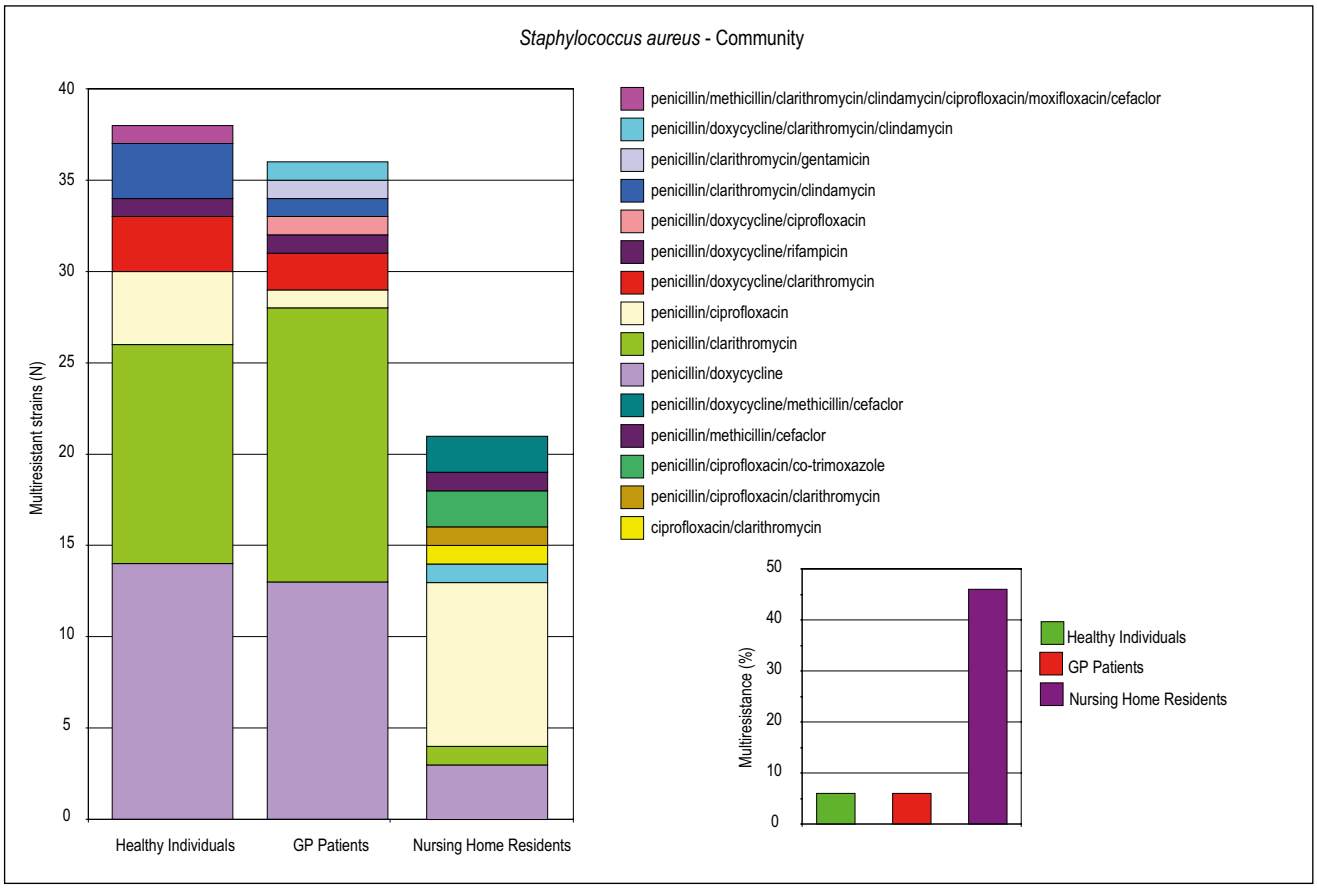


Figure 3. Multidrug resistance among *Staphylococcus aureus* from healthy individuals, GP patients in the community and nursing home residents.

tract infection visiting their general practitioner (GP) was determined. The study is still ongoing and the number of strains isolated until now is low. Therefore the results are difficult to interpret.

Carrier state and antibiotic resistance level of *Streptococcus pneumoniae* in healthy individuals

Two populations were studied: (I) children at the age of 9 year and (II) adults at the age of 60 years and more. Throat swabs were taken from 698 children and 593 adults. The carrier rate of *S. pneumoniae* in children (4%) was higher than in adults (2%) ($p<0.05$). Isolates of both study groups were susceptible to penicillin, amoxicillin, rifampicin, levofloxacin and moxifloxacin. Resistance to clarithromycin was 16% in children versus 9% in adults. Clindamycin-resistance was 11% in children versus 9% in adults. Chloramphenicol-resistance was 11% in children and was not observed in adults. In contrast, co-trimoxazole-resistance was higher in adults than in children (9% versus 5%), as was also doxycycline-resistance in adults (18%) versus 11% in children.

Carrier state and antibiotic resistance level of *Streptococcus pneumoniae* in patients with complaints of a lower respiratory tract infection

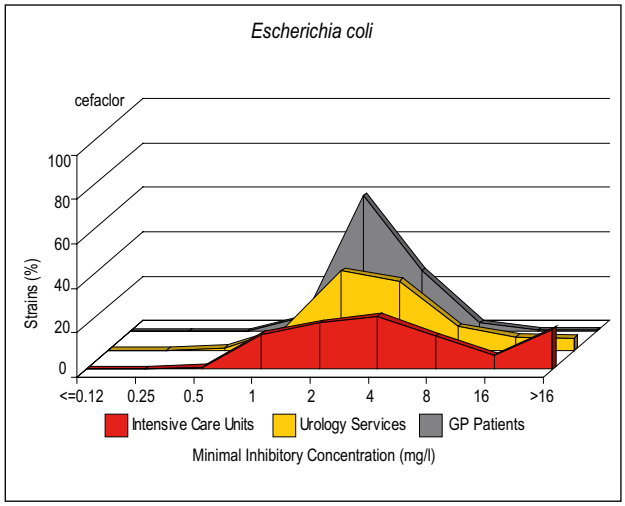
Thirty general practitioners (GP) from all over the Netherlands participated in the study. A total of 330 patients visiting their GP with complaints of a lower respiratory tract infection were included in the study (III). The carrier rate found was 4%, which is higher than that in healthy adults. No resistance to any of the antibiotics tested was found.

Escherichia coli

Resistance level for cefaclor in *Escherichia coli* from patients visiting their GP with complaints of uncomplicated urinary tract infection

A total of 365 *E. coli* strains isolated from urine from patients visiting their GP with complaints of an uncomplicated urinary tract infection in 2005 were tested for their susceptibility to cefaclor to get insight in the basic level of resistance to first generation cephalosporins in the community. This is of interest because first generation cephalosporins are used as routine prophylaxis in abdominal surgery. The resistance level was 0.5% (two strains were resistant; one of these was also resistant to cefuroxime). This is significantly lower than the resistance level in Urology Services (5%) and Intensive Care Units (18%) in the same year. The MIC distributions of cefaclor in strains from these study groups differ from each other (figure 4). The MIC distribution of the strains from GP patients showed a broad range with a sharp

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Firgure 4. MIC distribution of cefaclor tested for *Escherichia coli* from GP patients in the community and from patients in Urology Services and Intensive Care Units.

peak at 2 mg/l and an MIC_{90} of 4 mg/l, the distribution of the strains from patients of Urology Services was also unimodal, but showed a large population with MICs 4-16 mg/l and an MIC_{90} of 16 mg/l. In contrast the MIC distribution of the strains from Intensive Care Units was bimodal with a resistant population and MIC_{90} >16 mg/l. So far, there is no reason to change the prophylaxis policy for patients from the community admitted to the hospital for abdominal surgery or for patients from Urology Services (mostly outpatients), but first generation cephalosporins cannot be advised for abdominal surgery in patients from Intensive Care Units.

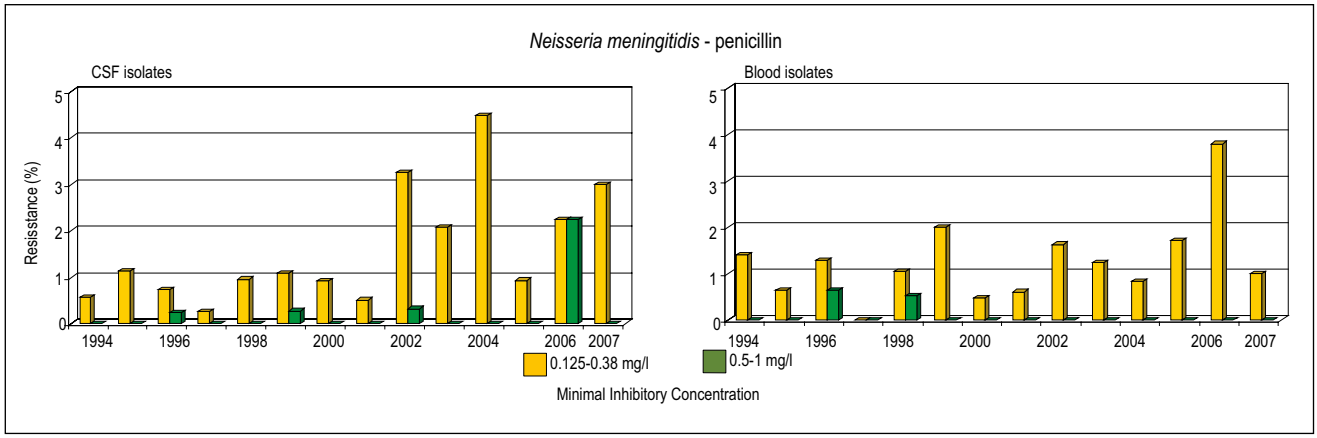
Neisseria meningitidis

From 1993-2007 a total of 4453 strains from cerebrospinal fluid and 2553 strains from blood were included in the surveillance project of the Netherlands Reference Laboratory for Bacterial Meningitis of the Academic Medical Centre, Amsterdam. Strains moderately susceptible to penicillin (MIC 0.125-0.38 mg/l) occurred in less than 1% of the strains before 2002. Thereafter 2-4% of these strains, both from CSF and blood, appeared moderately susceptible. Penicillin-resistance (MIC >=0.5 mg/l) was occasionally found in strains both from CSF and blood until 2002 (figure 5); 2% of the CSF strains from 2006 were resistant, none in 2007. All strains isolated in 2007 were susceptible to ceftriaxone and rifampicin.

Neisseria gonorrhoeae

In 1999 the nationwide surveillance of antibiotic resistance of gonococci was discontinued and since then insight in the susceptibility patterns of gonococci had been limited. Concern for increasing resistance to quinolones led to an annual RIVM questionnaire on resistance of gonococci from 2002 onwards. Complete data on the number of diagnoses and results of antimicrobial susceptibility testing for 2002-2006 were provided by 24 of all 39 microbiological laboratories. A remarkable increase in resistance to quinolones (recommended first line therapy until September 2003) was observed: from 6.6% (2002) to 26.4% in 2005, up to 38.0% in 2006 (figure 6).
Apart from this annual questionnaire, a Gonococcal Resistance to Antimicrobials Surveillance (GRAS) project has been implemented in the Netherlands from 2006 onwards. This surveillance consists of systematically collected data on gonorrhoea and standardised measurement of resistance patterns by using E-test, linked with epidemiological data. Isolates with unusual resistances are forwarded to the RIVM for conformation. Participants are STI clinics and associated laboratories that identify the majority of STI in high risk populations.
In June 2006, the GRAS project was implemented in the first STI clinic and at the end of 2006, GRAS was implemented in four regional STI clinics, and 177 isolates were tested for antimicrobial susceptibility so far. In 2007 most other STI clinics implemented the GRAS project and up to June 2007, 451 isolates have been tested for antimicrobial susceptibility.
Overall results show a prevalence of resistance to cipro-

Figure 5. Trends in penicillin susceptibility among clinical strains of *Neisseria meningitidis*.



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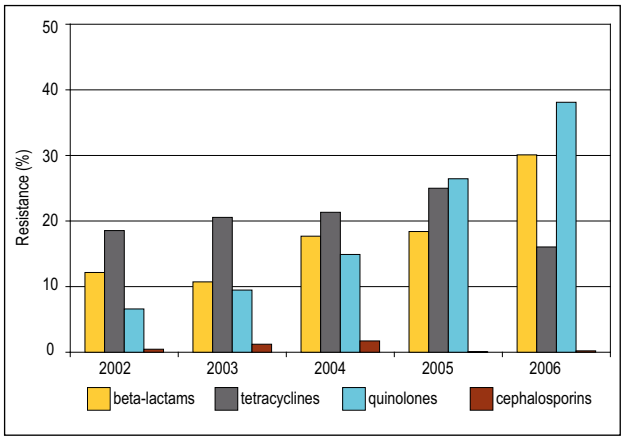


Figure 6. Prevalence of resistance among *Neisseria gonorrhoeae* in the Netherlands, 2002-2006 (Source: RIVM questionnaire among microbiological laboratories).

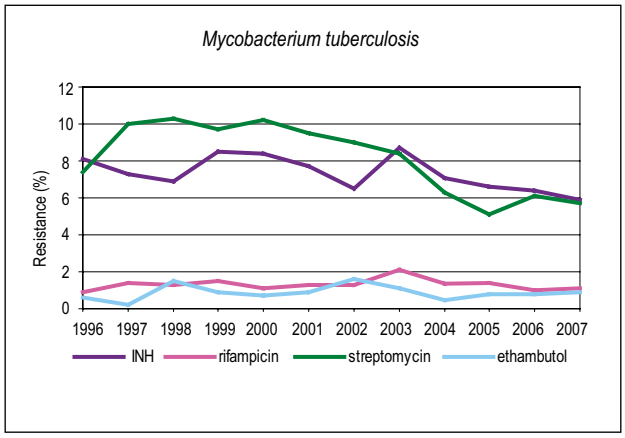
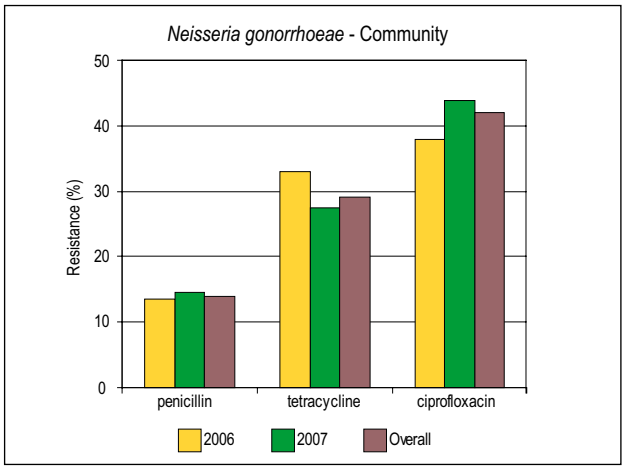


Figure 8. Trends in resistance to antibiotics among *Mycobacterium tuberculosis*.

floxacin of 42%, to tetracycline of 29% and to penicillin of 14%. Resistance to cephalosporins was not found (figure 7). Assuming a maximum of 5% resistance being acceptable for empiric therapy, none of the drugs mentioned above except cefotaxime and ceftriaxone can be used anymore for empiric therapy.
Ciprofloxacin-resistance increased from 38% in 2006 to 44% in 2007 (p=0.10), with the most marked increase in men who have sex with men (from 43% in 2006 up to 55% in 2007, p=0.04). In heterosexuals the prevalence of ciprofloxacin-resistance remained stable over 2006-2007 (men: 28%, women: 20%) but a very high resistance percentage in this group was observed in persons from Eastern Europe (12/17, 71%). Five of the twelve patients with resistant isolates worked as a commercial sex worker in the last six months.
The rapidly changing antibiotic resistance pattern of gonococci underlines the need for a continuous standardised surveillance of antimicrobial susceptibility.

Figure 7. Resistance to antibiotics among *Neisseria gonorrhoeae* in The Netherlands from 2006-2007 (GRAS project).



Understanding the distinct resistance patterns in different network groups, may add to understanding the transmission dynamics of *N. gonorrhoeae* in the population. Such knowledge will greatly support clinical care as well as public health to target and evaluate interventions.

Mycobacterium tuberculosis
A total of 11683 strains of *M. tuberculosis* were obtained during 1996-2007. In 2007 the number of isolates was 715. INH-resistance remained stable, 6% (figure 8). Streptomycin-resistance decreased from 10% in 2000 to 6% in 2006 and stayed at that level. The rifampicin-resistance level remained stable, 1% (figure 8). Ethambutol-resistance was 0.8% from 2005 on. Combined resistance to more than one drug was observed in 3% of all isolates (figure 9). Multiresistance (combined resistance to rifampicin and INH) was recorded in 1% of the strains and resistance to all four antimycobacterial drugs was 0.7% in 2007.

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 the strains collected and tested by 11 Regional Public Health Laboratories and four local laboratories covering 30% of the Dutch population (table 1 in Appendix). These are designated resistance rates in 'Unselected Hospital Departments'. Resistance rates in Unselected Hospital Departments were compared with the resistance rates among strains isolated from selected departments in 14 large referral hospitals (table 2 in the appendix). The latter study is a longitudinal national study for Surveillance of

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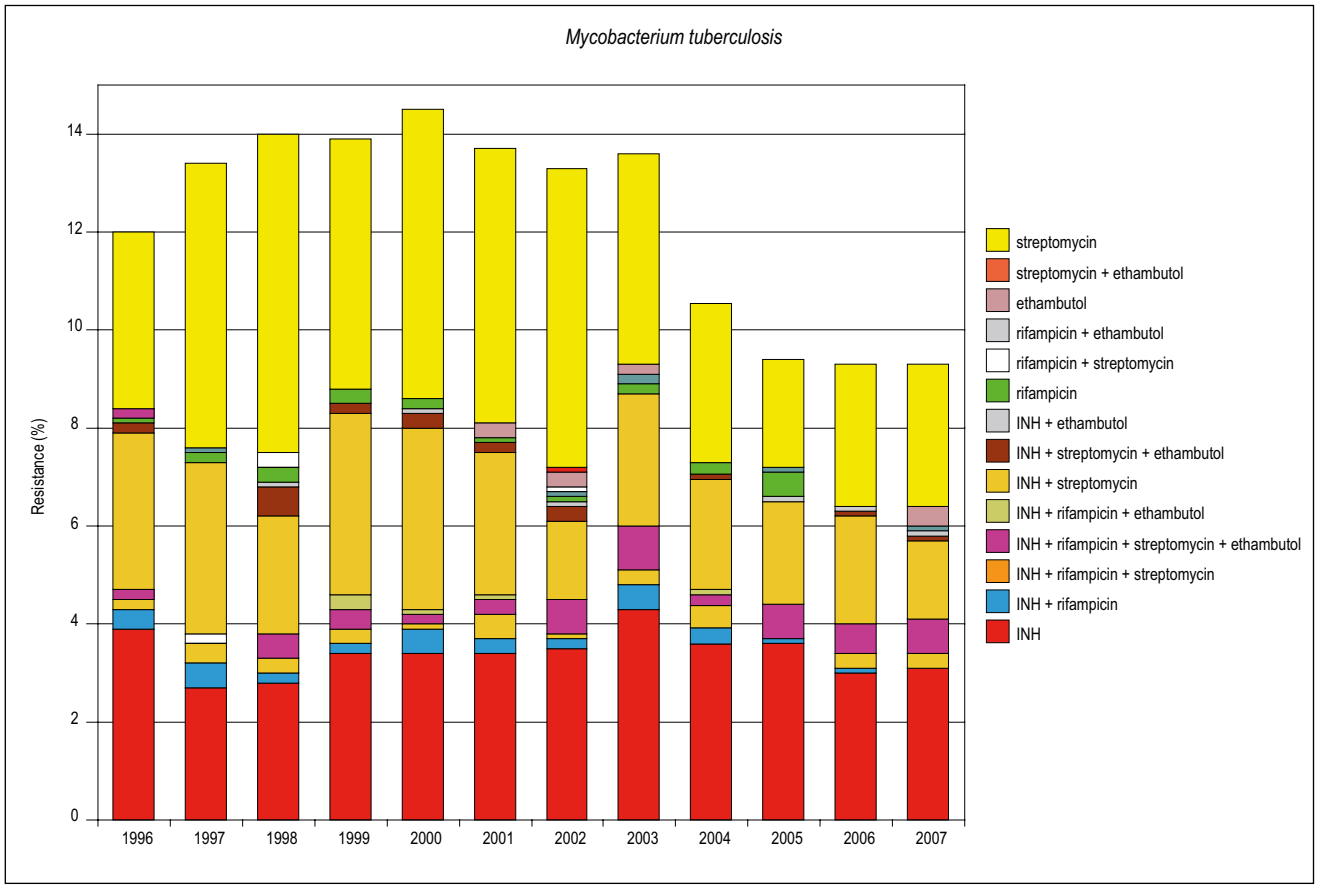


Figure 9. Trends of combined resistance among *Mycobacterium tuberculosis*.

Intramural Resistance in the Netherlands (SIRIN). The selected departments included the Intensive Care Units, being wards with high use of antibiotics and, consequently, high selective pressure favouring the emergence of resistance. Also included were the Urology Services and the Pulmonology Services, the latter two representing departments with frequent use of specific oral antibiotics. Results were analysed per species of common nosocomial pathogens and are presented in the accompanying figures. Resistance data obtained from the Intensive Care Units were used for further studies (project 1 and 2).

Escherichia coli

The overall prevalence of amoxicillin-resistance in Unselected Hospital Departments increased from 28 % in 1996 to 42% in 2007 (figure 10). Amoxicillin-resistance was higher in Intensive Care Units, it fluctuated around 42% until 2004 and showed a sharp increase to 56% in 2005, which stabilized in 2006. The resistance in Urology Services fluctuated around 40% from the beginning, but showed a slow increase to 46% in 2006.The distribution of MICs (figure 11) in Intensive Care Units showed two subpopulations: a susceptible one with a broad MIC range from 0.5-8 mg/l (peak at 2-4 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, 4-5% in Unselected Hospital Departments until 2000, but overall a slight increase could be observed resulting in 6% resistance in 2006 and 2007. The trend in the Urology Services was fluctuating but increasing from 4% in 1996 to 11% in 2006. Co-amoxiclav-resistance was much higher in Intensive Care Units, with fluctuations to 22% in 2005; the resistance in 2006 was 16% (figure 10). The MIC distribution of co-amoxiclav in Intensive Care Units was unimodal and showed a growing number of intermediate strains with MIC 16 mg/l (figure 11). The shape of the curve changed considerably over the years: until 2000 a real peak at 4 mg/l was observed, but this disappeared completely. The existence of a growing 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% which increased further in 2006 to 43%. The MIC distribution of piperacillin (figure 11) showed three subpopulations in 1998: one susceptible with MICs 0.5-4 mg/l, one moderately susceptible with MICs 8-64 mg/l and one resistant subpopulation with MICs >64 mg/l. From 2001 on a shift could be observed

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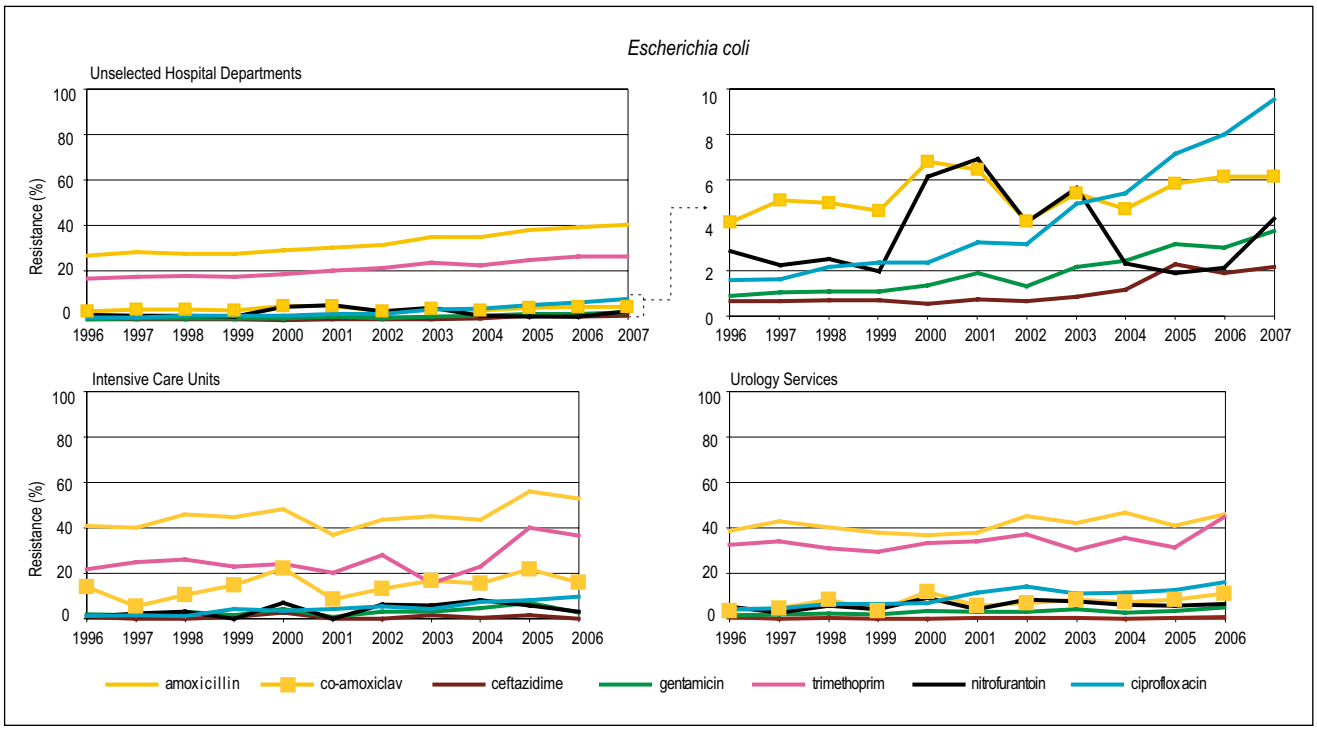
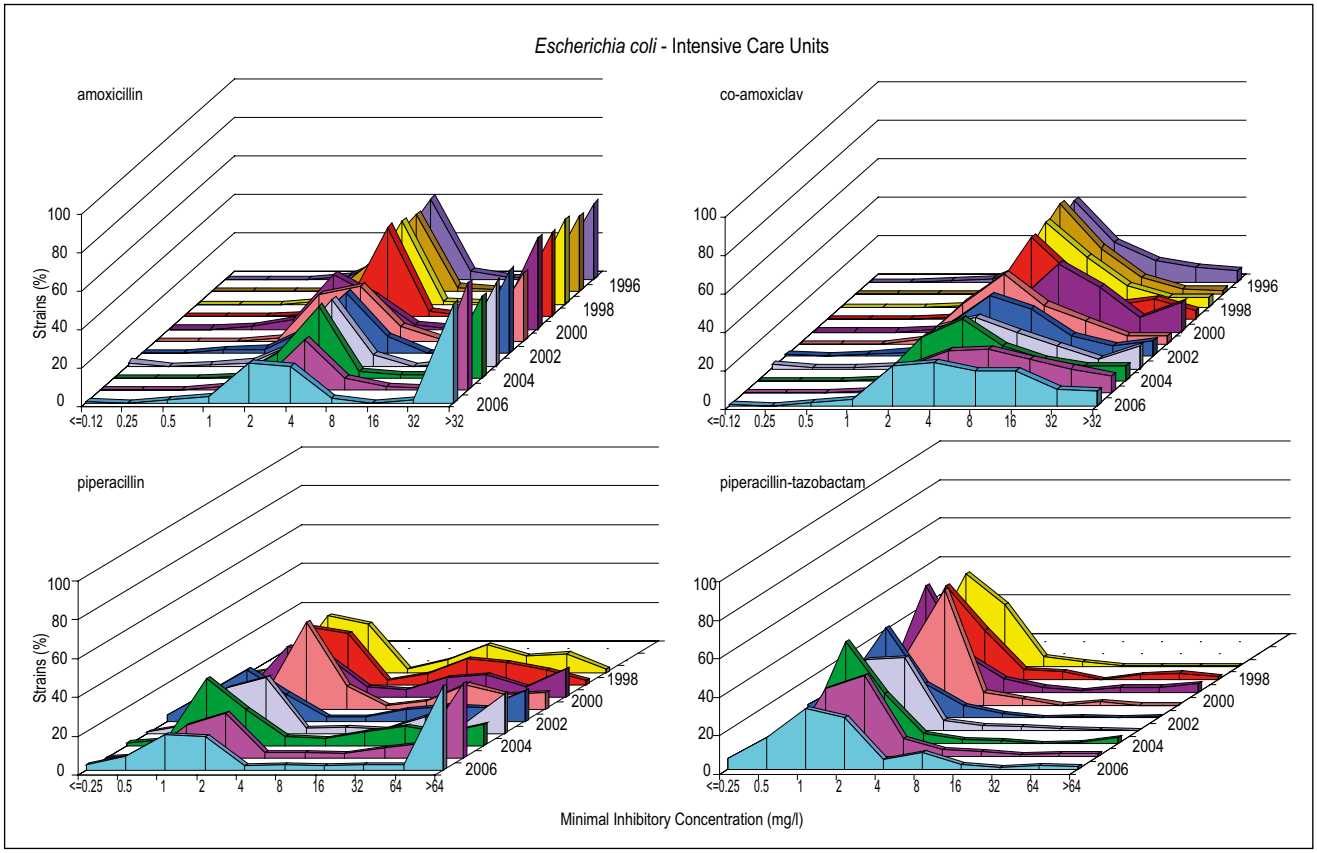


Figure 10. Trends in resistance to antibiotics among *Escherichia coli* from Unselected Hospital Departments, Intensive Care Units and Urology Services.

Figure 11. MIC distributions of beta-lactam antibiotics for *Escherichia coli* from Intensive Care Units.



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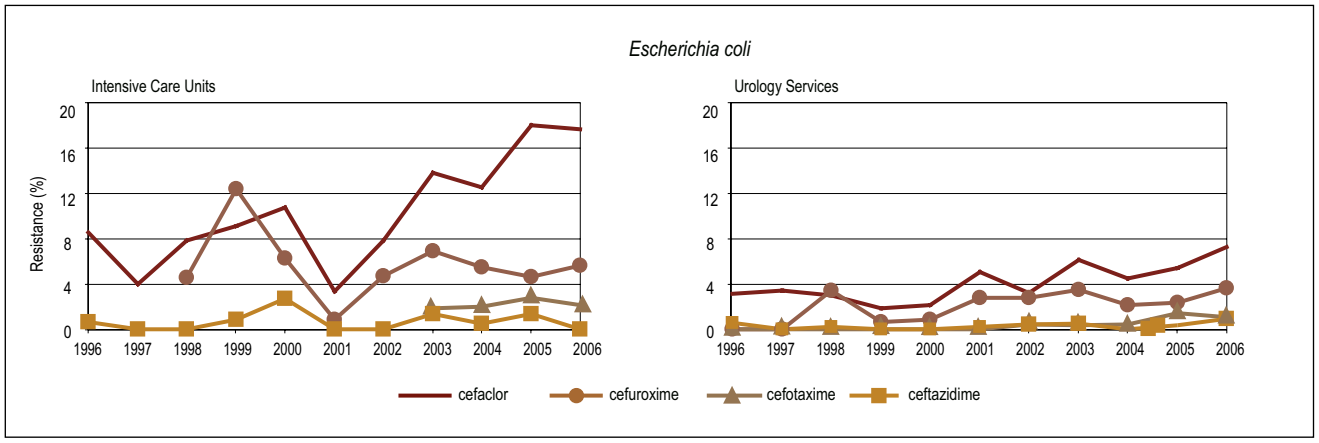
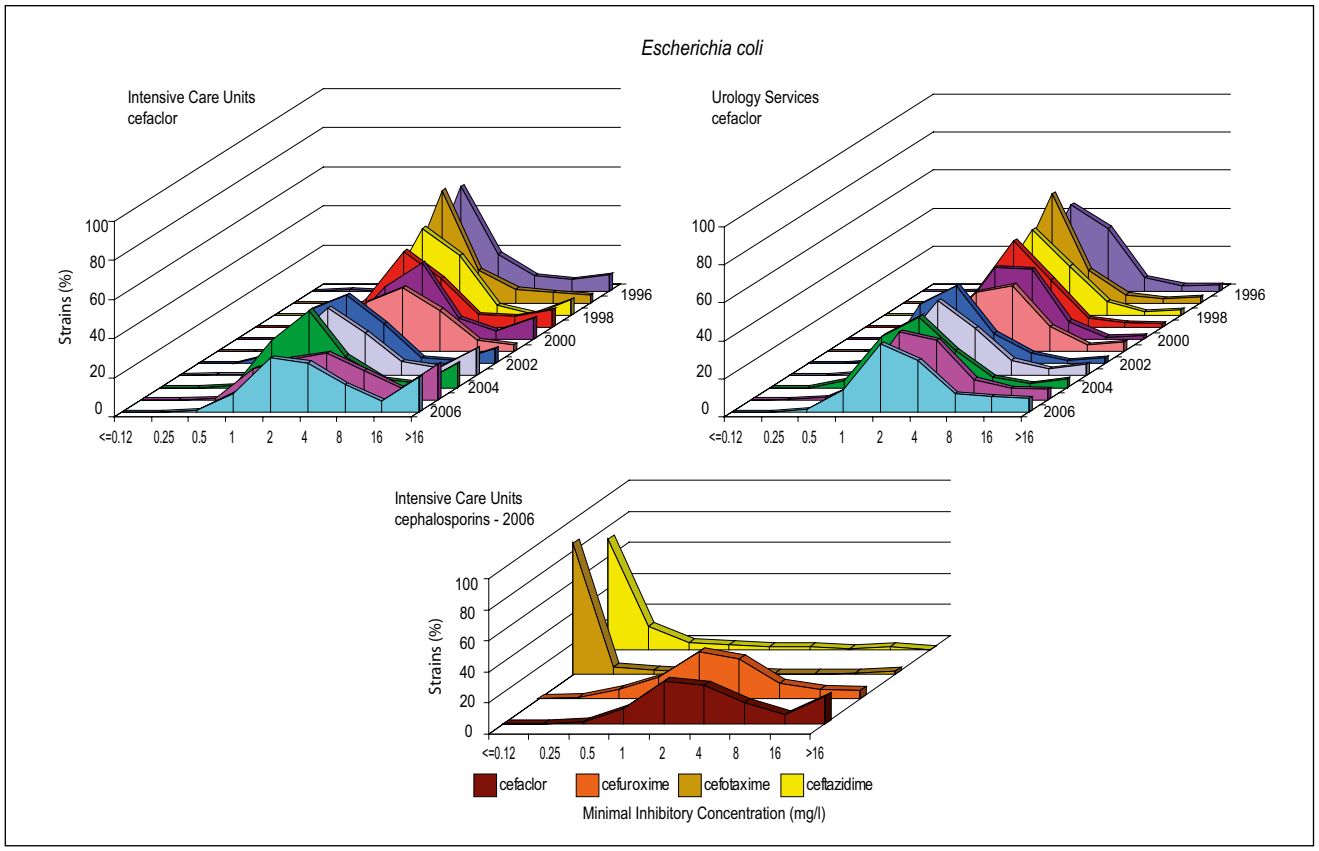


Figure 12. Trends in resistance to cephalosporins among *Escherichia coli* from Intensive Care Units and Urology Services.

from moderately susceptible to resistant. Then the shape of the distribution became bimodal. Piperacillin showed higher activity than amoxicillin towards the same subpopulation: the peak of MICs of piperacillin in the susceptible range was at 1-2 mg/l, that of amoxicillin at 2-4 mg/l (figure 11). Resistance to piperacillin-tazobactam was still exceptional (1.3% in 2006). The MIC distribution of piperacillin-tazobactam showed an almost complete disappearance of populations resistant or intermediate to piperacillin alone, but here less-susceptible strains with MICs 8-16 mg/l also emerged.

Ceftazidime-resistance in Unselected Hospital Departments was very low, but showed an increasing trend, being less than 1% until 2003, but 2% in 2007. The overall level in the Intensive Care Units and Urology Services was less than 1% and showed no increase. Intensive Care Units had consistently higher resistance rates for first and second generation cephalosporins than Urology Services (figure 12). Overall these increased in both departments, but more rapidly in Intensive Care Units. Cefaclor showed the highest resistance rate: increase from 8% in 1996 to 18% in 2005 and 2006 in Intensive

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



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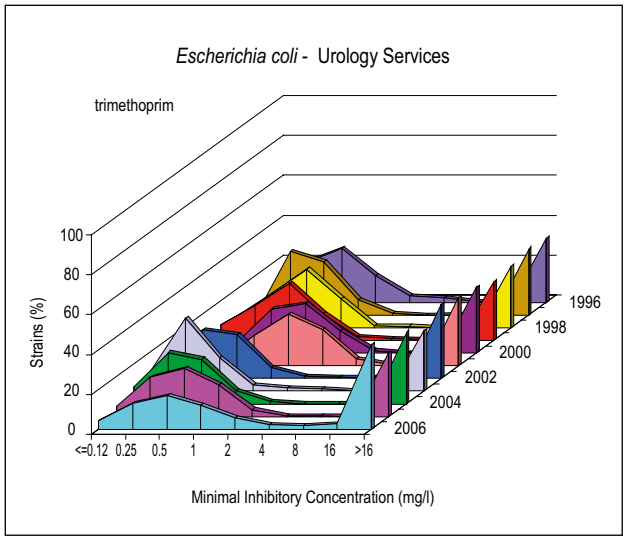


Figure 14. MIC distributions of trimethoprim for *Escherichia coli* from Urology Services.

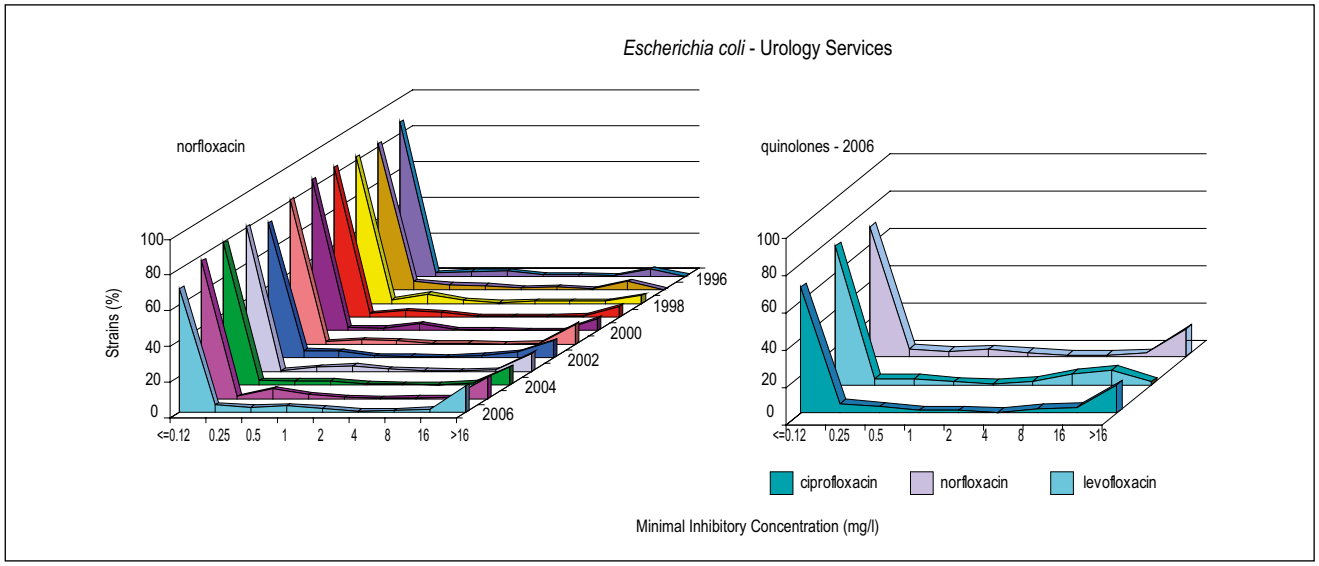
Care Units versus 3-7% in Urology services (figure 12). The MIC distribution of cefaclor in 2006 (figure 13) was almost unimodal over a broad range during 1996 and 1997 with a number of strains with an MIC just below the breakpoint of susceptibility and an MIC_{90} of 8-16 mg/l until 2000. From 2000 on highly resistant strains appeared, resulting in a bimodal shape of the curves with 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 13) showed a unimodal shape over a broad range (only shown for 2006), while 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 10). The level of trimethoprim-resistance in Intensive Care Units fluctuated around 20-25% until 2004, but in 2005 a sharp increase to 40% was found, which stabilized in 2006. The level of resistance in Urology Services was always significantly higher than in Intensive Care Units, it increased from 33% in 1996 to 45% in 2006. The MIC distribution (figure 14) showed that two subpopulations existed: one susceptible and one highly resistant. Co-trimoxazole-resistance followed this trend and was only 1-2% lower.

Nitrofurantoin-resistance fluctuated between 2-7% in Unselected Hospital Departments, equal to the figures in the community. Until 2000 the resistance level was around 2%. An increase to 7% was found in the following four years; from 2004 on it decreased to 2-4%. This pattern was also observed in Intensive Care Units: low resistance until 2000, then a slow increase to a mean of 6% until 2005 and a decrease to 3% resistance in 2006 (figure 10). The resistance level among strains from Urology Services was always higher; it fluctuated from 2-9%, with 7% resistance in 2006.

Ciprofloxacin-resistance increased steadily among *E. coli* from Unselected Hospital Departments, slowly during the first six years from 1-3%, then more rapidly during the next six years: from 3% in 2001 to 9% in 2007. This trend was also observed in the Intensive Care Units (figure 10). The resistance level in Urology Services however increased more rapidly from 4% in 1996 to 7% in 2000 and 16% in 2006. The resistance percentages and the MIC distributions of norfloxacin, levofloxacin and ciprofloxacin were similar (figure 15). 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 15. MIC distributions of quinolones for *Escherichia coli* from Urology Services.



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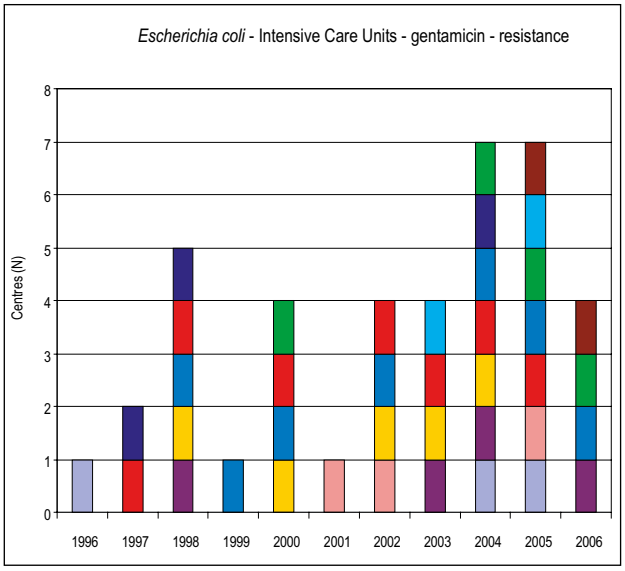
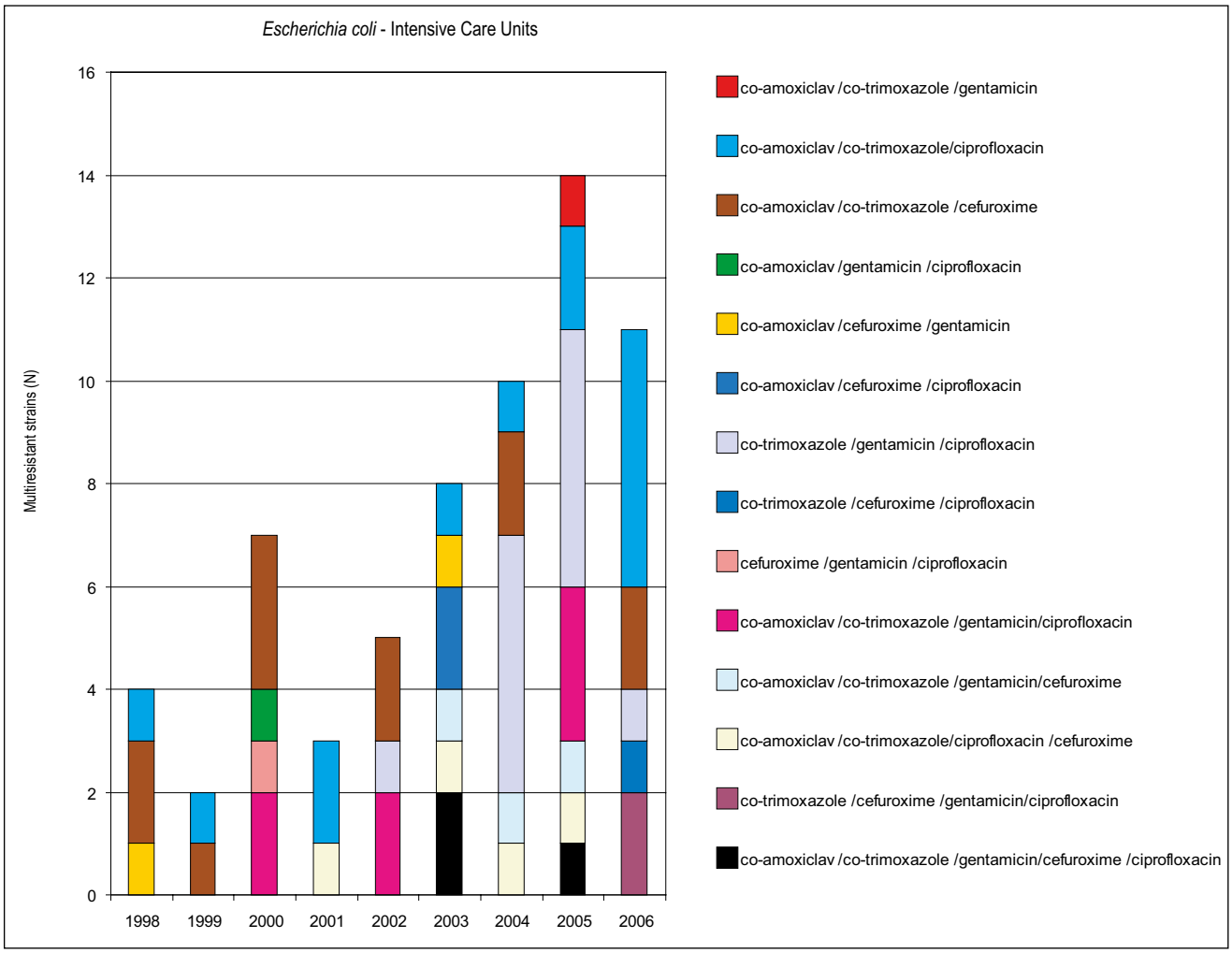


Figure 16. Number of centres with gentamicin-resistant *Escherichia coli* strains on Intensive Care Units. Each color represents one specific centre.

figure) and a small subpopulation of strains with MIC of >2 mg/l. 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 all from 2005 on. 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 3.5% in 2007, the resistance level in Intensive Care Units and Urology Services fluctuated between 2-5 % over the whole study period (figure 10). We found an overall 7% resistance in Intensive Care Units in 2005. This mean rate of gentamicin-resistance was associated with an unusual high resistance level in some centres (up to 15%), but in other centres gentamicin-resistant strains were rarely observed (figure 16). The number of centres with gentamicin-resistant strains (MIC >8 mg/l) varied considerably, only one centre in 1996, 1999 and 2001, but seven centres in 2004 and 2005. Three centres never had any resistant strains. Resistance was not associated with certain centres. There

Figure 17. Trends in multiresistance among *Escherichia coli* from Intensive Care Units.



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was no real national trend. This underlines the importance of local surveillance of resistance.

Multiresistance of *Escherichia coli* in Intensive Care Units

Resistance to three or more groups of antibiotics (multiresistance) in Intensive Care Units was recorded for various combinations, mostly at low levels. A total of 64 multiresistant strains were isolated from 1998 to 2006. 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 combination increased over the years (figure 17). Before 2000 only resistance to a combination of three antibiotics was found, thereafter resistance to four antibiotics or five antibiotics (from 2003 on) were recorded. Resistance to three antibiotics increased from 2% in 1998 and 1999 to 6% in 2005 and 5% in 2006. Resistance to the combination co-amoxiclav / co-trimoxazole + another drug was prevalent. The other drugs were cefuroxime, ciprofloxacin or gentamicin or a combination of them. Multiresistance to the combination co-amoxiclav / co-trimoxazole / ciprofloxacin was found yearly since 1998 (0.5 – 2% of the *E. coli* strains collected each year). Resistance to the combination co-amoxiclav / co-trimoxazole / cefuroxime emerged in 1998 and was demonstrated in 1-2% of the strains yearly thereafter, except in 2000, but since 2001 the resistance to this combination was expanded with resistance to ciprofloxacin as well.

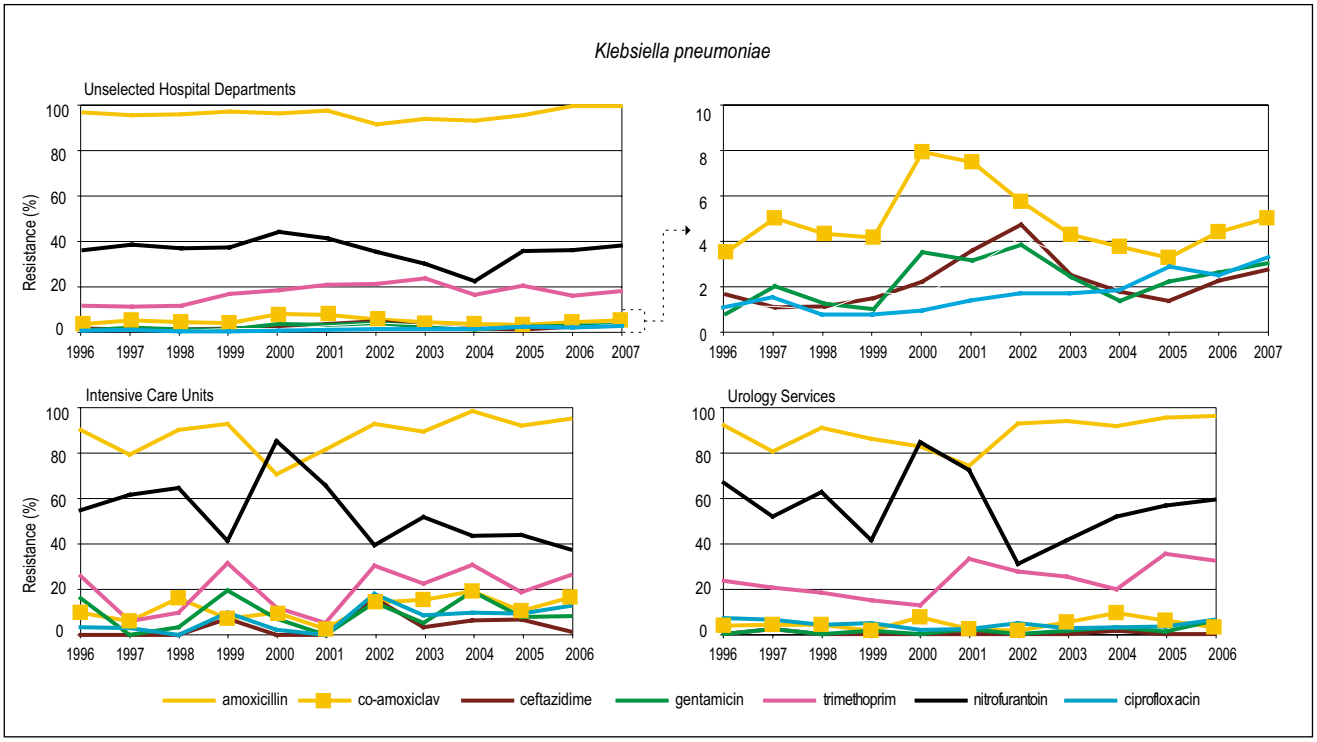
Similar observations were done with the co-trimoxazole combinations (others than those with co-amoxiclav). Resistance to the combination co-trimoxazole / gentamicin / ciprofloxacin emerged in 2002 in 1% of the isolates; it was observed in 2.5% in 2004 and 2005 and decreased to 0.5% in 2006. Resistance to five antibiotics was exceptional: two strains emerged in 2003, one in 2005, all in three different centres.

Klebsiella pneumoniae

Co-amoxiclav-resistance in *K. pneumoniae* from Unselected Hospital Departments was as low as that of *E. coli* (3-7%), it fluctuated but did not increase (figure 18). Co-amoxiclav-resistance in Intensive Care Units fluctuated at a much higher level (4-19%), but the trend was increasing from 8% in 1996 to 16% in 2006. Co-amoxiclav-resistance in Urology Services was similar to that in Unselected Hospital Departments.

Resistance to first- and second generation cephalosporin fluctuated in both Intensive Care Units and Urology Services. Resistance to cefaclor increased from 6% in 1996 to 18% in 2006 (figure 19). The trend showed an overall increase in resistance from 5% to 14% (figure 19). Cefuroxime-resistance did not change; it was around 6% with some fluctuations. 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. 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

Figure 18. Trends in resistance to antibiotics among *Klebsiella pneumoniae*.



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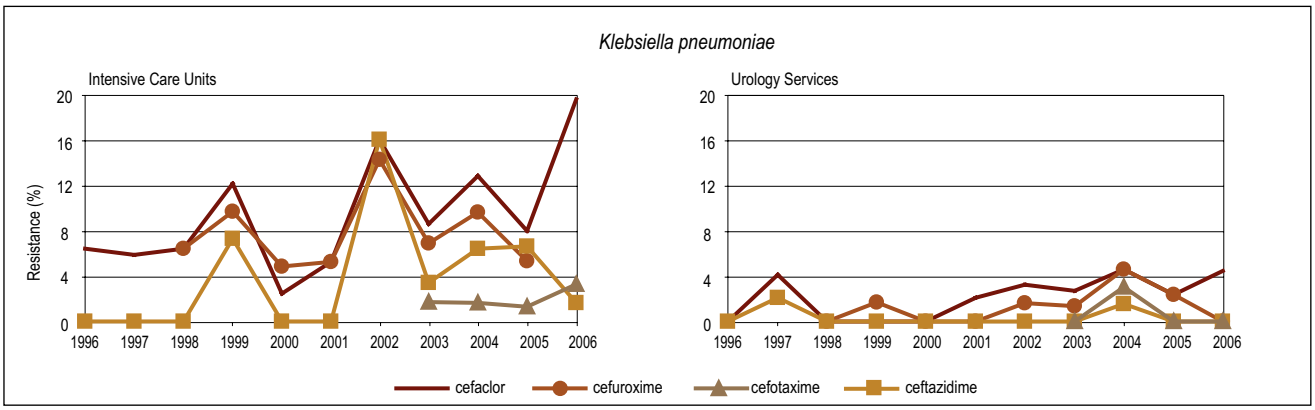


Figure 19. MIC distributions of cephalosporins for *Klebsiella pneumoniae* from Intensive Care Units and Urology Services.

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, 6% in 2004 and 2005 and again only 2% in 2006. Cefotaxime-resistance was 3% in 2006.

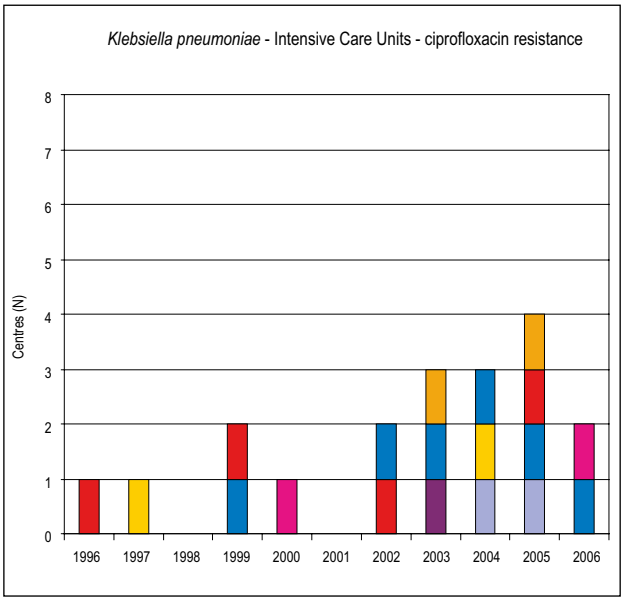
Trimethoprim-resistance increased with some fluctuations in Unselected Hospital Departments from 11% in 1996 to 18% in 2007 (figure 18). The level of resistance in Intensive Care Units fluctuated around 20%, but the trend indicated an increase from 14% in 1996 to 25% in 2006. In Urology Services an increase of resistance to around 35% was observed in 2005 and 2006. 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 23% in Intensive Care Units and 30% in Urology Services in 2006 (not shown). Co-trimoxazole is an alternative drug combination for Klebsiella infections in Intensive Care Units and it is often used for complicated urinary tract infections in Urology Services and Paediatrics. Reconsideration for use in these settings is wanted in view of these high resistance levels found.

Nitrofurantoin-resistance fluctuated in Unselected Hospital Departments (21-40%) (figure 18). The level of resistance in Intensive Care Units and Urology Services in 2006 was 38% or more.

Gentamicin-resistance was low and at a constant level (1-3%) in Unselected Hospital Departments (figure 18). Like ceftazidime *K. pneumoniae* strains resistant to gentamicin were not common. Gentamicin-resistant strains 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 and 2006 of 8%. Gentamicin-resistance in Urology Services was rare.

Ciprofloxacin-resistance among *K. pneumoniae* in Unselected Hospital Departments increased slowly, being lower than 1% until 2001, 1-2% from 2002-2004 and 3.5% in 2007 (figure 18). Ciprofloxacin-resistance had a sporadic character in Intensive Care Units and Urology Services and did not spread: resistant strains were found in 2-4 Intensive Care Units each year since 2000 (figure 20) and 2-3 Urology Services each year. The resistance levels in these centres exceeded sometimes 35%. The overall resistance level in Intensive Care Units increased from 3% in 1996 to 12% in 2006, but these percentages do not describe the rate of ciprofloxacin-resistance among *K. pneumoniae* in all Intensive Care Units in the Netherlands. So resistance should be surveyed locally. Multiresistance in Intensive Care Units was recorded in 3-13% of the strains isolated from 1998 on (figure 21). No real trend could be observed. Multiresistance was sporadic in six centres, the combination co-amoxiclav /

Figure 20. Number of centres with ciprofloxacin-resistant *Klebsiella pneumoniae* strains on Intensive Care Units. Each color represents one specific centre.



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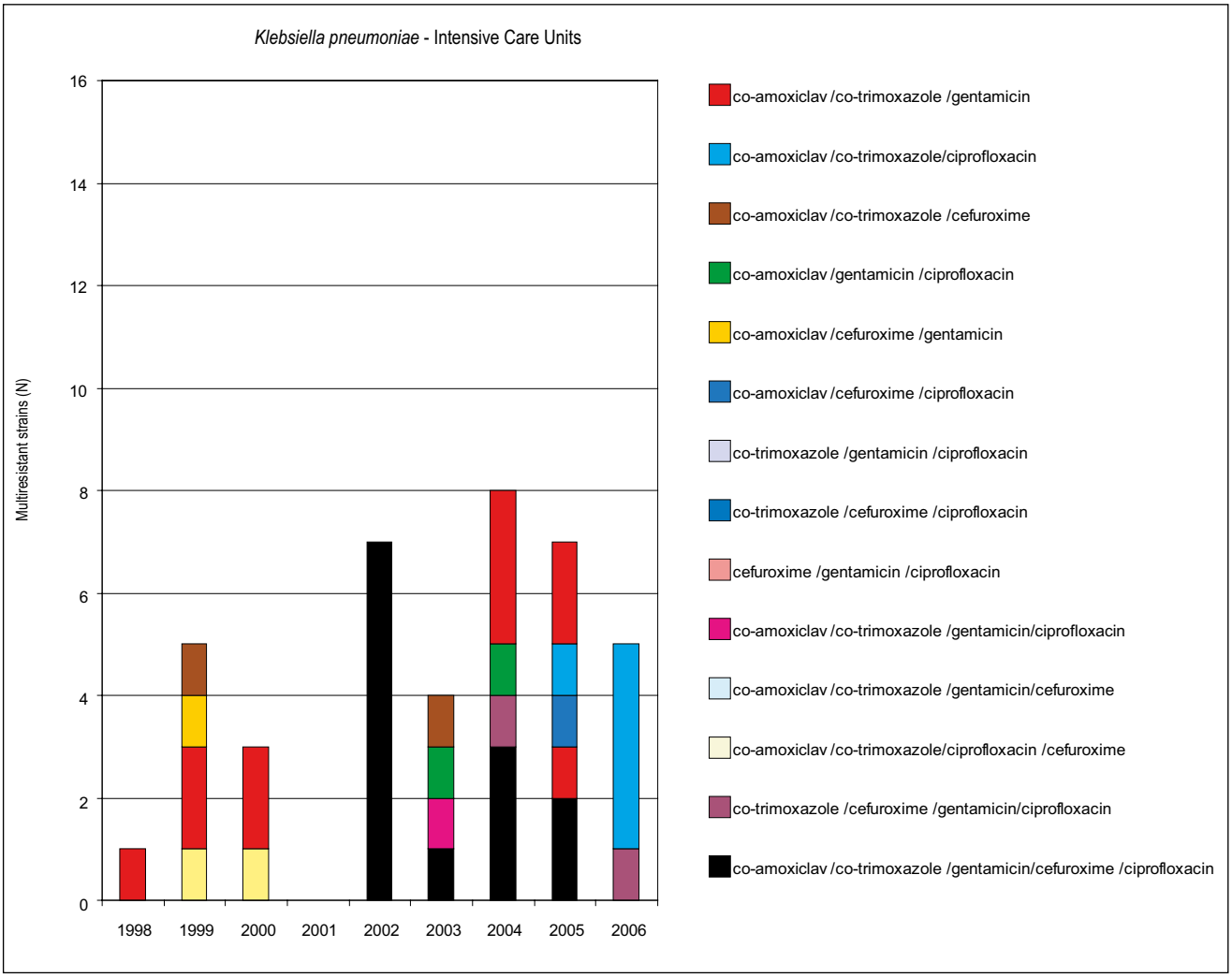


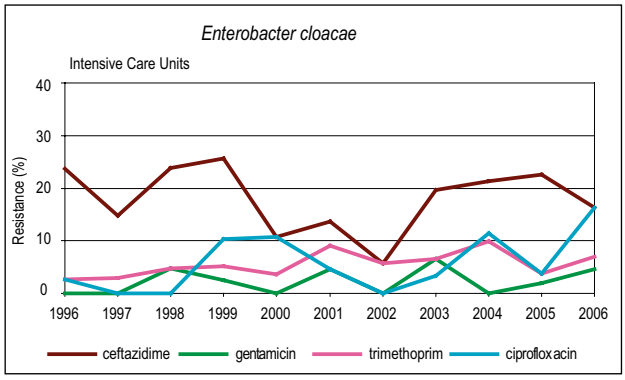
Figure 21. Trends in multiresistance among *Klebsiella pneumoniae* from Intensive Care Units.

co-trimoxazole / gentamicin and the combination co-amoxiclav /co-trimoxazole / ciprofloxacin were most often recorded. It was common in one Intensive Care Unit where most Klebsiella strains showed combined resistance to co-amoxiclav, cefuroxime, co-trimoxazole, gentamicin and ciprofloxacin from 2002 on.

Enterobacter cloacae

Ninety percent or more of *E. cloacae* strains from Intensive Care Units were resistant to co-amoxiclav. Piperacillin-resistance fluctuated around 20%; resistance to the piperacillin/tazobactam combination was les than 10%. No real trend was observed during the study period. Meropenem-resistance was once found in 2003 (3%). Resistance to ceftazidime fluctuated also around 20% without a clear trend (figure 22). Cefaclor-resistance increased from 60% in 1996 to 91 % in 2006 (figure 23); cefuroxime-resistance fluctuated between 30-45%, which was somewhat higher than the level of cefixime-resistance ((21-38%) and the rate of ceftibuten-resistance (18-30%). The percentage of the isolates resistant to cefotaxime was similar to the percentage resistant to ceftazidime. Resistance to cefepime was less than 5% which is due to its stability to the chromosomal AmpC beta-lactamase. The MIC distribution of ceftazidime (figure 24) was bimodal and showed two populations: one suscepti-

Figure 22. Trends in resistance to antibiotics among *Enterobacter cloacae* from Intensive Care Units.



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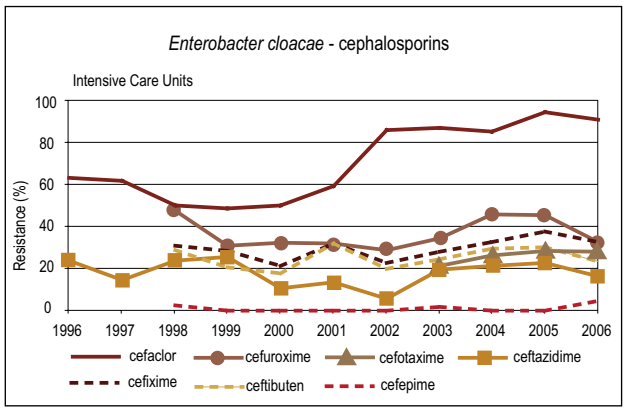
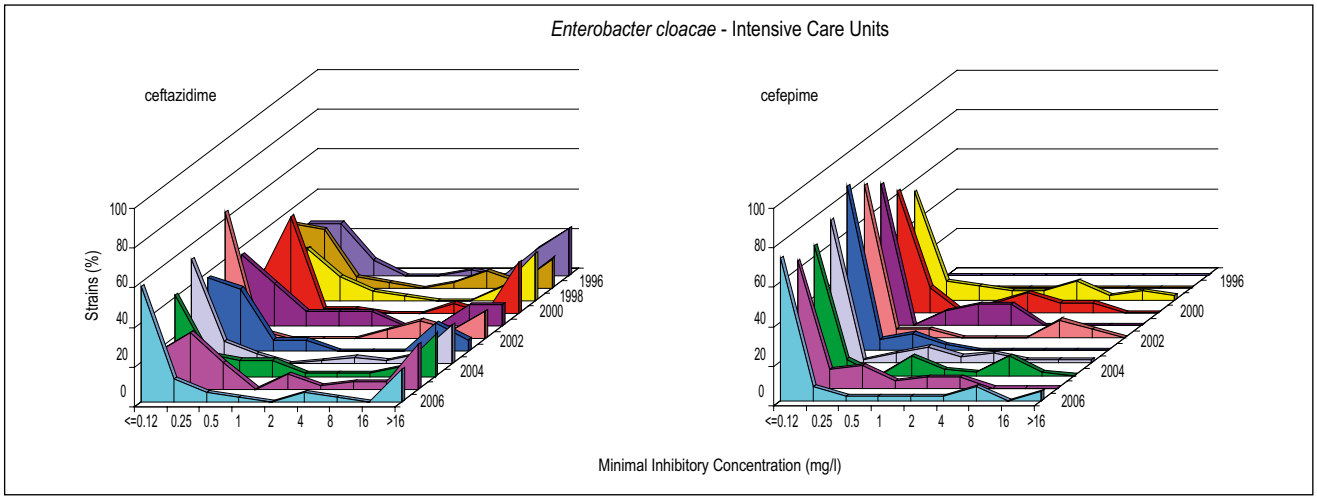


Figure 23. Trends in resistance to cephalosporins among *Enterobacter cloacae* from Intensive Care Units.

ble with MICs <0.12-2 mg/l and one resistant population with MICs >32 mg/l. In between, small populations with intermediate susceptibility were demonstrated. The MIC distribution of cefepime was not bimodal until 2006. It showed a susceptible population over a small range of MICs (<0.12-0.25 mg/l and existence of small populations with intermediate susceptibilities. In 2006 most intermediate-susceptible strains had disappeared and a small resistant population emerged, giving the picture a bimodal character. The presence of intermediate strains in such distribution may predict the move to resistant in the following years.
Trimethoprim-resistance fluctuated between 3-10% (figure 22).
Ciprofloxacin-resistance was 10% or less until 2006. Then a sudden increase to 16% resistance was observed.

Proteus mirabilis
Amoxicillin-resistance in Unselected Hospital Departments showed a steady increase, from 14% in 1996 to 24% in 2007. Amoxicillin-resistance in Intensive Care Units fluctuated highly. It was around 15-20 % until 2002, increased then to 45% in 2005, but dropped to 14% in 2006, the level of 2002 and before (figure 25). Amoxicillin-resistance was higher in Urology Services from the beginning (19%), and increased to 30% from 2003 on. The distribution of MICs of the strains from the Urology Services showed two subpopulations: a susceptible one and a resistant one with MICs >16 mg/l (figure 26). 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 moderately susceptible strains with MIC 16 mg/l emerged. In 2006 the distribution was clearly bimodal. 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), but in 2006 no co-amoxiclav-resistant strains were recorded. 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 26). In 2006 a small resistant population was observed.
Trimethoprim-resistance in *P. mirabilis* in Unselected Hospital Departments showed a significant increase from 27% in 1996 to 38% in 2007, equaling the levels found in Urology Services in 2006. The resistance level in Intensive Care Units increased rapidly from 28% in 2002 to 61% in 2005 (figure 25) and decreased to 19% in 2006.
Ceftazidime-resistance in *P. mirabilis* was less than 1%.
Gentamicin-resistance increased slowly in Unselected Hospital Departments to 4% in 2007. It had a sporadic character in Intensive Care Units and Urology Services.
Ciprofloxacin-resistance among *P. mirabilis* in Unselected Hospital Departments increased from 1-3% during the study period. The resistance level in Intensive Care Units remained low and sporadic.

Figure 24. MIC distributions of ceftazidime and cefepime for *Enterobacter cloacae* from Intensive Care Units.



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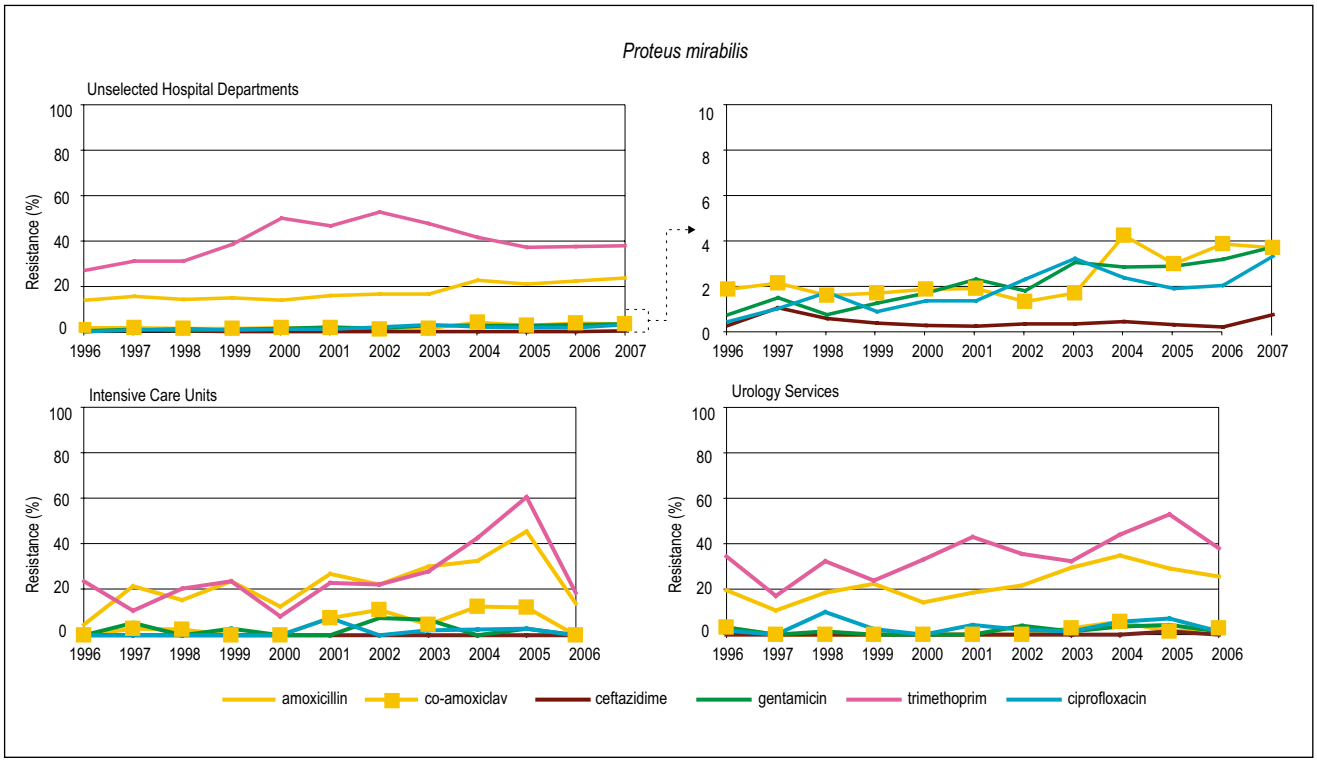
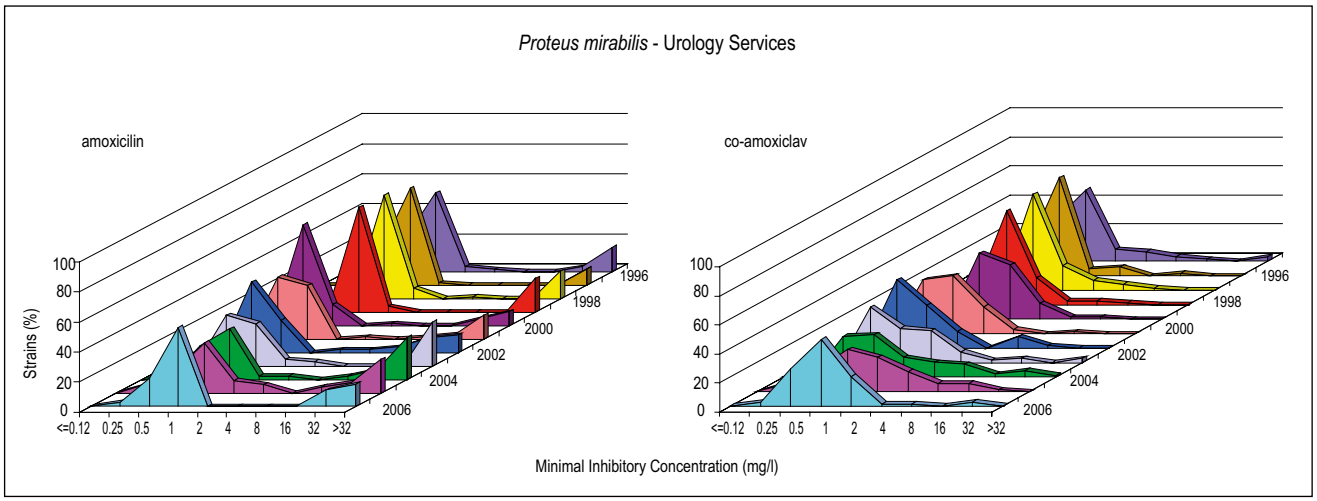


Figure 25. Trends in resistance to antibiotics among *Proteus mirabilis* from Unselected Hospitals, Intensive Care Units and Urology Services.

Pseudomonas aeruginosa

Ceftazidime-resistance among *P. aeruginosa* isolated in Unselected Hospital Departments and in Urology Services was consistently low (0-3%). Ceftazidime-resistance in Intensive Care Units remained below 2%. An incidental 10% resistance was recorded in 2002 (figure 27) because of an unusual high resistance rate in five centres. Piperacillin-resistance among *P. aeruginosa* isolated in Intensive Care Units was not found until 2000; then an increasing number of Intensive Care Units delivered resistant strains: two centres in 2000, five in 2002 and seven in 2003, 2005 and 2006. Resistant strains were permanently found in two centres and intermittently in nine centres; two centres had no piperacillin-resistant Pseudomonas strains. The proportion of resistant *P. aeruginosa* strains in the positive centres fluctuated between 20-30%. The overall percentage for all centres was calculated 4-14% from 2001 on (figure 27) without any trend. Piperacillin-resistance in Urology Services was accidental, fluctuating between 2-4%, affecting 2-3 centres in 2002-2004. The resistance to piperacillin/tazobactam followed that of piperacillin: it was found in two

Figure 26. MIC distributions of amoxicillin and co-amoxiclav for *Proteus mirabilis* from Urology Services.



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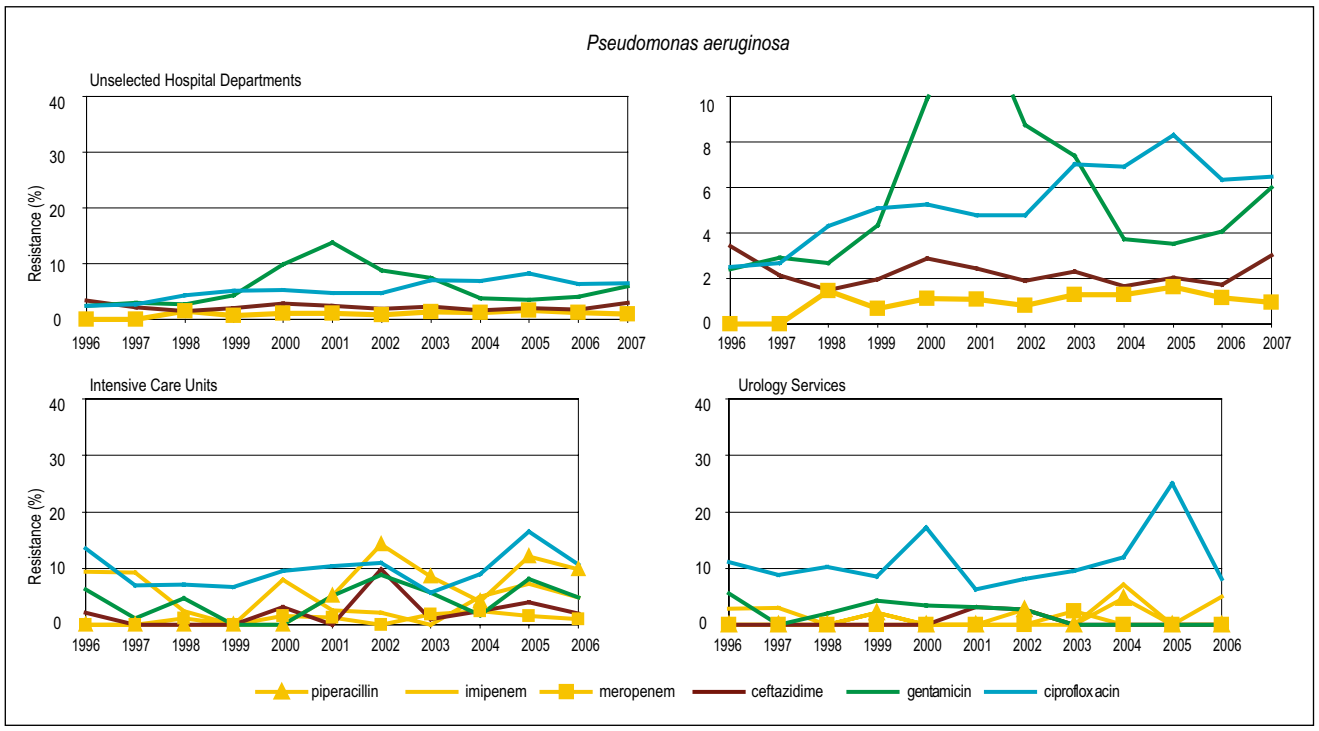
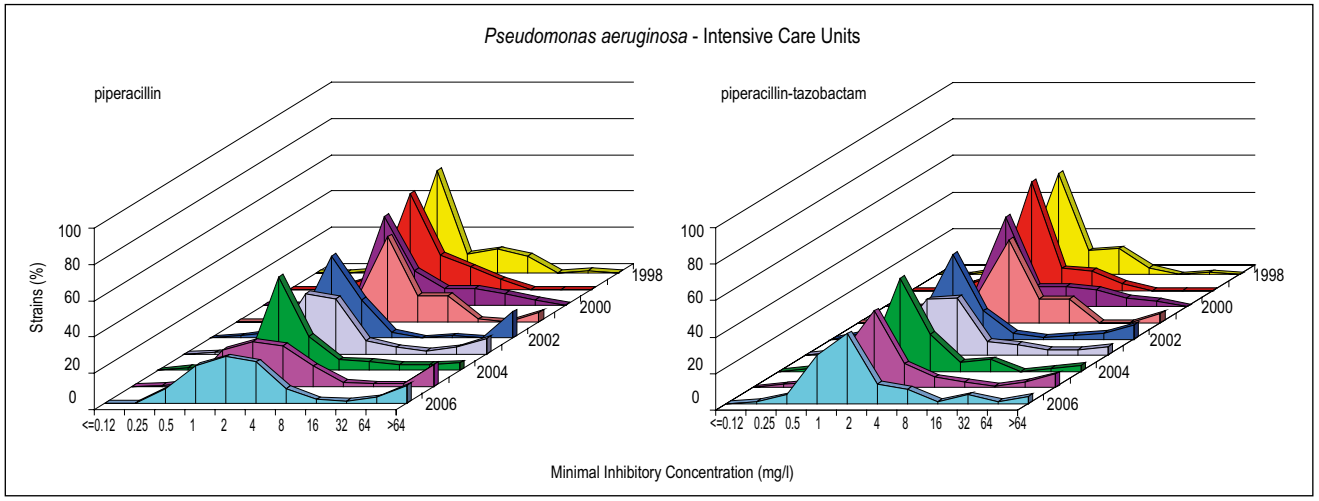


Figure 27. Trends in resistance to antibiotics among *Pseudomonas aeruginosa* from Unselected Hospitals, Intensive Care Units and Urology Services.

centres in 2001 and six in 2006 (not shown). The MIC distributions of piperacillin and piperacillin/tazobactam are given in figure 28. 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 on the MIC distributions became bimodal, 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 the disappearance of the "shoulder". The same phenomenon was observed for piperacillin/tazobactam.

Gentamicin-resistance increased to 6% in 2007 in Unselected Hospital Departments. Gentamicin-resistance was found sporadically in some Urology Services. Resistance was found yearly in one to six Intensive Care Units, responsible for the fluctuations in the overall resistance rate from 2-8%. Amikacin- and tobramycin-resistance were 4% and 6% respectively in 2006. The MIC distributions of the three aminoglycosides are presented in figure 29. 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

Figure 28. MIC distributions of piperacillin and piperacillin/tazobactam for *Pseudomonas aeruginosa* from Intensive Care Units.



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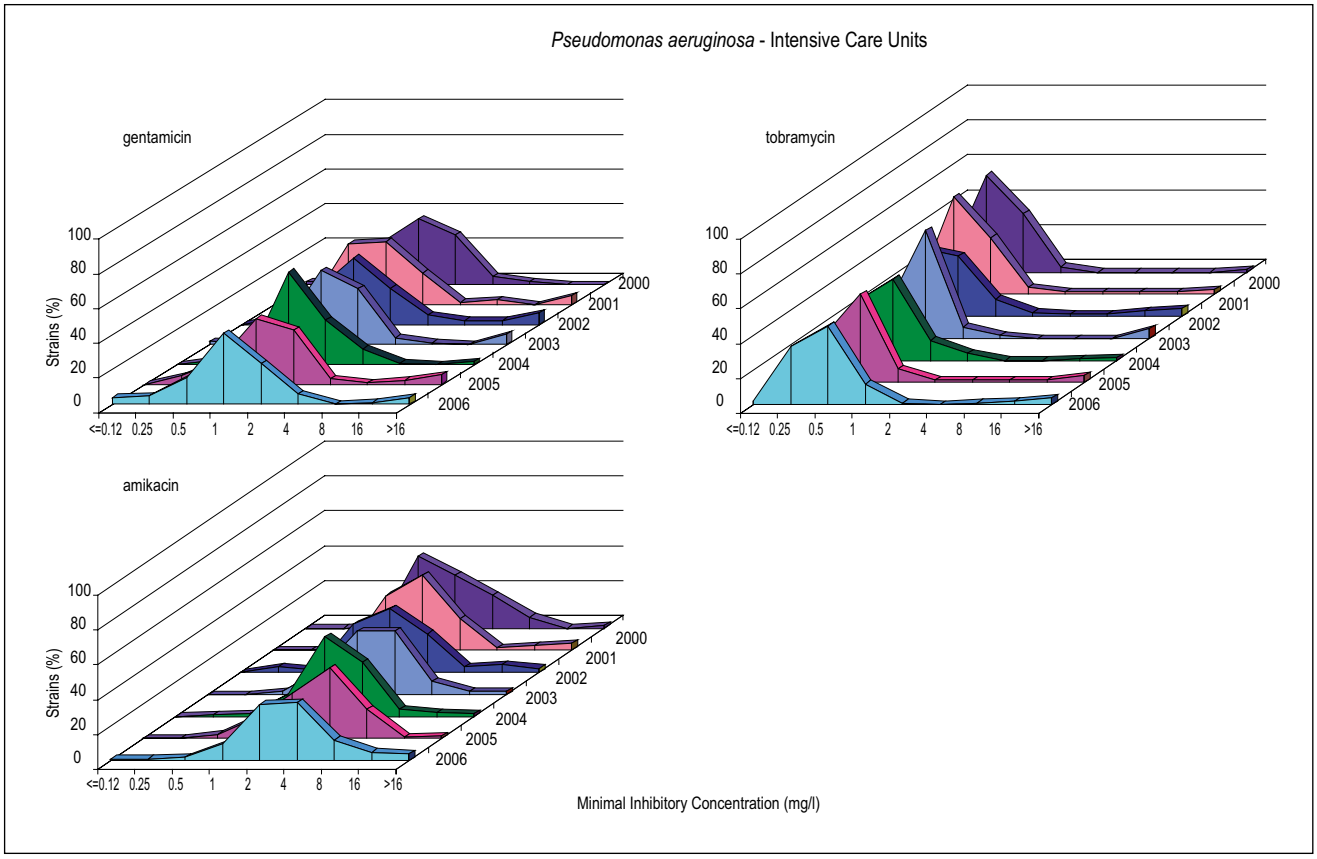


Figure 29. MIC distributions of aminoglycosides for *Pseudomonas aeruginosa* from Intensive Care Units.

gentamicin-resistant, but not always amikacin-resistant. Meropenem-resistance among *P. aeruginosa* remained lower than 2% in Unselected Hospital Departments and Intensive Care Units. It was found only once in Urology Services in 2003.

The prevalence of ciprofloxacin-resistance increased slowly in Unselected Hospital Departments: 2% in 1996 to 8% in 2005, then decreasing to 6% in 2006 and 2007 (figure 27). 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, increased in 2005 to 16%, but decreased again in 2006 to 11%. The trend in the Urology Services showed the same pattern: increasing until 2005 (23%) and then decreasing to 8% in 2006. Resistant strains have been found in all centres since 2005. The levels of resistance to levofloxacin paralleled those of ciprofloxacin.

Enterococcus faecalis

Before 2002 no amoxicillin-resistant *E. faecalis* were found in Intensive Care Units and Urology Services (figure 30). From 2002 on these strains have spread slowly over the country: one Intensive Care Unit was positive in 2002, two in 2003, four in 2004 and five in 2006. The resistance level fluctuated from 2-10%. The resistance in Urology Services fluctuated from 1-9% since 2002 and was found in a few centres: one in 2002, four in 2003, two in 2004 and one in 2006. 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 VanA gene positive strain. 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 30). It increased from 36% in 1996 to 66% in 2001 and decreased significantly thereafter to 24% in 2004 and 21% in 2005. Such levels were found consistently in Urology Services during the last ten years, but in 2006 resistance rose to 54%. The MIC distributions (figure 31) 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. The resistance rate in Urology Services was approximately 20% until 2003, it increased to 28% in 2004, but decreased to 18% in 2006 (figure 30). The shape of the MIC distribution of *E. faecalis* in Urology Services did

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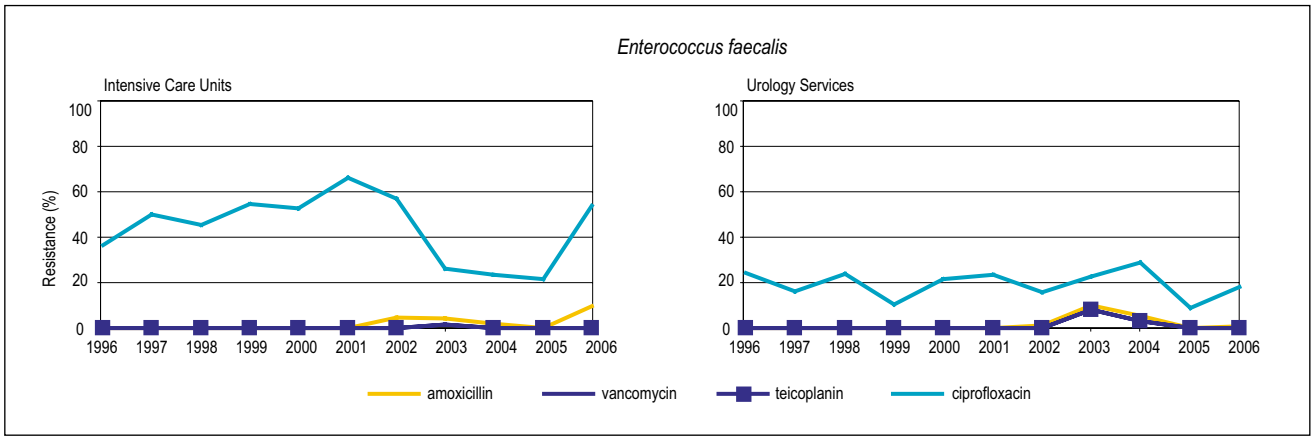


Figure 30. Trends in resistance to antibiotics among *Enterococcus faecalis* from Intensive Care Units and Urology Services.

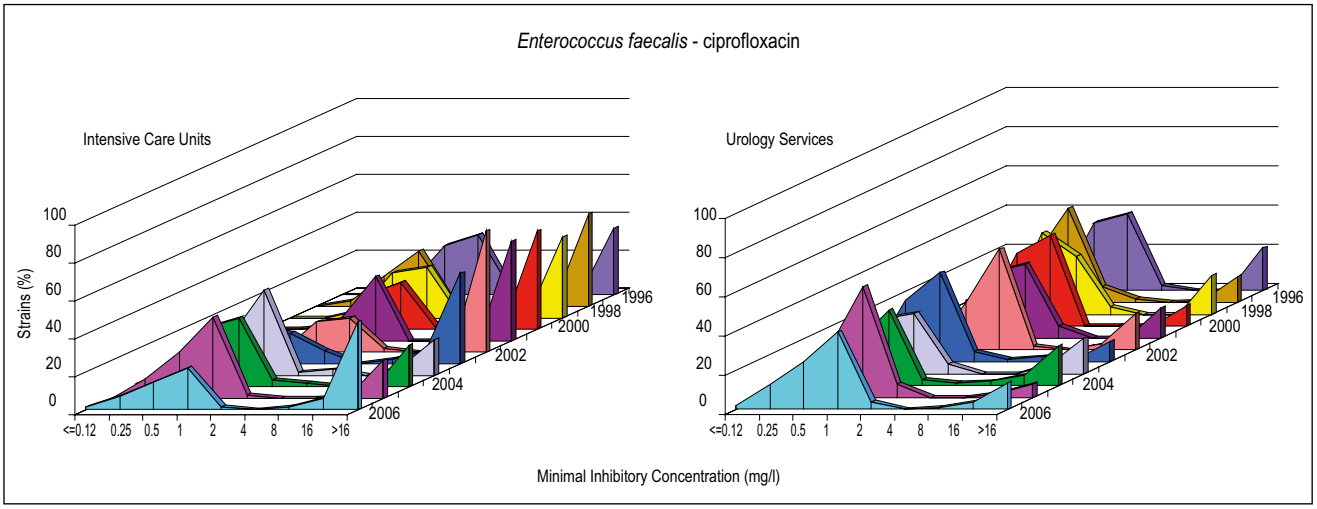
not change over the years, but the top of the susceptible cluster was also moving from 2 mg/l before 2001 to 1 mg/l from 2002 on (figure 31).

Staphylococcus aureus

In 2007 a total of 2733 MRSA isolates were forwarded to the National Institute of Public Health and the Environment (RIVM) for typing, which is an increase of 36% compared to 2006 (figure 32). The percentage of PFGE non-typeable (NT) strains was 29% in 2007 (14% in 2006). Ninety-two percent of new carriers of NT MRSA in hospitals participating in the study of Wassenberg et al. (in press) were detected by screening persons who had close contacts with pigs or calves as advised by the Dutch Working party on Infection Prevention since the second half of 2006. The remaining 8% of the NT MRSA was detected unexpectedly in routine clinical samples. A detailed epidemiological questionnaire was received for 1789 (65%) MRSA isolates. The proportion of persons who acquired MRSA abroad (through admission or work in a hospital abroad) was 9.1%. According to electronic surveillance (ISIS) 2.8% of the *S. aureus* strains isolated in the Netherlands in 2007, was MRSA, a 42% increase compared to 2006. The actual incidence of MRSA isolates per province in the Netherlands is reported at http://www.rivm.nl/mrsa.

Yearly a small number of MRSA were isolated from the Intensive Care Units (N = 24 from 1996-2006) and the Urology Services (N = 3 from 1996-2006) participating in the SWAB surveillance network. The overall percentage of MRSA in Unselected Hospital Departments increased to 2.8% in 2007, the percentage of MRSA in Intensive Care Units and Urology Services fluctuated between 0 and 4% from 1996-2006 without any trend (figure 33). Eleven out of 24 MRSA strains from Intensive Care Units were ciprofloxacin-resistant; three of them were also gentamicin-resistant. One of three strains from Urology Services was ciprofloxacin-resistant. Erythromycin-resistance in Unselected Hospital Departments was slowly increasing to 9% in 2006 and 2007. Clarithromycin-resistance among strains from Intensive Care Units increased from 9% in 2004 to 19% in 2005, but dropped in 2006 to 5%, comparable to the level of 2002 and earlier; the resistance rate in Urology Services

Figure 31. MIC distributions of ciprofloxacin for *Enterococcus faecalis* from Intensive Care Units and Urology Services.



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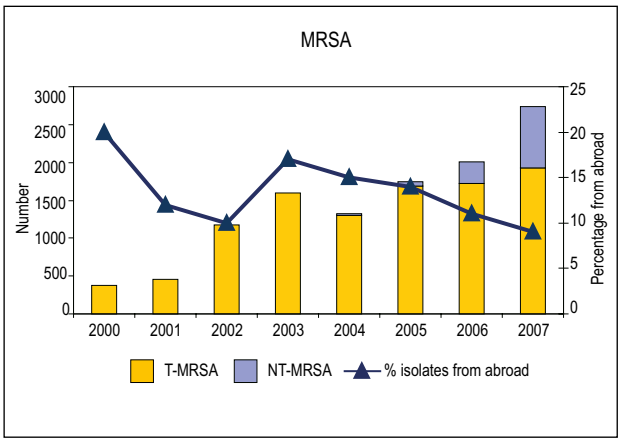


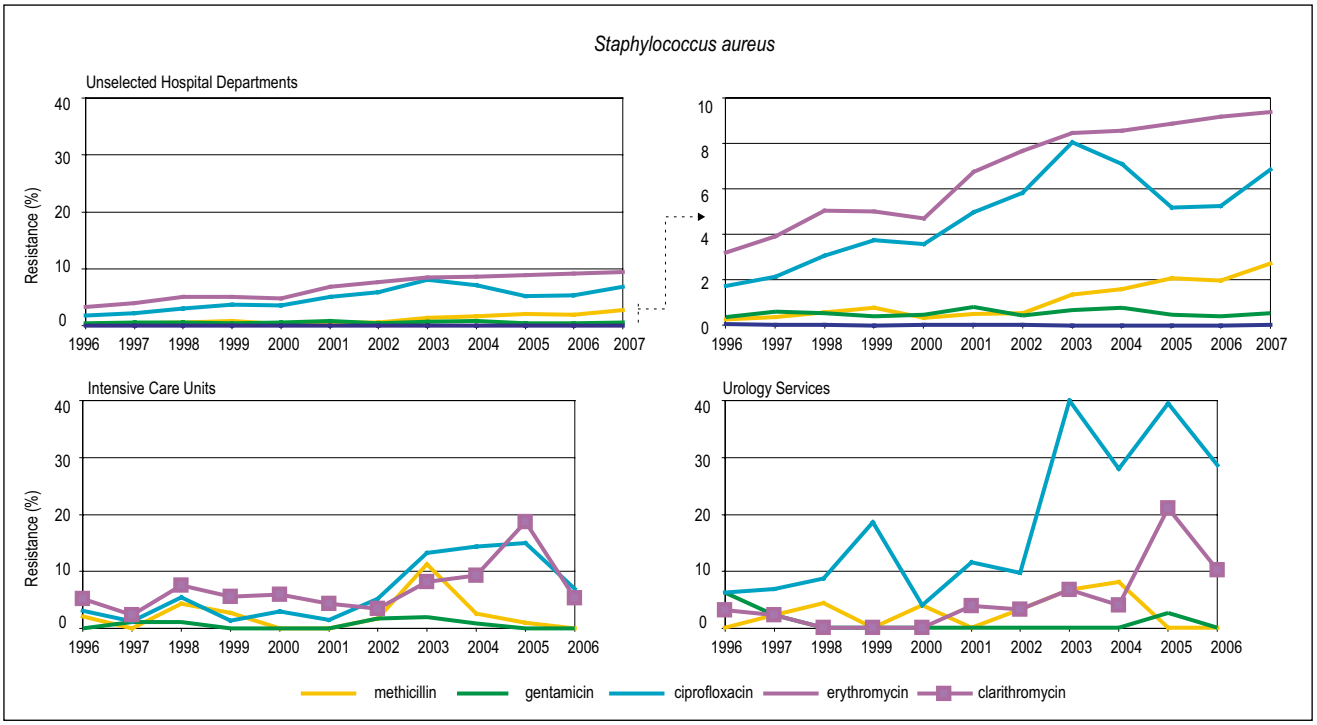
Figure 32. Numbers and origin of MRSA in The Netherlands.

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 7% in 2007 (figure 33). Resistance in Intensive Care isolates increased to 15% in 2005 and dropped to 7% in 2006. Strains from Urology Services showed high resistance rates from 2003 on, but the numbers of strains were very small (30 to 40 per year). Vancomycin-resistance was reported in 0.03% of the strains in 2007 in Unselected Hospital Departments (not confirmed). Vancomycin-resistant isolates were not found in the selected departments.
Gentamicin-resistance was 0.5% in Unselected Hospital Departments in 2006; it was sporadic in Intensive Care Units and Urology Services at levels of 0-2% during the whole study period.

Staphylococcus epidermidis

Methicillin-resistance (determined by oxacillin-resistance) was frequently found among hospital isolates of *S. epidermidis*. Methicillin-resistance in Unselected Hospital Departments reached 50% since 2004 (figure 34) and dropped to 42% in 2007. The number of *S. epidermidis* from Intensive Care Units in 2005 was low (23 strains). Ninety percent of 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 showed an increasing trend from 64% in 1996 to 70-80% from 1999 on. The MIC distribution was bimodal with a large cluster with MICs >16 mg/l and a very small cluster with MICs of 0.5 mg/l or less (figure 35). The peak of the susceptible cluster seems to move to higher MICs.
Gentamicin-resistance remained at a 55-65% level in Intensive Care Units. In contrast, the resistance to gentamicin in Unselected Hospital Departments was less than 30%. This may be explained by the existence of

Figure 33. Trends in resistance to antibiotics among *Staphylococcus aureus* from Unselected Hospitals, Intensive Care Units and Urology Services.



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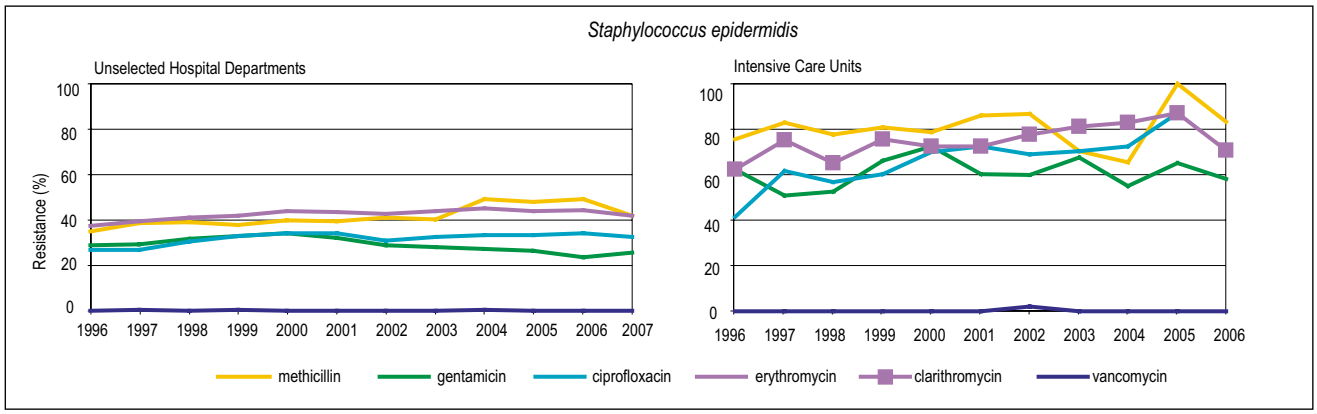
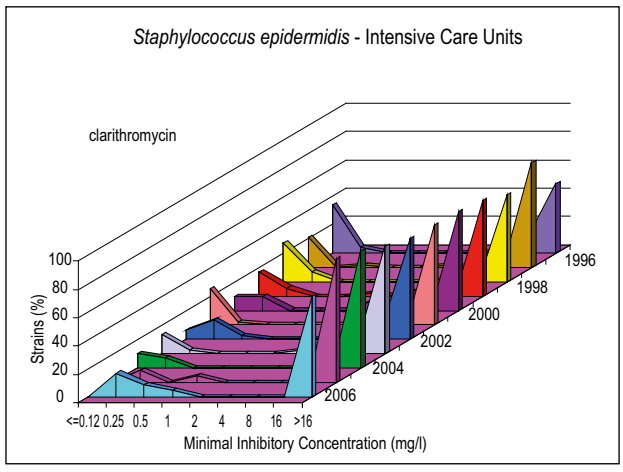


Figure 34. Trends in resistance to antibiotics among *Staphylococcus epidermidis* from Unselected Hospitals and Intensive Care Units.

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 result of high selective pressure in these wards. Often strains are circulating within these wards, colonizing many patients. Such populations may serve as a reservoir for multiresistance with the risk of exchange of resistance factors to other micro-organisms in the flora of patients and health care workers.
Ciprofloxacin-resistance in Intensive Care Units was much higher (60% or more) compared to that in Unselected Hospital Departments (33%).
Vancomycin-resistant strains were reported occasionally in Unselected Hospital Departments and once in one Intensive Care Unit in 2002. The vancomycin-resistant strain was also teicoplanin-resistant (MIC 256 mg/l).

Figure 35. MIC distributions of clarithromycin for *Staphylococcus epidermidis* from Intensive Care Units.



Streptococcus pneumoniae

Streptococcus pneumoniae strains non-susceptible to penicillin (intermediate plus resistant) are not often isolated in the Netherlands. Yet the trend was slowly increasing: the percentage was less than 1% in Unselected Hospital Departments until 1998; then it fluctuated between 1-2% until 2003, and increased to 2% in 2006 and 2007. The resistance rate in Pulmonology Services fluctuated at a higher level than that in the Unselected Hospital Departments until 2003 (5%); then it decreased to 2% in 2005 and 2006 (figure 36). The resistance to second and third generation cephalosporins remained at 6% or less during the study period with cefotaxime the most active against *S. pneumoniae* (figure 37). The MIC distributions for cefuroxime (figure 38) 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 small, but highly resistant (MIC >16 mg/l) subpopulation was observed, suggesting change to a bimodal shape of the distribution. This was not confirmed in 2006. Yet such observations induce alertness as such changes may predict the emergence of resistance in the next years.
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 7-10% both in Pulmonology Services and Unselected Hospital Departments from 2005 on respectively.
Ciprofloxacin-resistance in Unselected Hospital Departments fluctuated until 1999 between 10% and 26%; then a steady decrease was observed to a level of 4% in 2005 and 2006 with an increase to 16% in 2007. The ciprofloxacin-resistance rates (MIC ≤1 mg/l) in Pulmonology Services also showed large fluctuations, which cannot be read from the MIC distribution (figure 39). There no significant changes were observed. The fluctuations are method-dependant and are due to the ratio MIC and breakpoint. MICs of most pneumococci are 1-2 mg/l, which is at the breakpoint. Strains with MICs 2 mg/l for ciprofloxacin are recorded resistant; those with MICs 1

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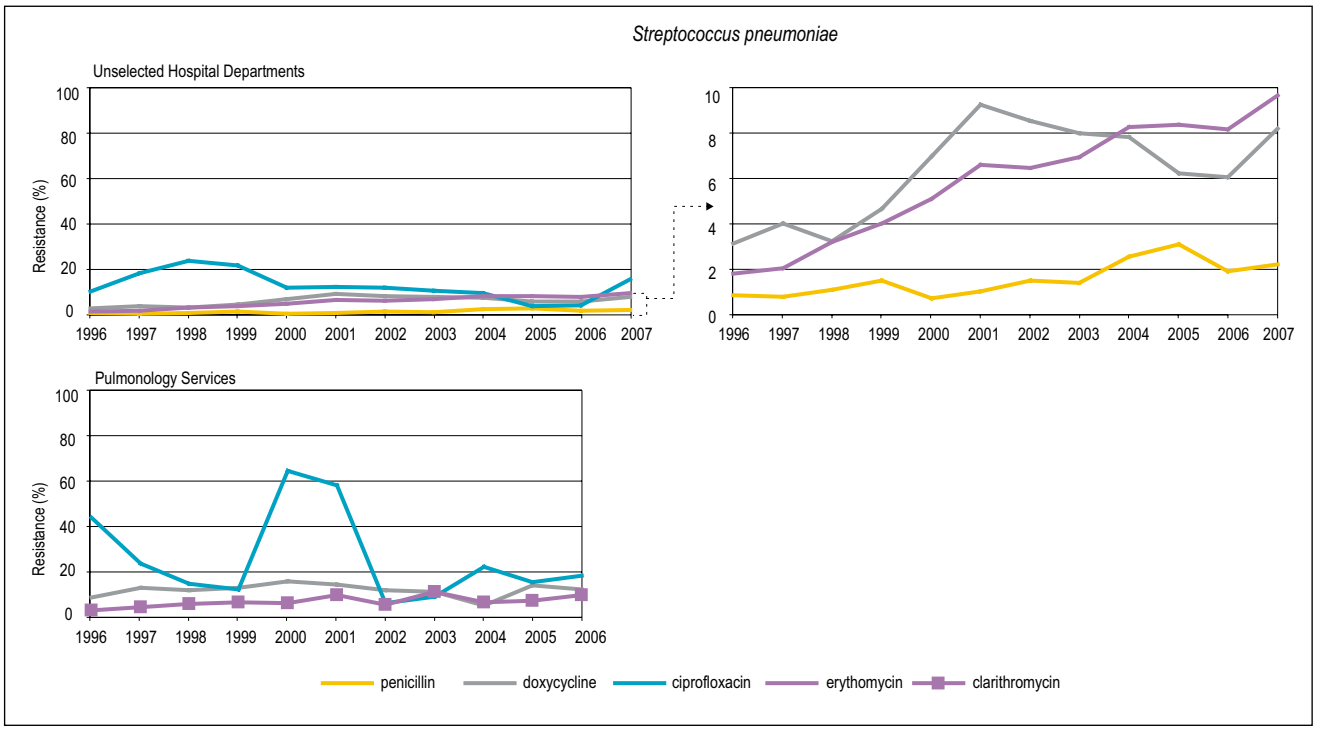


Figure 36. Trends in resistance to antibiotics among *Streptococcus pneumoniae* from Unselected Hospitals and Pulmonology Services.

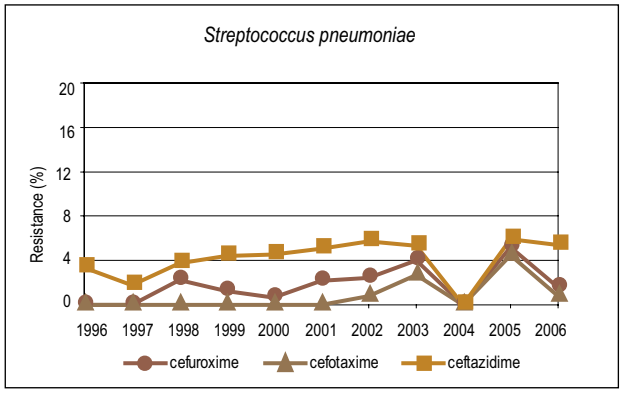


Figure 37. Trends in resistance to cephalosporins among *Streptococcus pneumoniae* from Pulmonology Services.

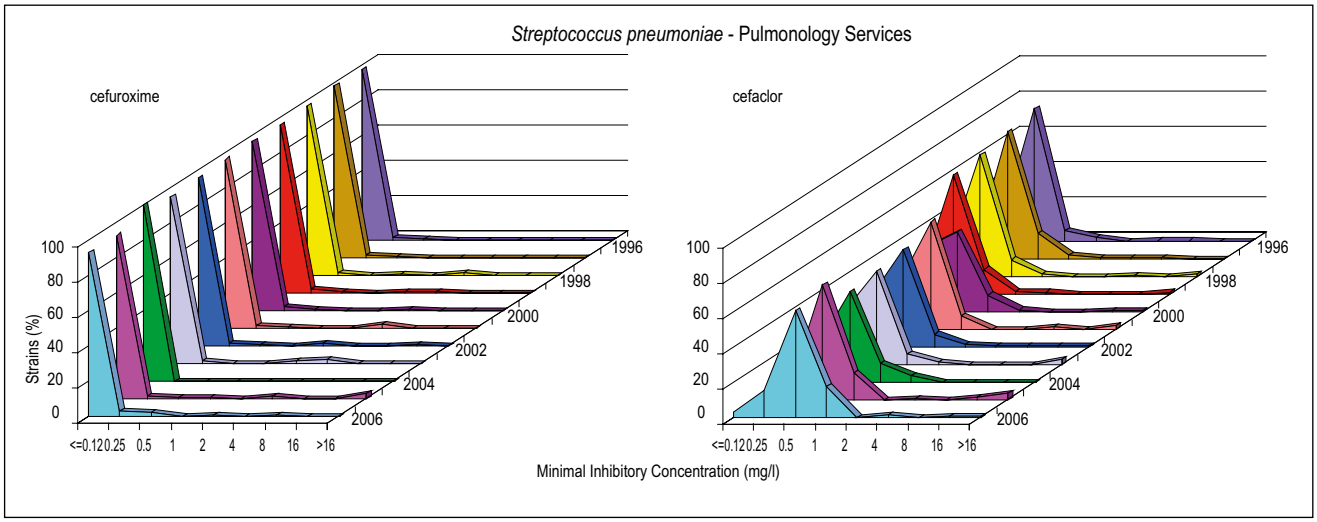


Figure 38. MIC distributions of cefaclor and cefuroxime quinolones for *Streptococcus pneumoniae* from Pulmonology Services.

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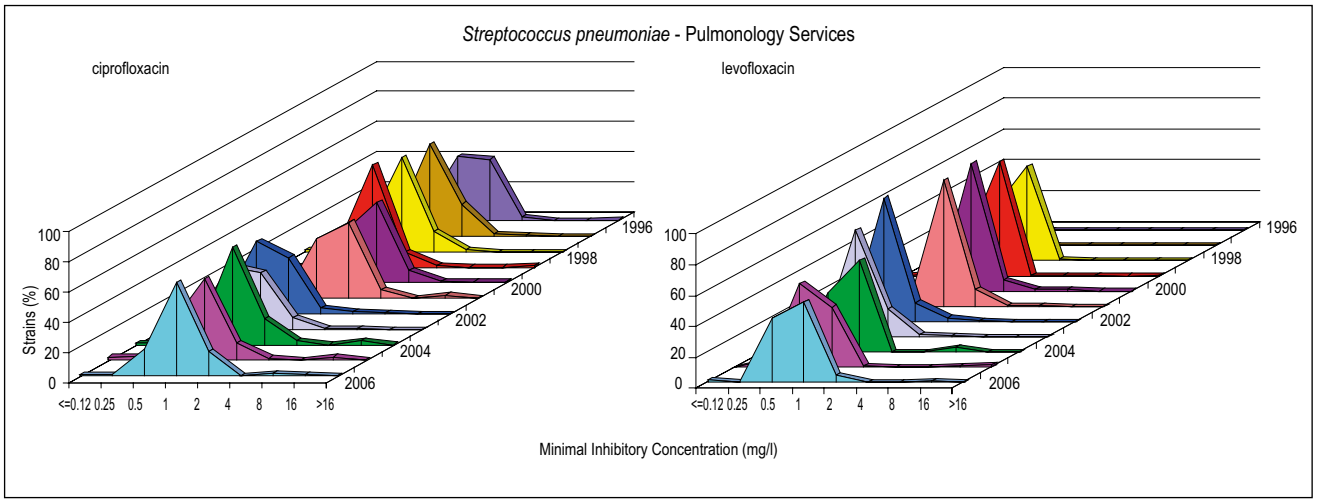


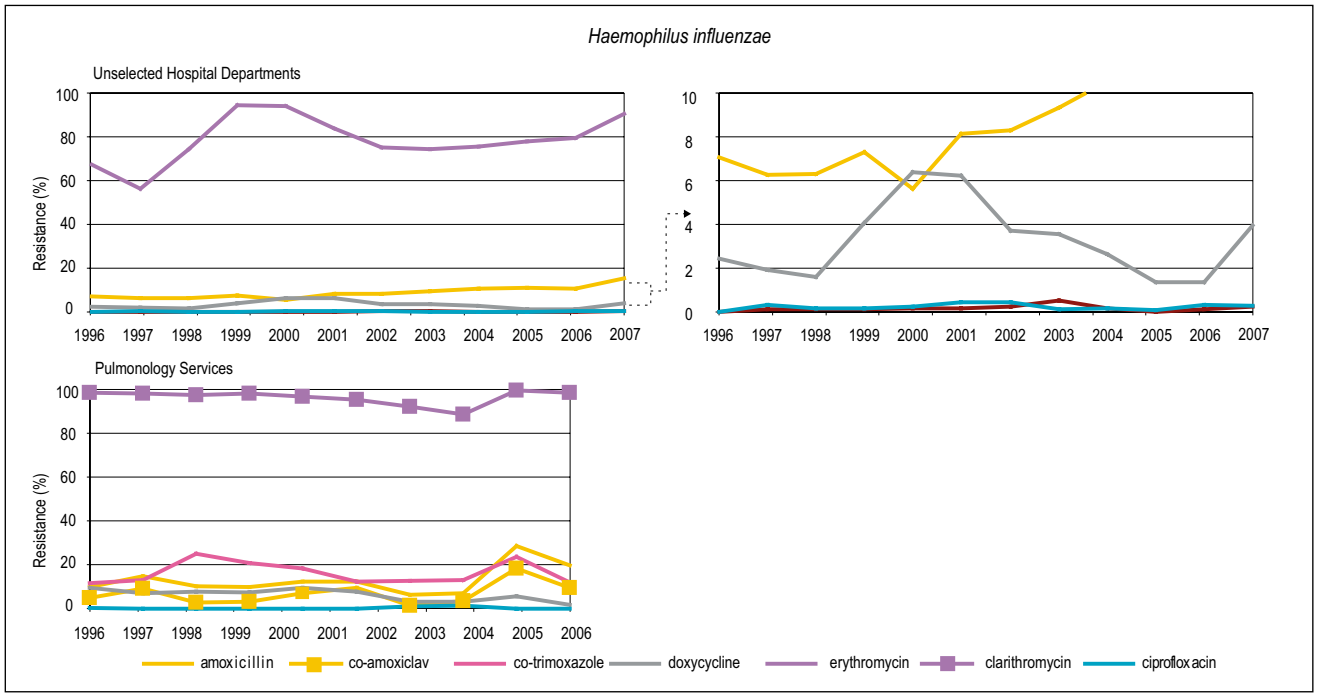
Figure 39. MIC distributions of quinolones for *Streptococcus pneumoniae* from Pulmonology Services.

mg/l are recorded susceptible. The variables within the micro-broth dilution method can easily induce a one-dilution step difference in the outcome of the test, which may categorize a pneumococcus susceptible on one day and resistant on the other day. This is nicely illustrated by the finding of the low resistance percentages of levofloxacin for the same strains which are also inhibited by 1-2 mg/l of levofloxacin but for which the breakpoint is one dilution step higher. So all strains with MIC 2 mg/l levofloxacin are susceptible. The MIC distributions of ciprofloxacin and levofloxacin are completely comparable (figure 39). Insight in the MIC distributions is much more informative for these borderline susceptibilities.

Haemophilus influenzae

The prevalence of amoxicillin-resistance among *H. influenzae* from Unselected Hospital Departments remained stable (6-7 %) until 2000. From 2001 on resistance increased to 15% in 2007. The data are shown in figure 40. The data for Pulmonology Services from the year 2004 were deleted because of the small numbers of strains tested. The resistance rate in Pulmonology Services was higher and fluctuated somewhat more (8-14%), but in 2005 a sudden increase to 28% resistance was found with a drop to 20% in 2006. About 50% of amoxicillin-resistance was based on beta-lactamase production; these strains were susceptible to co-amoxiclav. The other

Figure 40. Trends in resistance to antibiotics among *Haemophilus influenzae* from Unselected Hospitals and Pulmonology Services.



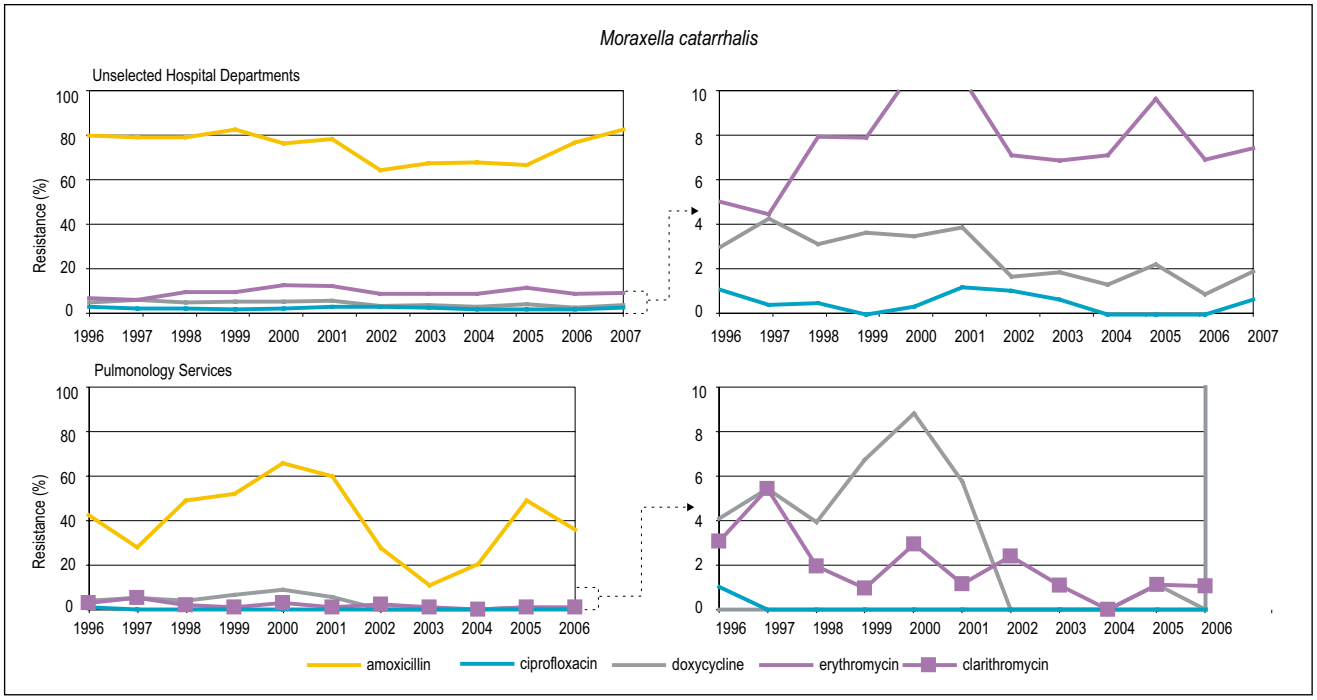
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strains must be recorded resistant due to other resistance-mechanisms; most had MICs for amoxicillin between 1-16 mg/l. The prevalence of erythromycin-resistance among *H. influenzae* from Unselected Hospital Departments was high (70-90%) if all strains with reduced susceptibility (MIC>0.5 mg/l) are counted as resistant. Clarithromycin instead of erythromycin was tested for isolates from the Pulmonology Services. Taking also the low breakpoint of 0.5 mg/l a 90-100% resistance to clarithromycin was recorded (figure 40).
Low prevalence resistance rates (2-6%) 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 from 2001 on to 2% in 2006. 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. Less use of doxycycline may be an explanation for decreased resistance rates in the last few years. A matter of concern is the fluctuating resistance to co-trimoxazole, which is one of the drugs used for COPD. The resistance level was 12 % in 1996-1997, raised to 25% in 1998, dropped to 13% in the following years but raised again in 2005 to 24% an dropped in 2006 to 12%. In 2005 the testing method (micro-broth dilution) was replaced by the E-test because of difficulties with the micro-broth dilution test. One resistance peak was recorded in the micro-broth dilution period, one in the E-test period. The numbers of strains tested each year are comparable (240-280), so the high resistance found in 1998 and in 2005 cannot be explained by mistakes or changes in the testing. Nevertheless the resistance level at all is too high for use of co-trimoxazole as empiric therapy in COPD if *H. influenzae* is the pathogen associated with an infectious event**.**

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 from 2006 were observed, resulting in a 82% resistance in 2007 (figure 41). The resistance in Pulmonology Services was 44% in 1996, raised to 60 % until 2001, dropped then to a level of around 20% from 2002 to 2004, but increased to 49% in 2005 and dropped to 36% in 2006. The difference in resistance levels between strains from Unselected Hospital Departments and those of Pulmonology Services is unclear. The resistance was completely due to beta-lactamase since resistance to co-amoxiclav did not occur. Resistance to erythromycin in Unselected Hospital Departments almost doubled from 4% in 1996 to 7% in 2007. Clarithromycin-resistance in Pulmonology Services was less than 5% 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. Resistance to doxycycline fluctuated between 2-4 % in

Figure 41. Trends in resistance to antibiotics among *Moraxella catarrhalis* from Unselected Hospitals and Pulmonology Services.



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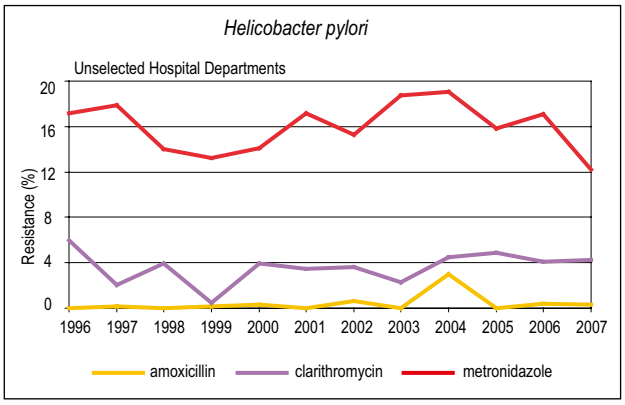


Figure 42. Trends in resistance to antibiotics among *Helicobacter pylori* from Unselected Hospitals.

Unselected Hospital Departments during the whole study period and was 4-8% in Pulmonology Services until 2001. Thereafter no resistance was found except in 2005 (1% resistance).

Helicobacter pylori

Amoxicillin-resistance among *H. pylori* was less than 3% over the years (figure 42). Clarithromycin-resistance was 1-6% (mean 4%) without a real tendency of increasing resistance, doxycycline-resistance was sporadic and metronidazole-resistance was stable over the years with 17% until 2006; in 2007 a resistance percentage of 12% was found.

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Project 1

Changes in the population structure of *Staphylococcus aureus* isolates of Intensive Care Unit patients in The Netherlands between 1996 and 2006

MIA Rijnders, RH Deurenberg, ML Boumans, JAA Hoogkamp-Korstanje, EE Stobberingh and the Susceptibility Surveillance Study Group

Methicillin-resistant *Staphylococcus aureus* (MRSA) prevalence is increasing in the Netherlands. This increase could be due to evolution of the methicillin-susceptible *S. aureus* (MSSA). MRSA may originate through the transfer of the mobile resistance element Staphylococcal Chromosome Cassette *mec* (SCC*mec*) into MSSA. In order to investigate the changes in the population structure of *S. aureus* and the evolution of MSSA in The Netherlands, MSSA isolates from ICU patients were analyzed. This study was carried out at the Department of Medical Microbiology, University Hospital Maastricht.

Staphylococcus aureus isolates (n=856) from ICU patients in The Netherlands were isolated between 1996 and 2006 within the national project on Surveillance of Intramural Resistance in the Netherlands (SIRIN). They were yearly collected from January until July in two university hospitals and twelve general hospitals. Only one isolate per patient was included. The minimal inhibitory concentration (MIC) of oxacillin was determined by the micro-dilution method according to CLSI guidelines. The genetic background of the isolates was determined with *spa* typing and the algorithm based upon repeat pattern (BURP).

Fifty eight new *spa*-types were identified out of 287 *spa*-types observed and three new *spa*-repeats were found among the new *spa*-types (figure 1). Among the *S. aureus* isolates, fourteen *spa*-clonal complexes were found. Ten isolates could not be clustered and were marked as singletons. Seventy isolates were excluded from the analyses.
A genetic background common to MRSA clones, e.g. MLST clonal complex CC1, CC5, CC8, CC22, CC30 and CC45 was observed among 46% of the isolates (N=393). The remaining isolates were associated with MLST CC7, CC15, CC25, CC26, CC51, CC97 and CC101.
Spa-types were clustered in *spa* clonal complexes (*spa*-CC's) using the BURP algorithm. The main *spa*-CCs were *spa*-CC 084 (19% of the isolates) and *spa*-CC 012 (18% of the isolates). *Spa*-CC 084 consisted of various MLST CCs. *spa*-CC 084 consisted mainly of CC15 (n=49, founder t084) and CC7 (n=53,founder t091). *Spa*-CC7 and *spa*-CC15 were connected through *spa*-type t1204. *Spa*-CC 012 consisted only of MSSA isolates of MLST CC30.

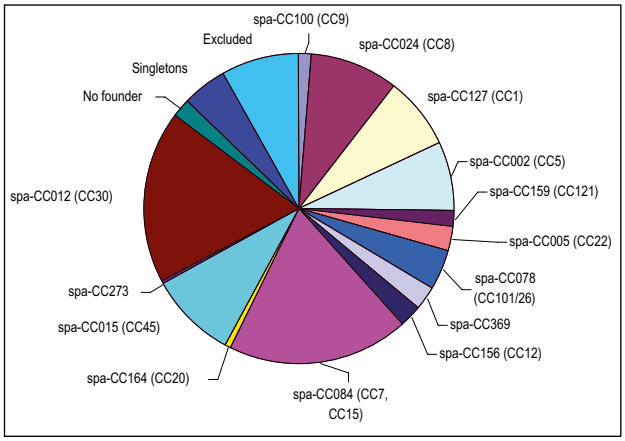


Figure 1. Distribution of *spa*-CCs (MLST CCs) among the MSSA isolates.

Conclusions

1. Half of the MSSA isolates (46%) had a genetic background common to MRSA clones.
2. The genetic background of the MSSA isolates was comparable with an earlier study in The Netherlands, where the genetic background of MSSA isolates of patients from multiple general practitioners was determined.
3. It was observed that MSSA isolates from ICU patients over a longer period of time had a heterogeneous genetic background, both common and uncommon to MRSA clones.
4. It was clear that BURP analyses can be improved and that further investigations are necessary.
5. The prevalence of oxacillin resistance was higher in this study than the prevalence found in The Netherlands. These isolates will be further analysed using SCCmec typing.

Presented as poster during the Annual Scientific Meeting of the Netherlands Society for Medical Microbioloy, 2008.

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Project 2

Prevalence of extended-spectrum β-lactamase among *Escherichia coli* and *Klebsiella pneumoniae* isolates from Intensive Care Units in the Netherlands 1998-2005

GJ Oudhuis, RHCA Deurenberg, A Verbon, JAA Hoogkamp-Korstanje, EE Stobberingh and the Susceptibility Surveillance Study Group

Outbreaks of extended-spectrum β-lactamase(ESBL)-producing *Enterobacteriaceae* strains on Intensive Care Units (ICUs), are associated with prolonged hospital admissions, delay of adequate antimicrobial therapy, and increased mortality. Therefore, reliable and rapid detection of these strains is important.
In this study, the prevalence of ESBL among *Escherichia coli* and *Klebsiella pneumoniae* isolated from 14 Dutch ICUs over an 8-year period was determined. The strains were collected within the national project Surveillance of Intramural Resistance in the Netherlands (SIRIN). The study on ESBL prevalence and diagnostic was carried out at the Department of Medical Microbiology, University Hospital Maastricht.

Unique *Escherichia coli* (N=1267) and *Klebsiella pneumoniae* isolates (N=402) from patients hospitalized on Intensive Care Units in the Netherlands were collected between 1998 and 2005 by the Susceptibility Surveillance Study Group. Minimal inhibitory concentrations (MICs) of broad-spectrum penicillins, cephalosporins, aminoglycosides, co-trimoxazole and fluoroquinolones were determined by broth micro-dilution with Mueller-Hinton II cation adjusted broth according to the Clinical Laboratory Standards Institute (CLSI) guidelines. Isolates with an MIC >=2 mg/L for ceftazidime and/or cefotaxime were considered putative ESBL producers. In these strains ESBL production was demonstrated by the double disk diffusion test (DDDT), as described by Jarlier et al., and the combination disk diffusion test (CDDT), according to the guidelines of the Dutch Society for Medical Microbiology. The presence of TEM- and/or SHV-genes was determined by PCR according to the method of Nyberg et al.

Sixty five *E. coli* strains and 35 *K. pneumoniae* strains had an MIC >=2 mg/L for ceftazidime and/or cefotaxime (table 1). A total of 14-18.5% of these *E. coli* strains and 63-77% of *K. pneumoniae* strains had one or two positive phenotypic tests, depending on the test used (table 1). The prevalence of ESBL producing *E. coli* among ICU isolates appeared 0.7-0.9% depending on the diagnostic method used; the prevalence of ESBL producing *K. pneumoniae* among ICU isolates was 5.5.-6.7% (table 2). The number of ESBL-positive isolates increased from 2002 onwards (figure 1). Overall the ESBL-prevalence among *E. coli* from 14 Dutch ICUs was significantly lower compared to that of *K. pneumoniae* ($p<0.001$). Seven *E. coli* and 20 *K. pneumoniae* strains which were positive with both DDDT and CDDT, contained a TEM- and/or SHV-gene. Five *E. coli* and two *K. pneumoniae* strains were positive with DDDT and/or CDDT, but did not carry any TEM- and/or SHV-gene.
Sixteen *E. coli* and eight *K. pneumoniae* isolates were negative with the phenotypic tests, but carried a TEM- and/or SHV-gene.
Further investigation regarding the presence of CTX-M β-lactamase, and characterisation of the TEM/SHV-genes with sequencing, is mandatory, to determine which phenotypic test is most accurate.

References

Jarlier V et al.: Rev Infect Dis 1988; 10: 867-878
Nyberg SD et al.: Scand J Infect Dis 2007; 39: 417-424

Presented as poster during the Annual Scientific Meeting of the Netherlands Society for Medical Microbioloy, 2008.

Table 1. Number of ESBL-producing strains among strains with MIC for ceftazidime and/or cefotaxime >=2 mg/l, determined by two phenotypic tests.

Species (N)	DDDT positive Number (%)	CDDT positive Number (%)
E. coli (N = 65)	12 (18.5)	9 (14)
K. pneumoniae (N = 35)	27 (77)	22 (63)

Table 2. Prevalence of ESBL-producing strains among Escherichia coli and Klebsiella pneumoniae from patients hospitalized in Intensive Care Units in the Netherlands.

Species (N)	ESBL (%) DDDT positive	ESBL (%) CDDT positive
E.coli (N = 1267)	0.9	0.7
K. pneumoniae (N = 402)	6.7	5.5

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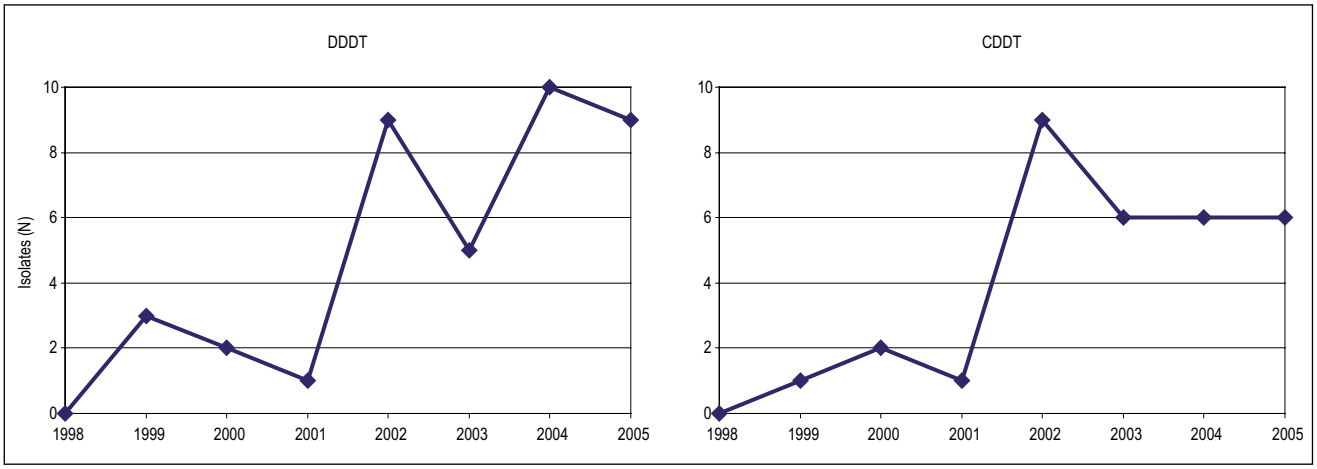


Figure 1. Number of ESBL producing isolates during the study period.

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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.

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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	7,10,33	1,5,8	1					5,8
Oxacillin	1,18,19,20								
Methicillin	3								
Flucloxacillin	7,10								
Ampicilin				3	2,27	2	8		
Amoxicillin		7,10	1	1,7,10,16, 25,28	17,25,26,30, 31,32			6	
Co-amoxiclav			9		1,2,4,17,30, 31,32	1,2	1,9		
Piperacillin	3			3	2,3,4,31,32	2,3,31			
Piperacillin/tazobactam	1,3		1	1,3	1,3,4,31,32	1,3,31	1		
Ticarcillin/clavulanate	3			3	1,2,3	1,2,3	1		
Mezlocillin					2	2			
Cefalothin		33							
Cefaclor					31				
Cefazolin					2,25,26,27	2			
Cefoxitin					4				
Cefuroxime	10	10			1,2,31	1,2	1		
Ceftriaxone			5,8		2	2	8		5,8
Cefotaxime		10	22		1,2,4,24,31	1,2,19,24	1		
Ceftazidime					1,2,3,4,17,24,31	1,2,3,17,19,24,31	1		
Cefpirome				16	4				
Cefepime					4,31				
Cefixime					31				
Ceftibuten					31				
Aztreonam					2	2			
Imipenem	1,3,11	11	1,11	1,3,11,16	1,2,3,17,31	1,2,3,17,31	1		
Meropenem	1,11	11	1,11	1,11,16	1,4,31	1,31	1		
Vancomycin	1,7,10,11	7,10,11	1,11,22	1,7,10,11,16, 19,25,28					
Teicoplanin	7,10,11	7,10,11	11	7,10,11,16					
Linezolid	14	14	14,22						
Gentamicin	1,3		1	1,10,16,25,28	1,2,3,4,17,25 26,27,31	1,2,3,17,31	1		
Tobramycin					2,4,31	2,31			
Netilmicin					4				
Amikacin	3				2,3,4,31	2,3,31			
Norfloxacin					17,30,32	17			
Ciprofloxacin	1,3,7,11,15	7,11,15	1,9,11,15	1,3,7,11,15,16, 25,28	1,2,3,15,17,25 26,27,31,32	1,2,3,15,17, 31	1,9,15		
Ofloxacin	7,15	7,15	15	7,15,16	4,15	15	15		
Levofloxacin			22		32				
Trovafloxacin	7	7		7,16				6	
Sparfloxacin	7,11	7,11	9,11	7,11,16			9		
Pefloxacin	7	7		7					
Moxifloxacin			22	16	32				
Clindamycin	1,10,11	10,33	1,22	1,10					
Erythromycin	1,10,11	10,11,29,33	1,11,22	1,10,11,15, 25,28					
Clarithromycin	10	10,11	9,11,22	10,11			9	6,12,21,23	
Telithromycin			22						
Tetracycline				25,28	25,26,27			6	
Minocycline				10					
Chloramphenicol			5,8	16	25,27		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					17,25,26,27,30,32				
Co-trimoxazole					17,30,32				
Nitrofurantoin					17,25,30,32				

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)
COPD	Chronic Obstructive Polumonary Disease
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
ESBL	Extended Spectrum Beta-lactamase
EU	European Union
GIP	Drug Information Project
GP	General practitioner
GRAS	Gonococcal Resistance to Antimirobials Surveillance
IPCI	Integrated Primary Care Information
ISIS	Infectious Diseases Information System
LINH	Netherlands Information Network in General Practice
MIC	Minimal Inhibitory Concentration
MRSA	Methicillin Resistant *Staphylococcus aureus*
MSSA	Methicillin Sensitive *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
SERIN	Surveillance of Extramural Resistance in the Netherlands
SFK	Foundation for Pharmaceutical Statistics
SIRIN	Surveillance of Intramural Resistance in the Netherlands
STI	Sexually Transmitted Infection
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
2007	16 357 992

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
2006	96	1736	11447	6.6

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
2006	8	218	1806	8.3

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
2006	88	1518	9641	6.4

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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 the 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 2008 includes data on the use of group J01 (antibiotics for systemic use) and group J02 (antimycotics 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 electronic format. The data are subsequently weighted statistically and extrapolated to cover 100% of the deliveries by community pharmacies. The total number of DDDs is divided by the total number of inhabitants that is registered by a community pharmacy (approximately 91.6% of the total number of inhabitants in the Netherlands). Data on the number of inhabitants in the Netherlands were 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.

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) were 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 nursing home residents was determined.
Residents from two nursing homes in Maastricht were asked to give informed oral consent to take a nasal swab from the anterior nostrils. The swabs were sent to the microbiological laboratory of the University Hospital Maastricht. The swabs were analysed for the presence of *S. aureus* using standard microbiological methods which include enrichment broth and the detection of catalase and coagulase enzymes. In addition, the susceptibility to the following antimicrobial agents was determined in micro-titre plates: penicillin, methicillin, erythromycin, tetracycline, clindamycin, cefaclor, rifampicin, ciprofloxacin, imipenem, meropenem, cefuroxime, linezolid and co-trimoxazole (MCS diagnostics, Swalmen, the Netherlands). The resistance to 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 the CLSI guidelines.
The study was approved by the Ethical Committee of the University Hospital Maastricht.
The results were compared with the results of the study on the prevalence of antibiotic resistance among *Staphylococcus aureus* in the indigenous flora of healthy volunteers and of patients visiting their general practitioner.
A total of 4000 individuals (age 18 – 75 years), taken from the municipal administration 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. In addition 2691 patients visiting their general practitioners for a non-infectious event were included in the study. A nose swab was taken from the anterior nostrils and sent to the microbiological laboratory of the University Hospital Maastricht. Most general practitioners (GPs) participated in the Sentinel project of the Netherlands institute for Healthy Services research (NIVEL).

Streptococcus pneumoniae

The carrier rate of *Streptococcus pneumoniae* in the indigenous flora of healthy children at the age of 9 years living in the southern part of the Netherlands and healthy adults at the age of 60 and higher from three general practitioners (one in the northern and two in the southern part of the Netherlands) was determined. The swabs from the children were taken in close cooperation with public health officers of the GGD Zuid-Limburg. Furthermore, throat swabs from patients all over the Netherlands visiting their general practitioner with complaints of a lower respiratory tract infection were analysed for the presence of *S. pneumoniae*.
The swabs were cultured by standard microbiological methods including use of a selective agar plate (Colistin Nalidixic acid). Strains were identified according to standard microbiological methods. The susceptibility was determined in micro-titre plates for the following antimicrobial agents: gentamicin, linezolid, ciprofloxacin, moxifloxacin, levofloxacin, clarithromycin, co-trimoxazole, trimethoprim, imipenem, vancomycin, teicoplanin, penicillin, amoxicillin, chloramphenicol, co-amoxiclav (ratio 4:1), meropenem, ceftazidime, cefaclor, cefuroxime, cefotaxime, clindamycin, rifampicin, tetracycline and cefixime (MCS diagnostics, Swalmen, the Netherlands).
Streptococcus pneumoniae ATCC 49619 was used as the reference strain. The breakpoints for resistance were according to the CLSI guidelines.
The study was approved by the Ethical Committee of the University Hospital Maastricht.

Neisseria gonorrhoeae

In 1999 the nationwide surveillance of antibiotic resistance of gonococci was discontinued and since then insight in gonococcal susceptibility patterns had been limited. Concern for increasing resistance to quinolones led to an annual RIVM survey of resistance of gonococci since 2002. Complete data on the number of diagnosis and results of antimicrobial susceptibility testing for 2002-2006 were provided by 24 of all 39 microbiological laboratories identified.
In 2006 a project called Gonococcal Resistance to Antimicrobials Surveillance (GRAS) has been implemented in the Netherlands. This surveillance project consists of systematically collecting data on gonorrhoea and standardised measurement of resistance patterns by using an E-test, linked with epidemiological data. Participants are STI clinics and associated laboratories that identify the majority of STI in high risk populations. Isolates are sent to the RIVM for further analysis.

Neisseria meningitidis

From 1993-2007 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.

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Mycobacterium tuberculosis
The first isolate of *M. tuberculosis* of each patient with tuberculosis in The Netherlands is routinely sent to the RIVM for susceptibility testing and confirmation of identification. Isolates obtained after more than 6 months from the same patient, are judged a new isolate. The susceptibility of the strains is tested quantitatively with a standard agar dilution assay according to the recommendations of the NCCLS. The antibiotics chosen for reporting are INH, rifampicin, streptomycin and ethambutol. Resistance rates represent the proportion of moderately and fully resistant strains.
The susceptibility data of 11683 strains, isolated from 1996-2007 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 were 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 2007 are given in table 1.
The susceptibility of the strains from the Unselected

Table 1. First isolates per clinical sample of patients in Unselected Hospital Departments in 2007.

Species (number of isolates)	Clinical material (number)			
	Blood (6257)	Pus and wound (27422)	Respiratory tract (14566)	Urine (31405)
Gram-positive cocci (31977)				
Staphylococcus aureus (14360)	823	10816	1621	1100
Coag neg. Staphylococcus (2831)	1510	695	66	560
Enterococcus spp. (6298)	392	1247	121	4538
Streptococcus pneumoniae (2906)	664	386	1856	0
Streptococcus agalactiae (4528)	97	2827	146	1458
Streptococcus pyogenes (1054)	94	822	68	70
Subtotal	3580	16793	3878	7726
Enterobacteriaceae (34037)				
Escherichia coli (19638)	1512	2558	1017	14551
Proteus mirabilis (4028)	151	975	298	2604
Klebsiella pneumoniae (3207)	264	475	478	1990
Klebsiella oxytoca (1819)	137	404	334	944
Enterobacter cloacae (1990)	143	695	514	638
Other Enterobacteriaceae (3355)	193	934	838	1390
Subtotal	2400	6041	3479	22117
Respiratory pathogens (6367)				
Haemophilus influenzae (4245)	43	467	3730	5
Haemophilus parainfluenzae (582)	8	106	465	3
Moraxella catarrhalis (1457)	7	80	1369	1
Neisseria meningitidis (83)	28	7	48	0
Subtotal	86	660	5612	9
Non-fermentors (5121)				
Pseudomonas aeruginosa (4825)	179	1659	1530	1457
Acinetobacter calcoaceticus (296)	9	124	67	96
Subtotal	188	1783	1597	1553
Helicobacter pylori (2148)	3	2145	0	0

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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 micro-dilution 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.

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 25500 strains were collected from 1996-2006, the results of 20730 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 micro-dilution assays using the recommendations of the CLSI for *E. coli*, *P. mirabilis*, *K. pneumoniae*, *P. aeruginosa*, *E. faecalis*, *S. aureus* and *S. epidermidis*. Resistance rates of these organisms likewise represent the proportion of fully resistant strains. For *H. influenzae*, *M. catarrhalis* and *S. pneumoniae* the lower breakpoints (MIC > lower breakpoint) were used to enable comparison with the data of strains from Unselected Hospital Departments. *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *H. influenzae* ATCC 49247 and *S. aureus* ATCC 25923 were used as control strains in the MIC tests performed in the central laboratory.

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

Table 2. Number of indicator strains (N=20730) isolated from patients admitted to specified hospital wards and tested for their susceptibility to antibiotics in the period 1996-2006.

Species	Intensive Care Units	Urology Services	Pulmonology Services
E. coli	1778	5601	
K. pneumoniae	528	665	
E. cloacae	456	174	
P. mirabilis	370	774	
P. aeruginosa	1025	427	
E. faecalis	739	1097	
S. aureus	991	350	
S. epidermidis	522	235	
S. pneumoniae			1548
H. influenzae			2379
M. catarrhalis			1071

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