NETHMAP 2005



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, Meibergdreef 9, AMC Afd. Infectieziekten, Tropische Geneeskunde en AIDS, F4-217, P.O. Box 22660, 1100 DD Amsterdam, the Netherlands, tel. 020 566 43 80, fax 020 697 22 86. NethMap is also available from the website of the SWAB: www.swab.nl. The suggested citation is: SWAB. NethMap 2005 – Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands.

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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:

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Preface

On behalf of the Dutch Working Party on Antibiotic Policy we are happy to present the third surveillance report, called NethMap 2005, on antimicrobial use and resistance in human medicine in the Netherlands. The Dutch Working Party on Antibiotic Policy was founded in 1996 by three societies of professionals highly involved in the management of infectious diseases in the Netherlands. Thus, the Netherlands Society for Infectious Diseases, the Netherlands Society for Medical Microbiology and the Netherlands Society of Hospital Pharmacists pooled their resources in this Working Party, locally known by its acronym: the SWAB (Stichting Werkgroep Antibiotica Beleid). SWAB's mission is to manage, limit and prevent the emergence of resistance to antimicrobial agents among medically important species of microorganisms in the Netherlands, thereby contributing to the proper care of patients in this country. The importance of the SWAB initiative taken by these professsional bodies was immediately clear to the health authorities of the Netherlands and resulted in the decision of the Ministry of Health, Welfare and Sports in 1997 to structurally support the SWAB's activities financially. This recognition and support of SWAB's work by the government continues to this day. SWAB has focused its activities on several major goals, one of which is the development of an integrated surveillancesystem regarding the use of antimicrobial agents and the prevalence of antimicrobial resistance among medically important species of microorganisms. These initiatives corresponded well with the recommendations from the Dutch Council on Health Research (2001) and the European Union (2001). Therefore the Ministry of Health, Welfare and Sports formally invited SWAB in May 2002 to develop such a surveillance system in close collaboration with the National Institute of Public Health and the Environment (its Dutch acronym is: RIVM). NethMap 2005 extends and updates the information in the previous two reports. We have added one or two more years to the trend lines, more species of microbes are monitored and several special analyses have been added that contribute to our insight in the usage data presented.

Importantly, two surveillance reports called MARAN 2002 and 2003 have been published regarding the use of antimicrobial agents and the development of antimicrobial resistance in animal husbandry (see www.cidc-lelystad.nl) by the Veterinary Antibiotic Usage and Resistance Surveillance Working Group. The MARAN 2004 report will appear in September 2005. Taken together the current and future NethMap- and MARAN-reports aim to constitute a comprehensive monitor of the consumption of antimicrobial agents and the prevalence of antimicrobial resistance in the Dutch medical and veterinary arena, respectively. The interaction between these two areas of antibiotic use and resistance is currently explored in a working group started in 2003 by the ministry of Health, Welfare and Sports and that of Agriculture, Nature and Food Quality. Both SWAB and its veterinary sister group are represented in this working group which discusses the evolution of antibiotic use and resistance in the Netherlands on the basis of our surveillance data.

We hope and trust that NethMap continues to contribute to our knowledge and awareness regarding the use of antibiotics and the resistance problems that may arise from it. We thank all who have contributed to the surveillance efforts of SWAB sofar, and express our hope that they will continue to do so.

The editors:

Prof dr Henri A. Verbrugh dr Han de Neeling

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1 Summary

NethMap 2005 is the third annual report of the SWAB containing information regarding the use of antimicrobial agents and the prevalence of resistance to these agents among common human pathogens isolated in the Netherlands. Trends in antibiotic use and resistance are presented in the form of serial annual data collected systematically from 1993 up to 2004.
The overall use of antimicrobial agents in primary health care has remained very stable over the years at levels just below 10 defined daily dosages (DDD) per 1000 inhabitants per day. However, subtle shifts in the patterns of use of the various classes of antibiotics can be observed. Thus, the use of beta-lactamase sensitive penicillin and of extended spectrum penicillin, primarily amoxicillin, is slowly declining, a trend that seems to be counterbalanced by increases in the use of the combination of amoxicillin with clavulanic acid, co-amoxiclav, and in the use of agents belonging to the macrolide class. The use of the fluoroquinolones in primary health care has remained stable, although within this class of agents substitutions seem to occur. Increased use of ciprofloxacin is offset by decreased use of ofloxacin and norfloxacin.
In this report antibiotic use data is for the first time further broken down with respect to prescribing physician, patient age and gender. These analyses clearly show that general physicians running a general practice have a prescription pattern that is different from that of medical specialists prescribing antibiotics to ambulatory patients, medical specialists being the ones that more often use broad spectrum agents including co-amoxiclav, co-trimoxazole and fluoroquinolones.
When analyzed by gender and age, antibiotic use by females exceeds that of males in all age categories except for the very young. For both genders it is true that antibiotic use increases with age and is much higher for those >65 years of age compared to younger age groups. At the level of individual antibiotics females receive nitrofurantoin and trimethoprim much more often than males, most probably a reflection of their greater susceptibility to uncomplicated urinary tract infection. This difference is, again, observed in all age categories except in the very young. In contrast, fluoroquinolone use is somewhat higher in males than in females, especially in the age group >65 years, reflecting most probably the use of these agents for complicated urinary tract infections that afflict both sexes.
In a separate analysis (Project 1) antibiotic use patterns in primary health care are presented in a so called directed animated graphical format. Such analysis allows a better insight in the prescription habits of physicians since it quantitatively depicts the transitions in antibiotic use of patients over time. The graph shows which antibiotics are preferentially used as first line agents, and to which antibiotic patients are transferred when second tier agent are needed in general practice. Thus, amoxicillin is the agent most often used as a first line agent and co-amoxiclav or clarithromycin are preferentially being used as follow-up treatments when patients apparently did not respond to amoxicillin.

In the two preceding NethMap reports (2003 & 2004) antibiotic use in hospital settings was expressed as DDD per 100 patient-days. This manner of expressing hospital use of antibiotics is in accordance with international convention. In this NethMap report 2005 it is argued that DDD/100 patient-days may not suffice as the sole indicator of antibiotic use in hospitals. It is shown that this indicator is sensitive to changes in the hospital resource data which are used to calculate the denominator, i.e. the number of patient-days. NethMap 2005, therefore, introduces a second indicator of antibiotic use in hospitals, i.e. the number of DDD/100 admissions. Whereas the number of DDD of antibiotics/100 patient-days steadily increased from 43 in 1999 to 52 in 2003 the number of DDD of antibiotics/100 admissions remained constant over this same period of time. The difference in trends between the two indicators could be ascribed to changes in hospital resource data, in this case to the steady decline in the mean length of stay per admission (down from 8.8 days in 1999 to 7.4 days in 2003). Thus, patients hospitalised in the Netherlands on average did not receive more antibiotics but, since they remained in the hospital for fewer days, the number of DDD/100 patient-days increased. Such an increase in DDD/100 patient-days may not necessarily represent an increase in the selection pressure exerted by antibiotic use, i.e. increase the risk of emergence of antibiotic resistance. Although it can be argued that increases in DDD/100 patient-days translate in increases in the density of antibiotic use in hospitals, this argument will only hold if the number of beds available and the bed occupancy rate remained stable, and this has not been the case. However, for several classes of antimicrobial agents increases in both DDD/100 patient-days and in DDD/100 admissions were observed, trends that are probably associated with increases in the selection pressure toward antibiotic resistance in hospitals. Such trends were observed for beta-lactamase-resistant penicillins, for co-amoxiclav, the carbapenems, the lincosamides and

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for nitrofurantoin. The opposite, i.e. trends toward less DDD/100 patient-days and less DDD/100 admissions, was observed for tetracyclines, extended spectrum penicillin (amoxicillin) and for the combination of sulfonamides with trimethoprim.
Although these trends were rather mild and our analysis do not show abrupt changes in antibiotic use patterns, subtle shifts may over the years accumulate to represent a significant change is usage and, therefore, have a major impact on the selection pressures present in the hospital setting.

The surveillance of antimicrobial resistance continued to include strains of *E. coli* isolated from patients presenting with urinary infection to their primary care physician in general practice, as well as strains of Gram-positive and Gram-negative species isolated in hospital settings.
In general practice the resistance of *E. coli* to amoxicillin was higher in 2003/2004 than in previous years (>30% versus approximately 20%). In addition, the trend toward higher rates of resistance to trimethoprim observed since 1997 continued so that in 2003/2004 23% of all isolates were resistant to this first line agent. Although there were regional differences trimethoprim resistance increased in all. Since trimethoprim is advocated as first line agent for uncomplicated urinary tract infection in general practice this observation is worrisome and may need to be taken into account when updating practice guidelines for this setting. Combination of trimethoprim with sulphonamide will not be an alternative since resistance rates to this combination run only 2% lower than for trimethoprim alone. However, *E. coli* resistance to nitrofurantoin, another first line agent, remains low as does its resistance toward co-amoxiclav. In contrast, resistance toward norfloxacin, often used as second tier agent for urinary infection, has been creeping up to a 3-4% level indicating that use of fluoroquinolones in general practice, even when stable over many years, may ultimately lead to resistance emergence among *E. coli*. Alternatively, resistant *E. coli* may be emerging in hospital settings where the density of fluoroquinolone use is much higher, and subsequently exported from hospitals to the community.
In hospitals, the surveillance system covers *E. coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Staphylococcus species, Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis,* and *Helicobacter pylori*. In addition, resistance data are presented for *Mycobacterium tuberculosis* and, new for this report, for *Neisseria meningitidis*. The overall impression is that of rather stable rates of resistance for most antibiotics among these pathogens. However, certain trends need to be addressed carefully. First, the rate of resistance to fluoroquinolones is clearly increasing among clinical isolates of *E. coli, P. aeruginosa* and *S. aureus*. In Urology services >10% of *E. coli and S. aureus* are now fluoroquinolone resistant, and in other hospital departments resistance to these agents has reached the 5-10% range. Importantly, fluoroquinolone resistant *E. coli* were observed in <5% of the isolates in the period up to the year 2000.
Another worrisome trend is the steadily increasing rate of resistance to macrolides among clinical isolates of *S. aureus and S. pneumoniae*, both are now approaching the 10% threshold above which their empiric use may be limited. However, the first line penicillin agents for these two important species of Gram-positive pathogens remain effective. Among clinical *S. aureus* isolates the proportion of methicillin resistance was 1-2% in 2003/2004, and only 2-3% of *S. pneumoniae* isolates had reduced susceptibility to penicillin. Although still low, these rates may be creeping up and continued vigilance in controlling resistant staphylococci and pneumococci is clearly warranted.
NethMap 2005 includes data on antibiotic resistance among *Helicobacter pylori* and *Neisseria meningitidis* for the first time. Again, the data generally show stable rates of resistance for *H. pylori* for 1995 until 2004.
For *N. meningitidis* rates of reduced susceptibility to penicillin were approximately 1% in the period 1993-2001. In 2002 and 2003 rates were higher (up to 3%) but it cannot yet be ascertained whether this is the beginning of a trend. Finally, resistance to antimicrobial agents among isolates of *Mycobacterium tuberculosis* showed them to be susceptible to all four agents tested in >85% of the cases. Resistance to INH was stable at 8-9% and multiple resistance was observed in 2-3% of the strains tested. Resistance to all four agents was rare but in 2003 occurred in almost 1% of the isolates. Again, trends of *M. tuberculosis* resistance need to be followed closely to discern the emergence of (multiple) resistance at an early stage.
In conclusion, NethMap aims to present information regarding the use of and resistance to antibiotics in the Netherlands in a manner that is useful for benchmarking and for detecting and following important trends.

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2 Samenvatting

NethMap 2005 is het derde jaarrapport van de SWAB en geeft informatie over het gebruik van antibiotica en het voorkomen van antibiotica resistentie in de meest voorkomende, voor de mens pathogene, bacteriesoorten in Nederland.
Op basis van systematisch verzamelde gegevens over het jaarlijkse gebruik aan antibiotica en het voorkomen van antibiotica resistenties kunnen trends worden beschreven. Over het geheel genomen is het gebruik aan antibiotica in de eerstelijns gezondheidszorg zeer stabiel. Het gebruik blijft net onder de 10 DDD per 100 inwoners per dag, voor Europa een laagte record. Binnen dit stabiele kader zijn wel enkele trends waarneembaar. Zo neemt het gebruik van beta-lactamase gevoelige penicilline en van breed spectrum penicilline langzaam af terwijl het gebruik van de combinatie co-amoxiclav en van antibiotica uit de groep macroliden toeneemt. Het gebruik van fluorchinolonen in de eerstelijns gezondheidszorg lijkt stabiel, maar binnen deze groep middelen zijn wel substituties waarneembaar. Er wordt meer ciprofloxacine gebruikt en minder ofloxacine en norfloxacine.
In dit rapport wordt voor de eerste keer onderscheid gemaakt in het antibioticagebruik door mannen en vrouwen, gebruik door verschillende leeftijdsgroepen en het voorschrijven van antibiotica door huisartsen en door medisch specialisten. Medisch specialisten schrijven vaker dan huisartsen een breed spectrum middel voor zoals co-amoxiclav, fluorochinolonen of cotrimoxazol voor hun ambulante patiënten. Het zou interessant zijn de indicatiestellingen daarbij te analyseren. Voor alle leeftijdgroepen behalve het eerste levensjaar is het gebruik van antibiotica door vrouwen hoger dan door mannen. De verschillen zijn vooral terug te voeren op het veel hogere gebruik van trimethoprim en nitrofurantoïne door vrouwen. Hoewel niet onderzocht, ligt de verklaring waarschijnlijk in de hoger frequentie van ongecompliceerde lage urineweginfecties bij vrouwen dan bij mannen, de indicatie voor het inzetten van deze middelen voor de behandeling. Op hogere leeftijden gebruiken mannen weer meer fluorochinolonen dan vrouwen, mogelijk als gevolg van het op die leeftijd voorkomen van gecompliceerde urineweginfecties bij mannen.
In een aparte analyse (Project 1) wordt het antibioticumgebruik in de eerstelijns gezondheidszorg op een bijzonder wijze gepresenteerd, namelijk in de vorm van een directionele grafische kaart die in de tijd varieert. Deze wijze van analyseren geeft een beter inzicht in de dynamiek van het gebruik van antibiotica.
Dergelijke kaarten laten zien welk antibioticum wordt gekozen als eerste middel bij de behandeling en in welke mate er vervolgbehandelingen gegeven worden en welke middelen men dan kiest. Zo blijkt amoxicilline vaak als eerste antibioticum voorgeschreven en, bij noodzaak tot een vervolgbehandeling, wordt dankzij deze analyse zichtbaar gemaakt dat de huisarts dan meestal kiest voor of co-amoxiclav of een macrolide antibioticum.

In de twee voorgaande NethMap rapporten (2003 & 2004) werd het antibioticumgebruik in het ziekenhuis weergegeven door de maat DDD/100 patiënten dagen (ligdagen). Het gebruik van deze maat is internationaal gemeengoed geworden. In NethMap 2005 wordt daarnaast een nieuwe maat geïntroduceerd, namelijk het aantal DDD/100 opnamen. Gesteld wordt dat het alleen weergeven van het aantal DDD/100 ligdagen niet voldoende is omdat die maat gevoelig is voor veranderingen in de zogenoemde kengetallen van ziekenhuiszorg, met name voor veranderingen in de gemiddelde opname duur. Deze kengetallen beïnvloeden de grootte van het noemergetal (aantal ligdagen) zeer. Zo is het antibioticumgebruik uitgedrukt in DDD/100 ligdagen gestegen van 43 in 1999 tot 52 in 2003 terwijl het aantal DDD/100 opnamen in dezelfde periode niet is gestegen. Het verschil in deze twee trendlijnen is geheel te verklaren door een afname in de gemiddelde duur per opname; deze was 8,8 dagen in 1999 en 7,4 dagen in 2003. Per opname, d.w.z. per patiënt, werden dus niet meer antibiotica voorgeschreven, maar omdat de patiënt gemiddeld steeds korter in het ziekenhuis verblijft neemt het aantal DDD/100 ligdagen wel toe. Meer DDD/100 ligdagen houdt derhalve niet perse in dat de selectiedruk van antibiotica in de ziekenhuizen is toegenomen. Men zou kunnen stellen dat wél sprake is van toegenomen selectiedruk, immers er worden meer antibiotica per ligdag gebruikt, maar op ziekenhuisniveau neemt daarmee de selectiedruk alleen toe als het aantal bedden en de bedbezetting constant zou zijn gebleven. Dat is echter niet het geval, er zijn tegenwoordig minder bedden beschikbaar in ziekenhuizen en de bedbezetting is afgenomen. Voor een aantal groepen antibiotica is het aantal DDD/100 ligdagen en het aantal DD/100 opnamen gestegen. Voor deze middelen is vermoedelijk wel sprake van een toegenomen selectiedruk. Het betreffen de beta-lactamase resistente penicillines, co-amoxiclav, de carbapenems, de lincosamiden en nitrofurantoïne. Een tegengestelde trend, minder DDD/100 ligdagen én minder DDD/100 opnamen, werd gevonden voor de tetracyclines, de breedspectrum penicillines

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(amoxicilline), en voor de combinatie van trimethoprim met een sulfonamide. Hoewel er geen sprake is geweest van een abrupte stijging of daling in het gebruik van de verschillende groepen antibiotica, kunnen de minder uitgesproken veranderingen in het gebruik op den duur wel degelijk een belangrijke wijziging in de selectiedruk van antibiotica in de ziekenhuizen opleveren.

De surveillance van antibioticaresistentie in de eerstelijns gezondheidszorg richt zich op *E. coli* geïsoleerd uit de urine van patiënten met urineweginfectie. Voor de ziekenhuizen werden zowel Gram-negatieve soorten en Gram-positieve soorten in de resistentie surveillance betrokken. De resistentie percentage van *E. coli* voor amoxicilline in de huisartsenpraktijk was in 2003/2004 hoger dan in de voorgaande jaren (>30% versus ongeveer 20%). Daarbij komt dat de al eerder waargenomen trend naar hogere niveaus van resistentie tegen trimethoprim zich heeft doorgezet en nu een niveau van 23% heeft bereikt. Er zijn weliswaar regionale verschillen in deze resistentiepercentage maar in alle regio's van Nederland is onder *E. coli* de resistentie tegen trimethoprim gestegen. Dat geeft te denken, omdat trimethoprim middel van eerste keuze is bij de behandeling van ongecompliceerde urineweg infectie. Het gebruik van cotrimoxazol levert geen soelaas omdat bij *E. coli* resistentie tegen cotrimoxazol maar 2% achterloopt op die tegen trimethoprim. Het resistentie percentage tegen nitrofurantoïne blijft gelukkig laag. Ook werd nauwelijks resistentie tegen co-amoxiclav waargenomen. Daarentegen lijkt het percentage resistentie tegen norfloxacine langzaam op te lopen (tot 3-4%). Dat kan het gevolg zijn van het langdurige gebruik van dit fluorochinolon in de huisartsenpraktijken, of er is sprake van resistentie ontwikkeling bij *E. coli* in de ziekenhuizen en export van dergelijke stammen naar de eerstelijns gezondheidszorg.

In de Nederlandse ziekenhuizen is het algemene resistentiebeeld redelijk stabiel. Toch zijn er belangrijke trends waar te nemen. Op de eerste plaats stijgen de resistentie percentages voor de fluorochinolonen onder klinische isolaten van *E. coli, Pseudomonas aeruginosa* en *Staphylococcus aureus*. In de afdelingen Urologie zijn >10% van de *E. coli* en *S. aureus* isolaten bijvoorbeeld ciprofloxacine resistent, en in de overige delen van de ziekenhuizen vindt men een resistentieniveaus van 5-10%. Dit is belangrijk anders dan in de periode voor de eeuwwisseling toen het resistentiepeil voor fluorochinolonen onder deze soorten nog lager dan 5% was. Een andere zorgwekkende trend is de toenemende resistentie tegen de macrolide antibiotica onder klinisch isolaten van *S. aureus* en *Streptococcus pneumoniae*. In beide gevallen bereiken ze bijna het niveau van 10% waarboven de bruikbaarheid van deze middelen voor de empirische behandeling van infecties beduidend minder wordt. Daartegenover staat dat het resistentieniveau tegen de middelen van eerste keuze bij de behandeling van infectieziekten met deze Gram-positieve bacteriën nog steeds laag is. Zo is het percentage meticilline resistentie onder *S. aureus* 1-2% van de klinische isolaten in de jaren 2003 en 2004. Voor *S. pneumoniae* geldt dat slechts 2-3% verminderd gevoelig was voor penicilline. Hoewel deze resistentie percentages als laag beschouwd moeten worden zijn zij niet eerder op dit niveau geweest en kan er dus sprake zijn van een beginnende trend naar hogere niveaus. Voortdurende waakzaamheid en controle van resistente isolaten van *S. aureus* en *S. pneumoniae* blijft aangewezen.

NethMap 2005 presenteert gegevens over de resistentie niveau bij *Helicobacter pylori* en voor het eerst bij *Neisseria meningitidis*. De gegevens voor *H. pylori* laten een stabiel beeld zien voor de periode 1995-2004. Voor *N. meningitidis* is het percentage stammen met een verminderde gevoeligheid voor penicilline ongeveer 1%; ook dit resistentie peil is nagenoeg stabiel in de periode 1993-2001. In 2002 en 2003 werden hogere percentages waargenomen (tot 3%), maar het is niet duidelijk of er sprake is van een beginnende trend naar hogere resistentie niveaus. Tenslotte worden voor de tweede keer resistentie gegevens van *Mycobacterium tuberculosis* gepresenteerd. Van alle geteste isolaten blijkt > 85% goed gevoelig te zijn voor de vier geteste tuberculostatica. Ook dit percentage is stabiel. INH resistentie wordt gevonden bij 8-9% van de isolaten, en 3-5% van de isolaten is resistent voor twee of meer van de vier middelen. Resistentie tegen alle vier middelen wordt slecht incidenteel waargenomen, hoewel in 2003 bijna 1% van de stammen uniform resistent was. Opnieuw een reden om de surveillance van resistentie bij *M. tuberculosis* te handhaven.

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3 Use of antibiotics

This part of the report considers the use of antimicrobial agents in human medicine only. Data on the use of such agents in animal husbandry and veterinary medicine are reported elsewhere (reference 1).
Human consumption is presented in two parts. One part describes the prescription and use of antibiotics in the community, also termed "Primary Health Care". The second part presents surveillance data on the use of antibiotics in the acute care hospitals in the Netherlands. See the Section "surveillance methods and susceptibility testing" in the Appendix for details regarding the structural acquisition and analysis of the antibiotic consumption data.
In addition to the routine surveillance of antibiotic use, data derived from an in-depth study are presented in this section.

Primary health care

Table 1 presents the use of antibiotics for systemic use in primary health care from 2000-2004. Over these years total antibiotic consumption remained almost constant. The overall use of antibiotics in primary health care is 10 DDD/1000 inhabitant-days.
The distribution of antibiotics by class in 2004 is presented in figure 1. Tetracyclines (mainly doxycycline) represented 22% 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 co-amoxiclav) and macrolides, representing 17%, 14% and 14% of the total use respectively.

The use of amoxicillin decreased from 1.88 in 2000 to 1.69 DDD/1000 inhabitant-days (-10.1%) in 2004. The use of co-amoxiclav increased from 1.15 in 2000 to 1.38 DDD/1000 inhabitant-days (+20%) in 2004 (figure 2).

The use of macrolides is presented in figure 3. Clarithromycin is still the most commonly used macrolide, and its use gradually increased to 0.84 DDD/1000 inhabitant-days. The use of azithromycin increased as well. Both the use of erythromycin and roxithromycin remained almost constant.

Total use of the fluoroquinolones did not change between 2000 and 2004 (table 1). Ciprofloxacin was the fluoroquinolone used most commonly. Between 2003 and 2004, the use of ciprofloxacin increased by 12%. From 2000 to 2004, the overall increase has been 35% (figure

Table 1. Use of antibiotics for systemic use (J01) in primary health care (DDD/1000 inhabitant-days), 2000 - 2004 (Source: SFK).

ATC group[a]	Therapeutic group	Year				
		2000	2001	2002	2003	2004
J01AA	Tetracyclines	2.47	2.39	2.33	2.23	2.22
J01CA	Penicillins with extended spectrum	1.88	1.82	1.78	1.77	1.69
J01CE	Beta-lactamase sensitive penicillins	0.52	0.49	0.45	0.44	0.42
J01CF	Beta-lactamase resistant penicillins	0.24	0.25	0.25	0.27	0.28
J01CR	Penicillins + beta-lactamase inhibitors	1.15	1.25	1.34	1.39	1.38
J01D	Cephalosporins and related substances	0.08	0.07	0.07	0.06	0.05
J01EA	Trimethoprim and derivatives	0.28	0.28	0.27	0.27	0.26
J01EC	Intermediate-acting sulfonamides	0.00	0.00	0.01	0.00	0.00
J01EE	Sulfonamides + trimethoprim	0.43	0.42	0.4	0.39	0.39
J01FA	Macrolides	1.13	1.22	1.24	1.27	1.31
J01FF	Lincosamides	0.04	0.05	0.06	0.06	0.07
J01GB	Aminoglycosides	0.00	0.01	0.01	0.02	0.02
J01MA	Fluoroquinolones	0.80	0.80	0.78	0.78	0.82
J01MB	Other quinolones	0.04	0.04	0.03	0.03	0.02
J01XB	Polymyxins	0.02	0.02	0.02	0.02	0.02
J01XE	Nitrofuran derivatives (nitrofurantoin)	0.68	0.71	0.74	0.78	0.80
J01XX05	Methenamine	0.06	0.06	0.04	0.03	0.02
J01	Antibiotics for systemic use (total)	9.84	9.90	9.81	9.81	9.77

[a] from the 2005 edition of the Anatomical Therapeutic Chemical (ATC) classification system

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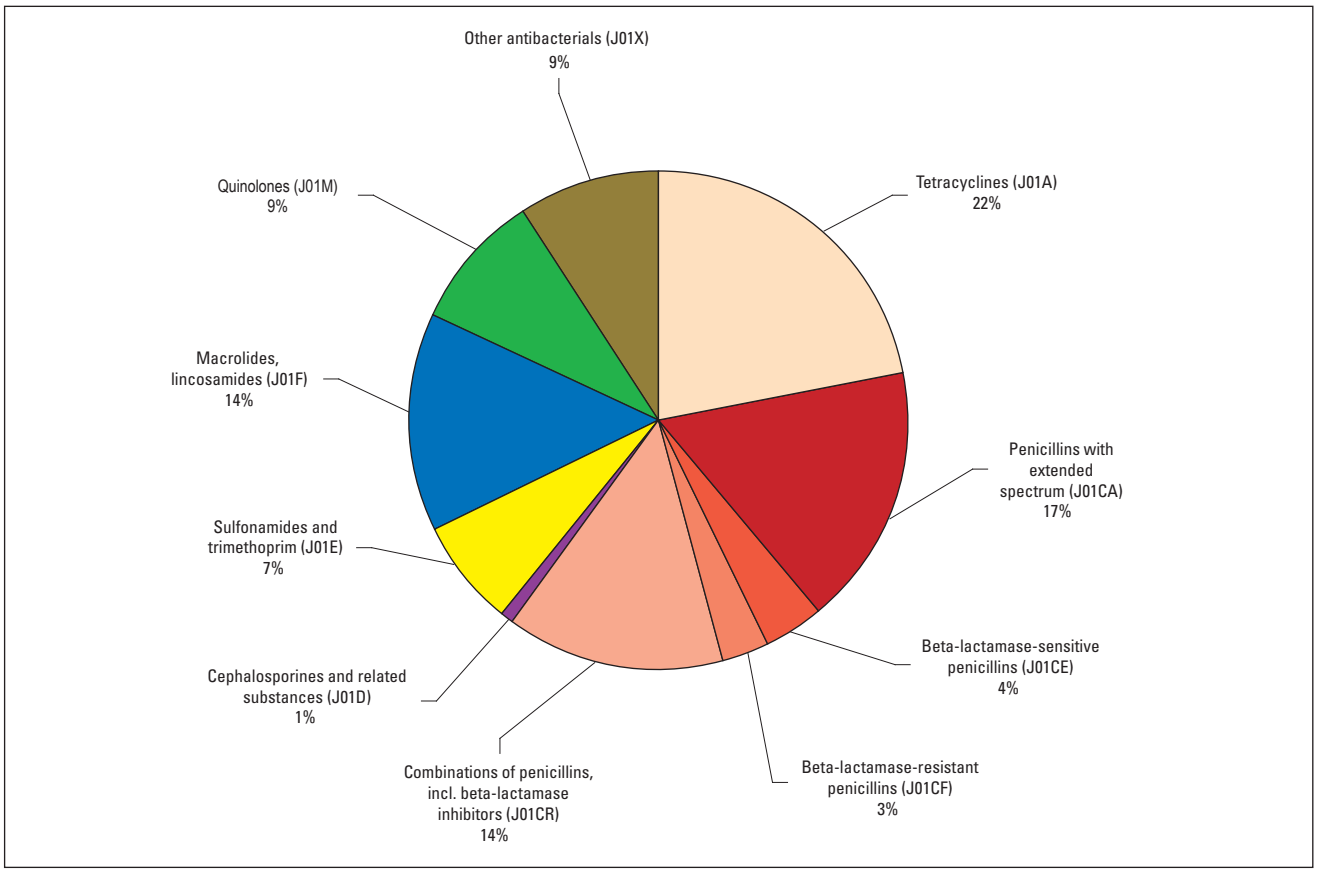


Figure 1. Distribution of the use of antibiotics for systemic use (J01, DDD) in primary health care, 2004 (Source: SFK).

4). Since 2002 the use of ciprofloxacin exceeded the use of norfloxacin.

The use of nitrofurantoin increased from 0.68 in 2000 to 0.80 DDD/1000 inhabitant-days in 2004 (table 1).

Figure 2. Use of amoxicillin and co-amoxiclav in primary health care, 2000 - 2004 (Source: SFK).

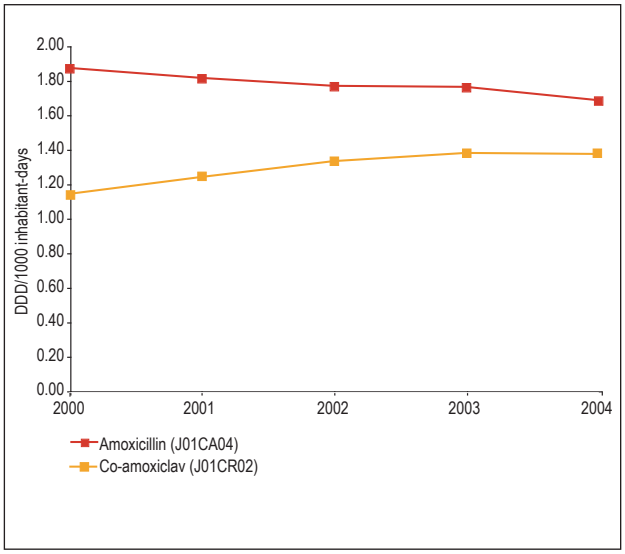
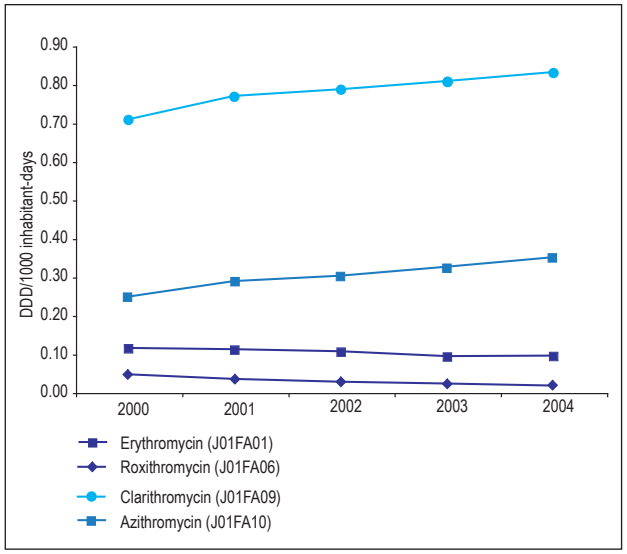


Figure 3. Use of macrolides for systemic use in primary health care, 2000-2004 (Source: SFK).



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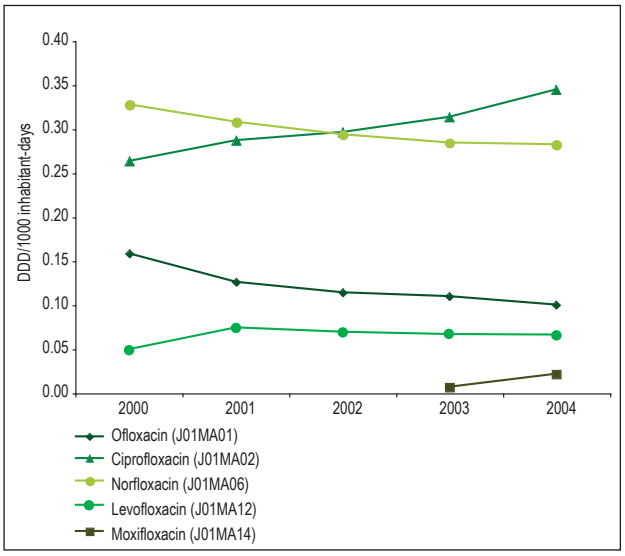


Figure 4. Use of fluoroquinolones for systemic use in primary health care, 2000 - 2004.

In the Netherlands 85% of the prescriptions and DDD's in primary health care is prescribed by general practitioners whereas 15% is prescribed by medical specialists to their outpatients.
In 2000, 27% of the antibiotics prescribed by general practitioners were tetracyclines and 19% were penicillins with extended spectrum (table 2). These proportions were lower for medical specialists. On the contrary, combinations of penicillins with beta-lactamase inhibitors, combinations of sulphonamides and trimethoprim and the fluoroquinolones were relatively more often prescribed by the medical specialists. Similar prescription patterns were observed in 2004. However, general practitioners are gradually substituting amoxicillin with co-amoxiclav.

Table 3 presents the use of antibiotics in 2004 by age and gender. Antibiotic use increased with age for the majority of therapeutic groups, in men as well as in women. Antibiotics were most often used by men and women over 65 years of age.
Antibiotics were on average more often used by women compared to men (figure 6A). Only in the age category of 0-1 year, boys used more antibiotics than girls.
Regarding the different subclasses of antibiotics only the combinations of sulfonamides and trimethoprim was more often prescribed to men whereas no differences in consumption between men and women were found for the beta-lactamase resistant penicillins, the combinations of penicillins including beta-lactamase inhibitors and the fluoroquinolones (Figure 5). Trimethoprim and derivatives, and nitrofuran derivatives were mainly prescribed to women (Figure 6B and 6C). In the age

Table 2. Relative use (% of total DDD/1000 inhabitant-days) of antibiotics for systemic use (J01) in primary health care by prescriber, 2000 and 2004 (Source: SFK).

ATC group[a]	Therapeutic group	Year			
		2000		2004	
		General practitioner	Medical specialist	General practitioner	Medical specialist
J01AA	Tetracyclines	27.0	20.1	24.1	17.8
J01CA	Penicillins with extended spectrum	18.8	8.9	15.5	7.2
J01CE	Beta-lactamase sensitive penicillins	5.7	1.8	4.8	1.4
J01CF	Beta-lactamase resistant penicillins	2.2	4	2.9	4.1
J01CR	Penicillins + beta-lactamase inhibitors	10.9	17.1	13.7	18.6
J01D	Cephalosporins and related substances	0.7	1.9	0.4	1.1
J01EA	Trimethoprim and derivatives	3.2	1.9	3.2	1.5
J01EC	Intermediate-acting sulfonamides	0.0	0.2	0.0	0.2
J01EE	Sulfonamides + trimethoprim	3.7	8.1	3.3	7.9
J01FA	Macrolides	11.9	11.6	13.8	14.5
J01FF	Lincosamides	0.1	1.8	0.2	2.7
J01GB	Aminoglycosides	0.0	0.2	0.1	0.7
J01MA	Fluoroquinolones	7.3	14.5	7.6	14.9
J01MB	Other quinolones	0.5	0.3	0.3	0.2
J01XE	Nitrofuran derivatives (nitrofurantoin)	7.3	6.3	9.6	6.3
J01X	Other antibiotics (= J01XE excluded)	0.7	1.3	0.4	0.9
J01	Antibiotics for systemic use (total)	100	100	100	100

[a] from the 2005 edition of the Anatomical Therapeutic Chemical (ATC) classification system

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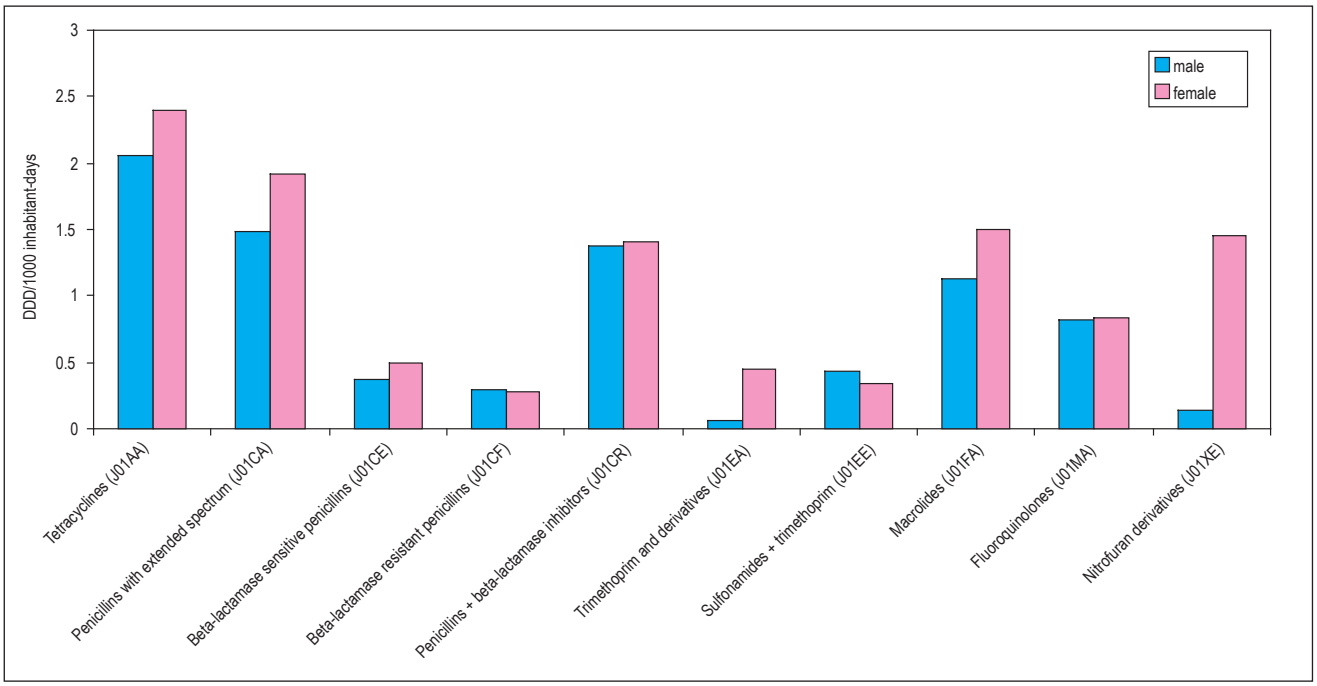


Figure 5. Use of antibiotics for systemic use (J01) in primary health care by gender, 2004 (Source: SFK).

category of 65 years and older, women used 4 to 6 times as much of these antibiotics compared to men. Up to twenty years of age, fluoroquinolones were more often prescribed to women whereas in the age category of 65 years and older fluoroquinolones were more often prescribed to men (figure 6D).

Discussion

From 1997 – 2004 total antibiotic consumption remained almost constant in the Netherlands. The use of antibiotics is approximately 10 DDD/1000 inhabitant days, which is lower than in any other European country (reference 2). In 2002, prescription of antibiotics in primary care

Table 3. Use of antibiotics for systemic use (J01) in primary health care (DDD/1000 inhabitant-days) by age category and gender, 2004 (Source: SFK).

ATC group[a]	Therapeutic group	Male					Female				
		0-1	2-10	11-20	21-64	≥ 65	0-1	2-10	11-20	21-64	≥ 65
J01AA	Tetracyclines	0.01	0.01	1.86	2.12	4.46	0.01	0.01	1.37	2.85	3.49
J01CA	Penicillins with extended spectrum	2.46	2.24	0.90	1.30	2.08	1.92	2.21	1.24	2.00	1.94
J01CE	Beta-lactamase sensitive penicillins	0.08	0.23	0.40	0.40	0.32	0.06	0.21	0.67	0.54	0.39
J01CF	Beta-lactamase resistant penicillins	0.00	0.05	0.18	0.32	0.54	0.00	0.05	0.17	0.28	0.57
J01CR	Penicillins + beta-lactamase inhibitors	0.61	0.69	0.62	1.29	3.45	0.43	0.82	0.77	1.40	2.46
J01D	Cephalosporins and related substances	0.01	0.02	0.02	0.03	0.08	0.01	0.03	0.02	0.04	0.14
J01EA	Trimethoprim and derivatives	0.05	0.03	0.02	0.04	0.28	0.03	0.08	0.30	0.37	1.16
J01EC	Intermediate-acting sulfonamides	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00
J01EE	Sulfonamides + trimethoprim	0.16	0.24	0.17	0.38	1.24	0.10	0.26	0.23	0.29	0.72
J01FA	Macrolides	0.65	0.99	0.75	1.06	2.17	0.50	0.93	1.01	1.60	2.04
J01FF	Lincosamides	0.00	0.00	0.02	0.07	0.22	0.00	0.00	0.02	0.06	0.19
J01GB	Aminoglycosides	0.01	0.03	0.06	0.01	0.02	0.00	0.02	0.06	0.01	0.02
J01MA	Fluoroquinolones	0.03	0.03	0.12	0.72	3.08	0.02	0.03	0.23	0.65	2.58
J01MB	Other quinolones	0.00	0.00	0.00	0.00	0.03	0.00	0.00	0.01	0.02	0.18
J01XE	Nitrofuran derivatives (nitrofurantoin)	0.04	0.04	0.05	0.09	0.62	0.03	0.23	0.82	1.21	3.91
J01XX	Other antibiotics (= J01XE excluded)	0.00	0.00	0.01	0.04	0.11	0.00	0.01	0.00	0.04	0.12
J01	Antibiotics for systemic use (total)	4.11	4.61	5.18	7.89	18.71	3.12	4.9	6.94	11.39	19.92

a) from the 2005 edition of the Anatomical Therapeutic Chemical (ATC) classification system

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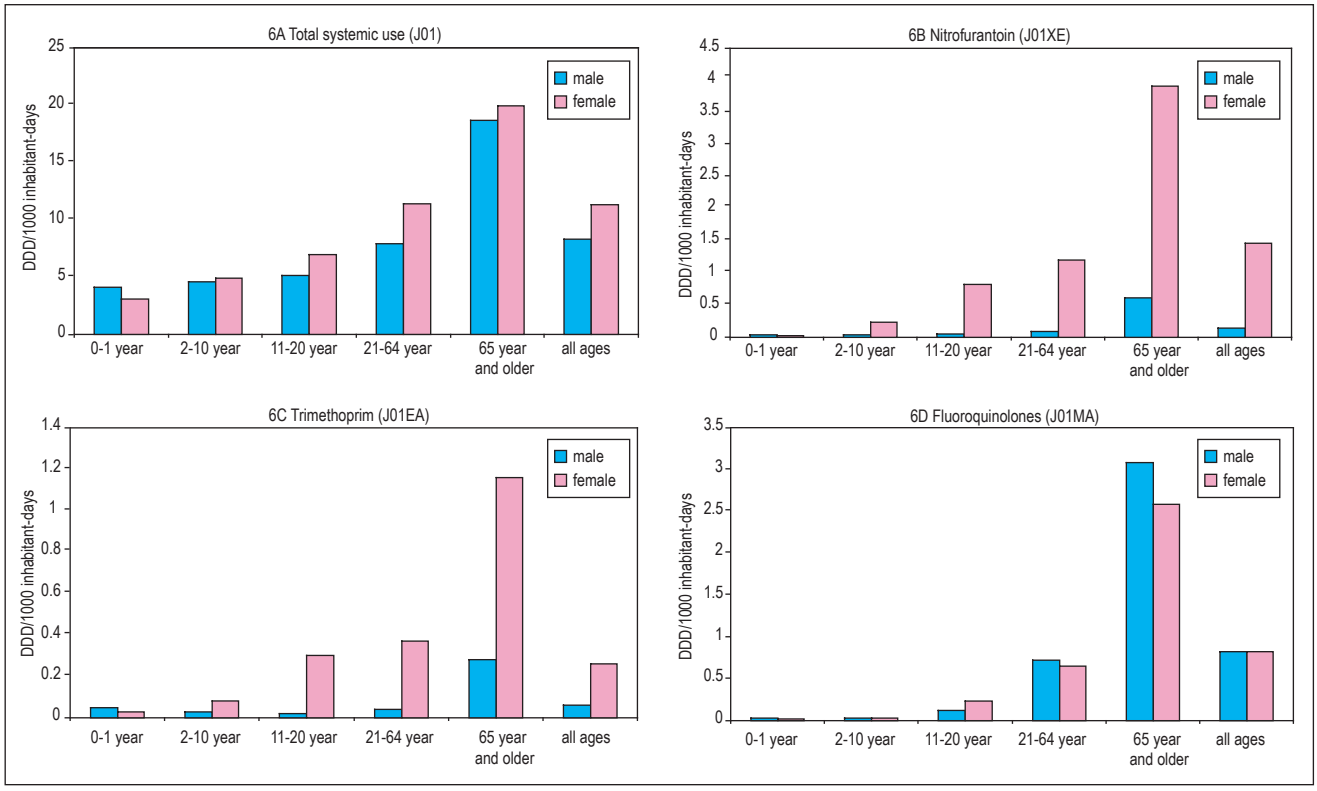


Figure 6. Use of antibiotics for systemic use (J01) in primary health care by age category and gender, 2004 (Source: SFK).

in Europe varied greatly; the highest rate was in France (32.2 DDD per 1000 inhabitants daily) and the lowest was in the Netherlands (10.0 DDD per 1000 inhabitants daily) (reference 2).
Compared to southern and eastern Europe, antibiotic use in the Netherlands is conservative.
However, over the past years we observed a growing use of some antibiotics, such as co-amoxiclav, clarithromycin and azithromycin, and ciprofloxacin. These increases were largely offset by the decreased use of doxycycline, fenethicillin and amoxicillin.
Reasons for this shift towards these newer antibiotics are unknown. To evaluate the higher use of these antibiotics insight into susceptibility patterns of causative microorganisms, prescription habits of general practitioners and medical specialists, and indications seem warranted.
In collaboration with the Foundation for Pharmaceutical Statistics (SFK) we developed a method to study the use of antibiotics at the patient level in the Dutch community (see project 1). With this method we analyse prescription habits in order to gain insight into first and second-line treatments. Data on indications may facilitate the understanding of observed- changes over the years and of patterns of usage by age category and gender.

Hospitals

Hospital resource indicators

Between 1999 and 2003 the mean number of admissions per hospital increased from 16,159 to 17,919 (+11%) in our cohort of hospitals. However, the mean length of stay decreased from 8.8 to 7.4 days (-18%). Thus the number of patient-days decreased from 125,498 to 115,054 (-8%). These trends in hospital resource indicators are consistent with the demographics of all acute care hospitals as registered by Statistics Netherlands (see appendix).

Hospital use

Data on antibiotic use in Dutch hospitals between 1999 and 2003 were expressed in DDD per 100 patient-days and in DDD per 100 admissions.
From our data it is evident that trends over time in DDD per 100 patient-days do not always correlate with trends in DDD per 100 admissions (table 4 and 5). Differences in trends between the two units of measurement are the result of changes in resource indicators over time.
In 1999 total systemic use of antibiotics in Dutch hospitals was 43.1 DDD per 100 patient-days, and increased by 20% to 51.9 DDD per 100 patient-days in 2003 (table 4). The mean number of total DDD per

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Table 4. Use of antibiotics for systemic use (J01) in hospitals[a] (DDD/100 patient-days), 1999-2003 (Source: SWAB).

ATC group[b]	Therapeutic group	1999	2000	2001	2002	2003
J01AA	Tetracyclines	1.6	1.6	1.6	1.7	1.4
J01CA	Penicillins with extended spectrum	6.3	5.8	6	6.1	6
J01CE	Beta-lactamase sensitive penicillins	1.0	1.1	1.3	1.2	1.2
J01CF	Beta-lactamase resistant penicillins	3.9	4.3	4.3	4.4	5.4
J01CR	Penicillins + beta-lactamase inhibitors	8.8	8.9	9.9	12.2	12.1
J01DA	Cephalosporins	5.6	5.6	6.1	6.3	6.5
J01DF	Monobactams	0.0	0.0	0.0	0.0	0.0
J01DH	Carbapenems	0.3	0.4	0.4	0.5	0.5
J01EA	Trimethoprim and derivatives	0.5	0.3	0.5	0.5	0.5
J01EC	Intermediate-acting sulfonamides	0.1	0.1	0.0	0.0	0.1
J01EE	Sulfonamides + trimethoprim	2.5	2.3	2.3	2.4	2.3
J01FA	Macrolides	2.2	2.1	2.3	2.7	2.4
J01FF	Lincosamides	1.1	1.2	1.3	1.5	1.6
J01GB	Aminoglycosides	2.1	2.1	2.0	2.1	2.5
J01MA	Fluoroquinolones	5.0	4.7	5.5	5.7	6.4
J01MB	Other quinolones	0.0	0.1	0.1	0.1	0.1
J01XA	Glycopeptides	0.4	0.5	0.5	0.5	0.5
J01XB	Polymyxins	0.2	0.3	0.1	0.1	0.1
J01XC	Steroid antibacterials (fusidic acid)	0.0	0.0	0.0	0.0	0.0
J01XD	Imidazole derivatives	1.2	1.1	1.3	1.5	1.6
J01XE	Nitrofuran derivatives	0.2	0.5	0.5	0.5	0.7
J01XX05	Methenamine	0.0	0.0	0.0	0.0	0.0
J01XX08	Linezolid	0.0	0.0	0.0	0.0	0.0
J01	Antibiotics for systemic use (total)	43.1	43	46.5	50.2	51.9

[a] Percentage of covered patient-days in 1999, 2000, 2001, 2002 and 2003 were 60, 58, 51, 62 and 72, respectively.
[b] from the 2005 edition of the Anatomical Therapeutic Chemical (ATC) classification system

hospital increased by 9% from 54,078 in 1999 to 59,666 in 2003.
However, total systemic use expressed as DDD per 100 admissions remained constant (table 5). So the average patient used the same number of DDD in 1999 and 2003. In 2003 patients were admitted to the hospital for a shorter period of time. This caused an intensification of antibiotic therapy per average patient-day.

Four main categories with regard to trends in antibiotic use over the years can be distinguished (table 4 and 5):

1. For the beta-lactamase resistant penicillins, combinations of penicillins including beta-lactamase inhibitors, carbapenems, lincosamides, fluoroquinolones, imidazole derivatives and nitrofuran derivatives we found an increase over the years for both units of measurement. This means that on average patients used more of these antibiotics than before, although they were hospitalized for a shorter time period. This resulted in an intensification of antibiotic therapy per patient-day.

2. For beta-lactamase sensitive penicillins, cephalosporins, macrolides, aminoglycosides and glycopeptides an increase in DDD per 100 patient-days and a constant or slightly decreased use in DDD per 100 admissions was observed.
So on average patients used the same or slightly decreased number of these antibiotics in a shorter period of time. This caused an intensification of antibiotic therapy per patient-day.

3. For tetracyclines, penicillins with extended spectrum and combinations of sulfonamides and trimethoprim a decrease in both units of measurement was found. This resulted in a decline of antibiotic therapy per patient-day. So on average patients used a significantly lower amount of antibiotics than before.

4. For trimethoprim and derivatives we found a decrease in the number of DDD per 100 admissions and a constant use expressed in DDD per 100 patient-days. So the patients used less antibiotics. The decrease in use was proportional to the decrease in the length of stay. So use per patient-day remained constant.

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Table 5. Use of antibiotics for systemic use (J01) in hospitals[a] (DDD/100 admissions), 1999-2003 (Source: SWAB).

ATC group[b]	Therapeutic group	1999	2000	2001	2002	2003
J01AA	Tetracyclines	12.5	12.0	11.3	11.2	8.8
J01CA	Penicillins with extended spectrum	48.6	44.2	41.5	41.2	38.6
J01CE	Beta-lactamase sensitive penicillins	8.1	8.1	9.2	8.2	7.8
J01CF	Beta-lactamase resistant penicillins	30.4	32.8	29.4	29.5	34.6
J01CR	Penicillins + beta-lactamase inhibitors	68.1	68.1	68.0	81.6	77.7
J01DA	Cephalosporins	43.1	42.8	42.3	42.0	42.0
J01DF	Monobactams	0.1	0.1	0.1	0.0	0.0
J01DH	Carbapenems	2.6	3.3	2.4	3.2	3.3
J01EA	Trimethoprim and derivatives	3.8	2.5	3.6	3.3	3.1
J01EC	Intermediate-acting sulfonamides	0.8	0.5	0.1	0.2	0.8
J01EE	Sulfonamides + trimethoprim	19.1	17.3	15.6	16.0	14.4
J01FA	Macrolides	17.2	15.4	15.7	17.9	15.4
J01FF	Lincosamides	8.4	9.0	9.2	10.0	10.2
J01GB	Aminoglycosides	16.2	16.2	14.0	14.2	15.8
J01MA	Fluoroquinolones	38.5	35.9	38.0	38.2	41.0
J01MB	Other quinolones	0.3	0.4	0.5	0.5	0.6
J01XA	Glycopeptides	3.5	3.8	3.2	3.4	3.4
J01XB	Polymyxins	1.9	2.3	0.8	0.4	0.5
J01XC	Steroid antibacterials (fusidic acid)	0.1	0.1	0.2	0.1	0.2
J01XD	Imidazole derivatives	9.5	8.5	9.0	9.7	10.1
J01XE	Nitrofuran derivatives	1.6	2.8	3.3	3.6	4.7
J01XX05	Methenamine	0.1	0.3	0.1	0.1	0.2
J01XX08	Linezolid	0.0	0.0	0.0	0.1	0.1
J01	Antibiotics for systemic use (total)	334.7	327.1	320.2	336.5	333.2

[a] Percentage of covered admissions in 1999, 2000, 2001, 2002 and 2003 were 59, 57, 54, 64 and 73, respectively.
[b] from the 2005 edition of the Anatomical Therapeutic Chemical (ATC) classification system

The distribution of antibiotics by class in 2003 is presented in figure 7. In 2003 all penicillins combined represented 46% of hospital antibiotic use in the Netherlands. Combinations of penicillins, including beta-lactamase inhibitors, mainly co-amoxiclav, represented 22% of hospital antibiotic use in the Netherlands.

The use of co-amoxiclav increased from 66.8 in 1999 to 75.5 DDD per 100 admissions in 2003 (+13%). From 1999-2003 the use of piperacillin with tazobactam increased from 1.3 to 2.3 DDD per 100 admissions (+77%). Amoxicillin use decreased from 44.7 in 1999 to 35.8 DDD per 100 admissions in 2003. Flucloxacillin is the only antistaphylococcal penicillin used to any extent in the Netherlands. The use of this antibiotic increased by 14% from 30.4 in 1999 to 34.6 DDD per 100 admissions in 2003. For these antibiotics similar trends were found when expressed in DDD per 100 patient-days.

Cephalosporins represented 12% of the total hospital use in 2003 (figure 7). The use of the various generations of cephalosporins is summarised in figure 8A and 8B. The use of the first generation cephalosporins increased from 10.6 in 2000 to 12.0 DDD/100 admissions in 2003 (+13%). Of these cefazolin was by far the most commonly used one. The use of cefazolin increased from 8.0 in 1999 to 11.2 DDD/100 admissions (+36%) in 2003. An increase was also found when expressed in DDD per 100 patient-days. The use of cefuroxime remained constant at 17.0 DDD/100 admissions. An increase was found when expressed in DDD per 100 patient-days. After an increase in use of the third generation cephalosporins in 2000 (13.4 DDD/100 admissions), use remained constant. However, when expressed in DDD per 100 patient-days a gradual increase has been observed.

Clarithromycin is now the most commonly used macrolide in the hospitals. Its use gradually increased from 7.5 in 1999 to 8.8 DDD/100 admissions in 2002 and decreased to 7.9 DDD/100 admissions in 2003 (figure 9A). The use of azithromycin also increased. Comparable trends were observed when expressed in DDD per 100 patient-days (figure 9B).

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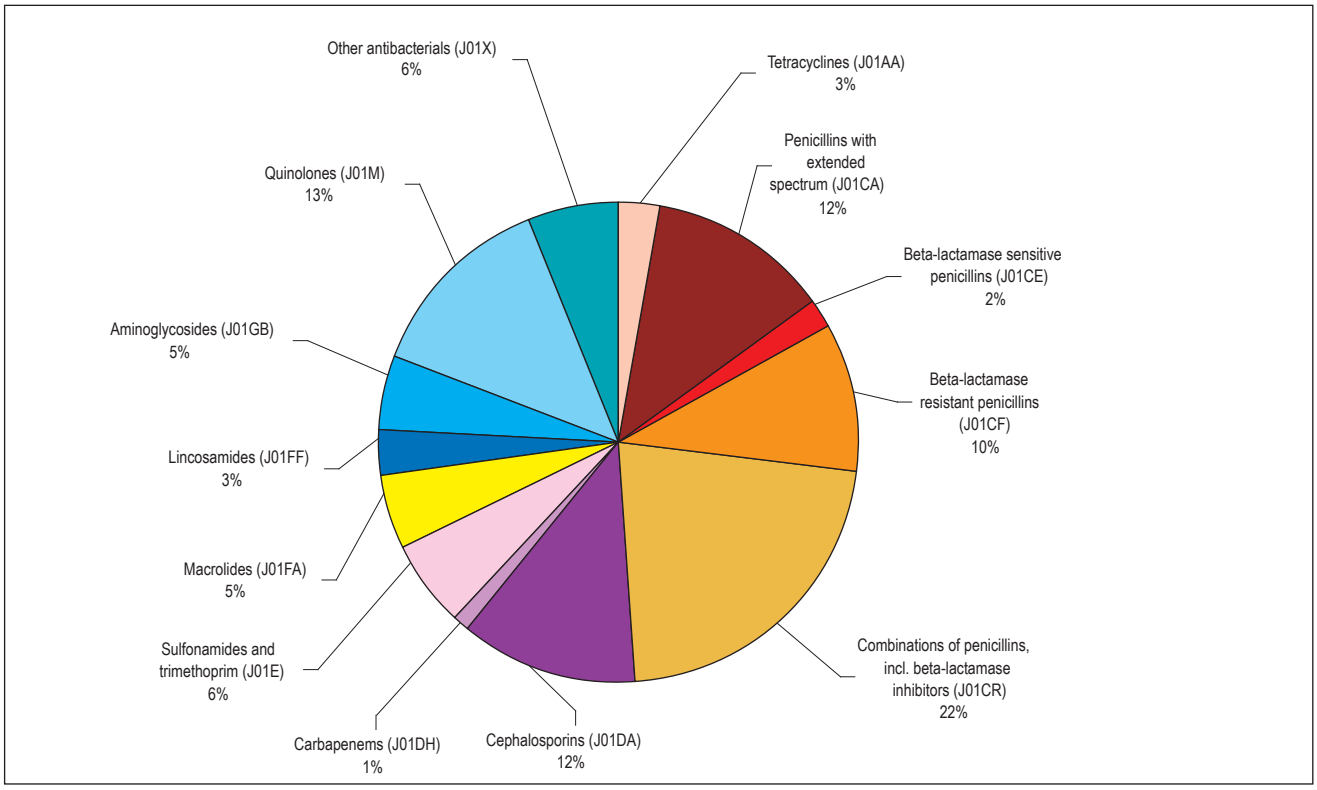


Figure 7. Distribution of the use of antibiotics for systemic use (J01, DDD) in hospitals, 2003 (Source: SWAB).

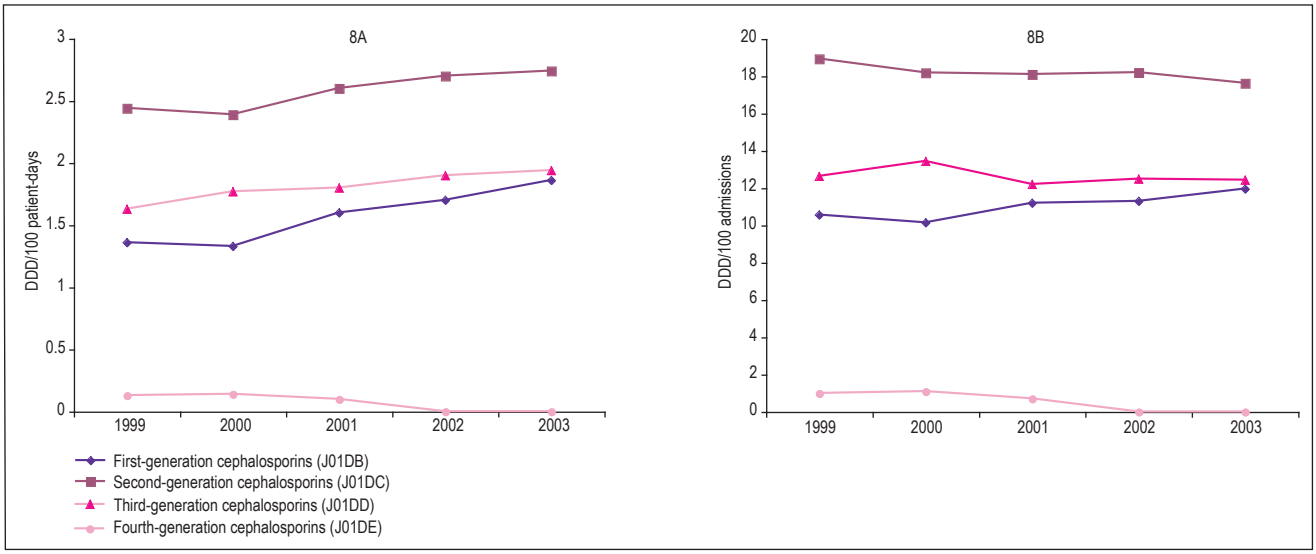
The use of clindamycin increased by 21% from 8.4 in 1999 to 10.2 DDD/100 admissions in 2001. The increase found when expressed in DDD per 100 patient-days was 49%.

Gentamicin was by far the most commonly used antibiotic of the aminoglycoside class (figure 10A and B).

A remarkable increase in use was found between 2002 and 2003.

Fluoroquinolones represented 13% of the total hospital use in 2003 (figure 7). Total use of the fluoroquinolones decreased in 2000 to 35.9 DDD/100 admissions, but increased with 5.1 DDD/100 admissions between 2000

Figure 8. Use of cephalosporins in hospitals, 1999-2003 (Source: SWAB).



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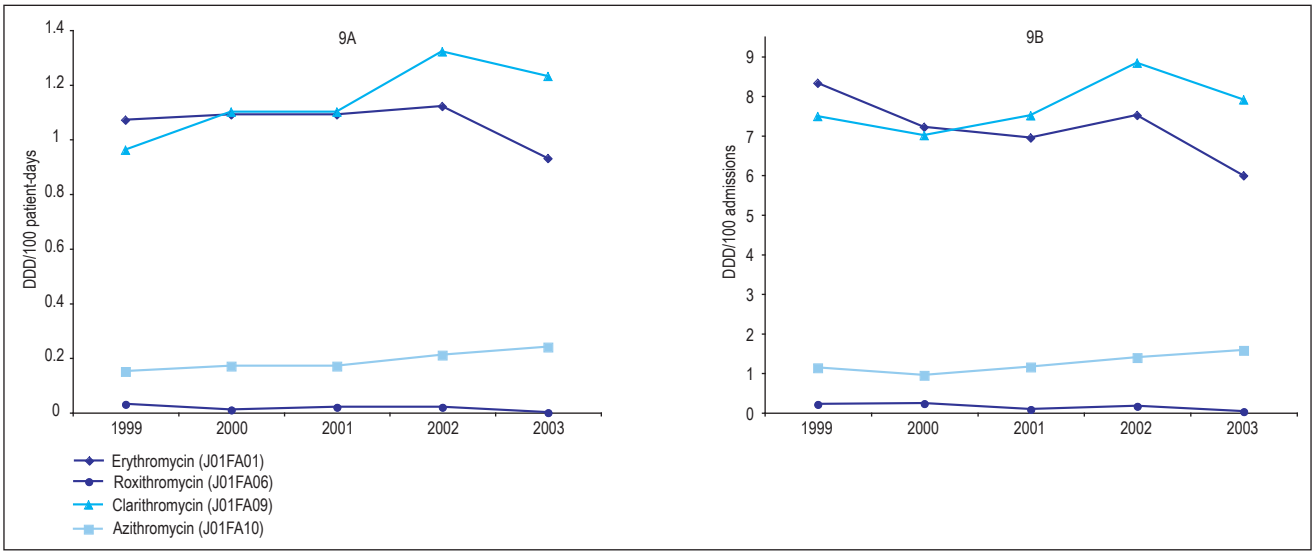


Figure 9. Use of macrolides in hospitals, 1999-2003 (Source: SWAB).

and 2003 (table 5). The use of ciprofloxacin increased by 42% to 29.2 DDD/100 admissions in 2003 (figure 11B). An increase of 72% was found when expressed in DDD per 100 patient-days (figure 11A).

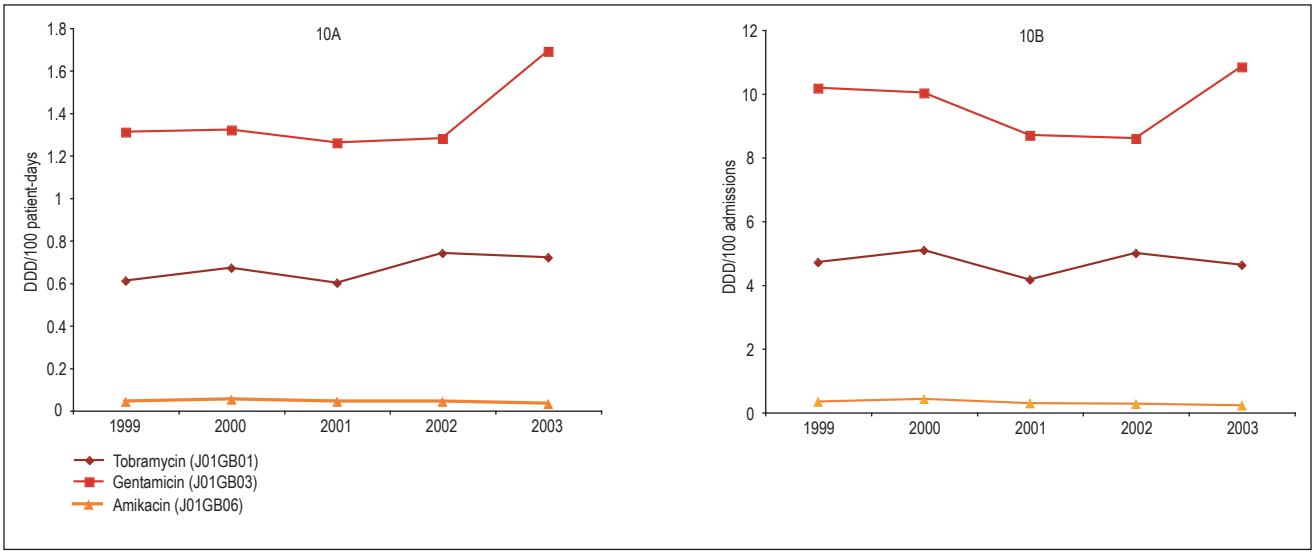
The use of vancomycin increased whereas the use of teicoplanin decreased. Similar trends were found for both units of measurement (figure 12A and B).

Discussion

The unit in which antibiotic usage is expressed does matter (reference 3). 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 (reference 4). The denominator should thus preferably include information on all these factors. However, there is a lack of studies to determine the correlation between different measures of antibiotic use and the level of antibiotic resistance.

In this edition of NethMap, data on antibiotic use in Dutch hospitals between 1999 and 2003 were expressed in DDD per 100 patient-days and in DDD per 100 admissions. Until recently an increase in the number

Figure 10. Use of aminoglycosides in hospitals, 1999-2003 (Source: SWAB).



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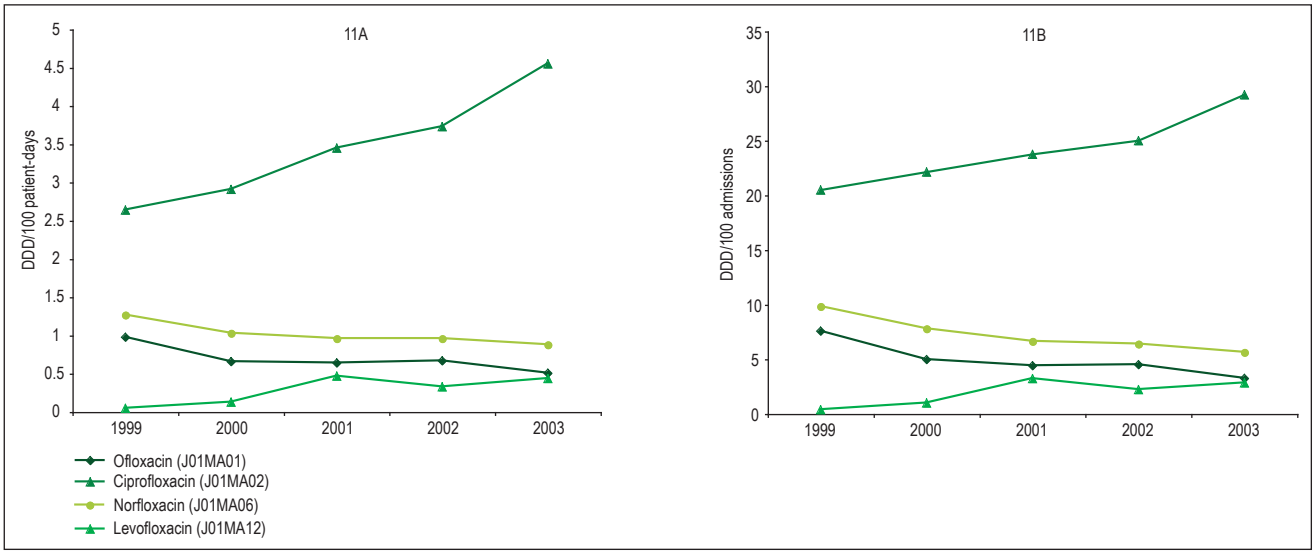
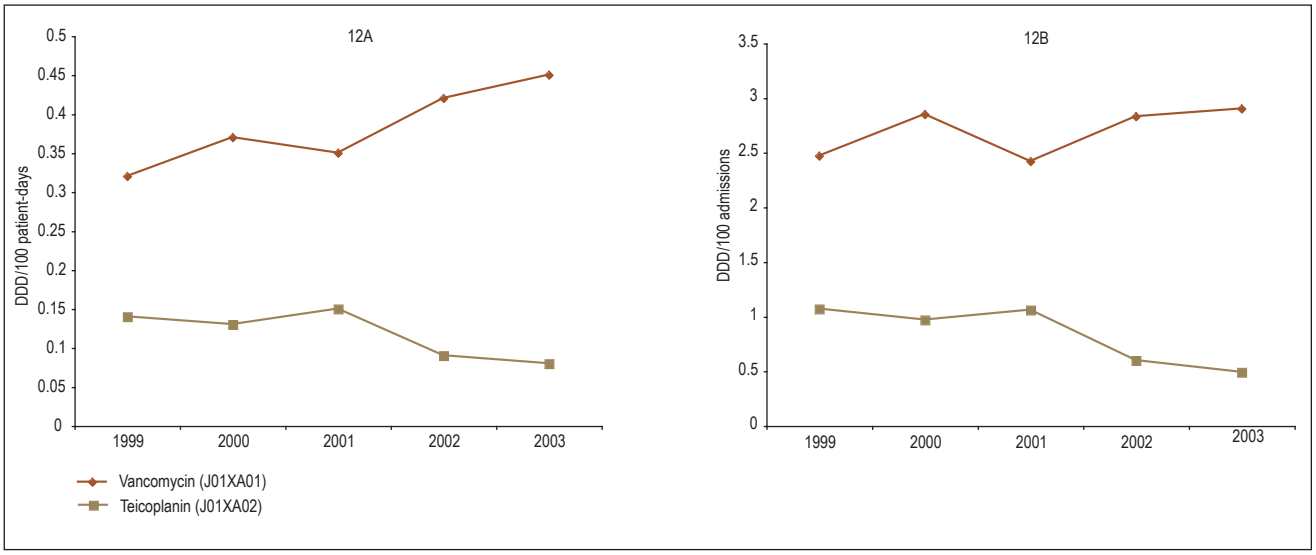


Figure 11. Use of fluoroquinolones in hospitals, 1999-2003 (Source: SWAB).

of DDD per 100 patient-days has been exclusively interpreted as worrisome with regards to the potential for antibiotic resistance development. We have distinguished four main categories with regard to the observed trends in antibiotic use. It is clear that an increase in both the number of DDD per 100 patient-days and the number of DDD per 100 admissions (category 1) is worrisome and no increase in either unit of measurement (category 3) is not worrisome in relation to resistance development. The trends in category 2 and 4 are less easy to interpret. A constant use per patient combined with an increase in the number of admissions (category 2) is indicative for an increase of the selection pressure exerted by antibiotics over the years. However, an intensification of antibiotic therapy per patient-day suggests a shortening of duration of antibiotic treatment. Short duration of therapy may lead to less selection of resistant microorganisms (reference 5).

In 2001 a remarkable increase in the use of cefazolin was observed. Cefazolin is an agent that is used for perioperative prophylaxis and the increased use in 2001 may be explained by a national intervention. In 2000 the SWAB published the guideline for perioperative antibiotic prophylaxis. In this quideline cefazolin is strongly recommended. In addition, in 1999 the CHIPS (surgical prophylaxis and surveillance) project, an audit and improvement programme looking at the quality of

Figure 12. Use of glycopeptides in hospitals, 1999-2003 (Source: SWAB).



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surgical prophylaxis, was started in the Netherlands (reference 7).

The consumption of beta-lactamase resistant penicillins and vancomycin continued to increase since 1999. This might be due either to an increased focus on staphylococcal infections or an increased incidence of these infections in primary health care.

The prescription of antimicrobials in Dutch hospitals presented a steady increase in the use of co-amoxiclav, fluoroquinolones and carbapenems. Monitoring antibiotic use patterns by specific populations within the hospital (e.g. intensive care and general ward patients, surgical and non-surgical patients) is warranted to estimate the rationality of these prescriptions.

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Project 1

Using directed animated graphs for examining subsequent use of antibiotics

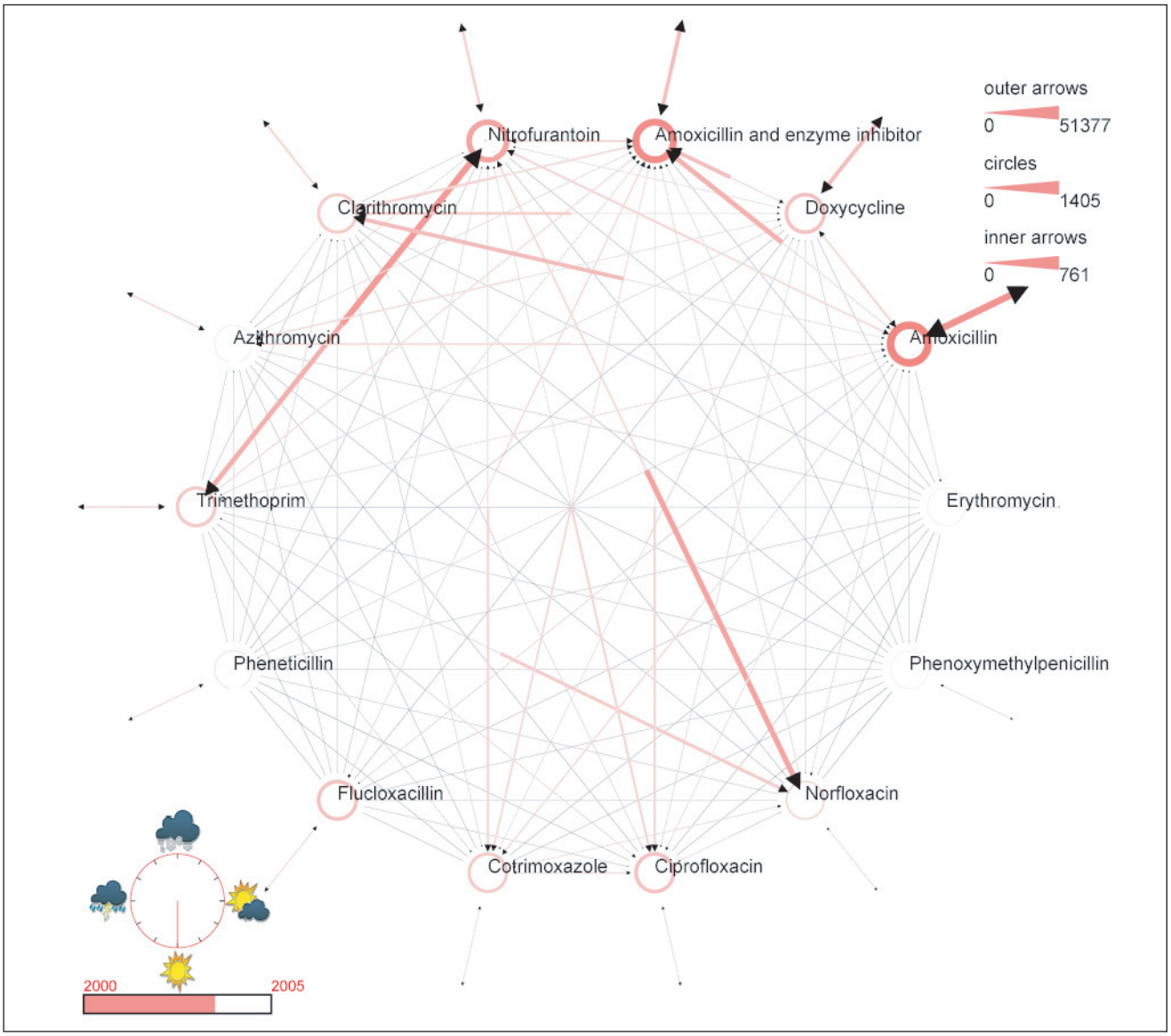
F Baart[1,2], S Natsch[2], PD van der Linden[2], AJ de Neeling[2]

[1]Foundation for Pharmaceutical Statistics (SFK), [2]SWAB's working group on the use of antimicrobial agents

Introduction

If a patient uses more than one course of antibiotics in a row, he or she has apparently not been cured. A subsequent course can have different causes. The preceding antibiotic may have caused adverse drug reactions. The preceding antibiotic may have failed in curing the patient from the infection or the bacteria causing the infection were reported to be resistant to the preceding prescribed antibiotic. A series of two antibiotics can be seen as a transition from the first antibiotic to another antibiotic. The most common way to display transitions is by using graphs. The SWAB working group on the use of antimicrobial agents developed a method to extensively study the

Figure 1. Transitions in antibiotic usage in July 2003.



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use of antibiotics in the Dutch community. This project describes how animated directed graphs can be used to gain insight into the subsequent use of antibiotics.

Method

The database of the Foundation of Pharmaceutical Statistics (SFK) was used for this project. In this database all prescriptions for an antibiotic over the years 2000 through 2004 were selected. The prescriptions were sorted by patient and prescription date. These series were transformed into four types of transitions. First the transition from no antibiotic to an antibiotic, second from an antibiotic to no antibiotic, third from one antibiotic to the same antibiotic and fourth from an antibiotic to another antibiotic. The 14 most frequently used antibiotics were plotted as evenly spaced small circles on the edge of a large ring. All four different kinds of transitions were plotted into the graph by connecting the circles with arrows:

1. The transition from no antibiotic to any antibiotic is plotted by an arrow from outside the main ring to the small circle representing that antibiotic. These are patients starting with a course of that antibiotic for the first time.
2. The transition from any antibiotic to no antibiotic is plotted using an arrow from that antibiotic circle to the outside of the main ring. These are patients stopping with a course of that particular antibiotic.
3. The transition from an antibiotic to the same antibiotic is represented by the thickness of the circles of each antibiotic. These patients start using the same antibiotic again.
4. The transition from an antibiotic to another antibiotic is plotted using the inner arrows between different antibiotic circles. These patients are switching between different antibiotics.

All arrows are built from two parts. The part pointing away implies patients switching from that antibiotic to another antibiotic or no more antibiotics. The part pointing towards implies patients switching to that antibiotic. The thickness of the arrows was used to represent the frequencies of the transitions.

Results

The dataset used in this study, consisted of 10 million antibiotic prescriptions from 2 million patients over the years 2000 through 2004. Using the described method a graph was created for each month in the 5 year period. The resulting 60 graphs were rendered into an animation. The full animation of the antibiotic usage from January 2000 through December 2004 can be viewed at the SFK website (http://www2.sfk.nl/svg/transitions). Figure 1 shows the directed graph representing the antibiotic usage in July 2003, as an example to illustrate the use of such a graph.

Some notable points in figure 1 are highlighted:

- Amoxicillin showed the biggest incoming outer arrow. Thus if a patient started using an antibiotic it was most often amoxicillin (n = 24,774);
- The least frequently used antibiotic (of the top 14) to start with was erythromycin (n = 1540);
- Amoxicillin/clavulanic acid, amoxicillin and nitrofurantoin have the thickest circles. So they were often prescribed two or more times in a row (n = 719, n = 658 and n = 536);
- Phenethicillin and azithromycin were seldom prescribed repeatedly (n = 126 and n = 103);
- The thickness of the inner rows shows that the most frequent transition was from trimethoprim to nitrofurantoin (n = 339);
- The transition from nitrofurantoin to norfloxacin was also quite common (n = 331).

Conclusion

Analysing transitions with animated graphs provides an in-depth analysis of patterns of usage, choices for first and second-line treatments and adherence to guidelines and policies. This information can be used as feedback to prescribers and policymakers.

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4 Resistance among common Pathogens

Surveillance of Antimicrobial Resistance in the Community

The prevalence of antibiotic resistance among bacteria causing community acquired infection was determined for strains collected from patients with complaints of an acute uncomplicated urinary tract infection visiting their general practitioner in communities in the Southern part of The Netherlands (1988-2001). This project was extended to other parts of The Netherlands from 2003-2004. See material and methods section for details regarding the acquisition and testing of isolates. The resistance patterns found among 1724 isolates of *Escherichia coli* in different areas in 2003-2004 are compared with the results found for the South of The Netherlands, obtained during the years before.

Escherichia coli

Escherichia coli isolates in 2003-2004 came from patients all over the Netherlands: from the North (78 strains, provinces Groningen and Drente), the East (393 strains, province of Gelderland), the West (882 strains, provinces of Utrecht, Noord Holland and Zuid Holland) and the South (371 strains, provinces Zeeland, Noord Brabant and Limburg). The results from the North were not analyzed separately and were not used for inter-regional comparison because of the low number of isolates.

The prevalence of amoxicillin resistance among *E. coli* strains from patients with acute urinary complaints was relatively stable (17-21%) until 2001 in the South, except for a much higher, unexplained prevalence in 1992 (figure 1). In 2003-2004 an overall resistance percentage of 33% was observed, varying from 31% (South and West) to 33% (East, figure 2). The amoxicillin resistance among *E. coli* in the community in 2001 was significantly lower than that in selected or Unselected Hospital Departments, but during 2002-2004 the resistance percentage equalled that of the Unselected Hospital Departments in 2001. The distribution of MICs of amoxicillin showed two subpopulations of strains, a susceptible one with MICs ranging from 1-16 mg/l and a highly resistant one (MIC>64 mg/l) (figure 3).

Resistance to co-amoxiclav was low, it was 3% or less in all provinces (figure 1). The MIC distribution showed a unimodal shape over a broad range from 1 to 32 mg/L (figure 3).

Trimethoprim resistance rates increased over the years, from 10% in 1988 to 17% in 2003-2004 (figure 1 and 2) in the South; the resistance rates in the East and West were significantly higher (22-24%, $p< 0.05$), making the overall figure of 23% for the whole country (figure 2). The prevalence of trimethoprim resistance among *E. coli* followed the trend in the Unselected Hospital Departments with a delay of two years. The resistance to co-trimoxazole followed that of trimethoprim, but was overall 2% lower. The MIC distribution for both compounds showed a bimodal distribution (figure 3) with a subpopulation of MICs over a broad range from 0.06 – 2 mg/l and one with MICs of 64 mg/l or higher.

Resistance to nitrofurantoin remained at a low level from 0.5% (East) to 1% (West) compared with 3% in the South. This is a significant difference ($p< 0.01$). The MIC

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

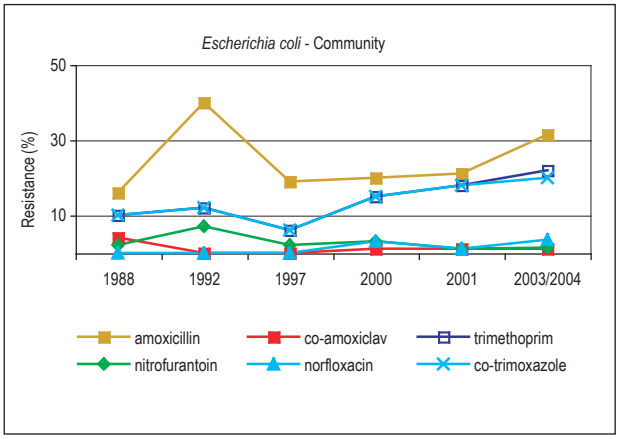
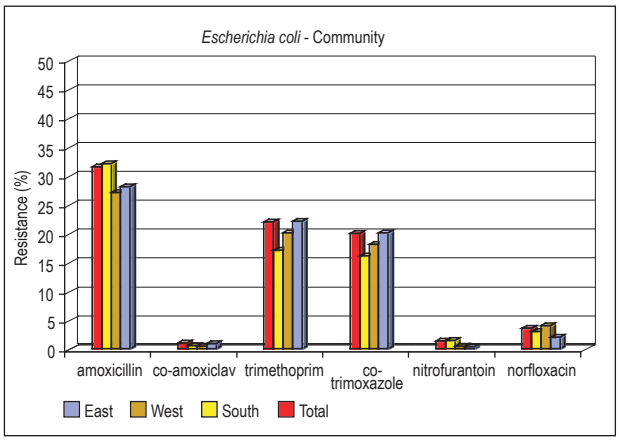


Figure 2. Regional and total resistance rates of antibiotics for *Escherichia coli* from the Community.



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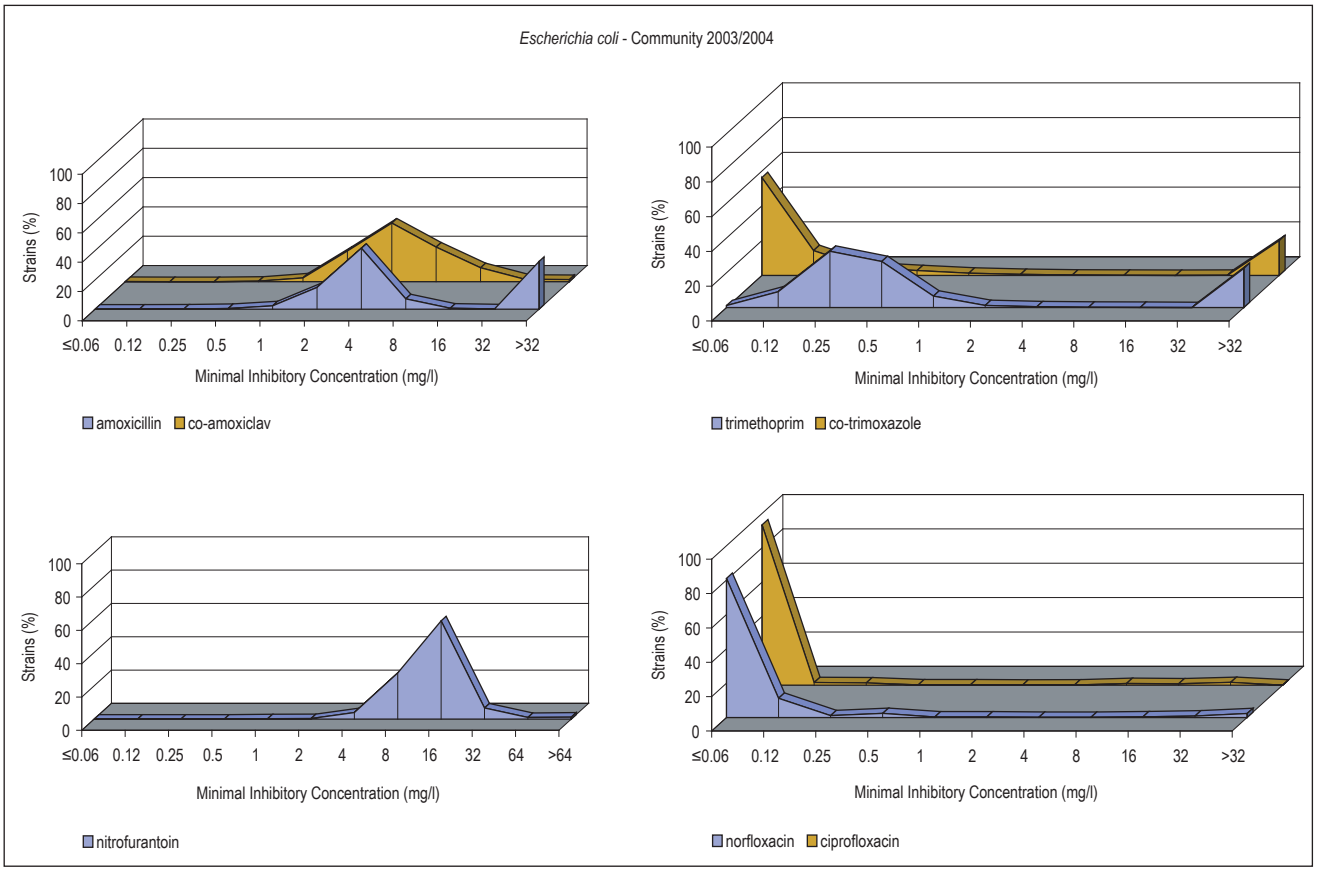


Figure 3. MIC distributions of antibiotics for *Escherichia coli* from the Community.

distribution showed a unimodal shape over a wide range from 2 to 256 mg/L, with a peak at 16 mg/L (figure 3). Norfloxacin resistant *E. coli* was at first found in 2000 and 2001 in the South, albeit at a rather low level (<3%, figure 1)). During 2003-2004 a slow increase in resistance (to 3.5 % overall) was observed, with rates ranging from 2% in the East to 4% in the other provinces (figure 1). There was complete cross-resistance with ciprofloxacin; The MIC distribution curves of both agents showed a large cluster of highly susceptible isolates and a few resistant ones (figure 3). The 3.5% quinolone resistance level is similar to that in Unselected Hospital Departments in 2001.

The differences in antibiotic susceptibility between the regions (figure 2) might be related to differences in antibiotic prescription (choice and duration) of the local general practitioners.
These data indicate that resistance to amoxicillin and trimethoprim among *E. coli* causing community acquired urinary tract infection are emerging in the community. These trends, if real, require further attention since trimethoprim is an agent of choice for the treatment of urinary tract infection (NHG standard) and amoxicillin may be used for paediatric complicated infection (i.e. relapsing and recurrent cases) in this setting. Higher number of isolates especially from the North and information as to the antibiotic therapy are necessary before firm conclusions can be drawn concerning regional differences in antibiotic susceptibility in relation to the antibiotic therapy prescribed.
These data also indicate that the rate of resistance in the community corresponds well with that in Unselected Hospital Departments a few years ago. There is no difference in trend and behaviour of resistance patterns, only a time delay of two years is observed.

Surveillance of Antimicrobial Resistance in Hospitals

The overall prevalence of antibiotic resistance in hospitals was estimated by using resistance data generated in routine clinical care. Unselected Hospital Departments and outpatients clinics were the sources of strains collected and tested by 11 Regional Public Health Laboratories and four local laboratories covering 30% of the Dutch population (table 1 in appendix). These

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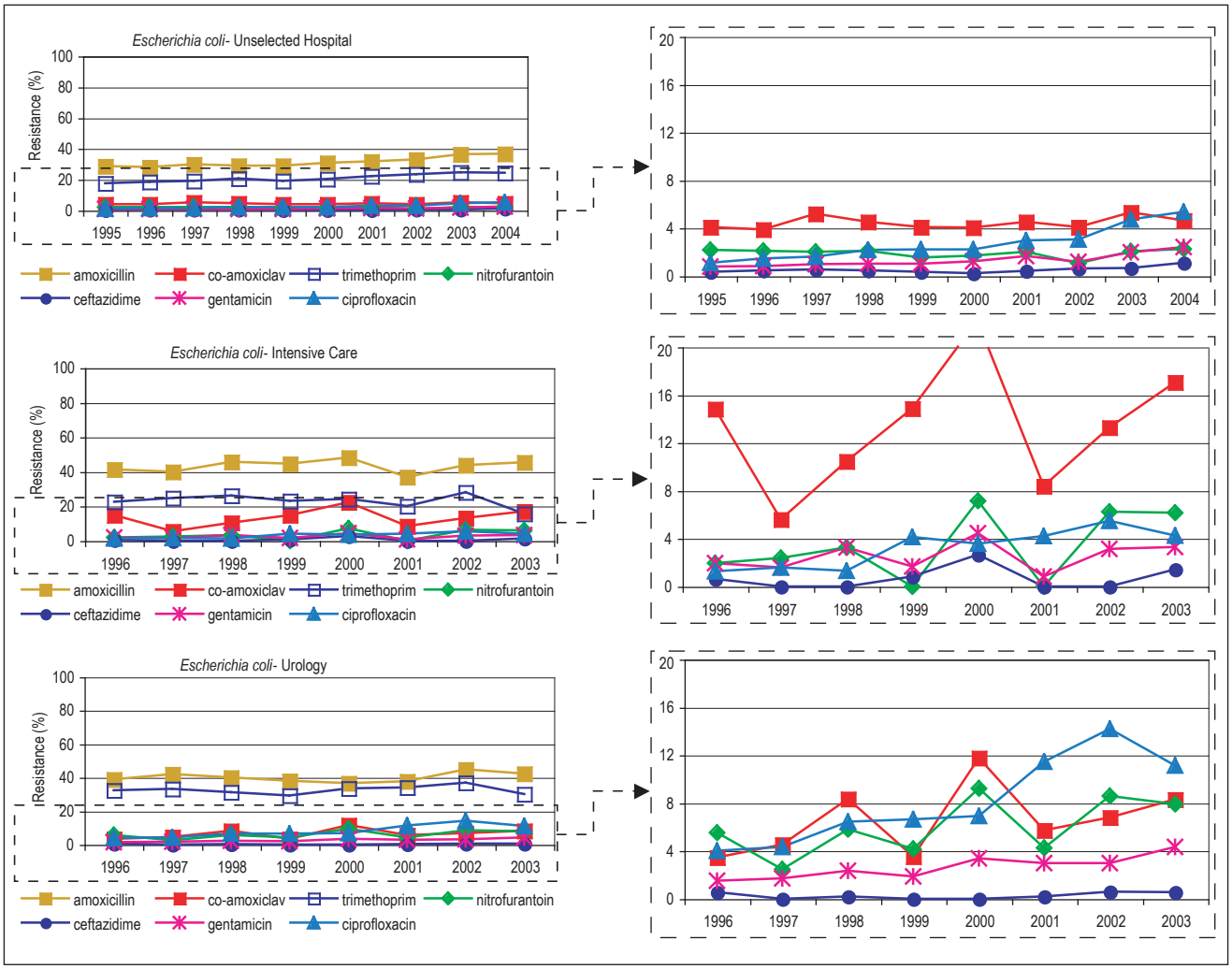


Figure 4. Trends in resistance to antibiotics among *Escherichia coli* derived from Unselected Hospital Departments, Intensive Care Units and Urology Services.

are designated resistance rates in 'Unselected Hospital Departments'. Resistance rates in Unselected Hospital Departments were compared with the resistance rates among strains isolated from selected departments in 14 large referral hospitals (table 2 in the appendix). These selected departments included the Intensive Care Units, being wards with high use of antibiotics and, consequently, high selective pressure favouring the emergence of resistance. Also included were the Urology Services and the Pulmonology Services, the latter two representing departments with frequent use of specific oral antibiotics. Results were analyzed per species of common nosocomial pathogens and are presented in the accompanying figures.

Escherichia coli

The overall prevalence of amoxicillin resistance in Unselected Hospitals Departments increased further from 29 % in 1995 to 37% in 2004 (figure 4). Amoxicillin resistance was higher in Urology Services (42%), but significantly and consistently the highest in Intensive Care Units. Starting in 1998 a steady increase in the prevalence of amoxicillin resistance was observed in Intensive Care Units reaching 45% in 2003. The distribution of MICs (figure 5) clearly showed that two subpopulations exist: a susceptible one with a broad MIC range from 0.25 -16 mg/l and a resistant one with MICs > 32 mg/l. The resistant subpopulation is steadily growing during the years.

Co-amoxiclav resistance was at a low level (4%) in Unselected Hospital Departments and in the Urology Services until 2000 (figure 4). Subsequently, an increase in the level of resistance was observed in the Urology Services, which stabilized at 8% in 2003. Co-amoxiclav resistance was much higher in Intensive Care Units and increased with fluctuations to >17% in 2003. The

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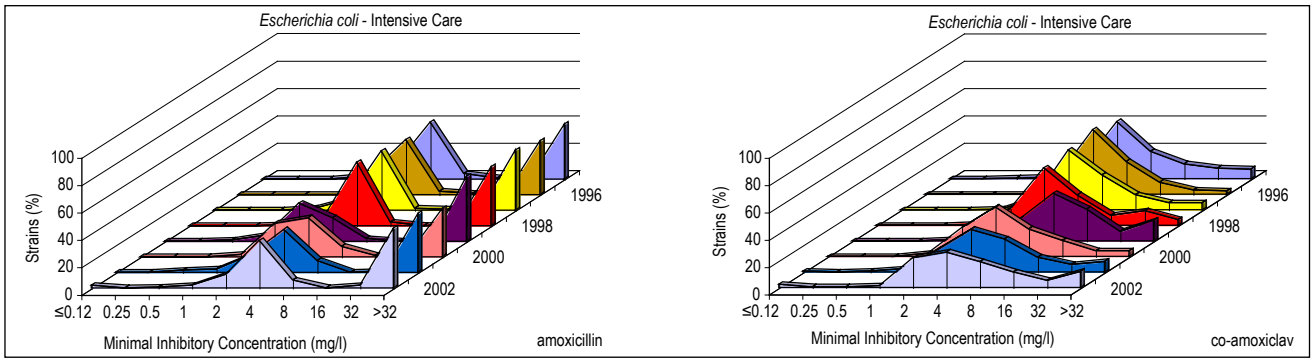


Figure 5. Trends in MIC distributions of amoxicillin and co-amoxiclav for *Escherichia coli* isolated from patients on Intensive Care Units.

MIC distribution of amoxicillin is comparable with that found for the community, but the MIC distribution of co-amoxiclav differs significantly from that in the community (figure 5). Here we find a considerable resistant subpopulation and a subpopulation in the area between susceptible and resistant.
Trimethoprim resistance increased slowly in Unselected Hospital Departments over the years from 18% to 25%. The level of trimethoprim resistance in Intensive Care Units fluctuated but followed this increasing tendency until 2002, when it was 28%. In 2003 a drop to 16% was observed. This may be explained by the extension of participating centres in 2002 and 2003. Three centres joined the surveillance, two of them in the South of The Netherlands, where the trimethoprim resistance in the community is also lower than in the rest of the country. This may have influenced the overall resistance rate. Trimethoprim resistance was significantly higher in the Urology Services. It remained at levels higher than 30% (figure 4). The trends in the various departments are presented in figure 6. The MIC distribution (figure 7) showed that two subpopulations exist: one susceptible and one highly resistant. A shift to higher MICs was already observed in 2000, resulting in a larger subpopulation of resistant strains in 2002 (37% vs 29% in 1999). Subsequently the susceptible subpopulation shifted "to the left" in 2002, which means that more strains had lower MICs. This stabilized in 2003 with a smaller subpopulation of resistant strains. Patterns of MIC distribution can, thus, give insight at an early stage of the emergence of resistance and of changes in subpopulations. This underlines the importance of quantitative susceptibility testing methodology when designing a surveillance system for antibiotic resistance. Similar differences in resistance rates between Intensive Care Units and the Urology services were observed for nitrofurantoin and the quinolones (figure 8), albeit at a lower prevalence levels. Nitrofurantoin resistance was about 2% in Unselected Hospital Departments, equal to the figures in the community. It was higher on Intensive Care Units (upto 2-6%), but the highest among strains from Urology Services (3-10%). No clear trend was

Figure 6. Trends of trimethoprim resistance in Unselected Hospital Departments, Intensive Care Units and Urology Services.

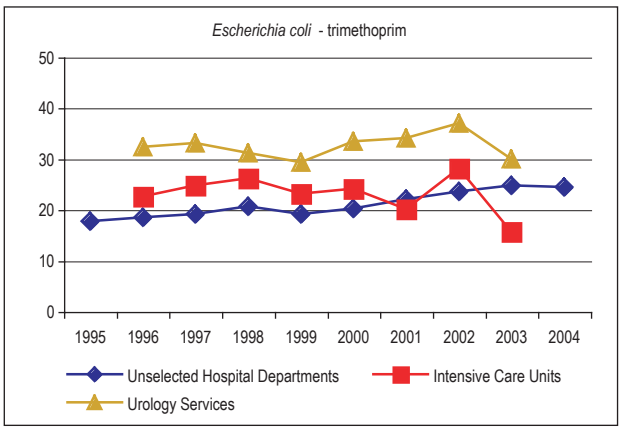
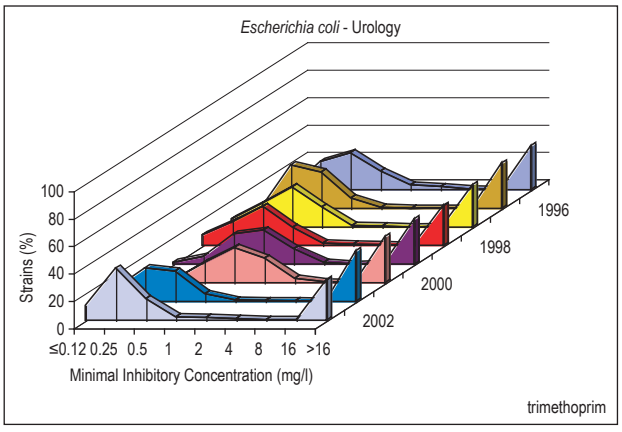


Figure 7. Trends in the MIC distributions of trimethoprim for *Escherichia coli* isolated from patients admitted to Urology Services.



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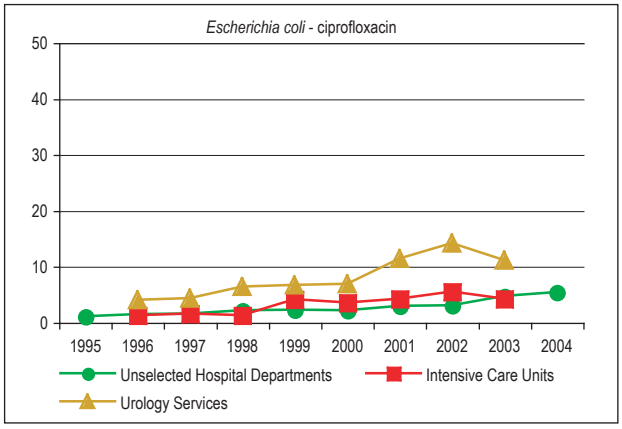


Figure 8. Trends in ciprofloxacin resistance in Unselected Hospital Departments, Intensive Care Units and Urology Services.

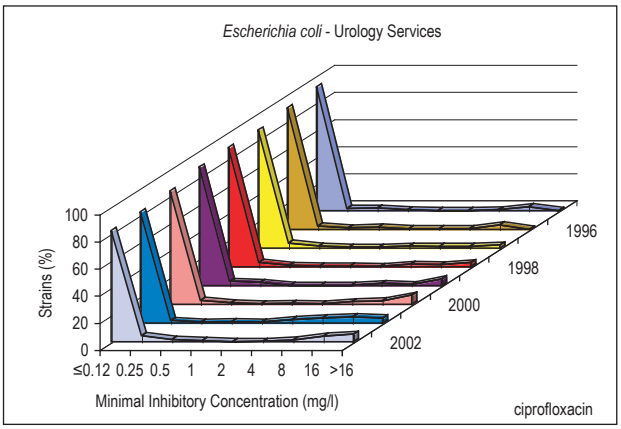
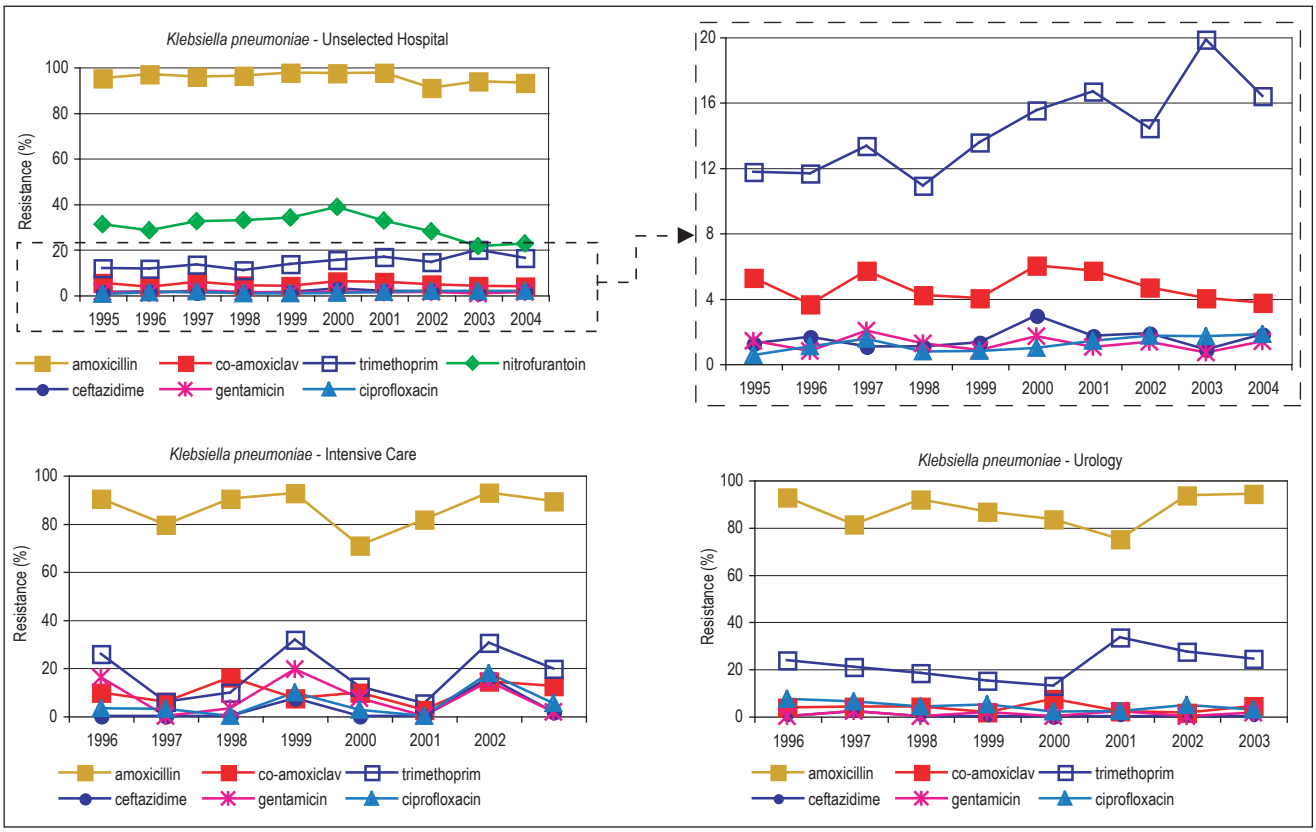


Figure 9. Trends in the MIC distributions of ciprofloxacin for *Escherichia coli* isolated from patients admitted to Urology Services.

observed.

Ciprofloxacin resistance increased slowly but steadily among *E. coli* from Unselected Hospital Departments to 4.5% in 2003 and 5% in 2004, thereby equalling the resistance rates on the Intensive Care Units which appeared 4.5% in 2003. The resistance level in Urology Services however increased rapidly from 7% in 2000 to 11% in 2003 with a peak of 14% in 2002 (figure 4 and figure 8). Ciprofloxacin resistant *E. coli* was isolated in the Urology Services of all hospitals from 1996 onwards. This may reflect intensive use of quinolones in patients with urinary tract problems during this period. Ciprofloxacin resistance spread slowly over the Intensive Care Units: in 1996 only two Units had these strains,

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



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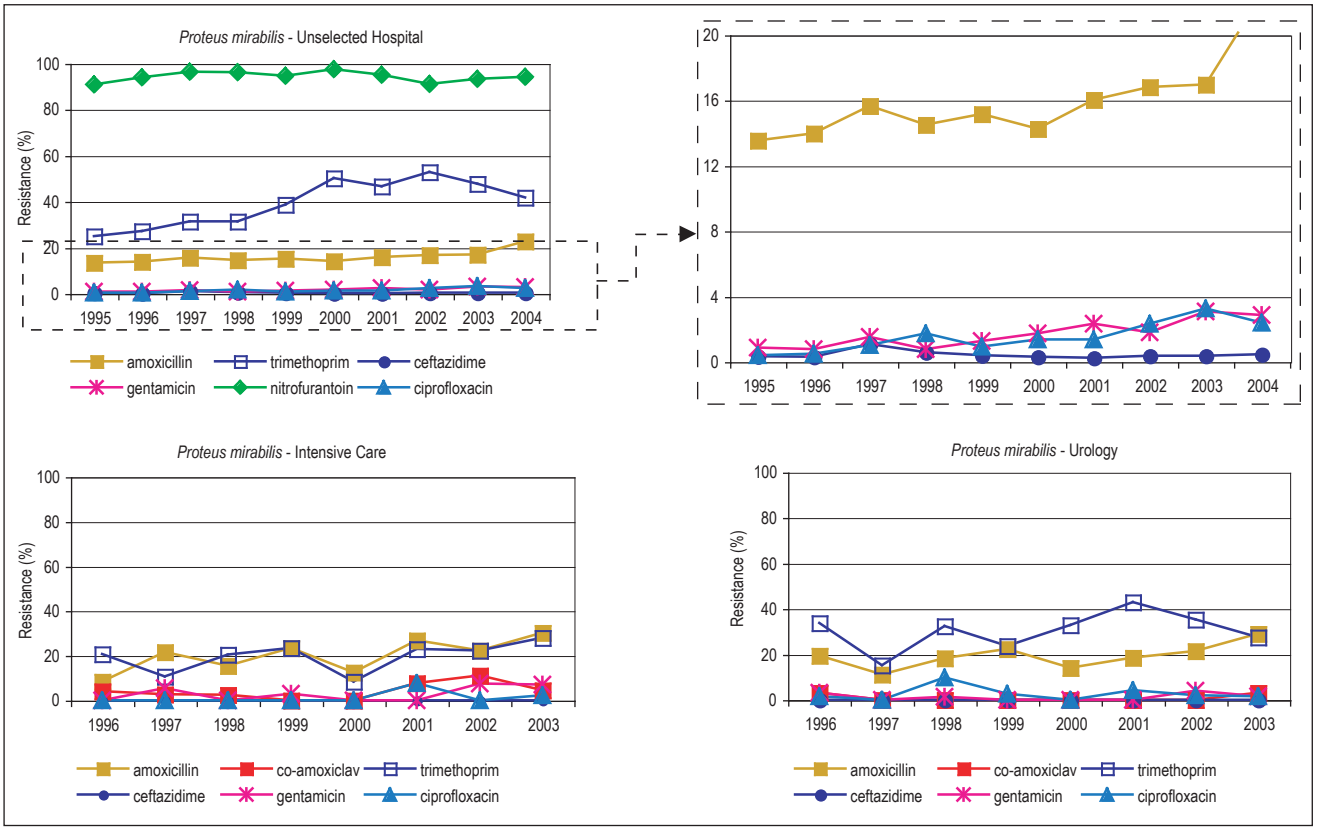
compared with five Intensive Care Units in 2002 and six in 2003.
The MIC distribution of ciprofloxacin showed a large susceptible subpopulation over a very small range (≤ 0.12-0.5 mg/l) with a small subpopulation of resistant strains (figure 9). The susceptible subpopulation for norfloxacin and levofloxacin had a broader range (≤ 0.12-2 mg/l). The breakpoints for resistance are 8 mg/l for norfloxacin, 2 mg/l for ciprofloxacin and 4 mg/l for levofloxacin. These imply similar resistance rates of 10-11%, although the number of strains in the moderately susceptible subpopulations differ.

Klebsiella pneumoniae

Co-amoxiclav resistance in *K. pneumoniae* from Unselected Hospital Departments and from the Urology Services was as low as that of *E. coli* (4%), it fluctuated but did not increase (figure 10). Co-amoxiclav resistance in Intensive Care Units fluctuated at a much higher level (mean 10%) with a resistance rate of 13% in 2003. The rather small number of Intensive Care derived strains tested (30-55 per year) may be responsible for the relatively large inter-annual fluctuations in resistance observed.

Trimethoprim resistance increased in Unselected Hospital Departments from 11% to 16% in 2004 (figure 10). The level of resistance in Intensive Care Units fluctuated around 17% with large inter-annual variations. Trimethoprim resistance in Urology Services was significantly higher, 24% in 2003. Trimethoprim is the drug of first choice in general practice and rarely used in Intensive Care Units. The resistance in Unselected Hospital Departments and Intensive Care Units may reflect resistance in the community. In contrast, the higher resistance rates observed in the Urology Services may reflect frequent use of this drug or co-trimoxazole by urologists. The resistance levels for this combination followed the trend of trimethoprim and appeared 22% in 2003.
Nitrofurantoin resistance fluctuated in Unselected Hospital Departments, it was 22% in 2003 and 2004 (figure 10). The level of resistance in Intensive Care Units and Urology Services in 2003 was 40% or more (not shown).
Ceftazidime resistance among *K. pneumoniae* in Unselected Hospital Departments remained lower than 3% over the years (figure 10). Ceftazidime resistant strains emerged occasionally in three Intensive Care

Figure 11. Trends in resistance to antibiotics among *Proteus mirabilis* derived from Unselected Hospital Departments, Intensive Care Units and Urology Services.



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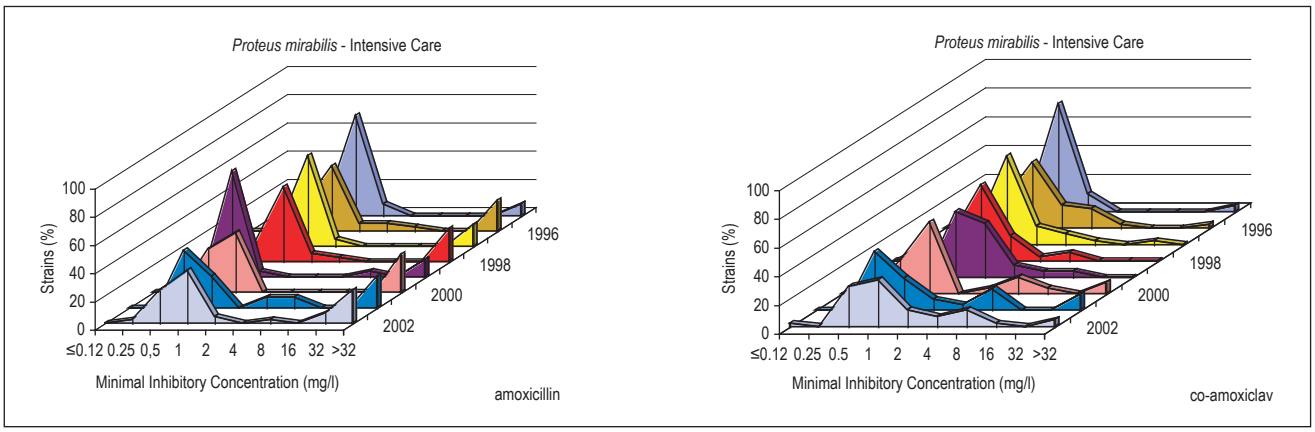


Figure 12. Trends in the MIC distributions of amoxicillin and co-amoxiclav for *Proteus mirabilis* isolated from patients admitted to Intensive Care Units.

Units and in one Urology Service. The 16% resistance observed in 2002 was exclusively caused by an extreme resistance rate in two Intensive Care Units. These strains disappeared in 2003, resulting in an overall resistance rate of less than 2%.

Gentamicin resistance was low and at a constant level in Unselected Hospital Departments (figure 10). Similar to ceftazidime *K. pneumoniae* strains resistant to gentamicin were observed in four Intensive Care Units, yielding large overall fluctuations in gentamicin resistance rates over the years of surveillance with an overall rate in 2003 of 2%. Gentamicin resistance in Urology Services was rare.

Ciprofloxacin resistance among *K. pneumoniae* in Unselected Hospital Departments did not follow the increasing trend of *E. coli*, it fluctuated from 1.5-1.8% without a clear increase (figure 10). Ciprofloxacin resistance had a sporadic character in Intensive Care Units and Urology Services and did not spread: resistant strains were found in 0-2 Intensive Care Units and 1-4 Urology Services each year.

The resistance peak in 2002 was exclusively due to resistance problems in two centres. Seven Intensive Care Units and eight Urology Services did not have any ciprofloxacin resistant *K. pneumoniae* during the entire study period.

Proteus mirabilis

Amoxicillin resistance in Unselected Hospital Departments showed a steady increase, from 14% in 1996 to 24% in 2004. Amoxicillin resistance in Intensive Care Units increased during the same period to 30% in 2003 (figure 11). Amoxicillin resistance was higher in Urology Services from the beginning (19%), and rose to 30% in 2003. The distribution of MICs showed that two subpopulations exist: a susceptible one and a resistant one (figure 12), but that an intermediate subpopulation is growing.

Co-amoxiclav resistance was exceptional in Urology Services. Co-amoxiclav resistance in Intensive Care Units was observed at a low level from 1996 to 2000. From 2001 on an increase of co-amoxiclav resistant strains was observed (up to 11%) whereafter it decreased to 5% in 2003 (figure 11). The MIC distribution of co-amoxiclav showed that not all amoxicillin resistant strains became susceptible by adding clavulanate (figure 12).

Trimethoprim resistance in *P. mirabilis* in Unselected Hospital Departments showed a significant increase until 2000 from 24% to more than 50%. In 2003 and 2004 a decrease was observed. These levels were even higher than those found for Urology Services (mean 30%). The resistance level in Intensive Care Units was consistently lower and equalled the resistance rate among *E. coli* in the community (around 20%).

Ceftazidime resistance in *P. mirabilis* was not detected.

Gentamicin resistance appeared sporadically in some Intensive Care Units and some Urology Services.

Ciprofloxacin resistance among *P. mirabilis* remained below 3%.

Pseudomonas aeruginosa

Ceftazidime resistance among *P. aeruginosa* isolated in Unselected Hospital Departments and in Urology Services was consistently low (2-3%). Ceftazidime resistance in Intensive Care Units was an exception. An incidental 10% resistance was recorded in 2002 (figure 13) in five centres.

Gentamicin resistance was low (<5%) in Unselected Hospital Departments. Sporadic resistance was found in Intensive Care Units, in three Intensive Care Units in 1996, thereafter only in one, but emerging in 2001 and 2002 in four Units responsible for a 7.5% resistance in

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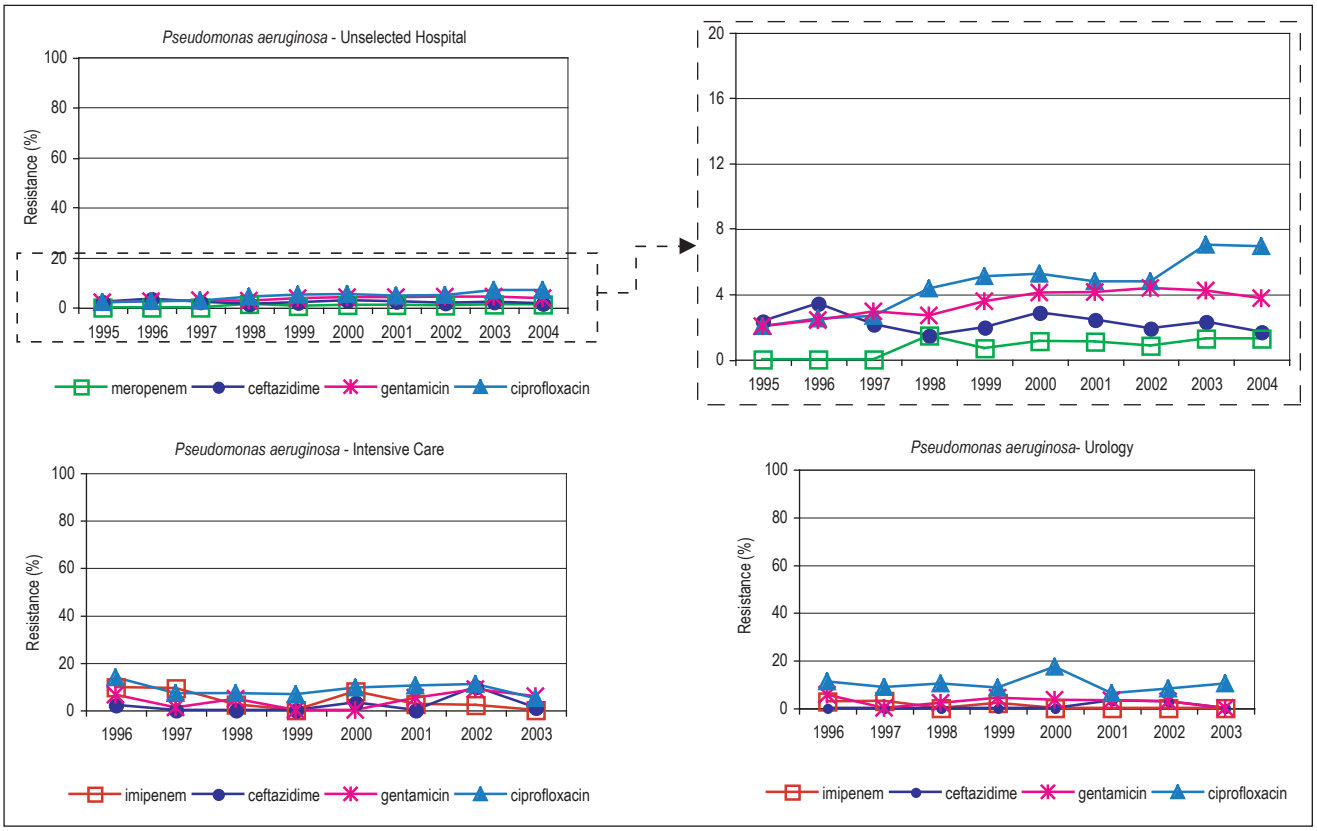


Figure 13. Trends in resistance to antibiotics among *Pseudomonas aeruginosa* derived from Unselected Hospital Departments, Intensive Care Units and Urology Services.

2002. Thereafter it decreased to 5% in 2003. Gentamicin resistance was found sporadically in some Urology Services.

Meropenem resistance among *P. aeruginosa* was exceptional in Unselected Hospital Departments, it was less than 2% during the whole study period. Selected departments showed similar results.

The prevalence of ciprofloxacin resistance increased slowly in Unselected Hospital Departments (2% in 1995 to 7% in 2004, figure 13). In addition, ciprofloxacin resistance was much higher in Intensive Care Units and Urology Services already in 1996. The rates in 2002 were 11% in Intensive Care Units and 10% in Urology Services but in 2003 a significant decrease of resistance to 5% in Intensive Care Units was recorded.

Pseudomonas infections are usually nosocomially acquired. Thus, increasing rates of ciprofloxacin resistance among *P. aeruginosa* may accurately reflect the increase use and subsequent selection pressure exerted by fluoroquinolone antimicrobials in hospitals. Alertness for increasing resistance rates and appropriate measures including a restrictive antibiotic policy may have resulted in a decreasing resistance rate in Intensive Care Units.

Staphylococcus aureus

The prevalence of methicillin resistant *S. aureus* (MRSA) has historically been very low in The Netherlands. The percentage of MRSA (percentage oxacillin resistance of *S. aureus*) in Unselected Hospital Departments increased to 1.5%, the percentage of MRSA in Intensive Care Units and Urology Services fluctuated between 2-4% from 1996-1998, was 0% until 2002 and again 4% in 2003 (figure 14). In contrast, the resistance to erythromycin in Unselected Hospital Departments was slowly increasing to almost 9% in 2004. This was also observed among isolates from the Intensive Care Units, where the resistance level reached 12% in 2003; the resistance rate in Urology Services fluctuated between 0-4%.

Ciprofloxacin resistance rose steadily among isolates from Unselected Hospital Departments to 8% in 2004. Similar percentages were found in Intensive Care isolates during the study period until 2003. Then a sudden increase to 16% resistance was recorded. The higher resistance level among *S. aureus* from Urology Services was found in only 25 strains.

Vancomycin resistant strains were not observed.

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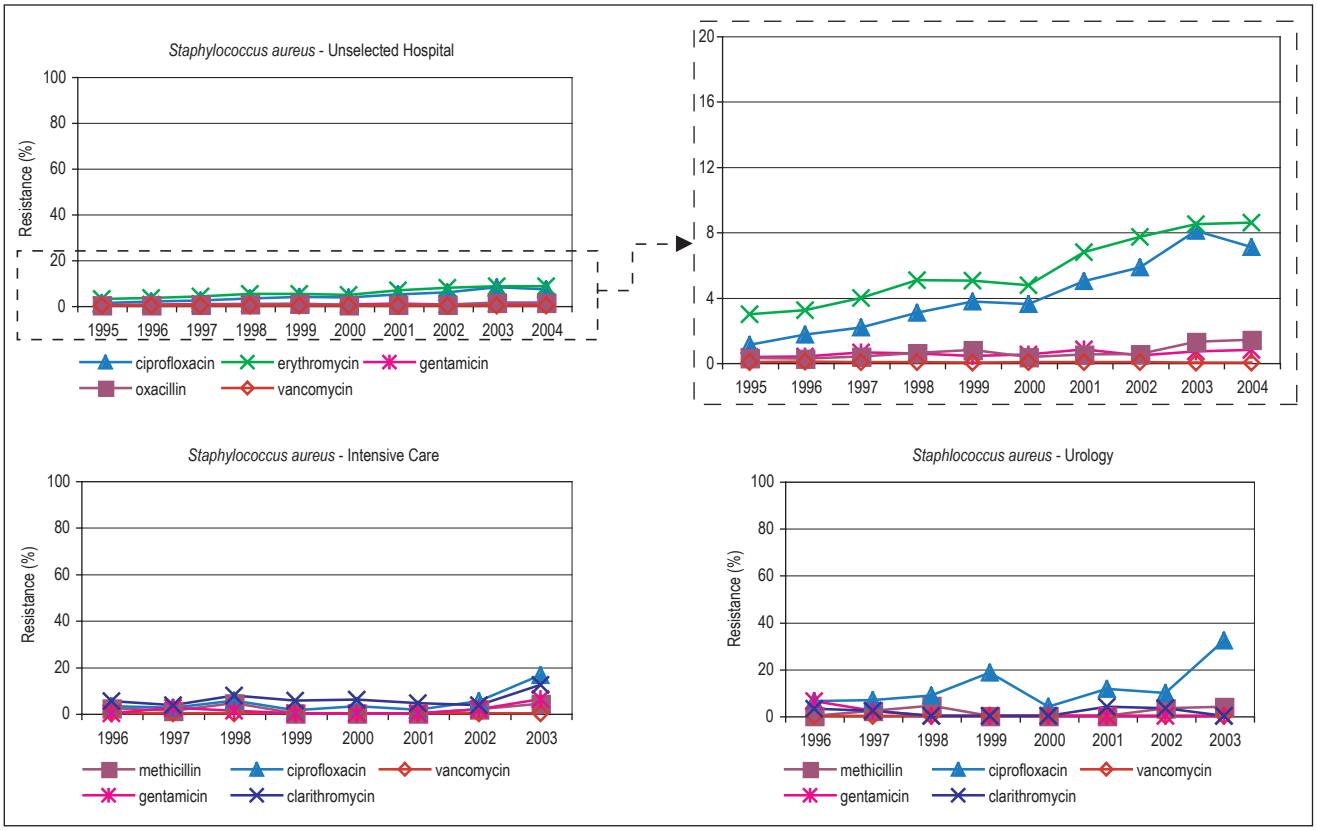


Figure 14. Trends in resistance to antibiotics among *Staphylococcus aureus* derived from Unselected Hospital Departments, Intensive Care Units and Urology Services.

Staphylococcus epidermidis

Methicillin resistance (determined by oxacillin resistance) was frequently found among hospital isolates of *S. epidermidis* (including other coagulase-negative species). Methicillin resistance among clinical isolates of *S. epidermidis* is still increasing in Unselected Hospital Departments and has reached 50% in 2004 (figure 15). Methicillin resistance in Intensive Care Units was almost 90% and it was fluctuating in patients from Urology Services (20-60% until 2000, thereafter decreasing to 30% in 2003); this fluctuation may be the result of low numbers of strains isolated at these departments. Methicillin resistant strains were often co-resistant to erythromycin, clarithromycin, gentamicin and ciprofloxacin in all departments.

Erythromycin resistance increased steadily in Unselected Hospital departments from 37% in 1996 to 45% in 2004, clarithromycin resistance in Urology Services was much lower, but in Intensive Care Unites it was much higher and increased from 64% in 1996 to 80% in 2003. Gentamicin resistance remained at a 60% level in Intensive Care Units. In contrast, the resistance rate of gentamicin in Urology Services was lower than 20%, in the same range or even lower than that found in Unselected Hospital Departments . This underlines the existence of specific populations circulating on Intensive Care Units, whereas the strains from Urology resemble those found in Unselected Hospital Departments.

Ciprofloxacin among strains from Intensive Care Units and from Urology was higher (60% or more) and increasing compared to that among strains from Unselected Hospital Departments (32%). High resistance levels to many drugs among *S. epidermidis* from Intensive Care Units are usual, apparently as result of high selective pressure in these wards. Often strains are circulating within these wards, colonizing many patients. The high ciprofloxacin resistance in Urology Services may reflect use of quinolones in these patients.

Vancomycin resistant strains were isolated occasionally in Unselected Hospital Departments.

Streptococcus pneumoniae

S. pneumoniae strains less susceptible to penicillin are not often isolated in The Netherlands. Yet the trend is slowly increasing: it was less than 1% in Unselected Hospital departments until 1998, then it fluctuated

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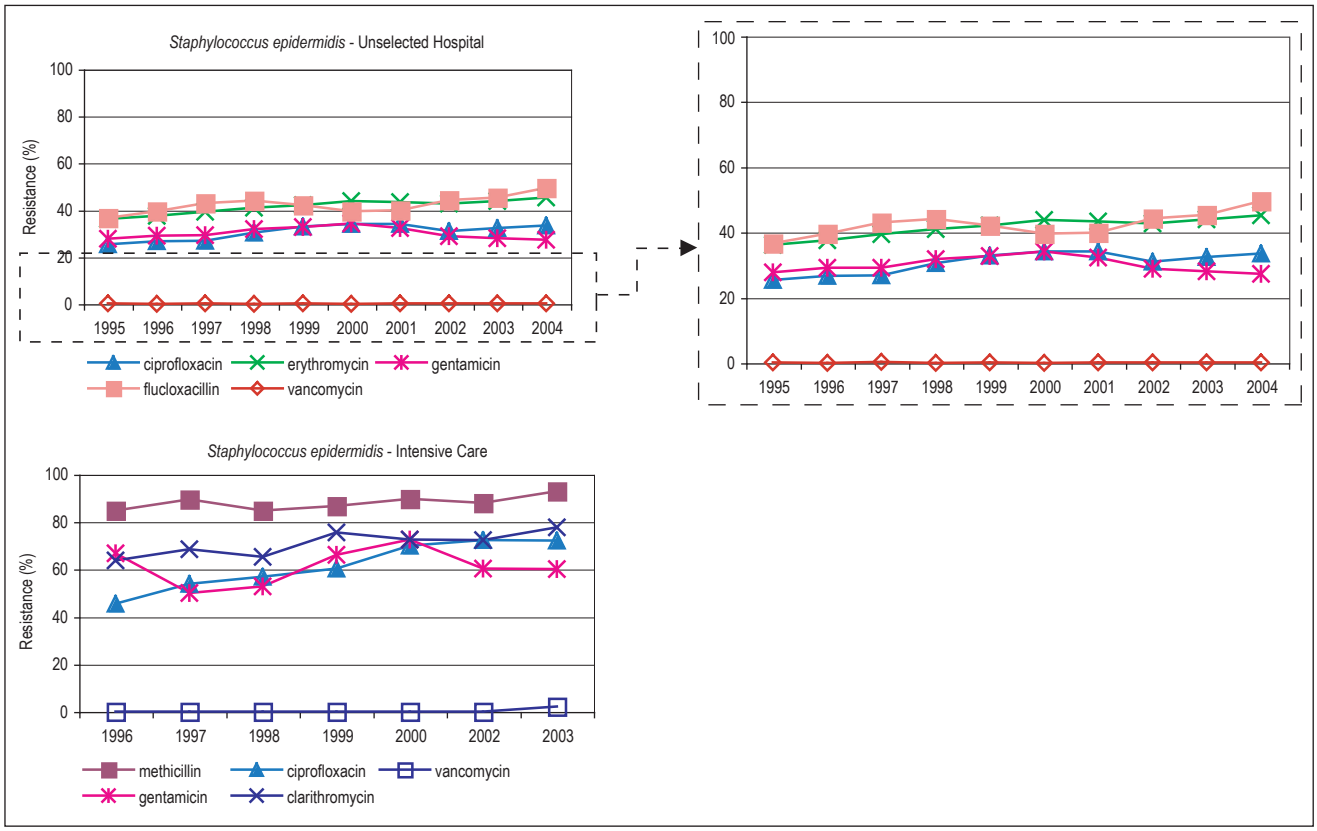


Figure 15. Trends in resistance to antibiotics among *Staphylococcus epidermidis* derived from Unselected Hospital Departments, Intensive Care Units and Urology Services.

between 1-2% until 2003 and it was 2.5% in 2004.
A comparable observation was made for strains from Pulmonology Services, where the resistance level was around 2% until 2000 and increased to 3.6% in 2001 and 6% in 2002 and 2003 (figure 16). This increase is significant ($p < 0.05$). There was a clear trend toward higher rates of erythromycin and clarithomycin resistance among clinical isolates of *S. pneumoniae* from all departments.
Ciprofloxacin resistance in Unselected Hospital Departments increased until 1999 to the level of 23% and decreased thereafter to 12% in 2000 and less than 10% in the following years. The ciprofloxacin resistance rates for the Pulmonology Services were initially much higher (in 1995 44%) compared to that of the Unselected Hospital Departments, then a decrease was observed over the ensuing years (being 13% in 1999) and again an increase to levels of 60% in 2000 and 2001. Thereafter a significant decrease followed until 7.7% in 2003, which is in the same range or even lower than that in Unselected Hospital Departments. It can be observed from the shape of the graphs that the peak of resistance in Unselected Hospital Departments was in 1998, whereas that in Pulmonology Services was later, in 2000 and 2001.

Analysis of the distribution of MICs showed that the decrease in the rate of ciprofloxacin resistance from 1999 on was primarily due to a shift from the fully resistant category to the intermediately susceptible category until 1999, whereas a shift to the intermediate and resistant category occurred in 2000 and 2001 (figure 17). In 2002 and 2003 a shift from the resistant and the intermediate category to the full-susceptible category was observed Resistance to ciprofloxacin among pneumococci apparently developed quickly in the early nineties. Ciprofloxacin is only moderately active against *S. pneumoniae* and most pulmonologists have stopped very soon to prescribe ciprofloxacin for suspected or proven pneumococcal infections. This change in prescribing behaviour may have reduced the selective pressure, and may have contributed to the shift in MIC distribution from fully resistant to intermediately and fully susceptible strains isolated from the Pulmonology Services.

Haemophilus influenzae

The prevalence of amoxicillin resistance among *H. influenzae* isolated in Unselected Hospital Departments has remained stable (8-10%) over the surveillance years.

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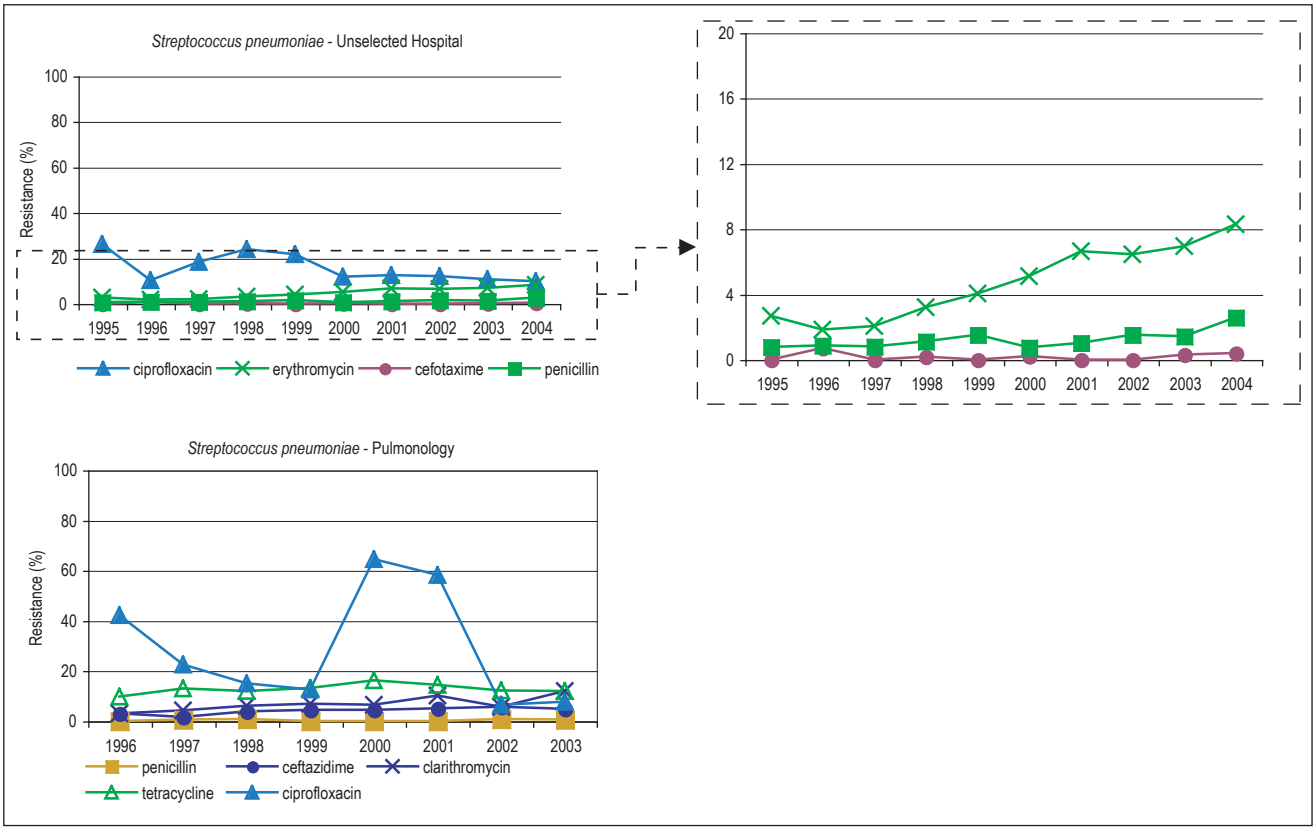


Figure 16. Trends in resistance to antibiotics among *Streptococcus pneumoniae* derived from Unselected Hospital Departments and from Pulmonology Services.

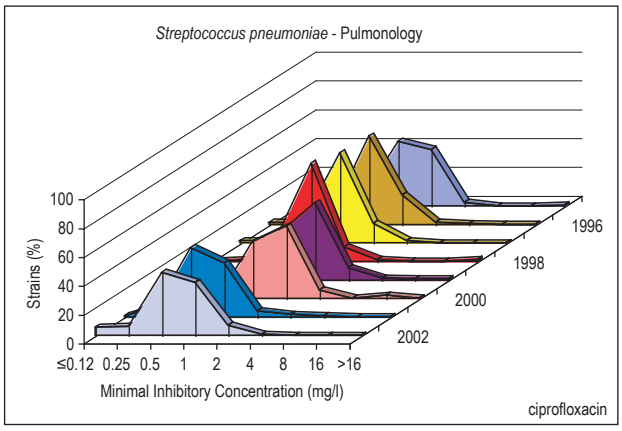
The resistance rate for *H. infuenzae* strains isolated from Pulmonology Services fluctuated somewhat more (8-14%), but again no trend toward increasing rates was discernible (figure 18).

The prevalence of erythromycin resistance among *H. influenzae* from Unselected Hospital Departments is high (70-90%) if all strains with reduced susceptibility (MIC>0.5 mg/L) are counted as resistant. The newer macrolide agent clarithromycin was tested for isolates from the Pulmonology Services instead of erythromycin. Taking the low breakpoint almost 100% resistance to clarithromycin was recorded (figure 18).

Increasing prevalence rates were found for doxycycline resistance among *H. influenzae* isolates from Unselected Hospital Departments from less than 2% in the preceding years to 6% in 2000 and 2001. Then a decrease in resistance followed until 2.7% in 2004. The resistance rates in the Pulmonology Services was higher from the beginning (7-9%), but the pattern over the years was the same, with a significant decrease in resistance in 2002 and 2003 to 3.5%. A shift in MIC distribution for strains isolated from Pulmonology Services was observed from 2000 on, with more strains with higher MICs, although still susceptible. These strains disappeared in 2002 and 2003 (figure 19).

Amoxicillin has been a drug of first choice for pulmonologists and has remained so over the years. The selective pressure that therefore occurs in this clinical setting may partly explain the higher resistance rates found among *H. influenzae* strains isolated from Pulmonology Services. The increased resistance rates

Figure 17. Trends in the MIC distributions of ciprofloxacin for *Streptococcus pneumoniae* isolated from patients admitted to the Pulmonology Services.



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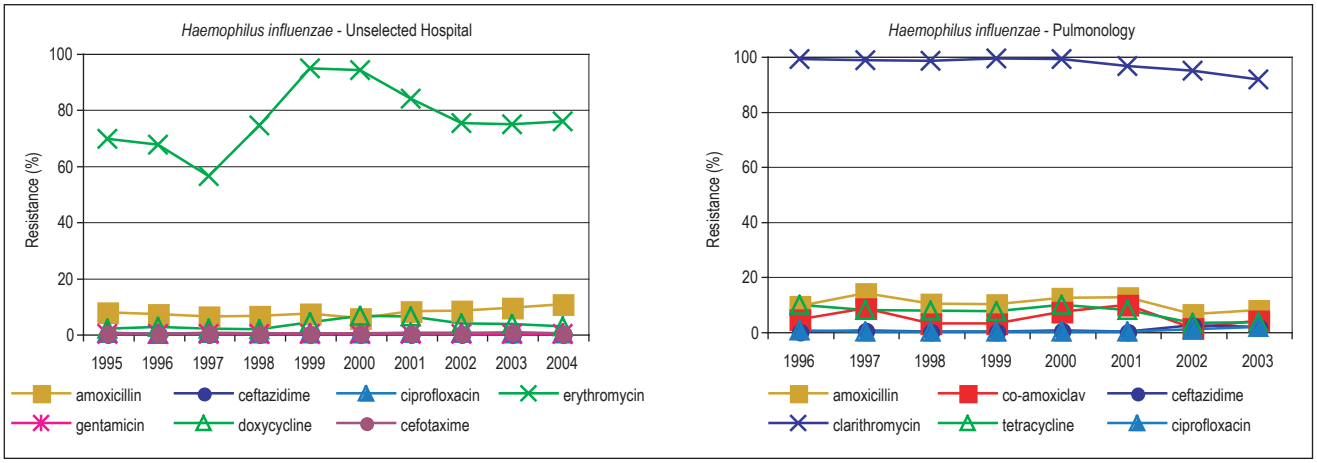
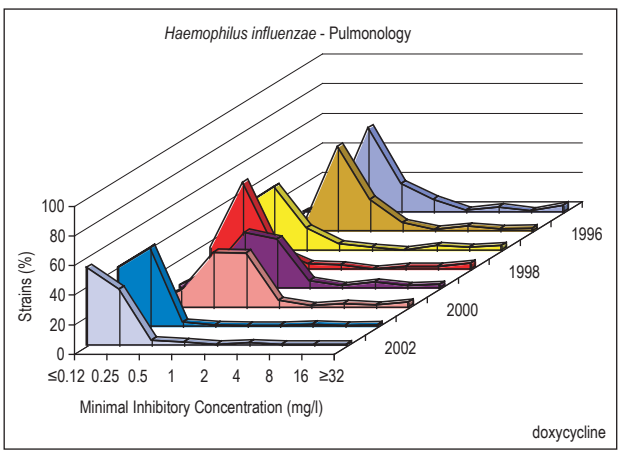


Figure 18. Trends in resistance to antibiotics among *Haemophilus influenzae* derived from Unselected Hospital Departments and from Pulmonology Services.

for doxycycline among *H. influenzae* isolated until 2001 may reflect doxycycline use in general practice and Pulmonology Services during the preceding years. The knowledge that doxycycline resistance was increasing together with the introduction of antibiotics like clarithromycin and levofloxacin advertised for treatment of respiratory tract infections might have led to a change in prescription behaviour. Lower use of doxycycline may be an explanation for decreased resistance rates in the last years.

In contrast, we observed emergence of quinolone-resistant *H. influenzae* (0.9%) in Pulmonology Services of two hospitals in 2002 and of three hospitals in 2003 (1.7%). These strains showed complete cross-resistance between ciprofloxacin and levofloxacin. This must reflect use of quinolones for some kinds of respiratory tract infections.

Figure 19. Trends in the MIC distributions of doxycycline for *Haemophilus influenzae* derived from Pulmonology Services.



Moraxella catarrhalis

The prevalence of amoxillin resistance among *M. catarrhalis* isolated in Unselected Hospital Departments has been about 80% since 1999 and remained stable (figure 20). The resistance in Pulmonology Services was decreasing from 2002 on. Resistance is completely beta-lactamase-based: resistance to co-amoxiclav did not occur. Resistance to erythromycin increased from 5% in 1996 to 11% in 2000 in Unselected Hospital Departments, but decreased again to 7% in 2002. Clarithromycin resistance in Pulmonology Services was low 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 are 2-4 fold lower than those of erythromycin, which may result in different resistance percentages at the same breakpoint. Resistance to ciprofloxacin (1% or less) and doxycycline (4% or less) remained stable during the surveillance period.

Helicobacter pylori

Amoxicillin resistance among *H. pylori* was 3% in 2004 (figure 21). Clarithromycin resistance was 1-6% without a real tendency of increasing resistance. Metronidazole resistance was stable over the years, 19% in 2004.

Mycobacterium tuberculosis

A total of 8435 strains of *M. tuberculosis* was obtained during 1996-2004. INH resistance remained below 8% among strains of *M. tuberculosis* (figure 22). Streptomycin resistance fluctuated between 8-10%, in 2004 it was 6.3%. The rifampicin resistance level was

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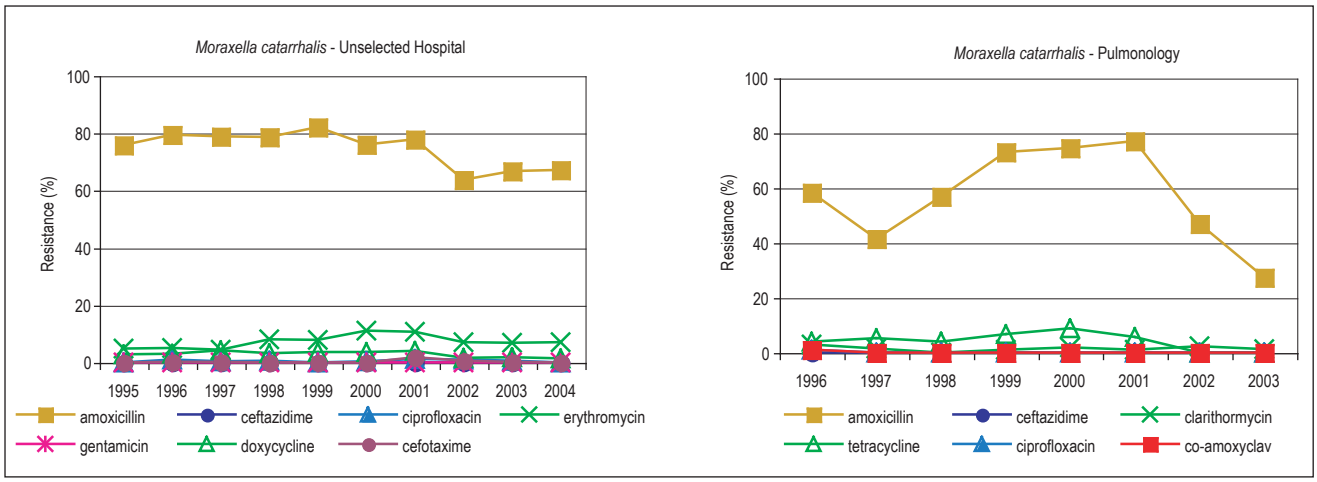


Figure 20. Trends in resistance to antibiotics among *Moraxella catarrhalis* derived from Unselected Hospital Departments and from Pulmonology Services.

stable, 1.1% in 2004 (figure 22). Ethambutol resistance did occur occasionally, but remained below 1.5%. Combined resistance to more than one drug was observed in 3-5% of all isolates (figure 23). INH resistance combined with streptomycin resistance occurred most frequently. Resistance to all four antimycobacterial drugs was low, 0.2% in 2004.

Neisseria meningitidis

From 1993-2003 a total of 4035 strains for cerebrospinal fluid and 2150 strains from blood were included in the surveillance project of the Netherlands Reference Laboratory for Bacterial Meningitis of the Academic Medical Centre, Amsterdam. Penicillin resistance (MIC > 0.38 mg/l) was occasionally found in strains both from CSF and blood (figure 24). The percentages of strains with moderate susceptibility (MIC 0.125-0.38 mg/l) fluctuated between 0.3 % and 3.25% during the study period, without indication of any trend.

Figure 21. Trends in resistance to antibiotics among *Helicobacter pylori* derived from Unselected Hospital Departments.

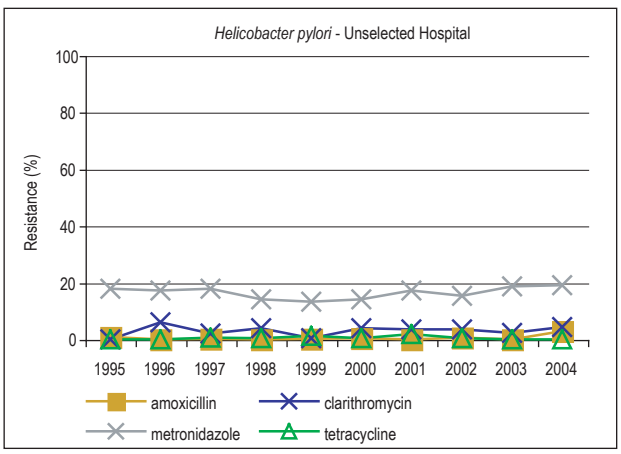
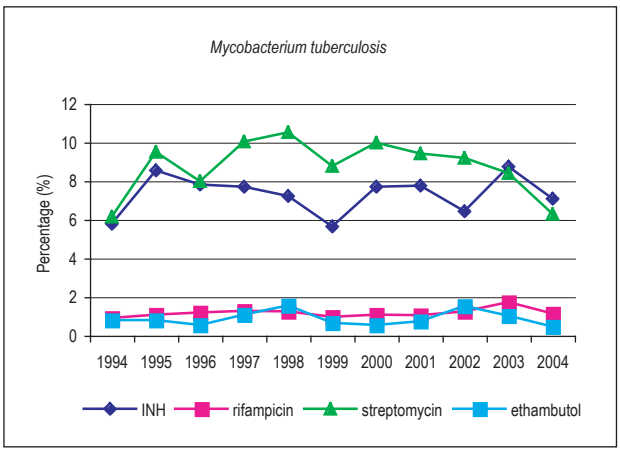


Figure 22. Trends in resistance to antibiotics among *Mycobacterium tuberculosis*.



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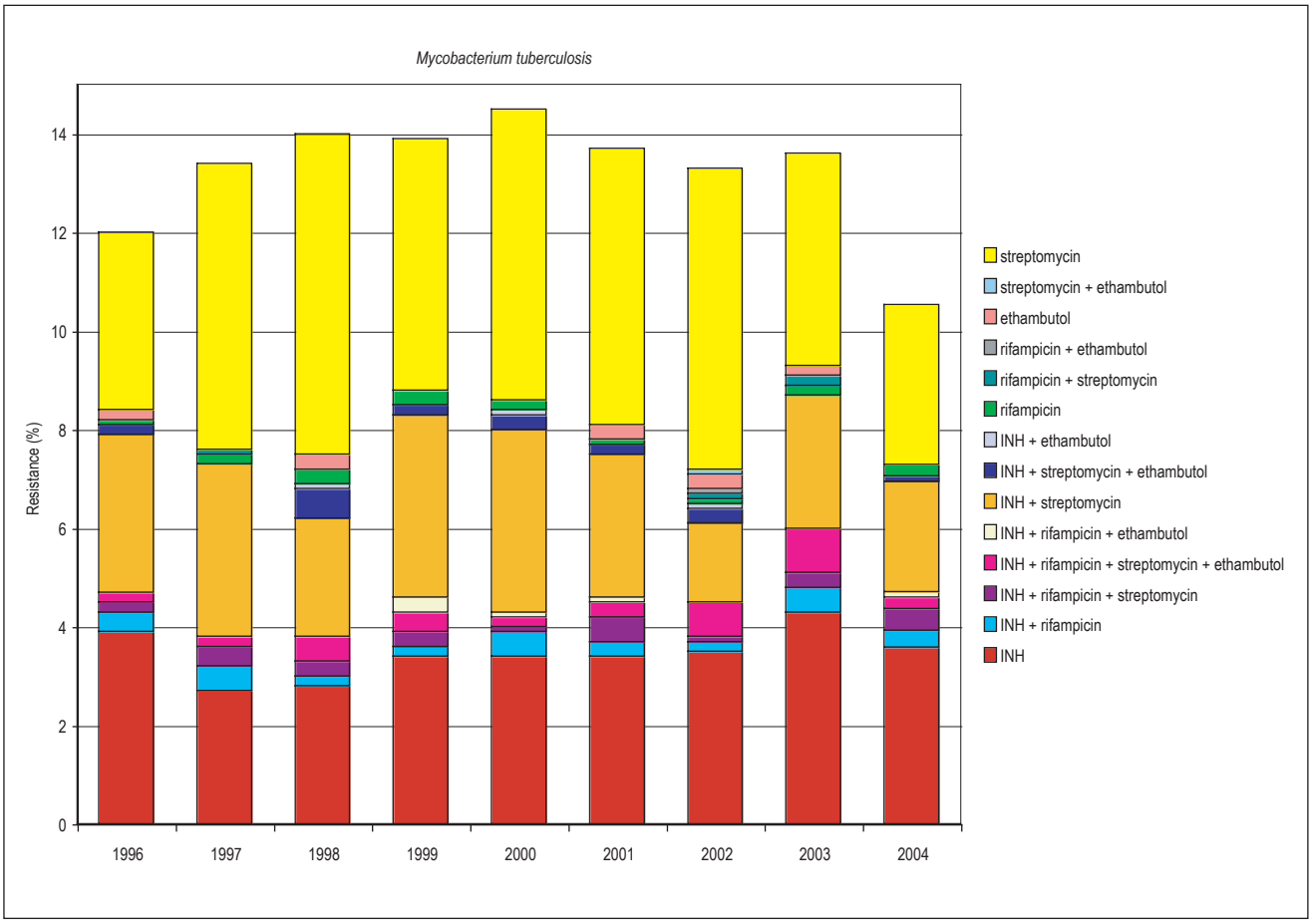
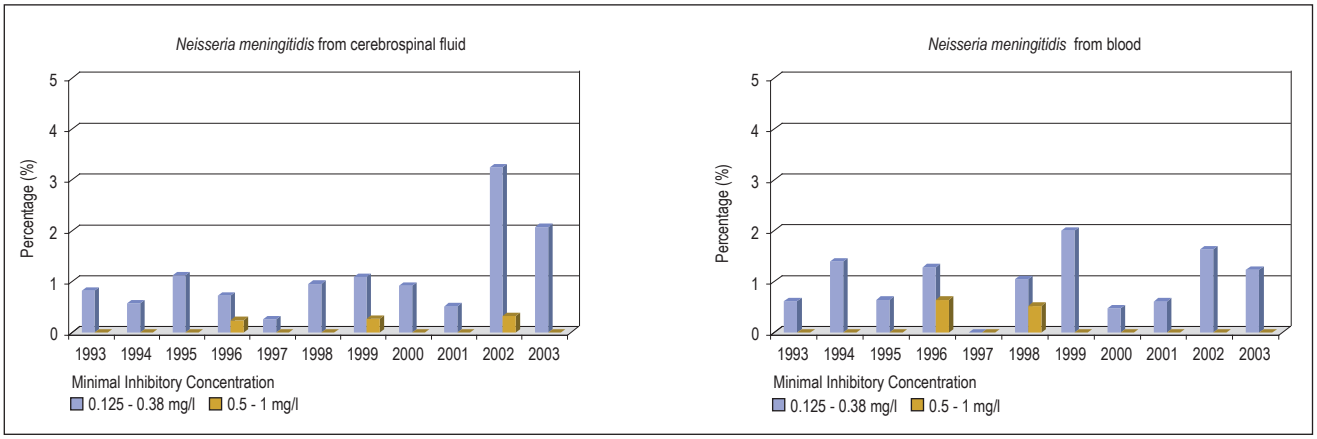


Figure 23. Trends of combined resistance of *Mycobacterium tuberculosis*.

Figure 24. Trends in penicillin susceptibility among clinical strains of *Neisseria meningitidis*.



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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 centers throughout the Netherlands and the studies were reported in peer-reviewed journals listed in the Medline database. Individually, and taken together, these studies provide further insight into the prevalence and emergence of antimicrobial resistance among medically important micro-organisms in the Netherlands. In addition to the list of studies readers are helped by a crosstable that reveals the combinations of 'bugs & drugs' for which MIC data were reported in each of the listed studies.

1. Endtz HP, Dijk WC van, Verbrugh HA et al. Comparative invitro activity of meropenem against selected pathogens fromhospitalized patients in the Netherlands. MASTIN Study Group. J Antimicrob Chemother (1997) 39: 149-56.

2. Buirma RJA, Horrevorts AM, Wagenvoort JHT. Incidence of multi-resistant gram-negative isolates in eight Dutch hospitals. Scand J Infect Dis (suppl) 78: 35-44, 1991.

3. Stobberingh EE, Maclaren DM et al. Comparative in-vitro activity of piperacillin-tazobactam against recent clinical isolates, a Dutch national multicentre study. J Antimicrob Chemother (1994) 34: 777-783.

4. Stobberingh EE, Arends J, et al. Occurrence of extended spectrum beta-lactamases in Dutch hospitals. Infection (1999) 27: 348-354.

5. Beek D van de, Hensen EF, et al. Meropenem susceptibility of *Neisseria meningitidis* and *Streptococcus pneumoniae* from meningitis patients in the Netherlands. J Antimicrob Chemother (1997) 40: 895-897.

6. Debets-Ossenkopp YJ, Herscheid AJ et al. Prevalence of *Helicobacter pylori* resistance to metronidazole, clarithromycin, amoxicillin, tetracycline and trovafloxacin in the Netherlands. J Antimicrob Chemother (1999) 43: 511-515.

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8. Enting RH, Spanjaard L et al. Antimicrobial susceptibility of *Haemophilus influenzae*, *Neisseria meningitidis* and *Streptococcus pneumoniae* isolates causing meningitis in the Netherlands 1993-1994. J Antimicrob Chemother (1996) 38:777-786.

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15. Bongaerts GPA, Hoogkamp-Korstanje JAA. In vitro activities of BAY Y3118, ciprofloxacin, ofloxacin and fleroxacin against Gram-positive and Gram-negative pathogens from respiratory tract and soft tissue infections. Antimicrob Ag Chemother (1993) 37: 2017-2019.
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21. Loffeld RJ, Fijen CA. Antibiotic resistance of *Helicobacter pylori*: a cross-sectional study in consecutive patients, and relation to ethnicity. Clin Microbiol Infect. (2003) 9: 600-4.

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

Numbers correspond with reference numbers 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
CRG	Dutch Committee on Guidelines for Susceptibility Testing
DDD	Defined Daily Dose
CVZ	College for Health Care Insurance's
EARSS	European Antimicrobial Resistance Surveillance System
ECCMID	European Congress on Clinical Microbiology and Infectious Diseases
ESAC	European Surveillance of Antibiotic Consumption
EU	European Union
GIP	Drug Information Project
ISIS	Infectious Diseases Information System
LINH	Netherlands Information Network in General Practice
MIC	Minimal Inhibitory Concentration
MSSA	Methicillin Sensitive *Staphylococcus aureus*
MRSA	Methicillin Resistant *Staphylococcus aureus*
NCCLS	National Committee for Clinical Laboratory Standards
NHG	Dutch College of General Practitioners
NIVEL	Netherlands Institute of Health Services Research
NVMM	Netherlands Society for Medical Microbiology
PRISMANT	Institute for Health Care Information and Consultancy
RIVM	Netherlands Institute for Public Health and the Environment
SFK	Foundation for Pharmaceutical Statistics
SWAB	Foundation of the Dutch Working Party on Antibiotic Policy
WIP	Working Party on Infection Prevention
WHO	World Health Organisation

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Demographics and denominator data

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

Year	Number of inhabitants
1996	15 567 107
1997	15 654 192
1998	15 760 225
1999	15 863 950
2000	15 987 075
2001	16 105 285
2002	16 192 572
2003	16 254 933
2004	16 292 353

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

Year	Hospitals	Beds	Admissions (x 1000)	Bed-days (x 1000)	Admissions /bed	Length of stay (mean in days)
1998	115	54 356	1 523	13 800	28	9.1
1999	109	53 786	1 497	12 985	27.8	8.7
2000	104	51 999	1 460	12 386	28.1	8.5
2001	101	50 037	1 457	11 912	29.1	8.2
2002	98	48 309	1 521	12 086	31.5	7.9
2003	97	47 777	1 579	11 800	33	7.5

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

Year	Hospitals	Beds	Admissions (x 1000)	Bed-days (x 1000)	Admissions /bed	Length of stay (mean in days)
1998	8	7 721	200	2 032	25.9	10.2
1999	8	7 715	200	1 914	25.9	9.6
2000	8	7 704	197	1 842	25.6	9.4
2001	8	7 933	192	1 805	24.2	9.4
2002	8	7 721	193	1 820	25	9.4
2003	8	7 723	199	1 837	25.8	9.2

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

Year	Hospitals	Beds	Admissions (x 1000)	Bed-days (x 1000)	Admissions /bed	Length of stay (mean in days)
1998	107	46 635	1 323	11 768	28.4	8.9
1999	101	46 071	1 297	11 071	28.2	8.5
2000	96	44 295	1 263	10 544	28.5	8.3
2001	93	42 104	1 265	10 107	30	8
2002	90	40 588	1 328	10 266	32.7	7.7
2003	89	40 054	1 380	9 963	34.5	7.2

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Surveillance of antibiotic use in humans

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; about 10 percent is delivered by general practitioners, mainly in rural areas (reference 8). This report includes data on the use of antibiotics provided by the Foundation for Pharmaceutical Statistics (SFK; http://www.sfk.nl). Sales data from approximately 90% of all 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. Data on the number of inhabitants in the Netherlands are obtained from Statistics Netherlands (CBS; http://www.cbs.nl). SFK data on antibiotic use do not include the use of antibiotics in hospitals and nursing-homes. Antibiotics prescribed by hospital based medical specialists to their outpatients are however included.

This report includes data on the use of antibiotics for systemic use, group J01 of the Anatomical Therapeutic Chemical (ATC) classification system, over the years 2000 through 2004. The use of antibiotics in primary health care is expressed as the number of Defined Daily Doses (DDD) per 1000 inhabitants and per day. The 2005 update of the ATC/DDD classification system is used to calculate the number of DDDs in this report.

Hospitals
Data on the use of antibiotics in Dutch hospitals between 1999 and 2003 were collected by the SWAB by means of a questionnaire distributed to all Dutch hospital pharmacists. The number of admissions and the number of days spent in the hospital (bed-days) are also registered in the questionnaire. The use of antibiotics for systemic use, group J01 of the ATC-system, is expressed as DDD/100 patient-days and in DDD/100 admissions (reference 3). The 2005 update of the ATC/DDD classification system is used to calculate the number of DDDs in this report. 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.

Data on the total number of bed-days and admissions in the Netherlands were obtained from Statistics Netherlands (CBS; http://www.cbs.nl). The percentage of covered patient-days was calculated for each year.

Surveillance of antimicrobial resistance

In the community

Isolates
During 1988, 1992, 1997, 2000 and 2001 strains of *Escherichia coli* were isolated from the urine of consecutive patients consulting their general practitioner in the Southern part of the Netherlands with new complaints compatible with acute uncomplicated urinary tract infection. In 2003 the study was expanded by a nation-wide inclusion of other centres. Thirty-one general practitioners from 21 sentinel stations participating in the sentinel project of the NIVEL joined the study. Patients presenting to their general practitioner with either dysuria, stranguria, urinary frequency or urgency were included irrespective of age and gender and / or presence of indwelling catheter or urinary tract infection in the past three months. Dip slides inoculated with patient's urine (clean voided urine) were sent to the Department for Medical Microbiology of the University Hospital Maastricht for culture and susceptibility testing of pathogens. A urine sample was considered positive if $>10^5$ colony forming units (CFU) per ml of one species were found. For isolation and identification of the isolated micro-organisms standard microbiological methods were used that included API 20E for Enterobacteriaceae.

Susceptibility testing
The quantitative antimicrobial susceptibility tests were performed by broth microdilution with the indicator antibiotics according to the SWAB standard. The microtiter plates were commercially prepared by MCS diagnostics (Swalmen, The Netherlands). *Escherichia coli* ATCC 25922 and ATCC 35218 were used as reference strains. The breakpoints for resistance used were those defined by the NCCLS and the SWAB Standard. *Escherichia coli* ATCC 25922 was used as the reference strain.

In 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

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collaborative agreement between the regional public health laboratories and the RIVM. Identification and susceptibility testing was routinely carried out in the regional public health laboratories. Only the first isolate of each species from a patient was used. The species distribution of isolates from various body sites appeared fairly stable during the period. Most isolates came from urine, respiratory tract, pus and wound and blood. The numbers of isolates per species and in each of these clinical materials in 2004 are given in table 1.
The susceptibility of the strains from the Unselected Hospital Departments was routinely determined according to the standard techniques used in the individual laboratories. These methods include standardised agar diffusion assays as well as home-made or commercial broth microdilution assays. The breakpoints defined by the NCCLS or by the CRG were used for calculating resistance rates. Resistance rates for *E. coli*, *P. mirabilis*, *K. pneumoniae*, *P. aeruginosa*, *S. aureus* and *S. epidermidis* represent the proportion of strains that were considered fully resistant. Resistance rates for *H. influenzae*, *M. catarrhalis* and *S. pneumoniae* include strains that showed intermediate susceptibility (I+R, MIC > lower breakpoint).
The results of susceptibility testing of the indicator strains, identified by the SWAB standard and belonging to this collection are presented in this report.

Specific Wards
Unique unrelated consecutive isolates isolated from various clinical materials of patients admitted to Intensive Care Units, from urine of patients admitted to Urology Services and from respiratory specimens of patients admitted to Pulmonology Services were yearly collected from March 1st to September 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

Table 1. Frequency and numbers of first isolates of each species per clinical sample of patients from Unselected Hospital Departments in 2004.

Species (numbers)	Frequency (%) per clinical material			
	Blood (N=3,853)	Pus/wound (N=20,188)	Resp. tract (N=11,056)	Urine (N=22,324)
Gram positive cocci				
Staphylococcus aureus (N=10,297)	12	38	14	3
Enterococcus sp. (N=4827)	5	5	2	15
Coag. neg. *Staphylococcus* (N=2598)	32	4	0	3
Streptococcus pneumoniae (N=2008)	10	2	12	0
Streptococcus agalactiae (N=1486)	2	3	1	3
Streptococcus pyogenes (N=794)	2	3	1	0
(Subtotal %)	62	55	30	24
Enterobacteriacae				
Escherichia coli (N=14,756)	21	15	7	46
Proteus mirabilis (N=3188)	2	4	2	9
Klebsiella pneumoniae (N=2772)	5	3	4	7
Enterobacter cloacae (N=1686)	2	4	3	2
Klebsiella oxytoca (N=1454)	2	2	2	3
Other Enterobacteriaceae (N=4036)	2	5	5	4
(Subtotal %)	34	33	24	71
Respiratory pathogens				
Haemophilus influenzae (N=3002)	0.8	2.0	23.2	0.0
Moraxella catarrhalis (N=1031)	0.1	0.4	8.6	0.0
Haemophilus parainfluenzae (N=562)	0.1	0.5	4.1	0.0
Neisseria meningitidis (N=72)	0.7	0.0	0.4	0.0
(Subtotal %)	1.6	3.0	36.2	0.0
Non-fermenters				
Pseudomonas aeruginosa (N=3884)	2.3	8.3	9.9	4.7
Acinetobacter calcoacet. (N=252)	0.1	0.8	0.3	0.3
(Subtotal %)	2.4	9.0	10.3	4.9

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Table 2. Number of indicator strains (N=13,019) isolated from patients admitted to specified hospital wards and tested for their susceptibility to antibiotics in the period 1996-2003.

Species	Intensive Care Units	Urology Services	Pulmonology Services
E. coli	1124	3980	
K. pneumoniae	328	446	
P. mirabilis	254	528	
P. aeruginosa	672	303	
S. aureus	638	233	
S. epidermidis	441	221	
S. pneumoniae			1232
H. influenzae			1826
M. catarrhalis			793

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 18,000 strains were collected from 1995-2003, the results of 10,738 indicator strains (table 2) are presented in this report.
The susceptibility of the strains from the specific wards was determined quantitatively, i.e. by MIC determinations by broth microdilution assays using the recommendations of the NCCLS for *E. coli*, *P. mirabilis*, *K. pneumoniae*, *P. aeruginosa*, *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. *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Haemophilus influenzae* ATCC 49247 and *Staphylococcus 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.

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 intermediate and fully resistant strains. The susceptibility data of 8435 strains, isolated from 1996-2004 are presented in this report.

Neisseria meningitidis
From 1993-2003 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 > 0.38 mg/l resistant.

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