NETHMAP 2004

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. 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. Some of these surveillance systems already existed and others were developed and sponsored directly by SWAB. NethMap, thus, is the result of collating and analysing data from various sources into relevant information regarding the dynamics in antibiotic usage and antimicrobial resistance in the Netherlands. SWAB is fully supported by a structural grant from the Ministry of Health, Welfare and Sports of the Netherlands.
The document was produced on behalf of the SWAB by the Studio of the RIVM.
NethMap can be ordered from the SWAB secretariat, p/a Erasmus MC, Department of Medical Microbiology & Infectious Diseases, Dr Molewaterplein 40, 3015 GD, Rotterdam, the Netherlands. NethMap is also available from the website of the SWAB: www.swab.nl.

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Editors:
Prof dr H. A. Verbrugh
Erasmus University Medical Center Rotterdam
Rotterdam
Dr A.J. de Neeling
National Institute for Public Health and the Environment
Bilthoven

The following persons were actively involved in writing parts of this report:
Drs P.M.G. Filius
Erasmus University Medical Center Rotterdam
Rotterdam
Prof dr J.A. A. Hoogkamp-Korstanje
University Medical Center St. Radboud
Nijmegen
Dr E.E. Stobberingh
University Hospital Maastricht
Maastricht

Centers contributing to the surveillance of antimicrobial resistance and their contact persons
The map represents the location by province of these centers throughout the Netherlands.

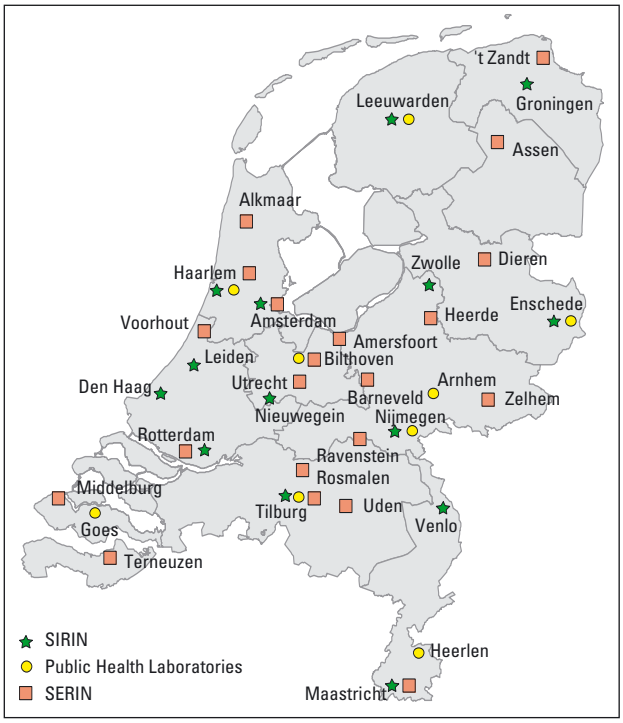
Groningen
General Practice 't Zandt
Martini Hospital, Groningen (Drs W.H.M. Vogels)

Friesland
Regional Laboratory for Public Health, Leeuwarden (Dr G.A. Kampinga)

Drente
General Practice Assen

Overijssel
Isala Clinics, Zwolle (Dr. P. Bloembergen)
Regional Laboratory for Public Health, Enschede (Dr M.G.R. Hendrix)

Gelderland
General Practice Barneveld
General Practice Dieren
General Practice Heerde
General Practice Zelhem
University Medical Centre St Radboud, Nijmegen (Dr T. Schülin)
Regional Laboratory for Public Health, Arnhem (Drs H. Nieste)



Geographical location of health care facilities participating in the *NethMap* surveillance program for antimicrobial resistance in the Netherlands.

Regional Laboratory for Public Health, Nijmegen (Dr A. Horrevorts)

Utrecht
General Practice Amersfoort
General Practice Utrecht
National Institute for Public Health and the Environment, Bilthoven (Dr A.J. de Neeling, M. Dessens)
Netherlands Institute for Health Services Research NIVEL, Utrecht (Dr A.I. Bartelds)
Sint Antonius Hospital, Nieuwegein (Dr B.M. de Jongh)

Noord Holland
General Practice Alkmaar
General Practice Amsterdam
General Practice Haarlem
General Practice Huizen
Onze Lieve Vrouwe Gasthuis, Amsterdam (Dr P.J.G.M. Rietra)
Kennemer Gasthuis, Haarlem (Dr A. Beunders / Dr E. IJzerman)
Regional Laboratory for Public Health, Haarlem (Dr E. Ligtvoet)

Zuid Holland
General Practice 's Gravenhage
General Practice Rotterdam
General Practice Voorhout
Bronovo Hospital, 's Gravenhage (Dr H.A. Bijlmer)
Diaconessenhuis, Leiden (Dr E.M. TerMeer-Veringa)
Medical Centre Rijnmond-Zuid, Rotterdam (Dr W.D.H. Hendriks)

Noord Brabant
General Practice Ravenstein
General Practice Rosmalen
General Practice Uden
Regional Laboratory for Public Health, Tilburg (Dr A. Buiting)

Limburg
General Practice Maastricht
VieCuri Medical Centre Noord-Limburg, Venlo (Dr T.H.M. Trienekens)
Regional Laboratory for Public Health, Heerlen (Dr J.H.T. Wagenvoort)
University Hospital, Maastricht (Dr E.E. Stobberingh)

Zeeland
General Practice Middelburg
General Practice Terneuzen
Regional Laboratory for Public Health, Goes (Dr L. Sabbe)

Centers contributing to the surveillance of the use of antimicrobial agents in the Netherlands

A] community usage
Foundation for Pharmaceutical Statistics SFK, The Hague.

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

Alkmaar, Medisch Centrum Alkmaar; Almelo, Ziekenhuisgroep Twente; Amersfoort, Meander Medisch Centrum; Amstelveen, Ziekenhuis Amstelveen; Amsterdam, Academisch Medisch Centrum; Amsterdam, VU Medisch Centrum; Amsterdam, BovenIJ Ziekenhuis; Apeldoorn, Gelre ziekenhuizen; Arnhem, Alysis Groep; Assen, Wilhelmina Ziekenhuis; Bergen op Zoom, Ziekenhuis Lievensberg; Boxmeer, Maasziekenhuis; Coevorden/Hardenberg, Streekziekenhuis; Delft, Reinier de Graaf Groep; Den Haag, Apotheek Haagse Ziekenhuizen; Deventer, Stichting Deventer Ziekenhuizen; Doetinchem, Slingeland Ziekenhuis; Dordrecht, Albert Schweitzer Ziekenhuis; Ede, Ziekenhuis Gelderse Vallei; Eindhoven, Catharina Ziekenhuis; Enschede, Medisch Spectrum Twente; Geldrop, St Annaziekenhuis; Goes, St Oosterschelde Ziekenhuizen; Gorinchem, Rivas Medizorg; Gouda, Groene Hart Ziekenhuis; Groningen, Academisch Ziekenhuis Groningen; Groningen, Martini Ziekenhuis; Haarlem, Haarlemse Ziekenhuizen; Harderwijk, Ziekenhuis St. Jansdal; Heerlen, Atrium Medisch centrum; Hengelo, Streekziekenhuis Midden-Twente; Hilversum, Ziekenhuis Hilversum, Hoorn, Westfries Gasthuis; Leeuwarden, Medisch Centrum Leeuwarden; Leiden, Diaconessenhuis; Leiden, Leids Universitair Medisch Centrum; Leiderdorp, Rijnland Ziekenhuis; Leidschendam, Medisch Centrum Haaglanden, lokatie Antoniushove; Maastricht, Academisch Ziekenhuis Maastricht; Nieuwegein St. Antonius Ziekenhuis; Nijmegen, Canisius Wilhelmina Ziekenhuis; Nijmegen, Universitair Medisch Centrum St. Radboud; Purmerend, Waterlandziekenhuis; Roermond, Laurentius ziekenhuis; Rotterdam, Erasmus Medisch Centrum, Rotterdam, Ikazia Ziekenhuis; Rotterdam, Medisch Centrum Rijnmond-Zuid; Sittard, Maaslandziekenhuis; Sneek, Antonius Ziekenhuis; Spijkenisse, Ruwaard van Putten Ziekenhuis; Terneuzen, Ziekenhuis Zeeuws-Vlaanderen; Tilburg, Apotheek Ziekenhuis Midden-Brabant; Utrecht, Diaconessenhuis; Utrecht, Universitair Medisch Centrum Utrecht; Veghel, Ziekenhuis Bernhoven; Veldhoven, Maxima Medisch Centrum; Venlo, St. Maartens Gasthuis; Venray, St.Elisabeth Ziekenhuis; Vlaardingen, Vlietland Ziekenhuis; Vlissingen, Ziekenhuis Walcheren; Weert, St. Jans Gasthuis; Woerden, Hofpoort Ziekenhuis; Zaandam, Zaans Medisch Centrum de Heel; Zeist, Lorentz Ziekenhuis; Zevenaar, Alysis Groep; Zutphen, Het Spittaal; Zwolle, Isalaklinieken.

Preface

On behalf of the Dutch Working Party on Antibiotic Policy we are happy to present the second surveillance report, called NethMap 2004, on antimicrobial use and resistance in human medicine in the Netherlands. The decision to form a Dutch Working Party on Antibiotic Policy was taken 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 professional 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. To achieve its goal 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. Since these initiatives corresponded well with the recommendations from the Dutch Council on Health Research (2001) and with the recommendations from the European Union (2001) the Ministry of Health, Welfare and Sports decided in May 2002 to formally invite SWAB to develop such surveillance system in close collaboration with the National Institute of Public Health and the Environment (its Dutch acronym is: RIVM). NethMap 2003 was the first publication of systematically gathered data on antibiotic use and resistance in the Netherlands and was published in april 2003. As indicated in the first report we intended future NethMap reports to become more comprehensive and informative. True to this policy one will find more information and data in this 2004 issue of NethMap. One more year has been added to the trend lines, more species of microbes are monitored and several special analyses have been added that contribute to our insight in the quality of the data presented and on the combined occurrence of resistance in some species. Importantly, a surveillance report called MARAN 2002 has been published in January 2004 regarding the use of antimicrobial agents and the development of antimicrobial resistance in animal husbandry by the Veterinary Antibiotic Usage and Resistance Surveillance Working Group (see www.cidc-lelystad.nl). 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 Netherlands in the medical and veterinary arena, respectively. The interaction between these two areas of antibiotic use and resistance will be explored in an interdepartemental 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 interdepartement working group where the evolution of antibiotic use and resistance in the Netherlands will be discussed 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 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 2004 describes antibiotic use and resistance to antibiotics in bacteria from humans in the Netherlands. It is the second edition of a similar report published in 2003.

Data on *antibiotic use outside hospitals* were collected by the Foundation for Pharmaceutical Statistics in The Hague and analyzed by the Working Party on Antibiotic Policy. These data included sales from pharmacies which supply medicines to 90% of the Dutch population outside hospitals. In the period 1998-2002 the use of antibiotics outside hospitals remained almost constant at 10 defined daily dosages (DDD) per 1000 inhabitant-days, which implies that approximately 1% of the Dutch population is using an antibiotic. This usage is the lowest of all European countries. The use of tetracyclines decreased monotonously from 2.6 to 2.3 DDD/1000 inhabitant-days. The use of co-amoxiclav increased from 0.95 to 1.3 DDD/1000 inhabitant-days substituting amoxicillin. The use of macrolides and fluoroquinolones, which increased in the past, leveled off at 1.2 and 0.85 DDD/1000 inhabitant-days respectively.
Tetracyclines, macrolides and co-amoxiclav were used in higher amounts in the winter season, indicating use for respiratory tract infections which occur more frequently in winter. However, the use of fluoroquinolones was equal in summer and winter, indicating that the use of these agents is still confined to urinary tract infections. Indeed in general practice only 8% of fluoroquinolone use was for respiratory tract infections compared with 80% for infections of the genito-urinary tract as shown by the account of a collaborative study of the Netherlands Information Network in General Practice and the Working Party on Antibiotic Policy [included in Dutch]. Quinolones were prescribed to 7% of the female patients at first time treatment of cystitis. Sixteen percent of the women treated with any antibiotic returned with complaints within four weeks and 18% of these were treated with a fluoroquinolone.

Antibiotic use in hospitals was surveyed by the Working Party on Antibiotic Policy by way of a questionnaire sent to hospital pharmacies. In the period 1998-2001 antibiotic use in hospitals increased from 48 to 55 DDD/100 patient-days. Because the length of stay shortened, the use of antibiotics per admitted patient remained stable at 4 DDD. Co-amoxiclav was used most frequently and its use continued to rise from 14 to 18 DDD/100 patient-days. The use of fluoroquinolones rose from 4.4 to 5.5 DDD/100 patient-days, but the use of co-trimoxazole decreased from 2.6 to 2.3 DDD/100 patient-days.

The *resistance to antibiotics* was monitored in unselected hospital departments by the National Institute of Public Health and the Environment gathering routine data from regional public health laboratories. Moreover the Department of Medical Microbiology at the University Hospital Maastricht performed quantitative susceptibility testing of a great number of bacterial isolates from intensive care units, and departments of urology and pulmonology. This department also sampled and analysed *Escherichia coli* isolates from general practices, a suvey which was extended in 2002 from the southern part to other parts of the Netherlands.
In *general practice* the resistance of *E. coli* from urinary tract infections to trimethoprim rose from 10% in the South in 1988 to 17-22% in 2002 in the whole of the country, but the resistance to fluoroquinolones remained lower than 3%. In *hospitals* the resistance of Gram-negative and Gram-positive bacteria to fluoroquinolones increased. The resistance to these compounds was higher in *E. coli* from urology departments (15% in 2002) than in isolates from intensive care units (5.5%). Similarly the resistance to trimethoprim of *E. coli* was higher in isolates from urological patients (37% in 2002) compared with isolates from intensive care units (28%). The resistance of *Staphylococcus aureus* and *Streptococcus pneumoniae* to macrolides increased in the period of investigation, from 3 to 8% and from 2 to almost 7% respectively. Intermediate and full resistance of *S. pneumoniae* to penicillin remained low (1.5% in 2002). These differences in resistance may be related to differences in use in the different settings and to increased use leading to higher resistance percentages after some time delay. The National Institute of Public Health and the Environment contributed data on the resistance of *Mycobacterium tuberculosis* to rifampicin, isoniazid, streptomycin and ethambutol since 1996. The resistance to rifampicin remained low, 1.2% in 2002, and co-resistance to all four antituberculosis drugs was 0.2-0.7%.

The resistance percentages in this report for hospitals have been determined in routine isolates sent to a laboratory. Such strains have often been isolated from patients who did not respond to earlier therapy. In such a collection of strains the percentage of resistance tends to be higher than if strains are sampled from unselected patients treated for the first time. The latter sampling procedure was applied for the isolates from general practice. On the other hand only one isolate per species per patient was included in the hospital surveillance. This excludes multiple isolates from patients treated repeatedly.

Resistance percentages are dependent on susceptibility breakpoints chosen by standardisation committees. From a clinical point of view, some breakpoint concentrations may be too low (e.g. the breakpoints for susceptibility and resistance to penicillin for pneumococci), others are probably too high (e.g. the breakpoint of clarithromycin for *Haemophilus*).
In conclusion the figures in NethMap on antibiotic use and resistance may be used as reference values. These may differ substantially from levels of antibiotic use and resistance in particular groups of patients.

2 Samenvatting

NethMap 2004 beschrijft het gebruik van antibiotica en de resistentie tegen antibiotica bij de mens in Nederland. Gegevens over het *gebruik buiten het ziekenhuis* zijn verzameld door de Stichting Farmaceutische Kengetallen te Den Haag, en voor NethMap geanalyseerd door de Stichting Werkgroep Antibioticabeleid. Deze gegevens betreffen de omzet van alle openbare apotheken, die ca. 90% van Nederlandse bevolking buiten de ziekenhuizen van geneesmiddelen voorzien. In de periode 1998-2002 bleef het gebruik van antibiotica buiten de ziekenhuizen nagenoeg constant, 10 gestandaardiseerde dagdoseringen (DDD) per 1000 inwoners per dag. Vrij vertaald betekent dit dat gemiddeld 1% van de Nederlanders een antibioticum gebruikt. Daarmee heeft Nederland het laagste gebruik buiten het ziekenhuis van alle Europese landen. Het gebruik van tetracyclines daalde monotoon van 2,6 naar 2,3 DDD per 1000 inwoners per dag. Het gebruik van amoxicilline met clavulaanzuur nam toe van 0,95 naar 1,3 DDD per 1000 inwoners per dag, terwijl het gebruik van amoxicilline alleen met een gelijk volume daalde. Het gebruik van macroliden en fluorochinolonen steeg nog maar licht, met 0,1 DDD per 1000 inwoners per dag tot respectievelijk 1,2 en 0,85 DDD per 1000 inwoners per dag en lijkt zich de laatste jaren te stabiliseren.

Het gebruik van sommige antibiotica is in de winter veel hoger is dan in de zomer, wat een aanwijzing is dat ze voor luchtweginfecties worden gebruikt, die immers meer voorkomen in de winter. Tetracyclines, macoliden en amoxicilline met of zonder clavulaanzuur worden meer gebruikt in de winter maar het gebruik van fluorochinolonen is ’s winters even hoog als in de zomer. Dit wijst erop dat het gebruik van fluorochinolonen in ons land nog voornamelijk beperkt blijft tot urineweginfecties. Een deelstudie met het Landelijk Informatie Netwerk van Huisartspraktijken bevestigde dit en bracht het gebruik van fluorochinolonen bij eerste en herhaalde behandeling van urineweginfecties door huisartsen in kaart.

Gegevens over het *gebruik in ziekenhuizen* zijn verzameld door de Stichting Werkgroep Antibioticabeleid met een enquête. Het gebruik in ziekenhuizen nam in de periode 1998-2001 toe van 48 tot 55 DDD per 100 patiënt-dagen. Omdat de opnameduur in dezelfde periode afnam, bleef het gebruik van 4 DDD per opgenomen patiënt nagenoeg gelijk. Het meest gebruikte antibioticum in het ziekenhuis was het eerder genoemde combinatie preparaat amoxicilline met clavulaanzuur. Het gebruik hiervan steeg van 14 naar 18 DDD per 100 patiëntdagen. Het gebruik van fluorochinolonen steeg van 4,4 naar 5,5 DDD per 100 patiënt dagen. Het gebruik van co-trimoxazol daalde licht, van 2,6 naar 2,3 DDD per 100 patiënt-dagen.

Gegevens over de *resistentie tegen antibiotica* kwamen uit de geautomatiseerde registratie door het RIVM van de resistentie van bacteriestammen uit klinieken en poliklinieken die werden onderzocht in acht streeklaboratoria. Verder werd het percentage resistente isolaten bepaald van grote aantallen stammen van afdelingen voor intensive care, urologie en longziekten. Dit gebeurde op een centraal adres, de afdeling Medische Microbiologie van de Universiteit van Maastricht. Deze afdeling peilde tevens de resistentie van *Escherichia coli* van urineweginfecties bij huisartspatiënten in het zuiden van het land, een surveillance die in 2002 werd uitgebreid naar huisartspraktijken in het hele land.

De resistentie bij *E. coli* van *huisartspatiënten* tegen het eerste keus middel trimethoprim steeg van 10% in 1988 in Zuid Nederland naar 17-22% in heel Nederland in 2002. De resistentie tegen fluorochinolonen bleef lager dan 3%. In het *ziekenhuis* steeg de resistentie tegen de fluorochinolonen zowel bij de Gram-negatieve bacteriën (*Escherichia coli, Klebsiella pneumoniae* en *Pseudomonas aeruginosa*) als bij *Staphylococcus aureus*. De resistentie tegen deze middelen bereikte hogere waarden bij *E. coli* van urologische patiënten (15% in 2002) dan bij patiënten van intensive care afdelingen (5,5%). Ook de resistentie tegen trimethoprim was hoger bij de

urologische patiënten (37% in 2002) dan bij patiënten op de intensive care (28%). De resistentie tegen macroliden bij *S. aureus* en *Streptococcus pneumoniae* steeg in de beschreven periode, respectievelijk van 3% naar 8% en van 2% naar bijna 7%. De resistentie van *S. pneumoniae* tegen penicilline bleef laag (1,5%). In het algemeen zijn de gevonden verschillen in resistentie te relateren aan lokale verschillen in antibiotica gebruik, of aan een toename van het gebruik die met een vertraging leidde tot hogere resistentiepercentages.

Nieuw in deze editie van NethMap zijn surveillance gegevens van het RIVM over de resistentie van *Mycobacterium tuberculosis*. Tuberculose wordt altijd met een combinatie van middelen behandeld om uitselectie van resistentie bacteriën tijdens de therapie te voorkómen. Resistentie tegen het meest actieve middel, rifampicine, was nog laag (1,2% in 2002), terwijl gelijktijdige resistentie tegen isoniazide, rifampicine, streptomycine en ethambutol bij 0,2-0,7% van de isolaten gevonden werd.

De resistentiepercentages in dit rapport uit ziekenhuizen zijn van kweken die door de behandelend artsen naar een laboratorium zijn gestuurd. Vaak zijn er dan al problemen bij de behandeling en is het percentage resistente bacteriestammen hoger bij deze wijze van stammenverzameling dan wanneer systematisch bij alle patiënten een kweek zou zijn afgenomen. Dat laatste is wel gebeurd bij de resistentiesurveillance van *E. coli* van huisartspatiënten. Anderzijds zijn bij de bepaling van het percentage resistente isolaten alleen de eerste isolaten van elke soort bacterie per patiënt meegenomen. Het risico op resistentie en falende therapie is groter bij patiënten die eerder langdurig met antibiotica zijn behandeld. Verder zijn resistentiepercentages afhankelijk van de door standaardisatie commissies gekozen breekpunten. Dit breekpunt is soms zo laag, dat bacteriën ten onrechte als resistent worden beschouwd. Een voorbeeld is het relatief lage resistentiebreekpunt van penicilline voor pneumokokken, waardoor luchtweginfecties en sepsis met resistente pneumokokken paradoxaal genoeg vaak nog goed te behandelen zijn met dit antibioticum, met name als hoge doseringen worden toegepast. Er zijn vaak grote verschillen in breekpunten tussen landen. Het Amerikaanse breekpunt van claritromycine voor *Haemophilus* is veel hoger dan het breekpunt dat in ons land wordt geadviseerd. Dit leidt er toe dat deze soort in Amerika als gevoelig wordt beschouwd, maar bij ons als resistent.

De gegevens in NethMap beogen dan ook primair een soort Nieuw Amsterdams Peil van gebruik en resistentie in Nederland te verschaffen. Wij hopen dat ze als zodanig voor de klinische praktijk en voor het antibioticabeleid bruikbaar zijn en houden ons aanbevolen voor suggesties en kritiek.

3 Use of antibiotics

This report considers the use of antimicrobial agents in human medicine only. Data on the use of such agents in animal husbandry and veterinary medicine is 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.
Besides the structural surveillance of antibiotic use, data derived from in-depth studies are presented in this section.

Primary health care
Table 1 presents the use of antibiotics for systemic use in primary health care from 1998-2002. Over these years total antibiotic consumption remained almost constant. The overall use of antibiotics in the Netherlands is 10 DDD/1000 inhabitant-days. The distribution of antibiotics by class in 2002 is presented in figure 1. As for previous years tetracyclines (mainly doxycycline) represented 23% 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, each representing 17%, 14% and 13% of the total use respectively.

The use of amoxicillin decreased from 2.13 in 1998 to 1.78 DDD/1000 inhabitant-days (-16%) in 2002. The use of co-amoxiclav increased from 0.95 in 1998 to 1.34 DDD/1000 inhabitant-days (+41%) in 2002 (figure 2). In 1998, the proportion of amoxicillin and co-amoxiclav was respectively 56 and 25% of the total penicillin use in the Netherlands. These proportions changed to respectively 47 and 35% in 2002.

The increased use of macrolides is presented in figure 3. Clarithromycin is still the most commonly used macrolide, and its use gradually increased to 0.79 DDD/1000 inhabitant-days. The use of azithromycin also increased. A decrease was found for both erythromycin and roxithromycin.

From 1998 to 2001 the use of fluoroquinolones increased by 10% (table 1). Between 2001 and 2002 total use and use of the individual drugs seemed to stabilize (figure 4). In 2002 the use of ciprofloxacin slightly exceeded the use of norfloxacin. Ciprofloxacin was the most used

Table 1. Use of antibiotics for systemic use (J01) in primary health care (DDD/1000 inhabitant-days), The Netherlands, 1998-2002 (Source: SFK).

ATC-group[a)]	Therapeutic group	Year				
		1998	1999	2000	2001	2002
J01AA	Tetracyclines	2.55	2.49	2.47	2.39	2.33
J01BA	Chloramphenicol	0.00	0.00	0.00	0.00	0.00
J01CA	Penicillins with extended spectrum	2.13	2.06	1.88	1.82	1.78
J01CE	Beta-lactamase sensitive penicillins	0.53	0.52	0.52	0.49	0.45
J01CF	Beta-lactamase resistant penicillins	0.22	0.23	0.24	0.25	0.25
J01CR	Combinations of penicillins, incl. beta-lactamase-inhibitors	0.95	1.04	1.15	1.25	1.34
J01DA	Cephalosporins and related substances	0.11	0.10	0.08	0.07	0.07
J01EA	Trimethoprim and derivatives	0.28	0.30	0.28	0.28	0.27
J01EC	Short-acting sulfonamides	0.00	0.01	0.01	0.01	0.01
J01EE	Combinations of sulfonamides and trimethoprim	0.46	0.46	0.43	0.42	0.40
J01FA	Macrolides	1.16	1.17	1.13	1.22	1.24
J01FF	Lincosamides	0.03	0.04	0.04	0.05	0.06
J01GB	Aminoglycosides	0.00	0.00	0.00	0.01	0.01
J01MA	Fluoroquinolones	0.79	0.85	0.85	0.87	0.85
J01MB	Other quinolones	0.05	0.04	0.04	0.04	0.03
J01XB	Polymyxins	0.02	0.02	0.02	0.02	0.02
J01XE	Nitrofuran derivatives	0.59	0.64	0.68	0.71	0.74
J01XX	Other antibiotics (= methenamine)	0.06	0.06	0.06	0.06	0.04
J01	Antibiotics for systemic use (total)	9.93	10.03	9.88	9.96	9.89

[a)] from the 2002 edition of the Anatomical Therapeutic Chemical (ATC) classification system

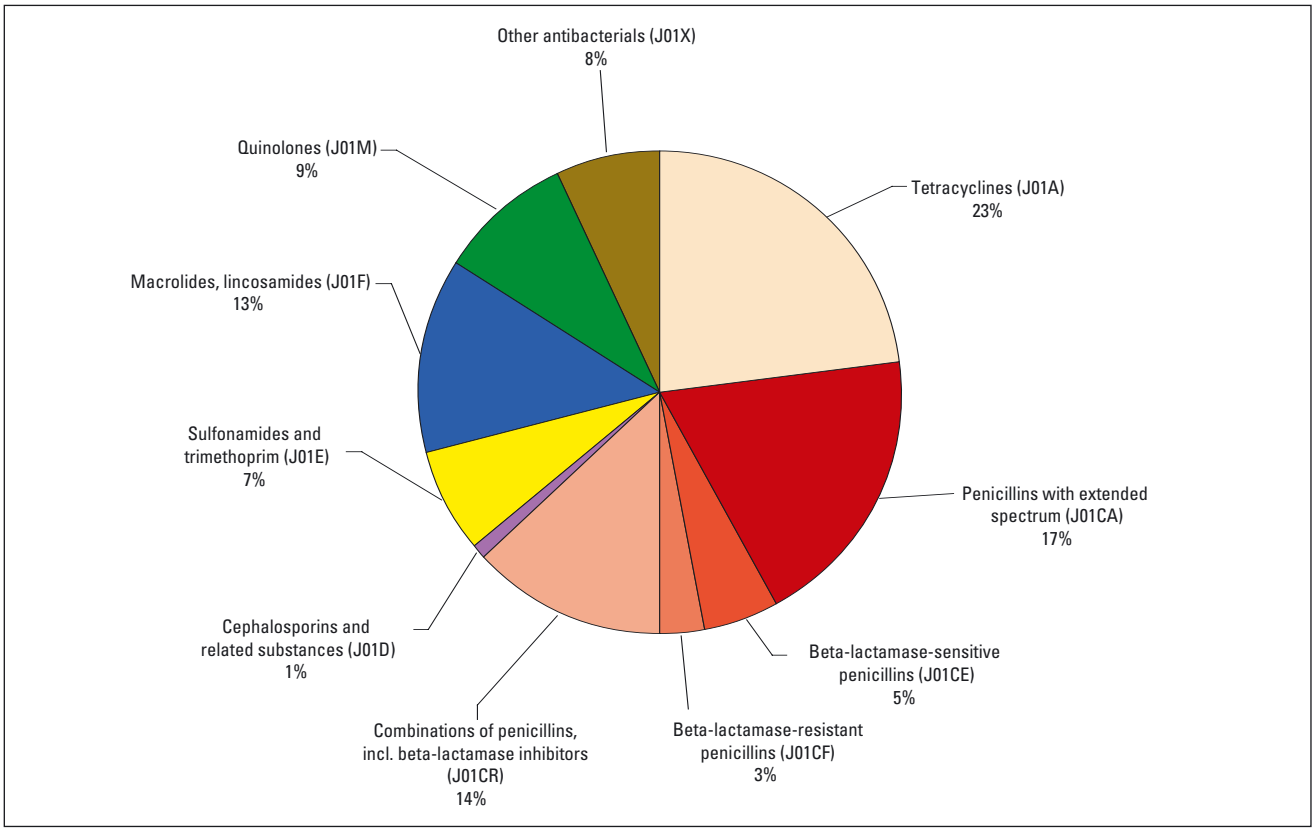


Figure 1. Distribution of the use of antibiotics for systemic use (J01) in primary health care, The Netherlands, 2002 (Source: SFK).

fluoroquinolone. The use of nitrofurantoin increased from 0.59 in 1998 to 0.74 DDD/1000 inhabitant-days in 2002 (table 1).

In figure 5 the quarterly number of prescriptions between 2000 and 2002 are depicted to assess the presence of seasonal fluctuations. These fluctuations were obvious for the beta-lactam antibiotics, tetracyclines and macrolides. No seasonal fluctations were observed for the fluoroquinolones.

Figure 2. Use of amoxicillin and co-amoxiclav in primary health care, The Netherlands, 1998 - 2002 (Source: SFK).

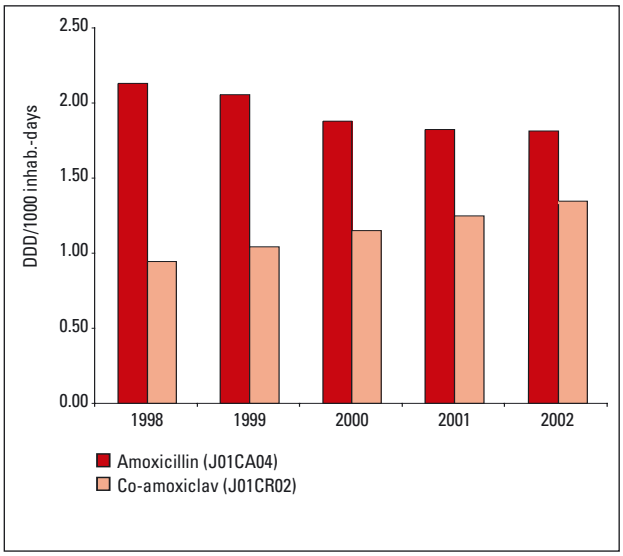
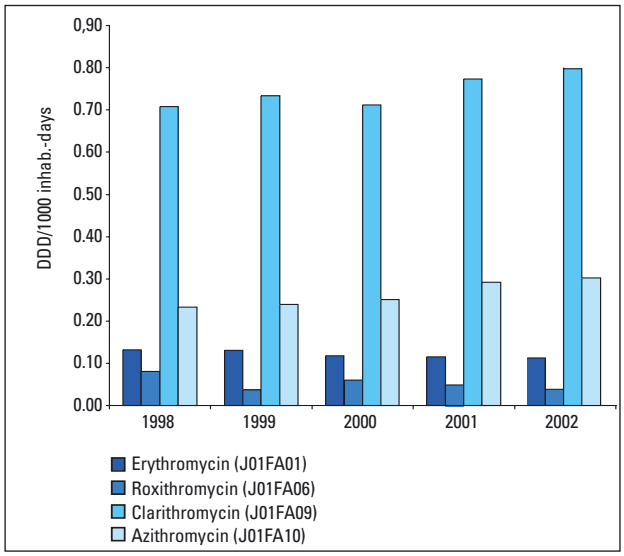


Figure 3. Use of macrolides for systemic use in primary health care, The Netherlands, 1998-2002 (Source: SFK).



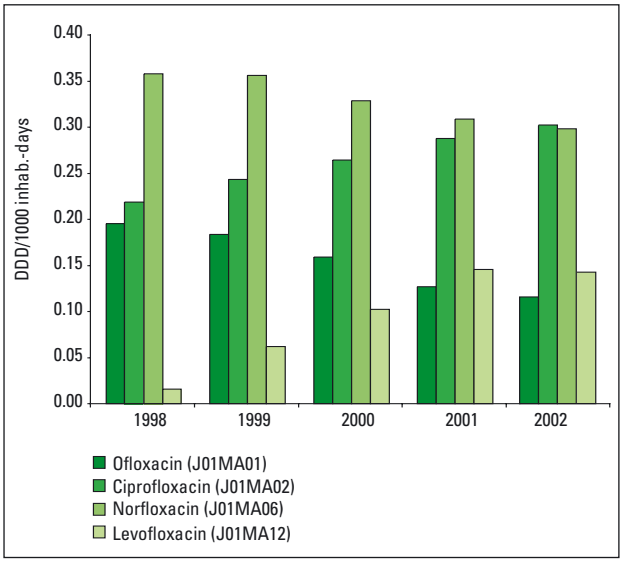


Figure 4. Use of fluoroquinolones for systemic use in primary health care, The Netherlands, 1998-2002 (Source: SFK).

Discussion

From 1998-2002 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). The use of co-amoxiclav still continued to rise in 2002 and showed seasonal fluctuations suggesting a pronounced role in the treatment of respiratory tract infections (figure 5). To evaluate the high use of these broad-spectrum antibiotics insight into indications and susceptibility patterns of causative micro-organisms seems warranted. Seasonal fluctuations were also found for the total group of beta-lactam antibiotics, tetracyclines and macrolides, but not for the fluoroquinolones. This indicates that in primary health care fluoroquinolones were hardly prescribed for respiratory tract infections.

Due to their broad spectrum, fluoroquinolones are definitely not the first choice for uncomplicated urinary tract infections presenting in the community. According to the guidelines developed by the Dutch College of General Practitioners fluoroquinolones are reserved in this setting for relapsing or recurrent infections caused by micro-organisms resistant to trimethoprim, nitrofurantoin or amoxicillin and be based on susceptibility testing of the causative microorganisms.

In collaboration with the Netherlands Information Network in General Practice (LINH) we assessed the use of fluoroquinolones in the treatment of uncomplicated urinary tract infections (see project 1). Eighty-two percent of the total fluoroquinolone use in women was prescribed for uncomplicated urinary tract infections. The majority of uncomplicated urinary tract infections in women was initially treated with nitrofurantoin or trimethoprim; fluoroquinolones were however chosen in 7% of infections treated for the first time. A second anti-

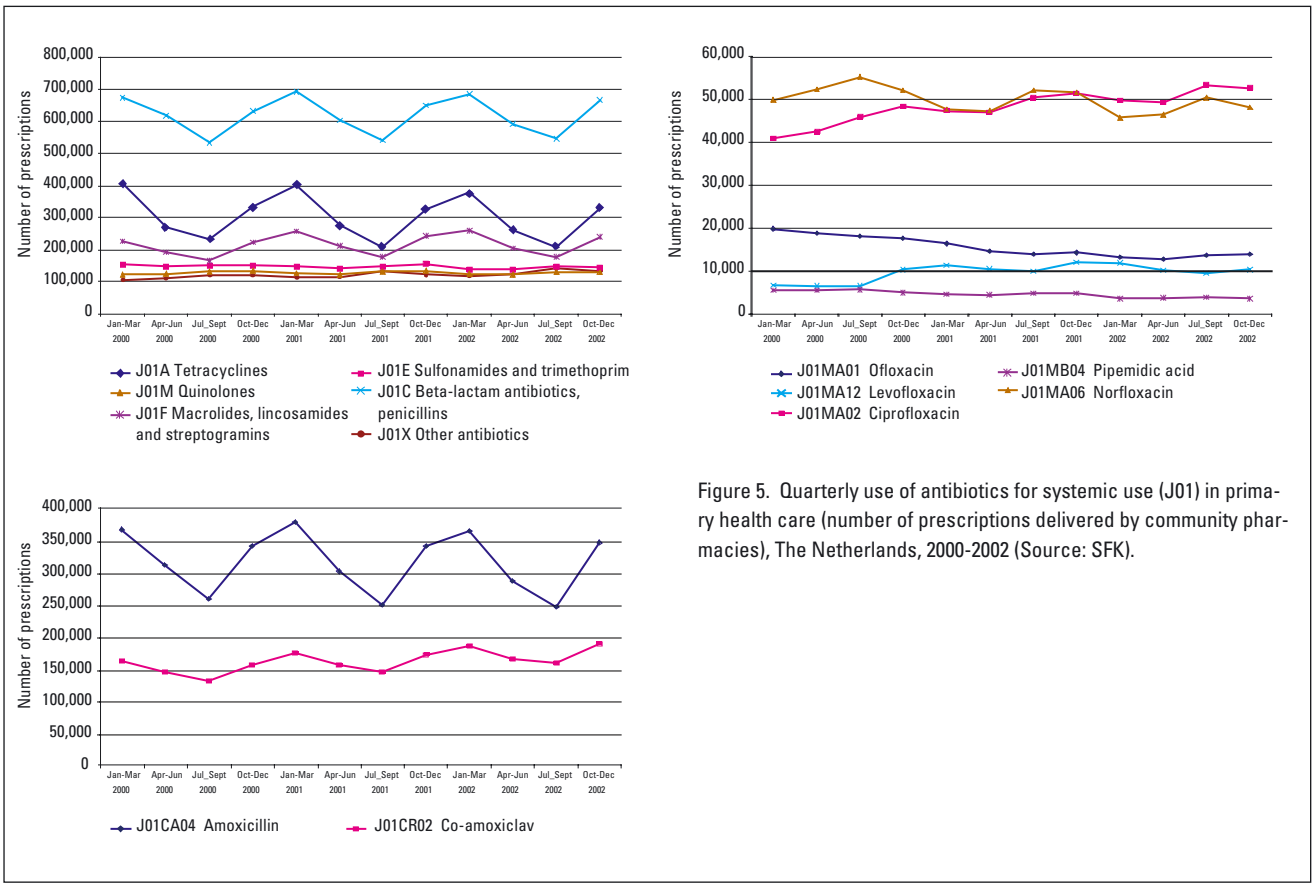


Figure 5. Quarterly use of antibiotics for systemic use (J01) in primary health care (number of prescriptions delivered by community pharmacies), The Netherlands, 2000-2002 (Source: SFK).

Table 2. Use of antibiotics for systemic use (J01) in Dutch hospitals[a] (DDD/100 patient-days), The Netherlands, 1998-2001 (Source: SWAB).

ATC-group[b]	Therapeutic group	Year			
		1998	1999	2000	2001
J01AA	Tetracyclines	1.6	1.7	1.6	1.6
J01BA	Chloramphenicol	0.0	0.0	0.0	0.0
J01CA	Penicillins with extended spectrum	6.5	6.4	6.0	6.1
J01CE	Beta-lactamase sensitive penicillins	1.0	1.1	1.1	1.4
J01CF	Beta-lactamase resistant penicillins	3.8	3.9	4.4	4.3
J01CR	Combinations of penicillins, incl. beta-lactamase-inhibitors	14.3	15.6	16.9	18.1
J01DA	Cephalosporins and related substances	5.5	5.6	5.9	6.1
J01DF	Monobactams	0.0	0.0	0.0	0.0
J01DH	Carbapenems	0.4	0.3	0.4	0.3
J01EA	Trimethoprim and derivatives	0.5	0.5	0.4	0.5
J01EC	Short-acting sulfonamides	0.1	0.1	0.1	0.0
J01EE	Combinations of sulfonamides and trimethoprim	2.6	2.5	2.4	2.3
J01FA	Macrolides	1.9	2.2	2.1	2.3
J01FF	Lincosamides	0.9	1.1	1.2	1.3
J01GB	Aminoglycosides	2.1	2.0	2.2	2.0
J01MA	Fluoroquinolones	4.4	5.0	4.9	5.5
J01MB	Other quinolones	0.1	0.0	0.1	0.1
J01XA	Glycopeptides	0.4	0.4	0.5	0.5
J01XD	Imidazole derivatives	1.2	1.2	1.2	1.3
J01XE	Nitrofuran derivatives	0.3	0.2	0.4	0.5
J01	Antibiotics for systemic use (total)	47.8	50.1	52.2	54.7

[a] percentage of covered patient-days in 1998, 1999, 2000 and 2001 were 61, 67, 63 and 53, respectively.

[b] from the 2002 edition of the Anatomical Therapeutic Chemical (ATC) classification system

biotic within 4 weeks was prescribed in 16% of these women of which 18% concerned a fluoroquinolone. Although it was impossible to verify whether these fluoroquinolone prescriptions were based on results of susceptibility testing, we strongly recommended to only prescribe these broad spectrum antibiotics in case of causative micro-organisms resistant to the first choice narrow spectrum antibiotics.

Hospitals

Table 2 presents the use of antibiotics for systemic use in Dutch hospitals from 1998-2001. Total use in hospitals was 47.8 DDD/100 patient-days in 1998 and increased to 54.7 in 2001.

The distribution of antibiotics by class in 2001 is presented in figure 6. In 2001 all penicillins combined represented 56% of hospital antibiotic use in the Netherlands. Combinations of penicillins, including beta-lactamase inhibitors, mainly co-amoxiclav, represented 34% of hospital antibiotic use in the Netherlands.

The use of co-amoxiclav increased from 14.2 in 1998 to 18.0 in 2001. From 1998-2000 the use of piperacillin with tazobactam increased from 0.12 to 0.19 DDD/100 patient-days, however in 2001 the use remained constant at 0.18 DDD/100 patient-days. Amoxicillin use decreased from 6.3 in 1998 to 5.5 DDD/100 patient-days in 2001. Flucloxacillin is the only antistaphylococcal penicillin used to any extent in the Netherlands. The use of this antibiotic increased from 3.8 in 1998 to 4.6 DDD/100 patient-days in 2001.

Cephalosporins represented 11% of the total hospital use in 2001 (figure 6). The use of the various generations of cephalosporins is summarised in figure 7. The use of the first generation cephalosporins increased from 1.3 in 2000 to 1.6 DDD/100 patient-days in 2001. Of these cefazolin was by far the most commonly used one. The use of cefazolin increased from 1.1 in 2000 to 1.5 DDD/100 patient-days (+36%) in 2001. The use of cefuroxime gradually increased to 2.5 DDD/100 patient-days. After an increase in use of the third generation cephalosporins (1.5 to 1.8 DDD/100 patient-days between 1998 and 2000), the use remained constant in 2001.

The use of clarithromycin increased between 1998 and 2001, bypassing that of erythromycin (figure 8). The use of clindamycin increased from 0.88 in 1998 to 1.3 DDD/100 patient-days in 2001. In 2001 gentamicin was

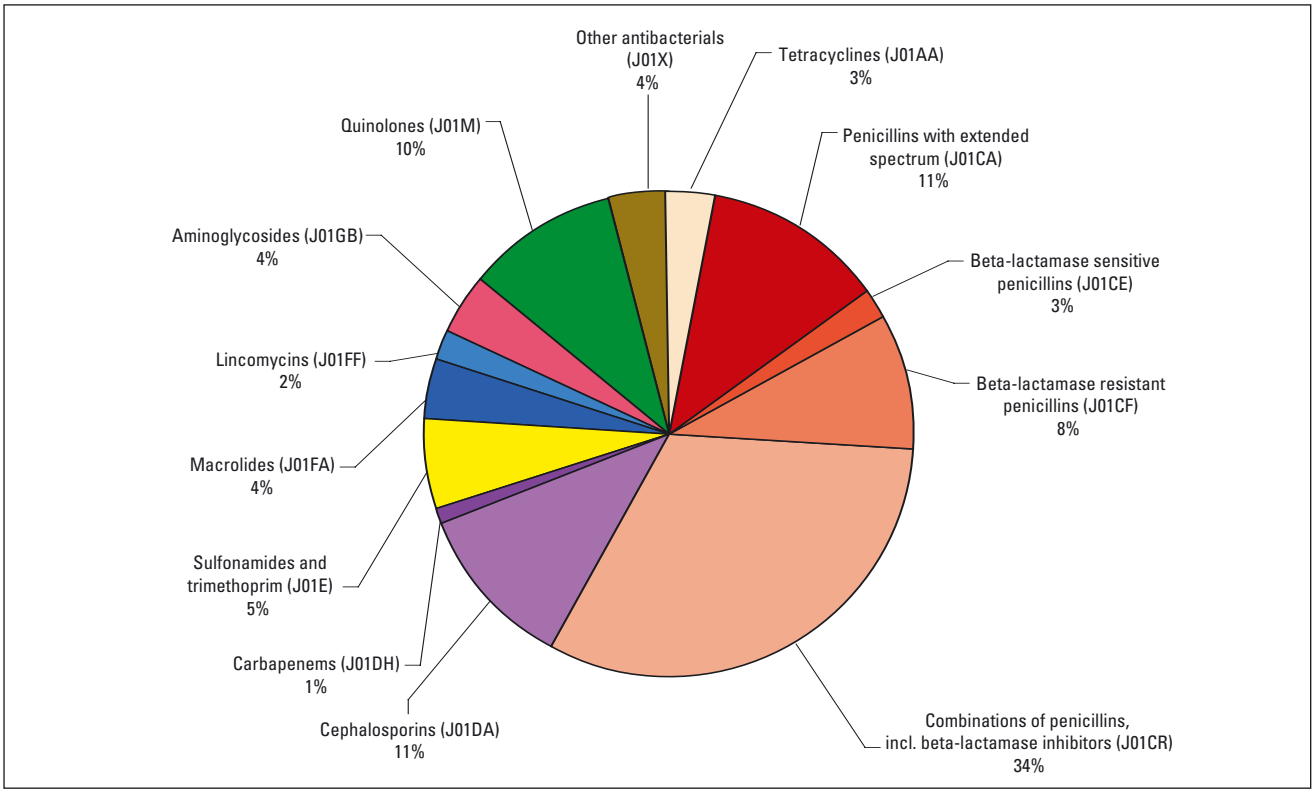


Figure 6. Distribution of the use of antibiotics for systemic use (J01) in Dutch hospitals, 2001 (Source: SWAB).

by far the most commonly used antibiotic of the aminoglycoside class (figure 9). Fluoroquinolones represented 10% of the total hospital use in 2001 (figure 6). Total use of the fluoroquinolones seemed to stabilise in 2000 at 4.9 DDD/100 patient-days, but increased 0.6 DDD/100 patient-days once again between 2000 and 2001 (table 2). Both the use of ciprofloxacin and levofloxacin increased in 2001 (figure 10). The use of the glycopeptides remained almost constant during the study period (figure 11).

Discussion

Total systemic use expressed as DDD/100 patient-days increased 14% during the period 1998-2001. However,

Figure 7. Use of cephalosporins in Dutch hospitals, 1998- 2001 (Source: SWAB).

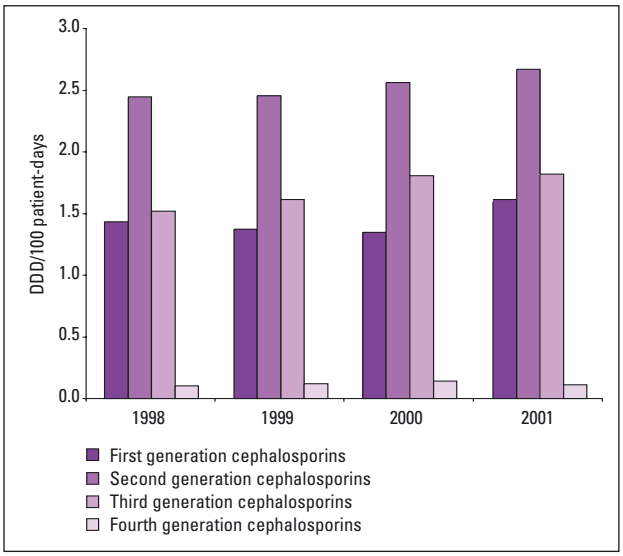
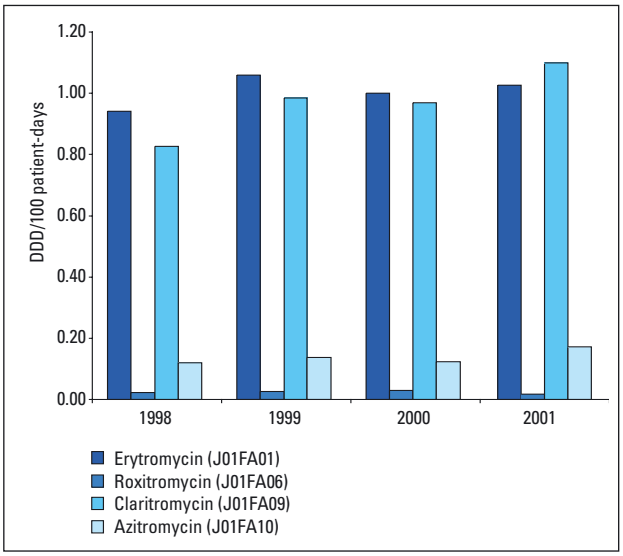


Figure 8. Use of macrolides in Dutch hospitals, 1998-2001 (Source: SWAB).



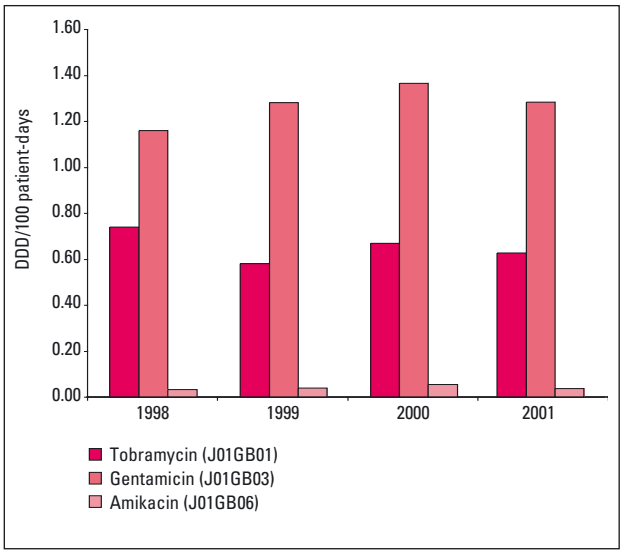


Figure 9. Use of aminoglycosides in Dutch hospitals, 1998-2001 (Source: SWAB).

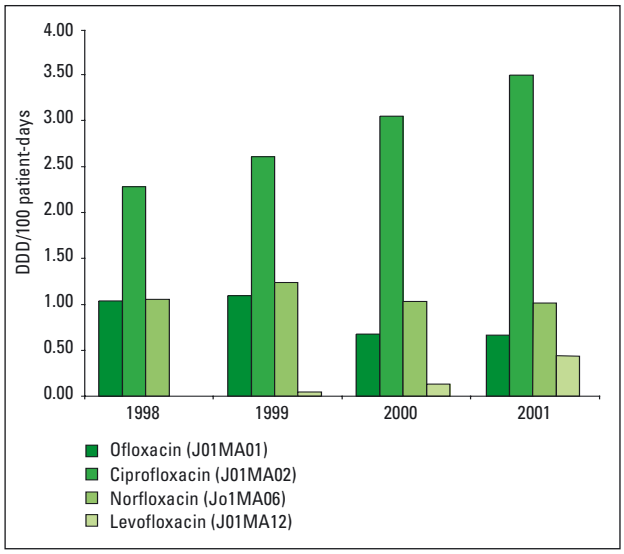
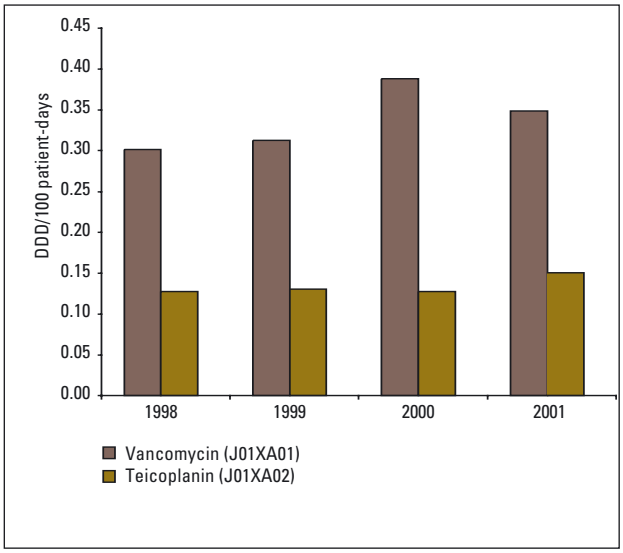


Figure 10. Use of fluoroquinolones for systemic use in Dutch hospitals, 1998-2001 (Source: SWAB).

total systemic use expressed as DDD/admission remained constant at approximately 4 because the average length of hospital stay decreased in this period from 9.0 to 8.0 days. So the decrease in average hospital stay is a confounding factor when hospital use of antibiotics is analysed solely on the basis of DDD/100 patient-days. Since average lengths of stay differ over time and between hospitals, geographical regions and countries, future comparisons in the hospital use of antibiotics should correct for this potential confounding effect.

In 2001 a remarkable increase in the use of cefazolin was observed. Cefazolin is an agent that is used for perioperative profylaxes and the increased use in 2001 may be explained by two national interventions. In 2000 the SWAB published the guideline for perioperative antibiotic profylaxis. In this guideline cefazolin is strongly recommended as this agent is not widely used as a therapeutic agent, is selective against micro-organisms most frequently isolated from surgical site infections and has a plasma half-life that makes single dosing possible for most operations (reference 3).In addition, in 1999 the CHIPS (surgical prophylaxis and surveillance) project, an audit and improvement programme looking at the quality of surgical prophylaxis, was started in the Netherlands (reference 4).

Figure 11. Use of glycopeptides in Dutch hospitals, 1998-2001 (Source: SWAB).



The use of piperacillin with tazobactam, the third generation cephalosporins, the carbapenems and vancomycin increased from 1998 to 2000, but fortunately remained constant between 2000 and 2001.

The increased use of the fluoroquinolones was caused by ciprofloxacin and the newer fluoroquinolone levofloxacin. The use of co-amoxiclav also continued to rise. It would be interesting to identify the hospitals departments in which these changes in antibiotic policies are being made. Subsequently rationality of the prescriptions and consequences for resistance frequencies should be studied.

PROJECT 1

Fluoroquinolones in the treatment of cystitis: can it be reduced?

(Source: LINH, published in Huisarts en Wetenschap 2003;46(7):353).

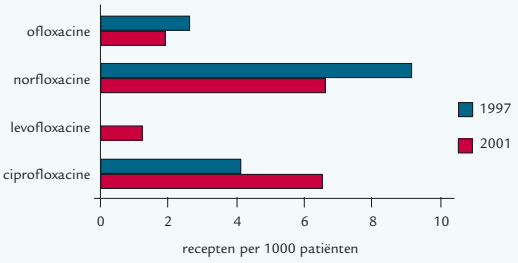
Fluorchinolonen bij cystitis: kan het minder?

Lea Jabaaij, Margreet Filius

Fluorchinolonen zijn breedspectrumantibiotica die alleen bij ernstige infecties moeten worden voorgeschreven zodat resistentieontwikkeling beperkt blijft. Het gebruik van fluorchinolonen stijgt, evenals de resistentie. Op dit moment bestaat al bij bijna 6% van de door de huisarts ingestuurde urinemonsters een resistentie voor E. *coli* tegen norfloxacine.

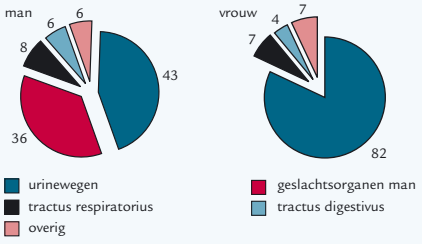
Het aantal recepten voor een fluorchinolon (norfloxacine, ciprofloxacine, ofloxacine en levofloxacine) is licht gestegen tussen 1997 en 2001: van 15,8 naar 16,2 per 1000 patiënten. Norfloxacine en ciprofloxacine worden het meest voorgeschreven (*figuur* 1).

Figuur 1 Aantal voorschriften fluorchinolonen in 1997 en 2001



Vrouwen krijgen vaker een fluorchinolon voorgeschreven dan mannen: 19,4 tegenover 12,1 recepten per 1000 patiënten in 2001. Het verschil zit vooral in het aantal norfloxacinerecepten.
Het aantal recepten voor fluorchinolonen verschilt aanzienlijk per praktijk: 10% van de praktijken schrijft niet meer dan 6 recepten uit per 1000 patiënten per jaar, terwijl eveneens 10% er meer dan 30 uitschrijft. Het is niet waarschijnlijk dat dit is te verklaren door verschillen in populatiesamenstelling.
Twee derde van de fluorchinolonrecepten die de huisarts uitschrijft, is bestemd voor de behandeling van urologische aandoeningen, 13% voor aandoeningen aan de mannelijke genitaliën, 7% voor respiratoire problemen en 5% voor aandoeningen aan het maagdarmkanaal. Er zijn grote verschillen tussen mannen en vrouwen (*figuur* 2).

Figuur 2 Aandoeningen (ingedeeld naar ICPC-hoofdstukken) waarvoor huisartsen in 2001 fluorchinolonen voorschrijven (als percentage van alle fluorchinolonrecepten)



Meer dan de helft van de fluorchinolonen is voorgeschreven voor ongecompliceerde urineweginfecties (ICPC-code U71). Bij vrouwen gaat het zelfs om driekwart van alle recepten. Dit is verrassend omdat de fluorchinolonen volgens de NHG-Standaard Urineweginfecties geen middelen van eerste keus zijn. Daarom zijn we vervolgens nagegaan wat huisartsen voorschrijven bij een urineweginfectie. We beperken ons hier tot vrouwen (*tabel*). De huisarts behandelt 7% van de vrouwen met een cystitis primair met een fluorchinolon; 16% van de vrouwen krijgt binnen 4 weken een tweede kuur, waarvan 18% met een fluorchinolon.

Tabel Welke plaats nemen de fluorchinolonen in bij de behandeling van een cystitis bij vrouwen met systemische antimicrobiële middelen (als percentage van alle recepten, 2001)?

	1e kuur*	2e kuur binnen 4 weken
trimethoprim	41,9	18,8
nitrofurantoïne	38,1	38,8
amoxicilline	5,1	6,5
trimethoprim/sulfamethoxazol	4,0	7,7
amoxicilline/clavulaanzuur	3,9	7,4
fluorchinolonen:		
– norfloxacine	4,6	12,6
– ciprofloxacine	1,4	4,6
– ofloxacine	0,4	1,0
– levofloxacine	0,2	0,7

* geen ander recept wegens cystitis 6 maanden voorafgaand aan deze kuur (5562 patiënten)

Om resistentieproblemen te vermijden, moeten artsen antimicrobiële middelen slechts mondjesmaat voorschrijven. De keuze voor een fluorchinolon bij bijna 20% van de patiënten met aanhoudende klachten is hoog en niet conform de NHG-Standaard. Wanneer niet gekweekt wordt bij de eerste vervolgkuur, moet er met een ander middel van eerste keuze, trimethoprim of nitrofurantoïne, worden behandeld. Om te voorkomen dat het therapeutisch arsenaal afneemt, kan niet sterk genoeg worden benadrukt dat bij aanhoudende ongecompliceerde urineweginfecties de keuze van het middel gebaseerd moet zijn op een kweek en resistentiebepaling.

Deze LINH-rubriek is tot stand gekomen in samenwerking met de werkgroep surveillance antibioticagebruik van de Stichting Werkgroep Antibioticabeleid (www.SWAB.nl). De hier beschreven analyses zijn uitgevoerd op LINH-gegevens. LINH is een project van WOK, NIVEL, LHV en NHG. In 2001 participeerden ruim 120 huisartsenpraktijken. Zie voor meer informatie over LINH en over de hier beschreven gegevens www.linh.nl. Reacties naar info@linh.nl.

PROJECT 2

Delivery of antibiotics by community pharmacies versus general practitioners with their own pharmacy

Introduction

All antibiotics for human use are prescription-only medicines in the Netherlands. The majority of prescriptions are delivered by community pharmacies. Direct delivery of medicines by general practitioners from their own pharmacy reaches approximately 10% of the Dutch population, mainly in rural areas. The SWAB surveillance system of antibiotic use in primary health care, as provided by the Foundation for Pharmaceutical Statistics, does not include data on deliveries of antibiotics by general practitioners. In the present study we examined whether the antibiotic deliveries by community pharmacies differs from deliveries by general practitioners from their own pharmacy.

Methodology

Data were obtained from the Dutch Drug Information Project (GIP) of the Health Care Insurance Board (CVZ). This institution registers drug use of patients insured by the Dutch Sickness Fund. Data are available for 2 million people in 1992 increasing to 7.5 million people in 2002, due to a growing number of participating regions. Prescriptions for antibiotics for systemic use (group J01 of the Anatomical Therapeutic Chemical (ATC) classification system) were selected for patients insured by the Dutch Sickness Fund from 1994 to 2002 and categorised to prescriptions declared by community pharmacies and by general practitioners.

In the Netherlands two-third of the population are covered for their medical care by the Dutch Sickness Fund and one-third is privately insured. In this study antibiotic use data were extrapolated by GIP to cover the total Dutch population (Dutch Sickness Fund and privately insured), using a model that corrects for differences in use, age en gender in the different populations. Antibiotic use was calculated as the number of defined daily doses (DDD) per 1000 inhabitants per day.

Results

Table 1 shows that over the years 1994 to 2002 the proportion of antibiotics delivered by general practitioners with a pharmacy equals the percentage of patients registered by these general practitioners. In 1994 and in 2002 no differences are observed in the proportion of the different antibiotic groups delivered by community pharmacies and general practitioners with a pharmacy (table 2).

Conclusion

The results of this study implies that data on antibiotic use calculated from prescriptions of community pharmacies can be extrapolated to the total use of antibiotics in the Netherlands as 1) the percentage of insured patients registered by general practitioners with a pharmacy equals the proportion of antibiotics delivered by these general practitioners and 2) no differences were found between the proportion of the different antibiotic groups delivered by community pharmacies and general practitioners with their own pharmacy.

Table 1. Use of antibiotics for systemic use (J01) in primary health care by distribution channel, the Netherlands, 1994-2002 (Source: Drug Information Project (GIP) / Health Care Insurance Board (CVZ)).

	Year				
	1994	1996	1998	2000	2002
Total use of antibiotics for systemic use (DDD/1000 inhabitant-days)	9.0	9.3	9.6	9.4	9.3
Antibiotics distributed by community pharmacy (DDD/1000 inhabitant-days, %)	8.0 (88.9)	8.3 (89.2)	8.6 (89.6)	8.4 (89.4)	8.4 (90.3)
Antibiotics distributed directly by general practitioner (DDD/1000 inhabitant-days, %)	1.0 (11.1)	1.0 (10.8)	1.0 (10.4)	1.0 (10.6)	0.8 (8.6)
Percentage of insured persons registered by general practitioner with pharmacy	10.7	10.4	10	9.7	9.3

Table 2. Relative use (% of DDD/1000 inhabitant-days) of antibiotics for systemic use (J01) in primary health care by distribution channel, the Netherlands, 1994 and 2002 (Source: Drug Information Project (GIP) / Health Care Insurance Board (CVZ)).

ATC-group[a]	Therapeutic group	Year			
		1994		2002	
		Community pharmacy	General practitioner	Community pharmacy	General practitioner
J01AA	Tetracyclines	28.9	30.8	24.3	25.8
J01BA	Chloramphenicol	0.0	0.0	0.0	0.0
J01CA	Penicillins with extended spectrum	22.8	23.1	18.1	19.1
J01CE	Beta-lactamase sensitive penicillins	6.5	4.7	4.7	3.1
J01CF	Beta-lactamase resistant penicillins	2.3	2.3	2.7	2.5
J01CR	Combinations of penicillins, incl. beta-lactamase-inhibitors	7.5	6.8	13.4	13.6
J01DA	Cephalosporins and related substances	1.6	1.6	0.6	0.8
J01EA	Trimethoprim and derivatives	2.9	2.3	2.8	3.1
J01EC	Short-acting sulfonamides	0.2	0.3	0.1	0.0
J01EE	Combinations of sulfonamides and trimethoprim	6.4	7.5	4.0	4.6
J01FA	Macrolides	6.0	5.7	11.9	10.2
J01FF	Lincosamides	0.2	0.1	0.6	0.5
J01GB	Aminoglycosides	0.0	0.0	0.1	0.1
J01MA	Fluoroquinolones	6.4	4.8	8.4	8.4
J01MB	Other quinolones	0.8	1.7	0.2	0.3
J01XE	Nitrofuran derivatives	6.6	7.8	7.5	7.1
J01XX	Other antibiotics (= J01XE excluded)	0.8	0.5	0.7	0.9
J01	Antibiotics for systemic use (total)	100	100	100	100

[a] from the 2003 edition of the Anatomical Therapeutic Chemical (ATC) classification system

4 Resistance among common Pathogens

Surveillance of Antimicrobial Resistance in the Community

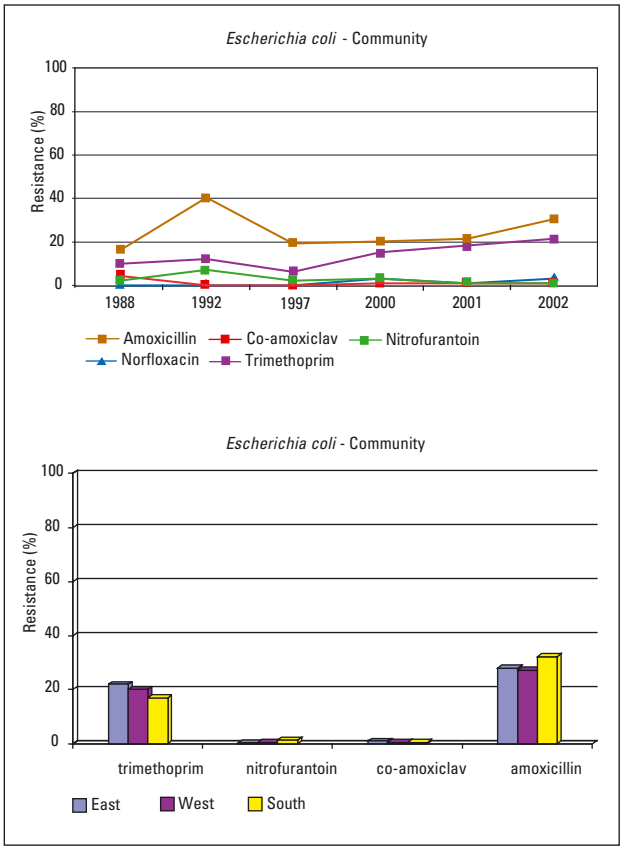
The prevalence of antibiotic resistance among bacteria causing community acquired infection was determined for strains collected from patients with complaints of an acute uncomplicated urinary tract infections visiting their general practitioner in communities in the Southern part of the Netherlands (1988-2001). This project was extended to other parts of the Netherlands in 2002. See material and methods section for details regarding the acquisition and testing of isolates. This report describes the resistance patterns found among 1080 isolates of *Escherichia coli* in different areas in 2002 and compares these data with the results in the South of the Netherlands, obtained during the years before.

Escherichia coli

Escherichia coli isolates in 2002 came from patients in the provinces Groningen and Drenthe (North, 51 strains), Gelderland (East, 329 strains), Utrecht, Noord- and Zuid Holland (West, 489 strains) and Zeeland, Noord Brabant and Limburg (South, 211 strains). The results from the North were not analysed further due to 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 2002 an overall resistance percentage of 30% (figure 1) was observed, varying from 27% (East and West) to 32% (South) (figure 2). The amoxicillin resistance among *E. coli* in the community in 2001 was significantly lower than that in selected or Unselected Hospital Departments (defined later), but in 2002 the resistance percentage equalled that of the Unselected Hospital Departments. The MIC distribution of amoxicillin showed two subpopulations of strains, one susceptible and one highly resistant (MIC>128 mg/l) (figure 3). Resistance to co-amoxiclav was relatively rare. The MIC distribution of co-amoxiclav (figure 3) showed a unimodal shape over a broad range (MIC 1-64 mg/l).

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



Trimethoprim resistance rates increased over the years, from 10% in 1988 to 17% in 2002 in the South (figure 1) which was lower than the rates in the West and the East (20-22%). The prevalence of nitrofurantoin resistance remained at a low level (< 1%) in all parts of the Netherlands.

Norfloxacin resistant *E. coli* was at first found in 2000 and 2001 in the South, albeit at a rather low level (<3%, figure 1)). This percentage persisted in 2002 and was equal to the rate in East and West (figure 2). There was cross-resistance with ciprofloxacin; the MIC distribution showed a large cluster of highly susceptible strains and sporadic highly resistant strains in each area (figure 3). The 3% quinolone resistance level is similar to that in Unselected Hospital Departments.

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 against amoxicillin and trimethoprim among *E. coli* causing community acquired urinary tract infection are emerging in the community. Since trimethoprim is an agent of choice for the treatment of urinary tract infection (NHG standard) and

Figure 2. Variation of resistance to antibiotics for *Escherichia coli* from the community in East, West and South of the Netherlands.

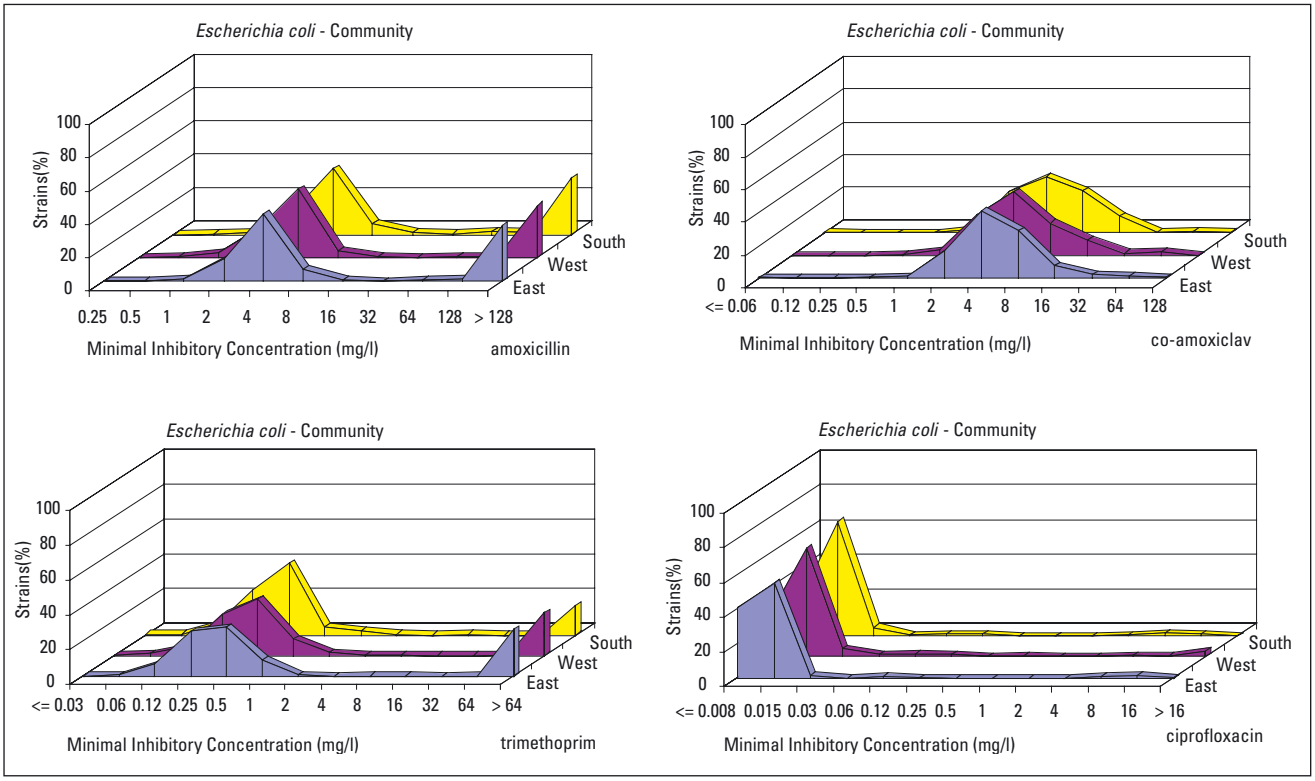


Figure 3. MIC distributions of amoxicillin, co-amoxiclav, trimethoprim and ciprofloxacin for *Escherichia coli* from the community in East, West and South of the Netherlands. Strains with MIC ≤ 8 mg/l for amoxicillin, co-amoxiclav and trimethoprim are susceptible, strains with MIC ≥ 32 mg/l for amoxicillin and co-amoxiclav and ≥ 16 mg/l for trimethoprim are resistant. Strains with MIC ≤1 mg/l for ciprofloxacin are susceptible and with MIC ≥ 4 mg/l are resistant.

amoxicillin may be used for paediatric complicated infection (i.e. relapsing and recurrent cases) in this setting these trends, if true, require further attention. These data also indicate that the resistance found 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 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 including outpatient clinics were the sources of strains collected and tested by eight Regional Public Health Laboratories covering 25% of the Dutch population (table 1 in appendix). These are designated resistance rates in 'Unselected Hospital Departments'. The resistance rates in Unselected Hospital Departments were compared with the resistance rates among strains (table 2 in appendix) isolated from selected departments in 13 large referral hospitals. 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 analysed per species of common nosocomial pathogens and are presented in the accompanying figures.

Escherichia coli

The overall prevalence of amoxicillin resistance in Unselected Hospital Departments increased slowly from 29% in 1995 to 33 % in 2002 (figure 4). Amoxicillin resistance was higher in Urology Services (39%), but significantly and consistently the highest in Intensive Care Units until 2001. Starting in 1998 a steady increase in the prevalence of amoxicillin resistance was observed in Intensive Care Units reaching 44% in 2002. In 2002 the amoxicillin resistance in Urology Services reached the level of that in Intensive Cares. The MIC distribution (figure 5) clearly showed a susceptible and a resistant subpopulation. Intermediate susceptibility to amoxicillin among *E. coli* isolates is rare. The resistant subpopulation is steadily growing during the years.
Co-amoxiclav resistance remained at a low level in

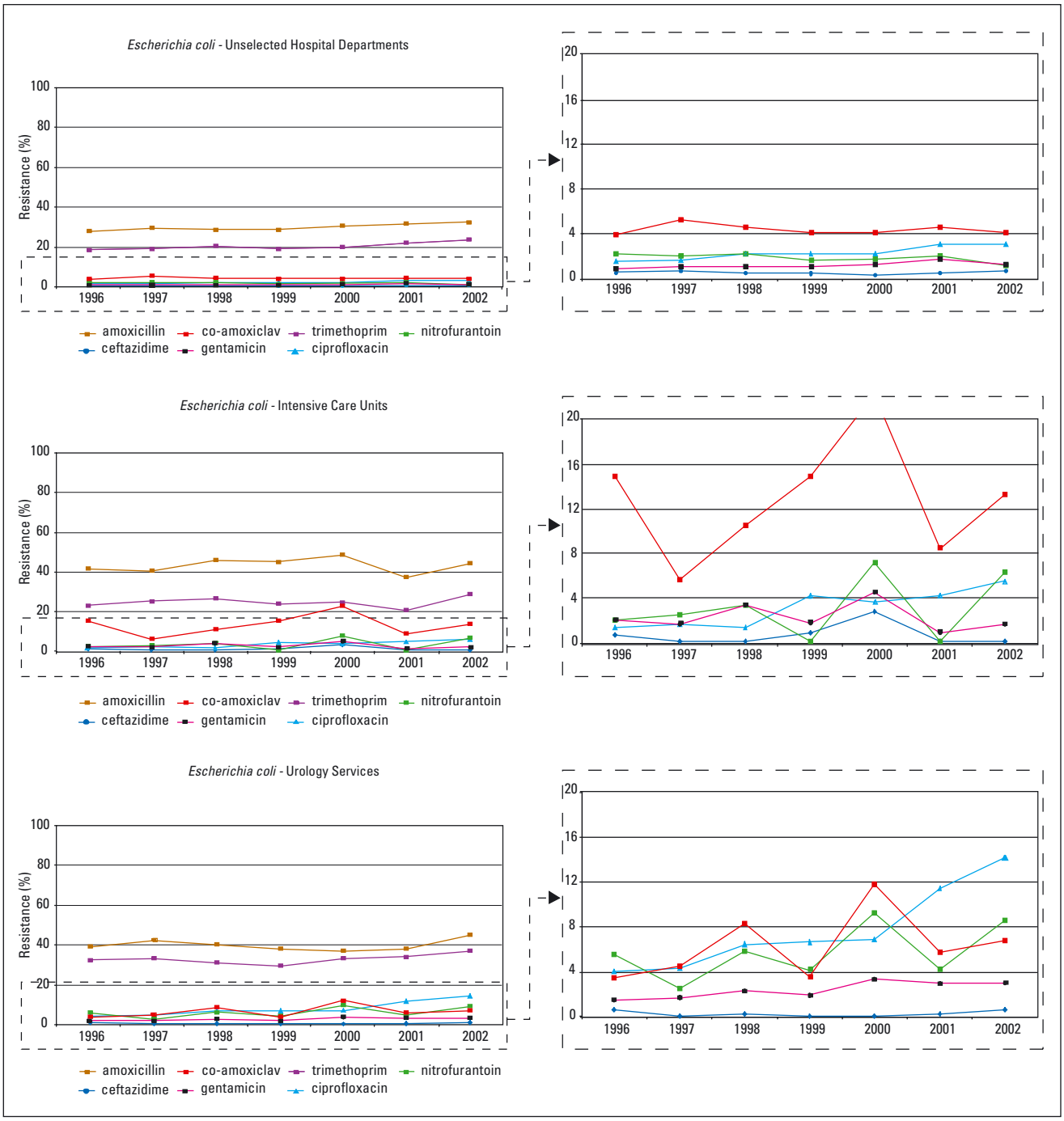


Figure 4. Trends in resistance to antibiotics among *Escherichia coli* derived from Unselected Hospital Departments, Intensive Care Units and Urology Services

Unselected Hospital Departments (4%) and in the Urology Services (4-12%) (figure 4). Co-amoxiclav resistance was much higher in Intensive Care Units (6-22%).

Trimethoprim resistance increased slowly in Unselected Hospital Departments over the years from 18% to 24%. The level of trimethoprim resistance in Intensive Care Units increased from 22% to 28%, but trimethoprim resistance was significantly higher in the Urology Services. It remained at a 33% level until 2001 and increased to 37% in 2002 (figure 4). The MIC distribution (figure 6) showed a susceptible and a highly resistant subpopulation.

The resistance to nitrofurantoin and the quinolones was much less frequent than the resistance to trimethoprim, but similar to trimethoprim, the resistance to nitrofurantoin and the quinolones was more frequent in the Urology Services than in the Intensive Care Units.

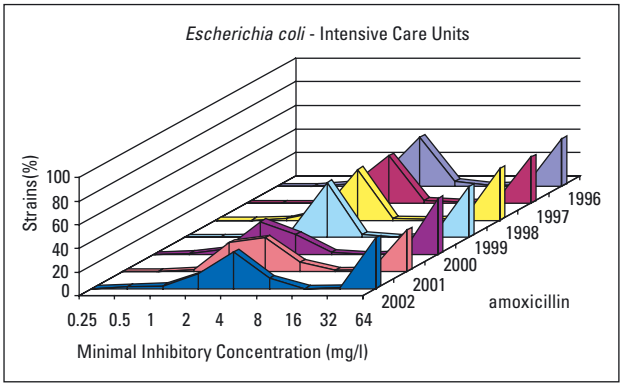


Figure 5. Trends in the MIC distribution of amoxicillin for *Escherichia coli* isolated from patients admitted to Intensive Care Units. Strains with MIC ≤ 8 mg/l are susceptible, strains with MIC ≥ 32 mg/l are resistant.

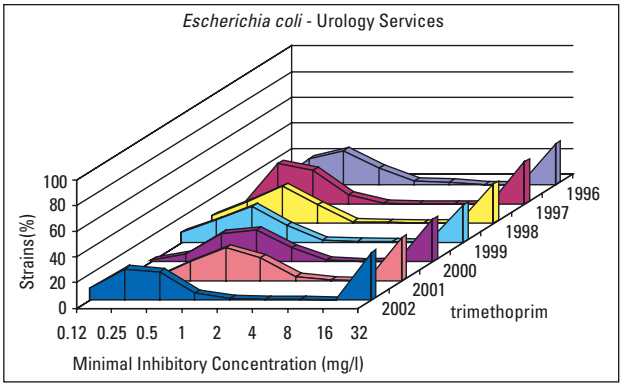


Figure 6. Trends in the MIC distribution of trimethoprim for *Escherichia coli* isolated from patients admitted to Urology Services. Strains with MIC ≤ 8 mg/l are susceptible, strains with MIC ≥ 16 mg/l are resistant.

Ciprofloxacin resistance increased slowly but steadily among *E. coli* from Unselected Hospital Departments to 3.5% and Intensive Care Units to 5.5% in 2002. The resistance level in Urology Services however increased rapidly from 7% in 2000 to 14.5% in 2002 (figure 4). 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, compared with five Intensive Care Units in 2002.

Klebsiella pneumoniae

Co-amoxiclav resistance in *K. pneumoniae* from Unselected Hospital Departments and from the Urology Services remained as low as that of *E. coli* (5%) (figure 7). Co-amoxiclav resistance in Intensive Care Units was higher (mean 9.5%). 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.

Trimethoprim resistance increased in Unselected Hospital Departments from 11% to 21% (figure 7). The level of resistance in Intensive Care Units fluctuated around 17%. Trimethoprim resistance in Urology Services was significantly higher and increased from 23% in 1996 to 27% in 2002. Trimethoprim is the drug of first choice in general practice and is rarely used in Intensive Care Units. So 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 the combination of trimethoprim with sulfamethoxazole by urologists.

Nitrofurantoin resistance fluctuated in Unselected Hospital Departments between 28 and 38% (figure 7). The level of resistance in Intensive Care Units and Urology Services was 40% or more (not shown).

Ceftazidime resistance among *K. pneumoniae* was low, but it has been increasing in Unselected Hospital Departments from 1% in 1999 to 5% in 2002 (figure 7). In the selected hospital departments ceftazidime resistant strains emerged occasionally in three Intensive Care 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.

Gentamicin resistance was low, but it is also increasing in Unselected Hospital Departments (figure 7). Likewise, *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. Gentamicin resistance in Urology Services was rare.

Ciprofloxacin resistance among *K. pneumoniae* followed the trend of that among *E. coli* in Unselected Hospital Departments. 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 1-3 Urology Services each year. The resistance peak in 2002 was exclusively due to resistance problems in two centres. Seven Intensive Care Units and five Urology Services had no ciprofloxacin resistant *K. pneumoniae* during the entire study period.

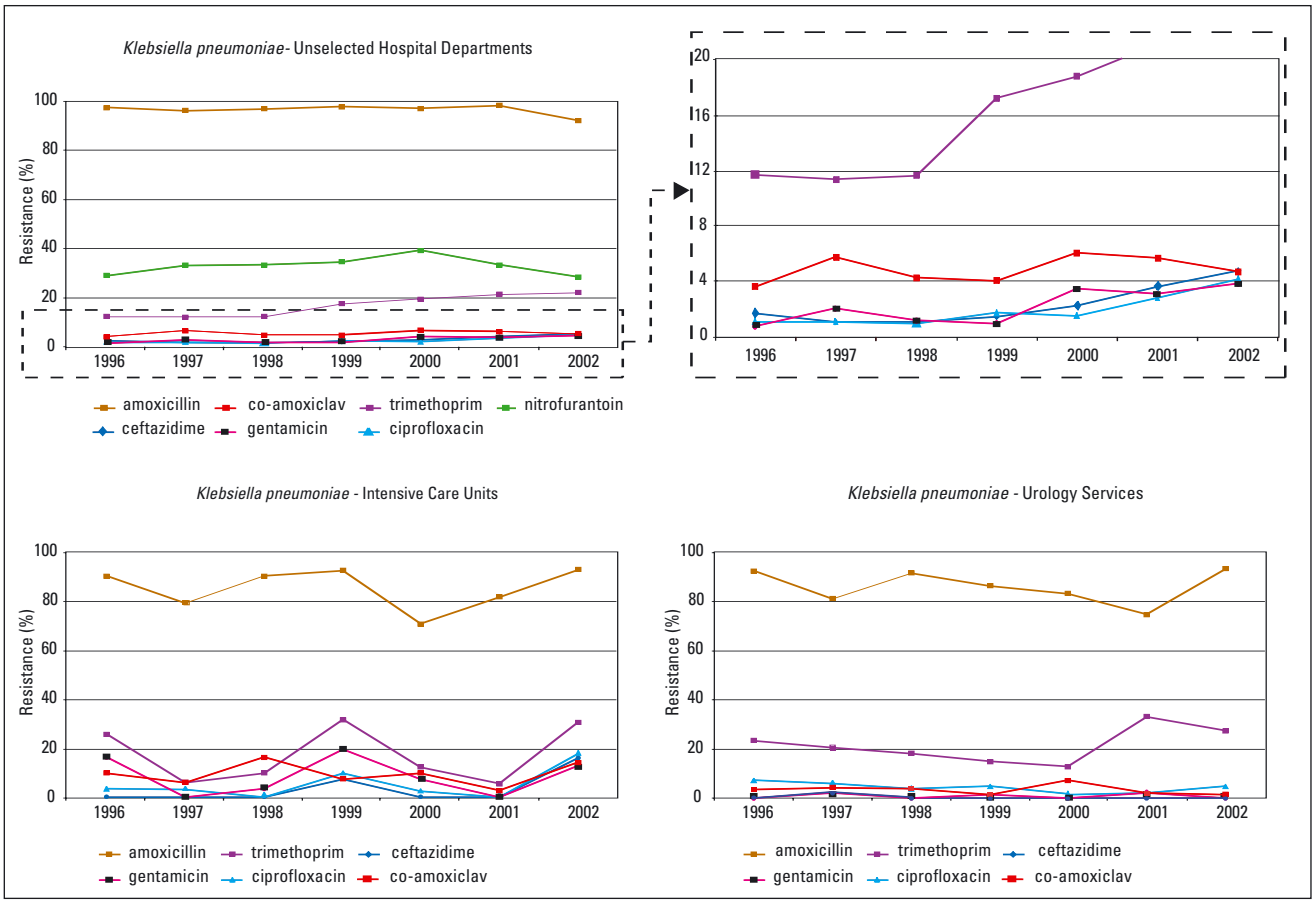


Figure 7. Trends in resistance to antibiotics among *Klebsiella pneumoniae* derived from Unselected Hospital Departments, Intensive Care Units and Urology Services

Proteus mirabilis

Amoxicillin resistance in Unselected Hospital Departments showed a slow, but steady increase, from 14% in 1996 to 17% in 2002. Amoxicillin resistance in Intensive Care Units and Urology Services was around 20% (figure 8). The MIC distribution showed a susceptible and a resistant population (figure 9). Intermediate susceptibility to amoxicillin among this species is rare. Co-amoxiclav resistance was exceptional in Urology Services. Co-amoxiclav resistance in Intensive Care Units was observed at a low level from 1996 to 1998. From 2001 on an increase of co-amoxiclav resistant strains was observed (up to 11%, figure 8). The MIC distribution of co-amoxiclav showed that not all amoxicillin resistant strains became susceptible by adding clavulanate (figure 9).

Trimethoprim resistance in *P. mirabilis* increased in Unselected Hospitals, from 24% to more than 50%. These levels were similar to those found in Urology Services (figure 8). The resistance level in Intensive Care Units was consistently lower and equalled the resistance rate in the community (around 20%).

Ceftazidime resistant *P. mirabilis* was very rare.

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

Ciprofloxacin resistance among *P. mirablis* occurred sporadically, it occurred more frequently in Urology Services, but did not increase.

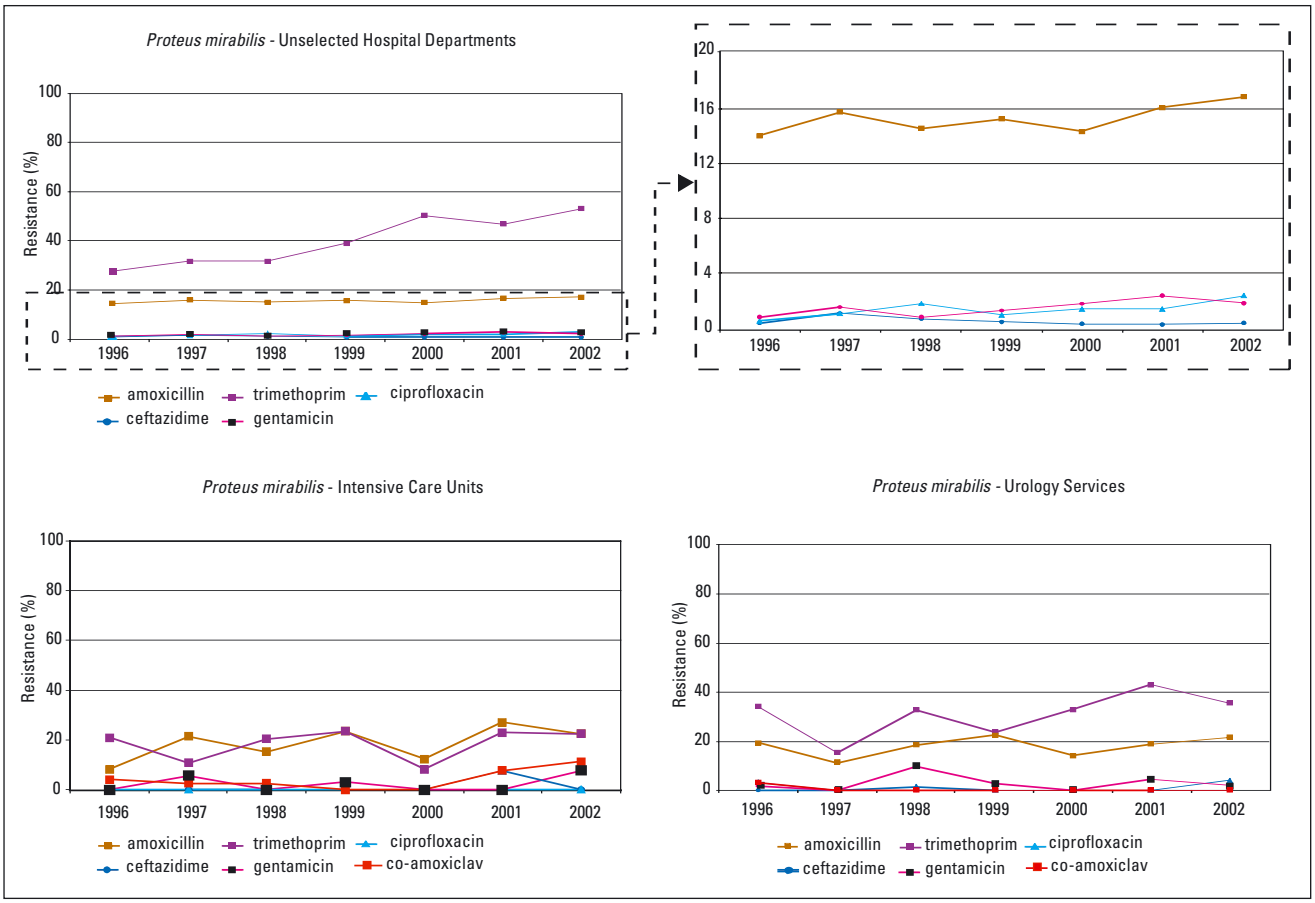


Figure 8. Trends in resistance to antibiotics among *Proteus mirabilis* derived from Unselected Hospital Departments, Intensive Care Units and Urology Services

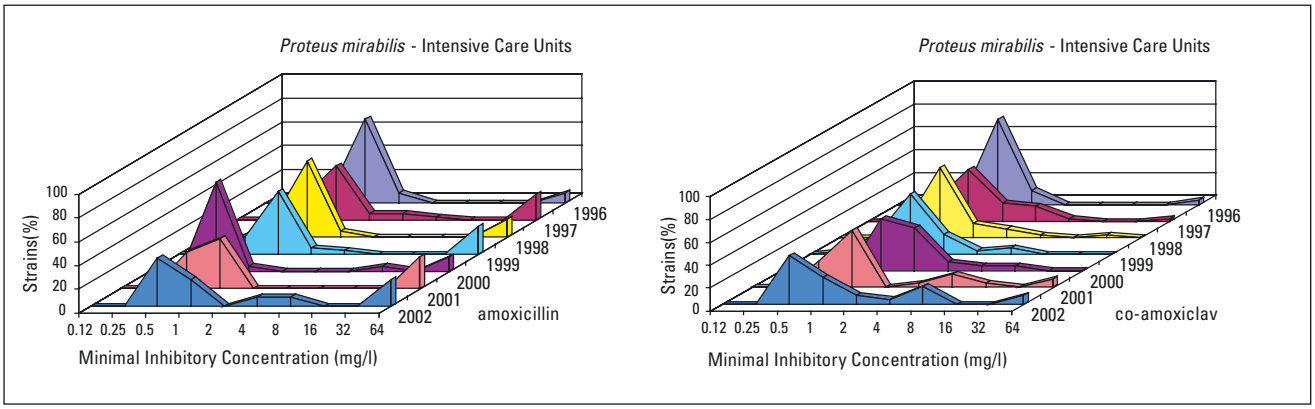


Figure 9. Trends in the MIC distribution of amoxicillin and co-amoxiclav for *Proteus mirabilis* isolated from patients admitted to Intensive Care Units. Strains with MIC ≤ 8 mg/l are susceptible, strains with MIC ≥ 32 mg/l are resistant.

Pseudomonas aeruginosa

Ceftazidime resistance among *P. aeruginosa* isolated in Unselected Hospital Departments and Urology Services was consistently low (2-3%). Ceftazidime resistance in Intensive Care Units was rare, but a 10% resistance was suddenly recorded in 2002 (figure 10) caused by emerging resistance in five centres.

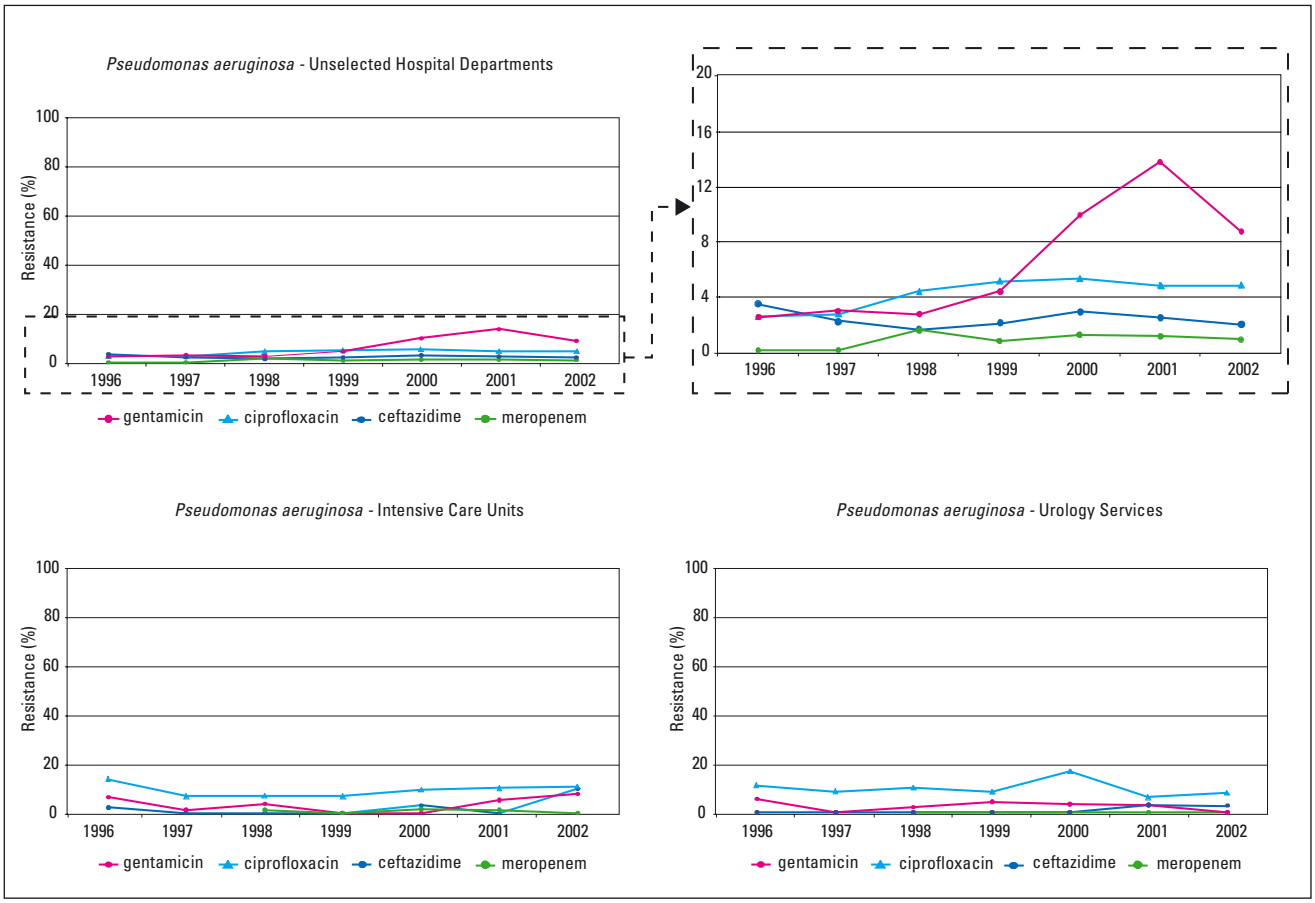
Gentamicin resistance was low (<5%) until 1999 in all departments. Subsequently a significant increase in the prevalence of gentamicin resistance among *P. aeruginosa* was recorded for Unselected Hospital Departments which persisted until 2002. Sporadic resistance was also found in Intensive Care Units, 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 2002. Gentamicin resistance was found sporadically in some Urology Services.

Meropenem resistance among *P. aeruginosa* in Unselected Hospital Departments was 1% throughout the period of investigation.

The prevalence of ciprofloxacin resistance increased slowly in Unselected Hospital Departments (2% in 1995 to 5% in the period 1999-2002, figure 10). Ciprofloxacin resistance was much higher in Intensive Care Units and Urology Services already in 1996. The rates of ciprofloxacin resistant *P. aeruginosa* in these latter two departments varied between 6-14% over the years of surveillance.

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 Dutch hospitals (see chapter on antibiotic use).

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



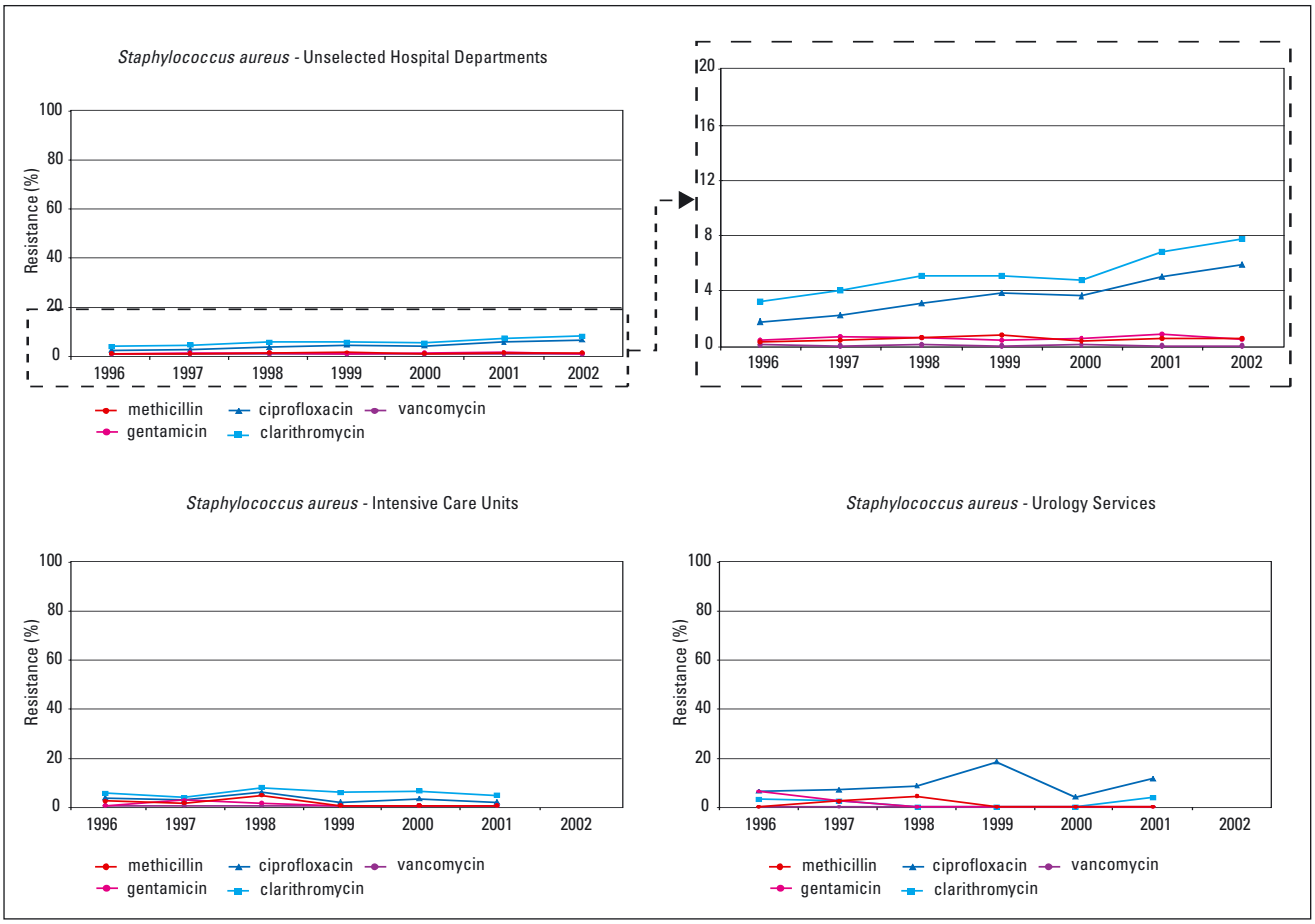


Figure 11. Trends in resistance to antibiotics among *Staphylococcus aureus* derived from Unselected Hospital Departments, Intensive Care Units and Urology Services.

Staphylococcus aureus

The prevalence of methicillin resistant *S. aureus* (MRSA) has historically been very low in the Netherlands. The prevalence of MRSA in Unselected Hospital Departments remained below 1%. The MRSA prevalence in Intensive Care Units and Urology Services fluctuated between 2-4% from 1996-1998 (figure 11). Thereafter no MRSA was isolated in this surveillance. In contrast, the resistance to erythromycin in Unselected Hospital Departments was slowly increasing to almost 8% in 2002. The resistance to clarithromycin in the isolates from Intensive Care Units and Urology services were in the same range.

Ciprofloxacin resistance increased slowly among isolates from Unselected Hospital Departments (1.5% to 5.8%), the same percentages were found in Intensive Care isolates (1.5-5.5%), but the resistance level was higher among *S. aureus* from Urology Services (6-18%, figure 11). This may confirm the selective pressure by use of these drugs in these patients.

Vancomycin resistant strains were not observed.

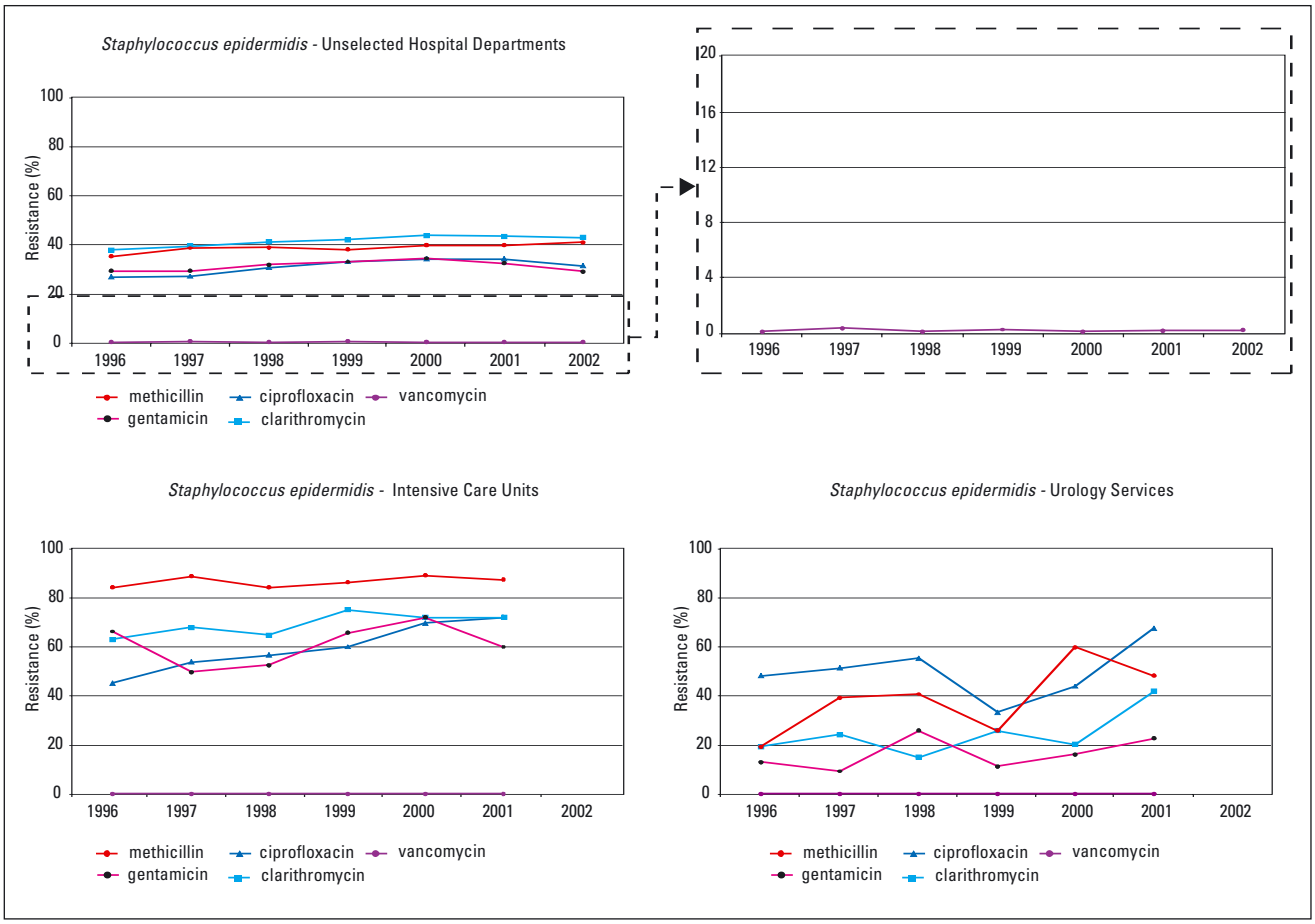


Figure 12. Trends in resistance to antibiotics among *Staphylococcus epidermidis* derived from Unselected Hospital Departments, Intensive Care Units and Urology Services.

Staphylococcus epidermidis

In contrast to *S. aureus*, resistance to methicillin and other beta-lactam antibiotics was frequently found among hospital isolates of *S. epidermidis* (including other coagulase-negative species). Methicillin resistance among clinical isolates of *S. epidermidis* from Unselected Hospital Departments increased from 32% in 1995 to 41% in 2002 (figure 12). Methicillin resistance in Intensive Care Units was almost 90% and it was fluctuating in patients from Urology Services (20-60%). This fluctuation may have been the result of low numbers of strains isolated at these departments. Methicillin resistance frequently showed co-resistance with erythromycin, clarithromycin, gentamicin and ciprofloxacin in all departments.

Erythromycin resistance increased steadily in Unselected Hospital departments from 37% in 1996 to 43% in 2002, clarithromycin resistance in Urology Services was comparable, but the level of resistance in Intensive Care Units was much higher and increased from 64% in 1996 to 73% in 2001. This pattern was also found for gentamicin. In contrast, the resistance rate of ciprofloxacin among strains from Intensive Care Units and from Urology was higher and increasing compared to that among strains from Unselected Hospital Departments. High resistance levels to many drugs among *S. epidermidis* from Intensive Care Units are usual, apparently as a result of the high selective pressure in these wards. Often strains are circulating there, colonizing many patients. The high ciprofloxacin resistance in Urology Services may reflect the use of quinolones in these patients.

Vancomycin resistant strains were isolated occasionally in Unselected Hospital Departments.

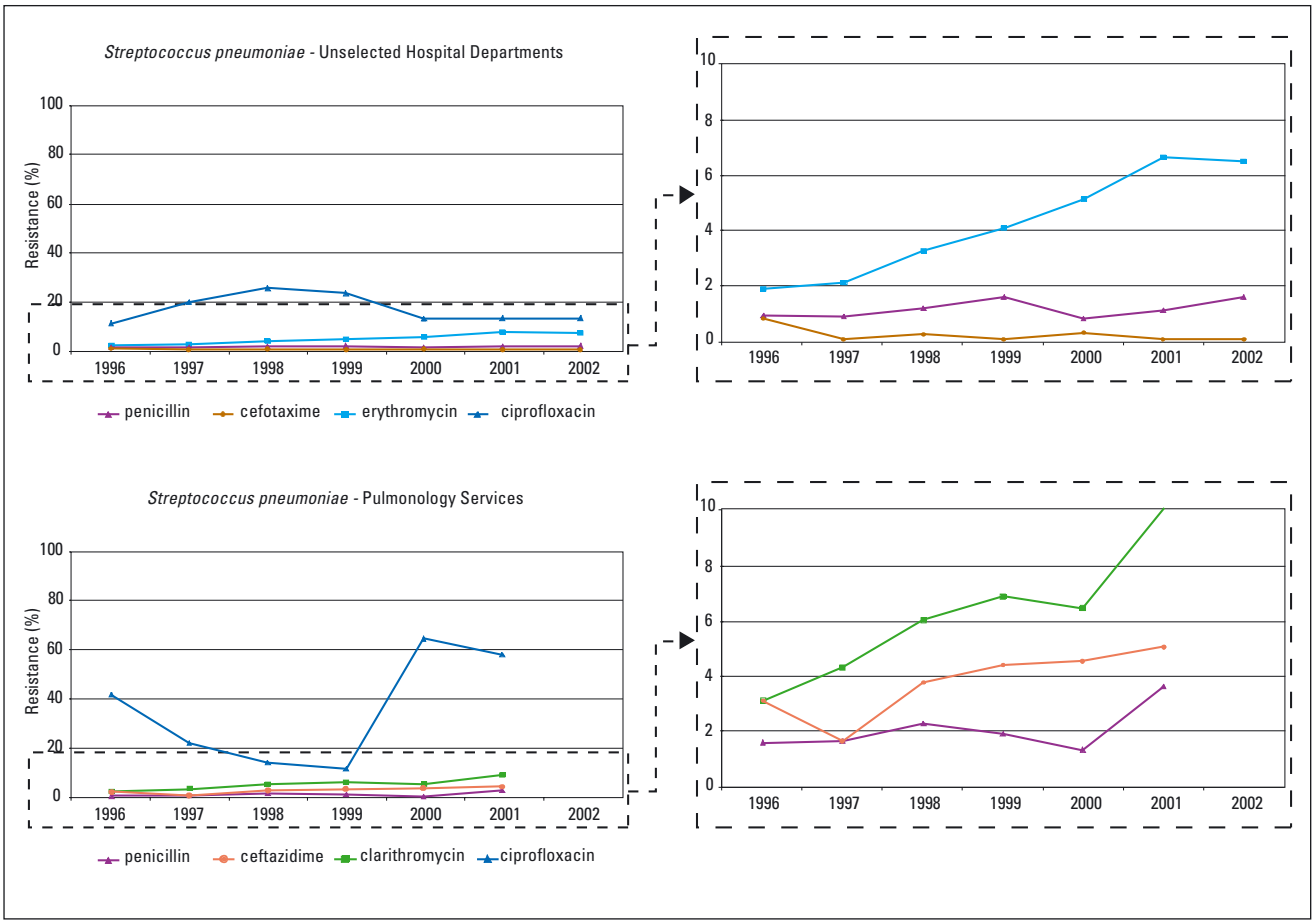
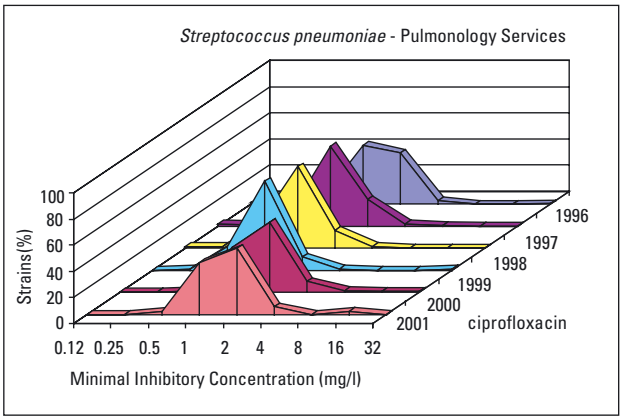


Figure 13. Trends in resistance to antibiotics among *Streptococcus pneumoniae* derived from Unselected Hospital Departments and Pulmonology Services.

Streptococcus pneumoniae

S. pneumoniae less susceptible to penicillin are not often isolated in the Netherlands. The highest yearly prevalence rate of strains with reduced penicillin susceptibility (MIC 0.1-1.0 mg/l) was 1.5% in 1999 and in 2002 in Unselected Hospital Departments; the resistance level in Pulmonology Services was around 2% until 2000 and increased to 3.6% in 2001 (figure 13). There was a clear trend toward higher rates of erythromycin and clarithromycin resistance among clinical isolates of *S. pneumoniae* from all departments. The prevalence of ciprofloxacin resistance in Unselected Hospital Departments was 10-24%, showing large fluctuations. Since the resistance breakpoint is near the centre of the natural MIC distribution, a relatively small shift in the MIC distribution causes a large change in the percentage of resistant strains (figure 14). Ciprofloxacin is only moderately active against *S. pneumoniae* and most pulmonologists have stopped prescribing ciprofloxacin for suspected or proven pneumococcal infections.

Figure 14. Trends in the MIC distributions of ciprofloxacin for *Streptococcus pneumoniae* isolated from patients admitted to the Pulmonology Services. Strains with MIC ≤ 1 mg/l are susceptible, strains with MIC ≥ 4 mg/l are resistant.



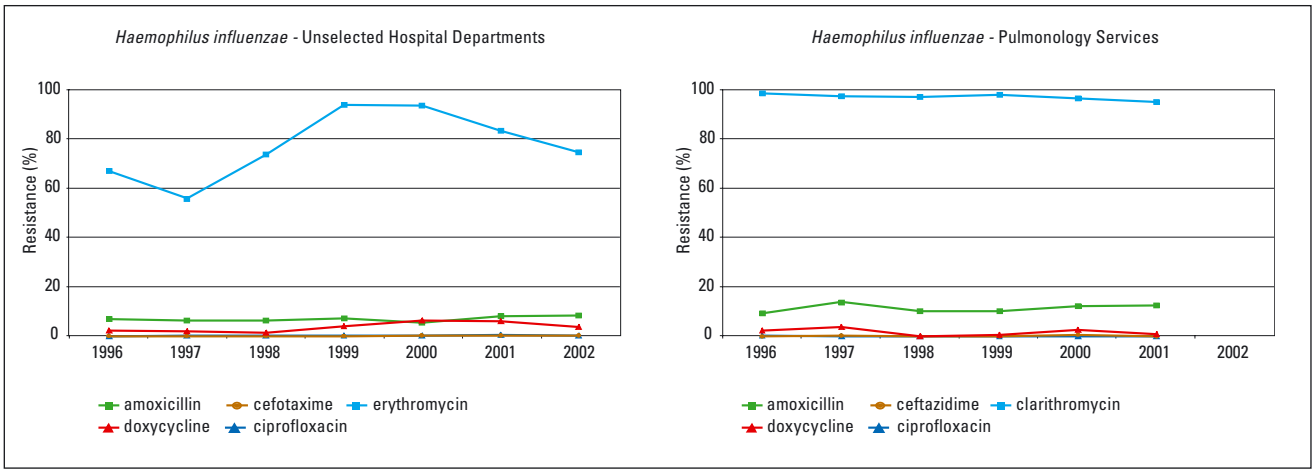


Figure 15. Trends in resistance to antibiotics among *Haemophilus influenzae* derived from Unselected Hospital Departments and from Pulmonology Services.

Haemophilus influenzae

The prevalence of amoxicillin resistance among *H. influenzae* isolated in Unselected Hospital Departments has remained stable (7%) over the surveillance years. For *H. influenzae* strains isolated from Pulmonology Services somewhat higher resistance rates (9-14%) were observed, but again no trend towards increasing rates was discernible (Figure 15).

The prevalence of erythromycin resistance among *H. influenzae* from Unselected Hospital Departments was high (70-90%) by including all strains with reduced susceptibility (MIC ≥ 0.5 mg/L). Instead of erythromycin the newer macrolide agent clarithromycin was tested for isolates from the Pulmonology Services. Taking also the low breakpoint of susceptibility, then almost 100% resistance to clarithromycin was recorded (figure 15). Since the NCCLS has established a much higher breakpoint for reduced susceptibility for clarithromycin (MIC ≥ 8 mg/l) the prevalence of clarithromycin resistance among *H. influenzae* strains isolated in these departments would be 18-23%.

Low resistance rates were found for doxycycline among *H. influenzae* isolates from Unselected Hospital Departments (6% in 2000 and 2001, 4% in 2002), and still lower percentages among strains isolated from the Pulmonology Services. Yet a shift in MIC distribution for

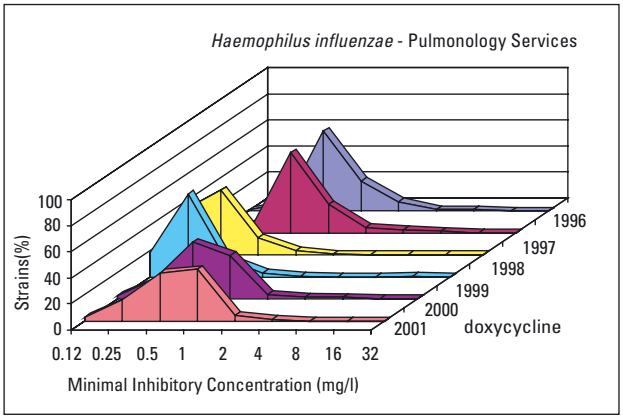


Figure 16. Trends in the MIC distributions of doxycycline for *Haemophilus influenzae* isolated from patients admitted to the Pulmonology Services. Strains with MIC ≤ 2 mg/l are susceptible, strains with MIC ≥ 8 mg/l are resistant.

strains isolated from Pulmonology Services was observed from 2000 on, with more strains with higher MICs, although still susceptible. This may predict the emergence of resistance in the next years (figure 16).

Amoxicillin has been a drug of first choice for pulmonologists and has remained so over the years in the Netherlands. Selective pressure may explain the higher resistance rates found among *H. influenzae* strains isolated from Pulmonology Services. The higher resistance rates for doxycycline among *H. influenzae* isolated in Unselected Hospital Departments may reflect doxycycline use in general practice.

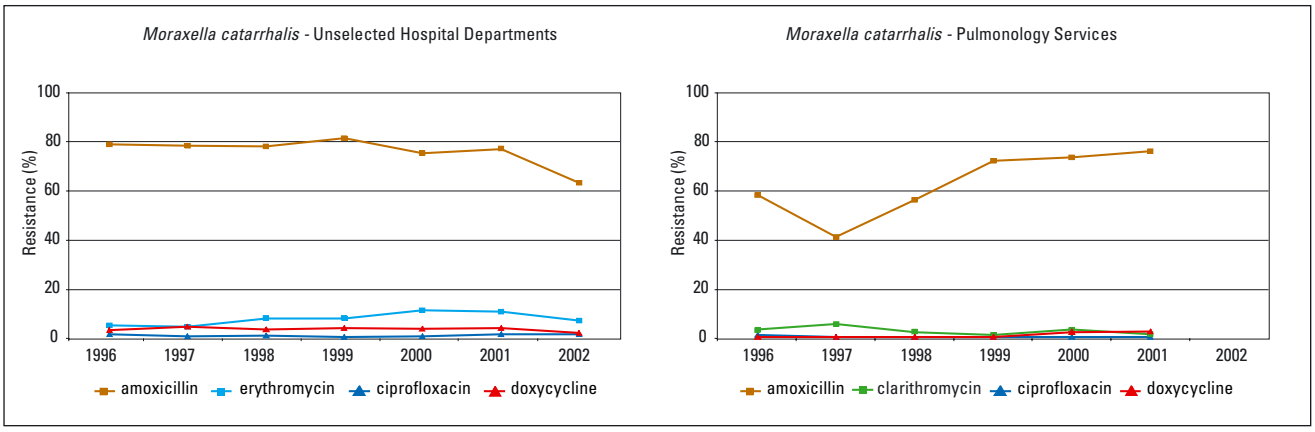


Figure 17. Trends in resistance to antibiotics among *Moraxella catarrhalis* derived from Unselected Hospital Departments and from Pulmonology Services.

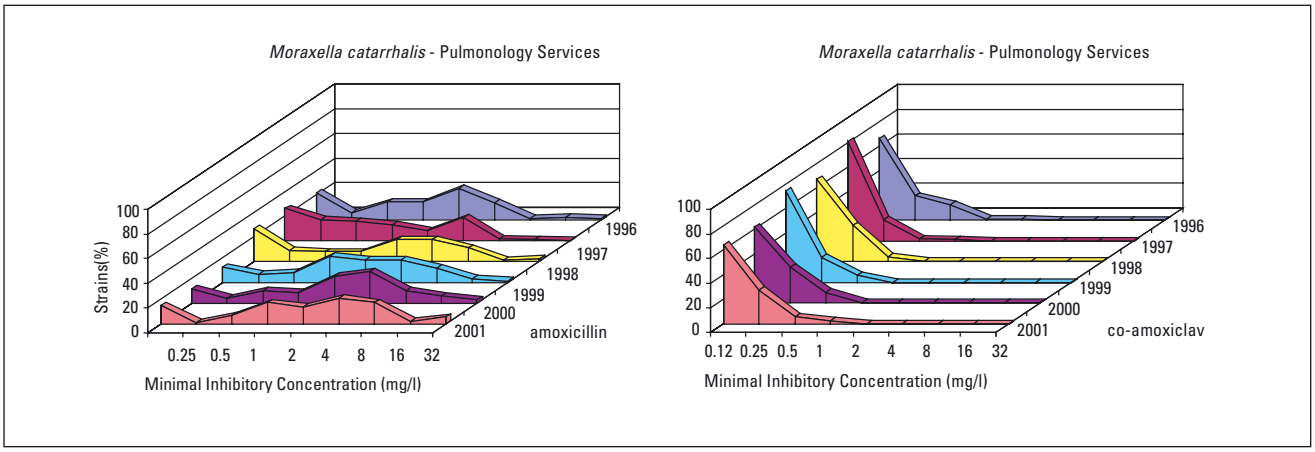


Figure 18. Trends in the MIC distributions of amoxicillin and co-amoxiclav for *Moraxella catarrhalis* isolated from patients admitted to Pulmonology Services. Strains with MIC ≤ 1 mg/l for amoxicillin and ≤ 4 mg/l for co-amoxiclav are susceptible, strains with MIC ≥ 4 mg/l for amoxicillin and ≥ 8 mg/l for co-amoxiclav are resistant.

Moraxella catarrhalis

The prevalence of amoxicillin resistance among *M. catarrhalis* isolated in Unselected Hospital Departments and Pulmonology Services has been about 80% since 1999 (figure 17). Resistance is completely beta-lactamase-based: resistance to co-amoxiclav did not occur as shown by the MIC distributions (figure 18).

Resistance to erythromycin was 5 to 11% in Unselected Hospital Departments. 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*: the MICs of clarithromycin are 2-4fold 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

From 1995 -2002 a total of 5886 strains of *H. pylori* were included in the surveillance project of the RIVM. Amoxicillin resistance among *H. pylori* was less than 1% during the surveillance period (figure 19). Tetracycline resistance fluctuated, but remained lower than 2%.
Clarithromycin resistance fluctuated as well from 1-6%. Metronidazole resistance was stable over the years (13-17%).

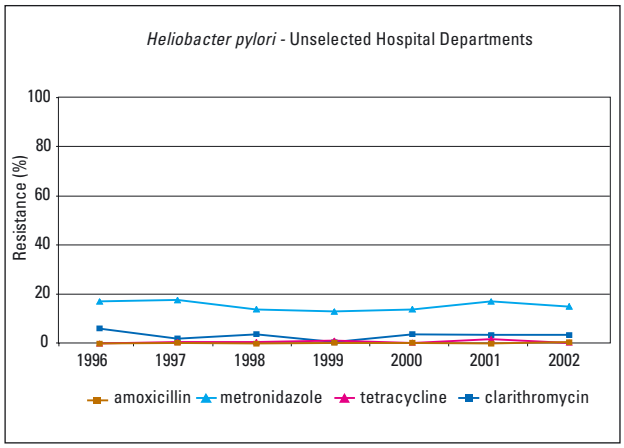


Figure 19. Trends in resistance to antibiotics among *Heliobacter pylori* derived from Unselected Hospital Departments.

Mycobacterium tuberculosis

Isoniazid (INH) resistance fluctuated from 6.5-8.5% among strains of *M. tuberculosis* during the surveillance period, there was no tendency of increase (figure 20). The MIC distribution showed one big susceptible cluster with small moderately resistant clusters (MIC 2->5 mg/l) every year (figure 21). Streptomycin resistance was 9-10% since 1997. The MIC distribution showed one large susceptible cluster with a very small resistant cluster (MIC > 5 mg/l) in every year (figure 21). The rifampicin resistance level was 1.2% in 2002 (figure 20). Ethambutol resistance occurred occasionally (0.1-0.4%). Combined resistance to more than one drug was observed in 3-5% of all isolates without any clear trend of increase during the years (figure 22). INH resistance combined with streptomycin resistance was most frequent. Resistance to all four antimycobacterial drugs was rare (0.2-0.7%).

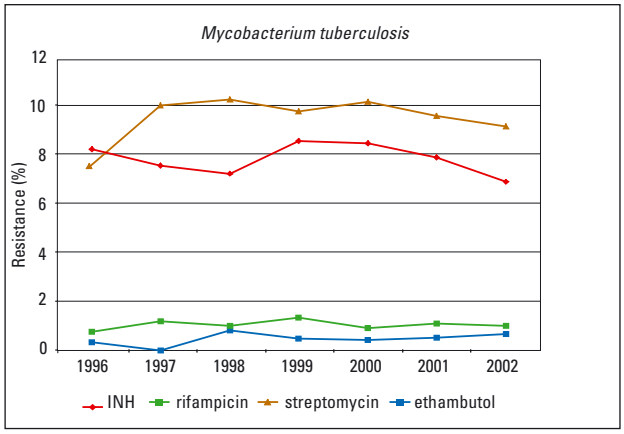


Figure 20. Trends in resistance to antibiotics among clinical strains of *Mycobacterium tuberculosis* in the Netherlands.

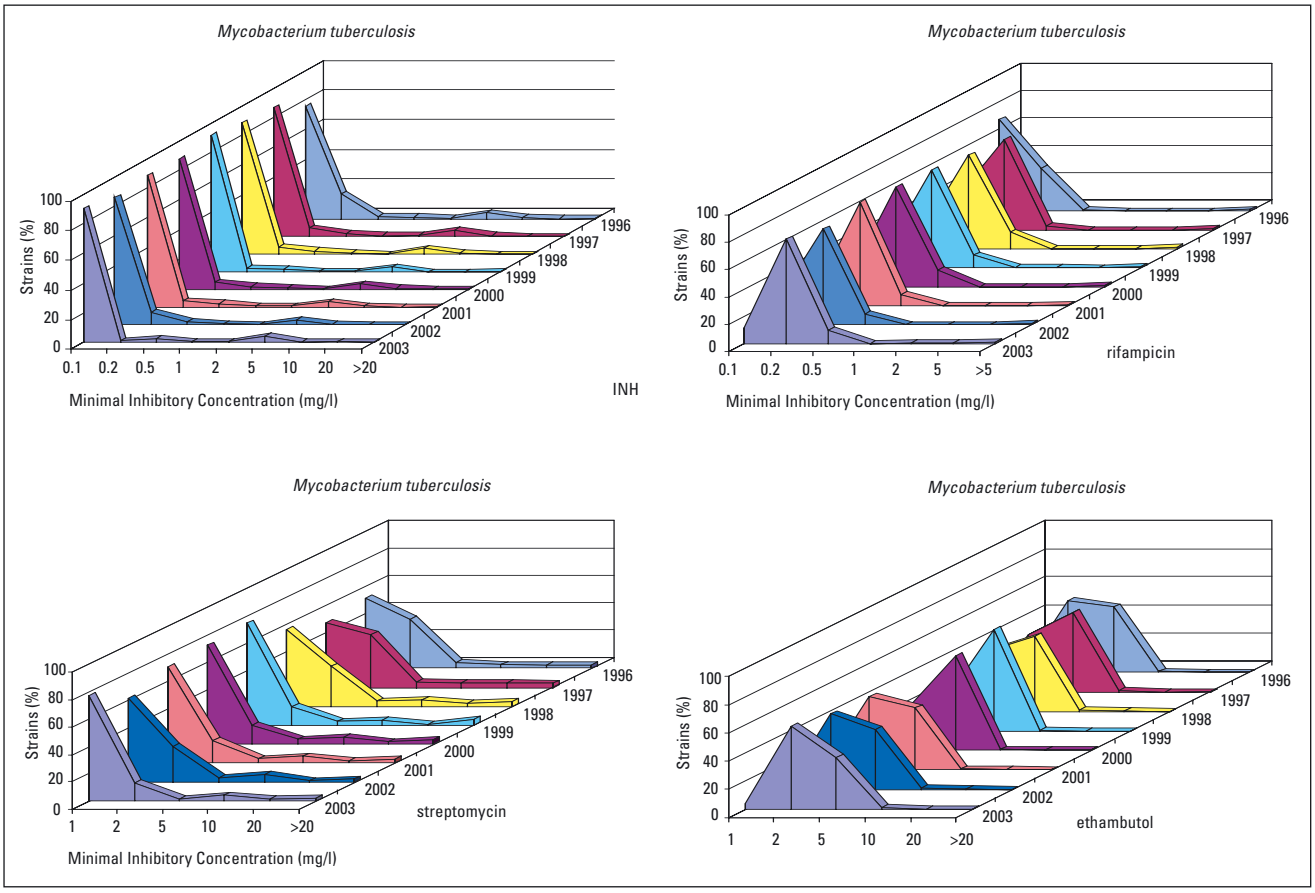


Figure 21. Trends in MIC distributions of INH, rifampicin, streptomycin and ethambutol for clinical strains of *Mycobacterium tuberculosis* in the Netherlands. Strains with MIC ≤ 0.2 mg/l for INH, with MIC ≤ 1 mg/l for rifampicin and with MIC ≤ 5 mg/l for streptomycin and ethambutol are susceptible, strains with MIC ≥ 0.5 mg/l for INH, with MIC ≥ 2 mg/l for rifampicin and with MIC ≥ 10 mg/l for streptomycin and ethambutol are resistant.

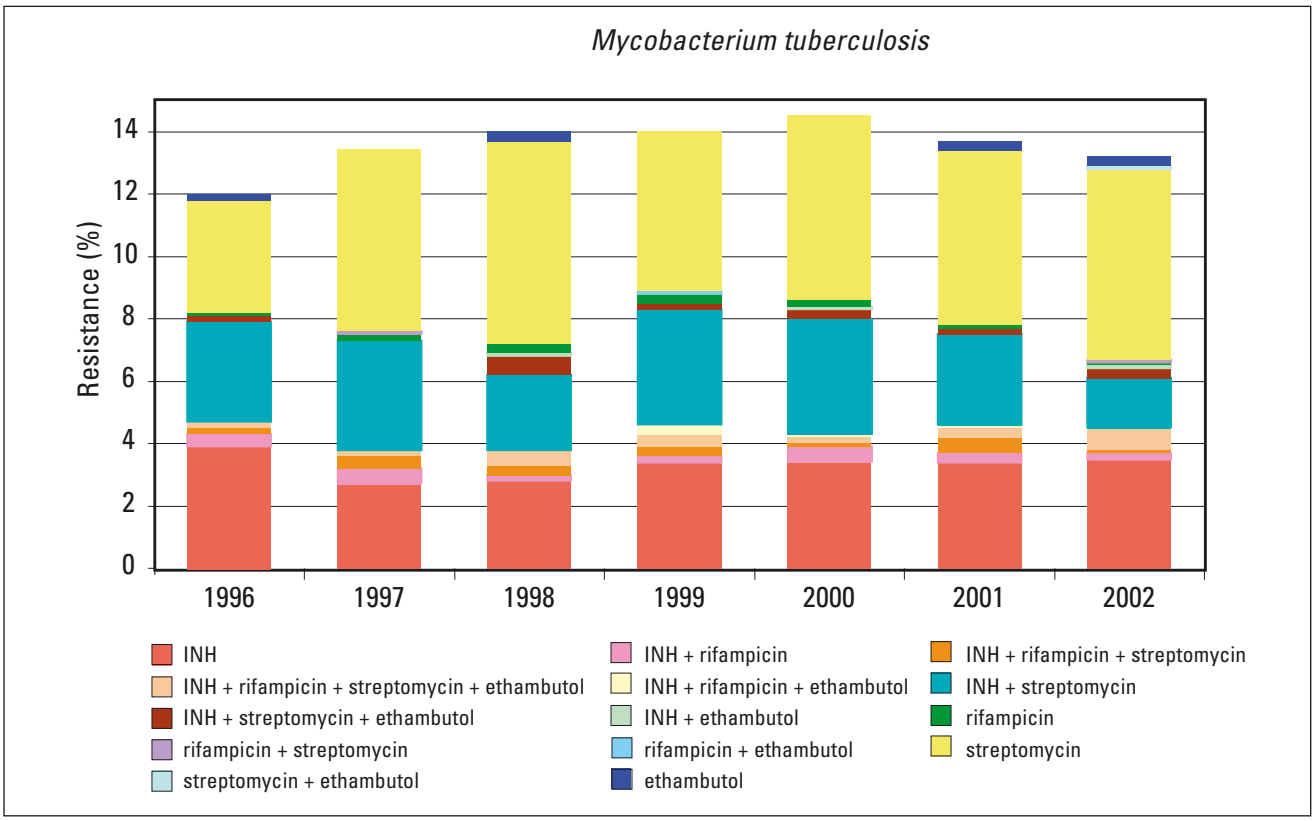


Figure 22. Trends of combined resistance for clinical strains of *Mycobacterium tuberculosis* in the Netherlands.

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 in the same time frame (the nineties). 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 Feb; 39(2): 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.

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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								
Methicillin	3								
Flucloxacillin	7,10								
Ampicillin				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	1		
Ceftazidime					1,2,3,4,17	1,2,3,17	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					
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	
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	
Trimethoprim					17				
Co-trimoxazole					17				
Nitrofurantoin					17				

Numbers correspond with referencenumbers listed above this crosstable .

5 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, an EU sponsored program
ECCMID	European Congress on Clinical Microbiology and Infectious Diseases
ESAC	European Surveillance of Antibiotic Consumption, an EU sponsored program
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

Demographics and numerator 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	16 192 842
2003	16 254 933

Table B Resource Indicators of acute Hospital care in the Netherlands (Source: Prismant)

Year	Hospitals	Beds	Admissions (x 1000)	Bed-days (x 1000)	Admissions /bed	Length of stay (mean in days)
1997	114	54 378	1 547	14 059	28.5	9.1
1998	109	54 119	1 520	13 689	28.1	9.0
1999	106	53 728	1 500	12 896	27.9	8.6
2000	104	51 288	1 465	12 330	28.6	8.4
2001	101	49 524	1 456	11 865	29.4	8.1

Table C Resource Indicators of University Hospital care in the Netherlands (Source: Prismant)

Year	Hospitals	Beds	Admissions (x 1000)	Bed-days (x 1000)	Admissions /bed	Length of stay (mean in days)
1997	8	7 586	203	2 016	26.8	9.9
1998	8	7 571	196	1 986	25.9	10.1
1999	8	7 691	200	1 867	26.0	9.4
2000	8	7 704	197	1 804	25.5	9.2
2001	8	7 933	192	1 773	24.2	9.2

Table D Resource Indicators of General Hospital care in the Netherlands (Source: Prismant)

Year	Hospitals	Beds	Admissions (x 1000)	Bed-days (x 1000)	Admissions /bed	Length of stay (mean in days)
1997	105	46 792	1 344	12 043	28.7	9.0
1998	101	46 548	1 324	11 703	28.4	8.8
1999	98	46 037	1 300	11 028	28.2	8.5
2000	96	43 584	1 268	10 525	29.1	8.3
2001	93	41 591	1 264	10 092	30.4	8.0

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 5). 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, between 1997-2002. 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 2003 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 1997 and 2001 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. The 2002 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 http://www.prismant.nl, previously known as SIG. The percentage of covered patient-days was calculated for each year.

Surveillance of antimicrobial resistance

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 2002 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. 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 CRG.

Surveillance of antimicrobial resistance 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 collaborative agreement between the regional public health laborato-

ries and the RIVM. Identification and susceptibility testing was routinely carried out in the regional public health laboratories. A total of 644,000 unique unrelated strains were collected from 1994-2002. Only the first isolate per species from a patient was used for the present study. 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 2002 are given in table 1. 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 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 January 1st to July 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°C and then sent to a single laboratory (department of Medical Microbiology of the University Medical Centre 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 1995-2002, the results of 10,738 indicator strains (table 2) are presented in this report.

Susceptibility testing

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

Table 1. Frequency and numbers of first isolates of each species per clinical sample of patients from Unselected Hospital Departments in 2002.

Species (numbers)	Frequency (%) per clinical material			
	Blood (N=3505)	Pus/Wound (N=18,116)	Resp tract (N=12,301)	Urine (N=16,609)
Grampositive cocci				
Staphylococcus aureus (N=9020)	12	35	13	4
Enterococcus sp. (N=3587)	3	6	1	14
S.epidermidis incl. coag. neg. Staphylococcus (N=2607)	34	4	0	4
Streptococcus pneumoniae (N=2360)	10	2	14	0
Streptococcus agalactiae (N=1866)	1	5	2	4
Streptococcus pyogenes (N=882)	2	3	2	0
(Subtotal %)	(63)	(54)	(33)	(26)
Enterobacteriaceae				
Escherichia coli (N=11,305)	19	16	6	42
Proteus mirabilis (N=2865)	2	5	2	10
Klebsiella pneumoniae (N=2228)	4	3	3	7
Enterobacter cloacae (N=1620)	2	4	3	2
Klebsiella oxytoca (N=1306)	2	3	2	3
Other Enterobacteriaceae (N=2407)	2	5	5	5
(Subtotal %)	(31)	(35)	(22)	(70)
Respiratory pathogens				
Haemophilus influenzae (N=3174)	0.6	2.2	22.4	0
Moraxella catarrhalis (N=1342)	0.2	0.4	10.2	0
Haemophilus parainfluenzae (N=377)	0.1	0.5	2.3	0
Neisseria meningitidis (N=137)	1.5	0	0.7	0
(Subtotal %)	(2.4)	(3.1)	(35.6)	(0)
Non-fermenters				
Pseudomonas aeruginosa (N=3078)	3.1	6.8	8.4	4.2
Acinetobacter baumannii (N=370)	0.3	1.2	0.6	0.4
(Subtotal %)	(3.4)	(8.1)	(9.0)	(4.6)

Table 2. Number of indicator strains (N=10,738) isolated from patients admitted to specific hospital wards and tested for their suspectibility to antibiotics in the period 1996-2002.

Species	Intensive Care Units	Urology Services	Pulmonology Services
E. coli	319	3,450	
K. pneumoniae	272	376	
P. mirabilis	211	466	
P. aeruginosa	568	264	
S.aureus	482	177	
S. epidermis	365	174	
S. pneumoniae			967 (1996-2001)
H. influenzae			1,420 (1996-2001)
M. catarrhalis			633 (1996-2001)

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 susceptibility of the strains from the specific wards was determined quantitatively, i.e. by MIC determinations, in one single laboratory by home-made 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 considered a new isolate. The susceptibility data of 7543 strains, isolated from 1996-2002 are presented in this report, 1033 strains in 2002.

Susceptibility testing
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.

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