NETHMAP
2003

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

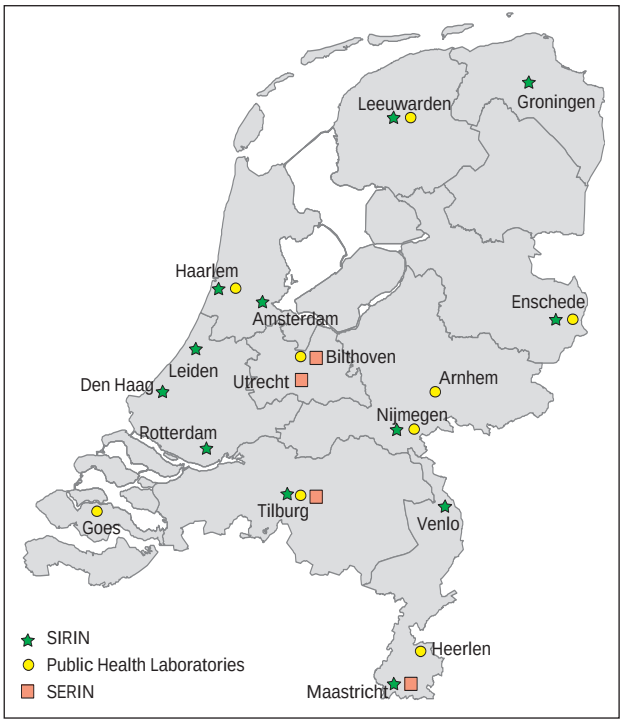
Overijssel
- Medisch Spectrum Enschede (Dr M.G.R. Hendrix)
- Regional Laboratory for Public Health Enschede (Dr M.G.R. Hendrix)

Gelderland
- UMC St Radboud Nijmegen (Prof Dr J.A.A. Hoogkamp-Korstanje)
- Regional Laboratory for Public Health Arnhem (Drs H. Nieste)
- Regional Laboratory for Public Health Nijmegen (Dr A. Horrevorts)

Noord Holland
- 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)

Utrecht
- National Institute for Public Health and the Environment (Dr A.J. de Neeling)
- Netherlands Institute for Health Services Research NIVEL (Dr A.I. Bartelds)

Zuid Holland
- Bronovo Hospital, 's Gravenhage (Dr H.A. Bijlmer)
- Diaconessenhuis Leiden (Dr W.C. van Dijk)
- MCRZ-Zuiderziekenhuis, Rotterdam (Dr W.D.H. Hendriks)



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

Noord Brabant
- St Elisabeth Ziekenhuis, Tilburg (Dr A. Buiting)
- Regional Laboratory for Public Health Tilburg (Dr A. Buiting)

Limburg
- St Maartens Gasthuis, Venlo (Dr W.H.J. Crombach)
- Regional Laboratory for Public Health, Heerlen (Dr J.H.T. Wagenvoort)
- University Hospital Maastricht (Dr E.E. Stobberingh)

Zeeland
- 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; Amsterdam, Academisch Medisch Centrum; Amsterdam, VU Medisch Centrum; Amsterdam, BovenIJ Ziekenhuis; Apeldoorn, Gelre ziekenhuizen; Arnhem, Ziekenhuis Rijnstate; Assen, Wilhelmina Ziekenhuis; Bergen op Zoom, Ziekenhuis Lievensberg; Coevorden/Hardenberg, Streekziekenhuis; Delft, Reinier de Graaf Groep; Den Haag, Haagse Ziekenhuizen; Deventer, Stichting Deventer Ziekenhuizen; Doetichem, Slingeland 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; Hilversum, Ziekenhuis Hilversum, Hoorn, Westfries Gasthuis; Leiden, Diaconessenhuis; Leiden, Leids Universitair Medisch Centrum; Leiderdorp, Rijnland Ziekenhuis; 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; Spijkenisse, Ruwaard van Putten Ziekenhuis; Terneuzen, Ziekenhuis Zeeuws-Vlaanderen; Tilburg, 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; Vlissingen, Ziekenhuis Walcheren; Woerden, Hofpoort Ziekenhuis; Zaandam, Zaans Medisch Centrum de Heel; Zeist, Lorentz Ziekenhuis; Zutphen, Het Spittaal; Zwolle, Isalaklinieken.

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Preface

On behalf of the Dutch Working Party on Antibiotic Policy we are happy to present the first result from its efforts in systematically collecting and collating data on the use of antimicrobial agents in human medicine and on the prevalence of resistance to antimicrobial agents among large collections of strains derived from patients in de open community as well as from those admitted to hospitals in the Netherlands.
This report, called ***NethMap***, is the direct result from several important strategic initiatives taken in the recent past. 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 micro-organisms 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 recognised by 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. 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 micro-organisms. Since these initiatives corresponded well with the recent recommendations from the Dutch Council on Health Research (RGO report, December 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 a surveillance system in close collaboration with the National Institute of Public Health and the Environment (its Dutch acronym is: RIVM). ***NethMap*** can, thus, be viewed as one more example of the workings of the Dutch 'poldermodel' in which governmental authorities and relevant stakeholders from society are able to find consensus regarding the management of emerging threats, in this case microbial threats to Health in the Netherlands.

Since this is our first effort, it should not be taken otherwise than a first effort. We do realise that the report has many deficits in content and, perhaps, may also harbour flaws in its execution. We invite all readers to note these deficits and report them as well as their suggestions for improvement of ***NethMap*** back to the SWAB. As a proper surveillance instrument updates of ***NethMap*** are planned on a regular basis, most probably every year. We foresee the content of ***NethMap*** to grow in quantity and quality, and invite all to contribute to its future.

The editors:
Prof dr Henri A. Verbrugh dr Han de Neeling

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I Introduction

The emergence of resistance to commonly used antimicrobial agents among medically important micro-organisms poses a threat to the health of the public. Antimicrobial resistance generally increases the morbidity and mortality of patients suffering from infection, and thereby increases the cost of health care delivery. Resistance emergence forces physicians to change their antibiotic prescribing policies not only in patients with proven infection but also in patients with suspected infection. Therefore, the economic impact of the emergence of antimicrobial resistance cannot be overstated. Resistance emergence drives the spiral of applying newer, ever more expensive antimicrobial agents that have the build-in paradox of being less prone to existing resistance mechanisms. Consequently, the newer agents have a broader range of activity, thus constituting a further selection pressure on the population of medically important microbial species in hospitals and the community.

The correlation between in vitro resistance and therapeutic failure is not perfect since the host's innate and specific immunity systems play important roles here as well. Nevertheless, there is now little doubt that resistance takes a heavy toll on society in terms of costs, morbidity and mortality. The emergence of methicillin resistant *Staphylococcus aureus* (MRSA) in virtually all parts of the world is a good paradigm of the problem. Recent analyses of the impact of MRSA on clinical medicine has shown MRSA infection to be more difficult to cure, to be associated with higher levels of morbidity and mortality and to incur much greater costs for the healthcare system compared to infection due to methicillin susceptible strains of *S. aureus* (MSSA). It is also evident that in regions or countries where MRSA has emerged to clinically significant levels (> 5-10%) the medical community has responded by switching their (empirical) antibiotic policies from the relatively inexpensive, safe and effective class of beta-lactam antibiotics to much more expensive, less safe and potentially less effective classes of antimicrobial agents, including the glycopeptide antibiotic vancomycin. In 2002 true vancomycin resistance has emerged in these settings, constituting the next step on the spiral of resistance among staphylococci.

Emergence of resistance to the level of a threat to the health of the public requires, for each combination of species and an antimicrobial agent, resistance to affect a significant proportion of patients with infection and, in some instances, the commensal microflora of healthy individuals. Thus, in some regions of the world resistant micro-organisms cause a significant proportion of infection in hospitals, but antimicrobial resistance has also spread to certain communities outside the hospitals where the rate of carriage of antibiotic resistant microbes among the public at large may be increasing.

In a general epidemiological model of the emergence of antimicrobial resistance two major events should be addressed, i.e. the rate of selection of resistant variants or mutants when a patient and his/her microflora is exposed to a given antimicrobial agent, and, once selection has taken place, the likelihood of dissemination of such resistant clones (or of their resistance genes) to produce outbreaks, epidemics and, finally, pandemics (figure 1). Apparently, resistant clones of normally sensitive microbial species arise occasionally in patients when under selective antibiotic pressure. However, it has been the successful spread of some of these resistant clones, first within the hospital setting and now beyond these confines, that has resulted in the global emergence

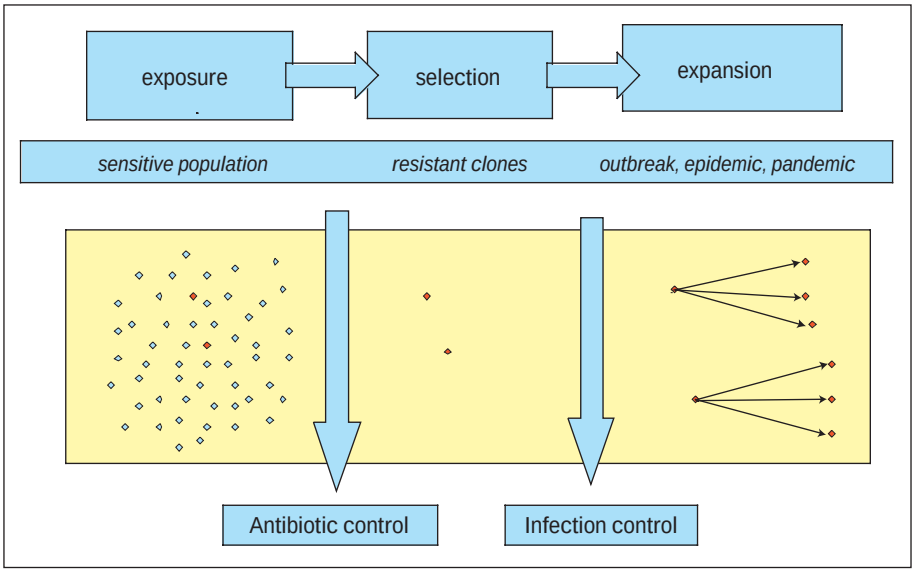


Figure 1. Model of resistance emergence and the crucial roles of antibiotic control and infection control in preventing outbreaks, epidemics and pandemics.

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of resistance problems. Microbial species that are not equipped to spread so easily are less likely to cause pandemics of resistant clones. However, they may still pose a threat if resistant variants or mutants emerge at high rates when patients are being treated with an antibiotic. Little is known about the dynamics of the emergence of resistance for each of the many clinically relevant combinations of microbial species with the various classes of antimicrobial agents, but we are learning fast. Clearly success rests with our efforts being directed at lessening the selection pressures exerted by the use of antimicrobial agents combined with efforts to limit the spread of resistant variants or mutant clones through proper infection control measures.

Information is needed to better focus our efforts to control and manage the emergence of antimicrobial resistance and to target our research activities in this field. Surveillance should ideally provide quantitative information on all usage of antimicrobial agents, in human medicine as well as in veterinary medicine and animal husbandry. Surveillance should likewise yield information on the prevalence and types of resistance among all species of microbes (bacteria, viruses, fungi and parasites) that are relevant to these sectors (including those species that may serve as a source of resistance genes). In addition, surveillance data on the use of antimicrobial agents on the one hand and the rates of resistances on the other should be collated in such fashion that use and resistance can be linked on several levels of detail. Levels of detail may pertain to certain locales (areas, counties, provinces, the whole country), types of populations sampled (hospital versus community, medical versus veterinary, various age groups and gender), species of micro-organisms, classes of antimicrobial agents and certain mechanisms of resistance.

Certainly, ***NethMap*** as it is presented here does not yet fulfil all criteria of an ideal source of surveillance information; many gaps are evident and remain to be filled in. However, the aim of ***NethMap*** is to develop over the years into such a comprehensive source of information on the use of antimicrobial agents and the prevalence of resistance to these agents in the Netherlands.

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II Summary

NethMap describes use of and resistance to antibiotics in bacteria isolated from humans in The Netherlands. The scope of ***NethMap*** is narrower than the scope of the DANMAP reports published by the Danish Statens Serum Institute and Veterinary Institutes yearly since 1997 (reference 3 in Appendix). A significant part of the Danish reports describes the surveillance of antibiotic usage in animals and resistance in zoonotic bacteria, which is not part of the first issue of ***NethMap***. The reader is referred to a recently published report by Mevius and Van Pelt who describe antimicrobial resistance among animal bacteria (ref. 7). Special human pathogens such as *Neisseria gonorrhoeae* and *Mycobacterium tuberculosis* are also not dealt with in this issue of ***NethMap***. However, future editions of ***NethMap*** shall include these topics.

The Foundation for Pharmaceutical Statistics (SFK) has gathered data on the use of antimicrobial agents outside hospitals. Their data include sales from pharmacies in the community, which are extrapolated to all pharmacies, thereby covering 90% of the prescriptions delivered to the Dutch population in the community outside the hospitals. These SFK data were analysed by the SWAB working group on antibiotic use surveillance. In the period 1997-2001 the use of antibiotics outside hospitals remained stable, 10 Defined Daily Doses (DDD) per thousand inhabitants per day. Loosely interpreted this implies that at any point in time approximately 1% of the Dutch population is using an antimicrobial agent. This usage is the lowest of all European countries. Tetracyclines were the antibiotics most frequently used. Their use decreased slightly from 2.6 to 2.4 DDD/1000 inhabitant-days. Compared to Scandinavian countries the Netherlands has a relatively high use of broad-spectrum penicillins. The use of one of these agents, co-amoxiclav, increased in the observed period from 0.9 to 1.3 DDD/1,000 inhabitant-days, while the use of amoxicillin alone, which has a smaller spectrum, decreased. The usage of macrolides and fluoroquinolones increased by only 0.1 DDD/1,000 inhabitant days to reach 1.2 and 0.9 DDD/1,000 inhabitant-days, respectively.

The Foundation of the Dutch Working Party on Antibiotic Policy (SWAB) collected data on the use of antibiotics inside hospitals by way of a questionnaire sent to hospital pharmacies. The use inside hospitals increased during the observation period from 47 to 52 DDD/100 patient-days. However, the use per patient admitted to hospitals remained constant at 4 DDD. This discrepancy was due a decrease in the average length of hospital stay in the same period in Dutch hospitals. The antibiotic most often used in hospitals was co-amoxiclav. Its use increased from 14.3 to 16.9 DDD/100 patient-days. The use of fluoroquinolones increased from 4.0 to 4.9 DDD/100 patient-days. Cotrimoxazole use decreased slightly, from 2.6 to 2.4 DDD/100 patient-days.

The National Institute for Public Health and the Environment (RIVM) collected data on the resistance of routine isolates from unselected hospital departments which were analysed by eight regional public health laboratories covering an estimated 25% of the country. The department of Medical Microbiology of the University Medical Center St. Radboud at Nijmegen collected strains from selected departments, i.e. the intensive care units, urology services and pulmonology services from hospitals located in various parts of the country. Quantitative susceptibility testing was performed centrally by the laboratory in Nijmegen. The department of Medical Microbiology of the University Hospital at Maastricht collected and tested strains from patients in the community. All surveillance systems registered a significant increase in the rates of resistance to the fluoroquinolones among Gram-negative bacteria (*Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa*) as well as *Staphylococcus aureus*. The level of fluoroquinolone resistance among *E. coli* attained higher percentages among isolates from urological patients (7%) than among those from patients admitted to intensive care departments (3-4%) and those from the community (1-3%). The macrolide resistance among *S. aureus* and *Streptococcus pneumoniae* also increased in the period under investigation, from 3% to 7% and from 2% to nearly 7%, respectively.

It is interesting to compare the surveillance data from ***NethMap*** with those from other countries in Europe, as presented in similar national reports (ref. 3, 5, 6) and on the website of the EARSS project (www.earss.rivm.nl). Denmark has a comparably low total use of antibiotics in the community outside hospitals, 13 DDD/1,000 inhabitant-days. The total use of antibiotics has been stable in that country as well over the years 1997-2001. However, the Danish people use twice as much penicillins and twice as much macrolides, but two times less tetracyclines as compared to the Netherlands. Similar to what we observed for the Netherlands, Denmark saw an increase in the percentage of macrolide-resistant *S. pneumoniae*, although the total use of macrolides in- and outside hospitals hardly increased. The DANMAP report ascribes the increase in macrolide-resistant pneumococci to the increased use of one of the macrolides, azithromycin. However, the use of this macrolide has not increased in our country in the last few years.
As a result of government intervention, quinolone use in the community outside hospitals has, in Denmark, decreased in the period 1997-2001 until a very low level (0.17 DDD/1000 inhabitant-days, five times lower than that in the Netherlands). In

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line with this low use, ciprofloxacin resistance among *E. coli* has remained at a very low level. A similarly low level of quinolone use was noted in Sweden, but they reported a mean quinolone resistance of *E. coli* of 3%, which is similar to the overall resistance rate in the Netherlands. Sweden reports a remarkably high usage of methenamine (1.6 DDD/1000 inhabitant-days), a compound used for treatment of urinary tract infections, especially in patients aged 80 years and older. It would be worthwhile to compare the efficacy and side effects of this policy to the treatments applied in the Netherlands.

In summary, the rate of resistance against fluoroquinolones and macrolide antibiotics among bacteria isolated from patients in Dutch hospital departments and outpatient clinics has clearly increased. Although the use of these two groups of antimicrobial agents has hardly increased in the period reported here, fluoroquinolone and macrolide usage did increase in the period immediately before the time frame observed in ***NethMap***. The use of quinolones doubled in the period 1990-1997 (ref. 9) and the use of macrolides doubled in the years 1994-1997 (ref. 10). Likewise, Janknegt et al. reported in 2000 that in hospitals the use of these two classes of agents doubled in the period 1991-1996 (ref. 2). Thus, there may be a considerable delay in time before changes in antibiotic usage become evident in changes in the level of antimicrobial resistance. This delay may, in part, be due to the fact that resistance rates are based on susceptibility test results for the first isolate of each patient only. The resistance rates among repeat isolates are higher than the resistance-rates among first isolates, probably because patients have been treated in between. Moreover, such patients have probably been treated more often with newer antibiotics. Also, the biology of resistance emergence among microbial species would predict some time delay between changes in the level of antibiotic exposure and the emergence of resistant clones as result of the selection pressures exerted by such exposures.
In some groups of patients antibiotic use is higher than in other groups. Thus, men use longer courses of quinolones for urinary tract infections than women and older women use more quinolones than younger women. This is reflected in the resistance rate of *E. coli* in these groups of patients. Children use hardly any quinolones and this low use results in very low resistance rates (ref. 9).

The information presented in ***NethMap*** illustrates the significance of early detection of changes in antibiotic use by different groups of patients, e.g. stratified by age, sex, countries, parts of the Netherlands, hospitals (general versus university) and departments of hospitals (medical specialty). In these compartments the determinants of use must be investigated. It would be interesting to relate these differences in use to differences in resistance and result of treatment. Do the large differences in use and resistance rates between countries in Europe lead to measurable differences in infectious diseases related morbidity and mortality? As yet integrated nation-wide reports on antimicrobial use and antibiotic resistance have only been produced by the Northern countries Norway, Sweden, Finland and Denmark. This is somewhat remarkable since the rates of antimicrobial resistance, and the clinical problems related to antimicrobial resistances, are so much higher in other parts of Europe.

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III Samenvatting

Dit rapport, ***NethMap*** genoemd, beschrijft het gebruik van antibiotica en de resistentie tegen antibiotica bij de mens in Nederland. Het blikveld van ***NethMap*** is vooralsnog minder breed dan dat van het Deense voorbeeld, DANMAP, dat sinds 1997 jaarlijks is verschenen (referentie 3 in de Appendix). Een belangrijk deel van het Deense rapport behelst het antibioticagebruik en de resistentie tegen antibiotica bij pathogenen in de veehouderij die in ***NethMap*** buiten beschouwing blijven. Zie hiervoor het recent verschenen rapport MARAN 2001 dat de resistentie bij bacteriën van dieren in Nederland beschrijft (ref. 7). Ook speciale humane pathogenen zoals *Mycobacterium tuberculosis* en *Neisseria gonorrhoeae* zijn in deze eerste editie van ***NethMap*** nog niet meegenomen. Toekomstige versies van ***NethMap*** zullen in deze zin worden uitgebreid.

Gegevens over het gebruik van antibiotica buiten het ziekenhuis zijn verzameld door de Stichting Farmaceutische Kengetallen (SFK) te Den Haag, en voor ***NethMap*** geanalyseerd door de SWAB. Deze gegevens betreffen de omzet van alle openbare apotheken, die ca. 90% van Nederlandse bevolking buiten de ziekenhuizen van geneesmiddelen voorzien. In de periode 1997-2001 bleef het gebruik van antibiotica buiten de ziekenhuizen nagenoeg constant, 10 gestandaardiseerde dagdoseringen (DDD) per 1000 inwoners per dag. Vrij vertaald betekent dit dat op elk moment ca. 1% van de Nederlanders een antibioticum gebruikt. Daarmee heeft Nederland het laagste gebruik buiten het ziekenhuis van alle Europese landen. De meest gebruikte antibiotica waren de tetracyclines. Het gebruik daarvan daalde licht van 2,6 naar 2,4 DDD per 1000 inwoners per dag. Ons land heeft een hoger relatief gebruik van breedspectrum penicillines dan de Scandinavische landen. Het gebruik van zo'n penicilline met verbreed spectrum, amoxicilline met clavulaanzuur, nam in de beschreven periode toe van 0,9 naar 1,3 DDD per 1000 inwoners per dag, terwijl het gebruik van amoxicilline alleen 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 0,9 DDD per 1000 inwoners per dag.

Gegevens over antibiotica gebruik in ziekenhuizen heeft de Stichting Werkgroep Antibioticabeleid (SWAB) verzameld met een enquête. Het gebruik in ziekenhuizen nam in de periode 1997-2001 toe van 47 tot 52 DDD per 100 patiënt-dagen. Omdat in dezelfde periode de opnameduur met hetzelfde percentage 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 14,3 naar 16,9 DDD per 100 patiënt-dagen. Het gebruik van fluorochinolonen steeg van 4,0 naar 4,9 DDD per 100 patiënt-dagen. Het gebruik van co-trimoxazol daalde licht, van 2,6 naar 2,4 DDD per 100 patiënt-dagen.

Gegevens over resistentie kwamen uit de geautomatiseerde registratie door het RIVM van de resistentie van bacteriestammen uit klinieken en poliklinieken die zijn onderzocht in acht streeklaboratoria. Tevens werden stammen verzameld uit geselecteerde afdelingen voor intensive care, urologie en longziekten. Laatstgenoemde stammen werden onderzocht op een centraal adres, de afdeling Medische Microbiologie van het Universitair Medisch centrum St. Radboud te Nijmegen. De afdeling Medische Microbiologie van de Universiteit van Maastricht verzamelde stammen van huisarts patiënten. Alle surveillance-systemen lieten een stijging zien van de resistentie tegen de fluorochinolonen zowel bij de Gramnegatieve bacteriën (*Escherichia coli, Klebsiella pneumoniae en Pseudomonas aeruginosa*) als bij *Staphylococcus aureus*. De resistentie tegen fluorochinolonen bereikte hogere waarden bij *E. coli* van urologische patiënten (7%) dan bij patiënten van intensive care afdelingen (3-4%) en de huisarts patiënten (1-3%). Ook de resistentie tegen macroliden bij *S. aureus* en *Streptococcus pneumoniae* steeg in de beschreven periode, respectievelijk van 3% naar 7% en van 2% naar bijna 7%.

Het is interessant onze resultaten te vergelijken met die van andere landen in Europa, zoals weergegeven in vergelijkbare nationale rapportages (ref. 3, 5, 6) en op de website van het EARSS project (www.earss.rivm.nl). Denemarken heeft ongeveer hetzelfde totale gebruik van antibiotica buiten ziekenhuizen, nl. 13 DDD per 1000 inwoners per dag. Ook in dat land is het gebruik in de jaren 1997-2001 nauwelijks gestegen. De Denen gebruiken twee maal zoveel penicillines, twee maal zo veel macroliden maar twee maal zo weinig tetracyclines. Net als wij zagen zij een toename in het percentage macrolide-resistente *S. pneumoniae*, hoewel het totale gebruik van macroliden in en buiten het ziekenhuis gemeten in DDD nauwelijks toenam in de periode 1994-2001. Zij schreven de toename van de macrolide-resistentie dan ook toe aan het toegenomen gebruik van één van de macroliden, nl. azitromycine (ref. 3), maar het gebruik van dit middel is in ons land in de periode 1997-2001 nauwelijks meer gestegen. Door overheidsmaatregelen is het chinolongebruik in Denemarken buiten de ziekenhuizen in de periode 1997-2001 gedaald tot slechts 0,17 DDD per 1000 inwoners per dag. Vijf maal zo laag als bij ons. In overeenstemming daarmee is er nauwelijks ciprofloxacine resistentie bij *E. coli* isolaten in Denemarken. Ook in Zweden ligt het chinolon gebruik veel lager dan bij ons (0,1-0,2 DDD per 1000 inwoners per dag). De resistentie bij *E. coli* ligt in dat land op ca. 3%, ongeveer even hoog als in Nederland. In Zweden wordt opmerkelijk veel

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methenamine gebruikt voor de behandeling van urineweginfecties, 1,6 DDD per 1000 inwoners per dag, met name bij patiënten van 80 jaar en ouder. Het zou interessant zijn het klinische effect hiervan (werking en bijwerkingen) te vergelijken met de behandelmethoden in ons land.

Resumerend is de resistentie bij bacteriën van patiënten in Nederlandse klinieken en poliklinieken tegen chinolonen en macroliden duidelijk gestegen. Het gebruik van deze twee groepen antibiotica is in de hier beschreven periode nauwelijks toegenomen, maar wel in de periode daarvóór. Het gebruik van chinolonen verdubbelde in de periode 1990-1997 (ref. 9) en dat van macroliden verdubbelde in de jaren 1994-1997 (ref. 10). Dit geldt niet alleen voor het gebruik bij huisartsen maar ook voor het gebruik in de ziekenhuizen (ref. 2). Er lijkt dus een vertraging te zijn tussen een toename in gebruik en een toename in resistentie. Die vertraging is mogelijk deels te verklaren doordat de hier beschreven resistentiebepalingen zijn uitgevoerd bij het eerste bacterie-isolaat van elke patiënt. Vervolgisolaten zijn in het algemeen vaker resistent omdat de patiënt intussen behandeld is en resistente bacteriën in die patiënt zijn uitgeselecteerd. Bovendien worden nieuwe middelen vaak pas toegepast nadat een eerste therapie heeft gefaald. Daarom is een stijging van resistentie eerder waar te nemen bij herhaalisolaten dan bij eerste isolaten per patiënt.

Bepaalde groepen patiënten lopen qua gebruik en bijbehorende resistentie voorop. Zo ligt het chinolon gebruik bij mannen veel hoger dan dat bij vrouwen en bij oudere vrouwen ligt het hoger dan bij vrouwen van middelbare leeftijd. Bij kinderen worden vrijwel geen chinolonen gebruikt. Men ziet dit terug in de resistentie van *E. coli* van deze groepen patiënten (ref. 9).
Dit illustreert het belang van een vroegtijdige signalering van het gebruik van antibiotica bij verschillende groepen patiënten, bijvoorbeeld verschillend op basis van leeftijd, sekse, landen, delen van Nederland, ziekenhuizen (algemene versus universitaire) en afdelingen van ziekenhuizen (medisch specialisme). In deze compartimenten zou gekeken moeten worden naar de determinanten van het gebruik. Het zou interessant zijn deze verschillen te koppelen aan verschillen in resistentie maar ook en vooral aan verschillen in behandelingsresultaat.
Een interessante vraag is bijvoorbeeld of de grote verschillen in gebruik en resistentie tussen de landen van Europa werkelijk leiden tot meetbare verschillen in ziektelast en/of sterfte ten gevolge van infectieziekten of dat alleen de resistentie statistieken in de veel gebruikende landen er beroerder uitzien. Tot nu toe zijn integrale rapporten over antibiotica gebruik en resistentie alleen gepubliceerd door de noordelijke landen, Noorwegen, Zweden, Finland en Denemarken. Dit is merkwaardig omdat juist in die landen de resistentieproblemen veel minder groot zijn dan in andere delen van Europa.

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IV 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 will be reported elsewhere. 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 "materials and methods" in the Appendix for details regarding the acquisition and analysis of the antibiotic consumption data.

Primary health care

Table 1 presents the use of antibiotics for systemic use in primary health care from 1997– 2001. 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 2001 is presented in figure 1. Tetracyclines (mainly doxycycline) represented 23% of total use in primary health care. Other frequently used antibiotics were penicillins with extended spectrum (mainly amoxicillin), macrolides and combinations of penicillins with beta-lactamase inhibitors (essentially co-amoxiclav), each representing 19%, 13% and 13% of the total use respectively. The distribution of the different classes of antibiotics according to DDD/1000 inhabitant-days corresponded well with the distribution of the number of prescriptions (data not shown).

During the study period the use of co-amoxiclav increased from 0.92 to 1.25 DDD/1000 inhabitant-days. Conversely, the use of amoxicillin decreased from 2.18 to 1.82 DDD/1000 inhabitant-days (figure 2). In 2001, the proportion of beta-lactamase sensitive penicillins, beta-lactamase resistant penicillins, penicillins with extended spectrum and combinations of penicillins with beta-lactamase inhibitors was 13, 7, 47 and 33%, respectively, of the total penicillin use in the Netherlands.

The increased use of macrolides is presented in figure 3. Clarithromycin is the most commonly used macrolide, and its use increased during the study period from 0.66 to 0.77 DDD/1000 inhabitant-days. The use of azithromycin also increased. A decrease was found for both erythromycin and roxithromycin. Clarithromycin, amoxicillin and pantoprazole, combined in a package with ATC-code A02BD04, are frequently used for the eradication of *Helicobacter pylori*. The use of this specific package was not included in the analysis of antibiotics of ATC

Table 1. Use of antibiotics for systemic use (J01) in primary health care (DDD/1000 inhabitant-days), The Netherlands, 1997-2001 (Source: SFK; data were analysed by SWAB).

ATC-group[a)]	Therapeutic group	Year				
		1997	1998	1999	2000	2001
J01AA	Tetracyclines	2.64	2.55	2.49	2.47	2.39
J01BA	Chloramphenicol	0.00	0.00	0.00	0.00	0.00
J01CA	Penicillins with extended spectrum	2.18	2.13	2.06	1.88	1.82
J01CE	Beta-lactamase sensitive penicillins	0.56	0.53	0.52	0.52	0.49
J01CF	Beta-lactamase resistant penicillins	0.23	0.22	0.23	0.24	0.25
J01CR	Combinations of penicillins, incl. beta-lactamase-inhibitors	0.92	0.95	1.04	1.15	1.25
J01DA	Cephalosporins and related substances	0.13	0.11	0.10	0.08	0.07
J01EA	Trimethoprim and derivatives	0.28	0.28	0.30	0.28	0.28
J01EC	Short-acting sulfonamides	0.00	0.00	0.01	0.01	0.01
J01EE	Combinations of sulfonamides and trimethoprim	0.48	0.46	0.46	0.43	0.42
J01FA	Macrolides	1.12	1.16	1.17	1.13	1.22
J01FF	Lincosamides	0.03	0.03	0.04	0.04	0.05
J01GB	Aminoglycosides	0.00	0.00	0.00	0.00	0.01
J01MA	Fluoroquinolones	0.78	0.79	0.85	0.85	0.87
J01MB	Other quinolones	0.06	0.05	0.04	0.04	0.04
J01XB	Polymyxins	0.01	0.02	0.02	0.02	0.02
J01XE	Nitrofuran derivatives	0.59	0.59	0.64	0.68	0.71
J01XX	Other antibiotics (= methenamine)	0.07	0.06	0.06	0.06	0.06
J01	Antibiotics for systemic use (total)	10.08	9.93	10.03	9.88	9.96

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

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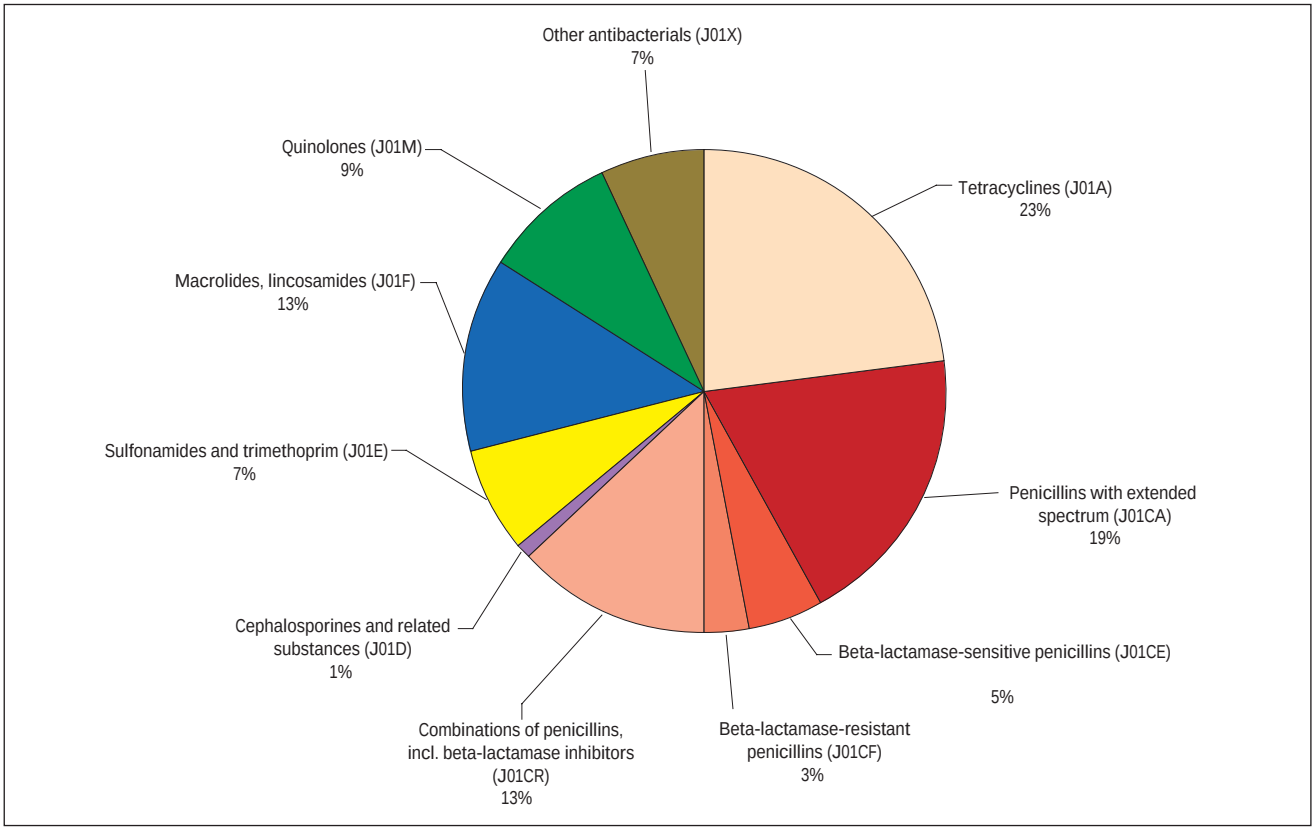


Figure 1. Distribution of the use of antibiotics for systemic use (J01) in primary health care, The Netherlands, 2001 (Source: SFK; data were analysed by SWAB).

group J01. In 2001, 16,385 prescriptions were registered, i.e. 3.9% and 1.3% of the total number of prescriptions of clarithromycin and amoxicillin, respectively.

From 1997 to 2001 the use of fluoroquinolones increased by 12% (table 1). In addition, the use of the individual drugs has changed during the past years (figure 4). A marked increase was

Figure 2. Use of amoxicillin and co-amoxiclav in primary health care, The Netherlands, 1997 - 2001 (Source: SFK; data were analysed by SWAB).

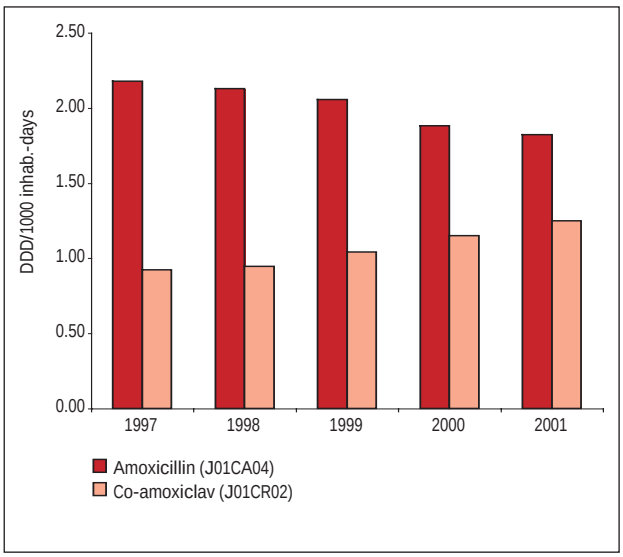
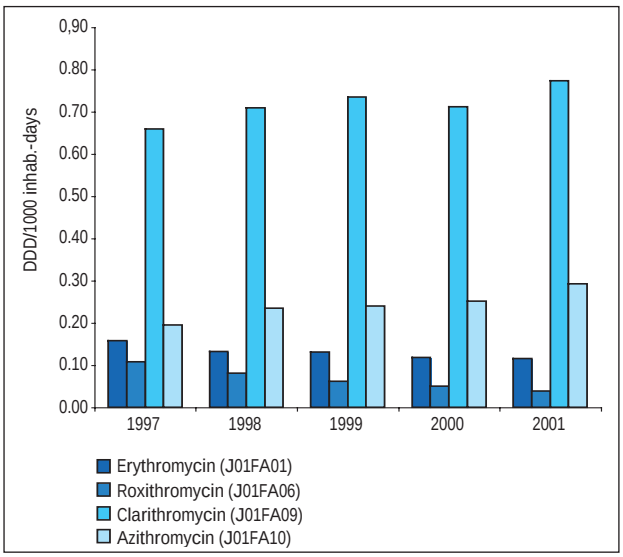


Figure 3. Use of macrolides for systemic use in primary health care, The Netherlands, 1997-2001 (Source: SFK; data were analysed by SWAB).



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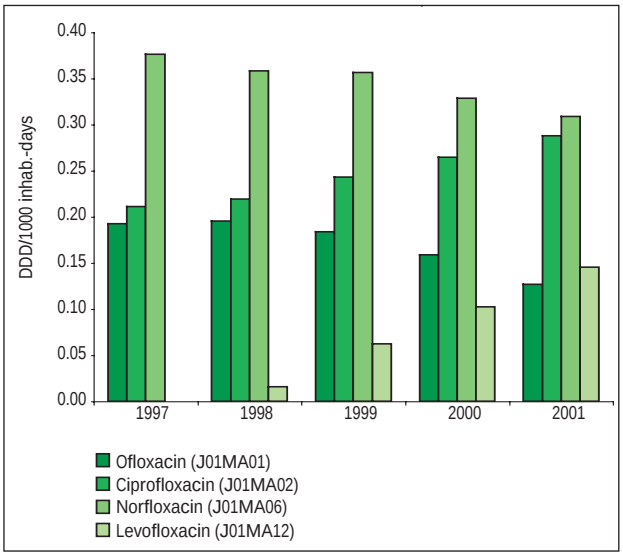


Figure 4. Use of fluoroquinolones for systemic use in primary health care, The Netherlands, 1997-2001 (Source: SFK; data were analysed by SWAB).

observed for the use of ciprofloxacin and levofloxacin. In 2001 the use of levofloxacin exceeded the use of ofloxacin. The use of ofloxacin and norfloxacin decreased from 0.19 to 0.13 and from 0.38 to 0.31 DDD/1000 inhabitant-days, respectively.

The use of nitrofurantoin increased from 0.59 to 0.71 DDD/1000 inhabitant-days (table 1).

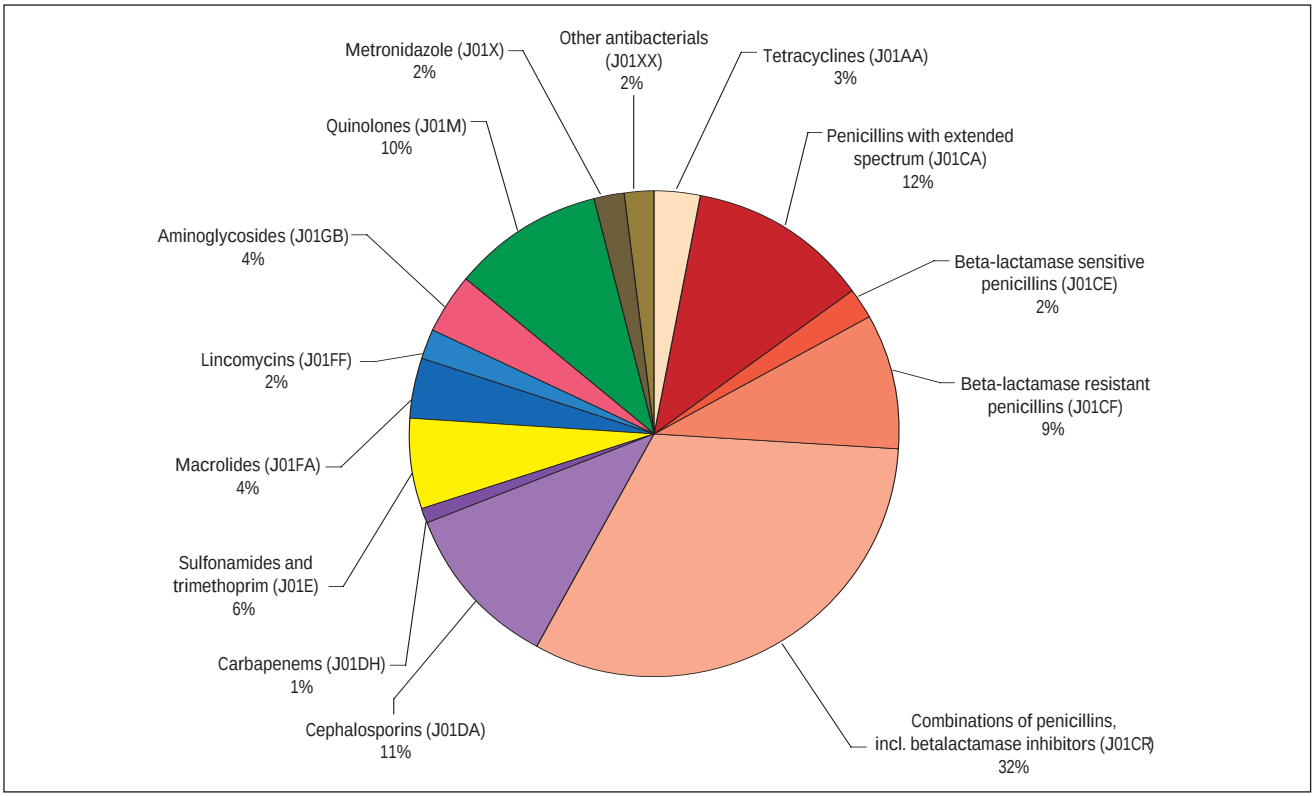
Discussion

From 1997-2001 total antibiotic consumption remained almost constant in the Netherlands. The use of antibiotics in community medicine is 10 DDD/1,000 inhabitant-days, which is lower than in any other European country (data from the European Surveillance of Antibiotic Consumption (ESAC) project; abstracts ECCMID 2003). The distribution of the different classes of antibiotics according to DDD/1,000 inhabitant-days corresponded well with the distribution of the number of prescriptions.

In 2001, the proportion of beta-lactamase sensitive penicillins, beta-lactamase resistant penicillins, penicillins with extended spectrum and combinations of penicillins with beta-lactamase inhibitors was 13, 7, 47 and 33%, respectively, of the total penicillin use in the Netherlands. In Denmark these proportions were 62, 7, 31 and 0.3%, respectively (ref. 3). This steady increase in the so-called "broad-spectrum" penicillins in the Netherlands may well be without proper rationale and deserves further scrutiny.

The increased use of the newer macolides clarithromycin and azithromycin may be related to their ease of administration and short treatment periods (twice or once daily for three to five days) as compared to erythromycin (three times daily for 7 days).

Figure 5. Distribution of the use of antibiotics for systemic use (J01) in Dutch hospitals, 2000 (Source: SWAB).



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Table 2. Use of antibiotics for systemic use (J01) in Dutch hospitals[a] (DDD/100 patient-days), The Netherlands, 1997-2000 (Source: SWAB).

ATC-group[b]	Therapeutic group	Year			
		1997	1998	1999	2000
J01AA	Tetracyclines	1.6	1.6	1.7	1.6
J01BA	Chloramphenicol	0.0	0.0	0.0	0.0
J01CA	Penicillins with extended spectrum	6.5	6.5	6.4	6.0
J01CE	Beta-lactamase sensitive penicillins	1.2	1.0	1.1	1.1
J01CF	Beta-lactamase resistant penicillins	4.1	3.8	3.9	4.4
J01CR	Combinations of penicillins, incl. beta-lactamase-inhibitors	14.3	14.3	15.6	16.9
J01DA	Cephalosporins and related substances	5.1	5.5	5.6	5.9
J01DF	Monobactams	0.0	0.0	0.0	0.0
J01DH	Carbapenems	0.4	0.4	0.3	0.4
J01EA	Trimethoprim and derivatives	0.5	0.5	0.5	0.4
J01EC	Short-acting sulfonamides	0.1	0.1	0.1	0.1
J01EE	Combinations of sulfonamides and trimethoprim	2.6	2.6	2.5	2.4
J01FA	Macrolides	1.9	1.9	2.2	2.1
J01FF	Lincosamides	0.8	0.9	1.1	1.2
J01GB	Aminoglycosides	2.0	2.1	2.0	2.2
J01MA	Fluoroquinolones	4.0	4.4	5.0	4.9
J01MB	Other quinolones	0.0	0.1	0.0	0.1
J01XA	Glycopeptides	0.4	0.4	0.4	0.5
J01XD	Imidazole derivatives	1.2	1.2	1.2	1.2
J01XE	Nitrofuran derivatives	0.2	0.3	0.2	0.4
J01	Antibiotics for systemic use (total)	47.2	47.8	50.1	52.2

[a] percentage of covered patient-days in 1997, 1998, 1999 and 2000 was 57, 61, 67 and 63, respectively.

[b] from the 2001 edition of the Anatomical Therapeutic Chemical (ATC) classification system

The increased use of fluoroquinolones in primary health care is worrisome. Due to their limited activity against pneumococci, fluoroquinolones are not the first choice for community acquired infections of the respiratory tract. Moreover, due to their broad spectrum, fluoroquinolones are definitely not the first choice for uncomplicated urinary tract infections occuring in the community. In this setting fluoroquinolones are reserved for (relapsing or recurrent) infections caused by micro-organisms resistant to amoxicillin, trimethoprim and nitrofurantoïn. The use of the fluoroquinolones in primary health care should preferably be restricted to complicated infection, and, when used, be based on a susceptibility report of the causative micro-organism. Further analysis on the increased use of these agents in primary health care seems warranted.

Hospitals

Table 2 presents the use of antibiotics for systemic use in Dutch hospitals from 1997-2000. Total use in hospitals was 47.2 DDD/100 patient-days in 1997 and increased to 52.2 DDD/100 patient-days in 2000. Overall there has been an increase of 10.6%. However, it should be noted that the average length of hospital stay decreased in the same period from 8.2 to 7.6 days. Thus, the average number of DDD per patient admitted to Dutch hospitals remained approximately the same, 3.96 DDD/patient admitted in 1997 versus 4.05 DDD/patient admitted in 2001.

The distribution of antibiotics by class in 2000 is presented in figure 5. In 2000 all penicillins combined represented 55% of hospital antibiotic use in the Netherlands. Combinations of penicillins, including beta-lactamase inhibitors represented 32% of total use in hospitals in 2000. Previous data reported by Janknegt et al. has revealed an increase in the use of co-amoxiclav from 3.93 in 1991 to 12.5 DDD/100 patient-days in 1996 (ref. 2). The use of co-amoxiclav continued to rise, from 14.3 in 1997 to 16.7 DDD/100 patient-days in 2000. The use of the combination of piperacillin with tazobactam increased from 0.08 in 1997 to 0.19 DDD/100 patient-days in 2000. Amoxicillin use decreased from 6.3 in 1997 to 5.8 DDD/100 patient-days in 2000 and represented 12% of total use in Dutch hospitals. Flucloxacillin is the only antistaphylococcal penicillin used to any extent in the Netherlands. The use of this antibiotic increased from 4.1 in 1997 to 4.4 DDD/100 patient-days and represented 9% of the total antibiotic use.

Cephalosporins represented 11% of the total hospital use in 2000 (figure 5). The use of the various generations of cephalosporins is summarised in figure 6. The use of the first generation cephalosporins remained fairly constant during the study period. Of these, cefazolin was by far the most commonly

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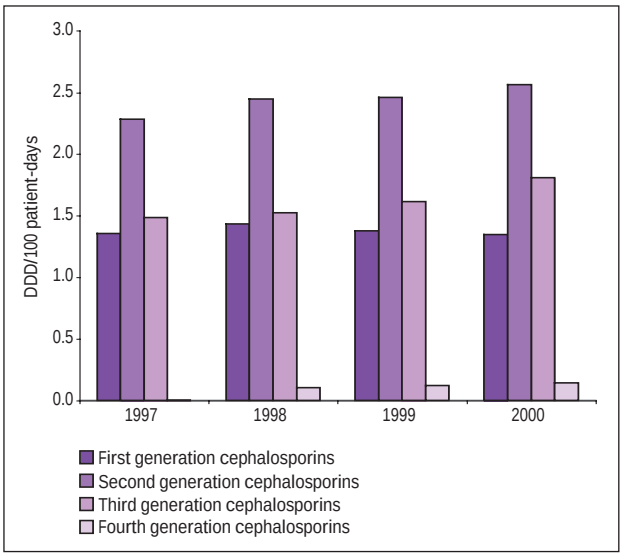


Figure 6. Use of cephalosporins in Dutch hospitals, 1997-2000 (Source: SWAB).

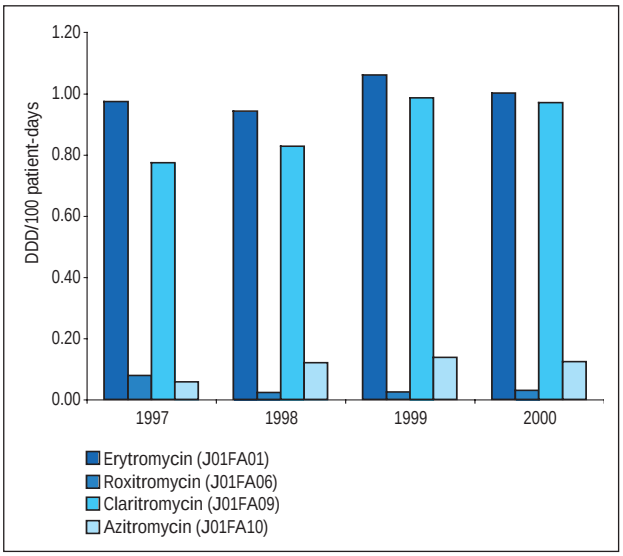


Figure 7. Use of macrolides in Dutch hospitals, 1997-2000 (Source:SWAB).

used one. The use of cefazolin increased from 0.9 in 1997 to 1.1 DDD/100 patient-days in 2000. In most Dutch hospitals cefazolin is restricted for surgical prophylaxis. The use of cefuroxime gradually increased to 2.4 DDD/100 patient-days in 2000. An increase was also found in the use of the third generation cephalosporins, mainly explained by an increase in the use of ceftazidime (0.56 to 0.66 DDD/100 patient-days) and ceftriaxone (0.46 to 0.67 DDD/100 patient-days). The use of carbapenems remained constant (table 2).

The use of clarithromycin increased between 1997 and 2000, approaching that of erythromycin (figure 7). The use of clindamycin increased from 0.8 in 1997 to 1.2 DDD/100 patient-days in 2000. Gentamicin was by far the most commonly used antibiotic of the aminoglycoside class (figure 8). Its use increased from 1.2 in 1997 to 1.4 DDD/100 patient-days in 2000. The use of tobramycin increased from 0.6 in 1997 to 0.7 DDD/100 patient-days in 2000. The relative contribution of the fluoroquinolones to the overall hospital use of antibiotics has been increasing since the early nineties, from 4.8% in 1991 to 7.7% in 1996 (ref. 2). This trend has continued such that in 2000 these antibiotics represented 9.4% of the total hospital use. The fluoroquinolone showing the largest increase in use was ciprofloxacin. Its use increased from 2.0 in 1997 to 3.1 DDD/100 patient-days in 2000 (figure 9).

Figure 8. Use of aminoglycosides in Dutch hospitals, 1997-2000 (Source: SWAB).

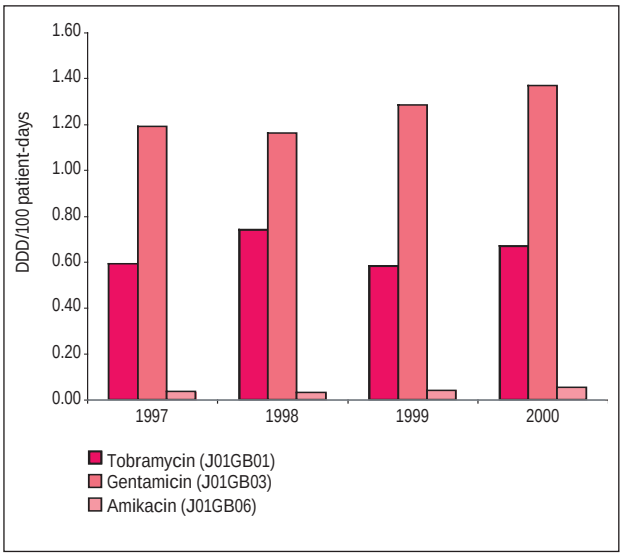
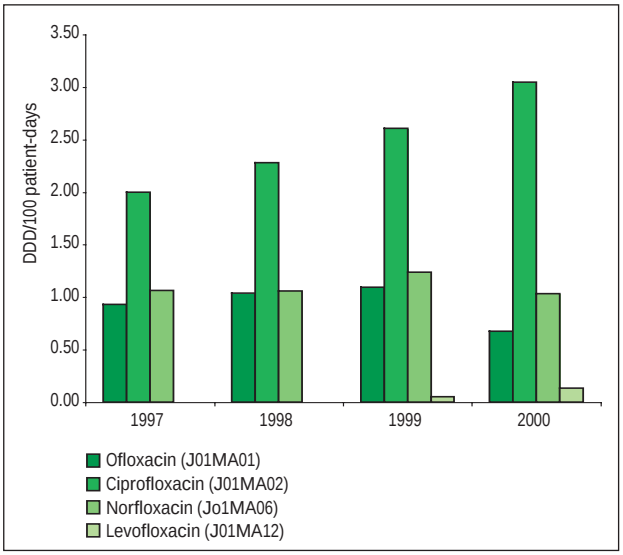


Figure 9. Use of fluoroquinolones for systemic use in Dutch hospitals, 1997-2000 (Source: SWAB).



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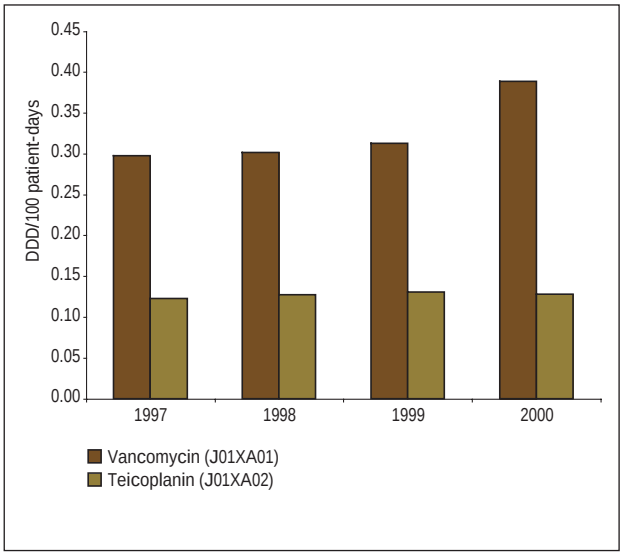


Figure 10. Use of glycopeptides in Dutch hospitals, 1997-2000 (Source: SWAB).

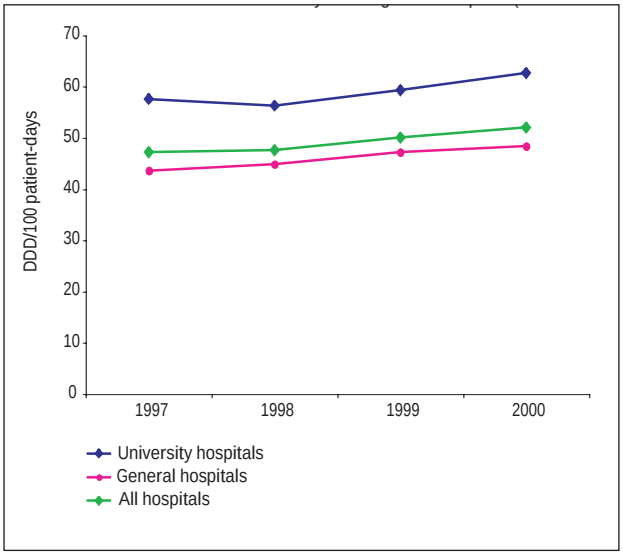


Figure 11. Total use of antibiotics for systemic use (J01) in Dutch hospitals: university versus general hospitals (Source: SWAB).

The use of glycopeptides showed a slight increase during the study period (figure 10). The use of vancomycin increased from 0.30 in 1997 to 0.39 DDD/100 patient-days in 2000, whereas the use of teicoplanin remained almost constant at 0.12-0.13 DDD/100 patient-days.

Discussion

The total use of antibiotics increased from 47.2 in 1997 to 52.2 DDD/100 patient-days in 2000. However, this increase in overall antibiotic use is largely explained by a similar reduction in the enumerators, i.e. the average length of stay. Thus, the average number of DDD/patient admitted to Dutch hospitals has remained constant over the years studied. However, shifts in the use of various classes of antibiotics did occur, indicating that changes in antibiotic policies are being made.

The increased use of co-amoxiclav, third generation cephalosporins, ciprofloxacin, clindamycin and vancomycin is of concern. It should be studied whether this originates from an increase in hospital infections, from more serious infections, from a decreased susceptibility to commonly used antibiotics or from frankly inappropriate use of antibiotics.

From 1997 to 2000 all eight university hospitals in the Netherlands participated in the SWAB surveillance project. The number of general hospitals varied from 41 to 50 (i.e. 43-52% of total).

In figure 11 the total use of antibiotics for systemic use (J01) is depicted for university versus general hospitals. The total use in university hospitals increased from 57.6 in 1997 to 62.7 DDD/100 patient-days in 2000, whereas in general hospitals the total use increased from 43.6 to 48.4 DDD/100 patient-days. From this figure it is clear that the ratio of the number of university and general hospitals affects the total use of antibiotics within a given country. When comparing data on hospital use between different countries, one should be aware of this ratio. In the future it will be interesting to make a separate analysis for both categories of hospitals to see whether the trends described before are similar in university as well as in general hospitals.

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V 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 acute respiratory tract infections and from patients with complaints of an acute uncomplicated urinary tract infections visiting their general practitioner in communities in the Southern parts of the Netherlands. See material and methods section for details regarding the acquisition and testing of isolates. This report describes the resistance patterns found among 1,697 isolates of *Escherichia coli* isolated from urine specimens. Respiratory tract specimens yielded strains of *Haemophilus influenzae* (N=12), *Staphylococcus aureus* (N=29) and hemolytic streptococci (N=55).

Escherichia coli

The prevalence of amoxicillin resistance among *E.coli* strains from patients with acute urinary complaints was relatively stable (17-21%) except for a much higher prevalence in 1992 (40%, figure 1). Except for the unexplained peak prevalence in 1992, amoxicillin resistance among *E.coli* causing infection in the community was significantly lower than that in selected or unselected hospital departments, where amoxicillin resistance rates are almost twice as high. The distribution of MICs of amoxicillin showed two small sub-populations of strains, one with reduced susceptibilities (MIC ~32 mg/L), and one that is highly resistant (MIC>256 mg/L) (figure 2). Resistance to co-amoxiclav, the combination of amoxicillin/clavulanate, was relatively rare, and in some years not detected.

Trimethoprim resistance rates, however, increased over the years, from 10% in 1988 to 18% in 2001 (figure 1). The prevalence of trimethoprim resistance among *E.*coli remained lower than that observed for hospital strains (see elsewhere). The prevalence of nitrofurantoin resistance remained at a low level over the years (~2%).

Norfloxacin resistant *E.coli* was not observed until 2000. However in 2000 and 2001 norfloxacin resistance was found, albeit at a rather low level (1-3%).

These data indicate that antibiotic resistance profiles among *E.coli* causing community acquired urinary tract infection remain rather constant so far, although surveillance data from 2000 and 2001 suggest that resistance against trimethoprim and against the fluoroquinolones may be emerging in the community. Since trimethoprim is an agent of choice for the treatment of urinary tract infection and norfloxacin may be used for complicated (i.e. relapsing and recurrent cases) infection in this setting these trends, if true, require further attention.

Pathogens isolated from the respiratory tract

Although the number of isolates tested so far are rather limited some remarks are made here. In case of *S.aureus*, these 29 strains were all found in throat samples from patients with respiratory tract disease, and none were resistant to methicillin, erythromycin, gentamicin, rifampicin, ciprofloxacin or vancomycin. Among the 12 *H.influenzae* strains the MIC values were not surprising with 8% of the strains being amoxicillin resistant and most erythromycin MICs falling in the 2-16 mg/L range. Among the 55 strains of hemolytic streptococci (both alpha and beta-hemolytic strains) no resistance against penicillin, cefotaxime or vancomycin was observed. 5% of the strains were resistant to erythromycin and 4% to ciprofloxacin.

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

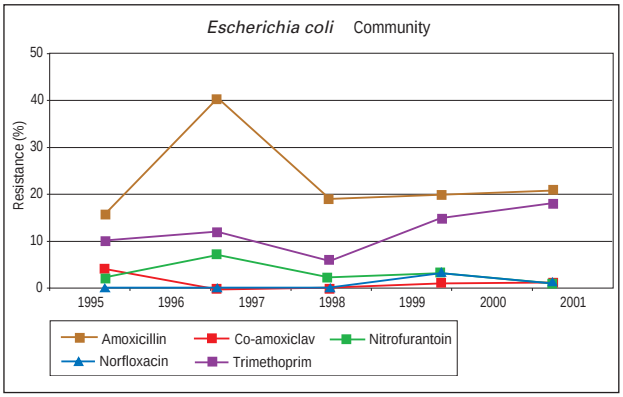
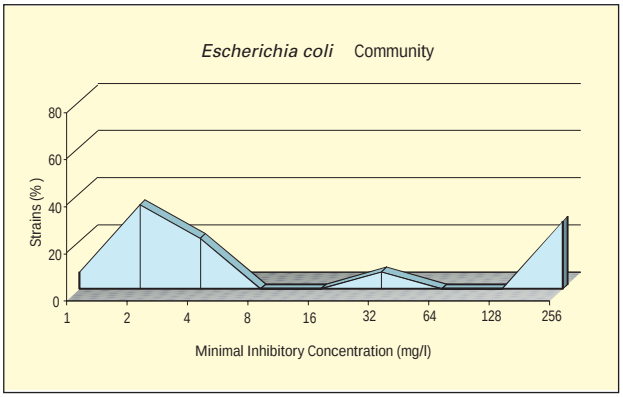


Figure 2. MIC distribution of amoxicillin for *Escherichia coli* from the community.



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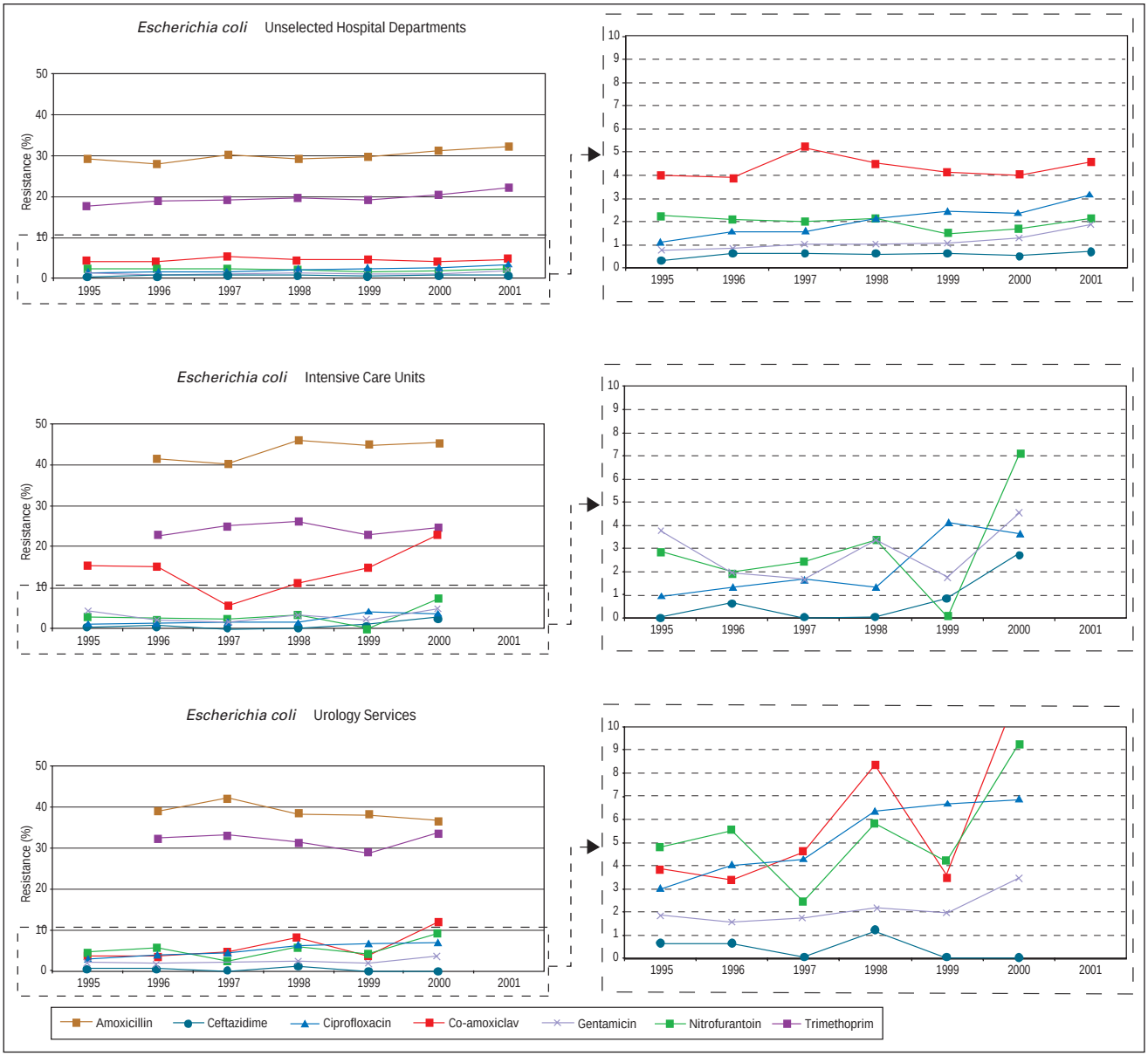
Surveillance of Antimicrobial Resistance in Hospitals

The overall prevalence of antibiotic resistance among bacteria isolated in hospitals was estimated by using resistance data generated in routine clinical care. Thus, unselected hospital departments and outpatients clinics were the sources of strains collected and tested by eight Regional Public Health Laboratories covering approximately 25% of the Dutch population (table 1 in Appendix). These overall hospital resistance rates are, in this report, designated resistance in 'unselected hospital departments'. Resistance prevalence among strains from unselected hospital departments were compared with the resistance rates among strains (table 2 in Appendix) isolated from selected departments in 10 large general or university hospitals. These selected departments included the Intensive Care Units, i.e. 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 hospitals increased slowly from 29% in 1995 to 32% in 2001 (figure 3).

Figure 3. Trends in resistance to antibiotics among *Escherichia coli* derived from Unselected Hospital Departments, Intensive Care Units and Urology Services.



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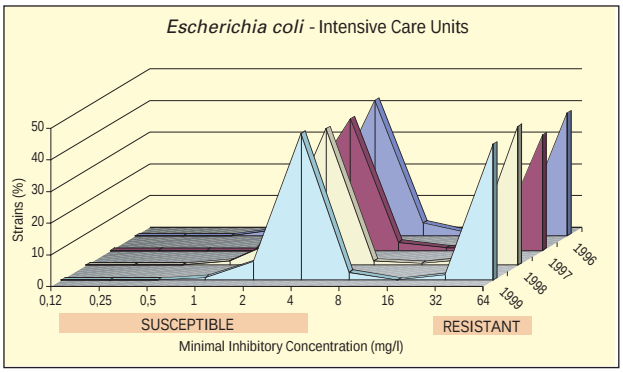


Figure 4. Trend in the MIC distribution of amoxicillin for *Escherichia coli* isolated from patients admitted to Intensive Care Units. The percentages indicate the proportion of strains susceptible to the concentration indicated. Strains with MIC≤8 mg/L are susceptible, and strains with MIC≥32 mg/L are resistant.

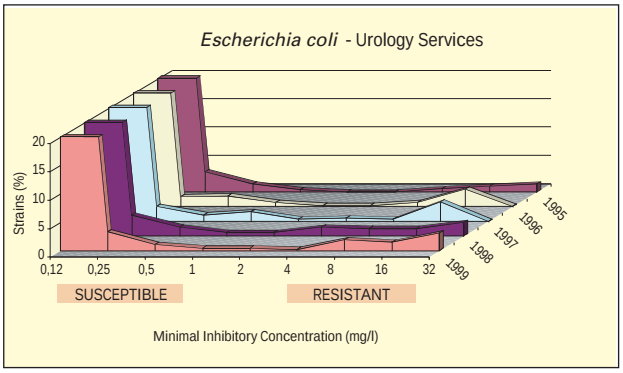


Figure 5. Trend in the MIC distribution of ciprofloxacin for *Escherichia coli* isolated from patients admitted to Urology Services. The percentages indicate the proportion of strains susceptible to the concentration indicated. Strains with MIC≤1 mg/L are susceptible and strains with MIC≥4 mg/L are resistant.

Amoxicillin resistance was higher in Urology Services, but significantly and consistently higher still among *E.coli* isolated from patients in Intensive Care Units during that period ($p<0.005$). Starting in 1998 a steady increase in the prevalence of amoxicillin resistance was observed in Intensive Care Units reaching 49% in 2000 ($p< 0.05$). The distribution of MICs (figure 4) clearly showed that two subpopulations exist: a susceptible one and a resistant one. Intermediate susceptibility to amoxicillin among this species is apparently rare. The resistant subpopulation is steadily growing during the years.

Co-amoxiclav (amoxicillin/clavulanate) resistance was at the same low level (4%) in unselected hospital departments and in the Urology Services until 2000. Subsequently, an increase in the level of resistance was observed in the Urology Services. Co-amoxiclav resistance was much higher in Intensive Care Units and increased to >20% in 2000.

Trimethoprim resistance increased in slowly in unselected hospital departments over the years from 18% to 22%. The level of trimethoprim resistance in Intensive Care Units fluctuated but was comparable (23-26%). It was significantly higher in the Urology Services (29-33%, $p<0.01$).

Trimethoprim is not frequently used in Intensive Care Units in the Netherlands. Thus, trimethoprim resistance rates among E.coli isolated in Intensive Care Units of hospitals may reflect resistance rates in the community rather than resulting from selection by antibiotic pressure in Intensive Care Units.

Similar differences between Intensive Care Units and the Urology Services were observed for nitrofurantoin, albeit at lower prevalence levels.

Ciprofloxacin resistance increased among *E.coli* from selected as well as from the unselected hospital departments. The resistance levels in unselected hospital departments and in the Intensive Care Units were comparable until 1998 (1-2%), thereafter the resistance in Intensive Care Units increased to 4%. Resistance spread slowly over the Intensive Care Units participating in the surveillance program. Only one Intensive Care Unit had ciprofloxacin-resistant *E.*coli strains isolated in 1995, whereas five had ciprofloxacin-resistant strains isolated in 1999 and 2000. The prevalence of ciprofloxacin resistance in the Urology Services was consistently higher from the beginning of the surveillance period in 1995. The MICs distribution of ciprofloxacin in Urology Services showed the emergence of highly-resistant *E.coli* strains already in 1995 with a slow shift of MICs to the more resistant range in the following years (figure 5). Patterns of MICs distribution can, thus, give insight at an early stage of the emergence of resistance. This underlines the importance of quantitative susceptibility testing methodology when designing a surveillance system for antibiotic resistance. Ciprofloxacin resistant *E.coli* was isolated in the Urology Services of all hospitals from 1996 onwards.

Pre-treatment with a quinolone in general practice and increased use of quinolones in Urology Services might be responsible for the higher resistance rates among *E.coli* strains isolated from patients at the Urology Services. Support for this assumption was the observation that some Urology Services recorded increases in quinolone resistance coincidentally with a decrease in trimethoprim resistance, suggesting a switch in antibiotic policy.

Klebsiella pneumoniae

Co-amoxiclav resistance in *K.pneumoniae* from unselected hospital departments and from the Urology Services was as low as that of *E. coli* (4%); in 2000 resistance increased (figure 6). Co-amoxiclav resistance among *K.pneumoniae* was much higher in the Intensive Care Units. The rather small number of Intensive Care derived strains tested (30-55 per year) may be responsible for the relatively large inter-annual fluctuations in resistance observed.

Trimethoprim resistance increased in unselected hospital departments from 11% to 21%. The level of resistance in Intensive Care Units fluctuated but was lower. Trimethoprim

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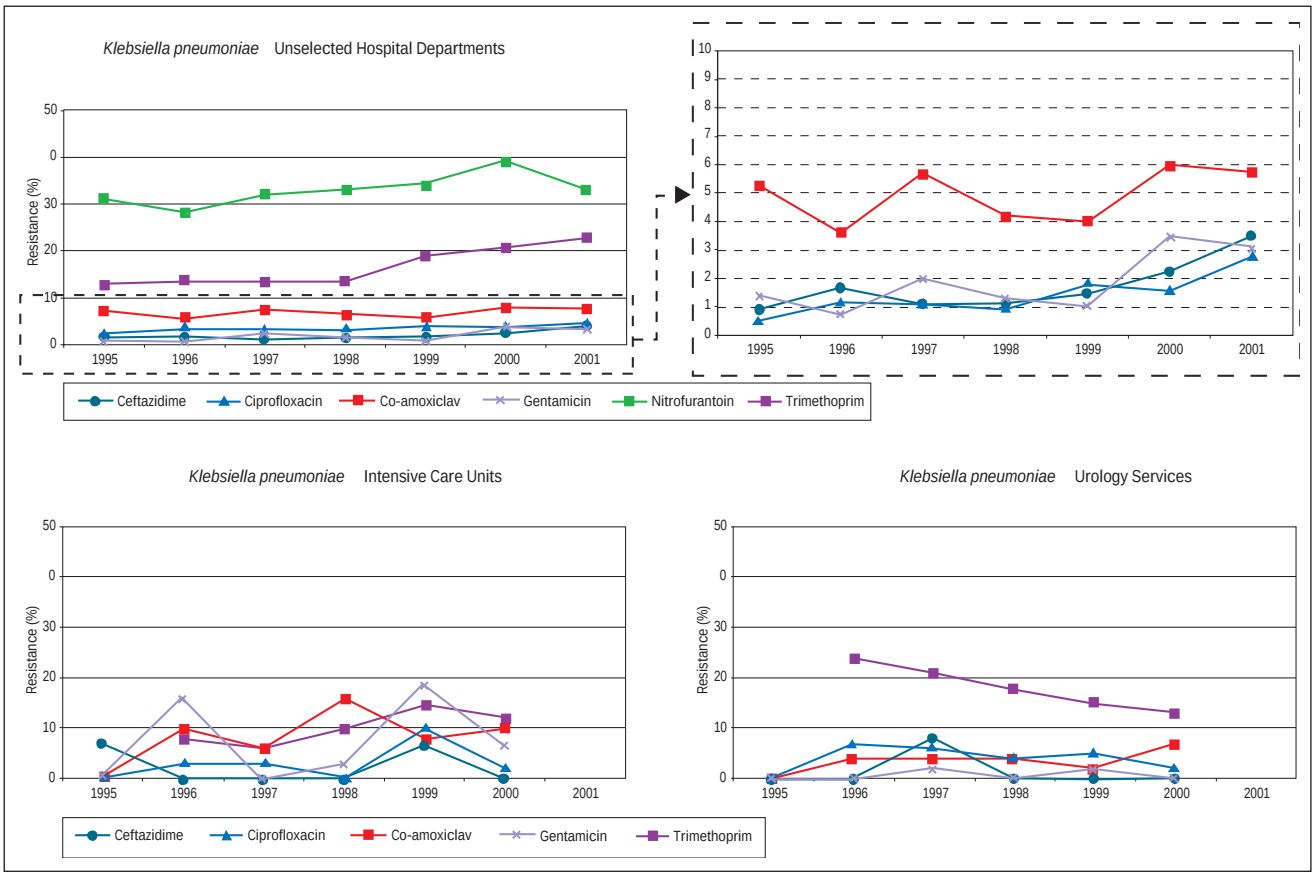


Figure 6. Trends in resistance to antibiotics among *Klebsiella pneumoniae* derived from Unselected Hospital Departments, Intensive Care Units and Urology Services.

resistance in Urology Services was significantly higher until 1998, thereafter the prevalence of resistance decreased to the level observed in Intensive Care Units. Trimethoprim is drug of first choice in general practice and rarely used in Intensive Care Units. The resistance in unselected hospital departments and Intensive Care Units may, thus, 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 the urologists. The decrease in resistance to trimethoprim parallels the increase in the prevalence of resistance to quinolones, a coincidence that is probably the result of a switch in antibiotic policy in Urology Services in the Netherlands.

The prevalence of ceftazidime resistance among *K.pneumoniae* was low, but it is increasing in unselected hospital departments. In the selected hospital departments ceftazidime resistant strains emerged occasionally in three Intensive Care Units and in one Urology Service.

The prevalence of gentamicin resistance was low, but it is also increasing in unselected hospital departments. 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 did not increase in Intensive Care Units or Urology Services and did not spread. Only three Intensive Care Units recorded ciprofloxacin resistant *Klebsiella* strains in 2000.

Pseudomonas aeruginosa

The prevalence of ceftazidime resistance among *P.aeruginosa* isolated in unselected hospital departments and in the Intensive Care Units was consistently low (2-3%). Ceftazidime resistance was not found among *P. aeruginosa* strains isolated in the Urology Services from 1996 onwards (figure 7).

Gentamicin resistance was low (<5%) until 1999 in all departments. However, a significant increase (>10%) in the prevalence of gentamicin resistance among *P.aeruginosa* was subsequently recorded for unselected hospital departments which persisted in 2001. Interestingly, such increasing rates in gentamicin resistance were not observed in the surveillance data derived from the selected departments, i.e. not in the Intensive Care Units nor in the Urology Services. Possibly, the use of gentamicin increased in other specialised wards (e.g. neonatal intensive

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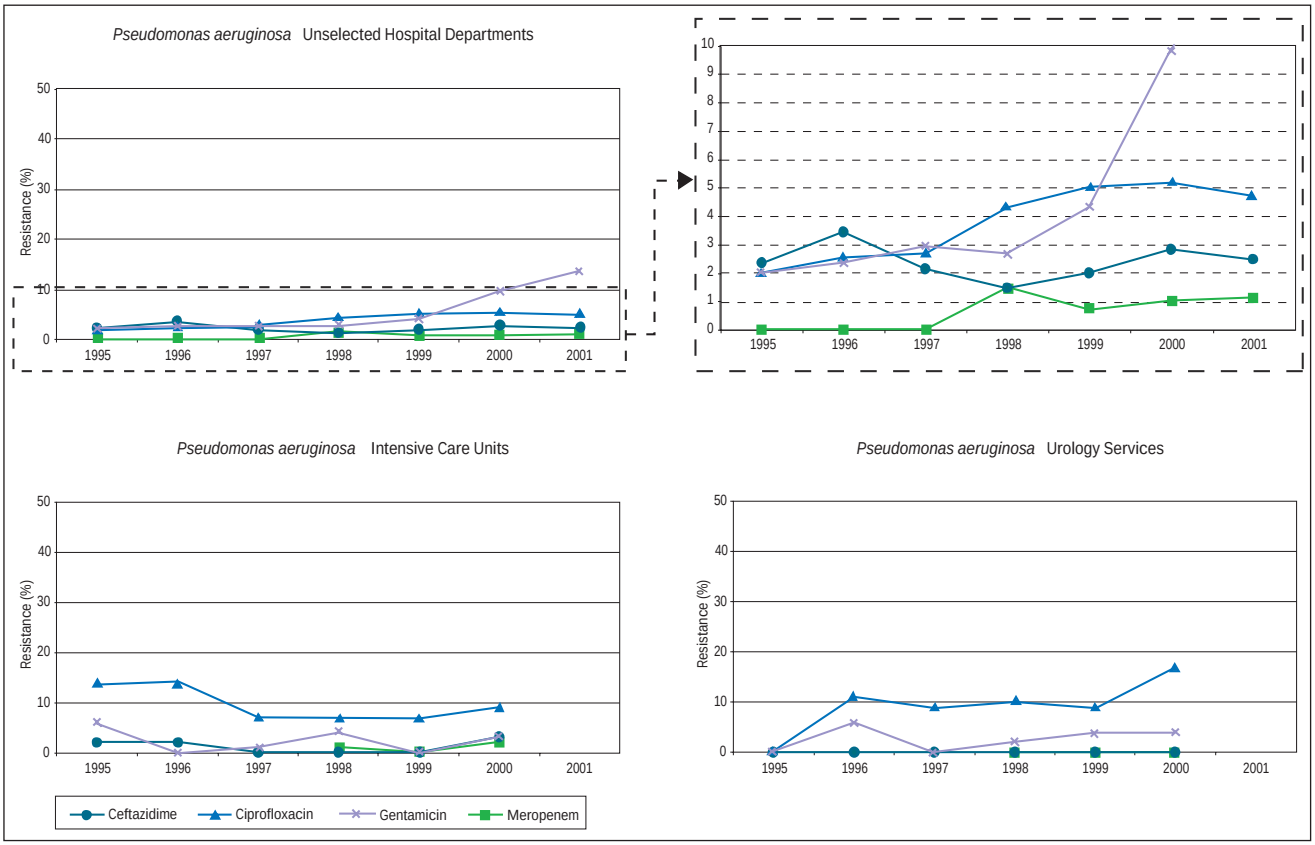


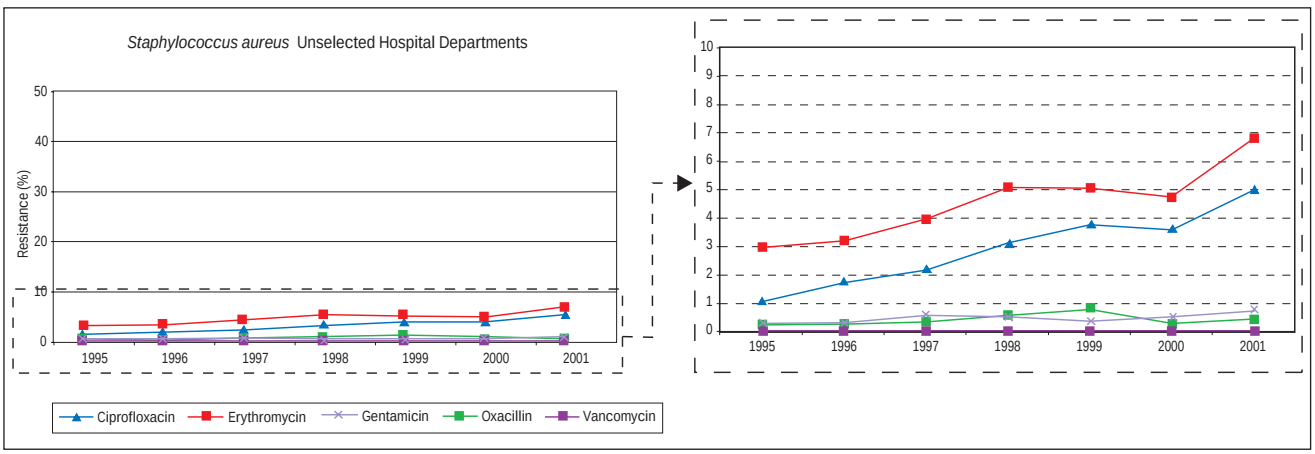
Figure 7. Trends in resistance to antibiotics among *Pseudomonas aeruginosa* derived from Unselected Hospital Departments, Intensive Care Units and Urology Services.

care units) and the emergence and spread of gentamicin-resistant strains of *P.aeruginosa* in some departments attributed to this change in the prevalence of gentamicin-resistance among *P.aeruginosa* in hospitals

Meropenem resistance among *P.aeruginosa* occurred only rarely, irrespective of the services selected in the hospitals. In contrast, the prevalence of ciprofloxacin resistance increased slowly in unselected hospital departments (2% in 1995 to 5% in 2001). In addition, ciprofloxacin resistance was much higher in Intensive Care Units and Urology Services already in 1995. The rates of ciprofloxacin resistant *P.aeruginosa* in these latter two departments varied between 8-18% over the years of surveillance.

Pseudomonas infections are usually nosocomialy acquired. Thus, increasing rates of ciprofloxacin resistance among

Figure 8. Trends in resistance to antibiotics among *Staphylococcus aureus* derived from Unselected Hospital Departments.



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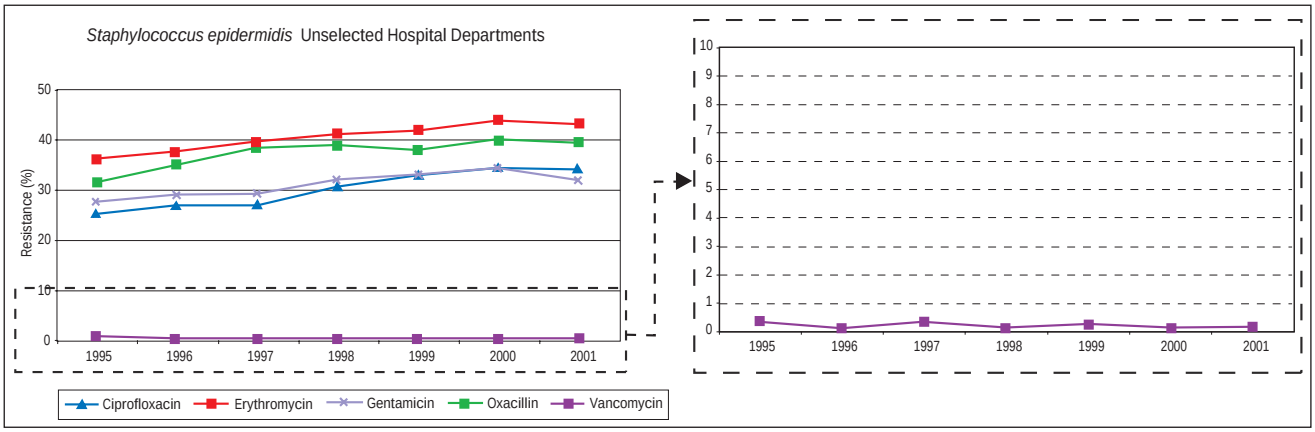


Figure 9. Trends in resistance to antibiotics among *Staphylococcus epidermidis* derived from Unselected Hospital Departments .

P.aeruginosa may accurately reflect the increase use and subsequent selection pressure exerted by fluoroquinolone anti-microbials in Dutch hospitals. See chapter on antibiotic use.

Staphylococcus aureus

The prevalence of methicillin resistant *S.aureus* (MRSA) has historically been very low in The Netherlands. In this surveillance report the prevalence of MRSA in unselected hospital departments remained below 1%. In addition no trend or significant increase in MRSA prevalence was observed during the surveillance period (figure 8). In contrast, the prevalence of resistance to erythromycin and ciprofloxacin were slowly increasing and reached 5-7% in 2001. However, *S.aureus* resistance to gentamicin remained less than 1%. The surveillance of *S.aureus* resistance rates among isolates derived from the Intensive Care Units and the Urology Services (data were available for 1995-1997) were highly similar to those for the unselected hospital departments (data not shown).

Staphylococcus epidermidis

In contrast to *S.aureus* methicillin resistance was frequently found among hospital isolates of *S.epidermidis* (includes all coagulase-negative species). Interestingly, the prevalence of methicillin among clinical isolates of *S.epidermidis* is still increasing in unselected hospital departments and has reached 40% (figure 9). The increase in methicillin resistance was paralleled by increasing rates in *S.epidermidis* resistance to erythromycin, gentamicin and ciprofloxacin. Vancomycin-resistance among *S.epidermidis* remained rare, but vancomycin-resistant strains were isolated occasionally.

Since staphylococci are species that primarily evolve along clonal lines or lineages, the emergence of clones resistant to one or more antimicrobial agents, especially MRSA, may well predict the future development of resistance problems in clinical medicine. Thus, the isolation of a resistant strain, especially of a strain of MRSA, should always be taken seriously, and acted upon along the guidelines of the Working Party on Infection Prevention (WIP).

Streptococcus pneumoniae

S.pneumoniae fully resistant to penicillin (MIC>1 mg/L) remain extremely rare in The Netherlands. When fully penicillin resistant strains and strains with reduced or intermediate susceptibility to penicillin (MIC: 0.1-1.0 mg/L) are taken together the highest yearly prevalence rate was 1.5% in 1999 in unselected hospital departments as well as in the Pulmonology Services (figure 10). There was no trend toward higher rates of penicillin resistance in this surveillance period. In contrast, there was a clear trend toward higher rates of erythromycin resistance among clinical isolates of *S.pneumoniae*, especially among strains isolated from unselected hospital departments. The prevalence of ciprofloxacin resistance was significant (10-30%) but fluctuated over the years of surveillance. Calculating the ciprofloxacin resistance rates for the Pulmonology Services it was shown that ciprofloxacin resistance among *S.pneumoniae* was initially much higher (44% in 1995) compared to that of the unselected hospital departments, but the prevalence of ciprofloxacin resistance decreased over the ensuing years (13% in 1999). Analysis of the distribution of MIC showed that the decrease in the rate of ciprofloxacin resistance was primarily due to a shift from the fully resistant category to the intermediately susceptible category (figure 11).

Resistance to ciprofloxacin among pneumococci apparently developed quickly in the early nineties. Ciprofloxacin is only moderately active against *S.pneumoniae* and most pulmonologists have stopped to prescribe ciprofloxacin for suspected or proven pneumococcal infections. This change in prescribing behaviour has reduced the use and, thereby, the selective pressure, and may, thus, have contributed to the shift in MIC distribution from fully resistant to intermediately susceptible strains isolated from Pulmonology Services.

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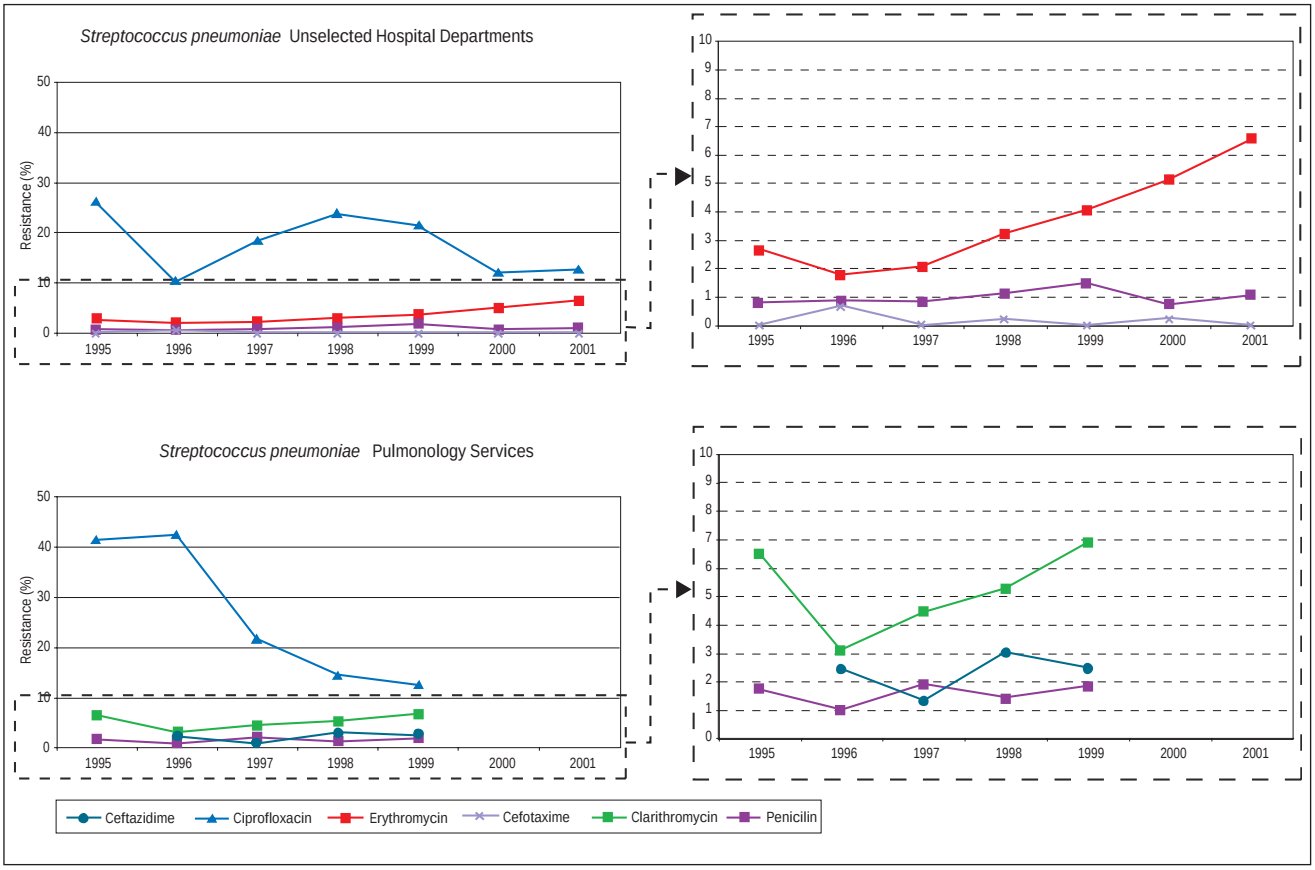
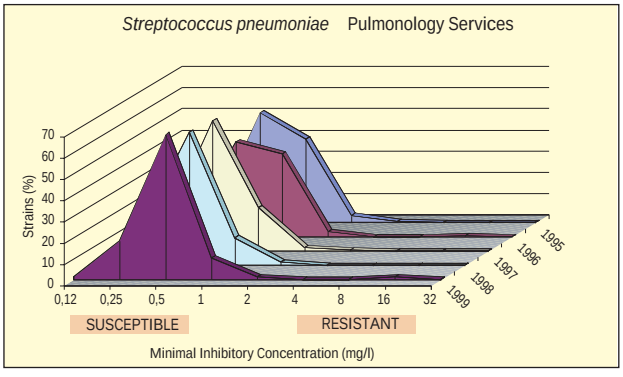


Figure 10. Trends in resistance to antibiotics among *Streptococcus pneumoniae* derived from Unselected Hospital Departments and Pulmonology Services.

Haemophilus influenzae

The prevalence of amoxicillin resistance among *H.influenzae* isolated in unselected hospital departments has remained stable over the surveillance years. For *H.infuenzae* strains isolated from Pulmonology Services somewhat higher resistance rates (9-14%) were observed, but again no trend toward increasing rates was discernible (Figure 12).

Figure 11. Trend in the MIC distribution of ciprofloxacin for *Streptococcus pneumoniae* isolated from patients admitted to the Pulmonology Services. The percentages indicate the proportion of strains susceptible to the concentration indicated. Strains with MIC≤1 mg/L are susceptible and strains with MIC≥4 mg/L are resistant.



The prevalence of erythromycin resistance among *H. influenzae* from unselected hospital departments is high (> 70%) when one includes strains with reduced susceptibility to erythromycin (MIC>0.5 mg/L). Instead of erythromycin the newer macrolide agent clarithromycin was tested for isolates from the Pulmonology Services. 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 was only 18-23% over the years.

Increasing prevalence rates were found for doxycycline resistance among *H.influenzae* isolates from unselected hospital departments, but not for strains isolated from the Pulmonology Services.

Amoxicillin has been a drug of first choice for pulmonologists and has remained so over the years. Thus, amoxicillin is frequently used by pulmonologists in the Netherlands. The selective pressure that, therefore, occurs in this clinical setting may partly explain the higher resistance rates found among *H.influenzae* strains isolated from Pulmonology Services. The higher resistance rates for doxycycline among *H.influenzae* isolated in unselected hospital departments compared to the Pulmonology Services, however, remain unexplained.

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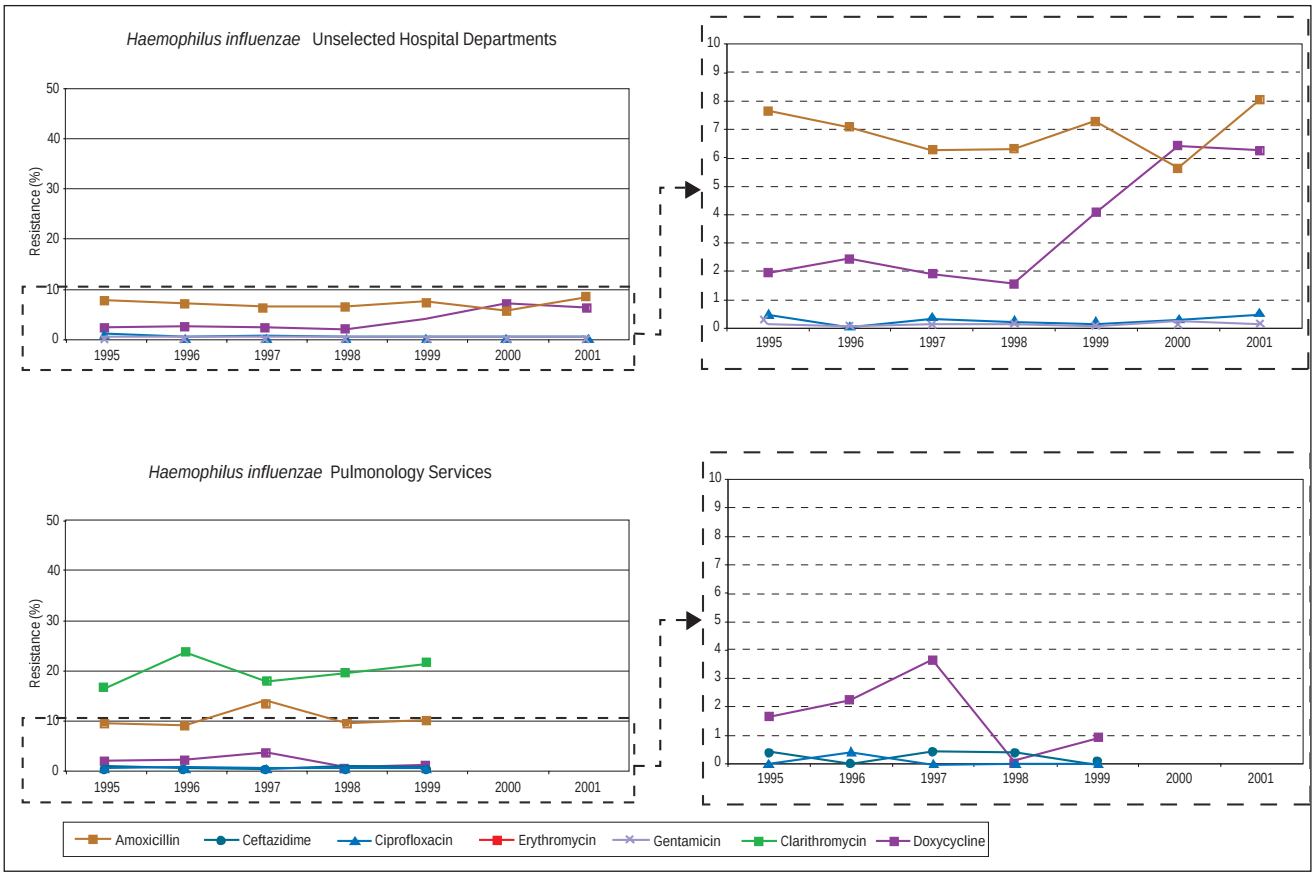


Figure 12. Trends in resistance to antibioticsto among *Haemophilus influenzae* derived from Unselected Hospital Departments and from the Pulmonology Services.

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) (table 1). 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 in-vitro activity of meropenem against selected pathogens from hospitalized 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. Stobbering 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	N. mening-itidis
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				6	
Co-amoxiclav			9		1,2,4	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	1,2,3	1		
Cefpirome					4				
Cefepime					4				
Aztreonam					2	2			
Imipenem	1,3,11	11	1,11	1,3,11	1,2,3	1,2,3	1		
Meropenem	1,11	11	1,11	1,11	1,4	1	1		
Vancomycin	1,7,10,11	7,10,11	1,11	1,7,10,11					
Teicoplanin	7,10,11	7,10,11	11	7,10,11					
Gentamicin	1,3		1	1,10	1,2,3,4	1,2,3	1		
Tobramycin					2,4	2			
Netilmicin					4				
Amikacin	3				2,3,4	2,3			
Ciprofloxacin	1,3,7,11	7,11	1,9,11	1,3,7,11	1,2,3	1,2,3	1,9		
Ofloxacin	7	7		7	4				
Trovafloxacin	7	7		7				6	
Sparfloxacin	7,11	7,11	9,11	7,11			9		
Pefloxacin	7	7		7					
Clindamycin	1,10,11	10	1	1,10					
Erythromycin	1,10,11	10,11	1,11	1,10,11					
Clarithromycin	10	10,11	9,11	10,11			9	6,12	
Tetracycline								6	
Minocycline				10					
Chlooramphenicol			5,8				8		5,8
Quinupristin/dalfopristin	10,11	10,11	11	10,11					
Rifampicin	10,11	11	11	11					5,8
Metronidazole								6,12,13	

Numbers correspond with referencenumbers listed above this crosstable .

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

7. Endtz HP, Mouton JW et al. Comparative in vitro activities of trovafloxacin (CP-99,219) against 445 gram-positive isolates from patients with endocarditis and those with other bloodstream infections. Antimicrob Ag Chemother (1997) 41: 1146-1149.

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

9. Hoogkamp-Korstanje JAA, Dirks-Go SIS, et al. Multicentre in-vitro evaluation of the susceptibility of Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis. J Antimicrob Chemother (1997) 39: 411-414.

10. Mouton JW, Endtz HP et al. In-vitro activity of quinupristin/dalfopristin compared with other widely used antibiotics against strains isolated from patients with endocarditis. J Antimicrob Chemother (1997) 39 Suppl A, 75-80.

11. Schouten MA, Hoogkamp-Korstanje. Comparative in-vitro activities of quinupristin-dalfopristin against gram-positive bloodstream isolates. J Antimicrob Chemother (1997) 40: 213-219.

12. Zwet AA van, Boer WA de et al. Prevalence of primary Helicobacter pylori resistance to metronidazole and clarithromycin in The Netherlands. Eur J Clin Microbiol Infect Dis (1996) 15: 861-864.

13. Wouden EJ van der, Zwet AA van et al. Rapid increase in the prevalence of metronidazole-resistant Helicobacter pylori in the Netherlands. Emerging Infectious Diseases (1997) 3 (3) 1-7.

14. Mouton JW, Jansz AR. The DUEL study: A multicenter in vitro evaluation of linezolid compared with other antibiotics in the Netherlands. Clin Microbiol Infect (2001) 7: 486-491.

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VI Strategic Initiatives in the Netherlands to Contain the Emergence and Spread of Resistance

In 1992 the Institute of Medicine of the United States of America published a landmark report regarding the emergence of infectious diseases and the threats these emerging diseases pose to the health in the United States (reference 11 in Appendix). The report recommended that the World Health Assembly take the lead in promoting the development and implementation of a comprehensive global infectious diseases surveillance system. Indeed, the World Health Organisation (WHO) responded and formulated their global strategy for the containment of emerging and re-emerging infectious diseases shortly thereafter. The major elements of the WHO strategy were:

1. the development and implementation of surveillance systems for microbial agents
2. promoting the surveillance of antimicrobial resistance among microbial pathogens
3. the upgrading of microbiology laboratories and microbiological expertise in many parts of the world
4. to foster applied research into the determinants of emerging infections, and
5. It emphasised prevention and control, rather than the treatment of diseases.

In 2001 the WHO recognised that special efforts should be directed at containing the rapid emergence of resistance against antimicrobial agents, and published their global strategy on the containment of antimicrobial resistance (ref. 12). This strategy largely concurs with the recommendations formulated at the same time by the European Union to address the menace of antimicrobial resistance (ref. 13). Awareness raised by these authorities and by the national and international professional societies in the biomedical sciences have had many countries, including the Netherlands, to review and amend their strategies regarding the management of infectious diseases. We here summarise the major strategic initiatives taken in the Netherlands to contain the emergence of infectious diseases and of the resistance to antimicrobial agents in particular. Some of these initiatives were taken and implemented long before international awareness was raised, other were implemented as a result of it.

Surveillance of antibiotic use

Monitoring the use of medicines including antibiotics in the Netherlands is performed by the Foundation for Pharmaceutical Statistics (www.sfk.nl), a government-sponsored non-profit organisation, which monitors the sales of pharmacies outside hospitals. These pharmacies cover approximately 90% of the Dutch population. The Geneesmiddelen en Hulpmiddelen Informatie Project (GIP) of the College for Healthcare Insurances (www.cvz.nl) monitors the use of medicines by 55% of the patients insured according to the non-profit Ziekenfonds system (i.e. 5.5 million inhabitants). Two third of the population are insured against healthcare costs via this system. For ***NethMap*** the SFK data on the use of antimicrobial agents outside hospitals were collated and analysed by SWAB. Data on the usage of antibiotics inside hospitals were collected, collated and analysed by SWAB (www.swab.nl). In the future SFK will collect hospital usage data of medicines as well.

Surveillance of pathogenic microbes and antibiotic resistance

Several institutions have started in the nineties to monitor antibiotic resistance in the Netherlands. Resistance in zoonotic pathogens has been monitored by the CIDC in Lelystad (www.cidc-lelystad.nl). Resistance among pathogens isolated in family practices outside hospitals is surveyed by the department of Medical Microbiology, University Hospital Maastricht, and their program has now been incorporated within the SWAB surveillance system. Resistance among pathogens from special hospital wards including intensive care units, urology and pulmonology services are surveyed by the department of Medical Microbiology, University Medical Center St.Radboud in Nijmegen since 1995 and their program has also been incorporated in the SWAB surveillance system. The National Institute for Public Health and the Environment (RIVM) initiated and coordinates the European Antibiotic Resistance Surveillance System (www.earss.rivm.nl). At present this system includes bloodisolates of a limited number of pathogens from the majority of European countries. The Infectious Diseases Information System (ISIS), run by RIVM, daily gathers (electronically and anonymously) all findings generated during routine microbiological examinations for patients from a limited but growing number of Dutch medical microbiological laboratories. These data are analysed, pooled and mined for relevant information. ISIS is, thus, a laboratory-based surveillance system for monitoring the incidence of a wide spectrum of infections. ISIS will replace a dedicated project for the surveillance of resistance among the most relevant pathogens isolated in eight regional public health laboratories, which has been running since 1989. Resistance of pathogens involved in meningitis is determined by the Netherlands Reference Laboratory for Bacterial Meningitis at Amsterdam (email: reflab@amc.uva.nl). Resistance of tuberculosis is continuously monitored by RIVM (email: d.van.soolingen@rivm.nl).

Importantly, the primary responsibility for the health of the public at large is, in the Netherlands, by law assigned to the

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municipal authorities. This responsibility has locally been translated into municipal public health departments. At the national level the Dutch Health Care Inspectorate (www.igz.nl) monitors the occurrence of several, law-specified, communicable diseases through mandatory reporting via the municipal health departments. To coordinate these public health efforts on a national level a coordinating body called LCI (www.infectieziekten.info) was started in 1995. Via the LCI the municipal public health authorities, the Health Inspectorate and the Netherlands Institute for Public Health and the Environment RIVM coordinate their efforts in case of outbreaks and epidemics. LCI also produces protocols and scenarios delineating actions to be taken for potential infectious disease threats to the public, including bioterrorist attacks. Surveillance data from these reportable communicable diseases are merged with the data gathered by ISIS to further complete the surveillance of infectious diseases in the Netherlands.

Upgrade microbiology laboratories and expertise

The quality of antimicrobial susceptibility and other tests in medical microbiological laboratories is secured by the work of the Netherlands Society for Medical Microbiology (www.nvmm.nl), which participates in the organisation for accreditation of healthcare laboratories (www.cckl.nl) and in the Foundation for Quality Improvement in Medical Microbiology (e-mail: skmm@lvf.nl), the latter of which aims to maintain and increase the quality of testing in medical microbiological laboratories by sending bacterial strains and critically analysing the testresults of these strains in the participating laboratories. The Dutch Committee on Guidelines for Susceptibility testing participates in the European Committee on Antimicrobial Susceptibility Testing for standardisation of testing of susceptibility to antimicrobial agents (www.escmid.org/sites/index_f.asp?par=2.4).

Foster applied research

Funding of research on infectious diseases and on antimicrobial agents has over the years been financed through several channels, including governmental, non-governmental non-profit organisations as well as commercial sources (pharmaceutical industry and venture capital). However, concerns about the level and depth of the infectious diseases expertise and research facilities available in the Netherlands has recently led the national organisation for medical research ZonMw (which is part of the Netherlands Organisation for Scientific Research NWO [www.nwo.nl]) to take the initiative in creating a separate funding program for infectious diseases and to establish a coordinating body to stimulate and integrate the infectious disease research efforts in this country. Also, the trainingprograms of scientists and practitioners in the field of medical microbiology and infectious diseases are expanding through directives from the government.

Emphasise prevention & control

The Foundation of the Working Party on Antibiotic Policy (SWAB) has from its beginnings in 1996 aimed to developed and published framework guidelines for the prudent use of antibiotic in hospitals (www.swab.nl). The Dutch College of general practitioners (NHG) has for many years been issuing guidelines for dealing with infectious diseases relevant in general practice outside hospitals, and intents to team up with SWAB to further those activities. Several of the NHG guidelines have been translated into English and put on their website (www.artsennet.nl/nhg). Professional organisations including those of the pulmonologists and paediatricians have published their own guidelines on antibiotic treatment of infections relevant at their respective fields. In addition, pharmacists and general practitioners all over the country participate in workshop-like sessions on the rational use of medicines including antibiotics. These local gatherings, called Farmacotherapeutisch Overleg (FTO), are supported by DGV, the Netherlands Institute for Appropriate Use of Medicines (www.medicijngebruik.nl). This organisation has published several booklets on the treatment of infections of the respiratory and urinary tract. The Institute for Quality in Healthcare CBO has issued and updated several guidelines for the treatment of meningitis and urinary tract infections (www.cbo.nl). To combat nosocomial infections including the prevention of the spread of resistant micro-organisms such as MRSA in health care institutions the Working Party on Infection Prevention WIP was created in 1982. Since then the WIP has been instrumental in guiding such efforts in Dutch Hospitals and nursing homes, primarily through the release of infection prevention guidelines and the provision of references and other types of guidance (www.wip.nl).

Clearly, many organisations and bodies have been put in place and are currently active in the Netherlands according to the strategies formulated by WHO a decade ago. The publication of ***NethMap*** by the SWAB in collaboration with the RIVM further adds to the strategic initiatives that have been taken to manage and control the emergence of infections and of antimicrobial resistance in this country. Surveillance of antimicrobial usage and antimicrobial resistance is key to our understanding of the resistance problems.

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VII 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 Insurances
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
ISIS	Infectious Diseases Information System
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	National Institute for Public Health and the Environment
SFK	Foundation for Pharmaceutical Statistics
SWAB	Foundation of the Dutch Working Party on Antibiotic Policy
WIP	Working Party on Infection Prevention
WHO	World Health Organisation

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Demographics and 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

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

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

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

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Surveillance methods and susceptibility testing

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 11 percent is delivered by general practitioners. This report includes data on the use of antibiotics provided by the Foundation for Pharmaceutical Statistics (SFK; http://www.sfk.nl) and analysed by the Working Party on Antibiotic Policy (SWAB; http://www.swab.nl). Sales data from approximately 90% of all community pharmacies are transferred monthly to SFK in an electronical 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 were 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 were excluded from the present analysis. Data from the Netherlands Institute for Health Services Research (NIVEL; http://www.nivel.nl), summarised in a report of the National Institute of Public health and the Environment (RIVM; http://www.rivm.nl), indicate that direct delivery of medicines by general practitioners reaches approximately 11% of the Dutch population, mainly in rural areas (ref. 1). This does not necessarily mean that the pharmacy sales of each of the different antibiotic groups may be multiplied by 100/89, because data derived from the Insurance Companies indicate that the proportion of direct delivery of antibiotics by general practitioners may be higher for conventional antibiotics such as sulfonamides and trimethoprim, but lower for newer ones such as macrolides and fluoroquinolones.

The present report includes data on the use of antibiotics for systemic use, group J01 of the Anatomical Therapeutic Chemical (ATC) classification system, between 1997-2001. The use of antibiotics in primary health care is expressed as:

The number of Defined Daily Doses (DDD) per 1,000 inhabitants and per day

The 2002 update of the ATC/DDD classification system was used to calculate the number of DDDs in this report.

Hospitals

Data on the use of antibiotics in Dutch hospitals between 1997 and 2000 were collected by the SWAB by means of a questionnaires distributed to all Dutch hospital pharmacists. The number of admissions and the number of days spent in the hospital (bed-days) were also registered in the questionnaires. The use of antibiotics for systemic use, group J01 of the ATC-system, is expressed as DDD/100 patient-days. The 2001 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 Prismant (http://www.prismant.nl), previously known as SIG. The percentage of covered patient-days was calculated for each year.

Surveillance of antimicrobial resistance

A] in the community

Respiratory tract pathogens

From October 2000 the Dutch influenza surveillance system was temporarily expanded into a case-control study on the etiology of acute respiratory infections among patients on roster with general practitioner offices (the ARI-EL study). General practitioners participating in the surveillance network of the Netherlands Institute for Health Services Research (NIVEL, head Prof dr J. van der Zee and network coordinator dr A.I. Bartelds) weekly sampled one case defined as a patient with complaints compatible with acute respiratory tract infection, and one control defined as a patient without such complaints. The microbiological samples were analysed for the presence of bacterial respiratory tract pathogens by culture in the Regional Laboratory of Public Health in Tilburg (head dr M.F. Peeters). The isolated bacteria were subsequently sent to the microbiological laboratory of the University Hospital Maastricht for quantitative susceptibility testing according to the guidelines of the surveillance study group of the SWAB. The analysis for the presence of viral respiratory tract pathogens was performed at the National Institute for Public Health and the Environment in Bilthoven (RIVM, dr B. Wilbrink).

Urinary pathogens

In indicated years of sampling 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. Dipslides inoculated with patient's urine were sent by mail to the Department for Medical Microbiology of the University Hospital Maastricht for culture and susceptibility testing of pathogens. The number of isolates ranged from 113 to 938, depending on the duration of the sampling period (several

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Table 1. Number of strains of major pathogenic species isolated from unselected hospital departments and tested for their susceptibility to the antibiotics indicated in the period 1995-2001.

species antibiotic	*E.coli*	*K.pneumoniae*	*P.aeruginosa*	*S.aureus*	*S.epidermidis*	*H.influenzae*	*S.pneumoniae*
Penicillin							21,694
Amoxicillin	76,418	14,929				27,908	
Co-amoxiclav	49,860	9,918					
Methicillin				62,661	19,214		
Cefotaxime						11,065	3,959
Ceftazidime	38,372	8,389	20,013				
Meropenem			3,903				
Gentamicin	55,837	11,266	16,615	43,922	13,548		
Erythromycin				59,877	17,887	22,688	18,521
Vancomycin				48,679	17,077		5,824
Doxycycline						10,597	5,541
Trimethoprim	36,834	6,471					
Ciprofloxacin	56,569	11,738	20,273	34,920	11,982	7,648	3,534
Nitrofurantoin	49,692	8,522					

months to more than one year) and the number of general practitioners participating in the network in that particular period.
A urine sample was considered positive if $\geq 10^5$ colony forming units (CFU) per ml of one species were found using the dipslide method. The micro-organisms were identified using standard bacteriological methods including the Analytic Profile Index (API 20E; API Biomerieux, France). The study was conducted in 1988, 1992, 1997, 2000 and 2001.

Susceptibility testing
The susceptibility of the strains was determined by broth microdilution with an inoculum size of 10^5 cfu/ml in Isosensitest broth (OXOID CM 473). The breakpoints for resistance used were those defined by the Dutch Committee on Guidelines for Susceptibility Testing. *Escherichia coli* ATCC 25922 was used as the reference strain.

B] 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 (see chapter on 'strategic initiatives'), partly on the basis of a longer standing collaborative agreement between the regional public health laboratory and the RIVM (see chapter on 'strategic initiatives'). Identification and susceptibility testing was routinely carried out in the regional public health laboratories. Identification and resistance data from a total of 243,000 unique, unrelated, strains were thus collected and collated from 1995-2001. The number of strains of each species tested for susceptibility to indicated antibiotics and for which the data were included in this surveillance report are given in table 1. *E.coli*, *K.pneumoniae* and *P.aeruginosa* were isolated from blood (6%), respiratory tract specimens (13%), wounds (17%), urine (49%) and other sites(15%). *S.aureus* strains were predominantly isolated from wounds and skin and soft tissue infection (65%), respiratory tract specimens (17%) and from bloodcultures (5%). *S.epidermidis* strains were primarily isolated from bloodcultures (50%), whereas *H.influenzae* and *S.pneumoniae* were predominantly from respiratory tract specimens.

Specific Wards
Unique, unrelated, consecutive strains isolated from various clinical materials of patients admitted to Intensive Care Units, from urine of patients admitted to Urology Services and from respiratory tract specimens of patients admitted to Pulmonology Services were yearly collected from January 1st until July 1st. A maximum of 100 isolates per ward were, thus, collected each year. The strains were identified at the local laboratory for clinical microbiology, stored at -20^0C and batchwise sent to a single laboratory (department of Medical Microbiology of the UMC St. Radboud, Nijmegen) for quantitative susceptibility testing. A total of 14,544 strains were, thus, collected in the period 1995-

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Table 2. Number of strains of pathogenic species isolated from patients admitted to specified hospital wards and tested for their susceptibility to antibiotics in the period 1995-2000.

species	Intensive Care Units	Urology Services	Pulmonology Services
E.coli	773	2.982	
K.pneumoniae	234	322	
P.aeruginosa	489	217	
S.aureus	241 (1995-1997)	106 (1995-1997)	
H.influenzae			1,256 (1995-1999)
S.pneumoniae			843 (1995-1999)

2000. The results of species identification and susceptibility testing of 6,974 strains (table 2) are presented in this report. *E.coli*, *K.pneumoniae* and *P.aeruginosa* isolated on Intensive Care Units originated from blood (23%), respiratory tract specimens (44%), wounds (20%) and from urine samples (13%).

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 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*, *K.pneumoniae*, *P.aeruginosa*, *S.aureus* and *S.epidermidis* represent the proportion of strains that were considered to be fully resistant. Resistance rates of *H.influenzae* and *S.pneumoniae* include strains that showed intermediate susceptibility (I+R, i.e. MIC> lower breakpoint).

The susceptibility of the strains from the specific wards was determined quantitatively, i.e. by MIC determinations, in one central laboratory by home-made broth microdilution assays using the recommendations of the NCCLS for *E.coli*, *K.pneumoniae* and *P.aeruginosa*. Resistance rates of these micro-organisms likewise represent the proportion of fully resistant strains. For *H.influenzae* and *S.pneumoniae* the guidelines of the CRG are used, thereby representing the proportion of strains that were considered to be fully resistant and those that showed intermediate susceptibility (I+R, i.e. MIC> lower breakpoint). *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Haemophilus influenzae* ATCC 49247 and *S.aureus* ATCC 25923 were used as control strains in the MIC tests performed in the central laboratory.

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

Data were statistically analysed using the Chi-square test for pair differences. Differences with a p value ≤ 0.05 were considered significant.

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