# NETHMAP 2010



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

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# NETHMAP
# 2010

## 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 Centre for Infectious Disease Control (CIb) at the National Institute for Public Health and the Environment (RIVM). SWAB is fully supported by a structural grant from the Ministry of Health, Welfare and Sports of the Netherlands. The information presented in NethMap is based on data from ongoing surveillance systems on the use of antimicrobial agents in human medicine and on the prevalence of resistance to relevant antimicrobial agents among medically important bacteria isolated from healthy individuals and patients in the community and from hospitalized patients. The document was produced on behalf of the SWAB by the Studio of the RIVM. NethMap can be ordered from the SWAB secretariat, c/o Academic Medical Centre, Dept. Infectious Diseases, Tropical Medicine and AIDS, F4-217, P.O. Box 22660, 1100 DD Amsterdam, the Netherlands, Tel. +31 20 566 60 99, Fax +31 20 697 22 86. NethMap is also available from the website of the SWAB: www.swab.nl. The suggested citation is: SWAB. NethMap 2010 – Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands.

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### Hospital usage

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*Centres contributing to the surveillance of resistance to antimicrobial agents*

| Province | Town | Name and type of centre | COM | IUP | ISIS | Men | Gon |
|---|---|---|---|---|---|---|---|
| Groningen | Delfzijl | Delfzicht Hospital | | | | 0 | |
| | Groningen | Academic Medical Centre | | | | 0 | 0 |
| | | Regional Laboratory for Public Health | | 0 | | 0 | 0 |
| | | Municipal Health Service Groningen | | | | | 0 |
| | Stadskanaal | Refaja Hospital | | | | 0 | |
| | Winschoten | St Lucas Hospital | | | | 0 | |
| | t Zandt | General practice | 0 | | | | |
| Friesland | Leeuwarden | Regional Laboratory for Public Health Izore | | 0 | 0 | 0 | 0 |
| | | Municipal Health Service Fryslan | | | | | 0 |
| Drente | Assen | General practice | 0 | | | | |
| | | Municipal Health Service Drenthe | | | | | 0 |
| | Emmen | Scheper Hospital | | | | 0 | |
| Overijssel | Deventer | Deventer Hospital | | | | | 0 |
| | | Regional Laboratory for Public Health | | | | 0 | |
| | Enschede | Regional Laboratory for Public Health | | 0 | 0 | 0 | 0 |
| | | Municipal Health Service Twente | | | | | 0 |
| | Hardenberg | Regional Laboratory for Public Health | | | | 0 | |
| | Zwolle | Isala Clinics | | | | | 0 |
| | | Hanze laboratory | | | | 0 | |
| | | Regional Laboratory for Public Health | | 0 | | | |
| Gelderland | Apeldoorn | Medical Laboraties ZCA | | | | 0 | |
| | Arnhem | Regional Laboratory for Public Health | | | 0 | 0 | 0 |
| | | Alysis Centre | | | | | 0 |
| | | Hulpverlening Gelderland Midden | | | | | 0 |
| | Barneveld | General practice | 0 | | | | |
| | Dieren | General practice | 0 | | | | |
| | Doetinchem | Slingeland Hospital | | | | 0 | |
| | Ede | Gelderse Vallei Hospital | | | | 0 | |
| | Harderwijk | St Jansdal Hospital | | | | 0 | |
| | Heerde | General practice | 0 | | | | |
| | Nijmegen | University Medical Centre St Radboud | | 0 | | 0 | 0 |
| | | Regional Laboratory for Public Health CWZ | | | 0 | 0 | 0 |
| | | Municipal Health Service Nijmegen | | | | | 0 |
| | Zelhem | General practice | 0 | | | | |
| Utrecht | Amersfoort | Meander Medical Centre | | | | 0 | 0 |
| | | General practice | 0 | | | | |
| | Bilthoven | National Institute for Public Health and the Environment | | | 0 | | |
| | Nieuwegein | Sint Antonius Hospital | | 0 | 0 | 0 | 0 |
| | Utrecht | Diakonessenhuis | | | | 0 | |
| | | General practice | 0 | | | | |
| | | Neth Institute for Health Services Research NIVEL | 0 | | | | |
| | | Mesos Medical centre | | | | 0 | |
| | | SALTRO | | | | | 0 |
| | | University Medical Centre | | | | 0 | 0 |
| | | Municipal Health Service Utrecht | | | | | 0 |
| | Zeist | Diakonessenhuis | | | | 0 | |
| Noord Holland | Alkmaar | General practice | 0 | | | | |
| | | Medical Centre Alkmaar | | | | 0 | 0 |
| | Amsterdam | Academic Medical Centre | | | | 0 | 0 |
| | | Academic Hospital VU | | | | 0 | 0 |
| | | General practice | 0 | | | | |
| | | Onze Lieve Vrouwe Gasthuis | | 0 | | 0 | 0 |
| | | Regional Laboratory for Public Health | | | | | 0 |
| | | Slotervaart Hospital | | | | 0 | |
| | | St Lucas Andreas Hospital | | | | 0 | |
| | | Municipal Health Service Amsterdam | | | | | 0 |
| | Baarn | Medical Centre I | | | | 0 | |
| | Haarlem | General practice | 0 | | | | |
| | | Regional Laboratory for Public Health | | 0 | 0 | | |
| | Hilversum | Central Bacteriological Laboratory | | | | 0 | |
| | Hoorn | Westfries Gasthuis | | | | 0 | |
| | Huizen | General practice | 0 | | | | |
| | Zaandam | Zaans Medical Centre | | | | 0 | 0 |



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*Table 1 Continued*

| Province | Town | Name and type of centre | COM | IUP | ISIS | Men | Gon |
|---|---|---|---|---|---|---|---|
| Zuid Holland | Capelle a/d IJssel | IJsselland Hospital | | | | 0 | |
| | Delft | SSDZ laboratories | | | | 0 | 0 |
| | 's-Gravenhage | Bronovo Hospital | | 0 | | 0 | |
| | | General practice | 0 | | | | |
| | | Leyenburg Hospital | | | | 0 | 0 |
| | | Regional Laboratory for Public Health | | | | 0 | |
| | | Rode Kruis / Juliana Children's Hospital | | | | 0 | |
| | | Medical Centre Haaglanden | | | | 0 | 0 |
| | | Municipal Health Service Den Haag | | | | | 0 |
| | Dordrecht | Regional Laboratory for Public Health | | | | 0 | 0 |
| | Gorkum | Regional Laboratory for Public Health | | | | 0 | |
| | Gouda | Groene Hart Hospital | | | | 0 | |
| | Leiden | Diakonessenhuis | | 0 | | 0 | |
| | | KML Laboratory | | | | 0 | |
| | | University Medical Centre | | | | | 0 |
| | Leiderdorp | Rijnland Hospital | | | | 0 | |
| | Rotterdam | General practice | 0 | | | | |
| | | Erasmus University Medical Centre | | | | 0 | 0 |
| | | Ikazia Hospital | | | | | 0 |
| | | Maasstadziekenhuis | | 0 | 0 | 0 | |
| | | Sophia Children's Hospital | | | | 0 | |
| | | St Franciscus Gasthuis | | | | 0 | |
| | | Municipal Health Service Rotterdam | | | | | 0 |
| | Schiedam | Vlietland Hospital | | | | 0 | |
| | Spijkenisse | Ruwaard vd Putten Hospital | | | 0 | 0 | 0 |
| | Voorhout | General practice | 0 | | | | |
| | Woerden | Zuwe Hofpoort Hospital | | | | 0 | |
| Noord Brabant | Bergen op Zoom | Lievensberg Hospital | | | | 0 | |
| | Breda | Amphia Hospital | | | | | 0 |
| | | Municipal Health Service West-Brabant | | | | | 0 |
| | Eindhoven | Municipal Health Service Eindhoven | | | | | 0 |
| | Helmond | Municipal Health Service Zuidoost Brabant | | | | | 0 |
| | 's Hertogenbosch | Jeroen Bosch Medical Centre | | | 0 | | 0 |
| | | Regional Laboratory for Public Health | | | | 0 | |
| | Ravenstein | General practice | 0 | | | | |
| | Roosendaal | Franciscus Hospital | | | | 0 | |
| | Rosmalen | General practice | 0 | | | | |
| | Tilburg | Regional Laboratory for Public Health | | 0 | 0 | 0 | 0 |
| | | Municipal Health Service Hart voor Brabant | | | | | 0 |
| | Uden | General practice | 0 | | | | |
| | Veldhoven | Laboratory for Medical Microbiology | | | | 0 | 0 |
| Limburg | Geleen | Municipal Health Service | 0 | | | | |
| | Heerlen | Regional Laboratory for Public Health | | | 0 | 0 | 0 |
| | | Atrium Medical Centre | | | | 0 | 0 |
| | | General practice | 0 | | | | |
| | | Nursing home Vivre location Klevarie | 0 | | | | |
| | | Nursing home De Zeven Bronnen | 0 | | | | |
| | | Academic Medical Centre | | 0 | | 0 | 0 |
| | | Municipal Health Service Zuid-Limburg | | | | | 0 |
| | | Laurentius Hospital | | | 0 | 0 | 0 |
| | Roermond | Maasland Hospital | | | | 0 | |
| | Sittard | VieCuri Medical Centre | | 0 | | 0 | 0 |
| | | Municipal Health Service Noord- en Midden Limburg | | | | | 0 |
| | | St Jansgasthuis | | | 0 | 0 | 0 |
| Zeeland | Goes | Regional Laboratory for Public Health | | 0 | 0 | 0 | 0 |
| | | Municipal Health Service Zeeland | | | | | 0 |
| | Middelburg | General practice | 0 | | | | |
| | Terneuzen | General practice | 0 | | | | |
| | | Regional Laboratory for Public Health | | | 0 | 0 | 0 |

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



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# Preface

This is NethMap 2010, the eight SWAB/RIVM report on the use of antimicrobial drugs and trends in antimicrobial resistance in the Netherlands in 2009 and previous years. NethMap is a cooperative effort by members of the Netherlands Society for Infectious Diseases (VIZ), the Netherlands Association of Hospital Pharmacists (NVZA), the Netherlands Society for Medical Microbiology (NVMM) and the Centre for Infectious Disease Control Netherlands (CIb) at the National Institute for Public Health and the Environment (RIVM). In 1996, the Dutch Working Party on Antibiotic Policy was created, better known as SWAB (Stichting Werkgroep Antibiotica Beleid). Its mission is to manage, limit and prevent the emergence of resistance to antimicrobial agents among medically important species of micro-organisms in the Netherlands, thereby contributing to the quality of care in the Netherlands. For this effort SWAB received in 2008 an award from prof Stuart Levy on behalf of the Alliance for the Prudent Use of Antibiotics (APUA) during the 48th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) held in Washington DC.
Because of the multidisciplinary composition of SWAB, this working group can be considered the Dutch equivalent of the Intersectoral Coordinating Mechanisms (ICM's), as recommended by the European Union (2001), to control emerging antimicrobial resistance and promote rational antibiotic use.
SWAB has started several major initiatives to achieve its goals. Among these are training programmes on rational prescribing of antimicrobial drugs, development of evidence-based prescription guidelines, implementation of tailor-made hospital guides for antibiotic prophylaxis and therapy and an integrated nationwide surveillance system for antibiotic use and resistance. CIb has set up an Infectious Disease Surveillance Information System on Antibiotic Resistance (ISIS-AR) in collaboration with the medical microbiological laboratories. These surveillance data form the basis of NethMap. The initiatives correspond well with the recommendations by the Netherlands Council of Health Research (2001). In line with these recommendations, SWAB is fully funded by a structural grant from the Ministry of Health, Welfare and Sport and CIb.

NethMap 2010 extends and updates the information of the annual reports since 2003. NethMap parallels the monitoring system of antimicrobial resistance and antibiotic usage in animals in the Netherlands, entitled MARAN – Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in the Netherlands, published annually by the Veterinary Antibiotic Usage and Resistance Surveillance Working Group VANTURES, see http://www.cvi.wur.nl. Recently, MARAN 2008 has been published. Jointly, NethMap and MARAN provide a comprehensive overview of antibiotic usage in the Netherlands in humans and in animal husbandry and therefore offer insight into the ecological pressure associated with emerging resistance.
The interaction between the human and animal areas of antibiotic use and resistance is explored in a working group started in 2003 by both Ministries of health, Welfare and Sport and of Agriculture, Nature and Food Quality. Both SWAB and VANTURES are represented in this interdepartmental working group in which the evolution of antibiotic use and resistance in the Netherlands is discussed on the basis of surveillance data as provided by SWAB and MARAN.
NethMap thus provides extensive and detailed insight in the Dutch state of medically important antimicrobial resistance, and compares well with the data of the European Antimicrobial Resistance Surveillance System (EARSS, see http://www.rivm.nl/earss/). EARSS collects resistance data of a limited number of invasive bacterial species for the majority of European countries, Israel and Turkey. EARSS has recently moved to the European Centre for Disease Prevention and Control (ECDC) and has been renamed EARS-net.
We believe NethMap continues to contribute to our knowledge and awareness regarding the use of antimicrobial drugs and the resistance problems which may arise. We thank all who have contributed to the surveillance efforts of SWAB, and express our sincere hope that they are willing to continue their important clinical and scientific support to SWAB.

The editors:
Prof dr John Degener
Dr Johan W. Mouton
Dr ir Mick N. Mulders



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# 1. Summary

NethMap is the annual report of SWAB about the use of antimicrobial agents and the prevalence of resistance to these agents among common human pathogens isolated in the Netherlands. Until 2009, this information was restricted to antibacterial agents and bacterial species. Besides these data on bacterial pathogens and antibacterial drugs, NethMap 2009 and 2010 contain data on use and resistance trends of antimycotic and antiviral drugs, the latter with focus on resistance in influenza virus.
The information provided in NethMap on antimicrobial drug use and trends in antimicrobial resistance is based on systematically collected and analysed data over a period from 1996 until now.

The overall use of antimicrobial agents in primary health care remained below 10 defined daily dosages (DDD) per 1000 inhabitants per day until 2005. In 2005, there was a slight increase in use, to 10.5 DDD/1000 inhabitant days, and since then there was a further increase to 11 DDD/1000 inhabitant days in 2008. This seems to have stabilised in 2009. The use in the Netherlands is still low in comparison to other European countries.
The distribution of antibiotic usage over the different classes of antibiotics varies per patient population. It is shown that 25% of the antibiotics used in general practice are tetracyclines, whereas these drugs are sporadically prescribed in hospitals. Nitrofurantoin use has been rising in recent years, most probably because of the increased resistance to trimethoprim in *Escherichia coli* causing urinary tract infections. This was reported in SWAB surveillance system and has resulted in subsequent changes in treatment guidelines. Consequently, a decrease is noticed in the use of trimethoprim and sulphonamide. Trimethoprim is nowadays a second choice antibiotic for treatment of urinary tract infections. NethMap 2010 reports a further substitution of amoxicillin by co-amoxiclav and an increase in macrolide and fluoroquinolone use. The background of some of these changes needs further study, since this is often not supported by evidence of less effectiveness of the current guidelines. Especially when considering the use of fluoroquinolones, particularly ciprofloxacine, more resistance is encountered, even in the general population. The use of antimicrobials against tuberculosis and other mycobacterial infections is in line with general principles. In the Netherlands resistance problems are limited in this field.

Between 2003 and 2008, the number of hospital admissions as well as the antibiotic use has increased with 22%. Total use and clinical activities are obviously running in parallel. From 2008 onwards, however, the total use decreased compared to the year before. Different trends within the given groups of antibiotics are recognisable when usage per bed day and usage per admission are compared. Observing a growing drug use during a constant number of occupied bed days and also a growing use with a growing number of hospital admissions, we can only conclude that the total use in individual patients is increasing and so does the antibiotic ecological pressure. In NethMap 2009 this was shown to happen for two classes of antibiotics: the aminoglycosides and fluoroquinolones. These are all antibiotics prescribed for serious infectious events. In NethMap 2010, however, a decrease was seen in all groups of antibiotics with the exception of the fluoroquinolones and the aminoglycosides. The origin of this remarkable shift in policy needs to be elucidated. Amoxicillin, co-amoxiclav, other penicillins and cephalosporins still account for almost half of all antibiotics used in Dutch hospitals.
The use of systemic antimycotic drugs in university medical centres is surpassing three times the use in general hospitals. This is a clear indication of the difference in patient populations between these two types of hospitals, the former harbouring a large group of severely immunocompromised patients.
NethMap 2010 shows a difference in the use of antiviral drugs between university hospitals and general hospitals, partly explained by the need for treatment and prophylaxis for opportunistic viral infections in transplant patients.

Like before, NethMap 2010 presents data on antimicrobial resistance in the community and in hospitals. The studies in the community focus on resistance of potential pathogens carried by healthy persons, resistance in isolates obtained from patients visiting general practitioners and resistance in bacterial species associated with public health related infections, *e.g.*, meningococci, gonococci and *Mycobacterium tuberculosis*.
Resistance in the community was studied in 489 strains of *Escherichia coli*, derived from 970 unselected uncomplicated urinary tract infections in general practice; the resistance rate for amoxicillin reached 34% (20% in 2000), for co-amoxiclav 12% (stable compared to 2004), for trimethoprim 19% (23% in 2004) and for nitrofurantoin 1% (stable). Also, a stable 3.5% of ciprofloxacin resistance is observed. ESBL-producing strains can sporadically be found in general practice nowadays, 5 strains (1%) in 2009; 3% of the *E. coli* strains were multiresistant to three classes of antibiotics, which will hamper the empiric choice of an effective oral drug by the general practitioner.

*Neisseria gonorrhoeae* resistance development is closely monitored in the so-called GRAS-project of the CIb/RIVM. *N. gonorrhoeae* has reached an ever



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increasing and alarmingly high level of resistance against ciprofloxacin of 52% in 2009 (46 % in 2008). This increase was mostly due to an increase among homosexual men, in whom the highest level of 60% was found. In 2009, the development of resistance against third generation cephalosporins is also observed. Incidental therapy failure of ceftriaxone has been reported.

According to the data collected by CIb/RIVM, resistance in *M. tuberculosis* strains appears to be constant. However, a slow rise in rifampicin-resistance is observed. The level of multiresistance in 2009 is 1.2%.

SWAB resistance surveillance data in specific patient populations are derived from the ISIS-AR system (Infectious Disease Surveillance Information System for Antibiotic Resistance), the inpatient SIRIN and the outpatient and community SERIN (Surveillance of Intra-/Extramural Resistance in the Netherlands) studies. In NethMap 2010, resistance data derived from these three initiatives are compared and discussed taking into account the different methods used to collect and to study these data obtained from different patient populations. Results are presented for *Escherichia coli, Klebsiella* species, *Enterobacter* species and *Proteus mirabilis*. Results for patients visiting the general practitioner, patients in hospital departments and patients in the intensive care are compared.
Most remarkable for *E. coli* is the continuing rise in ciprofloxacin resistance in hospitals to 12%. Increasing resistance was found in all study populations also for most other antibiotic classes. In this species multiresistance was not yet reported before 1998. This reached a peak value of 9% in 2008. ESBL-producing strains are a continuing threat from 2000 onwards (rates up to 6%), especially in intensive care units, where the carbapenem group and the toxic colistin are often the only remaining effective drugs to treat infections with such strains. Similar conclusions can be drawn for the *Klebsiella, Enterobacter* and *Proteus* strains studied. In these species carbapenem resistance is not found in the Netherlands, in contrast to other European countries. Increasing ceftazidime resistance, up to 9% in intensive care units, was found for *Pseudomonas aeruginosa*. The prevalence of carbapenem resistance is 3.0 % in *Pseudomonas* in intensive cares.

The results for *Staphylococcus aureus* were not much different from previous years. The proportion of methicillin resistant *S. aureus*, MRSA, strains remains less than 1.5% in unselected hospital departments. Vancomycin resistance in *S. aureus* is rarely encountered in the Netherlands. Vancomycin is still the rescue drug for resistant *S. aureus* infection. Livestock-associated MRSA isolates were approximately at the same level, 42%, as in 2008, 41%.

Data on pneumococci and *Haemophilus influenzae* were collected in hospitals. For the majority of these strains it can, by the nature of such public health related species, be suggested that these are community related rather than hospital acquired. Their resistance profiles may be considered a reflection of the situation in the general population.
Therefore it is of interest that in *H. influenzae* an increase of amoxicillin resistance to 15% as well as to co-amoxiclav (3%) was observed in unselected departments. In pulmonology services co-amoxiclav resistance reached a high of 17%. The increase is clearly not exclusively due to a rise in beta-lactamase producing strains, therefore indicating an increasing prevalence of so called Beta Lactamase Negative Amoxicillin Resistant (BLNAR) strains. Doxycycline is still a reasonable alternative choice to combat infections with BLNAR *H. influenzae*. In 2009, the rate of resistance against macrolides in pneumococci remained at a critical level of 10% and tetracycline resistance parallels this. Resistance to penicillin, the most important antibiotic prescribed for serious pneumococcal disease, remained at the low level of 1%, when intermediate resistant strains are included this was 3.6%.
In *Helicobacter pylori* increasing clarithromycin resistance is observed, which may be caused by a choice for clarithromycin as first treatment option for infection.

Studies in *Aspergillus* spp. indicate that resistance to azoles is increasing significantly. Susceptibility testing has been initiated only recently, but a large retrospective study at the UMC St Radboud, Nijmegen showed that azole resistance emerged in 2000. Since then, resistance increased slowly and is now over 5%. At the same time, the resistance mechanisms have been elucidated. It is expected that azole resistance will continue to rise in the near future. This will limit treatment option significantly.

Finally, data from surveillance studies of influenza viruses in the Netherlands are indicating treatment limitations due to emerging resistance against anti-influenza specific drugs such as oseltamivir.

Furthermore, NethMap 2010 provides an overview of more than 40 published studies on antibiotic resistance performed in the Netherlands since 1990.

We can conclude that, in general and on the basis of these and many more data presented in NethMap 2010, we can not be too optimistic about the situation of the emergence of antibiotic resistance in the Netherlands, while at the same time we are still better off than many countries surrounding the Netherlands, according to data of ISIS-AR (www.isis-web.nl) and those of the European Antimicrobial Resistance Surveillance System (EARSS).



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# 2. Samenvatting

NethMap is het jaarlijkse rapport van de SWAB over het gebruik van antimicrobiële middelen en resistentie in de meest voorkomende, voor de mens pathogene, micro-organismen in Nederland. Tot 2009 beperkte deze informatie zich tot antibiotica en verschillende voor de geneeskunde relevante bacteriesoorten. In NethMap 2009 en in de nu voor u liggende NethMap 2010 is deze informatie aangevuld met trends in het gebruik van middelen tegen diepe schimmelinfecties, antivirale middelen (bij influenzavirussen) en resistentie bij schimmels.
De data in NethMap zijn gebaseerd op sinds 1996 systematisch verzamelde en bewerkte gegevens over antimicrobiële middelen en de trends in resistentie daartegen.

Het gebruik van antibiotica in de Nederlandse eerstelijns gezondheidszorg is tot 2005 steeds onder de 10 standaard dagdoseringen (DDDs) per 1000 inwoners per dag gebleven. In 2005 was het gebruik iets hoger, 10,5 DDD/1000 inwoner-dagen, en het is sindsdien licht verder gestegen tot 11 DDD/1000 inwoner-dagen in 2008. In 2009 lijkt er een stabilisatie tot stand te zijn gekomen. Het antibioticagebruik in Nederland is nog steeds laag vergeleken met andere landen in Europa.
De verdeling van het gebruik van antibiotica bij de verschillende patiëntpopulaties is duidelijk heel verschillend. Zo is te zien dat tetracyclinen 25 % uitmaken van het gebruik buiten het ziekenhuis, terwijl deze middelen intramuraal slechts zelden worden toegepast. Het gebruik van nitrofurantoïne was al langere tijd aan het stijgen. Waarschijnlijk kwam dit door de toegenomen resistentie tegen trimethoprim van *E. coli* bij urineweginfecties en, als reactie daarop en mede ten gevolge van de resultaten van de SWAB surveillance, de aanpassingen in de richtlijnen voor huisartsen. We zien dan ook een gelijktijdige daling van het trimethoprim en sulfonamide gebruik optreden. Trimethoprim is nu een tweede keus middel geworden bij de behandeling van ongecompliceerde urineweginfecties.
Wat ook in 2009 weer opvalt, is de toenemende vervanging van amoxicilline door de combinatie van amoxicilline met de beta-lactamase remmer clavulaanzuur (co-amoxiclav).
Ook zien we een verder toenemend gebruik van macroliden en fluorochinolonen.
Het toenemende gebruik van co-amoxiclav en fluoro-chinolonen dient onderbouwd te worden, omdat gegevens over een grotere effectiviteit van deze middelen in de huisartspopulatie ontbreken. Gelet op de verder toenemende resistentie voor fluorochinolonen, en meer in het bijzonder ciprofloxacine, is er sprake van een zorg-wekkende ontwikkeling, ook in de algemene bevolking.

Het gebruik van middelen tegen tuberculose en tegen infecties veroorzaakt door andere mycobacteriën is in overeenstemming met de specialistische richtlijnen. Resistentie tegen deze middelen komt in Nederland beperkt voor.

Vanaf 2003 is zowel het aantal ziekenhuisopnames als het antibioticagebruik in DDD's gestegen met 22%. Het totale gebruik en de klinische activiteiten houden klaarblijkelijk gelijke pas. Echter, vanaf 2008 nam het totale gebruik af in vergelijking tot het voorgaande jaar. Tussen de verschillende groepen antibiotica zijn daarentegen verschillende trends zichtbaar als gebruik per opname en gebruik per beddag in ogenschouw worden genomen. Zien we bij een gelijk blijvend aantal beddagen een toename van het aantal opnames en voor beide parameters een toenemend gebruik dan is er sprake van een duidelijke stijging van de expositie aan antibiotica per patiënt in het ziekenhuis. In NethMap 2010 zien we deze ontwikkeling inderdaad gebeuren voor de chinolonen en de aminoglycosiden. Deze twee groepen van antibiotica nemen een belangrijke plaats in bij de behandeling van ernstige ziekenhuisinfecties. Kennelijk vindt er een verandering plaats in voorschrijfbeleid. Het is belangrijk te achterhalen wat hiervan de oorzaak kan zijn. Voor andere groepen antibiotica zien we juist een daling in het gebruik.
Bijna de helft van het antibioticagebruik in ziekenhuizen bestaat uit amoxicilline, al of niet in combinatie met de beta-lactamaseremmer clavulaanzuur, en andere middelen uit de penicillinengroep.
Het gebruik van systemische antimycotica ligt in universitaire centra tot 3 maal hoger dan in andere ziekenhuizen, wat het verschil in patiëntenpopulaties weergeeft. In universitaire centra worden meer oncologie en transplantatiepatiënten behandeld die extra vatbaar zijn voor infecties.

NethMap 2010 toont de verschillen in gebruik van antivirale middelen tussen universitaire centra en andere ziekenhuizen. Deze zijn opvallend. Ook dit is een reflectie van de verschillende patiëntenpopulaties in ziekenhuizen, waarbij het met name gaat om de noodzaak voor behandeling en profylaxe van opportunistische virale infecties bij transplantatiepatiënten.
Zoals voorheen presenteert NethMap ook nu gegevens over bacteriële resistentie in de bevolking en in ziekenhuizen. Het onderzoek bij de bevolking richt zich op het dragerschap van resistente, potentieel pathogene bacteriesoorten bij gezonde personen, resistente bacteriën gevonden in materialen afkomstig van patiënten die de huisarts bezoeken en resistentie in bacteriesoorten die een bedreiging vormen voor de publieke gezondheid zoals mycobacteriën (tuberculose), meningokokken en gonokokken.
Bij 489 stammen van *Escherichia coli*, verzameld uit



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970 urinemonsters van ongeselecteerde patiënten met ongecompliceerde urineweginfecties in huisartspraktijken werden in 2009 de volgende resistentiepercentages gevonden voor: amoxicilline 34% (20% in 2000), co-amoxiclav 12% (stabiel sinds 2004), trimethoprim 19% (23% in 2004) en nitrofurantoine 1% (stabiel). Voorts werd voor ciprofloxacine een stabiele 3,5% resistentie gevonden. ESBL-producerende stammen werden incidenteel waargenomen, 5 stammen (1%) in 2009. Van de *E. coli* stammen vertoonden 3% multiresistentie tegen 3 groepen antibiotica waardoor de empirische keuze van het juiste middel door de huisarts ernstig wordt belemmerd.

In het zogenaamde GRAS project van het CIb/RIVM wordt de resistentieontwikkeling van gonokokken nauwlettend in de gaten gehouden. De resistentie bij *Neisseria gonorrhoeae* begeeft zich steeds verder op een verontrustend hoog niveau. Ciprofloxacine heeft in 2009 een resistentie percentage van 52% (46% in 2008) bereikt. Deze stijging zien we in het bijzonder bij homoseksuele mannen, bij wie 60% van de gonokokken resistent is bevonden. Tegen derde generatie cefalosporinen wordt nu ook resistentie gevonden. Inmiddels is casuïstiek gepubliceerd van therapiefalen met ceftriaxon.

Resistentie van *Mycobacterium tuberculosis* stammen blijkt zich op hetzelfde niveau te handhaven als in vorige jaren op basis van de surveillance data door het CIb/RIVM verzameld. Er is een lichte stijging van rifampicine resistentie waarneembaar. Multiresistentie wordt slechts in 1,2% van de gevonden isolaten.

De SWAB surveillance gegevens van specifieke patiëntenpopulaties worden ontleend aan het ISIS-AR (Infectieziekten Surveillance Informatie Systeem – Antibiotica Resistentie), de SERIN en de SIRIN (Surveillance van Extra-/Intramurale Resistentie in Nederland) projecten. In NethMap 2010 worden de resistentie gegevens, die door deze drie initiatieven zijn verkregen, met elkaar vergeleken en besproken met inachtneming van de verschillende methodes die zijn toegepast om de data te kunnen verzamelen. Data worden gepresenteerd voor o.a. *Escherichia coli, Klebsiella* soorten en *Proteus mirabilis*. De resultaten van deze resistentiemetingen van isolaten die zijn gevonden bij patiënten uit de huisartsenpopulatie, uit algemene en specifieke afdelingen (urologie, intensive care, longafdeling) van ziekenhuizen worden met elkaar vergeleken. Bij *E. coli* is de voordurende stijging van ciprofloxacine resistentie in ziekenhuizen opmerkelijk (12%). In alle studiepopulaties wordt bij *E. coli* een stijging van de resistentie tegen vrijwel alle klassen van antibiotica gevonden. In deze soort werd vóór 1998 geen multiresistentie gerapporteerd. In 2008 werd een niveau van 9% multiresistentie waargenomen. ESBL-producerende stammen vormen sinds 2000 een bedreiging en percentages die nu oplopen naar 6% worden in intensive care units gevonden. Reserve antibiotica uit de carbapenem groep en het toxische colistine zijn nu de enige optie wanneer infecties met deze stammen moeten worden bestreden. Ongeveer hetzelfde kan worden gezegd voor *Klebsiella-, Enterobacter-* en *Proteus* soorten, die eveneens het ESBL resistentiemechanisme kunnen herbergen.
Resistentie tegen carbapenem wordt bij deze soorten in NethMap 2010 nog niet gerapporteerd. In een aantal Europese landen vormt dit inmiddels een ernstig probleem en met import moet rekening worden gehouden.
De resistentie tegen het derde generatie cefalosporine ceftazidime bereikte 9% bij *Pseudomonas aeruginosa* op intensive cares. Inmiddels wordt bij *Pseudomonas* op intensive cares 3,0% carbapenem resistentie gevonden.

*Staphylococcus aureus* gedraagde zich weinig anders dan in voorgaande jaren. De proportie Meticilline-resistente *S. aureus* stammen (MRSA) is minder dan 1,5% op ongeselecteerde ziekenhuisafdelingen. Vancomycine resistentie is uiterst zeldzaam. Vancomycine vormt het ultieme reservemiddel bij MRSA infecties. MRSA stammen die geassocieerd zijn met contact met vee (varkens, mestkalveren) vormen in 2009 42% van de isolaten.

In de ziekenhuizen zijn gegevens verzameld van pneumokokken en *Haemophilus influenzae*. Deze bacteriesoorten zullen in het overgrote deel community-acquired zijn en hun resistentieprofielen zullen daarom waarschijnlijk ook een redelijke afspiegeling vormen van die van stammen buiten het ziekenhuis. Opmerkelijk is de toename van resistentie bij *Haemophilus* tegen zowel amoxicilline (15%) als amoxicilline met clavulaanzuur (3%) op ongeselecteerde afdelingen. Op longafdelingen bereikte de resistentie tegen co-amoxiclav een niveau van 17%. Dit is een aanwijzing voor de verspreiding van zogenaamde Beta-Lactamase Negatieve Amoxicilline Resistente (BLNAR) stammen. Doxycycline is nog een redelijk alternatief bij dit type resistente *H. influenzae* infecties.. Resistentie tegen derde generatie cefalosporinen was zeldzaam (<1%).
Bij pneumokokken bleef de macrolide resistentie op 10% en is ongeveer gelijk aan de resistentie tegen tetracyclinen. Resistentie tegen penicilline, het belangrijkste middel tegen ernstige pneumokokkeninfecties, blijft in Nederland op een uniek laag niveau van 1%. Worden matig gevoelige (I) stammen meegerekend dan wordt het percentage 3,6% (I+R).
Bij *Helicobacter pylori* wordt een toename in resistentie waargenomen, mogelijk veroorzaakt door de keuze



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van clarithromycine als eerste behandeloptie voor een infectie.

Diepe schimmelinfecties met Aspergillus soorten vormen een ernstige bedreiging voor immuundeficiënte patiënten in het ziekenhuis. Azolen zijn belangrijke middelen om deze infecties te bestrijden. NethMap 2010 presenteert voor het eerst resistentieontwikkeling tegen azolen. Een grote retrospectieve studie in het UMC St Radboud, Nijmegen laat zien dat er een aanzienlijke resistentieontwikkeling is sinds 2000 tot 5%. Het mechanisme hierachter is totnogtoe onopgehelderd. Verwacht wordt dat deze ontwikkeling zich voortzet, waardoor de behandelopties voor dit type levensbedreigende infecties aanzienlijk worden beperkt.

Tenslotte geven de resultaten van surveillance studies naar influenzavirus in Nederland aan dat resistentie tegen antivirale middelen zoals oseltamivir stijgt.

NethMap 2010 biedt voorts een overzicht van de belangrijkste in Nederland bewerkte wetenschappelijke publicaties op het gebied van resistentieontwikkeling, meer dan 40 studies sinds 1990.
Helaas kan NethMap ook nu geen optimistisch beeld geven van de zich ontwikkelende resistentieproblematiek in Nederland, al is de situatie in vergelijking met vele andere ons omringende landen nog vrij gunstig. Zie voor deze vergelijking de websites van ISIS-AR (www.isis-web.nl) en van het European Antimicrobial Resistance Surveillance System (EARSS).



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# 3. Use of antimicrobials

This part of the report considers the use of antimicrobial agents in human medicine only. Data on the use of such agents in animal husbandry and veterinary medicine are reported elsewhere (1).
Human consumption is presented in two parts. One part describes the prescription and use of antibiotics in the community, also termed "Primary Health Care". About 85% of antibiotic use in primary health care is prescribed by general practitioners (2). The second part presents surveillance data on total hospital consumption of antimicrobial agents in acute care hospitals in the Netherlands. Details on the structural acquisition and analysis of these consumption data are presented in the Materials and Methods.

## 3.1 Primary health care

### 3.1.1 Use of antibiotics

From 1999-2004, the total use of antibiotics was 10 DDD/1000 inhabitant-days (table 1). From 2005 to 2008, the use gradually increased to 11 DDD/1000 inhabitant-days. In 2009, the use of antibiotics remained stable, compared to 2008. The distribution of antibiotics by class in 2009 is presented in figure 1. Tetracyclines (mainly doxycycline) represented 24% of total antibiotic use in primary health care. Other frequently used antibiotics were penicillins with extended spectrum (mainly amoxicillin), combinations of penicillins with beta-lactamase inhibitors (essentially co-amoxiclav) and macrolides, each representing 17%, 16% and 13% of the total use respectively.
Over the past 5 years, the use of amoxicillin remained stable at about 1.9 DDD/1000 inhabitant-days, while the use of co-amoxiclav further increased to 1.7 DDD/1000 inhabitant-days in 2009 (table 1 and figure 2).
The use of macrolides remained stable at 1.3 DDD/1000 inhabitant-days in 2009 (table 1). The use of subgroups of macrolides is presented in figure 3. Clarithromycin is still the most commonly used macrolide. The distribution of the use of the three macrolides remained stable in the past three years with clarithromycin at 0.7 DDD/1000 inhabitant-days, azithromycin at 0.5 DDD/1000 inhabitant-days and erythromycin at 0.1 DDD/1000 inhabitant-days.
The use of ciprofloxacin and levofloxacin remained stable at 0.48 and 0.06 DDD/1000 inhabitant-days respectively, while the use of ofloxacin and norfloxacin decreased slightly to 0.06 and 0.22 DDD/1000

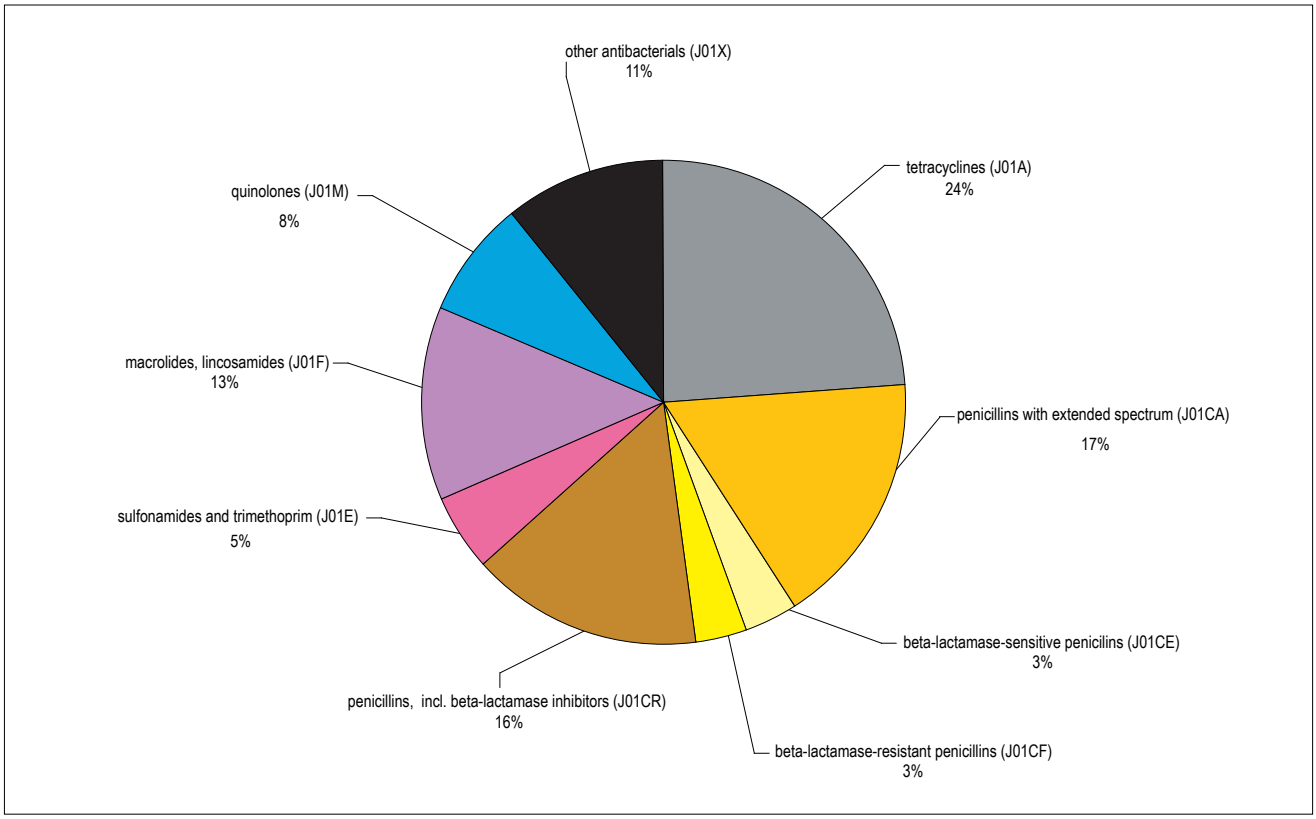



Figure 1. Distribution of the use of antibiotics for systemic use (J01) in primary health care, 2009 (SFK).



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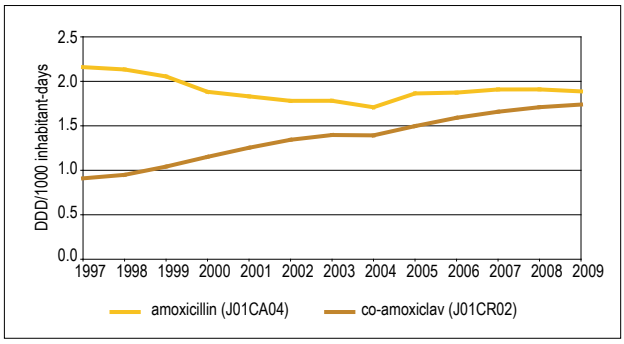



Figure 2. Use of macrolides for systemic use in primary health care, 1997-2009 (SFK).

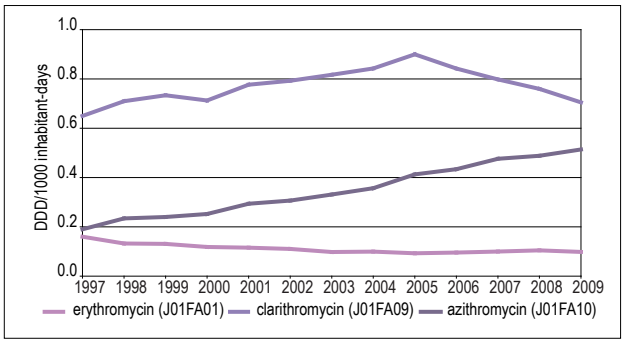



Figure 3. Use of quinolones for systemic use in primary health care, 1997-2009 (SFK).

inhabitant-days respectively (table 1 and figure 4). The use of moxifloxacin decreased in 2008 and it remained at the same level in 2009 with 0.04 DDD/1000 inhabitant-days.
The use of nitrofurantoin is still increasing to 1.17 DDD/1000 inhabitant-days in 2009, compared to 1.13 DDD/1000 inhabitant-days in 2008. The use of sulfonamides and trimethoprim (J01 EA and EE combined) remained stable in the past three years (table 1).

### 3.1.2 Use of antimycobacterials

Between 1998 and 2009 the use of antimycobacterials in primary health care remained relatively constant (table 2). Isoniazid is the most prescribed antimycobacterial followed by rifampicin. The use of ethambutol equals the use of pyrazinamide.

### 3.1.3 Use of antibiotics and chemotherapeutics for dermatological use

The use of fusidic acid increased from 1.31 DDD/1000 inhabitant-days in 1998 to 2.46 in 2007 and remained stable thereafter (Table 3 and Figure 5). The use of silver sulfadiazine decreased slightly. Since 2000, no use of topical acyclovir was registered. The use of metronidazole increased from 0.38 in 1998 to 0.75 DDD/1000 inhabitant-days in 2007 and remained stable thereafter.

### 3.1.4 Discussion

The antibiotic consumption in primary health care remained constant at 10 DDD/1000 inhabitant-days until 2004. From 2005 to 2008, the consumption gradually increased to 11 DDD/1000 inhabitant-days. In 2009,

*Table 1. 11-years data on the use of antibiotics for systemic use (J01) in primary care (DDD/1000 inhabitant-days), 1999-2009 (Source: SFK).*

| ATC Group* | Therapeutic group | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| J01AA | Tetracyclines | 2.49 | 2.48 | 2.40 | 2.34 | 2.24 | 2.24 | 2.41 | 2.37 | 2.57 | 2.66 | 2.67 |
| J01CA | Penicillins with extended spectrum | 2.05 | 1.88 | 1.83 | 1.78 | 1.78 | 1.71 | 1.86 | 1.87 | 1.91 | 1.91 | 1.89 |
| J01CE | Beta-lactamase sensitive penicillins | 0.52 | 0.52 | 0.49 | 0.46 | 0.44 | 0.43 | 0.44 | 0.50 | 0.46 | 0.42 | 0.39 |
| J01CF | Beta-lactamase resistant penicillins | 0.23 | 0.24 | 0.25 | 0.25 | 0.27 | 0.28 | 0.29 | 0.31 | 0.32 | 0.36 | 0.38 |
| J01CR | Penicillins + beta-lactamase-inhibitors | 1.04 | 1.15 | 1.25 | 1.34 | 1.40 | 1.39 | 1.50 | 1.59 | 1.66 | 1.71 | 1.74 |
| J01D | Cephalosporins | 0.10 | 0.08 | 0.07 | 0.07 | 0.06 | 0.05 | 0.05 | 0.04 | 0.05 | 0.04 | 0.04 |
| J01EA | Trimethoprim and derivatives | 0.30 | 0.28 | 0.28 | 0.27 | 0.27 | 0.26 | 0.25 | 0.23 | 0.22 | 0.21 | 0.21 |
| J01EC | Intermediate-acting sulphonamides | 0.00 | 0.00 | 0.00 | 0.01 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| J01EE | Sulphonamides + trimethoprim | 0.46 | 0.43 | 0.42 | 0.40 | 0.40 | 0.39 | 0.38 | 0.37 | 0.36 | 0.36 | 0.35 |
| J01FA | Macrolides | 1.17 | 1.14 | 1.23 | 1.24 | 1.27 | 1.32 | 1.42 | 1.39 | 1.39 | 1.36 | 1.33 |
| J01FF | Lincosamides | 0.04 | 0.04 | 0.05 | 0.06 | 0.06 | 0.07 | 0.08 | 0.09 | 0.10 | 0.11 | 0.12 |
| J01GB | Aminoglycosides | 0.00 | 0.00 | 0.01 | 0.01 | 0.02 | 0.02 | 0.02 | 0.03 | 0.03 | 0.03 | 0.03 |
| J01MA | Fluoroquinolones | 0.85 | 0.80 | 0.80 | 0.78 | 0.79 | 0.83 | 0.84 | 0.87 | 0.91 | 0.89 | 0.86 |
| J01MB | Other quinolones | 0.04 | 0.04 | 0.04 | 0.03 | 0.03 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.01 |
| J01XB | Polymyxins | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.00 | 0.00 | 0.00 | 0.00 |
| J01XE | Nitrofuran derivatives | 0.64 | 0.68 | 0.72 | 0.74 | 0.78 | 0.81 | 0.90 | 1.00 | 1.07 | 1.13 | 1.17 |
| J01XX05 | Methenamine | 0.06 | 0.06 | 0.06 | 0.04 | 0.03 | 0.02 | 0.02 | 0.03 | 0.03 | 0.02 | 0.03 |
| J01 | Antibiotics for systemic use (total) | 10.02 | 9.86 | 9.92 | 9.83 | 9.86 | 9.87 | 10.51 | 10.73 | 11.10 | 11.24 | 11.21 |

* from the 2008 edition of the Anatomical Therapeutic Chemical (ATC) classification system



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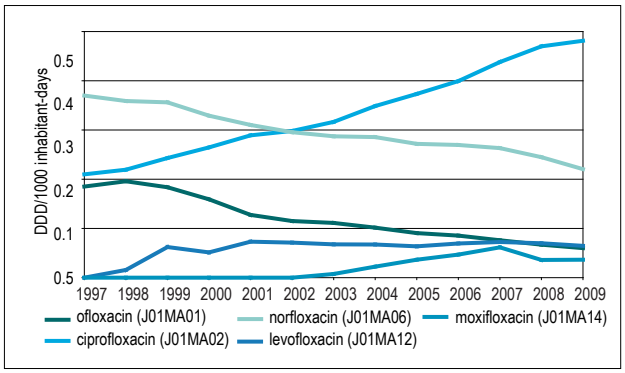



Figure 4. Use of quinolones for systemic use in primary health care, 1997-2009 (SFK).

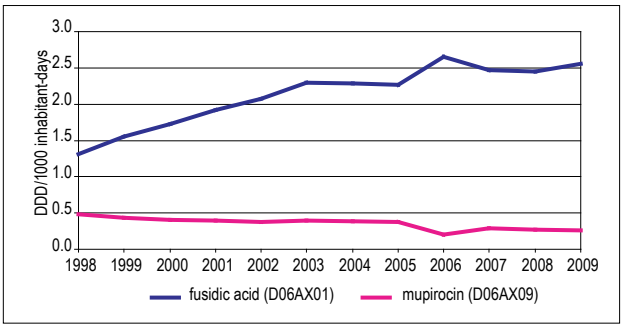



Figure 5. Use of fusidic acid and mupirocin in primary health care, 1998-2009 (SWAB).

the consumption remained stable compared to the use in 2008, at 11.2 DDD/1000 inhabitant-days. The use of antibiotics is still low if compared with that in other European countries (3).

The use of nitrofurantoin is still increasing; this may be explained by the national guidelines of the Dutch College of General Practitioners (NHG) (4) that have been changed in 2005 with regards to the empiric therapy of urinary tract infections. Trimethoprim was replaced then by nitrofurantoin as the drug of first choice (5 days treatment) because of lower resistance levels to nitrofurantoin in the community. Trimethoprim is ranked nowadays as a second choice antibiotic for treatment of urinary tract infection.

Moreover, subtle shifts in the patterns of use within the various classes of antibiotics were observed. The increased use of ciprofloxacin seemed to be offset by a decrease of ofloxacin and norfloxacin use. Since its market introduction in 2002, the use of moxifloxacin increased to 0.06 DDD/1000 inhabitant-days in 2007. After warnings about possible serious adverse side effects while using moxifloxacin, issued by the marketing authority in 2008, the use declined to 0.04 DDD/1000 inhabitant-days and remained stable at this level in 2009. Also within the class of the macrolides we saw a shift from erythromycin to the newer macrolides like clarithromycin and azithromycin. The use of azithromycin further increased in 2009, which may be due to its increasing use as an anti-inflammatory drug, e.g., for patients with cystic fibrosis. These trends may be relevant in the face of growing rates of resistance among common pathogens and therewith the rate of treatment failures.

*Table 2. 11-years data on antimycobacterial drugs in primary care (DDD/1000 inhabitant-days), 1998-2009 (Source: SFK).*

| ATC Group* | Antimycobacterials | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| J04AB02 | Rifampicin | 0.06 | 0.06 | 0.06 | 0.06 | 0.05 | 0.05 | 0.05 | 0.05 | 0.06 | 0.06 | 0.06 |
| J04AC01 | Isoniazid | 0.12 | 0.10 | 0.10 | 0.10 | 0.09 | 0.09 | 0.09 | 0.09 | 0.09 | 0.09 | 0.08 |
| J04AK01 | Pyrazinamide | 0.03 | 0.03 | 0.03 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.01 | 0.02 |
| J04AK02 | Ethambutol | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 |
| J04AM02 | Rifampicin and isoniazid | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 |
| J04BA02 | Dapson | 0.10 | 0.09 | 0.08 | 0.08 | 0.09 | 0.09 | 0.09 | 0.09 | 0.09 | 0.09 | 0.08 |

* from the 2008 edition of the Anatomical Therapeutic Chemical (ATC) classification system

*Table 3. 11-years data on the use of antimncrobials and chemotherapeutics for dermatological use in primary care (DDD/1000 inhabitant-days), 1998-2009 (Source: SFK).*

| ATC Group* | Antibiotics and chemotherapeutics | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| D06AA04 | Tetracycline | 0.04 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.04 | 0.03 | 0.03 | 0.03 |
| D06AX01 | Fusidic acid | 1.55 | 1.72 | 1.91 | 2.08 | 2.29 | 2.29 | 2.26 | 2.65 | 2.46 | 2.45 | 2.55 |
| D06AX09 | Mupirocin | 0.43 | 0.40 | 0.39 | 0.38 | 0.40 | 0.38 | 0.37 | 0.20 | 0.29 | 0.27 | 0.26 |
| D06BA01 | Silver sulfadiazine | 1.32 | 1.25 | 1.25 | 1.23 | 1.27 | 1.17 | 1.11 | 1.15 | 1.15 | 1.17 | 1.18 |
| D06BB03 | Acyclovir | 0.14 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| D06BB04 | Podophyllotoxin | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 |
| D06BX01 | Metronidazole | 0.44 | 0.50 | 0.56 | 0.60 | 0.61 | 0.64 | 0.67 | 0.68 | 0.75 | 0.78 | 0.80 |

* from the 2008 edition of the Anatomical Therapeutic Chemical (ATC) classification system



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The relative use of the antimycobacterials seems to be in line with the general principles of treatment and prophylaxis of tuberculosis. The constant use of these drugs over the years is suggestive for limited resistance problems over the past years.
To better understand the topical use of fusidic acid and mupirocin, an in depth analysis of indications is warranted. This is unfortunate, as mupiricin in particular is used as a first line agent in MRSA eradication and is important in the search-and-destroy strategy in the Netherlands. Since topical acyclovir is nowadays an over the counter drug, no use is registered by the community pharmacies anymore.
Increased resistance due to increased use may become a problem in the near future.

## 3.2 Hospitals

### 3.2.1 Hospital use of antibiotics

Data on antibiotic use are expressed in DDD per 100 patient-days as well as in DDD per 100 admissions, because trends over time in both units of measurement do not always correlate (tables 4 and 5).
In 2008, the total systemic use of antibiotics in our cohort of hospitals decreased to 58.1 DDD per 100 patient-days (-4.2% compared to 2007). The number of DDD per 100 admissions decreased by 10.5% from 335 DDD per 100 admissions in 2007 to 300 DDD per 100 admissions in 2008 (tables 4 and 5). This decrease was observed for all groups of antibiotics, except for the fluoroquinolones and the aminoglycosides. The distribution of antibiotics by class in 2008 is presented in figure 6. The relative use of different subclasses of antibiotics remained constant over the past years (table 4).
The use of fluoroquinolones increased from 7.6 DDD per 100 patient-days to 9.6 DDD per 100 patient-days, and from 41.9 to 49.8 DDD per 100 admissions. This increase was exclusively due to the steep increase in use of ciprofloxacin from 5.3 to 8.6 DDD per 100 patient-days (figure 7).
The use of aminoglycosides increased from 2.5 DDD per 100 patient-days to 3.3 DDD per 100 patient-days, and from 14 to 17.1 DDD per 100 admissions. This increase was due to the increase in use of tobramycin from 0.5 to 0.8 DDD per 100 patient-days and of gentamicin from 1.6 to 2.4 DDD per 100 patient-days (figure 8).
All categories of beta-lactam antibiotics showed a clear decrease in use compared to 2007 if measured as DDD per 100 admissions. Amoxicillin decreased from 39.3 DDD per 100 admissions to 27.8 DDD per 100

*Table 4. Use of antibiotics for systemic use (J01) in hospitals* (DDD/100 patient-days), 2002-2008 (Source: SWAB).*

| ATC group* | Therapeutic group | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 |
|---|---|---|---|---|---|---|---|---|
| J01AA | Tetracyclines | 1.7 | 1.4 | 1.5 | 1.6 | 1.6 | 1.4 | 1.4 |
| J01CA | Penicillins with extended spectrum | 6.1 | 6.0 | 6.0 | 6.7 | 7.6 | 7.3 | 5.5 |
| J01CE | Beta-lactamase sensitive penicillins | 1.2 | 1.2 | 1.4 | 1.4 | 1.4 | 1.2 | 1.1 |
| J01CF | Beta-lactamase resistant penicillins | 4.4 | 5.4 | 5.7 | 5.8 | 5.9 | 5.6 | 5.4 |
| J01CR | Combinations of penicillins. incl. beta-lactamase-inhibitors | 12.2 | 12.1 | 12.8 | 13.9 | 15.1 | 14.0 | 13.5 |
| J01DB -DE | Cephalosporins | 6.3 | 6.5 | 7.0 | 7.4 | 8.4 | 8.4 | 7.4 |
| J01DF | Monobactams | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.01 |
| J01DH | Carbapenems | 0.5 | 0.5 | 0.5 | 0.6 | 0.6 | 0.8 | 0.85 |
| J01EA | Trimethoprim and derivatives | 0.5 | 0.5 | 0.4 | 0.6 | 0.8 | 0.5 | 0.3 |
| J01EC | Intermediate-acting sulfonamides | 0.0 | 0.1 | 0.1 | 0.0 | 0.0 | 0.1 | 0.05 |
| J01EE | Combinations of sulfonamides and trimethoprim. incl. derivatives | 2.4 | 2.3 | 2.1 | 2.3 | 2.1 | 2.3 | 2.0 |
| J01FA | Macrolides | 2.7 | 2.4 | 2.3 | 2.8 | 2.5 | 2.7 | 2.3 |
| J01FF | Lincosamides | 1.5 | 1.6 | 1.8 | 1.9 | 2.0 | 2.1 | 1.8 |
| J01GB | Aminoglycosides | 2.1 | 2.5 | 2.2 | 2.6 | 2.5 | 2.5 | 3.3 |
| J01MA | Fluoroquinolones | 5.7 | 6.4 | 6.5 | 7.3 | 8.0 | 7.6 | 9.6 |
| J01MB | Other quinolones | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.0 | 0.05 |
| J01XA | Glycopeptides | 0.5 | 0.5 | 0.6 | 0.8 | 0.7 | 1.0 | 1.0 |
| J01XB | Polymyxins | 0.1 | 0.1 | 0.1 | 0.2 | 0.2 | 0.1 | 0.2 |
| J01XC | Steroid antibacterials (fusidic acid) | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.06 |
| J01XD | Imidazole derivatives | 1.5 | 1.6 | 1.7 | 1.5 | 1.7 | 1.8 | 1.4 |
| J01XE | Nitrofuran derivatives | 0.5 | 0.7 | 0.9 | 1.0 | 1.0 | 1.1 | 1.0 |
| J01XX05 | Methenamine | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.02 |
| J01XX08 | Linezolid | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.05 |
| J01 | Antibiotics for systemic use (total) | 50.2 | 51.9 | 53.8 | 58.3 | 62.2 | 60.9 | 58.1 |

* from the 2008 edition of the Anatomical Therapeutic Chemical (ATC) classification system



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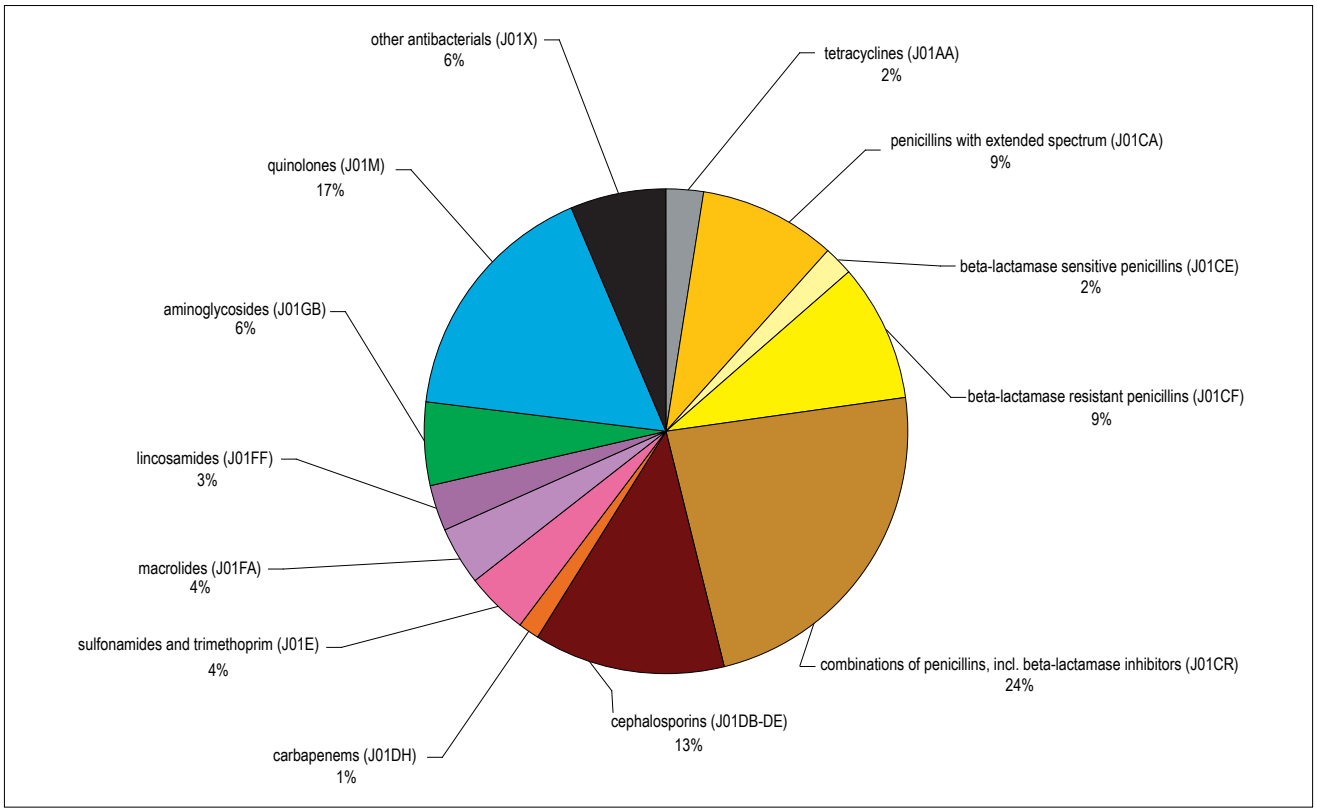



Figure 6. Distribution of the use of antibiotics for systemic use (J01) in hospitals, 2008 (SWAB).

admissions, for co-amoxiclav this decrease was from 73.9 DDD per 100 admissions to 66.7 DDD per 100 admissions. Per 100 patient-days, the use of amoxicillin/clavulanic acid increased slightly from 11.4 to 12.9 (figure 9).
The use of cephalosporins reduced from 8.4 to 7.4 DDD per 100 patient-days and from 46.3 to 38.2 DDD per 100 admissions (figure 10).
The use of macrolides, including that of azithromycin seemed to stabilise over the past years (figure 11).
Vancomycin use has been increasing since 1999. The use of teicoplanin remained constantly low (figure 12).

### 3.2.2 Hospital use of systemic antimycotics

Total use of antimycotics for systemic use was 3.4 DDD per 100 patient-days (table 6). It was the highest in university hospitals with 6.9 DDD per 100 patient-days compared to 2.1 DDD per 100 patient-days in general hospitals. Compared to 2007, the use of amphotericin B formulations in university hospitals has dramatically decreased from 4.4 DDD per 100 patient-days in 2007 to 1.0 DDD per 100 patient-days in 2008 (figure 13). For this reason, the total amount of antimycotic use as represented in DDD seems to have decreased. However, because of a flaw in the DDD systematic, this conclusion might not be justified. The DDD for amphotericin B was historically set at 35 mg. With the introduction of lipid formulations, however, the usual daily dose of amphotericin B has increased to about 350 mg, i.e., 10 DDD/day. With a shift from amphotericin B to voriconazol (1 DDD = 400 mg, more or less a usual therapeutic dose) as first line treatment, the total number of DDD has decreased.

### 3.2.3 Hospital use of systemic antimycobacterials

The total use of antimycobacterials for systemic use was 1.3 DDD/100 patient-days (table 7). The distribution of the different groups of drugs was more or less similar in university hospitals and general hospitals (table 7 and figure 14). The proportion of use made up by rifampicin, also used for staphylococci infections, was increased from approximately 50% of total use to about 60%.

### 3.2.4 Hospital use of systemic antivirals

The use of antivirals in 2008 was 1.6 DDD/100 patient-days on average. University hospitals used almost six times as much as general hospitals (4.0 vs. 0.7 DDD/100 patient-days; table 8). Nucleosides and nucleotides, with the exception of reverse transcriptase inhibitors, were used most frequently in both university and general hospitals (figure 15), accounting for almost half of the use of antivirals.

### 3.2.5 Discussion

The unit in which antibiotic usage is expressed matters (5). This is important when hospital resource indicators change over a study period. In relation to antibiotic resistance development, the measure of antibiotic use



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*Table 5. Use of antibiotics for systemic use (J01) in hospitals* (DDD/100 admissions) 2003-2008 (Source: SWAB).*

| ATC group* | Therapeutic group | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 |
|---|---|---|---|---|---|---|---|
| J01AA | Tetracyclines | 8.8 | 8.4 | 8.8 | 8.7 | 7.7 | 7.1 |
| J01CA | Penicillins with extended spectrum | 38.6 | 34.3 | 36.4 | 41.0 | 40.3 | 28.2 |
| J01CE | Beta-lactamase sensitive penicillins | 7.8 | 7.8 | 7.5 | 7.7 | 6.8 | 5.5 |
| J01CF | Beta-lactamase resistant penicillins | 34.6 | 33.0 | 31.4 | 31.8 | 31.0 | 27.8 |
| J01CR | Combinations of penicillins, incl. beta-lactamase-inhibitors | 77.7 | 73.1 | 75.4 | 81.7 | 77.3 | 69.7 |
| J01DB-DE | Cephalosporins | 42.0 | 39.4 | 39.8 | 45.3 | 46.3 | 38.1 |
| J01DF | Monobactams | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| J01DH | Carbapenems | 3.3 | 2.8 | 3.2 | 3.0 | 4.4 | 4.4 |
| J01EA | Trimethoprim and derivatives | 3.1 | 2.3 | 3.0 | 4.2 | 2.9 | 1.7 |
| J01EC | Intermediate-acting sulfonamides | 0.8 | 0.3 | 0.3 | 0.1 | 0.4 | 0.3 |
| J01EE | Combinations of sulfonamides and trimethoprim, incl. derivatives | 14.4 | 12.1 | 12.2 | 11.5 | 12.7 | 10.3 |
| J01FA | Macrolides | 15.4 | 13.4 | 15.1 | 13.4 | 14.8 | 11.7 |
| J01FF | Lincosamides | 10.2 | 10.2 | 10.5 | 10.8 | 11.5 | 9.3 |
| J01GB | Aminoglycosides | 15.8 | 12.5 | 13.9 | 13.7 | 14.0 | 17.1 |
| J01MA | Fluoroquinolones | 41.0 | 37.2 | 39.7 | 43.3 | 41.9 | 49.7 |
| J01MB | Other quinolones | 0.6 | 0.8 | 0.5 | 0.3 | 0.2 | 0.3 |
| J01XA | Glycopeptides | 3.4 | 3.5 | 4.1 | 3.9 | 5.3 | 5.0 |
| J01XB | Polymyxins | 0.5 | 0.6 | 1.1 | 0.9 | 0.7 | 1.0 |
| J01XC | Steroid antibacterials (fusidic acid) | 0.2 | 0.1 | 0.2 | 0.1 | 0.1 | 0.3 |
| J01XD | Imidazole derivatives | 10.1 | 9.6 | 7.9 | 9.0 | 9.9 | 7.3 |
| J01XE | Nitrofuran derivatives | 4.7 | 4.9 | 5.6 | 5.2 | 6.2 | 5.2 |
| J01XX05 | Methenamine | 0.2 | 0.4 | 0.1 | 0.1 | 0.1 | 0.1 |
| J01XX08 | Linezolid | 0.1 | 0.1 | 0.2 | 0.2 | 0.2 | 0.2 |
| J01 | Antibiotics for systemic use (total) | 333.2 | 306.8 | 316.9 | 335.9 | 335.0 | 300.1 |

* from the 2008 edition of the Anatomical Therapeutic Chemical (ATC) classification system

*Table 6. Use of antimycotics for systemic use (J02) in general hospitals, university hospitals and all hospitals (DDD/100 patient-days).*

| ATC group* | Therapeutic group | 2006 | | | 2007 | | | 2008 | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | general | university | total | general | university | total | general | university | total |
| J02AA01 | Antibiotics (amfotericin B) | 0.12 | 5.61 | 0.97 | 0.12 | 4.4 | 1.50 | 0.11 | 0.97 | 0.35 |
| J02AB02 | Imidazole derivatives (ketoconazole) | 0.03 | 0.03 | 0.03 | 0.01 | 0.1 | 0.04 | 0.05 | 0.09 | 0.06 |
| J02AC | Triazole derivatives | 1.38 | 6.41 | 2.16 | 1.59 | 5.2 | 2.74 | 1.83 | 5.52 | 2.87 |
| J02AX | Other mycotics for systemic use | 0.03 | 0.18 | 0.05 | 0.05 | 0.2 | 0.09 | 0.06 | 0.35 | 0.14 |
| J02 | Antimycotics for systemic use (total) | 1.56 | 12.23 | 3.21 | 1.76 | 9.93 | 4.38 | 2.10 | 6.90 | 3.40 |

* from the 2008 edition of the Anatomical Therapeutic Chemical (ATC) classification system

*Table 7. Use of antimycobacterials for systemic use (J04) in general hospitals, university hospitals and all hospitals (DDD/100 patient-days).*

| ATC group* | Therapeutic group | 2007 | | | 2008 | | |
|---|---|---|---|---|---|---|---|
| | | general | university | total | general | university | total |
| J04AB | Antibiotics (rifampicin) | 0.52 | 1.44 | 0.83 | 0.6 | 1.2 | 0.8 |
| J04AC | Hydrazides (isoniazide) | 0.22 | 0.39 | 0.28 | 0.1 | 0.3 | 0.2 |
| J04AK | Other drugs for treatment of tuberculosis | 0.18 | 0.38 | 0.25 | 0.1 | 0.3 | 0.2 |
| J04BA | Drugs for treatment of leprosy (dapson) | 0.14 | 0.53 | 0.27 | 0.0 | 0.3 | 0.1 |
| J04 | Antimycobacterials for systemic use (total) | 1.06 | 2.74 | 1.63 | 0.8 | 2.1 | 1.3 |

* from the 2008 edition of the Anatomical Therapeutic Chemical (ATC) classification system



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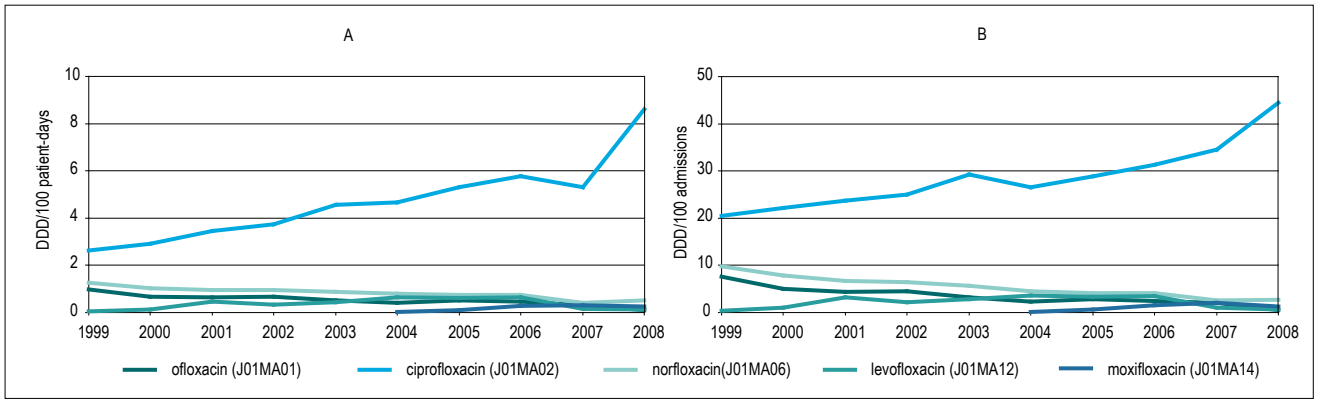



Figure 7. Use of fluoroquinolones in hospitals, expressed as DDD/100 patient-days (A) and DDD/100 admissions (B), 1999-2008.

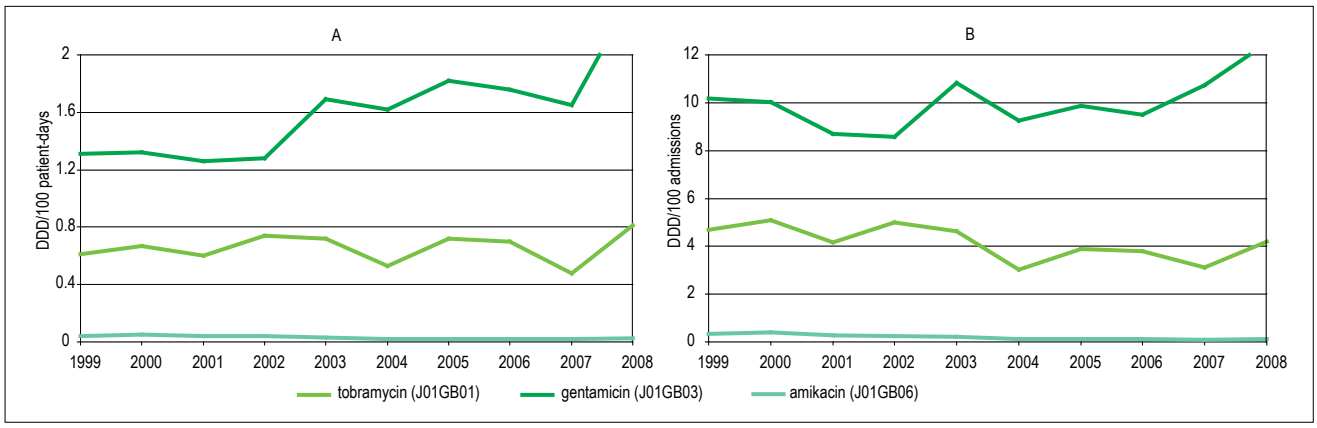



Figure 8. Use of aminoglycosides in hospitals, expressed as DDD/100 patient-days (A) and DDD/100 admissions (B), 1999-2008.

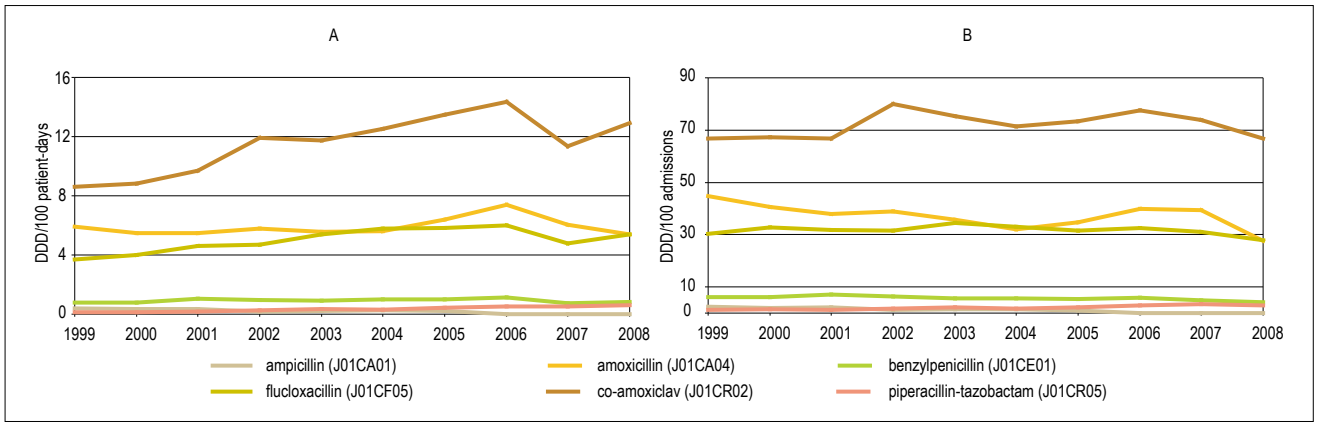



Figure 9. Use of penicillins in hospitals, expressed as DDD/100 patient-days (A) and DDD/100 admissions (B), 1999-2008.

should be a reflection of the antibiotic selection pressure exerted. At the population level the selection pressure is thought to depend on the volume of antibiotics used in a particular geographical area, the number of individuals exposed and the proportion of the population treated with antibiotics (6). The denominator should thus preferably include information on all these factors (6). However, there is a lack of studies to determine the correlation between different measures of antibiotic use and the level of antibiotic resistance.

Since NethMap 2004, data on antibiotic use in Dutch hospitals have been expressed in DDD per 100 patient-days and in DDD per 100 admissions. An increase in both the number of DDD per 100 patient-days and the number per 100 admissions is worrisome; if either unit does not increase, there is no reason to worry about development of resistance. When a constant use per patient is seen, and this is combined with an increase in the number of admissions, this is indicative for an increase of the selection pressure exerted by antibiotics in



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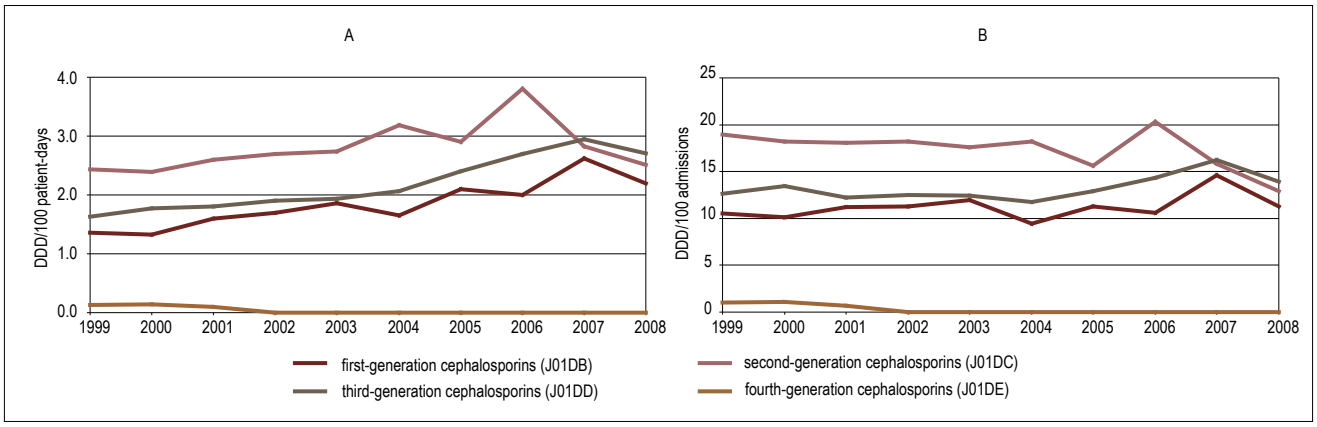



Figure 10. Use of cephalosporins in hospitals, expressed as DDD/100 patient-days (A) and DDD/100 admissions (B), 1999-2008.

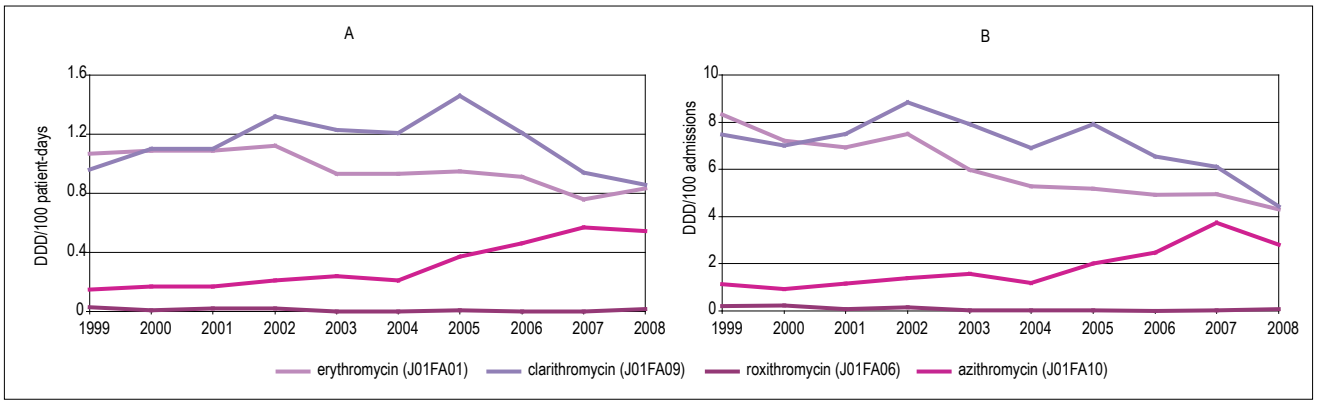



Figure 11. Use of macrolides in hospitals, expressed as DDD/100 patient-days (A) and DDD/100 admissions (B), 1999-2008.

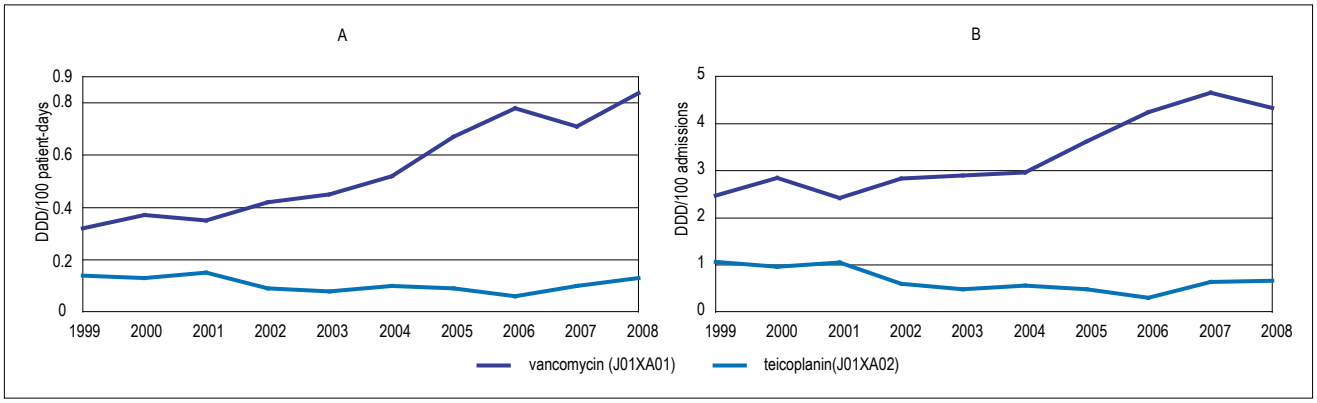



Figure 12. Use of glycopeptides in hospitals, expressed as DDD/100 patient-days (A) and DDD/100 admissions (B), 1999-2008.

hospitals over the years.
An intensification of antibiotic therapy per 100 patient-days, however, may be in part due to an increased number of admitted patients, and possibly a shortening of the duration of antibiotic treatment. Subsequently, such shortening of the duration of therapy may lead to a decreased selection of resistant micro-organisms (7).
In 2008, the total antibiotic use decreased referred to the year before when expressed in DDD/100 patient-days as well as in DDD per 100 admissions. This decrease was seen in all groups of antibiotics, except for the fluoroquinolones and the aminoglycosides.
All categories of beta-lactam antibiotics showed a clear decrease in use compared to 2007 if measured as DDD per 100 admissions. If these changes are due to the more widespread implementation of selective gut decontamination practices in the Netherlands following a large multicentre trial (8), and therefore changes in the antibiotic use policies (less use of beta-lactam antibiotics, in favour of use of quinolones) needs to be confirmed.



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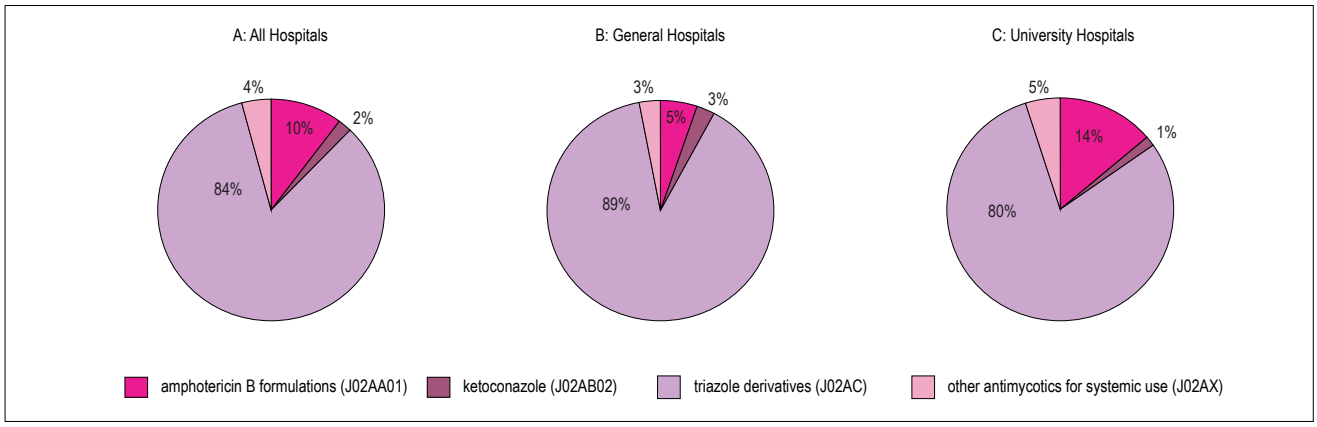



Figure 13. Distribution of the use of antimycotic drugs in all hospitals (A), General Hospitals (B) and University Hospitals (C) in 2008.

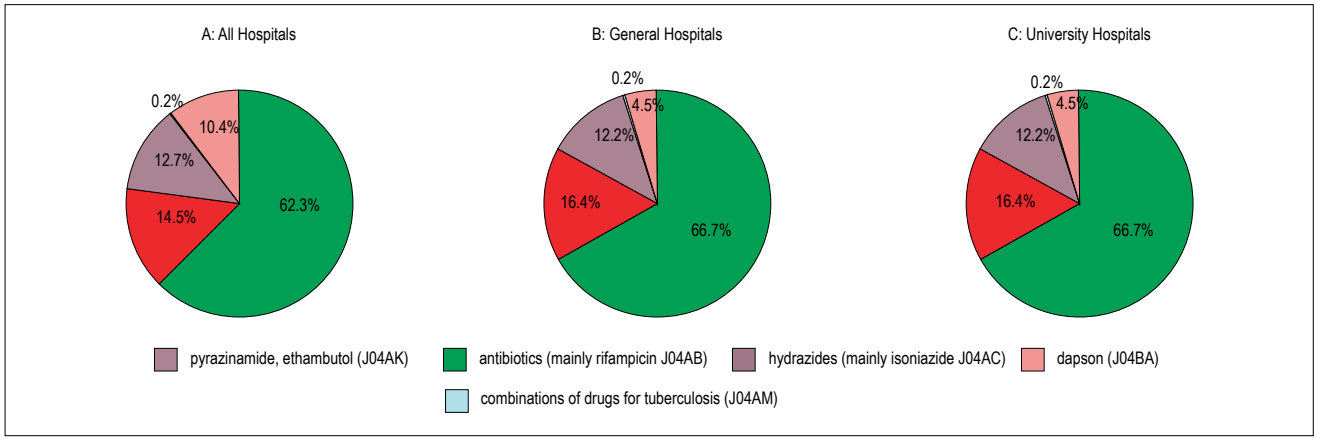



Figure 14. Distribution of the use of antimycobacterial drugs in all hospitals (A), General Hospitals (B) and University Hospitals (C) in 2008.

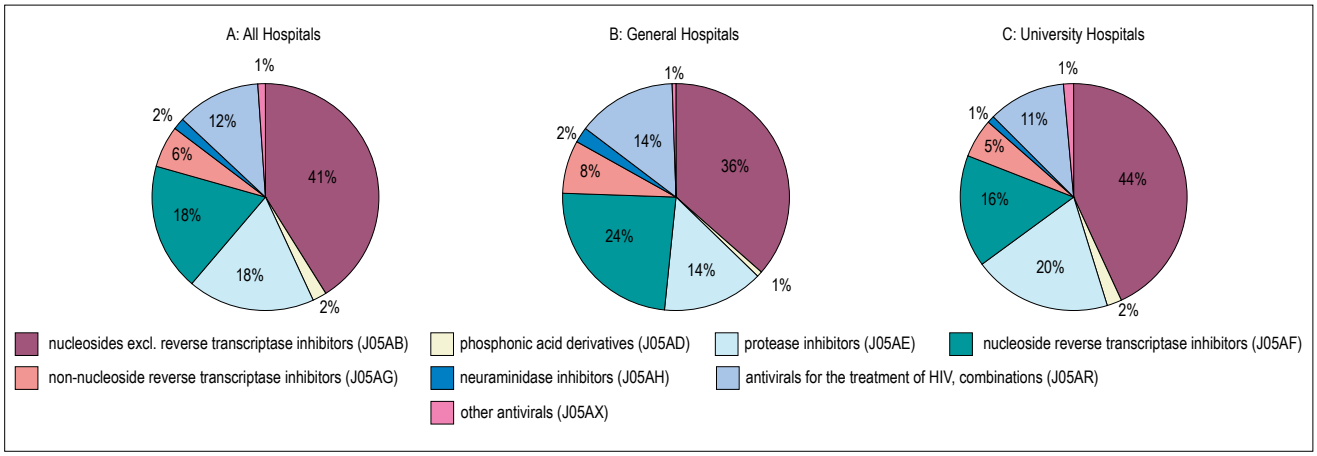



Figure 15. Distribution of the use of antiviral drugs in all hospitals (A), General Hospitals (B) and University Hospitals (C) in 2008.

The use of systemic antimycotics in university hospitals was almost three times higher compared to general hospitals. This is explained by the high concentration of haematology and oncology-patients in university hospitals. Although university hospitals used twice as much antimycobacterials, the distribution of the different groups was rather similar. The higher use in university hospitals might be explained by the fact that rifampicin is, besides its use for tuberculosis, also being used as an adjuvant in certain infections with Gram-positive staphylococci.

The treatment of tuberculosis in the Netherlands consists of a combination of a limited number of primary antimycobacterials, therefore, there is not much room for variation (9).

The use of dapsone is explained by its place in the



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*Table 8. Use of antivirals for systemic use (J05) in general hospitals, university hospitals and all hospitals (DDD/100 patient-days).*

| ATC group* | Therapeutic group | 2007 | | | 2008 | | |
|---|---|---|---|---|---|---|---|
| | | general | university | total | general | university | total |
| J05AB | Nucleosides and nucleotides excl reverse transcriptase inhibitors | 0.27 | 1.72 | 0.78 | 0.2 | 1.7 | 0.7 |
| J05AD | Phosphonic acid derivatives | 0 | 0.06 | 0.02 | 0 | 0.1 | 0 |
| J05AE | Protease inhibitors (PI's) | 0.06 | 0.70 | 0.28 | 0.1 | 0.8 | 0.3 |
| J05AF | Nucleosides and nucleotides reverse transcriptase inhibitors (NRTI's) | 0.14 | 0.83 | 0.35 | 0.2 | 0.6 | 0.3 |
| J05AG | Non-nucleosides reverse transcriptase inhibitors (NNRTI's) | 0.05 | 0.20 | 0.10 | 0.1 | 0.2 | 0.1 |
| J05AH | Neuraminidase inhibitors | 0 | 0.02 | 0.01 | 0 | 0 | 0 |
| J05AR | Anitvirals for the treatment of HIV, combinations | 0.07 | 0.33 | 0.15 | 0.1 | 0.5 | 0.2 |
| J05 | Antivirals for systemic use (total) | 0.59 | 3.86 | 1.81 | 0.7 | 4 | 1.6 |

prophylaxis and treatment of *Pneumocystis carinii* and toxoplasmic encephalitis.
The largest group of antivirals used were the nucleosides (excl. reverse transcriptase inhibitors) like (val)acyclovir and (val)ganciclovir. The difference in use between university hospitals and general hospitals can in part be explained by its use in prophylaxis and treatment of cytomegalovirus in transplant patients, who are usually treated in university hospitals.
All university hospitals and a few general hospitals are specialised in the treatment of HIV patients in the Netherlands.

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# 4. Resistance among Common Bacterial Pathogens

## 4.1 Introduction – the use of EUCAST criteria

In NethMap 2009, susceptibility criteria as defined by EUCAST were introduced to define resistance rates. However, not all laboratories in the Netherlands use EUCAST criteria at present – historically some laboratories use CRG criteria, some use their own criteria and many laboratories continue to use CLSI criteria, mainly because of the use of automated antimicrobial susceptibility testing using systems such as Vitek® and Phoenix®. As a consequence, resistance rates may differ by laboratory, based on the methods and criteria that are used. In 2009, the Netherlands Society for Medical Microbiology (NVMM) accepted a guideline to use EUCAST criteria. Laboratories should have implemented these guidelines by 1 January 2011. Thus, both 2009 and 2010 are transition years and it is expected that the majority of laboratories will use the EUCAST criteria by 2011. Since a number of laboratories did use CLSI criteria over the last years, resistance rates were recalculated using both EUCAST criteria as well as CLSI criteria in the previous NethMap 2009, and a discussion and comparison on the impact of resistance rates can be found in that issue. In this chapter, EUCAST criteria will be used whereever possible, but comparisons with CLSI are provided where appropriate. This allows comparisons for the future, but also with other countries in Europe that are using EUCAST criteria. However, for some data, in particular those where MIC values were not available for reinterpretation, alternatives have been used as indicated in the text.

## 4.2 Surveillance of Antimicrobial Resistance in the Community

The studies on resistance level in the community focus on three different goals, including estimation of resistance in:

(1) the indigenous flora of healthy persons in various circumstances and of various ages, giving information about the basic level of resistance in human reservoirs and
(2) patients visiting their general practitioner (GP) and
(3) special pathogens such as meningococci, gonococci and mycobacteria.

Several longitudinal multicentre studies within the national project Surveillance of Extramural Resistance in the Netherlands (SERIN) were carried out or are ongoing in various parts of the Netherlands in cooperation with the Department for Medical Microbiology, University Hospital Maastricht, the Netherlands Institute for Health Services research (NIVEL) and the Municipal Health Services (GGD).

In 2006, the RIVM started a surveillance of resistance of *Neisseria gonorrhoeae* among patients from outpatient-STD clinics, the so-called GRAS project.
Since 1993, the Netherlands Reference Laboratory for Bacterial Meningitis has been determining the resistance level of *Neisseria meningitidis* from patients admitted to the hospital for meningococcal disease.
The first isolate of *Mycobacterium tuberculosis* of each patient with tuberculosis in the Netherlands is routinely sent to the RIVM for susceptibility testing and confirmation of identification.
Results of all these studies are presented here.

### 4.2.1 Escherichia coli

The prevalence of antibiotic resistance among bacteria causing community acquired infection was determined for strains collected from patients visiting their general practitioner in the Netherlands in 2009. Urine was taken from patients with complaints of an acute uncomplicated urinary tract infection to determine the resistance level in *Escherichia coli*. Female, non-pregnant women aged 11 years and older who consulted the GP practice with symptoms indicating an acute uncomplicated UTI, i.e. stranguria, dysuria and pollakisuria, without the presence of fever >38°C were eligible for inclusion. Exclusion criteria were catheterization, urological or nephrological problems, diabetes mellitus or other immunocompromising diseases.
The materials were collected by 42 general practitioners distributed over the country and participating in the Sentinel Stations project of the Netherlands Institute for Health Services Research (NIVEL). See material and methods section for details regarding the acquisition and testing of isolates. The resistance patterns found among *E. coli* isolates were compared to the results found in previous years for comparable groups of patients.
A total of 970 urine samples were collected in 2009, of which 785 (81%) were positive; 489 revealed *E. coli* (62%). One hundred and nine samples contained two or more bacteria, most frequently in urine samples obtained from the age group of 70 year and older. The mean age of the patients was 52 + 23 y.
The trends of resistance from 2000 on are presented in figure 1. The breakpoints for resistance used from 2004 on were those according to the guidelines of EUCAST. They were compared to the results when applying also CLSI criteria for resistance. It is unknown which breakpoints were used before 2004, therefore the graphics contain a break between 2001 and 2004.
Amoxicillin resistance in the community increased from 20% in 2000 to 34% in 2009. If CLSI criteria with higher cut-off values would have been used, the resistance level in 2009 would have been 33%. In contrast to the



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results of 2004, we found the highest resistance in the age group less than 20 years of age (39%) and the lowest in the patients over 70 years of age (30%), although the difference was statistically not significant (figure 2). The overall resistance level of amoxicillin among *E. coli* from the community was lower than that among strains from Unselected Hospital Departments (46%, see below, figure 15), Outpatient Clinics and urine samples from General Practice sent to the laboratory on indication (selected GP patients). We assume that the latter were from selected patients with therapy failure, complicated and chronic infections or treated before, because general practitioners will never send in urine from patients with an acute uncomplicated UTI for culture and antibiogram determination. The MIC distribution of amoxicillin was bimodal with one subpopulation having MIC values ranging from 1-8 mg/l and another with MIC values >32 mg/l, without strains in the intermediate area of CLSI (figure 3).

Co-amoxiclav resistance was 12% in 2004 and remained stable in 2009. The resistance level in women >50 years of age is higher than that in younger women, but this difference is not statistically significant. In general, the resistance level was lower than that in Unselected Hospital Departments, Outpatient Clinics and selected GP patients during the same study period when using the EUCAST breakpoint for resistance (MIC > 8 mg/l). Application of the CLSI breakpoint for resistance (MIC > 16 mg/l) did influence the resistance rate: it should have been 1% in 2004 and 2% in 2009. Based on this, one may suppose that CLSI breakpoints were used in 2000 and 2001, as it is unlikely that the co-amoxiclav resistance should increase from 1% in 2001 to 12% in 2004. The 1% resistance in 2004 according to CLSI fits well with the 1% resistance found in 2000 and 2001.

The MIC distributions in 2004 and 2009 were similar, showing a unimodal shape with MIC values over a broad range from 1 - > 32 mg/l (figure 3).The existence of a number of strains with a MIC of 16 mg/l is responsible for the discrepancy between the levels calculated by the two different breakpoints. Strains with MIC of 16 mg/l are susceptible according to CLSI and resistant according to EUCAST criteria. Such strains are not found in the MIC distribution of amoxicillin, and no difference could be found.

Trimethoprim resistance rates increased from 15% in 2000 to 23% in 2004 and decreased to 19% in 2009. The resistance rate was the highest in the patients 51-70 years of age (23%) and the lowest among patients >70 years of age. The decrease in trimethoprim resistance may be the result of the change in the Dutch guidelines for treatment of urinary tract infections in general practice in 2005. It was already indicated in NethMap 2003 and 2004 that resistance to amoxicillin and trimethoprim for *E. coli* causing community acquired urinary tract infections had surpassed an acceptable level in the community, rendering these antibiotics as not useful for empiric therapy of community acquired urinary tract infections. The NHG changed its standard accordingly in 2005 and replaced trimethoprim by nitrofurantoin as the first choice for the empiric treatment of uncomplicated urinary tract infections. Since then the prescription rate of trimethoprim has been significantly lower and this may have contributed to a decrease in resistance rate. The MIC distribution showed a bimodal shape with a subpopulation over a broad range from 0.12 – 2 mg/l and one with MIC > 32 mg/l. The latter is smaller in 2009 as compared to 2004. Application of both CLSI and EUCAST breakpoints did not change the resistance rate. The resistance level in the community was significantly lower than that in hospitals, Outpatient Clinics and Selected GP patients (chapter 4.3).

The resistance rate of co-trimoxazole was 2 – 3% lower than that of trimethoprim and followed the same trend. The MIC distribution for co-trimoxazole showed a bimodal distribution with a subpopulation of MIC values

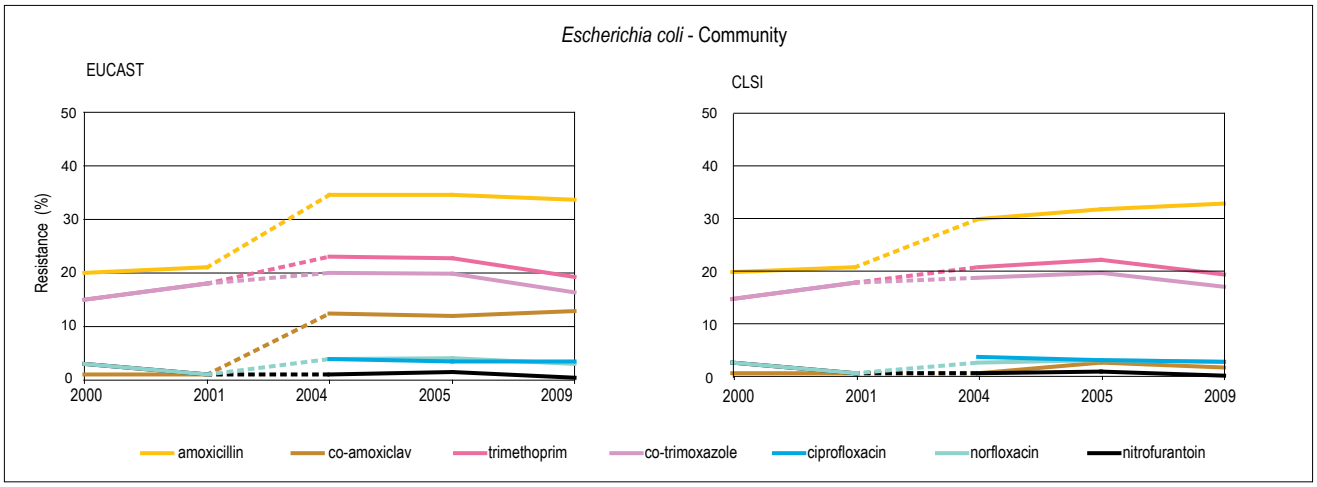



Figure 1. Trends in antibiotic resistance among *Escherichia coli* from patients in the community visiting the general practice for an uncomplicated urinary tract infection. Trends were calculated according to the breakpoints for resistance recommended by both EUCAST and CLSI.



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over a small range <0.06 – 0.12 mg/l and one with values of 32 mg/l or higher (figure 3).
Resistance to nitrofurantoin (figure 1) remained at a low level (mean 1.2%) in all age groups during the whole study period and was 0.4% (two strains) for the whole group in 2009. This is significantly lower than the resistance levels found in hospitals, Outpatient Clinics and Selected GP patients (see chapter 4.3). The MIC distribution showed a unimodal shape over a wide range from 2 to 256 mg/l, with a peak at 16 mg/l (not shown).

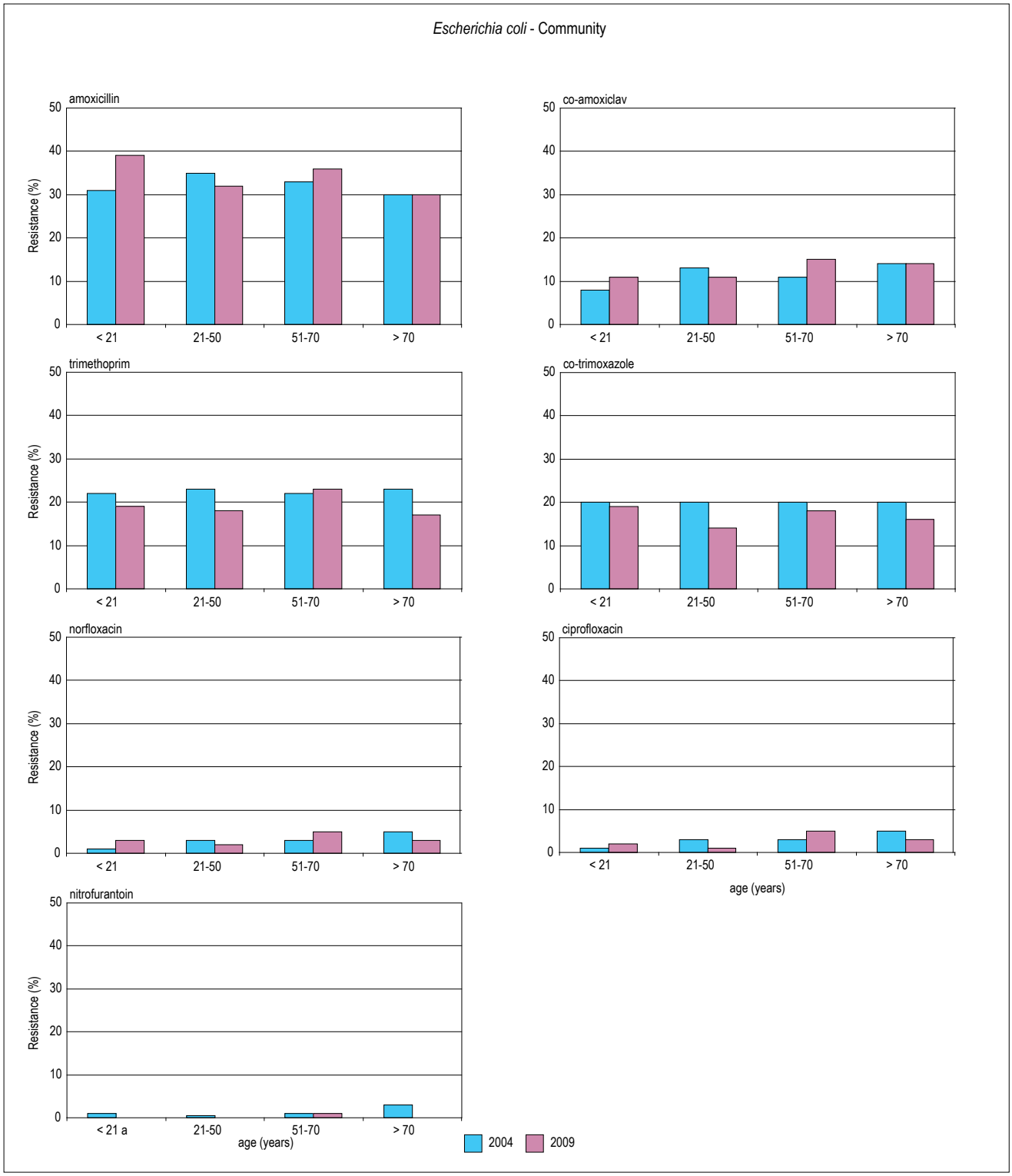



Figure 2. Resistance to antibiotics among *Escherichia coli* from patients of different age groups in the community. Resistance was calculated according to the breakpoints for resistance of EUCAST.



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Norfloxacin resistance level in the community increased slowly to 3.5% in 2004 with rates ranging 1 – 5%: 1% in the younger age group ≤20 years of age and 3 – 5% in the older age groups ($p < 0.05$), which may reflect more frequent use of this drug in the older ages. In 2009, the overall resistance level (3.5%) was not increased, although the resistance level in the younger women had increased from 1% to 3%. There was complete cross-resistance with ciprofloxacin (also 3.5% resistance in 2004 and 2009). Application of two breakpoints did not significantly change the resistance rates. The 3.5% quinolone resistance level in community isolates in 2004 and 2009 was significantly lower than that in hospitals, Outpatient Clinics and Selected GP patients. This lower level was observed in hospitals before 2002.
Resistance to fosfomycin was not found in the community.
Gentamicin resistance, measured in 2009, was 2.5% (not shown), which is significantly lower than that in hospitals, Outpatient Clinics and Selected GP patients.

**ESBL production**
*Escherichia coli* isolates resistant to co-amoxiclav were assessed for the presence of ESBL production. One strain in 2004 (0.1%) and five strains in 2009 (1%) appeared ESBL positive.

**Multiresistance**
To calculate resistance against various combinations of the different classes of antibiotics, co-trimoxazole was selected as representative for both trimethoprim and co-trimoxazole. A total of 63% of strains isolated in 2009 were susceptible to all classes of antibiotics tested (figure 4); 21.3% was resistant to one, most frequently to amoxicillin (11.5%) or co-amoxiclav (7.2%); 12.3.% was resistant two classes of antibiotics tested, most frequently to the combination amoxicillin/co-trimoxazole (7%) and co-amoxiclav/co-trimoxazole (4.3%); 2.7% was resistant to three classes of antibiotics (multiresistant) and 0.6% was even resistant to four or five classes of antibiotics.

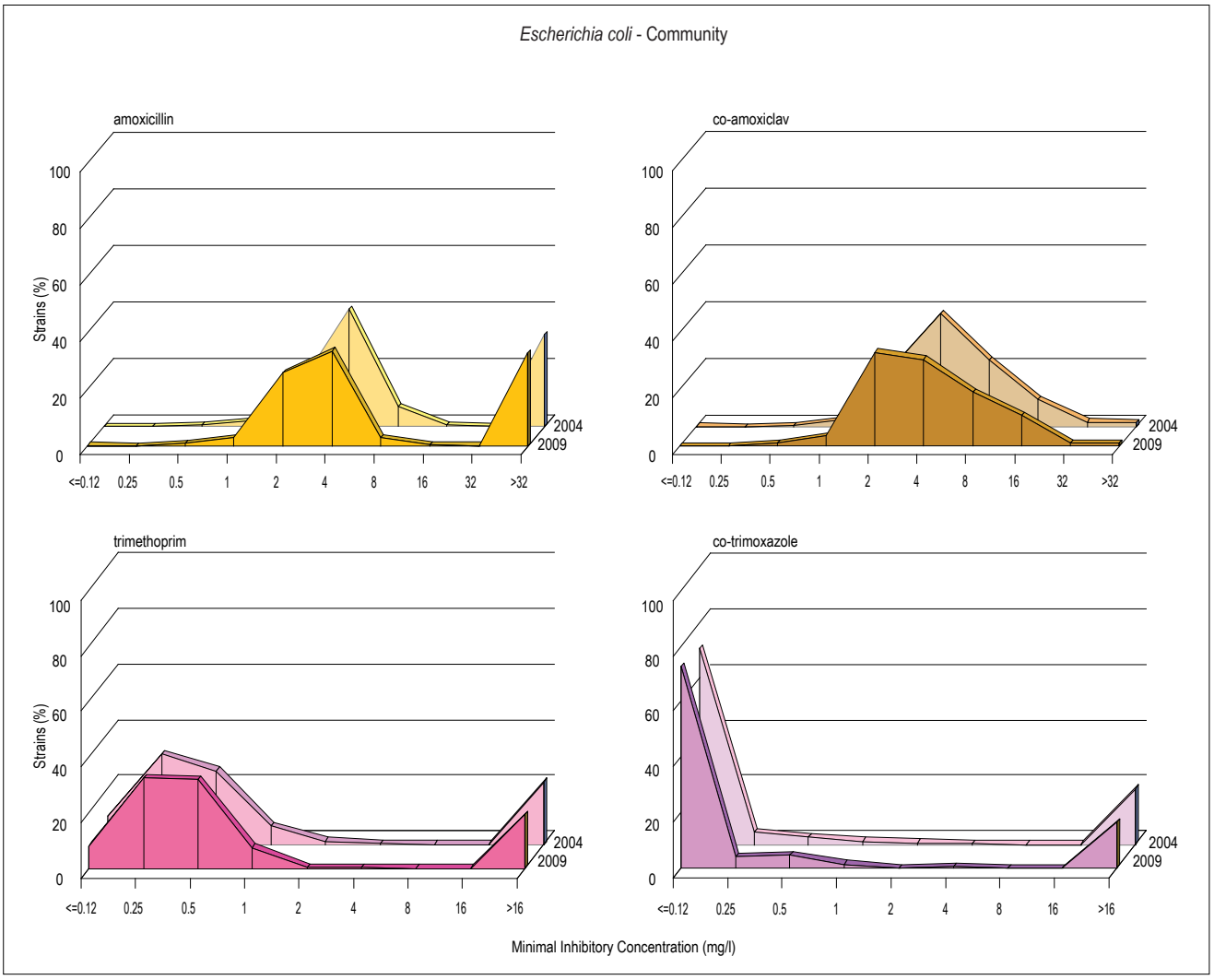



Figure 3. MIC distributions of amoxicillin, co-amoxiclav, trimethoprim and cotrimoxazole for *Escherichia coli* from the community.



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**Summary – *Escherichia coli***

1. Application of two breakpoints for resistance (EUCAST of CLSI) did influence the resistance level calculated for co-amoxiclav
2. Stable resistance to amoxillicin (34%), co-amoxiclav (12%), nitrofurantoin (1%) and quinolones (3.5%) since 2004
3. Decreasing resistance to trimethoprim and co-trimoxazole since 2004
4. ESBL producing strains in 1% of the isolates
5. Lower resistance levels to amoxicillin, co-amoxiclav, trimethoprim, co-trimoxazole, quinolones and gentamicin in patients with uncomplicated UTI from the community compared to those found in hospitals, Outpatient Clinics and Selected GP patients
6. Multiresistance (resistant to three or more classes of antibiotics) was 3.3% in 2009

### 4.2.2 Neisseria meningitidis

From 1994-2008 a total of 4566 strains from cerebrospinal fluid (CSF) and 2725 strains from blood were included in the surveillance project of the Netherlands Reference Laboratory for Bacterial Meningitis of the Academic Medical Centre, Amsterdam. Before 2002, less than 1% of the strains were moderately susceptible to penicillin (MIC 0.125-0.38 mg/l). After 2002, 2-4% of strains from CSF appeared moderately susceptible. The same pattern was observed in strains from blood until 2007, but in 2008 seven isolates (8%) and in 2009 four isolates (5%) appeared moderately susceptible with MIC > 0.125 mg/l (figure 5).
Five of these 11 strains (2008 and 2009) belonged to serogroup B, the other strains to the serogroups C (one of 12 isolates), W135 (four of five strains) and Y (one of 13 isolates), respectively. Penicillin resistance (MIC >0.5 mg/l) was occasionally found in strains both from CSF and blood in some years, the last time in 2006 (figure 5). All strains isolated in 2008 and 2009 were susceptible to ceftriaxone and rifampicin.

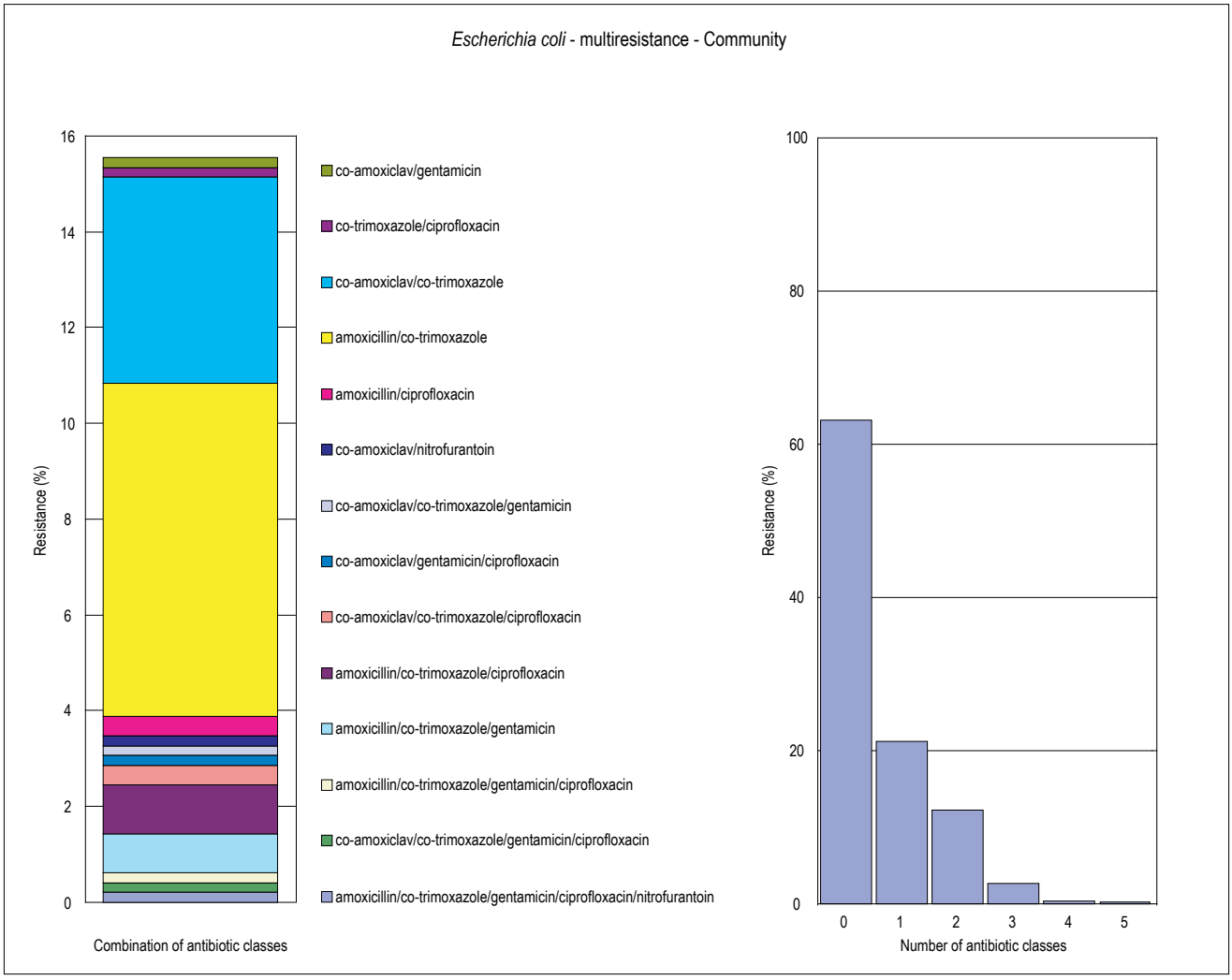



Figure 4. Multiresistance among *Escherichia coli* from the community in 2009. Resistance was calculated according to the breakpoints for resistance of EUCAST.



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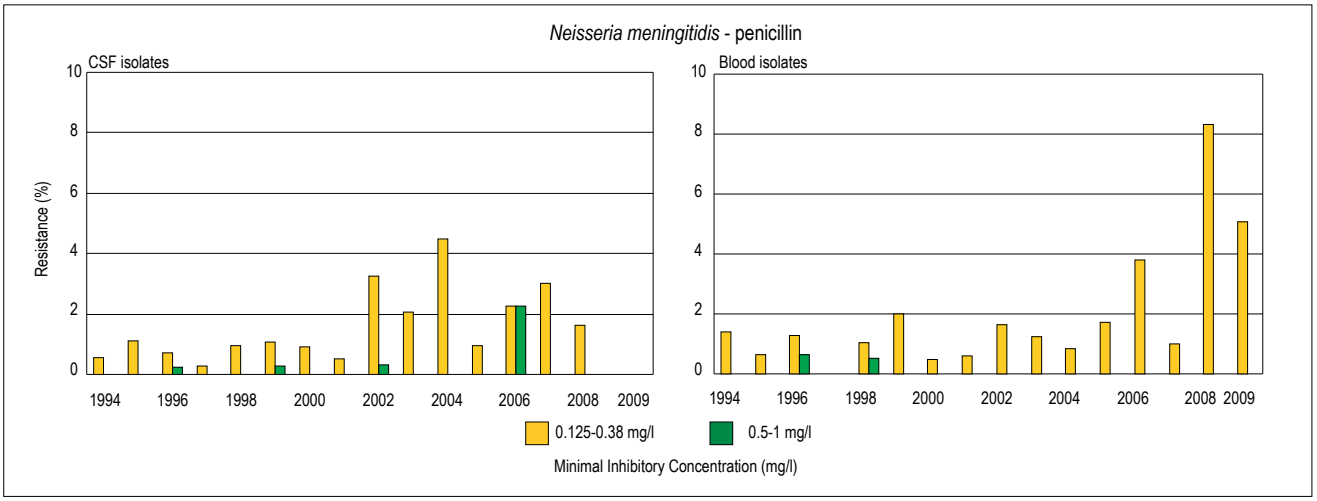



Figure 5. Trends in penicillin resistance among clinical strains of *Neisseria meningitidis*.

**Summary – *Neisseria meningitidis***

1. Penicillin resistance was not found since 2006
2. 5% of strains were moderately susceptible to penicillin in 2009.
3. Resistance to ceftriaxone and rifampicin was not found.

### 4.2.3 Neisseria gonorrhoeae

In 1999, the nationwide surveillance of antibiotic resistance in gonococci was discontinued and since then insight into the susceptibility patterns of gonococci has been limited.

In 2003, data of increasing quinolone resistance resulted in a revision of the guidelines from the Netherlands Dermatological and Venereological Society (Nederlandse Vereniging voor Dermatologie en Venereologie, NVDV), making cefotaxime the first-choice therapy for gonorrhoea infections. At the end of 2006, ceftriaxone was selected as primary therapy. Also, the NHG revised their guidelines in 2004, making cefotaxime their first choice, although ciprofloxacin remained second-choice therapy for gonorrhoea.

Concerns about the increasing resistance to ciprofloxacin resulted in the implementation of the national project Gonococcal Resistance to Antimicrobials Surveillance (GRAS) in 2006. This surveillance consists of systematically collected data on gonorrhoea from STI centres and standardised measurement of resistance patterns by using E-test (for penicillin, doxycycline, ciprofloxacin and cefotaxime), linked with epidemiological data. Isolates with unusual resistance patterns are forwarded to the RIVM for confirmation. STI centres and associated laboratories that identify the majority of STI in high risk populations participate in this surveillance.

In July 2006, GRAS was implemented in the first STI centre. Throughout the years, GRAS was further expanded and now includes most STI centres in the Netherlands, representing approximately 80% of the total population of STI centre attendees. From July 2006 through December 2009, the susceptibility of *N. gonorrhoeae* from 3117 patients was tested. Resistance levels were calculated using both the breakpoints for resistance according to the EUCAST guidelines, used from this year on and the CLSI guidelines (table 1), which were previously (2006-2008) used for interpretation of GRAS data. The breakpoints for resistance for ciprofloxacin and cefotaxime differ in both guidelines, those of penicillin and tetracycline are similar. Resistance proportions are shown in figure 6.

Overall penicillin resistance remained fairly stable between 8-10% over time according to both CLSI and EUCAST criteria (figure 6).

Tetracycline resistance increased from 33% in 2006 to 60% in 2009.

*Table 1. Resistance to antibiotics among Neisseria gonorrhoeae, calculated with application of breakpoints for resistance according to CLSI and EUCAST.*

| | CLSI | | | | | EUCAST | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Breakpoint | Resistance (%) | | | | Breakpoint | Resistance (%) | | | |
| Antibiotic | R (mg/l) | 2006 | 2007 | 2008 | 2009 | R (mg/l) | 2006 | 2007 | 2008 | 2009 |
| penicillin | >1 | 11 | 11 | 8 | 6 | >1 | 11 | 11 | 8 | 6 |
| doxycycline | >1 | 24 | 21 | 33 | 44 | >1 | 33 | 31 | 43 | 57 |
| ciprofloxacin | >0.5 | 35 | 42 | 45 | 49 | >0.06 | 46 | 48 | 49 | 53 |
| cefotaxime | >0.5 | 0 | 0 | 0 | 0 | >0.12 | 1 | 4 | 8 | 5 |



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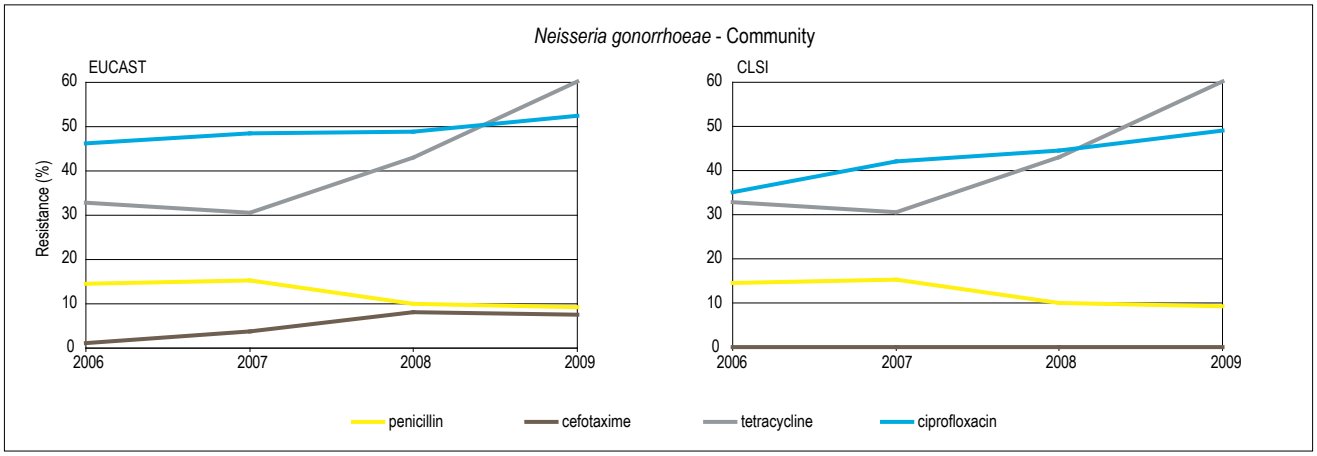



Figure 6. Trends in antibiotic resistance among *Neisseria gonorrhoeae* in The Netherlands, calculated according to the breakpoints for resistance recommend by both EUCAST and CLSI.

Ciprofloxacin resistance increased from 46% in 2006 to 52% in 2009 (EUCAST); with application of the CLSI breakpoint resistance levels should have been 35% and 49%, respectively. This increase was mostly due to increase in resistance among homosexual men, who had the highest level of resistance (up to 60%, figure 7). The prevalence of ciprofloxacin resistance in heterosexual men and in women remained stable during 2006-2008 (approximately 30%), but increased in 2009, although extremely high resistance levels were recorded in a small number of women from Eastern Europe (79%). At the same time, a survey among GPs found out that ciprofloxacin was still prescribed in approximately 40% of the cases in 2007 (47). GP guidelines will be updated in 2010, no longer recommending ciprofloxacin as second-choice therapy.

No resistance to cefotaxime was found from 2006-2009 when the CLSI breakpoints for resistance were applied (MIC > 0.5 mg/l). A few strains with MIC 0.5 mg/l, just below the breakpoint were found from 2007 onwards.

Using the EUCAST breakpoint for resistance (MIC > 0.12 mg/l), 1.5% – 8% of all strains were classified resistant from 2006 onwards, with 7.5% resistance among all isolates in 2009 (figure 6). The MIC distribution of cefotaxime (figure 8) showed a unimodal shape over a broad range (< 0.002 – 0.5 mg/l). The shape of the curve is changing: in 2006 a peak at the concentration of 0.008 mg/l was observed and 44% of strains had MIC values of 0.008 – 0.15 mg/l. In 2007, and following years the peak flattened with only 32% of strains with MIC between 0.008-0.015 mg/l in 2009 and with appearance of more strains in the area around and above the EUCAST breakpoint (0.12 mg/l) and around the CLSI breakpoint. Such changes predict upcoming resistance in a population. Although no reports of clinical failure have been reported with 3rd generation cephalosporins within GRAS, one STI centre not participating in GRAS reported a case of ceftriaxone-resistant gonorrhoea (MIC = 1mg/l) with initial failure of therapy. The patient (female, 64 yrs) was treated again but with a higher antibiotic dose. Resistance

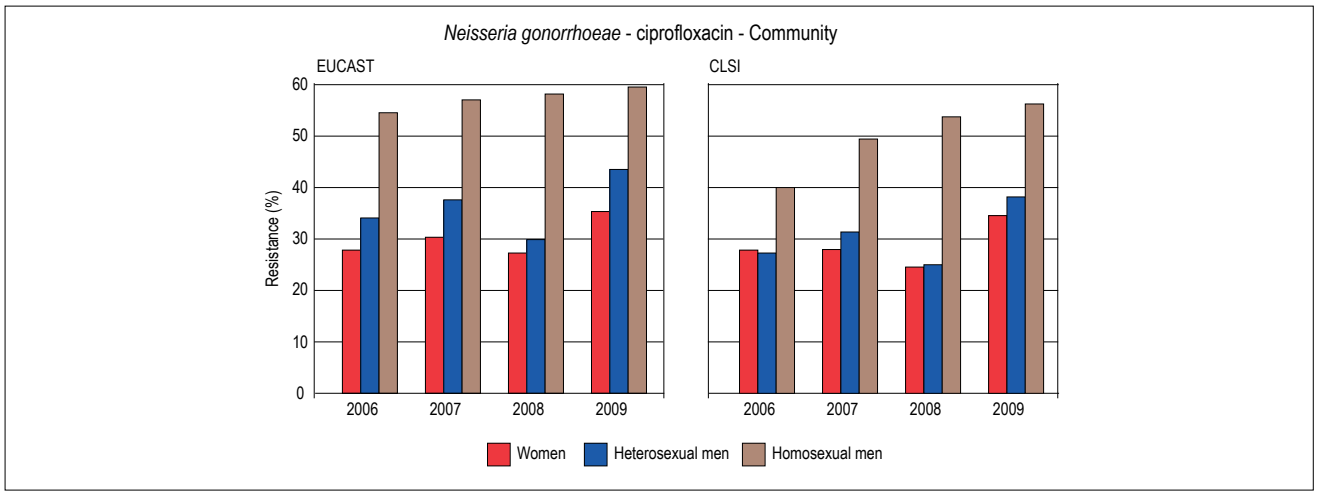



Figure 7. Trends in ciprofloxacin resistance among *Neisseria gonorrhoeae* in The Netherlands, 2006-2009 in different study groups. Trends were calculated according to the breakpoints for resistance recommended by both EUCAST and CLSI.



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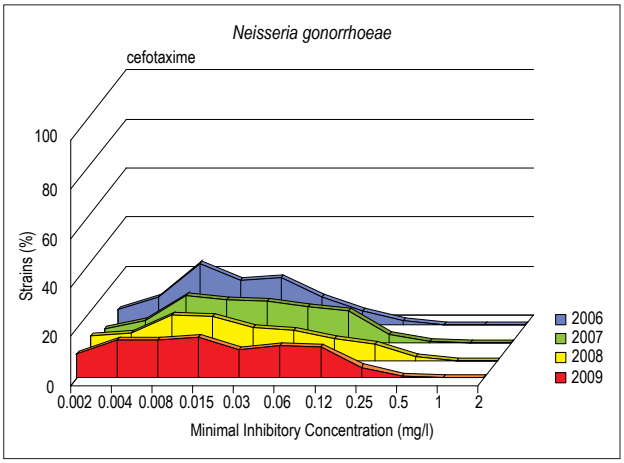



Figure 8. MIC distributions of cefotaxime for *Neisseria gonorrhoeae*.

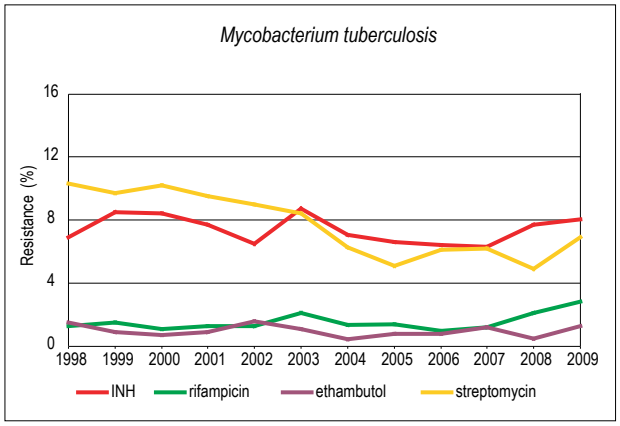



Figure 9. Trends in antibiotic resistance among *Mycobacterium tuberculosis*.

to ciprofloxacin and penicillin was also reported in this case. Cefotaxime resistance (according to EUCAST) was higher in isolates obtained from homosexual men (7%), compared to heterosexual men and women (both 3%). The changing antibiotic resistance pattern of gonococci underlines the need for a continuous standardised surveillance of antimicrobial susceptibility to detect changes in resistance patters which might necessitate modification of treatment guidelines, to explore risk factors for infection with such strains, and to understand high risk transmission patterns.

**Summary – *Neisseria gonorrhoeae***
1. Application of two breakpoints for resistance (EUCAST and CLSI) had influence on the resistance levels of cefotaxime and to a less extent on those of ciprofloxacin
2. Stable resistance to penicillin
3. Increasing resistance to tetracycline, ciprofloxacin and cefotaxime
4. Highest resistance among isolates from homosexual men

### 4.2.4 *Mycobacterium tuberculosis*

A total of 10,916 strains of *Mycobacterium tuberculosis* complex were collected and analysed at RIVM during 1998-2009; the number of isolates is steadily decreasing since 1999. Then the number of first isolates was 1109, in 2009 it was 775.
INH resistance remained stable, it was 8.1% in 2009 (figure 9), streptomycin resistance decreased from 10% in 1998 to 5% in 2008 and was 7% in 2009. Rifampicin resistance increased to 2.1% in 2008 and again to 2.8% in 2009. Ethambutol resistance remained low, 1.3% in 2009. Combined resistance to more than one drug in 2009 was observed in 4.6% of all isolates (figure 10), combined resistance to rifampicin and INH was recorded in 2.6% of the strains. Resistance to all four antimycobacterial drugs was 1.2% in 2009, which is the highest level found until now.

**Summary – *Mycobacterium tuberculosis***
1. Slightly increased resistance to rifampicin
2. Stable and low resistance levels to INH, streptomycin and ethambutol
3. Combined resistance to INH and rifampicin was 2.6%, multiresistance to the four drugs tested was 1.2% in 2009

## 4.3 Surveillance of Antimicrobial Resistance in Specific Patient Populations

**ISIS-AR**

In 2007, the new surveillance system ISIS-AR (Infectious Disease Surveillance Information System for Antibiotic Resistance) replaced the old ISIS system that started to collect data in 1998. ISIS-AR is coordinated by the Centre for Infectious Disease Control, the National Institute for Public Health and the Environment (RIVM) in Bilthoven, in collaboration with the Netherlands Society for Medical Microbiology (NVMM). It collects together with antibiotic resistance data now also all epidemiological data available in the laboratory information systems of participating laboratories. The additional epidemiological information allowed data collected from Outpatient Clinics and GP Patients from hospital departments to be separated and more insight in demographic and epidemiology data could be obtained. Furthermore, there is strong focus on the quality of data by national standardisation, structural quality control, and confirmation of unusual resistance data. The change to the new system also meant some laboratories stopped participating and others joined. Furthermore, the number of participating laboratories increased.



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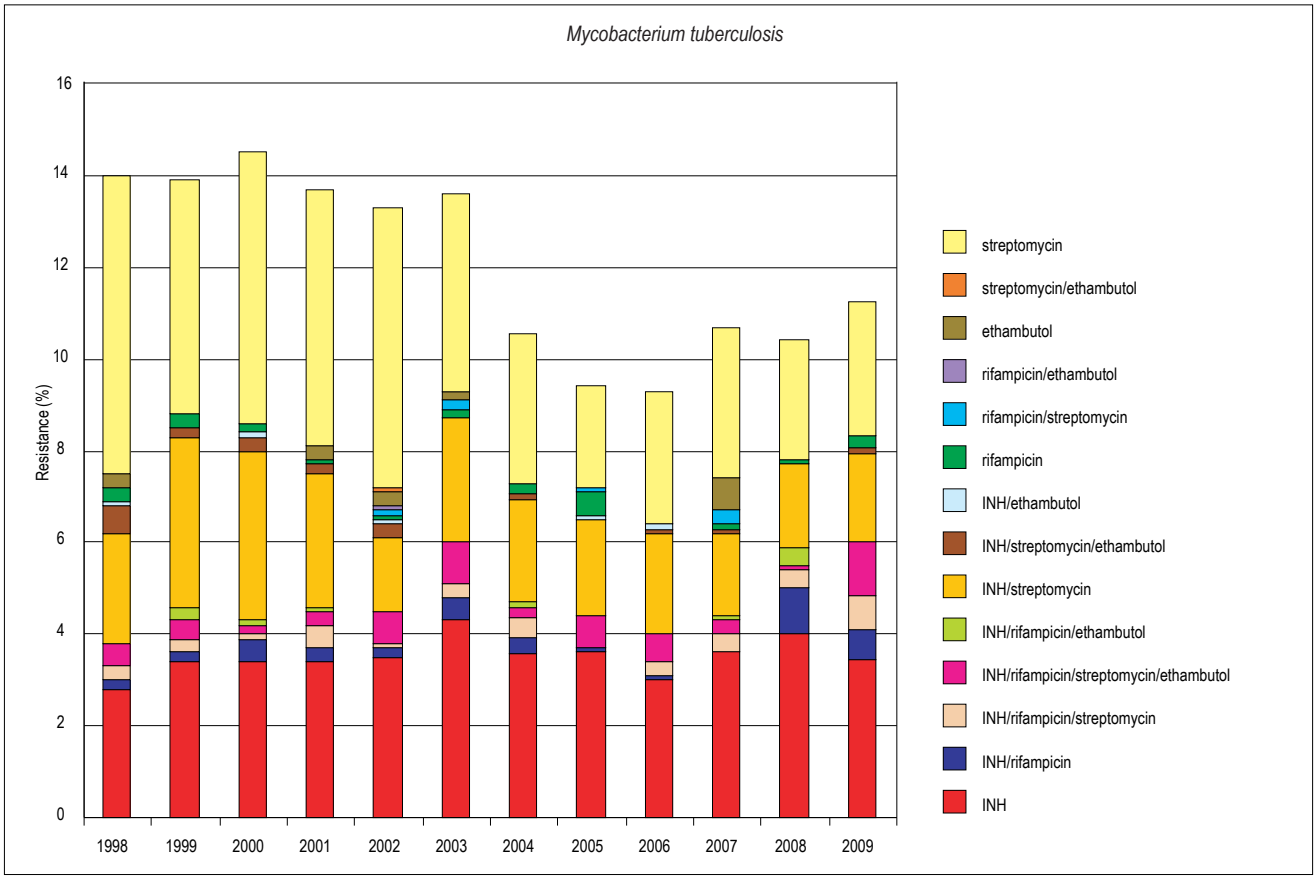



Figure 10. Trends in combined resistance among *Mycobacterium tuberculosis*.

The overall prevalence of antibiotic resistance in hospitals was estimated from the ISIS-AR dataset, based on routine antimicrobial resistance data interpreted as resistant, intermediate or susceptible by the participating laboratories in the Netherlands and reported as such. For analyses, the first isolate per species per patient was taken and the data are categorized as originating from Unselected Hospital Departments, Outpatient Clinics and selected GP patients. Further details can be found in the materials and methods section.
In this chapter, data is presented jointly from both the old ISIS and the new ISIS-AR systems. As these two systems have only limited comparability, the data is being represented in common graphs, but with a break between the years 2007 and 2008.

**SWAB-SIRIN**
Resistance in selected hospital departments was recorded by studying susceptibility patterns in 14 large referral hospitals participating in the longitudinal national SWAB study for Surveillance of Intramural Resistance in the Netherlands (SIRIN); the design of SIRIN differs significantly from ISIS-AR by generating quantitative susceptibility data, performed by the central laboratory of Medical Microbiology of the University Medical Centre Maastricht. The selected departments participating in SIRIN included the Intensive Care Units, being wards with high use of antibiotics and, consequently, high selective pressure favouring the emergence of resistance. Also included were the Urology Services and the Pulmonology Services, the latter two representing departments with frequent use of specific oral antibiotics. The quantitative data of all years were evaluated by use of EUCAST breakpoints according to the decision of SWAB in 2009 to adopt the EUCAST guidelines for susceptibility testing and surveillance. Results were analysed per species of common nosocomial pathogens and are presented in the accompanying figures.

We realized that it was problematic to compare the resistance data from the community (SERIN) and the specific hospital departments (SIRIN) with those reported by ISIS-AR, since most laboratories (12 out of 14) participating in ISIS-AR in 2009 use automated systems for qualitative susceptibility testing with breakpoints for resistance according to CLSI guidelines. In general, CLSI breakpoints for resistance (R) are higher than those of EUCAST, whereas the CLSI breakpoints for intermediate (I) are equal to the EUCAST breakpoints for resistance for most antibiotics. So we displayed the resistance rates I+R (low breakpoint of CLSI) reported by the participating laboratories of ISIS-AR and compared these with the resistance rates from specific wards and in the community calculated according EUCAST guidelines for resistance.



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Further a table was composed with the overview of the differences in resistance rates for the antibiotics and micro-organisms reported to the ISIS-AR database when using both R and I+R values (chapter 4.3.4).

### 4.3.1 Escherichia coli antimicrobial resistance patterns according to ISIS-AR

Due to the epidemiological data present in ISIS-AR it is now possible to select and compare resistance patterns from different well-defined patient populations in different settings. In the next two paragraphs 4.3.1.1 and 4.3.1.2 a number of examples of such analyses are presented to illustrate the possibilities of ISIS-AR. Firstly, resistance patterns in ICU and non–ICU patients settings was compared (4.3.1.1). Secondly, the extent of institution and age influence the resistance rates of *E. coli* against ciprofloxacin and ceftriaxone (4.3.1.2).

For the Netherlands, surveillance of antimicrobial resistance patterns of urinary tract pathogens is performed by both SERIN and ISIS-AR. In paragraph 4.3.1.3 we will show the (multi)drug resistance rates of *E. coli* in the general practice setting based on ISIS-AR data and SERIN data and relate the results to the guideline for urinary tract infections in the primary care setting[1]. In addition we compared the ISIS-AR data with the SERIN data to determine to what extent this difference in surveillance method leads to different resistance rates. Finally, we will show the extent of resistance absed on the ISIS-AR dataset in patients younger than 12 years visiting the general practitioner and compared to those obtained from older patients.

Surveillance of antimicrobial resistance patterns of pathogens causing infections at Dutch ICUs is performed by both SIRIN and ISIS-AR. No difference in patients groups or selection of isolates is made. The only difference is that in SIRIN the isolates are collected and the MIC values are determined by one laboratory. In chapter 4.3.1.4 we will discuss whether this difference leads to different resistance rates.

Details of methods and materials used for analyses can be found in chapter 7.2.2.1.

More results from the ISIS-AR database, on a selection of pathogens that serve as markers for clinically and epidemiologically meaningful developments in antibiotic resistance in the Netherlands, can be viewed at the interactive website ISIS web (www.ISIS-web.nl).

#### *4.3.1.1 Escherichia coli resistance patterns in ICU and non-ICU*

As in previous years, the resistance trends in hospitals described in chapter 4.3.3 are based on combined data from both Intensive Care Units (ICU) and other departments (non-ICU). The aim of the study described in this paragraph was to determine whether there are significant differences in resistance rates between isolates obtained from ICUs and non-ICUs.
The ISIS-AR database of 2009 contained at the moment of this analysis in total 17,612 *E. coli* isolates of which 2,955 (17%) were ICU-isolates. As shown in figure 11 resistance rates for beta-lactams of ICU-isolates were significantly higher than those of other non-ICU departments ($p<0.05$), although this was not the case for gentamicin and ciprofloxacin resistance rates. Due to the relative low number of ICU isolates in the total number of isolates the influence of these higher resistance rates on the overall resistance rates was small. The difference was 0.5% for co-amoxiclav, 0.3% for ceftazidime, 0.2% for ceftriaxone, 0.1% for piperacillin/tazobactam and for ciprofloxacin, and 0.0% for gentamicin. However, since Nethmap resistance rates may be used to determine empiric therapy regimens in hospitals these results indicate that resistance rates of ICUs and non-ICUs should be analysed separately.

#### *4.3.1.2 Resistance rates of Escherichia coli in different settings and distinguished patient populations*

Guidelines on empiric antimicrobial therapy may take into account the institution (general practitioner, out-patient department, long-term care facility or hospital) the patient is visiting or the age of the patient. We studied the influence of institution and age on the resistance rates of *E. coli* against ciprofloxacin and ceftriaxone.
The 2009 ISIS-AR database contained at the moment of the analysis resistance patterns of 50,465 isolates agaist ceftriaxone and 46,611 against ciprofloxacin; 50% of the isolates were obtained from patients in general practice, 25% from clinical patients, 21% from patients visiting outpatient clinics, and 4% from nursing homes residents. Of all patients, 6% were children 1-5 years old, 7% were 6-18 years old, 37% were 19-64 years old and 50% was 65 years of age or older. Almost all isolates were derived from urine (90%).

As shown in figure 12, ceftriaxone resistance rates were higher among isolates obtained in nursing homes and the hospital than in isolates obtained at the outpatient clinics and at the GP. Ciprofloxacin resistance rates, however, were highest in nursing homes, followed by outpatient clinics, clinic, and GP, respectively (figure 13). No significant difference is seen in ceftriaxone resistance rates between age groups above patients older than 5 yrs (figure 12). This is in stark contrast with the ciprofloxacin resistance rates, where a strong correlation between age and resistance rates exists.
These differences between settings and age groups and resistance rates per antimicrobial agent may reflect

[1] http://nhg.artsennet.nl/kenniscentrum/k_richtlijnen/k_nhgstandaarden/NHGStandaard/M05_std.htm#Medicamenteuzebehandeling



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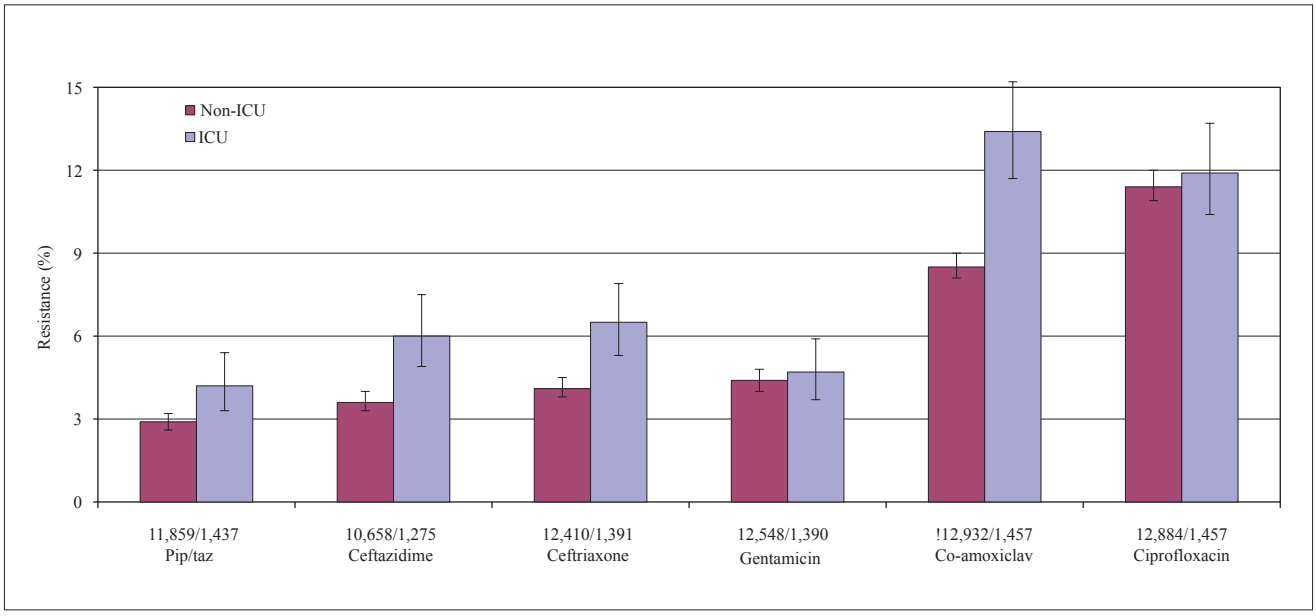



Figure 11. Resistant rates of *E. coli in* ICU and non-ICU departments. The number of isolates tested per department is displayed on the X-axis.

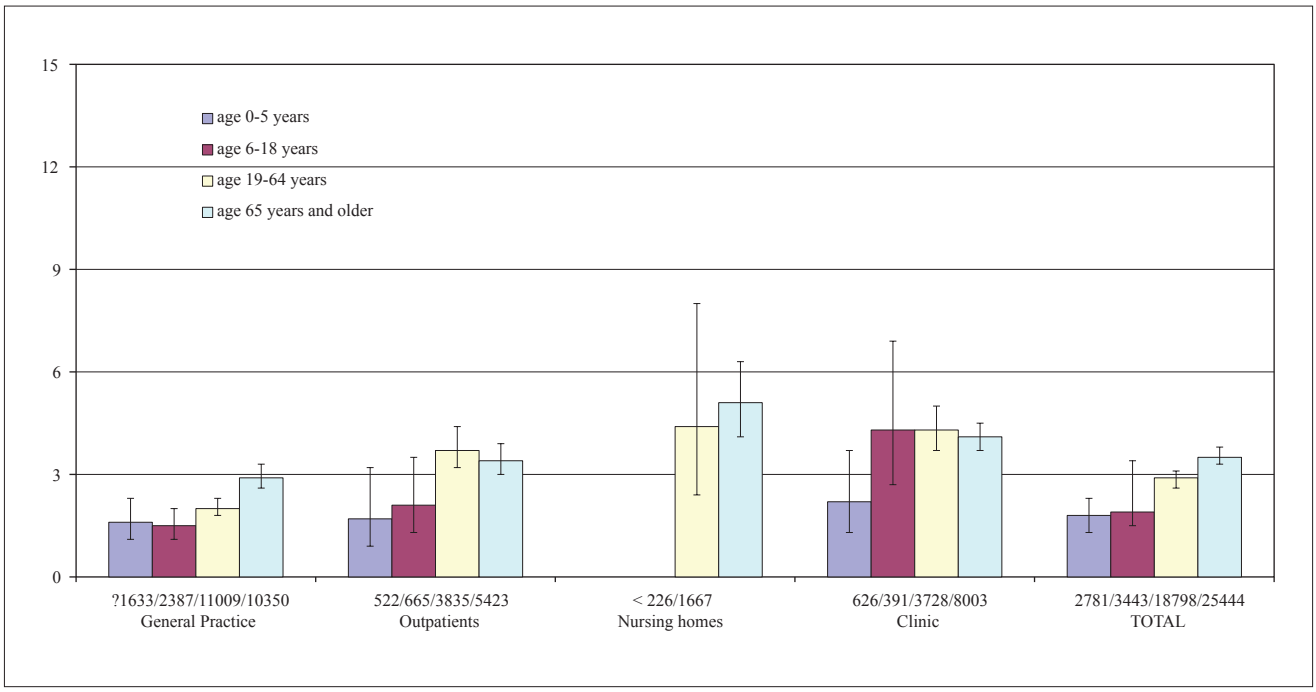



Figure 12. Ceftriaxone resistance rates of *E. coli* per setting and age group. The number of isolates tested per setting per age group is displayed on the X-axis.

different antibiotic usage in the different settings, the way resistance is predominantly acquired, either by transmission or de novo development, the rate in which resistance is lost.

#### *4.3.1.3 Escherichia coli resistance rates in urinary tract samples in the primary care setting*

The resistance percentages among *E. coli* isolates from GP patients reported to ISIS-AR in 2009 were analyzed for age groups and compared with the results from the 2009 SERIN study (chapter 4.2.1). We assessed the resistance rates to the antibiotics recommended by the NHG for the treatment of urinary tract infections in general practice setting.

*Results from ISIS-AR*

Results from 44,011 urinary isolates were reported to the ISIS-AR database in 2009, of which 25,086 (57%) were *E. coli*. Of the total number of isolates, 20% were obtained from males and 80% from females, whereas



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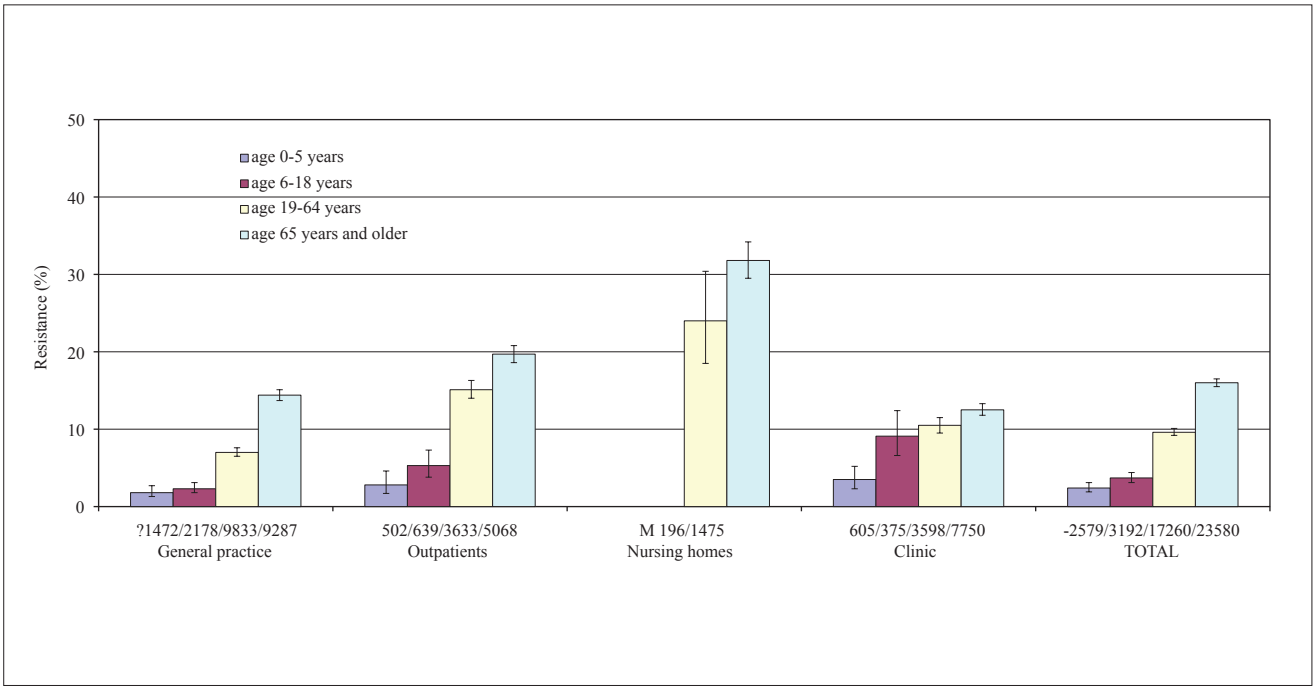



Figure 13. Ciprofloxacin resistance rates of *E. coli* per setting and age group. The number of isolates tested per setting per age group is displayed on the X-axis.

from children up to 18 years of age, only 10% was male. Resistance to one or more classes of antibiotics were calculated. Co-trimoxazole and trimethoprim were considered as one class since 92% of the isolates resistant to trimethoprim were also resistant to co-trimoxazole, and vice versa where co-resistance was 99%. Norfloxacin and ciprofloxacin were also combined, as 99% of isolates resistant to norfloxacin were also resistant to ciprofloxacin, and vice versa where co-resistance was 95%.

Of all strains, 35% was resistant to one or more classes of antibiotics. Resistance to co-trimoxazole was 30.5%, to fluoroquinolones 9.6%, to co-amoxiclav 5.7%, and to nitrofurantoin 2.3%. Table 2 shows percentages of *E. coli* isolates resistant to one, two, three or four classes of antibiotics. Fosfomycin was tested only in two laboratories and was not included in this analysis, although the resistance to this drug appeared low (0.5%). Furthermore, 10.4% of the strains was resistant to two

*Table 2. (Multi) drug resistance rates of Escherichia coli from urine of patients in primary care, ISIS-AR, 2009*

| Antibiotic class | % resistance (n=25,086) | |
|---|---|---|
| Susceptible | 64.6 | |
| Resistance to one class | | |
| Nitrofurantoin | 0.6 | |
| Co-trimoxazole/trimethoprim | 20.7 | |
| Ciprofloxacin/ norfloxacin (fluoroquinolones) | 2.0 | |
| Co-amoxiclav | 1.6 | |
| total | | 25.0 |
| Resistance to two classes | | |
| Nitrofurantoin + co-trimoxazole/trimethoprim | 0.7 | |
| Nitrofurantoin + fluoroquinolones | 0.1 | |
| Nitrofurantoin + co-amoxiclav | 0.1 | |
| Co-trimoxazole/trimethoprim + fluoroquinolones | 5.0 | |
| Co-trimoxazole/trimethoprim + co-amoxiclav | 2.0 | |
| Fluoroquinolones + co-amoxiclav | 0.3 | |
| total | | 8.2 |
| Resistance to three classes | | |
| Nitrofurantoin + co-trimoxazole/trimethoprim + fluoroquinolones | 0.5 | |
| Nitrofurantoin + co-trimoxazole/trimethoprim +co-amoxiclav | 0.1 | |
| Nitrofurantoin + fluoroquinolones + co-amoxiclav | 0.0 | |
| Fluoroquinolones + co-trimoxazole/trimethoprim + co-amoxiclav | 1.4 | |
| total | | 2.0 |
| Resistance to four classes | 0.2 | |



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or more classes of antibiotics: 8.2% to two, 2.0% to three classes of antibiotics and 0.2% to four classes of antibiotics. All isolates (n=40) resistant to four classes of antibiotics were confirmed to be ESBL-positive, also indicating resistance to third generation cephalosporins (e.g. ceftriaxon, ceftazidime). Fortunately, they were still susceptible to carbapenems.

*Comparison of ISIS-AR and SERIN data*
For the Netherlands, surveillance of antimicrobial resistance patterns of urinary tract pathogens is performed by both SERIN and ISIS-AR. In SERIN resistance patterns of *E. coli* isolates causing uncomplicated UTI in unselected patients older than 11 years visiting the general practitioner are collected. The MICs of these isolates are determined centrally. In ISIS-AR resistance patterns of *E. coli* urine isolates represent both complicated and uncomplicated UTIs. Any age group can be selected. The MICs are determined and interpreted by the participating laboratories which most often followed the CLSI guidelines. Resistance percentages for SERIN were recalculated from the MIC values using CLSI breakpoints to be able to compare both results.
We determined if and to what extent the different surveillance methods would lead to different resistance rates in patients older than 11 years. Again, resistance rates were compared against the antibiotics recommended by the NHG for the treatment of urinary tract infections in the general practice setting.

The resistance percentages found for GP patients in the community by ISIS-AR were significantly higher than those found by SERIN for the antibiotics indicated (table 3). These differences are likely the result of the difference in patients groups in both surveillance systems. Patients with uncomplicated UTI are in the ISIS-AR database less prevalent than in the SERIN database and patients with uncomplicated UTI are less likely to have had prior antibiotic treatment or admittance to health care facilities.
From these data it can also be concluded SERIN data are necessary to provide the information needed to determine the empiric therapy for uncomplicated UTIs in the general practice.

Nitrofurantoin is the first choice antibiotic for uncomplicated UTI according to the Dutch guidelines for primary care. Trimethoprim and fosfomycin are recommended as second and third choice, and norfloxacin and ciprofloxacin are considered as spare antibiotics. Based on these resistance rates, the recommendation of the Dutch guideline for primary care to prescribe trimethoprim as an empiric antibiotic for *uncomplicated* UTIs should be reconsidered.
For complicated UTI, co-amoxiclav is the first choice, while co-trimoxazole and a fluoroquinolone (norfloxacin or ciprofloxacin) are recommended as alternative agents. Based on these resistance rates the recommendations of the Dutch primary care guideline for complicated UTIs should be revised as well. The resistance rates to the first drug of choice, co-amoxiclav, has increased to nearly 6% and to the alternative agents ciprofloxacin and co-trimoxazole to alarming rates of respectively 10% and 28%. It should be noted that these percentages are flattered since the ISIS-AR data are a combination of urine from complicated and uncomplicated UTIs.

*Resistance rates of E. coli isolates obtained from patients younger and older than 12 yrs*
Since SERIN surveillance does not include data from patients younger than 12 years, it is unknown whether the SERIN resistance data can also be used for antibiotic guidelines for children younger than 12 years. To determine whether resistance rates in this younger age group differ significantly from the older population, resistance rates were compared between patients younger and older than 12 yrs visiting the general practitioner (table 4). From all isolates tested, 12% were obtained from children below 12 years of age. For all antibiotics tested the resistant rates were higher in isolates from patients above 12 years. These results indicate that the SERIN surveillance should be extended to children younger than 12 yrs.

#### *4.3.1.4 Comparison between data from ISIS-AR and SIRIN on 2008 data – Resistance rates in Intensive Care Units*

Surveillance of antimicrobial resistance patterns of pathogens causing infections at Dutch ICUs is performed by both SIRIN and ISIS-AR. The aim of this study was to compare the resistance patterns from ICU collected through SIRIN and those present in ISIS-AR in 2008.
In SIRIN, resistance rates are assessed by MIC values obtained by a micro broth dilution method of isolates collected by SWAB and analyzed in a central laboratory. The laboratories participating in ISIS-AR mostly use automated microdilution systems (VITEK, Phoenix). Since 2009, the interpretation of the MIC values in SIRIN is based on EUCAST breakpoints (Nethmap 2009; data from 2008) while in ISIS-AR, the interpretation of the MIC values by the participating laboratories is based on CLSI (twelve laboratories) or CRG breakpoints (two laboratories). Table 5 shows the different breakpoints for CRG, EUCAST and CLSI. For most antibiotics, isolates considered “Intermediate” according to CLSI guidelines, should be recorded “Resistant” when using EUCAST guidelines, except for cefotaxime, co-trimoxazole and nitrofurantoin.
The number of isolates tested per antimicrobial agent was 227 in SIRIN and the mean number of isolates tested per antimicrobial agent in ISIS-AR was 1237. As cefotaxime was tested in SIRIN, but the ISIS-AR laboratories only reported ceftriaxone resistance, these antibiotics were left out of the comparison.



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*Table 3. Resistance patterns of E. coli in urinary tract isolates in primary care; data from SERIN and ISIS-AR, 2009*

| Antibiotic | % resistance (95%CI) | |
|---|---|---|
| | ISIS-AR (n=25,086) | SERIN (n=489) |
| Nitrofurantoin | 2.3 (2.1-2.4) | 0.4 (0.1-1.5) |
| Co-trimoxazole | 28.2 (27.6-28.7) | 17.2 (14.1-20.8) |
| Trimethoprim | 30.3 (29.8-30.9) | 19.6 (16.4-23.4) |
| Ciprofloxacin/ norfloxacin | 9.6 (9.2-9.9) | 3.1 (1.9-5.0) |
| Co-amoxiclav | 5.8 (5.5-6.0) | 2.0* (1.1-3.7) |
| Fosfomycin | 0.5 (0.4-0.6)# | |

* When CLSI I+R should be taken, 12.8% of isolates would be resistant to co-amoxiclav. This large difference is caused by a high number of isolates with MIC=16 mg/l, classified as I according to CLSI.

\# Only two laboratories tested for fosfomycin (N=9,671 isolates).

*Table 4. Comparison of resistance rates between children younger than 12 years old and patients above 12 years of age of E. coli urinary tract isolates in primary care using ISIS-AR data of 2009*

| Antibiotic class | % resistance (95%CI) | |
|---|---|---|
| | < 12 years old (n=3,138) | ≥12 years old (n=22,300) |
| Susceptible (to the antibiotics included in the analysis) | 74.3 (72.8-75.8) | 63.2 (62.6-63.8) |
| Nitrofurantoin | 0.5 (0.3-0.8) | 2.5 (2.3-2.7) |
| Co-trimoxazole/ trimethoprim | 23.3 (21.8-24.8) | 31.6 (31.0-32.2) |
| Ciprofloxacin/ norfloxacin | 2.0 (1.5-2.6) | 10.6 (10.2-11.0) |
| Amoxicillin | 39.0 (37.3-40.7) | 43.0 (42.3-43.6) |
| Co-amoxiclav | 4.1 (3.5-4.9) | 6.0 (5.7-6.3) |

*Table 5. CRG, EUCAST and CLSI breakpoints for Escherichia coli*

| Antibiotic class | CRG | | *EUCAST* | | CLSI | | |
|---|---|---|---|---|---|---|---|
| | S ≤ | R > | S ≤ | R > | S ≤ | I | R ≥ |
| Ampicillin | 2 | 16 | | 8 | 8 | 16 | 32 |
| Amoxicillin | 2 | 16 | | 8 | 8 | 16 | 32 |
| Co-amoxiclav | 2 | 16 | | 8 | 8 | 16 | 32 |
| Piperacillin | 16 | 64 | 8 | 16 | 16 | 32-64 | 128 |
| Piperacillin-tazobactam | 16 | 32 | 8 | 16 | 16 | 32-64 | 128 |
| Cefaclor | | | - | - | 8 | 16 | 32 |
| Cefotaxime | 4 | 16 | 1 | 2 | 8 | 16-32 | 64 |
| Ceftazidime | 4 | 16 | 1 | 8 | 8 | 16 | 32 |
| Cefuroxime | 4 | 16 | 8 | 8 | 8 | 16 | 32 |
| Ciprofloxacin | 1 | 2 | 0.5 | 1 | 1 | 2 | 4 |
| Gentamicin | 1 | 4 | 2 | 4 | 4 | 8 | 16 |
| Nitrofurantoin | 32 | 32 | 64 | 64 | 32 | 64 | 128 |
| Trimethoprim | 1 | 2 | 2 | 4 | 8 | | 16 |
| Co-trimoxazole | 1 | 2 | 2 | 4 | 2 | | 4 |

*ISIS-AR compared with SIRIN using interpreted data*

As the majority of laboratories in ISIS-AR used CLSI breakpoints in 2008, the CLSI categories I and R were combined in order to compare the results with the SIRIN results based on EUCAST breakpoints. The resistance rates in SIRIN and ISIS-AR were comparable (overlapping confidence intervals) for all antibiotics tested, except nitrofurantoin and cefuroxime (table 6). The difference for cefuroxime originated from the use of different breakpoints. Two laboratories using CRG breakpoints reported 32 isolates with a MIC of 8 mg/l to be intermediately resistant while these isolates are susceptible according to both EUCAST and CLSI criteria. If these isolates were interpreted susceptible, cefuroxime resistance for ISIS-AR would have been 12.5% instead of 15%, and comparable with the resistance rate determined by SIRIN.

For nitrofurantoin, the higher resistance percentages in ISIS-AR could also be explained by differences in breakpoints. In ISIS-AR, 58 isolates with a MIC-value of 64 mg/l were reported intermediate according to CLSI breakpoints. According to EUCAST these isolates are susceptible. Deduction of these isolates from the resistant isolates resulted in a 5% lower resistance percentage for nitrofurantoin in ISIS-AR, which would result in a similar percentage as determined in SIRIN.

*ISIS-AR data compared with SIRIN using re-interpreted MICs*

Most laboratories participating in ISIS-AR and using automated systems for susceptibility deliver MIC values from a limited test range (the range is determined by the breakpoint criteria used). These MIC values were available for 90% of all isolates and were re-interpreted



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*Table 6. Resistance among Escherichia coli in Intensive Care Units from SIRIN (EUCAST) and ISIS-AR*

| Antibiotic class | SIRIN *(% resistance, 95%CI)* | ISIS-AR *(% resistance, 95%CI)* | |
|---|---|---|---|
| | | Interpreted by laboratories* | Re-interpretation using EUCAST |
| Amoxicillin/Ampicillin | 47.6 (41.2-54.1) | 48.9 (46.4-51.4) | 49.0 (45.4-52.7) |
| Co-amoxiclav | 24.7 (19.5-30.7) | 23.3 (21.2-25.5) | 23.6 (21.5-25.9) |
| Piperacillin | 41.0 (34.8-47.5) | 35.5 (33.0-38.1) | 33.9 (31.4-36.5) |
| Piperacillin/tazobactam | 1.3 (0.5-3.8) | 3.8 (3.0-5.0) | 2.9 (2.1-3.9) |
| Ceftazidime | 1.8 (0.7-4.4) | 4.3 (3.3-5.6) | 2.4 (1.7-3.5) |
| Cefuroxime | 8.4 (5.4-12.7) | 15.0 (13.2-17.1) | 12.2 (10.5-14.1) |
| Ciprofloxacin | 15.4 (11.3-20.7) | 11.9 (10.3-13.6) | 11.6 (10.1-13.4) |
| Gentamicin | 4.0 (2.1-7.4) | 5.9 (4.8-7.2) | 5.4 (4.3-6.6) |
| Nitrofurantoin | 0.4 (0.1-2.5) | 5.7 (4.5-7.2) | 0.7 (0.4-1.4) |
| Trimethoprim | 30.4 (24.8-36.7) | 29.0 (26.4-31.6) | 29.7 (27.0-32.5) |
| Co-trimoxazole | 29.1 (23.6-35.3) | 27.7 (25.5-30.0) | 27.7 (25.5-30.1) |

* intermediate susceptible isolates are added to the resistant isolates

using EUCAST breakpoints in accordance with SIRIN. As can be seen in table 6, no significant differences were found for any of the antibiotics tested.

From these analyses it can be concluded that surveillance results from SIRIN and ISIS-AR are very comparable. The observed small (not significant) differences in resistance rates are likely due to the different ICUs that were monitored in both systems.
These analyses also confirm previous studies that the use of different breakpoints leads to significantly different resistant rates. For the analysis re-interpretation of the MICs was necessary. These findings emphasize the need for participating laboratories to implement the EUCAST breakpoints as has been recommended by NVMM, VIZ and RIVM in the fall of 2009.

#### *4.3.1.5 The incidence of highly resistant microorganisms (HRMO)*

The occurrence of highly resistant micro-organisms (HRMO) among clinical isolates was investigated for the year 2009 from the ISIS-AR database. Screening and inventory isolates were excluded from the analysis. In total 2,113 HRMO were reported among almost 50,000 strains (4%), which means 71 HRMO per 100,000 patient days.
The majority of HRMO included *E. coli* resistant to 3rd generation cephalosporins (34%), to the combination fluoroquinolones/aminoglycosides (27%), and *Klebsiella spp*. resistant to 3rd generation cephalosporins (11%). Half of the HRMO found were ESBL positive (table 7). The impact of HRMO on patient treatment and health care is clear; limited possibilities for treatment are left and extreme control measures are required to prevent circulating and spread. These figures may help to support infection control measures and strategies as developed by the Dutch Working Party on Infection Prevention (WIP)[2].

### 4.3.2 Surveillance of resistance in outpatient clinics and selected patients from primary care

Data of strains from urine of patients visiting Outpatient clinics and from urine sent for culture by the general practitioner could be distinguished from strains of other origin in 2008 and 2009. Patients visiting the Outpatient Clinics belong to a special category since it is not possible in the Netherlands to visit the Outpatient Clinics without referral by GP or specialist or on indication of a specialist after treatment or hospitalization. This means that they have a medical history and may have been treated for infections before. Further, general practitioners send urine specimens for culture only in case of therapeutic failure or in chronic and complicated urinary tract infections. This group of patients is called 'selected GP patients'. Most of the patients in these categories have been treated with antibiotics before and are not representative for patients visiting the GP for an uncomplicated urinary tract infection. Resistance levels in these patient groups have been compared with results from patients of other study groups and may give insight in use of empiric treatment before.

#### *4.3.2.1 Escherichia coli*

The numbers of strains tested in 2008 and 2009 ranged from 10.000-60.000, depending on the antibiotic tested. Resistance to co-amoxiclav was 16% in 2008 and 2009 (figure 14), which is significantly higher than that found in urinary strains from patients from the community visiting the GP for the first time ($p < 0.05$). Co-amoxiclav is not a drug of first choice for uncomplicated urinary tract infection according to the standard for general practice in the Netherlands (NHG standard), but advised for treatment of complicated urinary infections. Also the rates found for trimethoprim and co-trimoxazole were much higher (30%) than those found in the community. These levels are comparable with those found in isolates

[2] http://www.wip.nl/free_content/Richtlijnen/BRMO.pdf



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*Table 7. HRMO reported to ISIS-AR, 2009*

| | *HRMO (N)* | *HRMO (% of tested)* | *HRMO/ 100,000 patient days* |
|---|---|---|---|
| *E.coli* 3rd generation cephalosporin resistant | 713 | 4.97 | 24.13 |
| *Klebsiella ssp.* 3rd generation cephalosporin resistant | 222 | 5.78 | 7.51 |
| Other Enterobacteriaceae ESBL positive | 115 | | 3.89 |
| *Citrobacter ssp.* ESBL positive | (26) | | (0.88) |
| *Enterobacter cloacae* ESBL positive | (76) | | (2.57) |
| *E.coli* fluoroquinolones and aminoglycosides resistant | 577 | 4.03 | 19.53 |
| *Klebsiella spp.* fluoroquinolones and aminoglycosides resistant | 96 | 2.53 | 3.25 |
| Other Enterobacteriaceae resistant to fluoroquinolones, aminoglycosides and co-trimoxazole* | 113 | 1.97 | 3.82 |
| *E.coli* carbapenem resistant§ | 0 | 0.00 | 0.00 |
| *Klebsiella spp.* carbapenem resistant§ | 1 | 0.03 | 0.03 |
| Other Enterobacteriaceae (excl. *Proteus spp.*) carbapenem resistant§ | 2 | 0.06 | 0.07 |
| *P. mirabilis* meropenem# resistant§ | 0 | 0.00 | 0.00 |
| *Acinetobacter spp.* carbapenem resistant | 24 | 6.35 | 0.81 |
| *Acinetobacter spp.* resistant to fluoroquinolones/ceftazidime / aminoglycosides* | 1 | 1.35 | 0.03 |
| *S. maltophilia* co-trimoxazole resistant | 31 | 5.30 | 1.05 |
| Other non-fermenters *(P. aeruginosa)* resistant to fluoroquinolones, ceftazidime, aminoglycosides, carbapenems, piperacillin** | 142 | 4.16 | 4.81 |
| *P. aeruginosa* resistant to colistine | 45 | 1.82 | 1.52 |
| *S. pneumoniae* penicillin resistant | 22 | 1.40 | 0.74 |
| *S. pneumoniae* vancomycin resistant | 0 | 0.00 | 0.00 |
| *Enterococcus faecium* penicillins† and vancomycin resistant | 6 | 0.44 | 0.20 |
| Other *Enterococcus spp.* penicillins† and vancomycin resistant | 3 | 0.07 | 0.10 |
| **Total** | **2,113‡** | | **71.49** |

* combined resistance for at least two indicated antibiotic groups or agents.

** combined resistance for at least three indicated antibiotic groups or agents.

\# meropenem is tested, as testing with imipenem incorrectly shows resistant isolates.

§ published only after explicit confirmation.

† (benzyl)penicillin, piperacillin, amoxicillin, or ampicillin.

‡ from 431 patients more than one HRMO was isolated. For other ESBL positive Enterobacteriaceae, the percentage of isolates tested is not displayed, as 97% of these isolates were not tested.

from Unselected Hospital Departments (see 4.3.3). Norfloxacin- and ciprofloxacin resistance appeared 11% in both years, which was significantly higher than those found in the community (3.5%). The levels in Outpatient Clinics and in selected GP patients were also comparable to those found for Unselected Hospital Departments. Nitrofurantoin resistance was 6% in 2008 and 2009, which was higher than that found in the community (1%) and equal to the level found in Urology Services (see 4.3.3). Fosfomycin resistance was less than 1%.

*4.3.2.2 Klebsiella pneumoniae*

The numbers of strains tested in 2008 and 2009 ranged from 1300-7400. Co-amoxiclav resistance was 9% in 2008 and 2009 (figure 14), which was somewhat lower than the level found for strains from hospitalized patients (12%). Trimethoprim resistance (25% in 2008 and 26% in 2009) was significantly higher in this group of patients compared to that among strains from patients of Unselected Hospital Departments ($p<0.05$) and was equal at the level found for patients from Urology Service in 2008 (see 4.3.3). The resistance rate to co-trimoxazole was 20%, which was also comparable with the resistance level in Urology patients. Norfloxacin- and ciprofloxacin resistance was 5-6%, which was also in the range found for patients from Unselected Hospital departments and Urology Services. Data of resistance levels among patients from the community are not available. Nitrofurantoin resistance (79%) was similar to that reported for patients from Unselected Hospital Departments. Fosfomycin resistance was 5% in 2008 and 9% in 2009. Fosfomycin is third choice for the treatment of uncomplicated urinary tract infections in general practice. Finding 9% resistance among *K. pneumoniae* from urine is highly suggestive for previous treatment with this drug and failure with other drugs like nitrofurantoin and trimethoprim. Failures with these drugs suggest existence of complicated, invasive urinary tract infections for which fosfomycin is not the appropriate drug. Inappropriate use may increase development of resistance.

*4.3.2.3 Klebsiella oxytoca*

The numbers of strains tested in 2008 and 2009 ranged from 1200-2400, depending on the antibioticum tested. Co-amoxiclav resistance was 12%, which was higher than the resistance level among *K. pneumoniae* ($p<0.05$). In contrast, the resistance percentages to trimethoprim,



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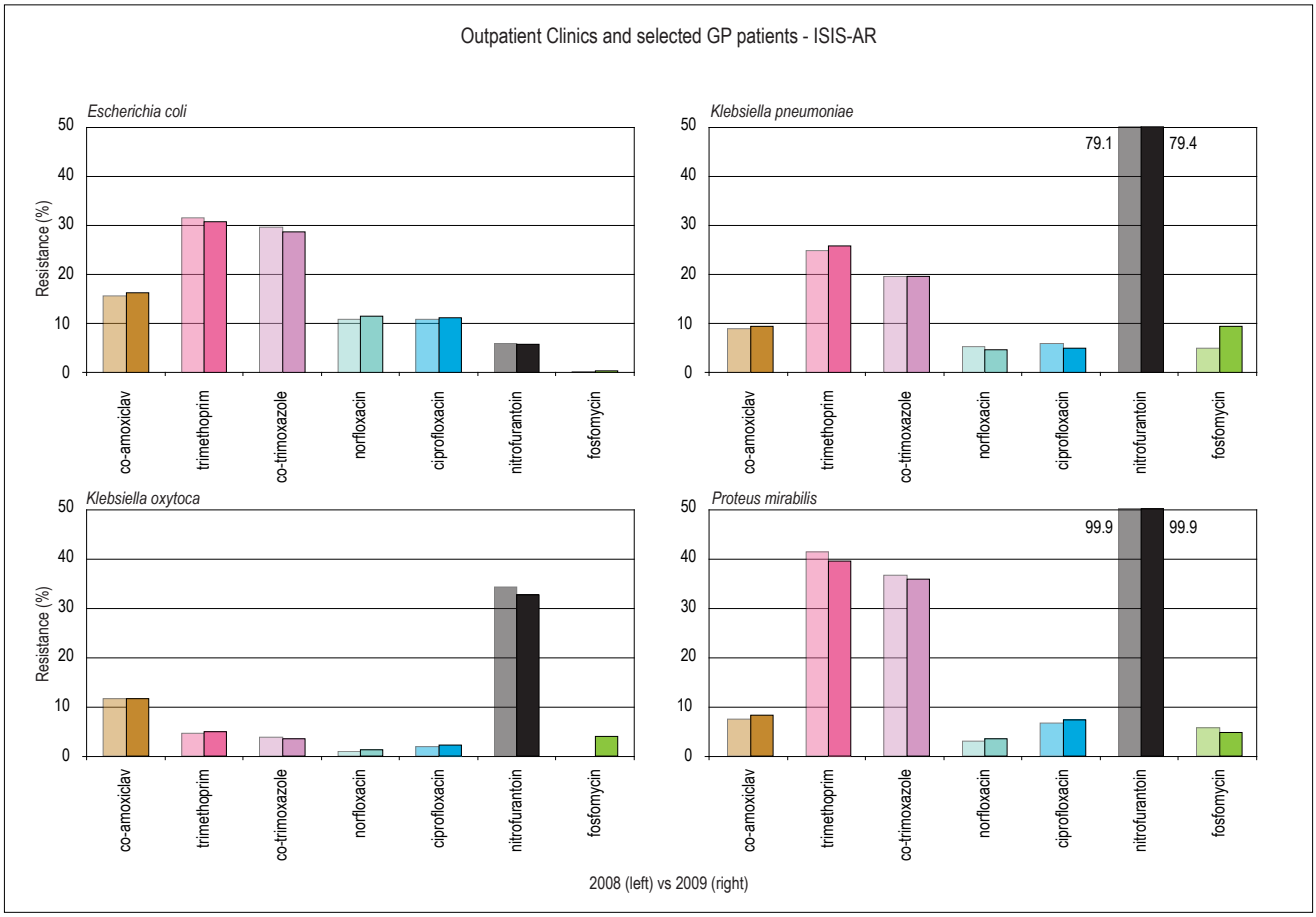



Figure 14. Antibiotic resistance among Enterobacteriaceae from selected patients of general practice and patients from outpatient clinics, reported to ISIS-AR in 2009.

co-trimoxazole (4-5%), the quinolones (1-2%), nitrofurantoin (34%) and fosfomycin (4%) were lower than those for *K. pneumoniae* in the same study group.

*4.3.2.4 Proteus mirabilis*

The number of strains tested in 2008 and 2009 ranged from 1200-3500, depending on the antibiotic tested. Co-amoxiclav resistance (figure 14) was 7% in 2008 and 8% in 2009, being as high as that reported for patients in Unselected Hospital Departments and Urology Services. Trimethoprim- and co-trimoxazole resistance were high (around 40% and 36%, respectively), similar to the levels found in Urology Services in previous years and higher than those found for patients in Unselected Hospital Departments. *Proteus mirabilis* is associated with complicated urinary tract infections. So the high resistance rates must be the result of previous treatments. Resistance to quinolones reported (I+R) was 3% for norfloxacin and 7% for ciprofloxacin. An explanation for this discrepancy could not be found. Differences in breakpoints may have been the cause of it. Fosfomycin resistance was 5-6%.

### 4.3.3 Surveillance of antimicrobial resistance in hospitals

*4.3.3.1 Escherichia coli*

The numbers of strains from Unselected Hospital Departments participating in ISIS-AR, tested for each antibiotic varied roughly from 10,000 – 20,000 during the years; not all strains were tested for all antibiotics. Details of drug/bug combinations for 2009 are given in table 9 as an example of the collection obtained.

The overall prevalence of amoxicillin resistance in Unselected Hospital Departments showed an increasing trend from 36% in 1998 to 47% in 2009 (figure 15). Amoxicillin resistance in ICUs was already higher in 1998 (46%), it showed considerable fluctuations between 2005 and 2007 and it increased slightly to 48% in 2008 (figure 16). The numbers of strains tested were much lower annually (200-225) than those obtained by ISIS-AR and this may be the reason for the incidental fluctuations. The distribution of MICs (figure 17) in ICUs showed two subpopulations: a susceptible one with a broad MIC range from 0.5-8 mg/l (peak at 2-4 mg/l) and a resistant one with MICs >32 mg/l. The resistant subpopulation was steadily growing during the years, whereas the peak of the susceptible one was gradually becoming more flat. The numbers of strains from Urology Services were higher



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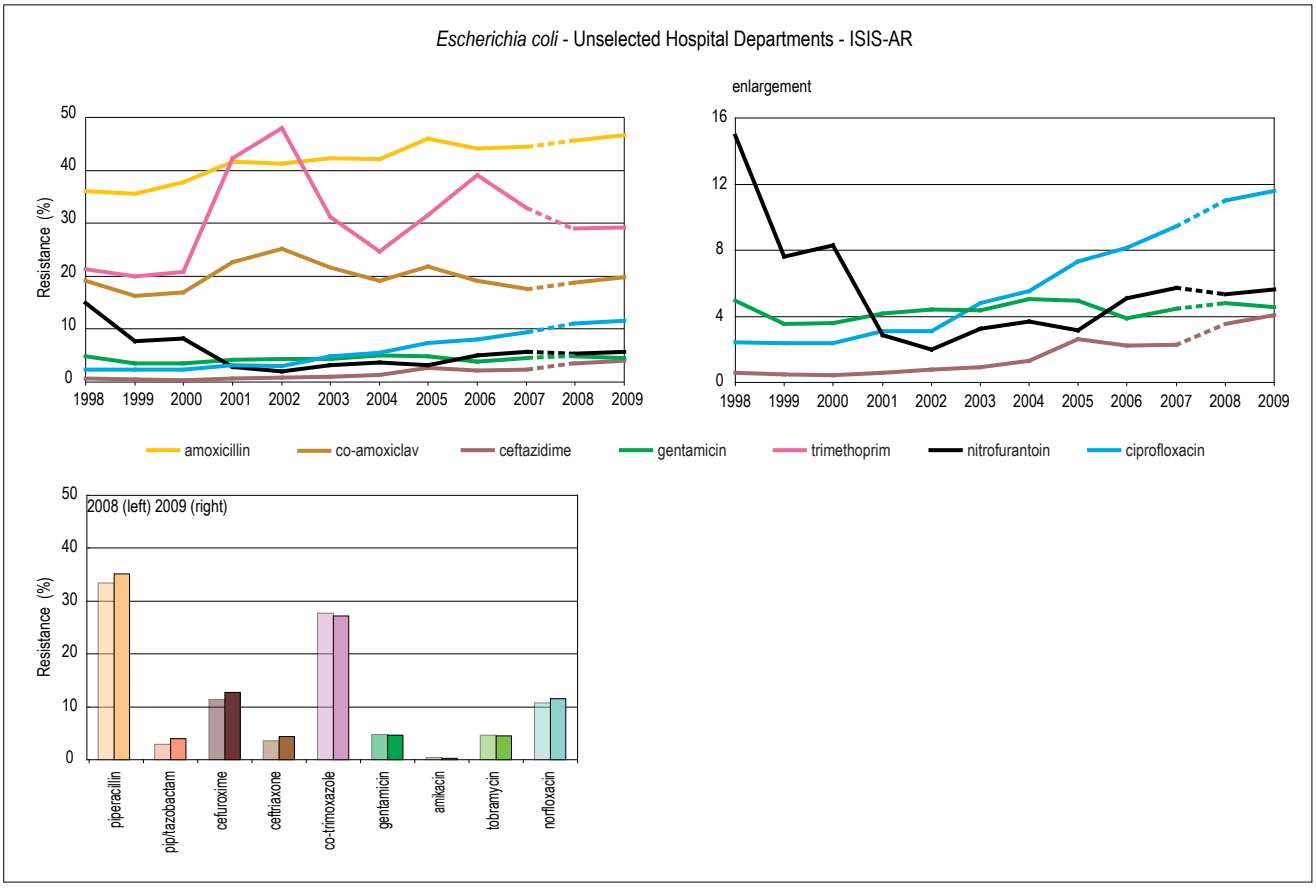



Figure 15. Trends in antibiotic resistance (1998-2009) among clinical strains of *Escherichia coli* (N= 82.000-170.000) from Unselected Hospital Departments, calculated from the values for intermediate susceptibility and resistance (I+R) reported to ISIS-AR. Additional antibiotics tested in 2008 and 2009 are presented as columns.

(600-700 annually). The resistance in Urology Services fluctuated around 40% from the beginning and showed a slow increase to 46% in 2008.
Co-amoxiclav resistance was around 19% during the whole study period with peaks in 2001 (23%), 2002 (25%) and in 2005 (22%), respectively (figure 15).
The trend in the Urology Services was fluctuating but increasing from 19% in 1998 to 24% in 2008. Co-amoxiclav resistance was higher in ICUs and increased from 22% in 1998 to 25% in 2008 (figure 16).
The MIC distribution of co-amoxiclav among strains from ICUs (and Urology Services) was unimodal and showed a growing number of strains with MIC = 16 mg/l (figure 17), the breakpoint for resistance as recommended

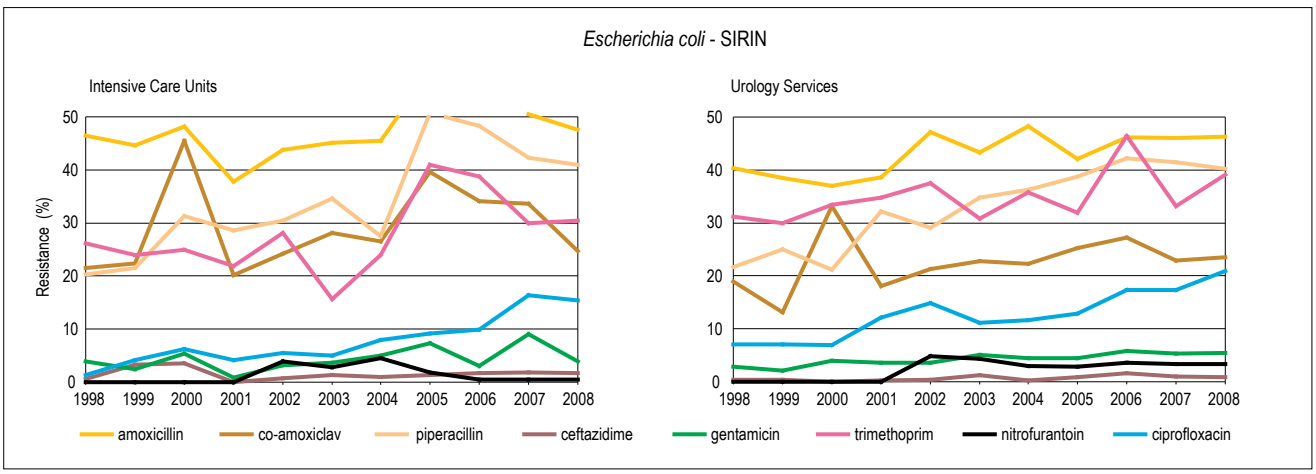



Figure 16. Trends in antibiotic resistance among clinical strains of *Escherichia coli* from Intensive Care Units (N=2.223) and Urology Services (N=6.769), calculated according to the breakpoints for resistance of EUCAST.



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*Table 9. Numbers of clinical isolates of Escherichia coli, tested for each antibiotic indicated and the reported values of resistance (R) and resistant + intermediate susceptible (I+R), ISIS-AR.*

| Antibiotic | Strains (N) | *R (N)* | *R (%)* | *I + R (N)* | *I+R (%)* |
|---|---|---|---|---|---|
| amoxicillin/ampicillin | 13939 | 6407 | 46.0 | 6510 | 46.7 |
| co-amoxiclav | 13991 | 1218 | 8.7 | 2777 | 19.8 |
| piperacillin | 11338 | 3227 | 28.5 | 3979 | 35.1 |
| piperacillin/tazobactam | 12902 | 376 | 2.9 | 510 | 4.0 |
| carbapenem | 12992 | 2 | 0.0 | 3 | 0.0 |
| ceftazidime | 11605 | 436 | 3.8 | 470 | 4.0 |
| ceftriaxone | 13790 | 574 | 4.2 | 602 | 4.4 |
| cefuroxime | 12644 | 765 | 6.1 | 1604 | 12.7 |
| gentamicin | 13554 | 581 | 4.3 | 621 | 4.6 |
| tobramycin | 11533 | 248 | 2.2 | 520 | 4.5 |
| amikacin | 10803 | 8 | 0.1 | 35 | 0.3 |
| trimethoprim | 13022 | 3785 | 29.1 | 3795 | 29.1 |
| co-trimoxazole | 13991 | 3790 | 27.1 | 3800 | 27.2 |
| nitrofurantoin | 13039 | 243 | 1.9 | 736 | 5.6 |
| ciprofloxacin | 13944 | 1575 | 11.3 | 1616 | 11.6 |
| norfloxacin | 10346 | 1105 | 10.7 | 1193 | 11.5 |

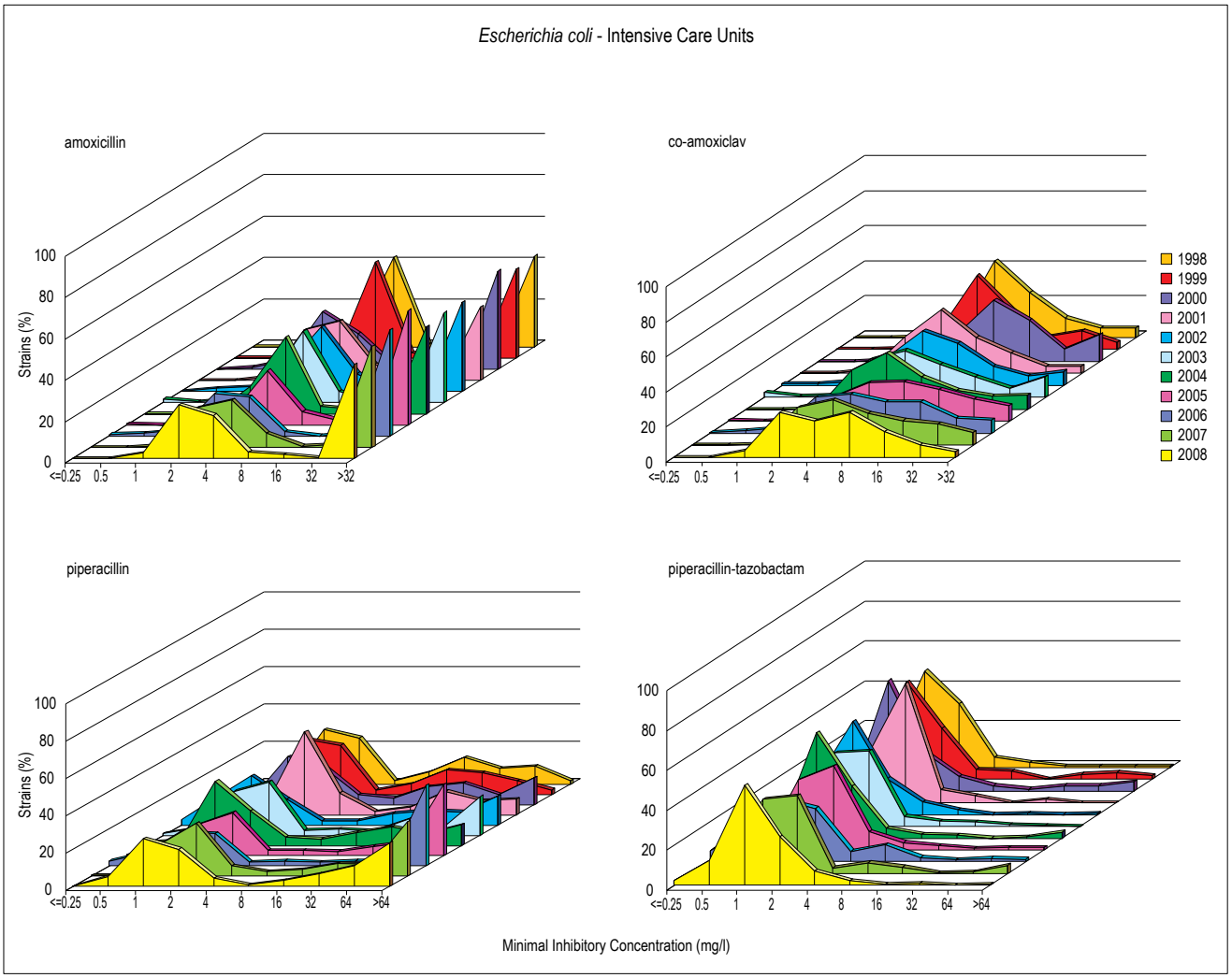



Figure 17. MIC distributions of beta-lactams for *Escherichia coli* from Intensive Care Units.



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by EUCAST, but classified as intermediate susceptible by CLSI. The shape of the curves changed considerably over the years: until 2000 a real peak at 4 mg/l was observed, but later this disappeared completely. The existence of a growing intermediate population may be a predictor for increasing resistance.

Piperacillin resistance was not determined for strains from Unselected Hospital Departments until 2008. It was 33% and 35% in 2008 and 2009, respectively (figure 15). Resistances rate varied between the ICUs, some had high resistance rates (30%), others low (15%) until 2004, but from 2003 onwards the resistance levels increased in all ICUs, resulting in an overall level of 41% in 2008. The MIC distribution of piperacillin in 1998 was bimodal over a broad range with one subpopulation with MICs 0.5-4 mg/l and one over a broad range with MICs 8 - >64 mg/l with a small peak at MIC of 16 mg/l (figure 17). This second population included susceptible (MIC < 16 mg/l) and resistant strains (MIC > 16 mg/l). From 2001, the number of strains with MIC values close to the breakpoint of 16 mg/l became lower and an increasing number of strains with MIC > 64 mg/l could be observed. The curves showed a clear bimodal shape. Thus the increase of resistance level calculated in 2003 could be predicted already in 2001. Piperacillin showed higher activity than amoxicillin towards the same subpopulation: the peak of MICs of piperacillin in the susceptible range was at 1-2 mg/l, that of amoxicillin at 2-4 mg/l (figure 17). Resistance to piperacillin-tazobactam was 0-4% during the whole study period. The MIC distribution of piperacillin-tazobactam showed an almost complete disappearance of populations resistant or intermediate to piperacillin alone, but less-susceptible strains with MICs 8-16 mg/l also emerged together with some strains with MIC > 64 mg/l, possibly predicting a change in shape of the distribution from a unimodal to a bimodal one in the future.

Imipenem and meropenem resistance was found occasionally in Unselected Hospital Departments in 2009 and in ICUs in 2000 and 2005.

Cefuroxime resistance in Unselected Hospital Departments was 11% and 13% in 2008 and 2009, respectively (figure 15). The trends of resistance of six cephalosporins among strains from ICUs and Urology Services are given in figure 18. The resistance levels of cefuroxime among strains from ICUs varied from 4-16%, the trend indicated a slightly increase in resistance from 9% in 1998 to 11% in 2008; this agreed well with the levels measured in the Unselected Hospital Departments taking the lower breakpoint. The levels among strains from Urology Services were much lower, increasing from 5% in 1998 to 8% in 2008 (figure 18). Cefaclor resistance increased in both departments, although the level in ICUs was much higher (10-25%) than in Urology Services (5-15%).

Ceftazidime resistance in Unselected Hospital Departments increased from less than 0.5% in 1998 to 4% in 2009 (figure 15). The resistance level in strains from ICUs increased from 0.5% in 1998 to 2% in 2008 (figure 16 and 18).

Ceftriaxone resistance in Unselected Hospital Departments was equal to that of ceftazidime in 2009 (figure 15).

The MIC distribution of cefuroxime for strains of ICUs was almost unimodal over a broad range (MIC 0.5 - >16 mg/l until 2006, except in 1999. Over the years the range broadened, the peak at 4 mg/l lowered (from 60% of strains in 1998 to 35% of strains in 2008) and a cluster of strains with high MIC values appeared in 2007, resulting in a real bimodal distribution. Cefotaxime and ceftazidime showed a unimodal MIC distribution over a very small range in 2008 (<= 0.12-0.5 mg/l) (figure 19). The resistance levels to all cephalosporins tested were higher among strains from ICUs compared to Urology Services. Resistance to cefaclor, cefuroxime and

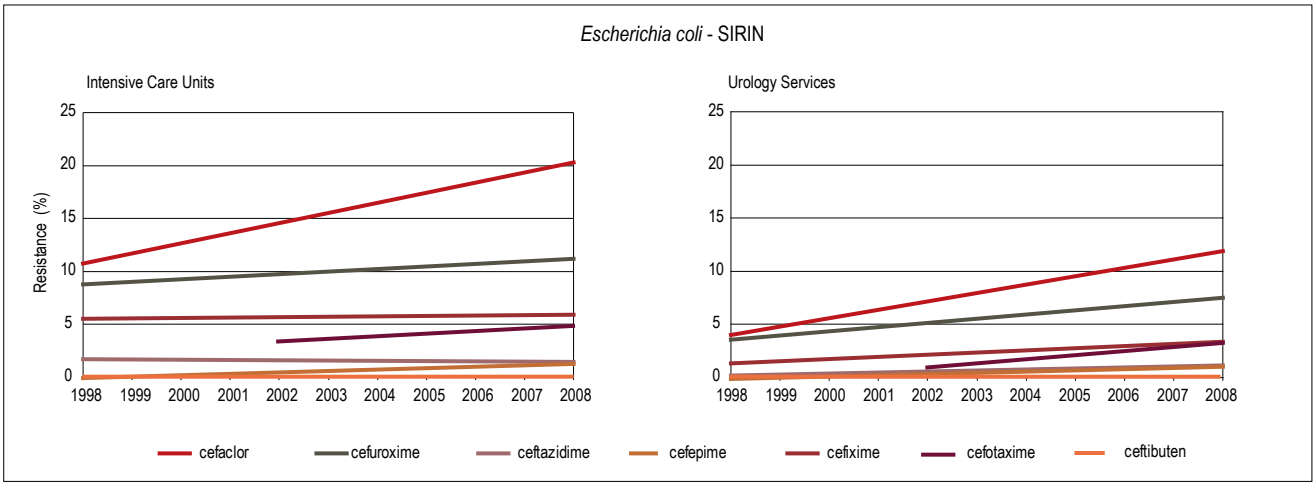



Figure 18. Trends in cephalosporin resistance among *Escherichia coli* from Intensive Care Units and Urology Services, calculated according to the break-points for resistance of EUCAST.



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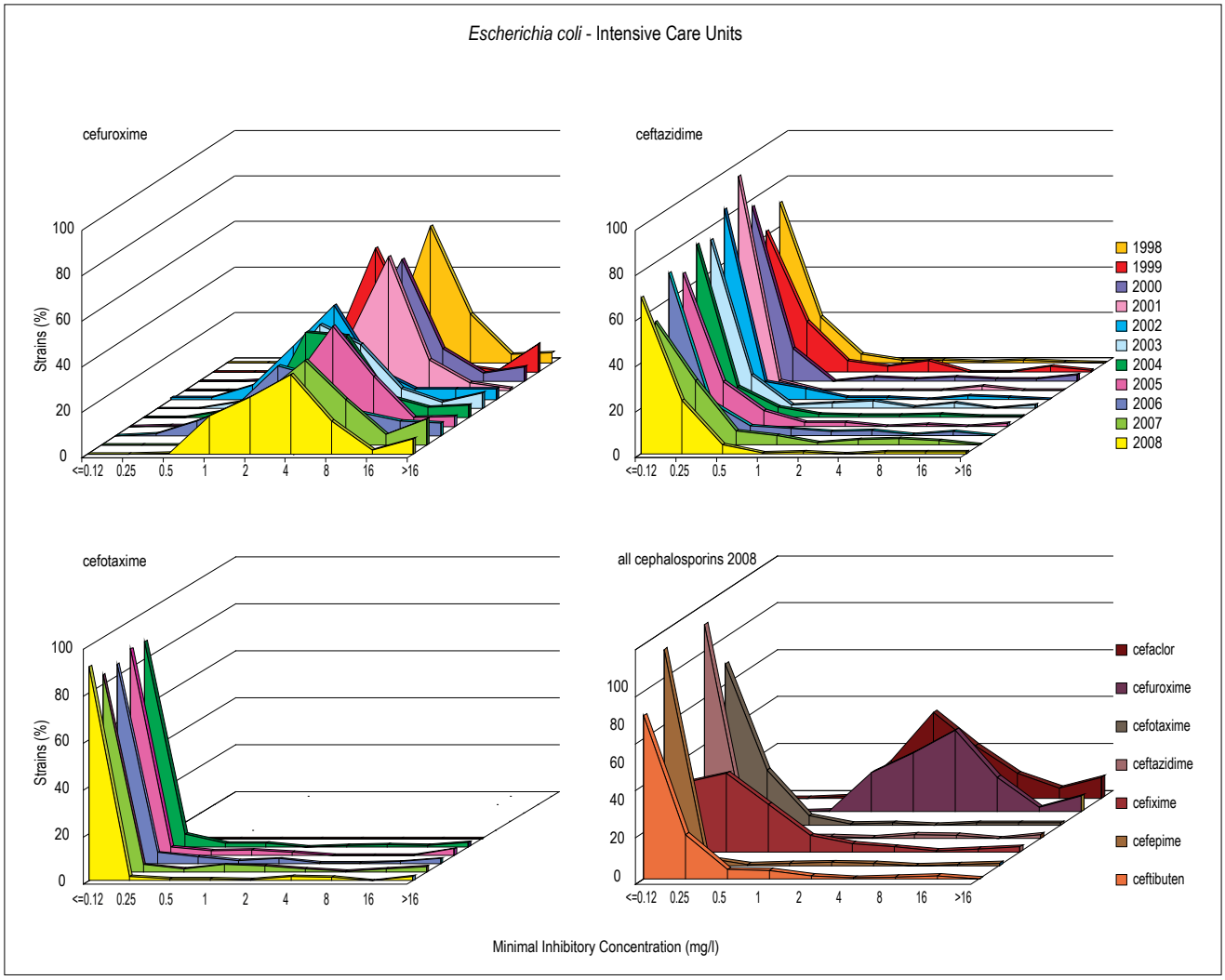



Figure 19. MIC distributions of cephalosporins for *Escherichia coli* from Intensive Care Units.

cefotaxime was slowly increasing, those to ceftazidime (2%), cefepime (0.5%), ceftibuten (0%) and cefixime (5%) were stable.

Trimethoprim resistance increased steadily in Unselected Hospital Departments over the years from 21% in 1998 to 29% in 2009 (figure 15) with peaks upto 40% or more in 2001, 2002 and 2006. This may suggest existence of strains with MIC values near to the breakpoint, like we also observed for ICUs. One year, strains are susceptible with MIC just below the breakpoint and the next year resistant with MIC just above the breakpoint. The level found in Urology Services was higher, as it fluctuated around 31%-35% until 2005 and showed an increase to 39% in 2008 (figure 16). The level of trimethoprim resistance in ICUs increased with some fluctuations from 22% in 1998 to 30% in 2008 (figure 16), which was in line with the rates found for Unselected Hospital Departments.

Co-trimoxazole resistance in Unselected Hospital Departments was not determined until 2007. It was 28% and 26% in 2008 and 2009, respectively and almost equal to the resistance found in ICUs (28%). The resistance trend in ICUs followed that of trimethoprim, being around 22% in 1998 and increasing to 29% in 2008.The resistance in Urology Services was always higher and increasing from 30% in 1998 to 37% in 2008 with some fluctuations during the years. The MIC distributions for trimethoprim and co-trimoxazole (figure 20) for strains from Urology Services showed a bimodal shape with two subpopulations: one susceptible and one highly resistant, with an increasing number of resistant strains (MIC > 4 mg/l). The MIC distribution of strains susceptible to trimethoprim ranged from < 0.12 mg/l to 2 mg/l, that of co-trimoxazole had a high and sharp peak at 0.12 mg/l.

Nitrofurantoin resistance reported for Unselected Hospital Departments was 15% in 1998, it came down to 2% in 2002 and increased to 5% in 2008 and 6% in 2009. The high levels found 10 years ago might be the result of interpretation on the basis of older and lower breakpoints (CRG). Nitrofurantoin resistance among strains from Intensive Cares fluctuated (3-7%) and it was 3% in 2008, that among strains from Urology Services was



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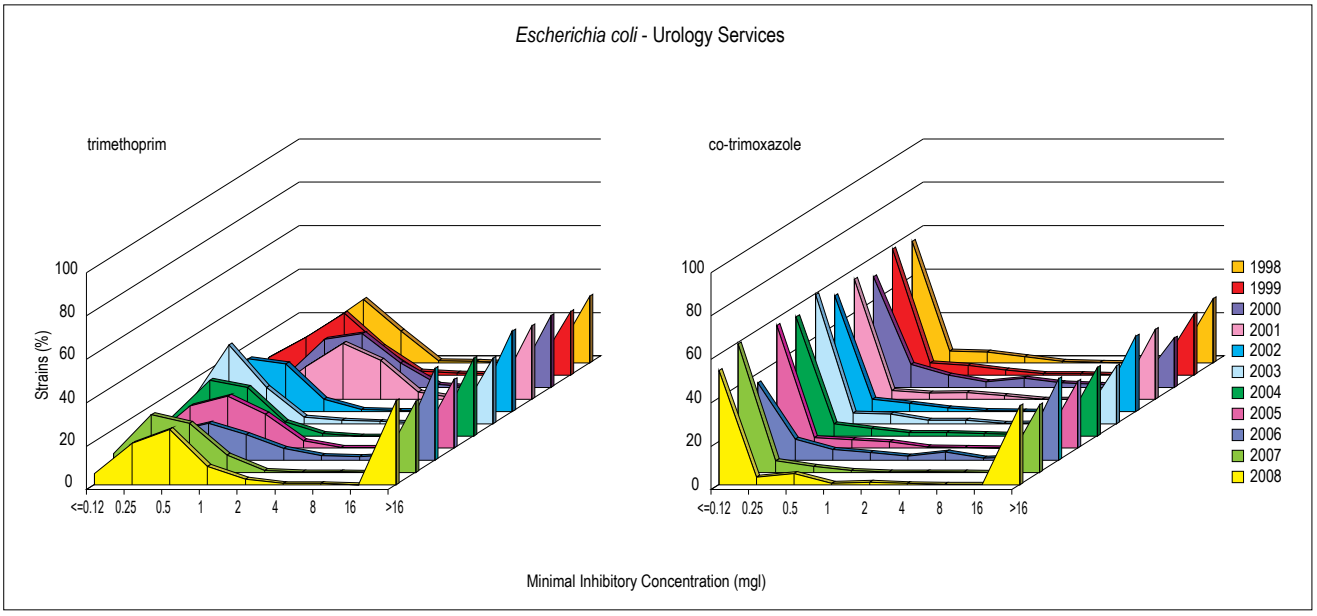



Figure 20. MIC distributions of trimethoprim and co-trimoxazole for *Escherichia coli* from Urology Services.

consistently higher (4-9%) with 5% in 2008 (figure 16). Ciprofloxacin resistance increased steadily among *E. coli* from Unselected Hospital Departments, slowly during the first four years from 1-3%, then more rapidly during the next six years: from 3% in 2001 to 12% in 2009 (figure 15). Increasing resistance was also observed in the ICUs from 1% in 1998 to 15% in 2008 for ciprofloxacin (figure 15). The resistance level in Urology Services increased more rapidly from 7% in 1998 to 21% in 2008. The resistance percentages of norfloxacin, levofloxacin and moxifloxacin were equal to those of ciprofloxacin for isolates from ICUs and Urology Services. The MIC distributions of the quinolones for *E. coli* from ICUs (not shown) and Urology Services (figure 21) were bimodal with a large susceptible subpopulation over a small range) and a small subpopulation of strains with MIC >8 mg/l. The intrinsic activity of ciprofloxacin was superior to that of the other quinolones with 74% susceptible to <0.03 mg/l in 2007 compared to 61% for levofloxacin, 38% for moxifloxacin and 6% for norfloxacin. Only few strains had MIC values in the intermediate area. The majority of the resistant strains had MICs > 16 mg/l. Quinolone resistance was common in all departments in 2008, but the level of quinolone-resistant *E. coli* varied between the centres from 3-25%.

Gentamicin resistance in Unselected Hospital Departments was low, but increasing from 1% until 2002 to around 5% over the whole period (figure 15). The resistance level in ICUs increased slowly from 2% in 1998 to 4% in 2008 (figure 16). This overall increase of gentamicin resistance was associated with an unusual high resistance level in some centres (up to 15%). The number of centres with gentamicin-resistant strains (MIC >8 mg/l) varied considerably, only one centre in 1999 and 2001, but seven centres in 2004 en 2005, four in 2006 and six in 2007 and 2008 (figure 22). Resistance was not associated with certain centres and it was not permanent in most centres. Therefore the increasing trend presented does not reflect a real national trend. This underlines the importance of local surveillance of resistance.

*Multiresistance of Escherichia coli in Intensive Care Units and Urology Services*

Increasing levels of resistance to three or more classes of antibiotics (multiresistance) in Intensive Care Units (ICU) within SIRIN were observed for various drug-combinations. Before 1998, no multiresistance was observed. The annual percentages of multiresistant strains were less than 7% from 1998-2004 it increased to 11% in 2005 and 16% in 2007 and decreased to 9% in 2008 (figure 23). A total of 155 multiresistant strains were isolated between 1998 and 2008. Resistance to the combination co-amoxiclav/co-trimoxazole with another drug was prevalent. These other drugs were either cefuroxime or ciprofloxacin or gentamicin (less frequent) or a combination of them. Multiresistance to the combinations co-amoxiclav/co-trimoxazole/cefuroxime and to co-amoxiclav/co-trimoxazole/ciprofloxacin was found yearly since 1998 (each 1 – 3% of the *E. coli* strains collected yearly); since 2000, resistance to all four antibiotics was found and from 2002 onwards this combination was expanded with resistance to gentamicin as well.

Similar observations were made with the co-trimoxazole combinations (others than those with co-amoxiclav). Resistance to the combination co-trimoxazole/gentamicin/ciprofloxacin with or without cefuroxime emerged since 2002 in 1-1.5% of the isolates. Multiresistance to four and five antibiotics was recorded from 2000 on at low percentages (2-5% of the total), but increased greately in 2007 to 8% of the total amount of



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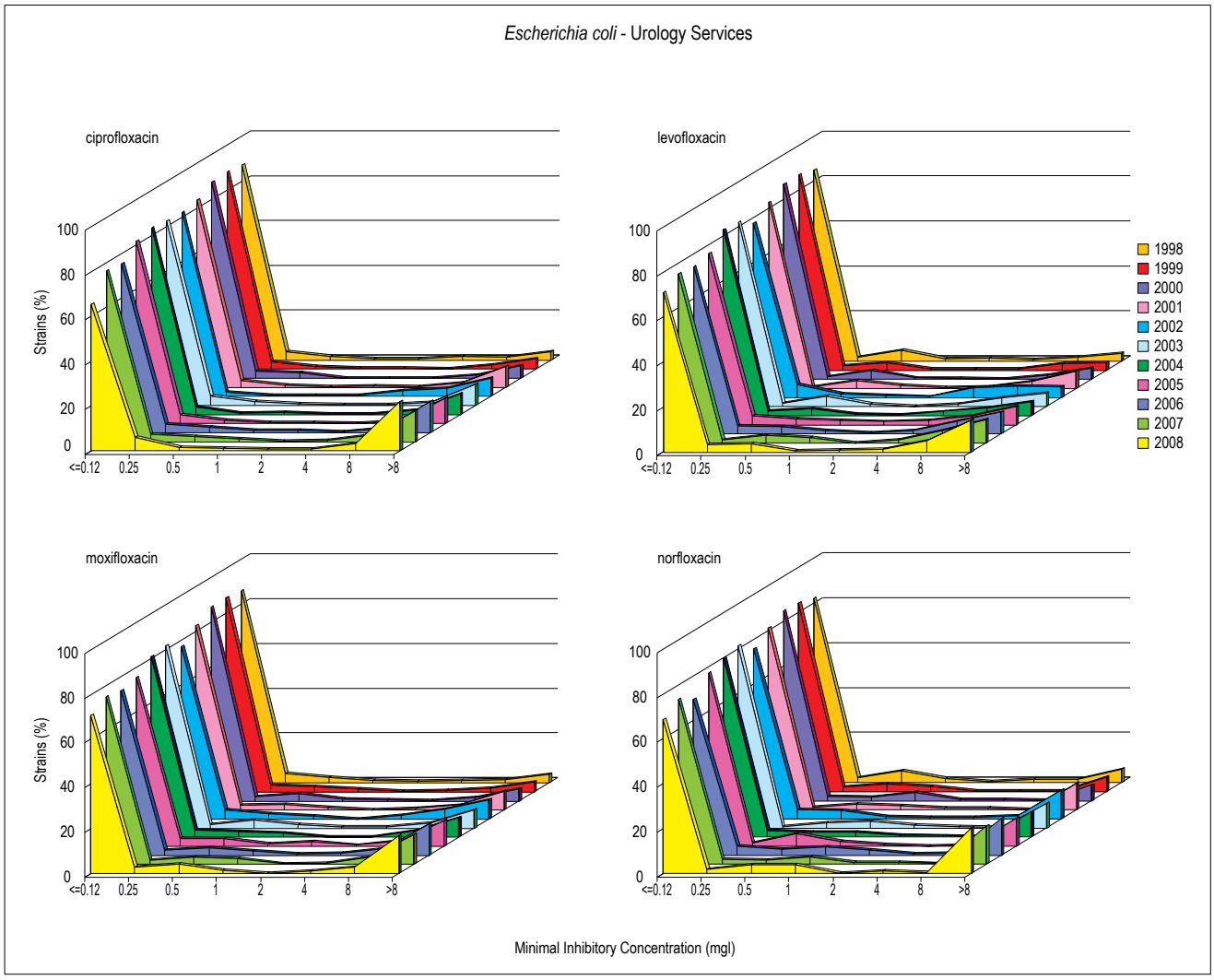



Figure 21. MIC distributions of quinolones for *Escherichia coli* from Urology Services.

strains collected in that year ($p < 0.02$) and decreased to less than 5% in 2008. These fluctuations can be explained by the incidental appearance of such strains in some ICUs. It appeared that the number and the origin of ICUs with multiresistant strains varied over the study period.

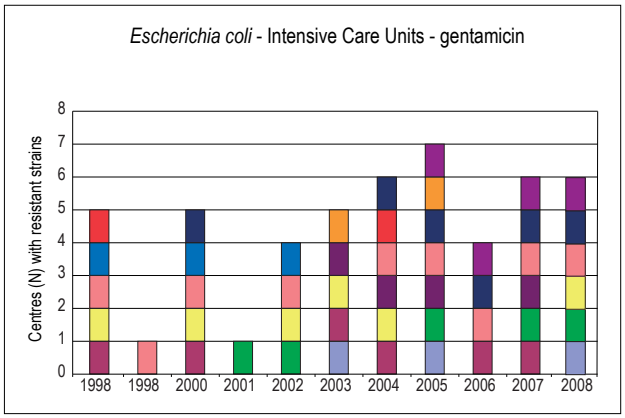



Figure 22. Number of centres with gentamicin-resistant *Escherichia coli* on Intensive Care Units, calculated according to the breakpoints for resistance of EUCAST. Each color represents one specific centre.

Multiresistance to four of more classes of antibiotics was observed in a limited number of ICUs per year (figure 24). The high resistance rate in 2007 may be due to a local problem in three Units (A C and P), which did not occur in the years before. Multiresistance was not observed in Unit C in 2008, it stayed in the Units A and P. So we have to conclude that multiresistance in ICUs is more a local than a national problem.
Surprisingly, a higher rate of multiresistance was found in Urology Services compared to ICUs (figure 24).
It increased from 6% of all strains in 1998 to 14% in 2008. Resistance to the combination co-amoxiclav/co-trimoxazole/ciprofloxacin was most prominent increasing from 1% of all strains tested in 1998 to 4% in 2008.
From 1998 onwards, resistance to four of more classes of antibiotics was recorded, which also increased from 2% in 1998 to 4.5% of all strains in 2008. Most frequent was the combination co-amoxiclav/co-trimoxazole/ciprofloxacin with gentamicin or cefuroxime or both. This affected almost all centres since 2006 (figure 24) and is therefore not a local problem, but rather a national one.



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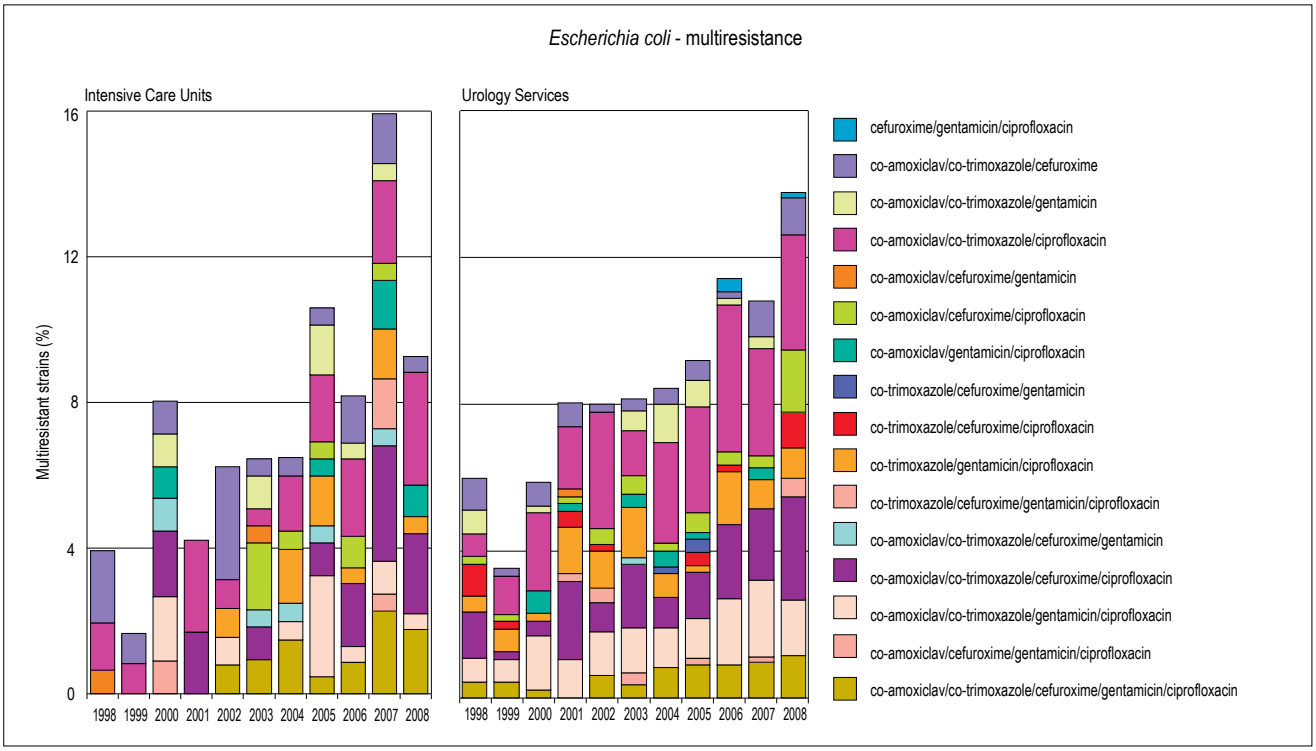



Figure 23. Trends in multiresistance among *Escherichia coli* from Intensive Care Units and Urology Services, calculated according to the breakpoints for resistance of EUCAST.

*ESBL*

Because of the emergence of ESBL producing strains in the Netherlands, the data of previous years were re-evaluated and putative ESBL producers retested. All isolates from ICUs with MICs ≥1 mg/l for ceftazidime and/or cefotaxime were considered putative ESBL producers. A total of 110 strains were found from 1998 to 2008 (3-9% of all isolates per year). ESBL production was demonstrated in 37 of the 110 strains by the combination disk diffusion test (CDDT) according to NVMM guidelines and by PCR. The prevalence per year is presented in figure 25. Suspected strains were found in 11 of 14 centres at varying numbers using the CDDT test (figure 26). The double disk diffusion test did not detect all suspected strains. ESBL producering bacteria were isolated from 2000 onwards at a rate of 0.5-2% until 2005. Thereafter it increased to 5.9% in 2007 and decreased again to 2.6% in 2008. Until 2005, ESBL producing strains were found in one to three centres annually, representative of a local problem. However, they came from six centres in 2006 from eight centres in 2007 and five centres in 2008. ESBL-producing strains, therefore, may become a general problem for ICUs in time.

The presence of TEM-, SHV and CTM-X genes among ESBL producers from 1998-2007 was determined by PCR and is also presented in figure 25 (PCR data from 2008 were not yet available). The TEM-gene predominated from 1998 until 2005 and disappeared thereafter. The SHV-gene was only found in 1998, 1999 and 2004. The CTM-X-gene emerged in 2000 and 2005 and it was exclusive found in 2006 and 2007. This indicated a significant shift to another class of beta-lactamases which express greater activity to cefotaxime than the TEM- and SHV- beta-lactamases.

**Summary – *Escherichia coli***

1. Increasing resistance to amoxicillin, co-amoxiclav, piperacillin, cefaclor, cefuroxime, trimethoprim, co-trimoxazole, gentamicin and ciprofloxacin was found in all study populations
2. Consistent higher resistance levels of penicillins, cephalosporins and gentamicin in Intensive Care Units compared to those in Unselected Hospital Departments and Urology Services
3. Consistent higher resistance levels of trimethoprim and ciprofloxacin in Urology Services compared to those in Unselected Hospital Departments and Intensive Care Units
4. Multiresistance is increasing in Intensive Care Units and Urology Services
5. ESBL producing strains in Intensive Care Units were demonstrated from 2000 on at varying percentages (0.5-5.9%) in one to eight centres. The TEM- and SHV-genes which were common from 1998 on, were replaced by the CTX-M gene in 2006



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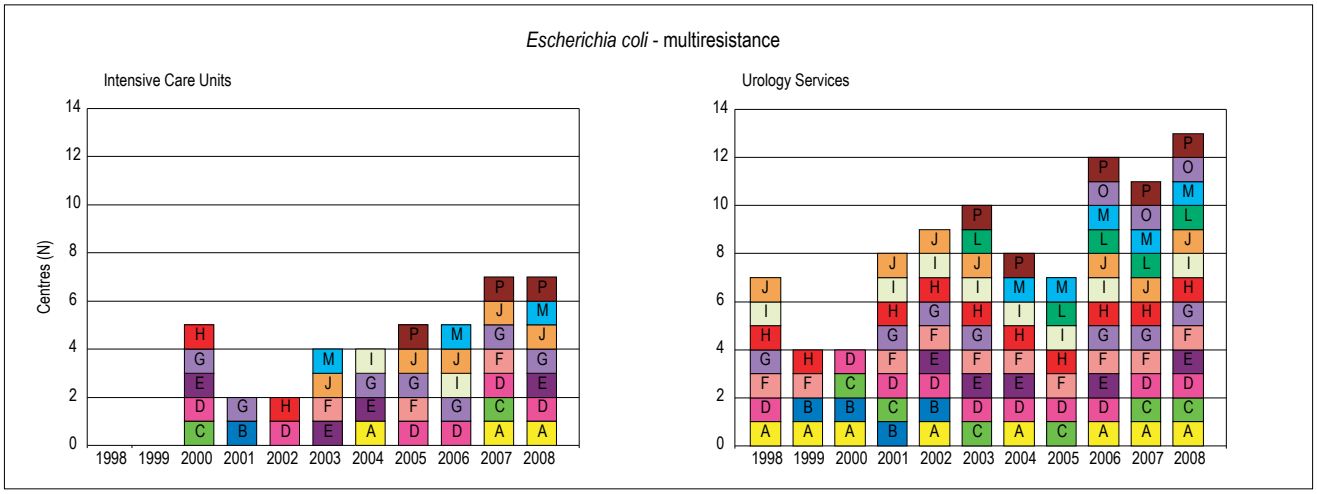



Figure 24. Number of centres with multiresistant *Escherichia coli* on Intensive Care Units and Urology Services, calculated according to the breakpoints for resistance of EUCAST. Each color represents one specific centre. The centres are indicated by characters (A-P).

*4.3.3.2 Klebsiella pneumoniae*

Co-amoxiclav resistance in *K. pneumoniae* from Unselected Hospital Departments fluctuated between 10-15% during the whole study period without a clear increase (figure 27). Co-amoxiclav resistance in ICUs was much higher; it fluctuated but showed an increasing trend from18% in 1998 to 26% in 2008 (figure 28). Co-amoxiclav resistance in Urology Services was lower compared to that in ICUs but showed also an increasing trend from 7% in 1998 to 13 % in 2008

Overall, piperacillin-tazobactam resistance in ICUs varied from 0-15% over the years without significant increase (not shown). Piperacillin-tazobactam resistance was sporadically found in some centres. We recorded 2-4 centres per year with resistant strains without a clear pattern. No centre had a "clear piperacillin-tazobactam problem" over time. This may explain the fluctuations during the study period. Piperacillin-tazobactam resistance in Urology Services fluctuated in the same way but at a lower level (0-5%) with only a few centres yearly delivering resistant strains. So the piperacillin-tazobactam resistance found did not reflect the resistance level for all ICUs and Urology Services.

Carbapenem resistance was rare in ICUs. It was found once in 2006 in one centre.

Resistance to cefuroxime was not determined regularly in Unselected Hospital Departments before 2008; it was 11% in 2008 and 13% in 2009.

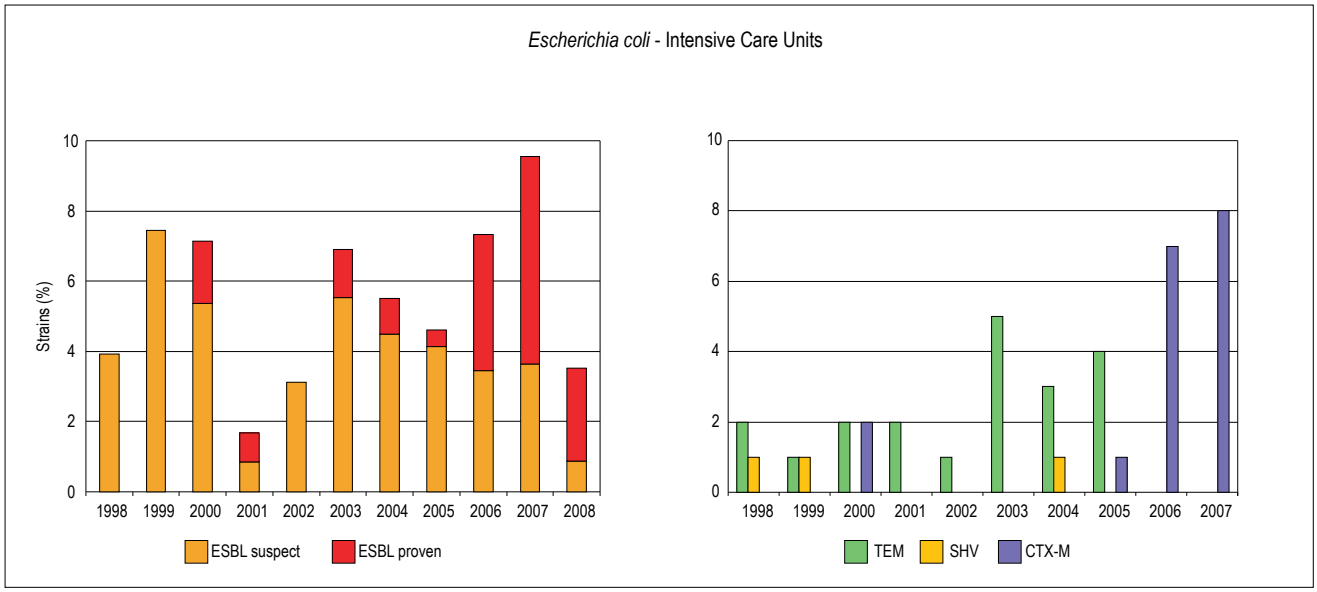



Figure 25. Prevalence of ESBL producing strains (suspect and proven) among *Escherichia coli* from Intensive Care Units (1998-2008) and the occurrence of TEM-, SHV- and CTX-M genes among ESBL producing strains.



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Resistance to 1st and 2nd generation cephalosporins fluctuated during the years in both ICUs and Urology Services, but the trends in ICUs (figure 29) showed an overall increase in resistance to cefaclor from 8% in 1998 to 16% in 2008 and to cefuroxime from 8% in 1998 to 13% in 2008, equal to the resistance level found in Unselected Hospital Departments. The MIC distributions of cefaclor and cefuroxime differed slightly (figure 30). That of cefaclor was clearly bimodal with one subpopulation with MIC < 4 mg/l and another subpopulation with MIC > 16 mg/l. The MIC distribution for cefuroxime showed an almost unimodal shape over a broad range (0.5-16 mg/l) and only a small number of strains with higher MICs resembling the profile of *E. coli*. Resistance to ceftazidime in Unselected Hospital Departments increased from 1% in 1998 to 5% in 2009 (figure 27). Ceftazidime-resistance was not always present in all ICUs. It fluctuated between 0% (1998 and 2001) and 16% (2002) and it was 6% in 2008 (figure 28). The high rate and fluctuations were exclusively due to a high resistance rate in two ICUs in 2002 and four others occasionally thereafter. So the resistance level is not representative for the ICUs as a whole. Resistance in Urology Services was found in four centres only once in different years. Resistance level to ceftriaxone was 5%

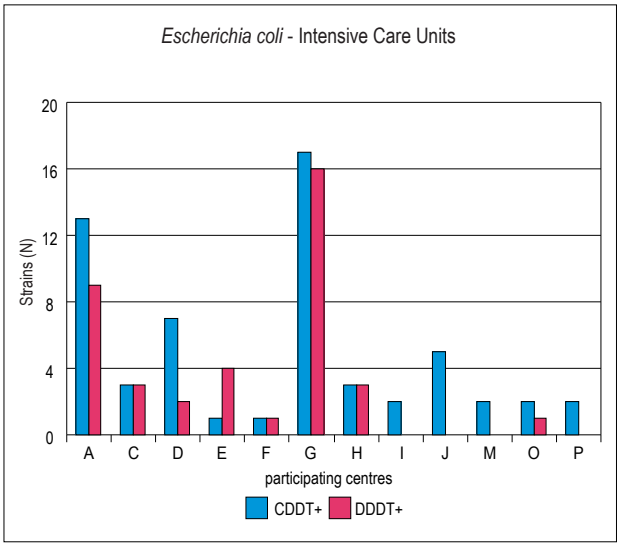



Figure 26. Prevalence of ESBL producing *Escherichia coli* strains in Intensive Care Units of centres indicated (A-P), determined by the combination disk diffusion test (CDDT) or double disk diffusion test (DDDT).

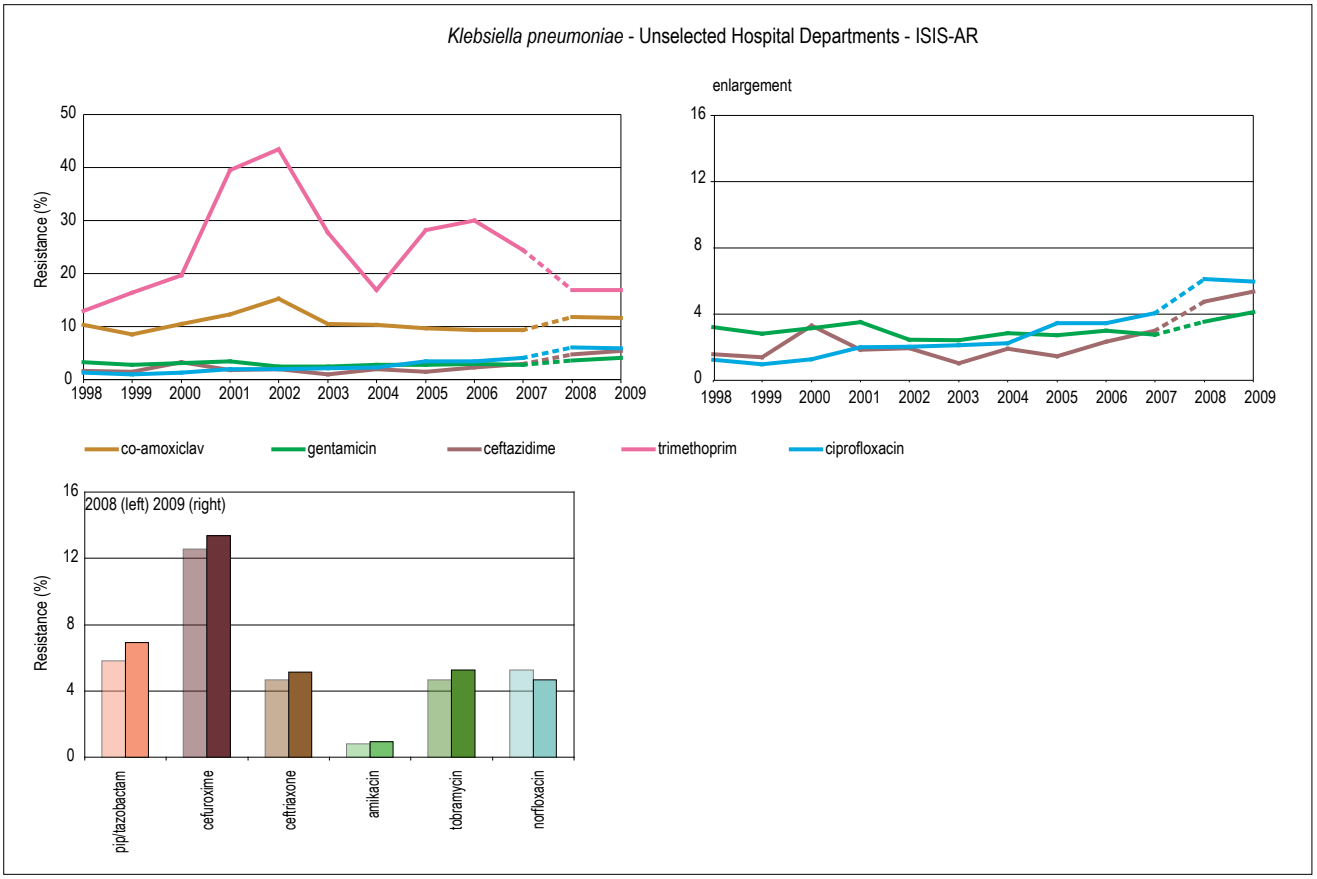



Figure 27. Trends in antibiotic resistance among clinical strains of *Klebsiella pneumoniae* (N= 13.000-29.000) from Unselected Hospital Departments, calculated from the values for intermediate susceptibility and resistance (I+R) reported to ISIS-AR. Additional antibiotics tested in 2008 and 2009 are presented as columns.



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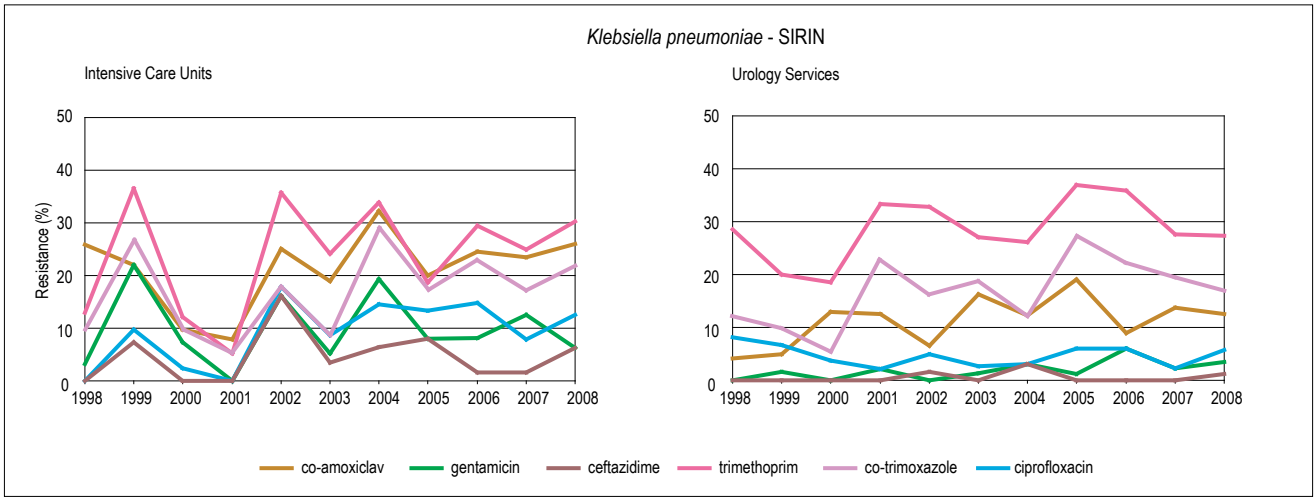



Figure 28. Trends in antibiotic resistance among clinical strains of *Klebsiella pneumoniae* from Intensive Care Units (N=687) and Urology Services (N=838), calculated according to the breakpoints for resistance of EUCAST.

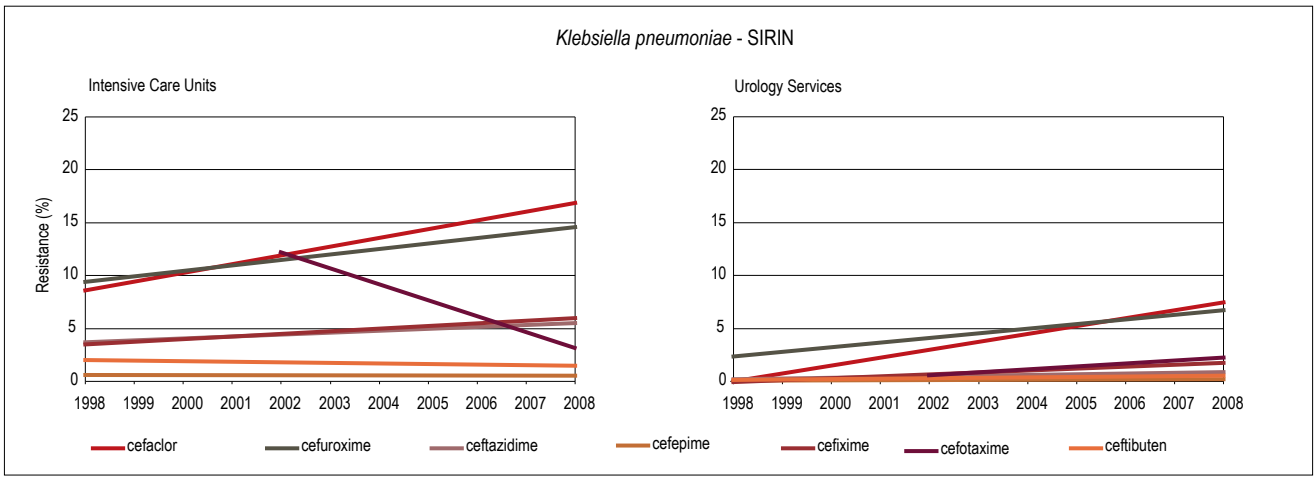



Figure 29.Trends in cephalosporin resistance among *Klebsiella pneumoniae* from Intensive Care Units and Urology Services, calculated according to the breakpoints for resistance of EUCAST.

in 2008 and 2009 in Unselected Hospital Departments (figure 27); that of cefotaxime was measured since 2003 in ICUs, it fluctuated around 8%. Cefotaxime resistance in Urology Services occurred occasionally. The MIC distributions of all cephalosporins tested are given in figure 30. It can be concluded that the intrinsic activity of cefotaxime, cefixime, cefepime and ceftibuten is higher against *K. pneumoniae* with 90% of strains with MIC < 0.12 mg/l compared to ceftazidime with only 50-60% with MIC < 0.12 mg/l and 30% with MIC 0.2-0.5 mg/l. Trimethoprim resistance in Unselected Hospital Departments increased gradually from 11% in 1998 to 17% from 2007 on, although high fluctuations were observed in some years (figure 27). This might be explained by the existence of many strains in the population with MICs around the breakpoint, like we also observed for *E. coli*. The resistance levels in ICUs were in the same range although also here considerable fluctuations could be observed (figure 28). Those found in Urology Services fluctuated around 28%. Trimethoprim was the drug of first choice in GP patients until 2005. The higher resistance rates observed in urinary strains from Urology Services may reflect frequent use of this drug alone or in the combination co-trimoxazole in the previous years. The fluctuations may be explained by the distribution of MICs (figure 31). That of trimethoprim looks bimodal with one subpopulation with MICs 0.25-2 mg/l and one subpopulation with MICs > 16 mg/l, but there is another subpopulation in between with MICs 4-8 mg/l, around the breakpoint for resistance. Variations in laboratory procedures or number of strains per year may result in strains in the intermediate area are categorized resistant or susceptible and thus influence the resistance level in a given year.

The resistance to co-trimoxazole followed the trend of trimethoprim; the resistance rate in Unselected Hospital Departments was 15% in 2008 and 2009 (figure 27). The resistance level in ICUs increased from 13% in



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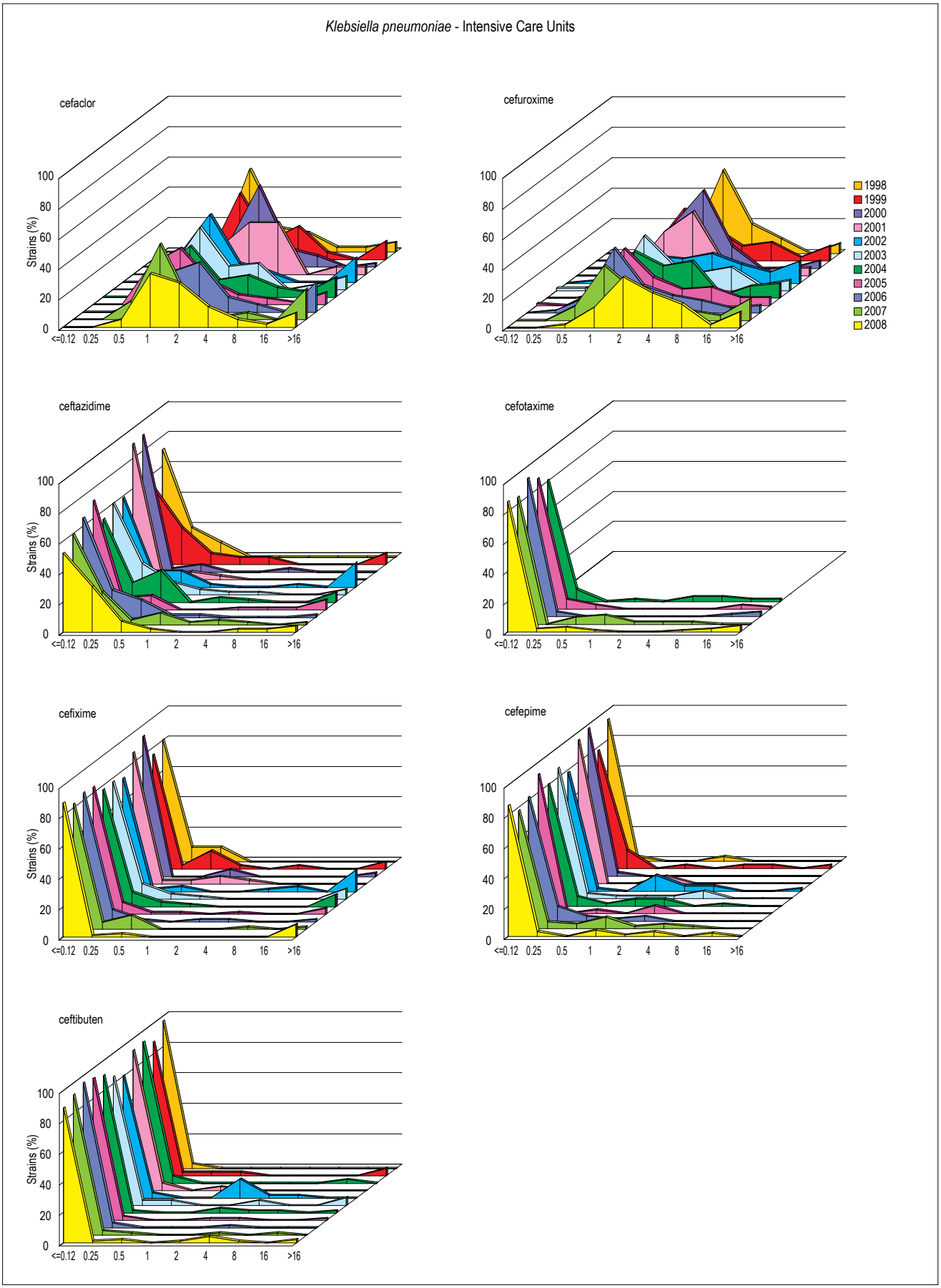



Figure 30. MIC distributions of cephalosporins for *Klebsiella pneumoniae* from Intensive Care Units.



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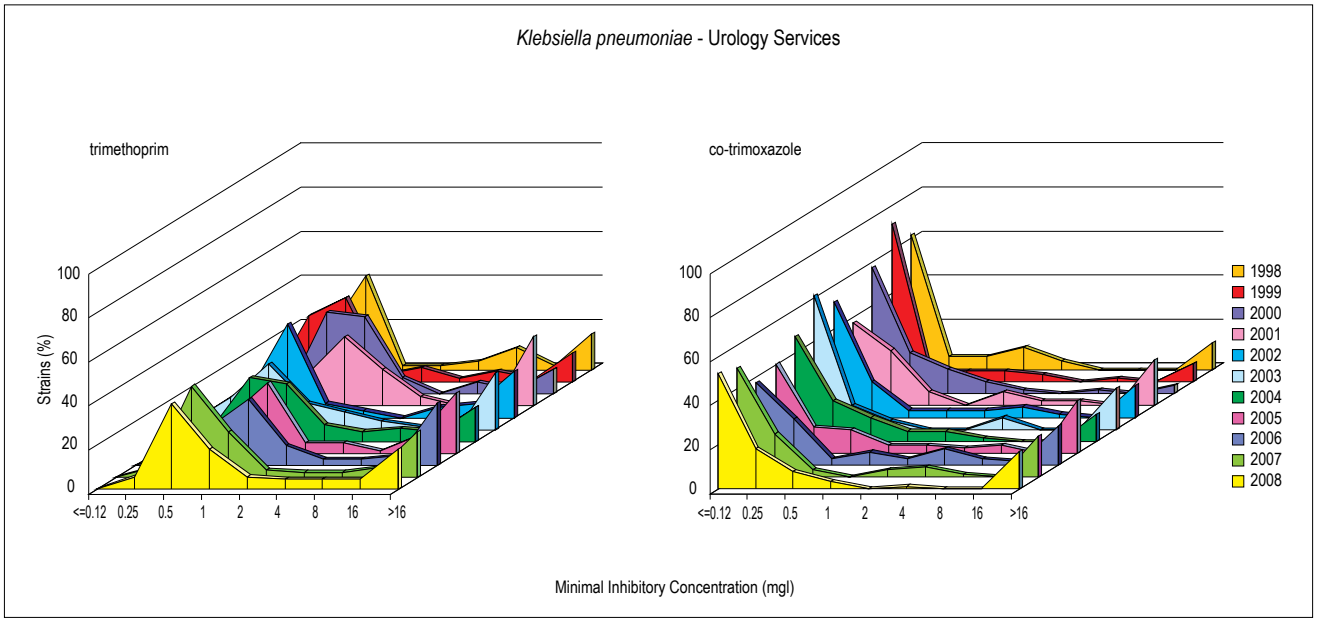



Figure 31. MIC distributions of trimethoprim and co-trimoxazole for *Klebsiella pneumoniae* from Urology Services.

1998 to 22% in 2008 and from 12% to 17% in Urology Services (figure 28). Co-trimoxazole is an alternative drug combination for *Klebsiella* infections in ICUs and it is often used for complicated urinary tract infections in Urology Services and Paediatric Departments. Use of co-trimoxazole in these settings should be reconsidered in view of the high resistance levels found. The MIC distribution of strains from Urology Services (figure 31) showed a clear bimodal shape without the intermediate subpopulation as we noticed for trimethoprim.

Nitrofurantoin resistance fluctuated around 75% in Unselected Hospital Departments without a visible trend (figure 27). The resistance levels in ICUs and in Urology Services resembled those of the levels in Unselected Hospitals (not shown).

Gentamicin resistance in Unselected Hospital Departments was low but increased slowly from 1% in 1998 to 4% in 2009 (figure 27). Gentamicin-resistant strains were observed continuously in two ICUs from 1999 onward and sporadically in four others resulting in large fluctuations in gentamicin resistance rates (0-16%) over the years of surveillance with a mean resistance rate of 6% in 2008 (figure 28). These figures are therefore not representative for all ICUs. This underlines the need for local surveillance. Gentamicin resistance in Urology Services was less than 3% and not common in all Urology Services.

Ciprofloxacin resistance among *K. pneumoniae* in Unselected Hospital Departments increased slowly from less than 1% in 2001 to 6% in 2009 (figure 27). Ciprofloxacin resistance in ICUs showed an increasing trend from less than 1% in 1998 to 13% in 2008 (figure 28). In contrast, ciprofloxacin resistance in Urology Services decreased from 8% in 1998 to 6% in 2008, a level comparable with that in Unselected Hospital.

The MIC distributions of all quinolones tested showed a susceptible subpopulation over a broad range (MIC < 0.03 – 0.5 mg/l) and a small subpopulation with MIC 1-8 mg/l whereas only few strains had MICs > 16 mg/l (figure 32). This differed from the MIC distributions of quinolones for *E. coli* where a real bimodal distribution was observed.

*Multiresistance of Klebsiella pneumoniae in Intensive Care units*

Multiresistance (resistance to three or more classes of antibiotics) in Intensive Care Units was recorded yearly except in 2001 at varying percentages (3-23% of all *K. pneumoniae* strains). A real trend was not visible, although the percentages of multiresistance remained 12% or more from 2005 onwards, suggesting a more stable situation compared to the years before (figure 33). The highly fluctuating numbers of multiresistant strains may be associated with high resistance levels, e.g., for gentamicin in some ICUs in some but not all years, as described above. The antibiotic combinations for which resistance was recorded differed in some way from those found in *E. coli* strains. For *E. coli* the combinations co-amoxiclav/cotrimoxazole with either cefuroxime or ciprofloxacin predominated whereas the combination co-amoxiclav/co-trimoxazole/gentamicin for *K. pneumoniae* predominated with or without cefuroxime or ciprofloxacin. Unlike in *E. coli* the proportion of strains resistant to four or five classes of antibiotics was higher (3-14% of all *K. pneumoniae* isolates).

Multiresistance in Urology Services occurred (6% in 2008), but to a much less extend than that in ICUs. It never reached the level found for *E. coli* strains in Intensive care units (figure 33).



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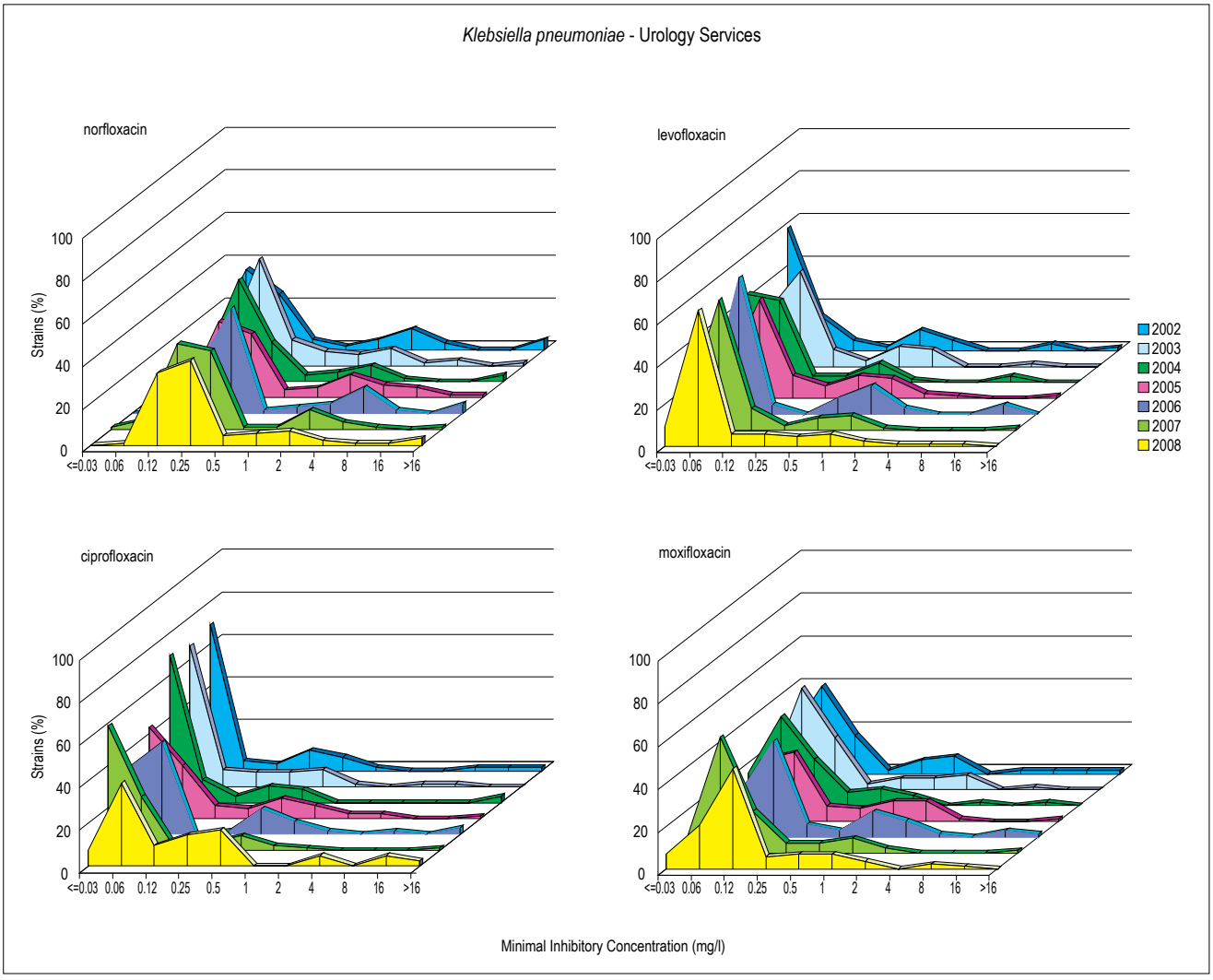



Figure 32. MIC distributions of quinolones for Klebsiella pneumoniae from Urology Services.

*ESBL*

All isolates from ICUs with MIC ≥ 1 mg/l for ceftazidime and/or cefotaxime were considered putative ESBL producers. A total of 43 were found from 1998 to 2007. ESBL production was demonstrated in 27 strains. The prevalence per year is presented in figure 34. It turned out that suspected strains were found every year at varying percentages. ESBL producers were demonstrated in 1999 and from 2002 onwards. The level in 2002 was high (16%) and decreased to 3-6% annually. It appeared that these ESBL producers were a local problem of some centres and not at all a nationwide problem. They occurred sporadically: in centre C only in 1998, in centres A and G annually from 2002 onwards, in centre O once in 2004, and in centre D once in 2006. TEM and SHV genes predominated until 2005 but were replaced by the CTM-X gene in 2006, like was observed among ESBL producing *E. coli* strains. PCR data of 2007 were not available.

**Summary – *Klebsiella pneumoniae***

1. Increasing resistance to trimethoprim, co-trimoxazole and ciprofloxacin in Unselected Hospital Departments and Intensive Care Units
2. Decreasing resistance to ciprofloxacin in Urology Services
3. Consistent higher resistance to co-amoxiclav, cotrimoxazole, gentamicin and ciprofloxacin in Intensive Care Units compared to Unselected Hospital Departments and Urology Services
4. 12 -23% multiresistance in Intensive Care Units from 2004 onwards; 5% multiresistance in Urology Services
5. ESBL producing strains demonstrated yearly from 2002 on at varying prevalence; 3-6.5% from 2003 on without a trend.
6. Resistance to imipenem and meropenem was not found



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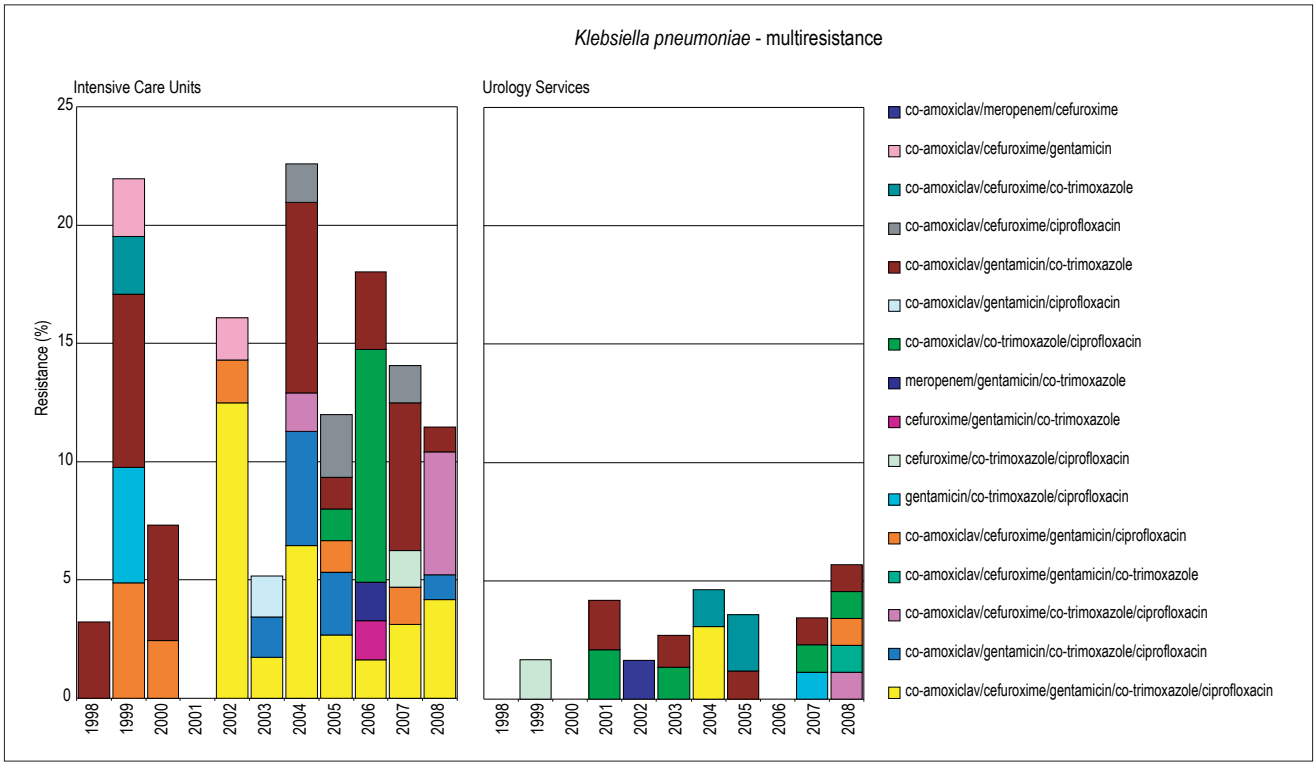



Figure 33. Trends in multiresistance among *Klebsiella pneumoniae* from Intensive Care Units and Urology Services, calculated according to the break-points for resistance of EUCAST.

*4.3.3.3 Enterobacter cloacae*

The number of strains isolated from patients in Urology Services was less than 20 per annum and therefore excluded from the comparison with ICUs and Unselected Hospital Departments. Between 1998 and 2008, 90% or more of *E. cloacae* strains from ICUs were resistant to co-amoxiclav. Resistance in Unselected Hospitals was only reported from 2008 onwards; hence yearly trends are not available.

Resistance to piperacillin-tazobactam in Unselected Hospital Departments increased from 22% in 2008 to 28% in 2009 (figure 35). The resistance level in ICUs varied considerably over the years ranging from 6-25% with 21% resistance in 1998 and 25% in 2008 (figure 35). The fluctuation was clearly related to the emergence of resistant strains in some ICUs. These strains were recorded occasionally in all centres, but often only for a short period and not every year. Therefore the overall resistance percentage does not reflect the general situation in ICUs and does not indicate a trend.

Meropenem resistance was exceptional in Unselected Hospital Departments (0.1% in 2008) and only once found in 2003 (3%) in ICUs (not shown).

Cephalosporin (2nd, 3rd, and 4th generation) resistance among *E. cloacae* strains from ICUs was approx 30% or more except for cefepime (less than 5%) during the whole study period (not shown). Any cephalosporin is therefore not recommended as empiric therapy in Intensive Cares with circulating *E. cloacae* strains.

Co-trimoxazole resistance in Unselected Hospital Departments increased from 5% in 2008 to 8% in 2009 (figure 35). The resistance level in ICUs increased with annual fluctuations from 7% in 1998 to 11% in 2008.

Gentamicin resistance increased from 5% in 2008 to 6% in 2009 in Unselected Hospital Departments (figure 35). The resistance level in Intensive Care fluctuated around 5% from 1998 to 2007. In 2008, an unusual high resistance level of 19% was recorded. This was due to exclusive emergence of resistant strains in three ICUs; these strains were also resistant to tobramycin. Resistant strains were found in these centres from 2004 on. The MIC distribution for gentamicin was bimodal with a susceptible subpopulation with MIC < 2 mg/l) and a small resistant one with MIC > 16mg/l (figure 36). From 2003 onwards, small subpopulations with MIC 4- 8 mg/l appeared, predicting upcoming resistance and in 2008 a real cluster with MIC 4-16 mg/l existed between the two subpopulations. These strains circulated exclusively in the three centres mentioned before. Therefore, longitudinal evaluation of the MIC distributions may give information on emergence of resistance long before this will become apparent. There was no complete cross resistance between the two aminoglycosides.

Amikacin resistance was exceptional in both Unselected Hospital Departments (0.1% in 2008) and in ICUs (3% in 2000 and 2003). The MIC distribution of tobramycin resembled that of gentamicin, although the resistant subpopulation was larger in 2008. The MIC distribution of amikacin (figure 36) showed sporadic resistant strains (MIC > 16 mg/l). It was clear that the intrinsic activity



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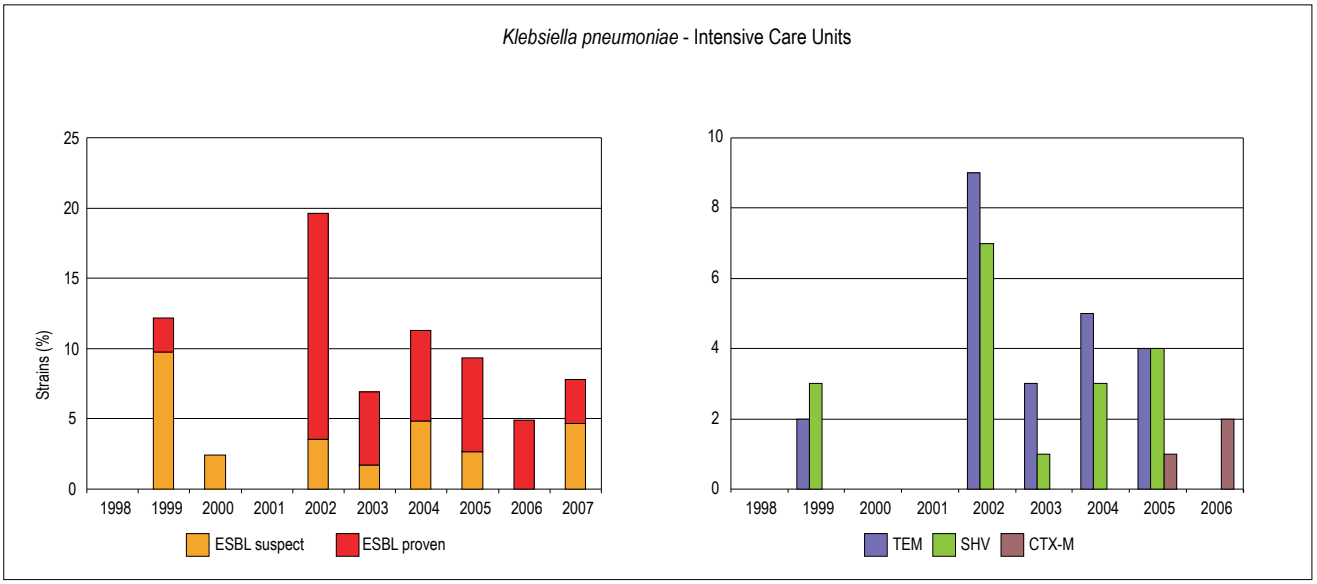



Figure 34. Prevalence of ESBL producing strains (suspect and proven) among *Klebsiella pneumoniae* from Intensive Care Units (1998-2007) and the occurrence of TEM-, SHV- and CTX-M genes among ESBL producing strains (1998-2006).

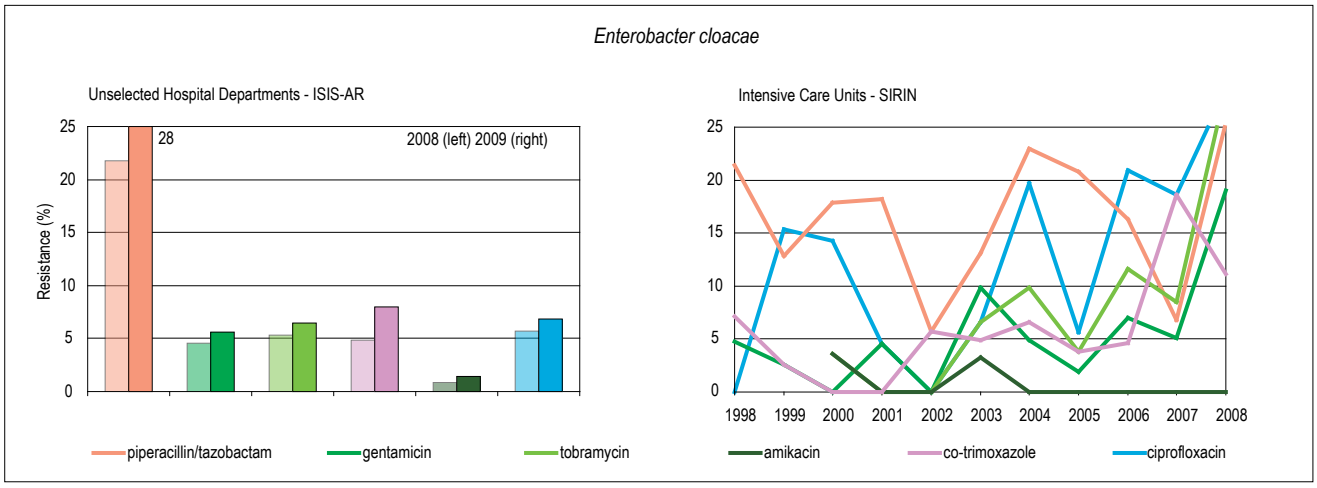



Figure 35. Resistance among clinical strains of *Enterobacter cloacae* (N= 2.500-3.100) from Unselected Hospital Departments in 2008 and 2009, calculated from the values for intermediate susceptibility and resistance (I+R) reported to ISIS-AR (left) and trends in antibiotic resistance among clinical strains of *Enterobacter cloacae* from Intensive Care Units (right, N=579), calculated according to the breakpoints for resistance of EUCAST.

of amikacin was less than that of gentamicin. Fifty eight percent of strainds were inhibited by 0.25 mg/l gentamicin compared with 55% by 1 mg/l amikacin. Ciprofloxacin resistance reported for Unselected Hospital Departments was 6% in 2008 and 7% in 2009 (figure 35). Resistance in ICUs was not found in 1998, but raised to 15% in 1999 and increased, highly fluctuating, to 28% in 2008. These fluctuations were due to the existence of strains with MICs around the breakpoint for resistance. Co-resistance with gentamicin and tobramycin occurred in 50% or more of ciprofloxacin-resistant strains.

**Summary – *Enterobacter cloacae***

1. Higher resistance rates of piperacillin-tazobactam, co-trimoxazole, gentamicin and ciprofloxacin in Intensive Care Units compared with Unselected Hospital Departments
2. Increasing resistance to piperacillin-tazobactam, gentamicin, tobramycin and ciprofloxacin in Intensive Care Units, attributed to the emergence of resistant clones in some centres
3. Resistance to imipenem and meropenem was not found



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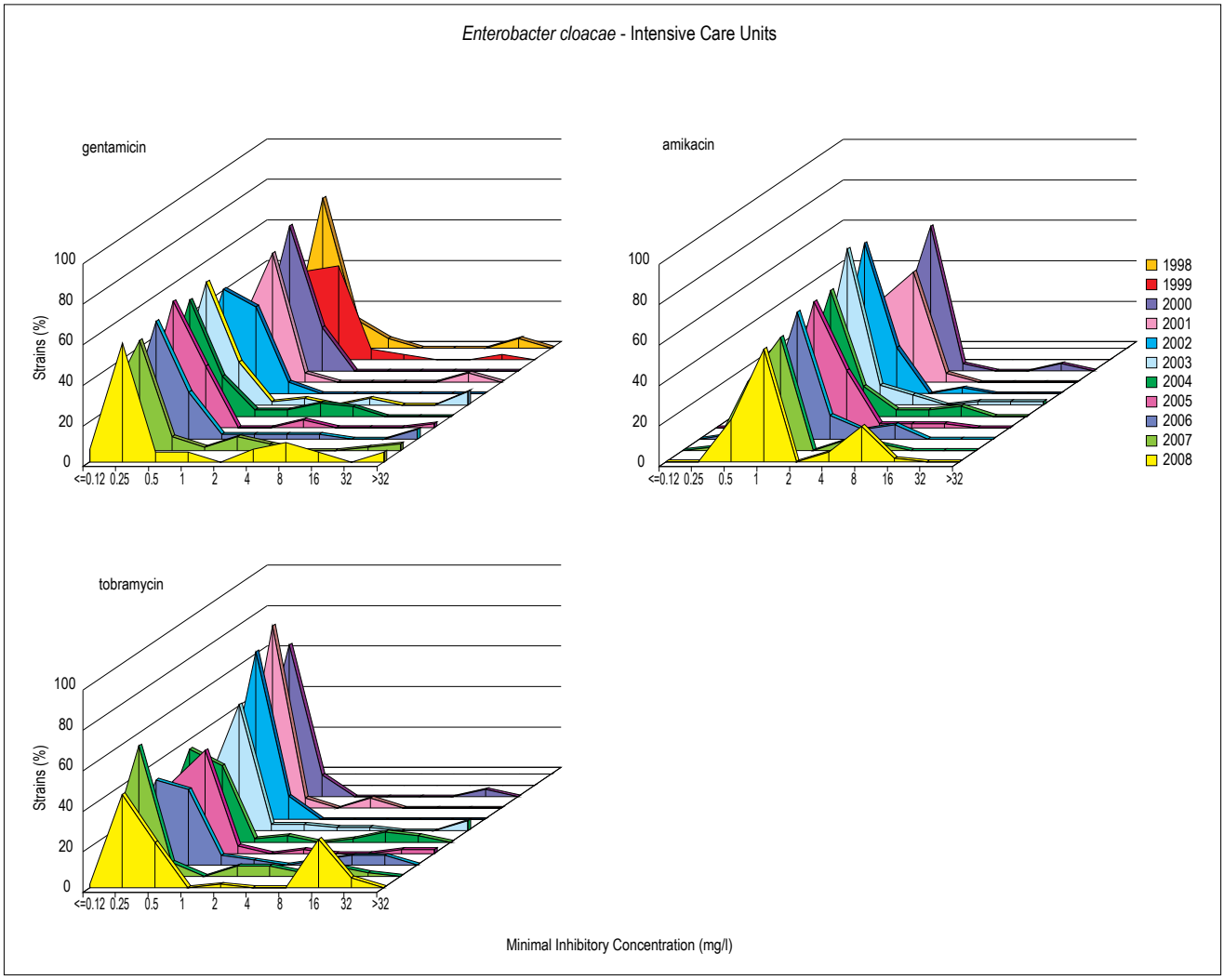



Figure 36. MIC distributions of aminoglycosides for *Enterobacter cloacae* from Intensive Care Units.

*4.3.3.4 Proteus mirabilis*

Amoxicillin resistance in Unselected Hospital Departments showed a continuous increase from 13% in 1998 to 24% in 2009 (figure 37). The number of strains collected from ICUs was less than 40 per year and therefore excluded from evaluation. Amoxicillin resistance in Urology Services increased from 18% in 1998 to 28% in 2008 (figure 38). The distribution of MICs of the strains from Urology Services was bimodal and showed two subpopulations: a susceptible one over a small range during most years (MIC 0.5-1.0 mg/l) and a resistant one with MICs >8 mg/l (figure 39). Co-amoxiclav resistance in Unselected Hospital Departments increased from 5% in 1998 to 8% in 2009. The resistance level in Urology Services increased from 1% in 1998 to 5% in 2008. The MIC distribution of co-amoxiclav (figure 39) showed a change starting in 2000 with a broadening of the susceptible subpopulation (MIC 0.25-8 mg/l) and flattening of the peak at 1 mg/l with appearance of small subpopulations with MIC >16 mg/l. This continued in the years after 2002 resulting in a resistance rate of 5-6%. So the increase of resistance observed in 2003 could already be predicted three years earlier by analyzing the MIC distributions. This underlines the importance of quantitative susceptibility testing.

Cefuroxime resistance in Unselected Hospital Departments was 2% in 2008 and 2009, equal to that in Urology Services during the whole study period (figure 37). Ceftazidime- and cefotaxime resistance in *P. mirabilis* was less than 1% in all hospital departments. Trimethoprim resistance in *P. mirabilis* in Unselected Hospital Departments was higher than 50% until 2002 and it decreased thereafter to 41% in 2007 and 34% in 2009 (not shown). The high resistance level before 2002 is not well-understood, unless we have to assume that other breakpoints have been applied in that time. The resistance level in Urology Services was similar to that in Unselected Hospital Departments.

Co-trimoxazole resistance in Unselected Hospitals was 31% in 2008 and 2009 (figure 37). The resistance levels in Urology Services fluctuated around 30-35% (figure 38).



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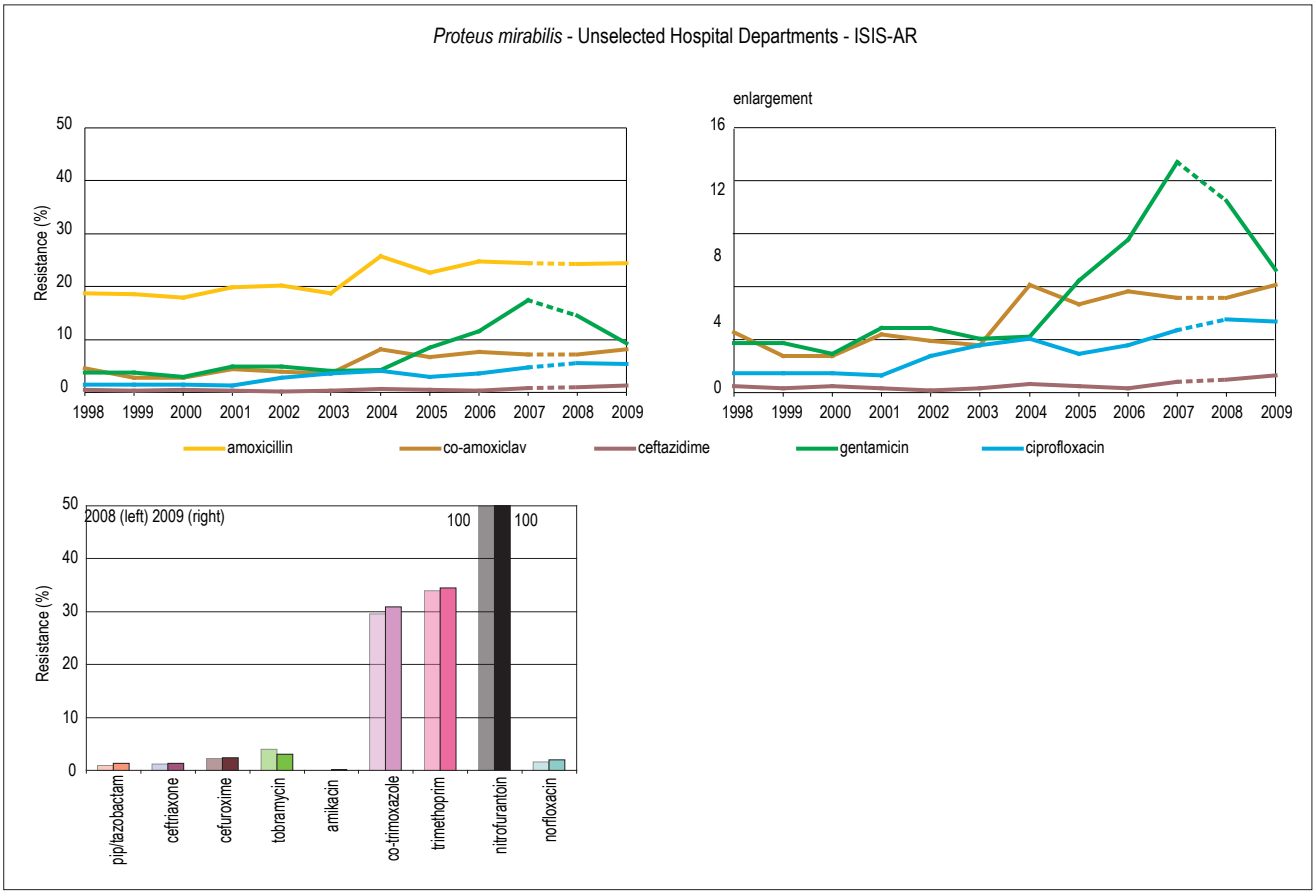



Figure 37. Trends in antibiotic resistance among clinical strains of *Proteus mirabilis* (N= 17.000-34.000) from Unselected Hospital Departments, calculated from the values for intermediate susceptibility and resistance (I+R) reported to ISIS-AR. Additional antibiotics tested in 2008 and 2009 are presented as columns.

Gentamicin resistance increased slowly with fluctuations in Unselected Hospital Departments from 4% in 1998 to 9% in 2009. In 2007, an unusual high resistance level (17%) was observed. We have no explanation for this finding. Gentamicin resistance in Urology Services increased from 3% in 1998 to 8% in 2008 (figure 38). Ciprofloxacin resistance among *P. mirabilis* in Unselected Hospital Departments increased from 2% in 1998 to 7% in 2009. The resistance level in Urology Services fluctuated between 5% and 13% over the years without a significant trend.

**Summary – *Proteus mirabilis***

1. Increasing resistance to amoxicillin, co-amoxiclav, ciprofloxacin and gentamicin in all study populations

*4.3.3.5 Pseudomonas aeruginosa*

Piperacillin resistance among *P. aeruginosa* isolated in Unselected Hospitals was not routinely recorded until 2007. The resistance level in 2008 and 2009 was 3-4% (not shown). Resistance in ICUs was not found until 2000; then resistant strains were isolated in an increasing number of ICUs, leading to an overall increase trend to 18% in 2008 (figure 40). Piperacillin resistance in Urology Services was accidental, fluctuating between 2% and 7%. The resistance to piperacillin-tazobactam followed that of piperacillin (not shown). The MIC distributions of piperacillin are given in figure 41. They were unimodal from 1998 to 2000. In 2001, a shoulder in the area MIC 8-16 mg/l and a small subpopulation of strains with MIC > 64 mg/l emerged. The following year the resistant subpopulation had increased and the distribution became bimodal. In 2005, the distribution broadened over the area 0.25-8 mg/l with a shift of the median to higher MIC values and in 2007 a shoulder appeared again in the range 8-32 mg/l, which flattened in 2008 with again a shift to the right. The same phenomenon was observed for piperacillin-tazobactam. Meropenem resistance among *P. aeruginosa* remained less than 2% in Unselected Hospital Departments during the years. It was less than 2% in ICUs until 2006, but 4% resistance was recorded in 2008 (figure 40). Resistant strains were found in five of 14 centres only, and this resistance figure reflected a local problem in some ICUs and was therefore not representative for the Netherlands as a whole. Meropenem resistance was found only once in Urology Services in 2003.



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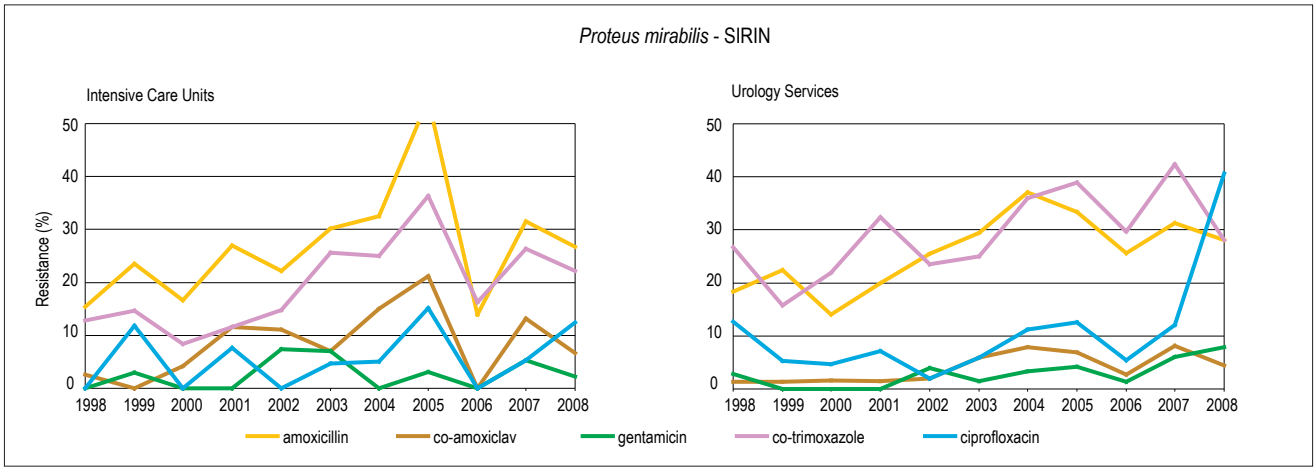



Figure 38. Trends in antibiotic resistance among *Proteus mirabilis* from Intensive Care Units (N=450) and Urology Services (N=949), calculated according to the breakpoints for resistance of EUCAST.

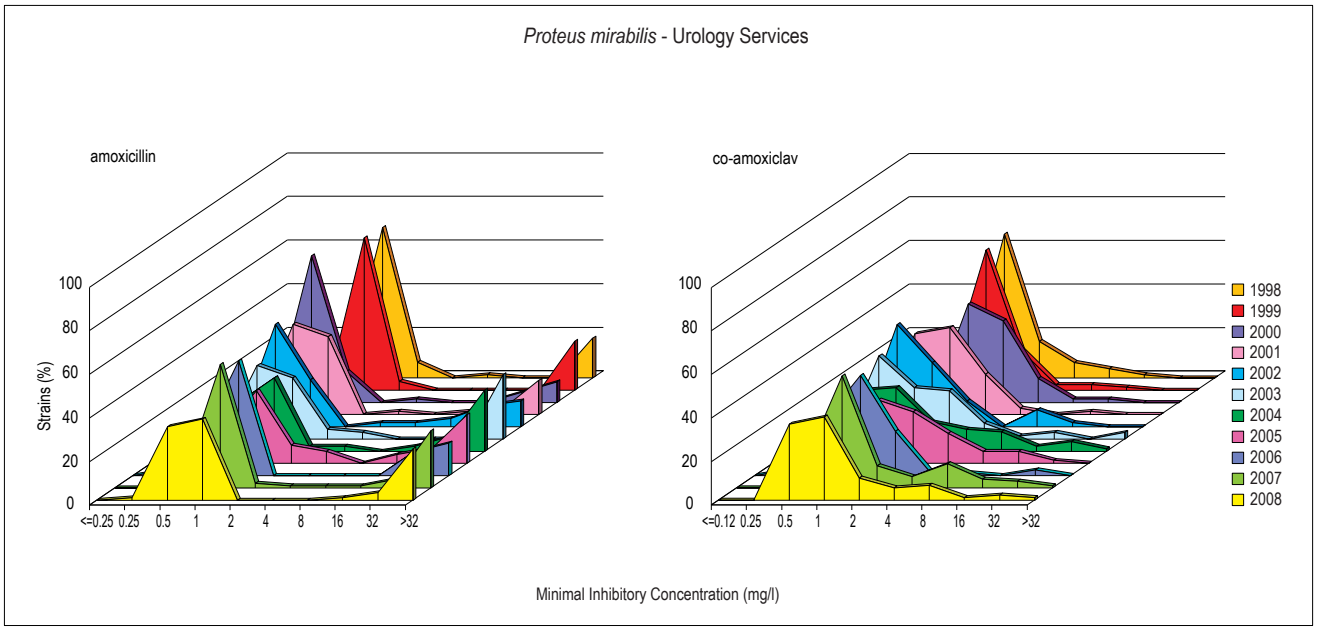



Figure 39. MIC distributions of amoxicillin and co-amoxiclav for *Proteus mirabilis* from Urology Services.

Ceftazidime resistance among *P. aeruginosa* isolated in Unselected Hospital Departments increased slowly from 2% in 1998 to 7% in 2009 (figure 40). Ceftazidime resistance in ICUs fluctuated, but the trend was increasing from 1% in 1998 to 9% in 2008. An incidental 12% resistance was recorded in 2002 because of an unusual high resistance rate in five centres. Six of 14 centres had delivered ceftazidime-resistant strains in 2008. The current resistance levels are not representative for ICUs in general but reflect a local problem with a highly resistant population. This underscores the importance of local surveillance. The resistance rate in Urology Services was consistently low (0-5%) without a trend.

Gentamicin resistance data for Unselected Hospital Departments is available as of 2005. Before that time one of eight participating laboratories had methodologic problems and reported an unusual high amount of gentamicin-resistant strains which could not be confirmed. These data were excluded from this evaluation. Gentamicin resistance in Unselected Hospitals was 2-4% without a trend (figure 40). Resistance in ICUs was found every year in one to six centres responsible for the fluctuations in the overall resistance rate of 5% (figure 40). Gentamicin resistance was found sporadically in some Urology Services.

Amikacin- and tobramycin resistance in Unselected Hospital Departments was 2% in 2008 and 2009; amikacin resistance in Intensive Care was less than 4% during the whole study period whereas that of tobramycin showed more fluctuations (1-9%) reflecting local problems in some ICUs rather than a general trend. There was no complete cross-resistance between the three aminoglycosides: 39% of gentamicin-resistant



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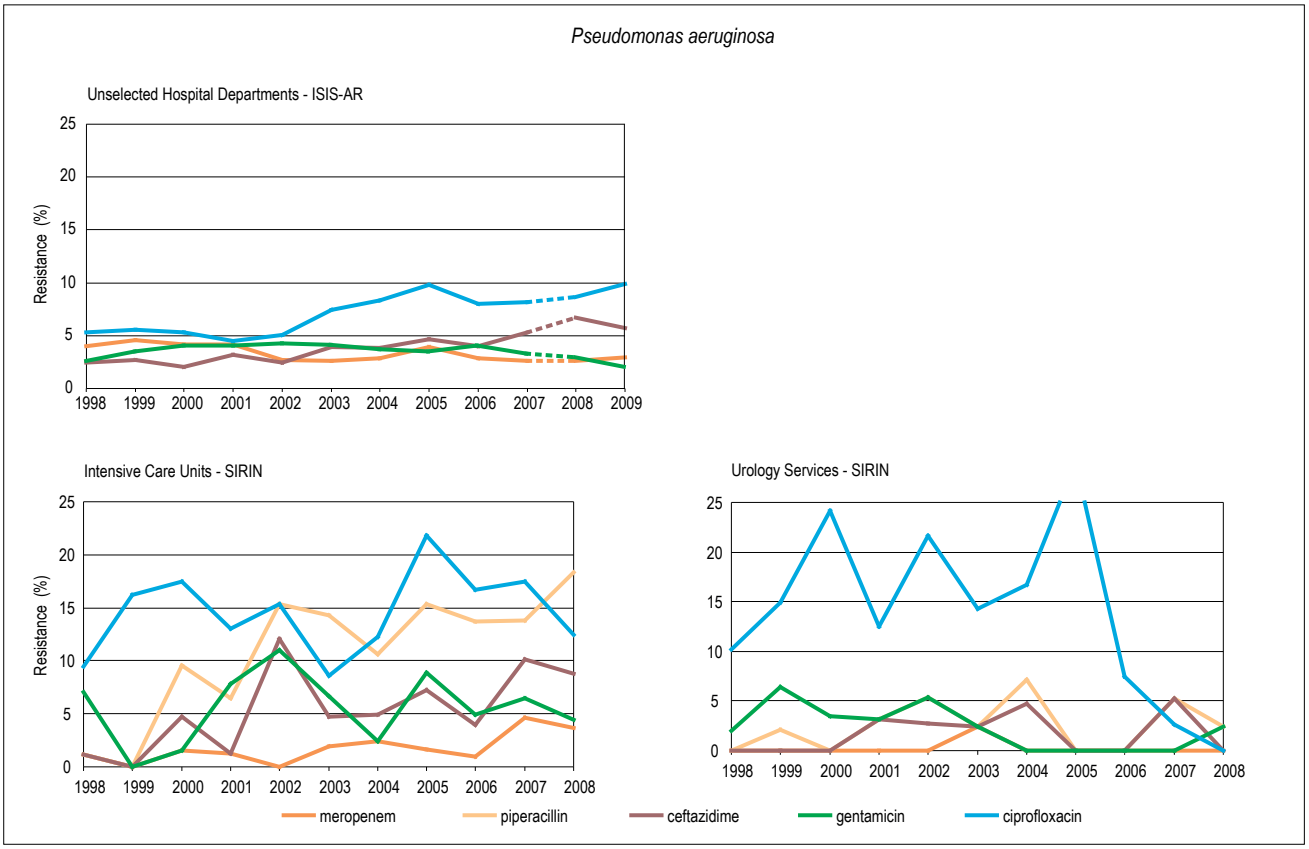



Figure 40. Trends in antibiotic resistance among clinical strains of *Pseudomonas aeruginosa* (N= 2.500-3.100) from Unselected Hospital Departments, calculated from the values for intermediate susceptibility and resistance (I+R) reported to ISIS-AR and trends in antibiotic resistance among clinical strains of *Pseudomonas aeruginosa* from Intensive Care Units (N=1.270) and Urology Services (N=505), calculated according to the breakpoints for resistance of EUCAST.

strains were also tobramycin-resistant and 24% were amikacin resistant. Tobramycin-resistant strains were also gentamicin-resistant but not always amikacin-resistant. The MIC distributions of gentamicin and tobramycin were bimodal with one subpopulation with MICs over a broad range from 0.12-4 mg/l and a very small subpopulation with MIC > 16 mg/l (figure 42). The MIC distribution of amikacin was unimodal over a broad range from 0.5-> 16 mg/l. In general MICs of tobramycin were two-fold lower than those of gentamicin, reflecting its higher intrinsic activity against *P. aeruginosa* and four-fold lower than those of amikacin.

Ciprofloxacin resistance showed a slowly increasing trend in Unselected Hospital Departments from 4% in 1998 to 9% in 2009 (figure 40). Ciprofloxacin resistance in ICUs was higher and fluctuated around 15% (figure 40). The resistance level in Urology Services fluctuated strongly between 10% in 1998 and 28% in 2005, but showed a remarkable decrease thereafter to 7% in 2006 3% in 2007 and 0% in 2008. The levels of resistance to levofloxacin paralleled those of ciprofloxacin but were mainly 2-3% higher with 5% resistance in 2008. The MIC distributions of strains from ICUs were unimodal over a broad range of MIC values; those of Urology Services were bimodal until 2006 and turned to unimodal in 2007 and 2008 with the disappearance of the resistant subpopulation with MIC > 16 mg/l (figure 43). This pattern was also found for levofloxacin. The intrinsic activity of ciprofloxacin was higher than that of levofloxacin: $MIC_{50}$ for ciprofloxacin was 0.12 mg/l, and for levofloxacin was 0.5 mg/l.

**Summary – *Pseudomonas aeruginosa***

1. Increasing resistance to ceftazidime and ciprofloxacin in Unselected Hospital Departments
2. Ciprofloxacin resistance rate was higher in Intensive Care Units than in Unselected Hospital Departments
3. Decreasing resistance to ciprofloxacin in Urology Services
4. Local problems with resistant clones in a limited number of Intensive Care Units might have influenced the overall resistance level of piperacillin, meropenem, gentamicin and ceftazidime in a given year. This underlines the importance of local surveillance



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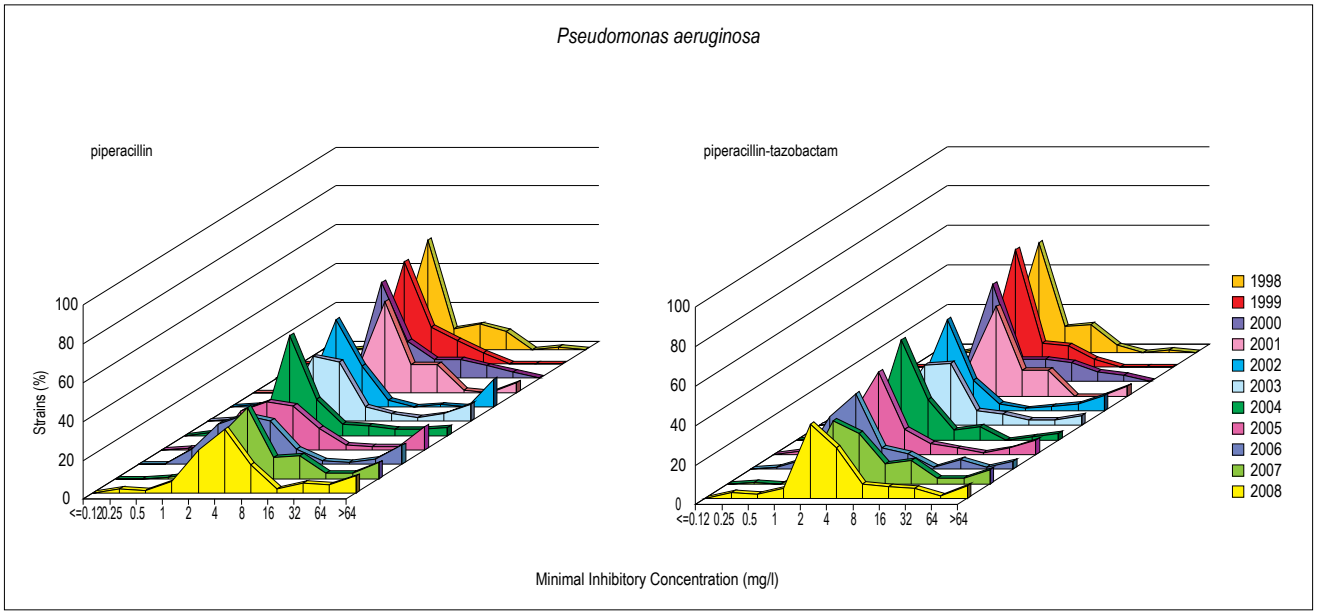



Figure 41. MIC distributions distributions of piperacillin and piperacillin-tazobactam for *Pseudomonas aeruginosa* from Intensive Care Units.

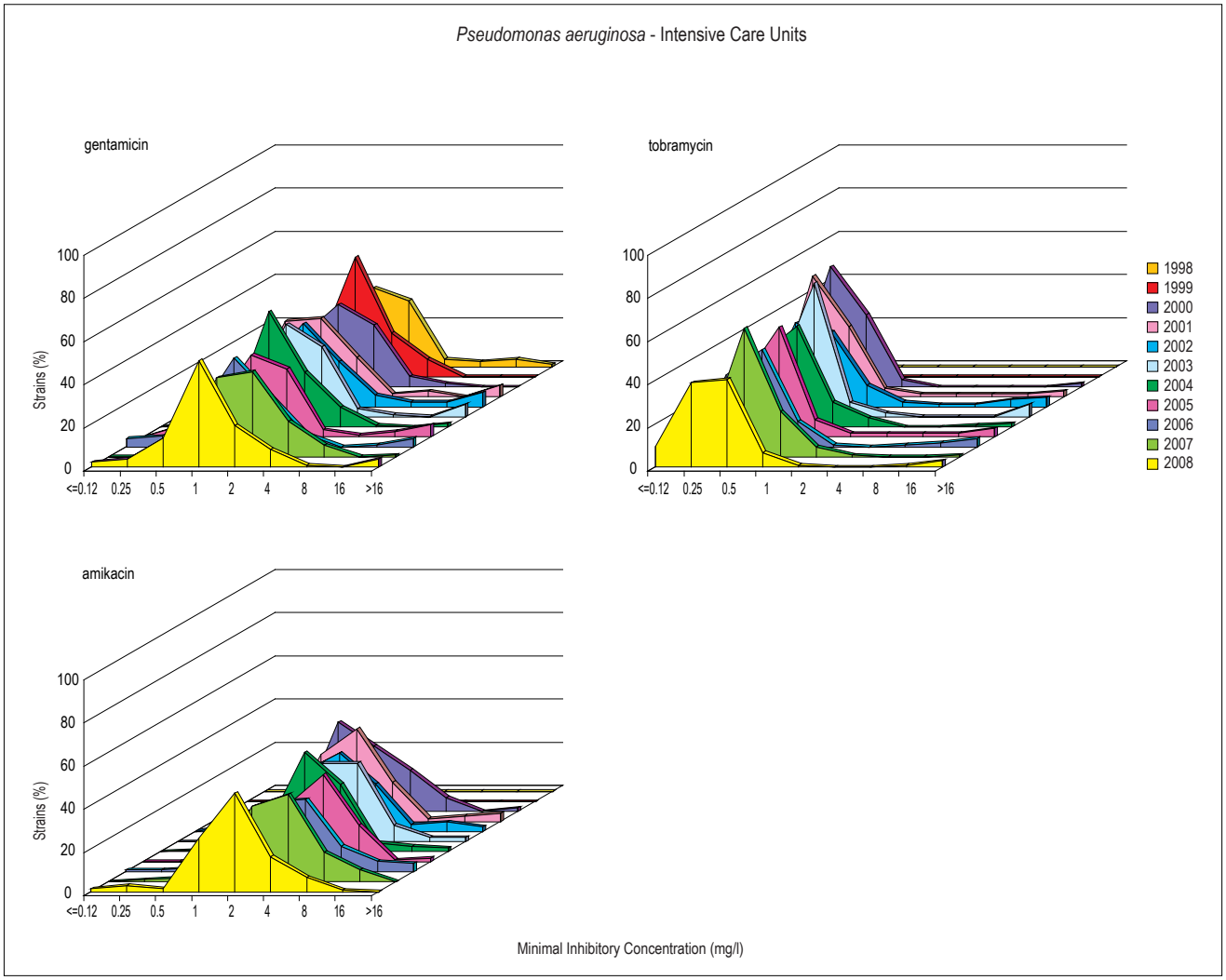



Figure 42. MIC distributions of aminoglycosides for *Pseudomonas aeruginosa* from Intensive Care Units.



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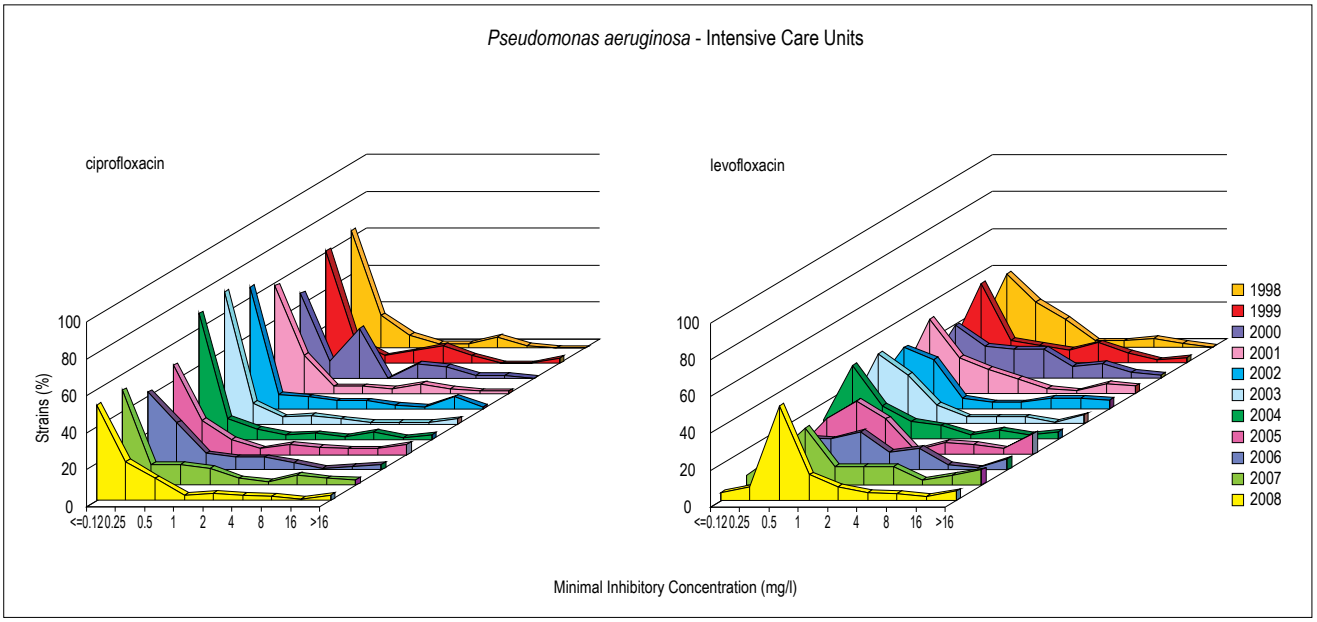



Figure 43. MIC distributions of ciprofloxacin and levofloxacin for *Pseudomonas aeruginosa* from Intensive Care Units.

*4.3.3.6 Staphylococus aureus*

In 2009, a total number of 2970 MRSA isolates were forwarded to the Centre for Infectious Disease Control Netherlands ath the National Institute of Public Health and the Environment (RIVM) for typing, which is 277 isolates more then the number received in 2008 (figure 44). The percentage of CC398 strains, as derived from spa-type, was 42% in 2009 compared to 41% in 2008. Part of the strains were livestock-associated, derived from screening projects among farmers and their families.

The overall percentage of MRSA in Unselected Hospital Departments increased slowly from 0.5% in 1998 to 1.6% (82 strains) in 2009 (figure 45). Sporadically, MRSA strains were isolated from the ICUs (N = 10 from 1998-2008) and the Urology Services (N = 7 from 1998-2008). Six out of ten MRSA strains from ICUs were ciprofloxacin resistant of which five were also clarithromycin-resistant, one was also gentamicin-resistant.

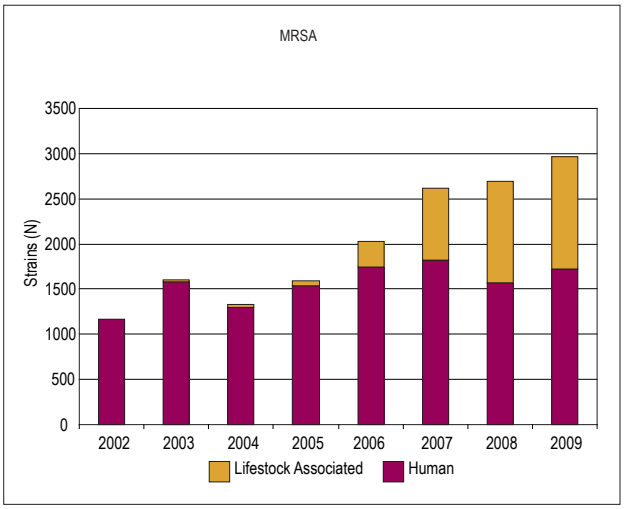



Figure 44. Numbers and origin of MRSA in The Netherlands.

Cefuroxime resistance in ICUs was rare, 2% or less and not recorded yearly (figure 45).

Erythromycin resistance in Unselected Hospital Departments was slowly increasing from 5% in 1998 to 11% in 2009 (figure 45). Clarithromycin resistance among strains from ICUs increased from 5% in 1998 to 10% in 2008; the resistance rate in Urology Services paralleled that of the ICUs. No data on clindamycin resistance in Unselected Hospital Departments were available from 1998-2007, it was 8% in 2008 and 9% in 2009, respectively (figure 45). Clindamycin resistance in ICUs was lower, and fluctuated around 3-4% over the years without a shift or clear trend.

Ciprofloxacin resistance rose among isolates from Unselected Hospital Departments from 3% in 1998 to 11% in 2009 (figure 45). Ciprofloxacin resistance in ICUs increased from 4% in 1998 to 16% in 2005 and decreased thereafter to 8% in 2008. Moxifloxacin resistance followed that of ciprofloxacin resistance, although at a lower level (7% in 2008). Strains from Urology Services showed high resistance rates from 2003 on (30-40% not shown,) but the numbers of strains were very small (30 to 40 per year).

Gentamicin resistance remained les than 1% in Unselected Hospital Departments without a trend; it was higher in ICUs (1-4%) from 1998 to 2004 and not found thereafter. Vancomycin resistance in Unselected Hospital Departments remained less than 0.1% during the whole study period and it was not found every year. Vancomycin resistance was once recorded in the ICUs in



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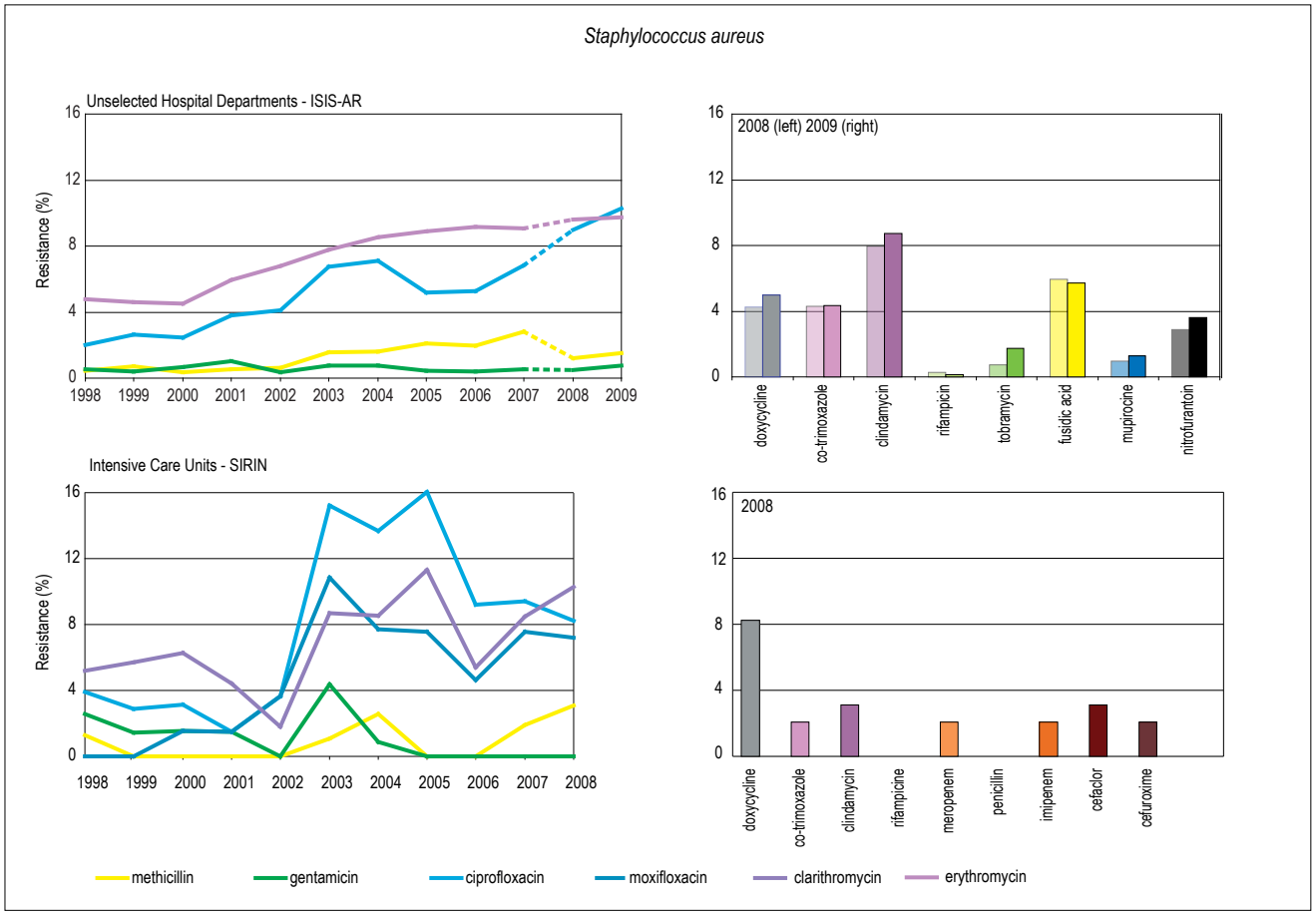



Figure 45. Trends in antibiotic resistance among clinical strains of *Staphylococcus aureus* (N=75.000-110.000) from Unselected Hospital Departments, calculated from the values for intermediate susceptibility and resistance (I+R) reported to ISIS-AR and trends in antibiotic resistance among clinical strains of *Staphylococcus aureus* from Intensive Care Units (N=1.148), calculated according to the breakpoints for resistance of EUCAST. Additional antibiotics tested in 2008 are presented as columns. Additional antibiotics tested in 2008 and 2009 are presented as columns.

2006. Teicoplanin resistance was not tested in Unselected Hospital Departments before 2008; it was 0.2% in 2009; teicoplanin resistance was once found in ICUs in 2003 being less than 0.1%.
Fusidic acid resistance was 6% in Unselected Hospital Departments in 2008 and 2009. Resistance percentages to additional antibiotics in Unselected Hospital Departments tested from 2008 onwards are given in figure 45. Looking at the resistance percentages found in ICUs in the same year it appeared that the resistance rate of doxycycline in ICUs in 2008 was higher (8%) than that found for Unselected Hospital Departments (5%). The opposite was found for co-trimoxazole with 2% resistance in ICUs and 4% in Unselected Hospital Departments.
Resistance rates to carbapenem, rifampicin, linezolid and quinupristin/dalfopristin were less than 1% (not shown).

**Summary – *Staphylococcus aureus***

1. Prevalence of MRSA was slowly increasing, but remained less than 1.5% in Unselected Hospital Departments; MRSA occurred occasionally in Intensive Care Units
2. Increasing resistance to macrolides in Unselected Hospital Departments and Intensive Care Units
3. Increasing resistance to ciprofloxacin in Unselected Hospital Departments
4. Decreasing resistance to ciprofloxacin in Intensive Care Units to levels lower than in Unselected Hospital Departments
5. Vancomycin- and teicoplanin resistance were sporadic in all hospital departments



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Figure 46. Trends in antibiotic resistance among clinical strains of *Staphylococcus epidermidis* (N=24.000-31.000) from Unselected Hospital Departments, calculated from the values for intermediate susceptibility and resistance (I+R) reported to ISIS-AR and trends in antibiotic resistance among clinical strains of *Staphylococcus epidermidis* from Intensive Care Units (N=566), calculated according to the breakpoints for resistance of EUCAST. Additional antibiotics tested in 2008 are presented as columns.

*4.3.3.7 Staphylococcus epidermidis*

Methicillin-resistance (determined by oxacillin-resistance) was frequently found among hospital isolates of *S. epidermidis*. Methicillin-resistance in Unselected Hospital Departments increased from 41% in 1998 to 55% in 2009 (figure 46). About 80% of all strains from ICUs were methicillin-resistant. Methicillin-resistant strains were often co-resistant to erythromycin, clarithromycin, gentamicin, ciprofloxacin and meropenem. The emergence of resistance to meropenem in ICUs was impressive being less than 20% until 2001 and increasing to 32% in 2008. The MIC distribution (figure 47) was more or less bimodal until 2005 with a small subpopulation of strains with MIC < 0.25 mg/l and another subpopulation over a large range (MIC 1- >16 mg/l) with the median at 2 mg/l. A clear shift to higher MIC values was observed from 2002 onwards with disappearance of the small susceptible subpopulation and appearance of a cluster of strains with MIC > 8 mg/l.

Erythromycin resistance increased steadily in Unselected Hospital Departments from 40% in 1998 to 50% in 2009; clarithromycin resistance in ICUs was much higher and showed an increasing trend from 70% in 1998 to 80% from 2000 on. The MIC distribution was bimodal with a large cluster with MICs >16 mg/l and a very small cluster with MICs of 0.5 mg/l or less (figure 47). The peak of the susceptible cluster seemed to flatten and to move to higher MIC values. Clindamycin resistance in Unselected Hospitals was 42% in 2009 compared to 54% among strains from ICUs in 2008 (figure 46).

Gentamicin resistance in Unselected Hospital Departments fluctuated around 32% during the whole study period. Gentamicin resistance in ICUs fluctuated around 70% with a peak of 94% in 2008.

Ciprofloxacin resistance in Unselected Hospital Departments increased slowly from 30% in 1998 to 39% in 2009. Ciprofloxacin resistance in ICUs was much higher from the beginning (57%); it fluctuated and increased to 90% in 2007 and decreased again to 64% in 2008.

Co-trimoxazole- and rifampicin resistance rates were significant higher among strains from ICUs compared to those from Unselected Hospital Departments, in contrast with doxycycline resistance which was 22% in all departments (figure 46).

Vancomycin-resistance was less than 1% in Unselected



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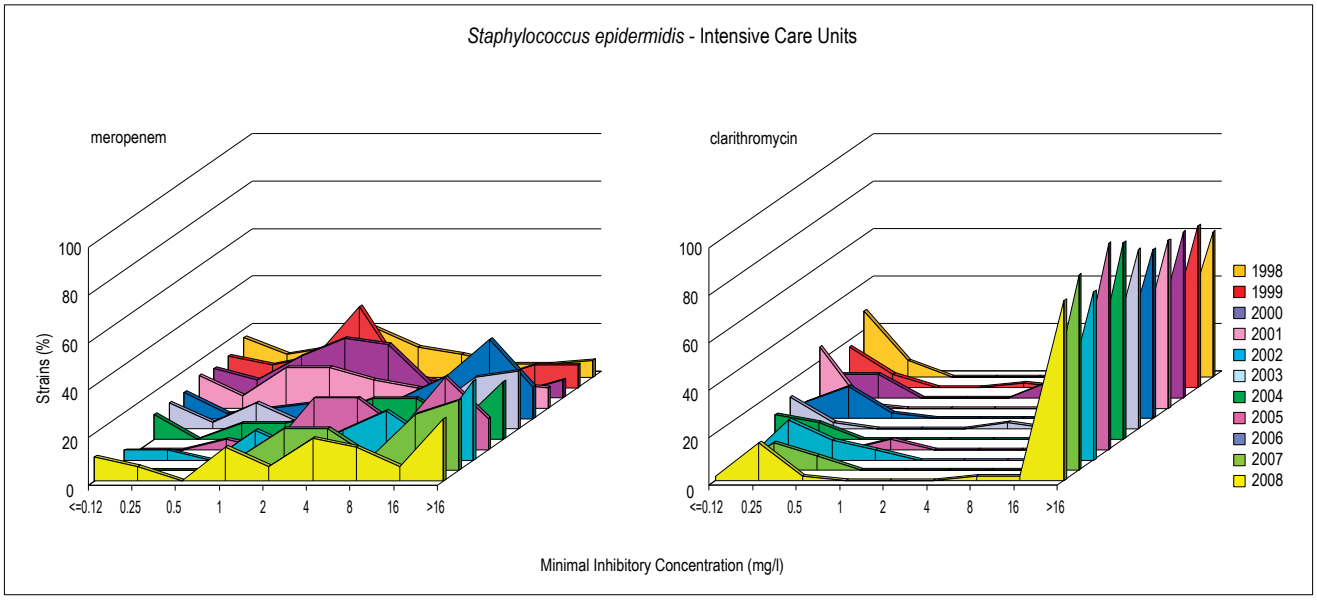



Figure 47. MIC distributions of meropenem and clarithromycin for *Staphylococcus epidermidis* from Intensive Care Units.

Hospital Departments; it was occasionally found in ICUs in 1-2 centres per year from 2002 on. Two vancomycin-resistant strains were also teicoplanin-resistant (MIC 256 mg/l). Linezolid resistance was not recorded.
High resistance levels to many drugs among *S. epidermidis* from ICUs are common apparently as result of high selective pressure in these wards. Often these strains belong to specific populations circulating in ICUs and colonizing many patients. Such populations may serve as a reservoir for multiresistance with the risk of exchange of resistance factors to other micro-organisms in the commensal flora of patients and health care workers.

**Summary – *Staphylococcus epidermidis***

1. High resistance levels to macrolides, gentamicin, ciprofloxacin, cotrimoxazole and rifampicin and multiresistance were common among strains from Intensive Care Units especially
2. Increasing resistance to methicillin and macrolides in Unselected Hospital Departments and Intensive Care Units
3. Increasing resistance to meropenem in Intensive Care Units
4. Glycopeptide resistance was sporadic in all hospital departments

*4.3.3.8 Streptococcus pneumoniae*

*Streptococcus pneumoniae* strains resistant to penicillin (MIC > 2 mg/l) are not often isolated in the Netherlands. In 2009, 1% of all pneumococci from Unselected Hospital Departments were resistant whereas another 2.5% was categorized as intermediate. Taking resistant and intermediate strains together over the years an increase was observed from 1% in 1998 to 3.5% in 2009 (figure 48). The resistance level in Pulmonology Services was lower (1%) and did not increase. This difference might be due to different patient populations from which the strains came.
The resistance to cefaclor increased to 50% or more in Pulmonology Services, and cefuroxime-resistance was less than 4% during the whole study period. The MIC distribution (figure 49) showed a shift to higher MIC values in 2007 and 2008, increasing the number of resistant strains with MIC > 0.5 mg/l. The MIC distribution of cefuroxime showed no change over the years. Cefotaxime was the most active against *S. pneumoniae* in Unselected Hospital Departments and Pulmonology Services with less than 1% resistance during the whole study period (not shown).
Increasing resistance to macrolides among clinical isolates of *S. pneumoniae* from all departments was observed from 2000 on, resulting in 10% resistance to erythromycin in Unselected Hospitals in 2009 and 10% clarithromycin resistance in Pulmonology Services in 2008.
Resistance rates of doxycycline in Unselected Hospitals increased slowly to 11% in 2009 with some fluctuations. The resistance level in Pulmonology Services was already 12% in 1998, but remained at that level during the whole study period with some fluctuations (figure 48). The MIC distributions (figure 50) showed a change from 2001 onwards. Until that year a large subpopulation with MIC < 0.25 mg/l and a small subpopulation over a broad range (MIC 1-16 mg/l) were observed. These small subpopulations are responsible for the fluctuations, as they are around the breakpoint for resistance and may fall into the susceptible category one year and into the resistant category the other year when their MIC is one



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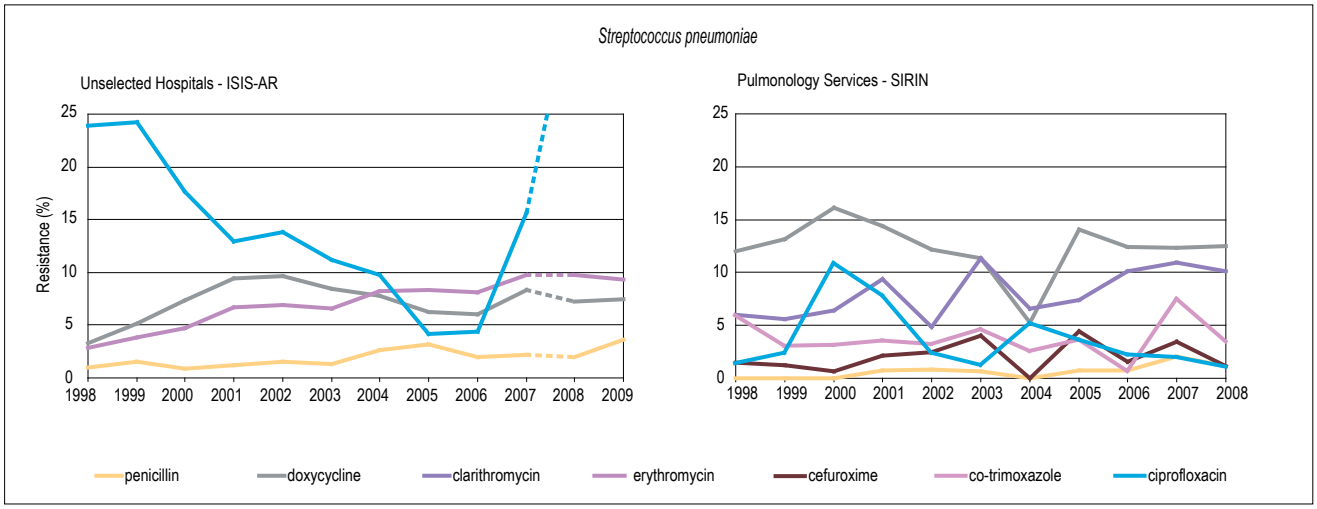



Figure 48. Resistance among clinical strains of *Streptococcus pneumoniae* (N=5.000-21.000) from Unselected Hospital Departments, calculated from the values for intermediate susceptibility and resistance (I+R) reported to ISIS-AR and trends in antibiotic resistance among clinical strains of *S. pneumoniae* from Pulmonology Services (N=1.858), calculated according to the breakpoints for resistance of EUCAST.

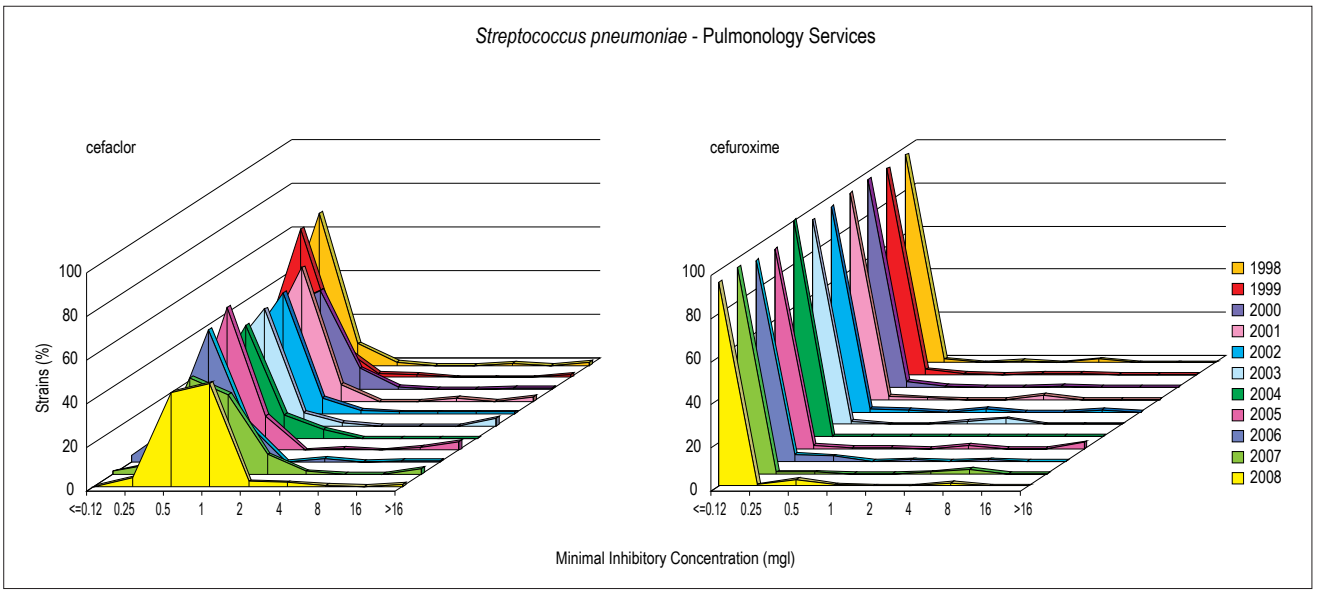



Figure 49. MIC distributions of cefaclor and cefuroxime for *Streptococcus pneumoniae* from Pulmonology Services.

dilution step higher. From 2002 onwards, the distribution became bimodal with one susceptible subpopulation (MIC < 0.5 mg/l) and one resistant with MIC > 16 mg/l. Co-trimoxazole resistance was 6% in Unselected Hospital Departments in 2009, which is much lower than that reported in 2008 (14%, not shown). We have no explanation for this difference as the number of strains in both years are comparable (953 and 773 respectively), although different laboratories participated. Maybe the patient groups differed as well. It is important to explore this further. Co-trimoxazole is one of the drugs used as alternative for penicillins and doxycycline in patients with RTI for both adults and children. When the resistance level exceeds 10%, it is not useful anymore for empiric therapy. The levels found for Pulmonology Services were less than 6% during the whole study period with 4% resistance in 2008.

Ciprofloxacin resistance recorded in Unselected Hospital Departments fluctuated considerably over the years (4-15%) until 2007 and it was reported 37% in 2008 (figure 48). Results of ciprofloxacin testing were not available for 2009. The resistance to levofloxacin reported was 0% in 2008 and 2009. The big difference in resistance levels of ciprofloxacin and levofloxacin is probably a matter of breakpoints applied. The MIC distributions of levofloxacin and ciprofloxacin are similar with the majority of strains having MIC 1-2 mg/l. This is around the breakpoint for resistance for ciprofloxacin, but within the susceptible area for levofloxacin as the CLSI breakpoint for intermediate resistance for levofloxacin



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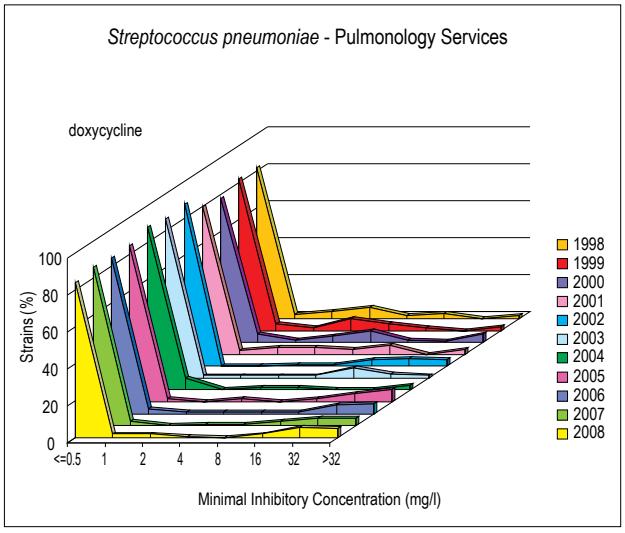



Figure 50. MIC distributions of doxycycline for *Streptococcus pneumoniae* from Pulmonology Services.

is twice as high compared to that for ciprofloxacin. The breakpoint for susceptibility recommended by EUCAST for ciprofloxacin is very low (MIC < 0.125 mg/l). This reflects the low exposure of ciprofloxacin due to its pharmacokinetic profile. This implies that less than 1% should have been categorized really susceptible and that all wild type *S. pneumoniae* strains (MIC 0.25-1 mg/l) are categorized as intermediate (see also figure 51). The breakpoint for susceptibility recommended by CLSI is higher (MIC < 1 mg/l). Depending on the breakpoints used the susceptibility percentages may vary considerably. Ciprofloxacin resistance (MIC > 2mg/l) in Pulmonology Services showed some fluctuations, but remained less than 5% from 2002 on with 1% in 2008. Moxifloxacin resistance was very low (1-3%) during the whole study period. Resistance percentages are not informative on changes and shifts in susceptibility patters. MIC distributions of ciprofloxacin showed no significant changes during the whole study period, but 90% of the strains had MIC values of 0.5-1 mg/l in the intermediate area (figure 51). The MIC distribution of moxifloxacin showed a unimodal distribution with 90% of MICs 0.06-0.12 mg/l.

**Summary – *Streptococcus pneumoniae***

1. Penicillin resistance remained less than 3.5% in Unselected Hospital departments and 1% in Pulmonology Services.
2. Increase of resistance to macrolides in all departments.
3. Consistent higher resistance level to doxycycline in Pulmonology Departments compared to that in Unselected Hospital Departments.
4. Increasing resistance to cefaclor in Pulmonology Departments

*4.3.3.9 Haemophilus influenzae*

Amoxicillin resistance among *H. influenzae* from Unselected Hospital Departments showed an increasing trend to 15% in 2009 (figure 52). Co-amoxiclav was not tested until 2007, it was 3% in 2009, which implied that 80% of the total amoxicillin-resistance was based on beta-lactamase production. Amoxicillin resistance in Pulmonology Services was consistently higher and increased from 8% in 1998 to 30% in 2008, whereas co-amoxiclav resistance increased from 3% in 1998 to 17% in 2008. Data from 2004 were excluded from evaluation because of the low number of strains collected that year.

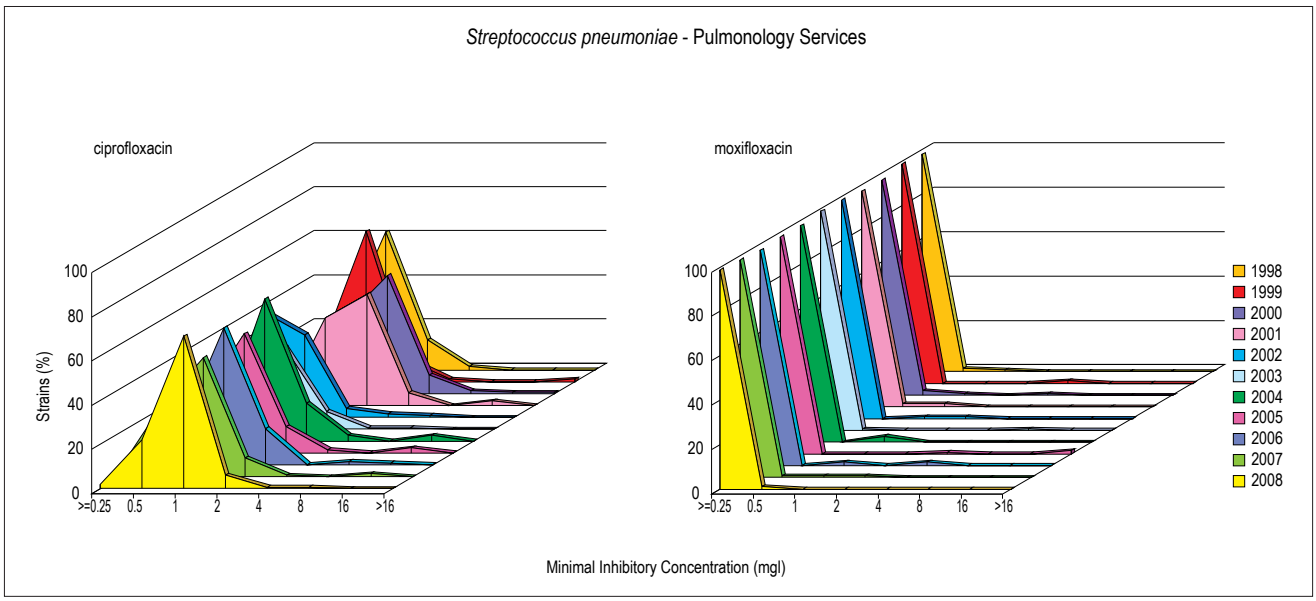



Figure 51. MIC distributions of ciprofloxacin and moxiflocacin for *Streptococcus pneumoniae* from Pulmonology Services.



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The MIC distributions (figure 53) of amoxicillin showed a shift in 2005; before that time the distribution showed an almost unimodal shape over a broad range (MIC 0.1-1 mg/l) with some strains with MIC > 16 mg/l. This shape changed in 2005 with appearance of a bimodal shape and a shift to higher MIC values of the susceptible subpopulation now showing one subpopulation with an MIC range 0.5-2 mg/l and a second subpopulation with MIC > 16 mg/l. The same shift was observed for co-amoxiclav, which resulted in higher resistance levels, as the breakpoint for resistance is MIC > 2mg/l. The increasing amoxicillin- and co-amoxiclav resistance is a matter of concern.
Resistance to cefotaxime among strains from Unselected Hospital Departments was less than 1% during the whole study period. This was also found for cefuroxime and ceftazidime in strains from Pulmonology Services until 2005 (not shown). Thereafter cephalosporin resistance was not routinely tested for this department.
Resistance to erythromycin in strains from Unselected Hospital Departments increased from 69% in 1998 to 98% in 2009 (figure 52). Clarithromycin resistance in Pulmonology Services increased with fluctuations from 3% in 1998 to 12% in 2008. Apparently, the intrinsic activity of clarithromycin is higher than that of erythromycin.
Low resistance rates (1-2%) without a trend were found for doxycycline among *H. influenzae* isolates from Unselected Hospital Departments (figure 52). The resistance rates in Pulmonology Services were higher from the beginning (8%) and decreased to 2% in 2006, but increased again to 8% in 2008.
A matter of concern is the high resistance to co-trimoxazole, which is one of the drugs used in COPD exacerbations. Data on co-trimoxazole resistance in Unselected Hospital Departments are only available for 2008 and 2009. They were 18% and 17%, respectively. The resistance level in Pulmonology Services (EUCAST) fluctuated between 11-24% with 22% resistance in 2008. These resistance levels in both Unselected Hospitals and Pulmonology Services are too high for use of co-trimoxazole as empiric therapy.
Ciprofloxacin resistance occurred sporadically in Unselected Hospital Departments and Pulmonology Services.

**Summary – *Haemophilus influenzae***

1. Increasing resistance to amoxicillin in Unselected Hospital Departments and Pulmonology Services and to co-amoxiclav in Pulmonology Services are matters of concern
2. High resistance to co-trimoxazole in Unselected Hospital Departments (15-17%) and Pulmonology Services (22%)
3. Erythromycin resistance in Unselected Hospital Departments was more than 95%; clarythromycin resistance in Pulmonology Services increasing to 12% in 2008
4. Consistent higher resistant levels of doxycycline in Pulmonology Services (8%) compared to Unselected Hospital Departments (1-2%)
5. Ciprofloxacin resistance was sporadic

### *4.3.3.10 Moraxella catarrhalis*

Amoxicillin resistance among *M. catarrhalis* isolated in Unselected Hospital Departments increased from 82% in 1998 to 88% in 2009. Amoxicillin resistance

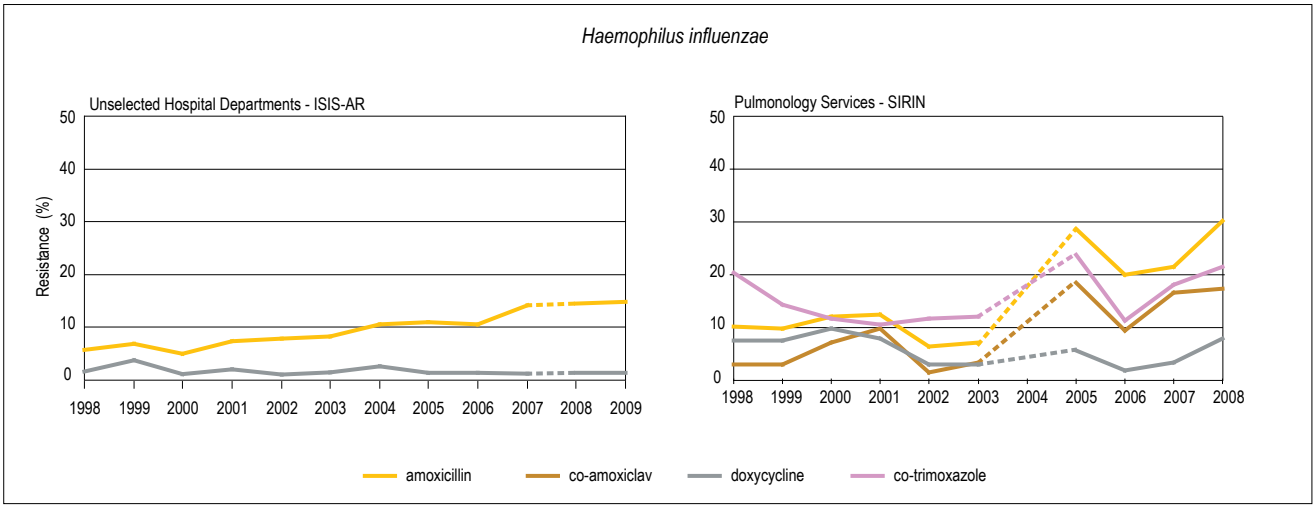



Figure 52. Resistance among clinical strains of *Haemophilus influenzae* (N=12.000-38.000) from Unselected Hospital Departments, calculated from the values for intermediate susceptibility and resistance (I+R) reported to ISIS-AR and trends in antibiotic resistance among clinical strains of *Haemophilus influenzae* from Pulmonology Services (N=2.870), calculated according to the breakpoints for resistance of EUCAST.



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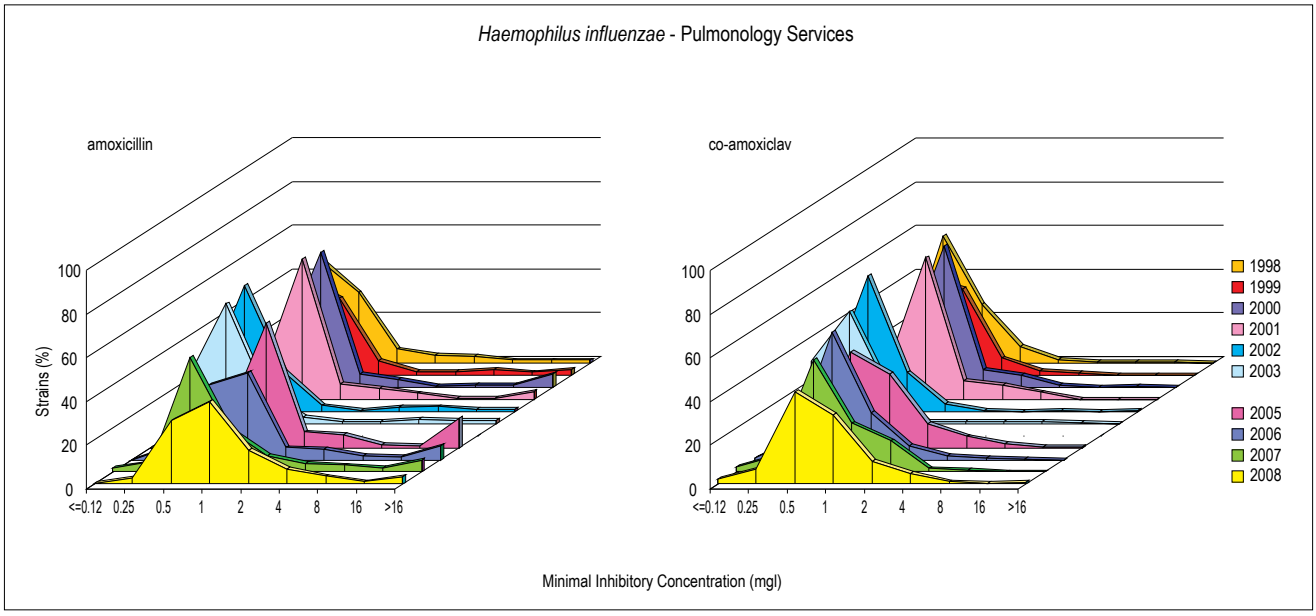



Figure 53. MIC distributions of amoxicillin and co-amoxiclav for *Haemophilus influenzae* from Pulmonology Services.

in Pulmonology Services fluctuated around 45% over the whole study period (figure 54). The difference in resistance levels between strains from Unselected Hospital Departments and those from Pulmonology Services could not be explained. Knowledge of breakpoints used might clarify this. Co-amoxiclav was not tested in Unselected Hospital departments before 2008; seven resistant strains were reported in 2008 en 2009. The resistance in Pulmonology Services was completely due to beta-lactamase since resistance to co-amoxiclav did not occur there.

Cephalosporin resistance was low in all hospital departments. Cefaclor resistance in Pulmonology Services decreased from 8% in 1998 to 1% or less in 2007 and increased to 4% in 2008. Cefuroxime resistance was 0-5% over the years, apparently without a clear trend, but when looking at the MIC distribution a clear shift was observed in 2004 (figure 55). The MIC distributions were unimodal over a broad range from < 0.03-0.5 mg/l in 2003 and 2004. More recently, a complete shift to MIC values of 0.5-4 mg/l was observed, with a clear peak at MIC = 2 mg/l. This is just below the breakpoint for resistance when using EUCAST breakpoints. Cefotaxime- and ceftazidime resistance was less than 1% in all hospital departments during the whole study period. The MIC distributions for ceftazidime for strains from Pulmonology Services showed a unimodal shape over a small range, without a change over time. $MIC_{90}$ was 0.12 mg/l, $MIC_{50}$ was 0.03 mg/l.

Resistance to erythromycin in Unselected Hospital Departments fluctuated from 6-10% over the study period without a specific trend. Clarithromycin resistance in Pulmonology Services was 1-3% and did not show any trend of development of resistance. The lower resistance rate to clarithromycin in Pulmonology Services compared to that to erythromycin in Unselected Hospital Departments may be explained by a higher intrinsic activity of clarithromycin towards *M. catarrhalis*.

Ciprofloxacin resistance was occasionally found in all departments but not every year. Moxifloxacin resistance was tested for strains from Pulmonology Services but not observed.

Resistance to doxycycline fluctuated between 1-3 % in Unselected Hospital Departments (figure 54). Doxycycline resistance was 4-8% in Pulmonology Services until 2001. Thereafter the resistance dropped to 1% or less.

**Summary – *Moraxella catarrhalis***

1. Why amoxicillin resistance in Unselected Hospital Departments (88%) is higher than in Pulmonology Services (45%) is not understandable.
2. Resistance to erythromycin in Unselected Hospital Departments (6-10%) was higher than that of clarithromycin in Pulmonology Services (1-3%)
3. Resistance to cephalosporins, ciprofloxacin and doxycycline remained less than 2% during the last seven years.

*4.3.3.11 Helicobacter pylori*

The number of isolates varied considerably over the years; they were 300-700 yearly, but not all strains were tested for susceptibility to all indicator antibiotics: metronidazole, clarithromycin and amoxicillin were almost always tested, doxycycline was not. Further, the ISIS-AR data obtained in 2008 and 2009 came



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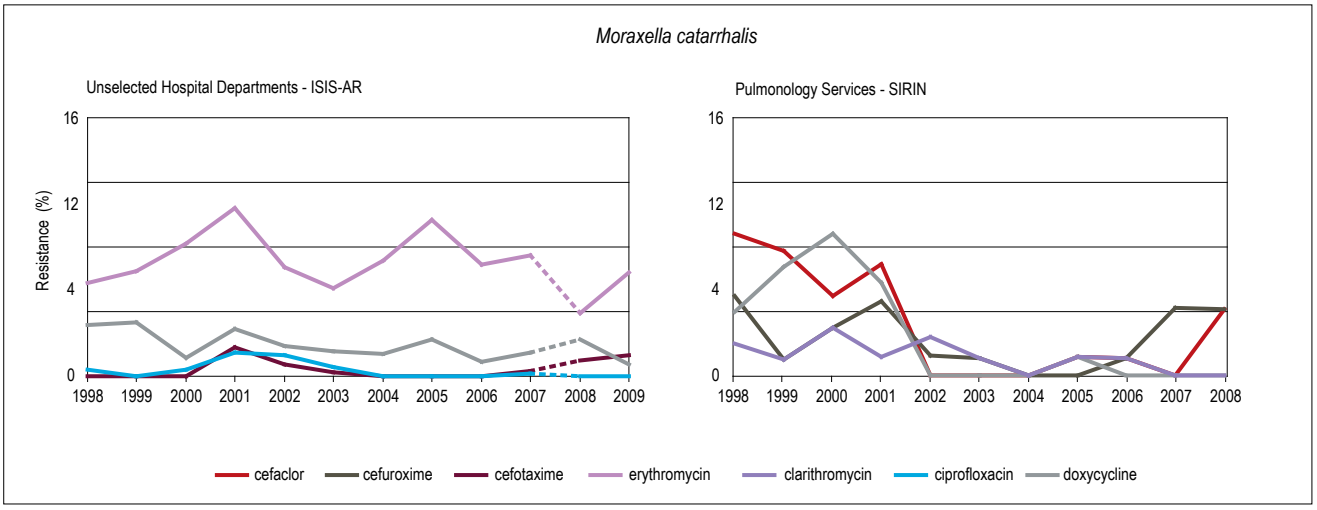



Figure 54. Resistance among clinical strains of *Moraxella catarrhalis* (N=3.500-19.000) from Unselected Hospital Departments, calculated from the values for intermediate susceptibility and resistance (I+R) reported to ISIS-AR and trends in antibiotic resistance among clinical strains of *Moraxella catarrhalis* from Pulmonology Services (N=1.230), calculated according to the breakpoints for resistance of EUCAST.

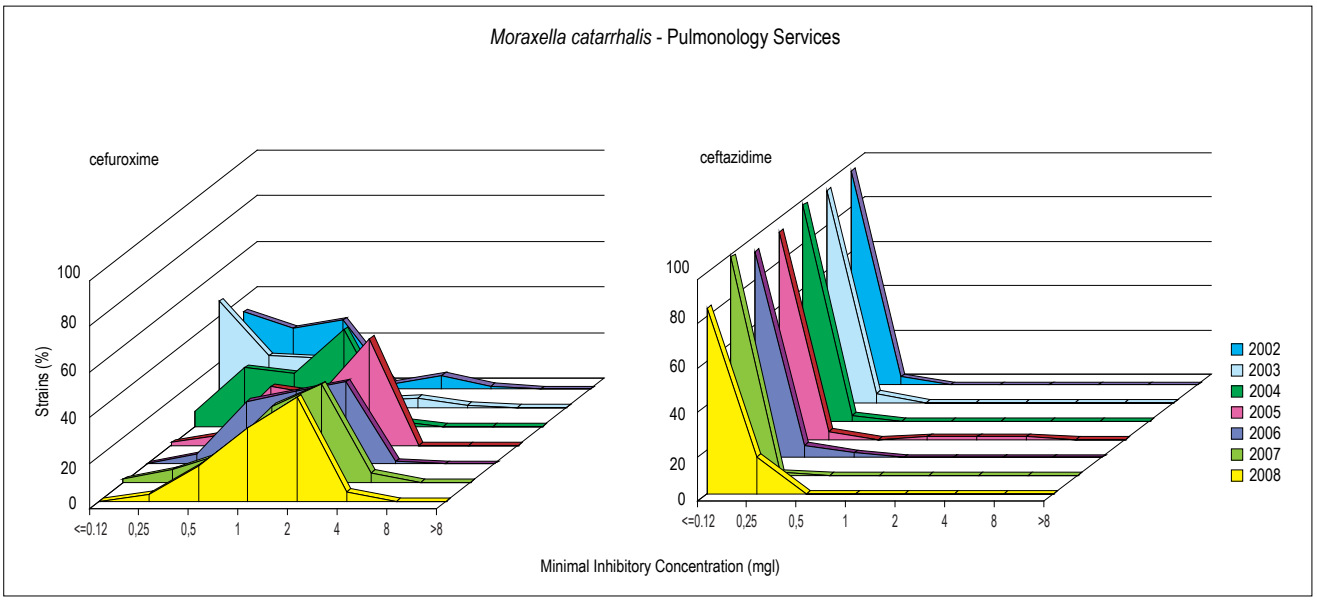



Figure 55. MIC distributions of cefuroxime and ceftazidime for *Moraxella catarrhalis* from Pulmonology Services.

predominantly from one laboratory and, therefore, results should be interpreted with caution.

Amoxicillin resistance among *H. pylori* from Unselected Hospital Departments was 3% or less (figure 56) for both hospitalized patients and patients from Outpatient Clinics over the years. Clarithromycin resistance was 1-5% (mean 4%) until 2007 but increased to 6% in 2008 and 2009 for all patients. Taking the clinical isolates alone this should have been 8% and 7%, respectively, but this difference is statistically not significant.

Doxycycline resistance was less than 2% until 2004 and not tested anymore until 2009. Then again 2% resistance was found.

Metronidazole resistance fluctuated between 12-19% over the years until 2006 without a real trend; thereafter a decrease was observed to 6.5% in 2009 for all isolates. Taking the clinical isolates alone the resistance levels should have been 13%. This difference is significant ($p<0.05$). Probably the hospitalized patients have been treated before with metronidazole with development of resistance as result. The overall decrease of metronidazole resistance together with the increase of clarithromycin resistance may be caused by replacement of metronidazole by clarithromycin for initial treatment of *H. pylori* infections.



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**Summary – *Helicobacter pylori***
1. Increasing resistance to clarithromycin
2. Decreasing resistance to metronidazole

### 4.3.4 Lower (I+R) and high (R) breakpoints – impact on resistance levels of ISIS-AR

The resistance levels in Unselected Hospital Departments presented in chapter 4.3.3 are calculated from the I+R values reported by the participating laboratories. When taken only the R values for resistance, the resistance levels changed significantly for some antibiotics and some micro-organisms. Table 10 summarizes the findings for the indicator strains and antibiotics used. These differences may also be representative for the differences found when comparing breakpoints for resistance according to CLSI and EUCAST criteria.
Clear patterns were not found. The use of two breakpoints had impact on the resistant rates for co-amoxiclav, cefuroxime, ciprofloxacin, nitrofurantoin and aminoglycosides for most *Enterobacteriaceae*. Co-trimoxazole resistance changed for the three respiratory pathogens tested, resistance to macrolides changed for *S. pneumoniae* and *M. catarrhalis*. Such changes are understandable when most strains of a population have MICs around the lower breakpoint. They will be judged resistant by use of the lower breakpoint and susceptible by use of the higher breakpoint. Effective treatment from an infectious disease depends on many factors, but one is the inverse relationship between the MIC of an organism and the antibiotic concentration. The lower the MIC, the higher the cure rate. Strains with MIC values around the breakpoints are potentially less susceptible to an antibiotic because of the low ratio between MIC and antibiotic concentration and they may therefore contribute to failure. From the studies on MIC distributions over time, we concluded that strains in this area are often shifting to higher MIC values in subsequent years, becoming fully resistant. Reporting these strains susceptible by taking high breakpoints may also hide upcoming resistance.

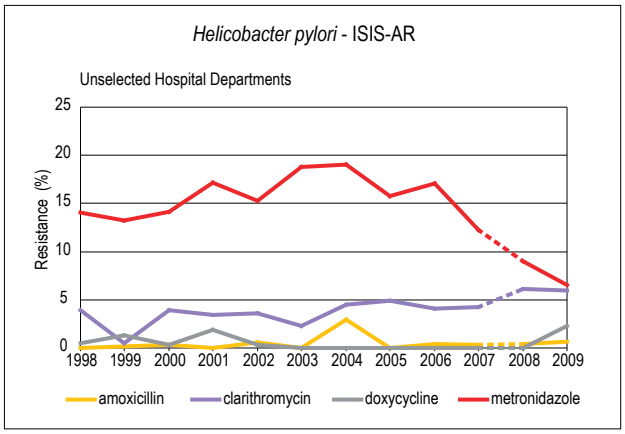



Figure 56. MIC distributions of doxycycline for *Streptococcus pneumoniae* from Pulmonology Services.

## 4.4 Surveillance studies on bacterial pathogens isolated in the Netherlands

Apart from the surveillance data presented in NethMap on the basis of the surveillance system developed by SWAB, several individual studies by other authors have reported on the occurrence of antimicrobial resistances among various bacterial species in the Netherlands. These studies were selected for inclusion in NethMap based on the following criteria: (1) all studies reported on resistance rates based on the measurements of MIC values, *i.e.* quantitative susceptibility tests were performed on all strains; (2) all strains were collected from patients in multiple centres throughout the Netherlands and (3) 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 cross table (table 11) that reveals the combinations of "bugs & drugs" for which data were reported in each of the listed studies.

1. Buirma RJA, Horrevorts AM, Wagenvoort JHT. Incidence of multiresistant Gram-negative isolates in eight Dutch hospitals. Scand J Infect Dis (suppl) 1991; 78: 35-44.
2. Bongaerts GPA, Hoogkamp-Korstanje JAA. In vitro activities of BAY Y3118, ciprofloxacin, ofloxacin and fleroxacin against Gram-positive and Gram-negative pathogens from respiratory tract and soft tissue infections. Antimicrob Agents Chemother 1993; 37: 2017-2019.
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. 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.
5. 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.



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*Table 10. Impact on resistance rate when using R or I+R breakpoints for resistance for indicator strains from Unselected Hospital Departments reported to ISIS-AR. x = difference between R and I+R; 0 = no difference.*

| Antibiotic | Micro-organisms | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *E. coli* | *K. pneumoniae* | *E. cloacae* | *P. mirabilis* | *P. aeruginosa* | *S. aureus* | *S. epidermidis* | *S. pneumoniae* | *H. influenzae* | *M. catarrhalis* | *H. pylori* | *N. gonorrhoeae* |
| penicillin | | | | | | | | x | | | | 0 |
| methicillin | | | | | | 0 | 0 | | | | | |
| amoxicillin | 0 | | | 0 | | | | | x | 0 | 0 | |
| co-amoxiclav | x | x | | x | | | | | | 0 | | |
| piperacillin | x | | | | 0 | | | | | | | |
| piperacillin-tazobactam | 0 | 0 | x | 0 | 0 | | | | | | | |
| cefaclor | | | | | | | | | | | | |
| cefuroxime | x | x | | 0 | | | | | | | | |
| ceftriaxone | 0 | 0 | 0 | 0 | | | | | | 0 | | x |
| ceftazidime | 0 | 0 | | 0 | x | | | | | | | |
| doxycycline | | | | | | 0 | x | x | | 0 | 0 | 0 |
| trimethoprim | 0 | 0 | | | | | | | | | | |
| cotrimoxazole | 0 | 0 | 0 | 0 | | 0 | 0 | x | x | x | | |
| nitrofurantoin | x | x | | 0 | | | | | | | | |
| ciprofloxacin | 0 | 0 | x | x | x | 0 | x | 0 | | | | x |
| gentamicin | x | 0 | 0 | x | x | 0 | x | | | | | |
| tobramycin | x | x | x | 0 | 0 | 0 | x | | | | | |
| amikacin | 0 | 0 | 0 | 0 | x | | | 0 | | | | |
| macrolides | | | | | | 0 | 0 | | x | x | 0 | |
| fusidic acid | | | | | | x | x | | | | | |
| mupirocin | | | | | | 0 | 0 | | | | | |
| metronidazole | | | | | | | | | | | 0 | |
| rifampicin | | | | | | 0 | 0 | | | | | |


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*Table 11. Cross table 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-ferm Gram-bacteria | *Haem-philus influenzae* | *Helico-bacter pylori* | Meningo cocci | Gono cocci |
|---|---|---|---|---|---|---|---|---|---|---|
| Penicillin | 7,8,11 | 8,11 | 4,6,7 | 7 | | | | | 4,6 | |
| Oxacillin | 7 | | | | | | | | | |
| Methicillin | 3,40,41, 43,44,45 | | | | | | | | | |
| Flucloxacillin | 8,11,44,45 | | | | | | | | | |
| | | | | | | | | | | |
| Ampicilin | | | | 3 | 1,25,33 | 1 | 4 | | | |
| Amoxicillin | | 8,11 | 7 | 7,8,11,16, 20,29 | 20,21,22, 32,35,36, 46 | | | 15 | | |
| Co-amoxiclav | | | 10 | | 1,7,22, 32,33,35, 36, 46 | 1,7 | 7 | | | |
| Piperacillin | 3 | | | 3 | 1,3,17, 35,36 | 1,3,36 | | | | |
| Piperacillin/tazobactam | 3,7 | | 7 | 3,7 | 1,3,17, 35,36 | 1,3,36 | 7 | | | |
| Ticarcillin/clavulanate | 3 | | | 3 | 1,3,7 | 1,3,7 | 7 | | | |
| Mezlocillin | | | | | 1 | 1 | | | | |
| | | | | | | | | | | |
| Cefaclor | | | | | 37 | | | | | |
| Cefazolin | | | | | 1,20,21,25 | 1 | | | | |
| Cefoxitin | | | | | 17 | | | | | |
| Cefuroxime | 11 | 11 | | | 1,7,36 | 1,7 | 7 | | | |
| Ceftriaxone | | | 4,6 | | 1 | 1 | 4 | | 4,6 | |
| Cefotaxime | | 11 | | | 1,7,17, 31,36 | 1,7,32 | 2 | | | |
| Ceftazidime | | | | | 1,3,7,17, 22,36 | 1,3,7, 22,36 | 2 | | | |
| Cefpirome | | | | 16 | 17 | | | | | |
| Cefepime | | | | | 17 | | | | | |
| Cefixime | | | | | 37 | | | | | |
| Ceftibuten | | | | | 37 | | | | | |
| | | | | | | | | | | |
| Aztreonam | | | | | 1 | 1 | | | | |
| Imipenem | 3,7,12 | 12 | 7,12 | 3,7, 2,16 | 1,3, 7,22 | 1,3,7,22,36 | 2 | | | |
| Meropenem | 7,12 | 12 | 7,12 | 7,12,16 | 7,17 | 7,36 | 7 | | | |
| | | | | | | | | | | |
| Vancomycin | 7,8,11,12 | 8,11,12 | 7,12 | 7,8,11,12, 16,20,29 | | | | | | |
| Teicoplanin | 8,11,12 | 8,11,12 | 12 | 8,11,12,16 | | | | | | |
| Linezolid | 19 | 19 | 19 | | | | | | | |
| | | | | | | | | | | |
| Gentamicin | 3,7,44,45 | | 7 | 7,11,16, 20,29 | 1,3,4,7, 17,22,20, 21,25,36 | 1,3,7,22,36 | 7 | | | |
| Tobramycin | | | | | 1,17 | 1,36 | | | | |
| Netilmicin | | | | | 17 | | | | | |
| Amikacin | 3 | | | | 1,3,17 | 1,3,36 | | | | |
| | | | | | | | | | | |
| Norfloxacin | | | | | 22,32,35, 33,46 | 22 | | | | |
| Ciprofloxacin | 2,3,7,8,12 | 2,8,12 | 2,7,10,12, | 2,3,8,7, 12,16,20, 29 | 1,2,3,7, 22,20,21, 25,35,36, 46 | 1,2,3,7, 22,36 | 2,7,10 | | | 42 |
| Ofloxacin | 2,8 | 2,8 | 2 | 2,8,16 | 2,17 | 2 | 2 | | | |



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*Table 11. Cross table of combinations of species of bacteria and antibiotics for which MIC data are presented in the individual studies listed above (continued).*

| | Staphylo cocci | Strepto cocci | Pneumo cocci | Entero-cocci | *Entero-bacte-riaceae* | Non-ferm Gram-bacteria | *Haem-philus influenzae* | *Helico-bacter pylori* | Meningo cocci | Gono cocci |
|---|---|---|---|---|---|---|---|---|---|---|
| Levofloxacin | | | | | 35 | | | | | |
| Trovafloxacin | 8 | 8 | | 8,16 | | | | 15 | | |
| Sparfloxacin | 8,12 | 8,12 | 10,12 | 8,12,16 | | | 10 | | | |
| Pefloxacin | 8 | 8 | | 8 | | | | | | |
| Moxifloxacin | | | | 16 | 35 | | | | | |
| | | | | | | | | | | |
| Clindamycin | 7,11,12 | 11 | 7 | 7,11 | | | | | | |
| Erythromycin | 7,11,12 | 11,12,30 | 7,12 | 2,7,11,12, 20,29 | | | | | | |
| Clarithromycin | 11 | 11,12,34 | 10,12 | 11,12 | | | 10 | 5,15 | | |
| | | | | | | | | | | |
| Tetracyclin | | | 20,29 | 20,29 | 20,21,25 | | | 15 | | |
| Minocyclin | | | | 11 | | | | | | |
| | | | | | | | | | | |
| Chloramphenicol | | | 4,6 | 16 | 20,25 | | 4 | | 4,6 | |
| Quinupristin/dalfopristin | 11,12 | 11,12 | 12 | 2,11,12 | | | | | | |
| Rifampicin | 11,12 | 12 | 12 | 12 | | | | | 4,6 | |
| Metronidazole | | | | | | | | 5,13,15 | | |
| Trimethoprim | | | | | 20,21,22, 25,32,33, 35,46 | | | | | |
| Co-trimoxazole | | | | | 2,32,35, 46 | | | | | |
| Nitrofurantoin | | | | | 20,22,32, 33,35 | | | | | |
| Fosfomycin | | | | | 46 | | | | | |

Numbers correspond with reference numbers listed above this cross table .



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# 5 Resistance to influenza antiviral drugs

## 5.1 Introduction

Infection by influenza A(H1N1), A(H3N2) or B viruses, results in substantial morbidity and excess mortality each year. Vaccination against seasonal influenza is the key control measure used in the Netherlands and Europe to minimize morbidity and mortality, especially in the risk groups for development of complications upon influenza virus infection. However, antigenic mismatch between vaccine components and circulating viruses does occur every few years requiring the vaccine to be reformulated. This together with sub-optimal vaccine uptake in recommended patient groups, non-responders to vaccination and waning immunity during the season provides the rationale for the use of antiviral drugs in the prophylaxis and treatment of influenza under special circumstances (1, 2). In addition, preparations have been made for provision of antiviral treatment and prophylaxis in case of a pandemic and the government has stockpiled oseltamivir and zanamivir. These preparations came into effect when in 2009 the first influenza pandemic of the 21$^{th}$ century occurred, caused by a triple reassortant virus from swine origin, the A(H1N1) 2009 pandemic virus (3).

## 5.2 Prescriptions of influenza antivirals

Two classes of influenza antiviral drugs are available for treatment and prophylaxis, the M2 ion-channel blockers (M2Bs), amantadine (Symmetrel®) and rimantadine (Flumadine®, not registered in the Netherlands), and the neuraminidase inhibitors (NAIs), oral oseltamivir (Tamiflu®) and inhaled zanamivir (Relenza®). M2Bs have been available since 1964, but their usefulness have been limited because of adverse effects, rapid development of resistance (full cross-resistance for both drugs) and lack of activity against influenza B virus infections. M2Bs are also indicated for Parkinson disease. In our previous report, we showed that during influenza outbreaks there is no significant increase in amantadine prescriptions in the Netherlands, consistent with the limited usefulness of this type of influenza antiviral drugs (4).
The introduction in 1999 of NAIs, which are active against both type A and B influenza viruses, was a major breakthrough in treatment and prophylaxis of influenza using antiviral drugs. In addition, because of different molecular interactions of both drugs with the neuraminidase, a limited number of mutations result in full cross-resistance, and if resistance mutations occur these mostly adversely affect infectiveness and transmissibility of the mutated virus. According to prescription data, NAIs are not widely used in the Netherlands during seasonal epidemics (Figure 1).
Highest prescription of 6,641 courses oseltamivir was noted in October 2005 (Figure 1), possibly due to personal stockpiling in response to the emergence of highly pathogenic avian influenza A(H5N1) in Turkey. In Europe the number of prescriptions by country is in general low, but the Netherlands is among the lowest (5). During the first wave in summer 2009 of the A(H1N1) 2009 pandemic, oseltamivir was widely prescribed for therapy and prophylaxis on indication fitting the case definition, mainly to limit the spread of the pandemic virus (Figure 1). During the epidemic phase, oseltamivir was used mainly for treatment of severe cases (Figure 1). However, a substantial amount of prescriptions as precaution cannot be excluded (6).

## 5.3 Surveillance for resistance

Details about surveillance for influenza antiviral resistance has been described previously (4). Briefly, in the Netherlands, monitoring of antiviral susceptibility is since the 2005/2006 season embedded in the integrated clinical and virological surveillance of influenza using general practitioner (GP) sentinel stations, which is carried out by the Netherlands Institute for Health Services Research (NIVEL) and the National Influenza Centre location Bilthoven, Centre for Infectious Disease Control, National Institute for Public Health and the Environment. In special circumstances, like during the emergence of oseltamivir resistant A(H1N1) virus during the 2007/2008 season and the during the 2009 pandemic, this system is extended to include viruses detected in hospital and peripheral laboratories with special attention for viruses detected in patients treated with antivirals who show prolonged shedding of influenza virus. Techniques used to monitor antiviral resistance in influenza viruses are determination of the 50 percent inhibitory concentration ($IC_{50}$) in cell-ELISA virus growth inhibition assay or plaque reduction assay and Sanger sequencing, pyrosequencing or site-specific polymerase chain reaction (PCR) assay for known resistance markers for both the M2Bs and NAIs (7, 8). For NAIs the $IC_{50}$ can also be determined using an enzyme inhibition assay (9, 10). In the absence of known NAI resistance mutations detected by genotypic assays, determination of the $IC_{50}$ is the only way to determine the drug susceptibility of a virus.

## 5.4 Resistance

Previously we described the emergence of M2B resistance in A(H3N2) viruses and A(H1N1) viruses, although for A(H1N1) a lineage of M2B sensitive viruses gradually replaced the resistant lineage (4,11). In addition, the emergence of oseltamivir resistant



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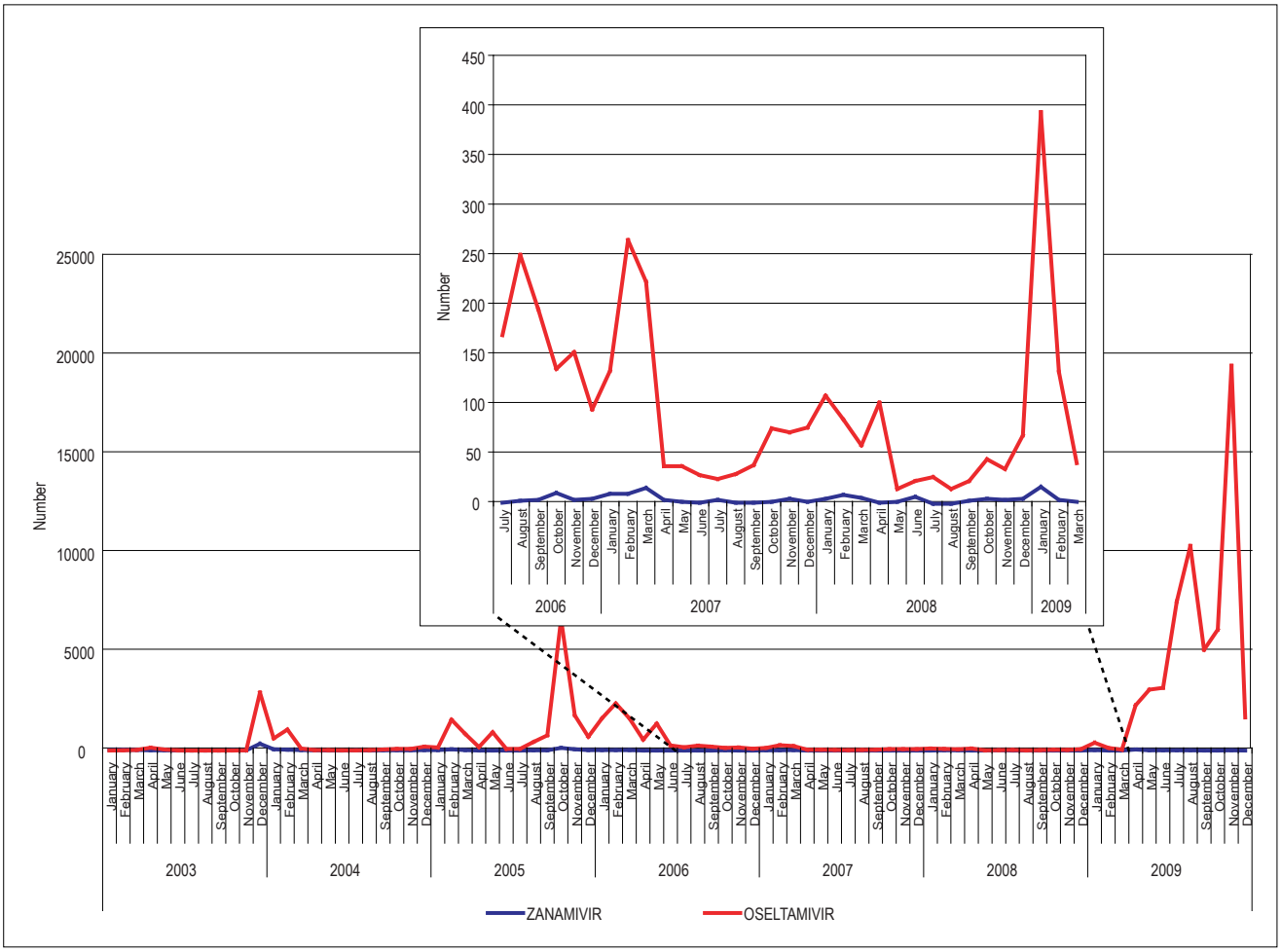



Figure 1. Monthly prescription data for zanamivir and oseltamivir for the Netherlands, 2003 –2009. Inset shows zoomed in time period July 2006 – March 2009. Source: Stichting Farmaceutische Kengetallen, Den Haag, the Netherlands for commercial prescriptions and the Dutch Vaccine Institute, Bilthoven, the Netherlands for prescriptions from the national stockpile during the 2009 pandemic.

A(H1N1) viruses during the 2007/2008 season was described. Preliminary data for the 2008/2009 season in the Netherlands in our previous report have been supplemented with additional data on seasonal viruses. However, the overall pattern did not change (Table 1). During the aftermath of the 2008/2009 seasonal influenza epidemic, infections of humans with a triple reassortant A(H1N1) influenza virus from swine origin were detected in Mexico and the USA in April 2009 (3). Subsequently, this virus spread world-wide causing the first pandemic of the 21$^{th}$ century. The first A(H1N1) 2009 pandemic virus in the Netherlands was detected April 30. Because the pandemic virus initially was classified as a biosafety level 3 (BSL-3) organism, antiviral resistance was primarily done by direct sequencing of clinical specimens. Pandemic viruses cultured at BSL-3 were inactivated using a procedure with Triton X-100 developed at the RIVM for subsequent $IC_{50}$ determination at BSL-2 (12). Because of the generally mild disease caused by the pandemic virus and the endemic presence in the Netherlands, pandemic viruses are cultured and used for $IC_{50}$ determination at BSL-2 since March 2010. Sentinel surveillance for antiviral resistance was immediately supplemented with analysis of viruses derived from case finding, contact tracing and from 15 August 2009 onwards from hospitalised and deceased pandemic A(H1N1) 2009 patients. Implementation of H275Y single nucleotide polymorphism real-time PCR made it possible for hospital and peripheral laboratories to screen for the major resistance marker for oseltamivir (13). To keep track of emergence of resistance and to implement timely appropriate public health measures, patients with resistant pandemic virus had to be notified from then on. During the summer wave of the pandemic no resistant pandemic viruses were detected in the Netherlands, despite extensive use of oseltamivir (Table 1, Figure 1). However, during the subsequent wave of the pandemic in autumn and early winter of 2009 in the Netherlands, 18 patients with oseltamivir resistant pandemic virus harbouring the H275Y mutation in the neuraminidase were detected. Fourteen of these patients were immune suppressed, of which 10 with a hematopoietic disorder, resulting in prolonged shedding of virus. Three other



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*Table 1. Resistance of influenza viruses to NAIs and M2Bs in the Netherlands, 2005/2006 – 2009/2010*

| Season | A(H3N2) | | A(H1N1) | | A(H1N1) 2009 | | B |
|---|---|---|---|---|---|---|---|
| | NAI | M2B | NAI | M2B | NAI | M2B | NAI |
| 2005/2006 | 1/39 (3%)[2] | 29/39 (74%) | NA | NA | NA | NA | 2/48 (4%)[3] |
| 2006/2007 | 0/50 | 38/51 (75%) | 0/5 | 0/6 | NA | NA | 0/3 |
| 2007/2008 | 0/10 | 12/12 (100%) | 47/172 (27%)[4] | 0/49 | NA | NA | 1/81 (1%)[2] |
| 2008/2009 | 5/74 (7%)[5] | 8/8 (100%) | 5/5 (100%) | ND | 0/431 | ND | 0/16 |
| 2009/2010[6] | NA | NA | NA | NA | 19/506 (4%)[7] | ND | NA |

(1) Combined results obtained with phenotypic (virus isolates) and genotypic (clinical specimens) assays. Season defined as week 40 of the first year to week 39 of the following year. Abbreviations: NA = not applicable as there were no viruses of the given type or subtype tested; ND = viruses available, but analysis was not done.
(2) The resistant virus had an extreme outlier $IC_{50}$ for oseltamivir and mild outlier $IC_{50}$ for zanamivir.
(3) Both resistant viruses had outlier $IC_{50}$ values for oseltamivir as well as zanamivir.
(4) Viruses resistant to oseltamivir only. Viruses were sensitive to zanamivir and M2Bs.
(5) The 5 viruses had mild outlier $IC_{50}$ values for oseltamivir but normal $IC_{50}$ values for zanamivir.
(6) Preliminary data; analysis of the viruses from the 2009/2010 season is ongoing.
(7) Eighteen viruses were resistant to oseltamivir and not to zanamivir with H275Y mutation. One other virus had a 3-fold increased $IC_{50}$ for oseltamivir and a 5-fold increased $IC_{50}$ for zanamivir.

patients had another underlying disease explaining prolonged viral shedding. These 17 patients developed resistance under oseltamivir therapy within on average 12 days (range 5-27) days between onset of disease and detection of resistance. These results underline previous results about the impact of antiviral resistance, especially in immune suppressed patients (4). The importance of lymphocyte reconstitution for clearance of the virus as we described before (14) was again illustrated in a patient with Acute Lymphoblastic Leukemia (ALL) under chemotherapy. Lifting chemotherapy for one week resulted in restored lymphocyte counts and clearance of the pandemic virus. One of the immune suppressed patients following reversion of the virus to wildtype under zanamivir therapy, developed reduced susceptibility to zanamivir (10-fold) and oseltamivir (46-fold) due to an amino-acid mutation at position 223 in the neuraminidase. Previously, amino-acid mutations at the 223 (N1 numbering) or 222 (N2 numbering) position in the neuraminidase have been reported in A(H5N1) and seasonal influenza viruses associated with reduced susceptibility or an enhanced level of resistance in combination with other resistance mutations (e.g. H275Y), for oseltamivir only or for both oseltamivir and zanamivir (15). Contact investigation of the 18 patients did not reveal transmission of resistant viruses. Resistant pandemic viruses with the H275Y mutations are highly likely impaired in their capacity to transmit and cause infection. Similar observations were made previously with the naturally occurring oseltamivir resistant seasonal A(H1N1) virus variants.

## Conclusion

Emergence of natural resistance to M2Bs and NAIs in circulating A(H3N2) and A(H1N1) seasonal influenza viruses has resulted in considerable limitations in possibilities to treat severe influenza cases and for (post exposure) prophylaxis. Emergence of oseltamivir resistance in A(H1N1) 2009 pandemic virus is still sporadic, however, the emergence of natural resistance against oseltamivir in seasonal A(H1N1) viruses has set the scene. Therefore, continuous alertness using sentinel surveillance and close monitoring of patients under therapy and their contacts is needed for early warning and timely action to limit spread of resistant viruses.

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# 6 Azole resistance in *Aspergillus* species

## 6.1 Introduction

The saprophytic fungus *Aspergillus fumigatus* is the primary cause of opportunistic fungal infections in immunocompromised patients. Invasive *Aspergillus* disease is a frequent infectious complication of hematopoietic stem cell transplantation (HSCT), cytotoxic chemotherapy for hematological malignancy, solid organ transplantation and conditions which require corticosteroid-based treatment especially if these are given for long periods of time or at high doses. Invasive aspergillosis has a significant morbidity and mortality rate, depending on the underlying condition and the extent of the infection (1).
The diagnosis of invasive aspergillosis is often difficult as cultures are positive in only 30% to 50% of patients and invasive procedures are precluded due to severe thrombocytopenia (2). Increasingly, non-culture based diagnostic methods are used for the diagnosis including the detection of circulating *Aspergillus* antigen, galactomannan, and of *Aspergillus* DNA by polymerase chain reaction (3,4). In addition, imaging techniques such as high resolution CT scan are used to diagnose invasive aspergillosis (5).
There are a limited number of antifungal drugs with evidence-based efficacy in invasive aspergillosis. These include the polyenes (amphotericin B), the azoles (itraconazole, voriconazole and posaconazole) and the echinocandins (caspofungin). For primary therapy of invasive aspergillosis voriconazole is considered the first choice drug, and a liposomal amphotericin B as alternative (6). Posaconazole has been shown to be effective in chemoprophylaxis in patients with neutropenia during therapy of acute myeloid leukemia and myelodysplastic syndrome, and in patients with graft-versus-host disease following HSCT (7,8). Amphotericin B, the azoles and caspofungin can be used in salvage therapy of invasive aspergillosis. The azoles are the only class that exhibit efficacy in invasive aspergillosis and can be administered orally.
Besides invasive disease, aspergilli may cause a range of other diseases in humans, including chronic cavitating aspergillosis, aspergilloma and acute bronchopulmonary aspergillosis (ABPA). The azoles play an important role in the management of these patients, most notably itraconazole.

## 6.2 Emergence of azole resistance in *A. fumigatus* in the Netherlands

Until recently, in vitro susceptibility testing in aspergilli was not performed in clinical microbiology laboratories due to the fact that acquired resistance was very rare. However, there are two developments that will change this practice in the near future. First, the taxonomy of *A. fumigatus* and many other clinically relevant *Aspergillus* species has changed dramatically in recent years. The use of sequence-based identification of fungi has changed the classification of molds and revealed new sibling species that could not be identified using conventional methods based on morphological characteristics. For instance, *Aspergillus* section Fumigati, previously identified as *A. fumigatus* based on macroscopic and microscopic morphology, now contains as many as 25 different species, 8 anamorphs and 17 teleomorphs based on sequence-based identification (9). Although the ability of these new sibling species to cause infections in humans remains unclear, the susceptibility profiles differ significantly from that of *A. fumigatus*, with many species being less susceptible to antifungal agents (10). This indicates that clinical microbiology laboratories should perform species identification of clinically relevant *Aspergillus* isolates by sequencing of household genes such as β-tubulin, or that in vitro susceptibility testing should be performed in order to detect intrinsic resistance.
A second important development is the emergence of acquired resistance to azoles in *A. fumigatus*. In the Netherlands, resistance to medical triazoles was first noted in patients with invasive aspergillosis (11,12). All infections were caused by *A. fumigatus* isolates that were not susceptible to itraconazole, and showed non-wild type susceptibility to voriconazole and posaconazole. Following this observation, the fungus culture collection of the Radboud University Nijmegen Medical Center was investigated in order to determine the prevalence of azole resistance in historical clinical isolates. Analysis of 1,908 clinical *A. fumigatus* isolates from this collection, obtained between 1994 and 2007, showed that azole-resistance had emerged since the year 2000 and that between 1.7% and 6% of patients carried a resistant isolate (Figure 1)(13). Among *A. fumigatus* isolates sent to Nijmegen from other Dutch hospitals a higher prevalence of resistance (12.8%) was found, which was thought to be due to different selection criteria compared to those analyzed from the culture collection. The Nijmegen culture collection included all isolates that had been cultured from patients irrespective of the clinical relevance, while the isolates sent to Nijmegen were from patients with *Aspergillus* diseases that were probably failing to antifungal therapy. A prospective surveillance study was recently completed that monitored azole resistance in seven Dutch University Medical Centers. In this study 2,062 clinical isolates were screened and in all University Medical Centers azole resistance was observed. The prevalence ranged between 0.8 and 8.5%. Eighty-two azole-resistant isolates were cultured from



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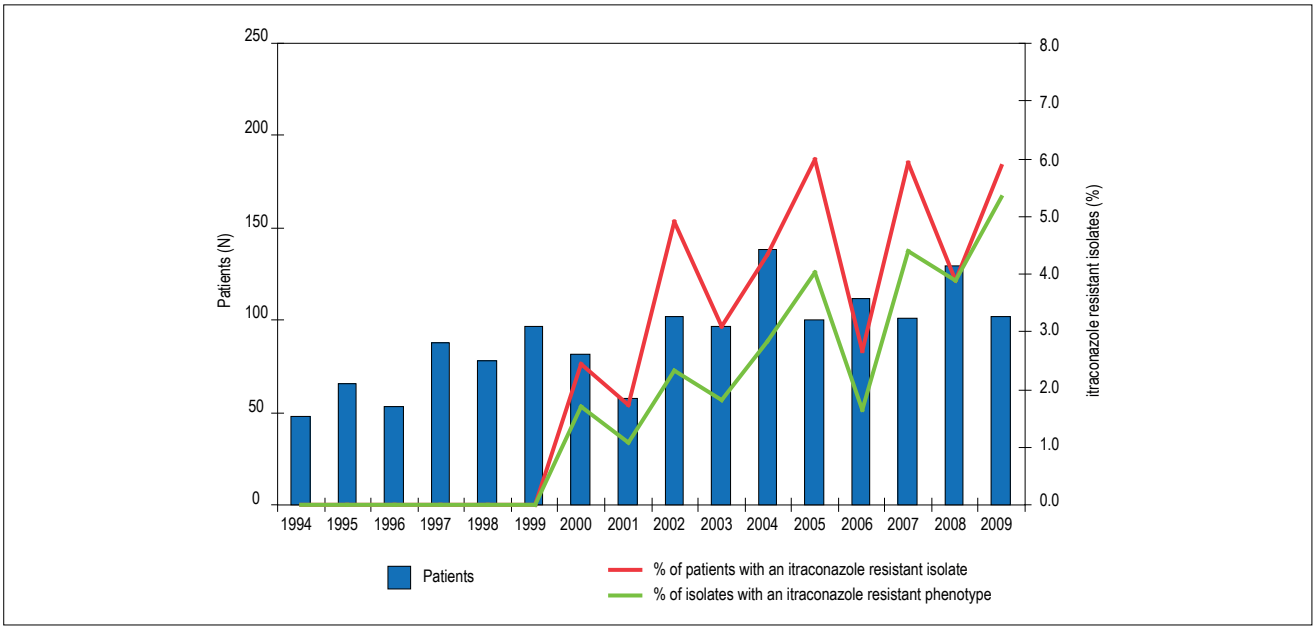



Figure 1. Trends in resistance to itraconazole among 2223 clinical isolates of *Aspergillus fumigatus* in 1451 patients.

64 patients, of which 23 (36%) had *Aspergillus* disease. Of patients with azole-resistant invasive aspergillosis the failure rate was 86%, indicating that azole resistance is associated with treatment failure. Also in 62% of patients there was no record of azole therapy in the three months prior to culture of the resistant isolate (14). Several studies have shown that azole-resistant isolates are capable of causing invasive aspergillosis (15-17), and that resistance is associated with treatment failure (14-18).

## 6.3 Mechanisms of azole resistance

The mechanism of action of azoles is interference with the biosynthesis of ergosterol which is an essential component of the fungal cell membrane. In *A. fumigatus* that target enzyme of antifungal azoles is 14α-sterol demethylase. It appears that mutations in the corresponding gene, the Cyp-gene, prevents or at least complicates docking of the antifungal azole thereby resulting in resistance or decreased susceptibility to azoles. Numerous point mutations in the Cyp51A-gene have been associated with an azole-resistant phenotype (19). Point mutations have been shown to develop in *A. fumigatus* in patients during azole therapy. These patients were commonly treated with itraconazole for aspergilloma (18). Different Cyp51A-mutations are associated with distinct phenotypes in vitro, characterized by partial or complete loss of susceptibility to one or more of the mold-active azoles. Each patient appeared to develop unique resistance mechanisms, and sometimes multiple resistance mechanism were found in different colonies from a single patient. Resistance development due to azole therapy is therefore characterized by a high diversity of resistance mechanisms.
The distribution of resistance mechanisms in *A. fumigatus* in the Netherlands was very different as a single highly dominant resistance mechanism was found in over 90% of clinical isolates (13,14). This resistance mechanism was characterized by two genomic changes: a substitution of leucine for histidine at codon 98 of the Cyp51A gene in combination with a 34 base pair tandem repeat in the promoter region of this gene (TR/L98H). The tandem repeat increases the expression of the Cyp-gene and it was shown that both changes were required for the resistant phenotype (20). The presence of a dominant resistance mechanism cannot be explained through resistance development in epidemiologically unrelated patients, as *Aspergillus* disease are not contagious and therefore spread of resistance or of a resistance mechanism is very unlikely to occur.

## 6.4 An environmental route of resistance development

Several clues pointed towards an environmental route of resistance development. These included the presence of a dominant resistance mechanism and the absence of azole exposure in approximately two-thirds of patients from whom an azole-resistant isolate was cultured. In the Nijmegen culture collection also 250 *A. fumigatus* isolates that were cultured from patient rooms were screened for azole resistance and five were found to be resistant (21). This prompted an environmental survey, which showed that *A. fumigatus* resistant to medical triazoles could be cultured from the environment including soil, compost and seeds obtained at a commercial garden center (20). These isolates also harbored the TR/L98H resistance mechanism and appeared to be genetically related to azole-resistant clinical isolates. Evidence is therefore accumulating that



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Table 1. Proposed breakpoints (mg/l) for azole resistance in *Aspergillus fumigatus*

| Drug | Susceptible | Intermediate | Resistant |
|---|---|---|---|
| Itraconazole | <2 | 2 | >2 |
| Voriconazole | <2 | 2 | >2 |
| Posaconazole | <0.5 | 0.5 | >0.5 |

an environmental route of resistance development exists (22). Azoles are commonly used for crop protection and for material protection. The mode of action of these compounds is similar to that of the medical triazoles, and *A. fumigatus* is a saprophytic fungus and therefore abundantly present in the environment. It is now thought that through exposure to azole fungicides, *A. fumigatus* is becoming cross-resistant to the medical triazoles (21,22). The volume of use of azoles is the environment is much higher than used in clinical medicine, amounting to a 300 fold difference in the Netherlands in 2004 (22). Azole resistance is also found in plant pathogenic molds and mutations in the Cyp51A-gene are commonly found sometimes in combination with transcriptional enhancers, such as a tandem repeat, in the gene-promoter (22). If this route of resistance development indeed exists one can anticipate that resistance mechanism will continue to emerge as has been observed in plant pathogenic molds. At present no data are available on the presence of azole resistance in non-*A. fumigatus* species or in other opportunistic molds.

## Conclusions

Azole resistance is an emerging problem in *A. fumigatus*, which has important consequences for patient management. Surveillance programs are clearly warranted to monitor for trends in existing resistance mechanisms or to detect new emerging resistance mechanisms. The prevalence of azole resistance in other *Aspergillus* species is unknown as is the case in other opportunistic molds. One problem is that at present interpretative breakpoints are not available for *Aspergillus* species. Recently breakpoints and nomenclature were proposed for azoles (table 1) and *A. fumigatus* in order to facilitate research and communication (19), but clearly these proposed breakpoints need to be validated. More research is warranted to understand the mode of resistance development in the environment and the impact of resistance on the management of patients with *Aspergillus* diseases.

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# 7 Materials and Methods

## 7.1 Surveillance of antibiotic use in humans

Data on the consumption of antibiotics were collected by a pre-established protocol, using the ATC/DDD classification that is developed by WHO Collaborating Centre for Drug Statistics Methodology (http://www.whocc.no). The Defined Daily Dose (DDD) is the assumed average maintenance dose per day for a drug used for its main indication in adults. The DDD is a unit of measurement and does not necessarily reflect the recommended or prescribed daily dose. It enables however comparison of drug consumption statistics at international and other levels (1). The 2009 update of the ATC/DDD classification system is used to calculate the number of DDDs in this report.

### 7.1.1 Primary health care

All antibiotics for human use are prescription-only medicines in the Netherlands. The majority of antibiotics are delivered to patients by community pharmacies. Direct delivery of medicines by general practitioners from their own pharmacy reaches approximately 8.4% of the Dutch population, mainly in rural areas (2).

Data on the use of antibiotics in primary health care were obtained from the Foundation for Pharmaceutical Statistics (SFK; http://www.sfk.nl) and expressed as the number of Defined Daily Doses (DDD) per 1000 inhabitants per day. Sales data from approximately 90% of all community pharmacies are transferred monthly to SFK in an electronically format. The data are subsequently weighted statistically and extrapolated to cover 100% of the deliveries by community pharmacies. The total number of DDDs is divided by the total number of inhabitants that is registered by a community pharmacy (approximately 91.6% of the total number of inhabitants in the Netherlands). Data on the number of inhabitants in the Netherlands are obtained from Statistics Netherlands (CBS; http://www.cbs.nl). SFK data on antibiotic use do not include the use of antibiotics in hospitals. Antibiotics prescribed by hospital based medical specialists to their outpatients are, however, included. Deliveries from community pharmacies to nursing-homes as an institute are not covered.

### 7.1.2 Hospitals

Data on the use of antibiotics in Dutch hospitals were collected by the SWAB by means of a questionnaire distributed to all Dutch hospital pharmacists. The number of admissions and the number of days spent in the hospital (bed-days) are also registered in the questionnaire. The use of antibiotics is expressed as DDD/100 patient-days and in DDD/100 admissions (3).

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.

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## 7.2 Surveillance of antibiotic resistance and susceptibility testing

### 7.2.1 Community

*7.2.1.1 Escherichia coli*

The prevalence of antibiotic resistance among *E. coli* was determined for strains collected from patients visiting their general practitioner in communities of the Netherlands from 2009. General practitioners (n=42) from the Sentinel Stations Network of NIVEL participated in the study for the recruitment of the patients. The Network is nationally representative by age, gender, regional distribution and population density. Urine was taken from patients with complaints of an acute uncomplicated urinary tract infection to determine the resistance level in *E. coli*. Female, non-pregnant women aged of 11 years and older who consulted the GP practice with symptoms indicating an acute uncomplicated UTI, *i.e.*, stranguria, dysuria and pollakisuria, without the presence of fever >38°C were eligible for inclusion. Exclusion criteria were catheterization, urological or nephrological problems, diabetes mellitus or other immunocompromising diseases. The period for inclusion lasted from January 2009 until July 2009.

A dipslide from a fresh urine sample was prepared according to the manufacturer's instructions and sent by mail to the Laboratory of Medical Microbiology of the University Hospital Maastricht for identification and antimicrobial susceptibility testing. The dipslides were considered positive when bacterial growth was observed



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of >$10^2$ cfu/ml. Dipslides showing growth of 2 or more bacterial species were excluded from the final analysis. Antimicrobial susceptibility was determined using the microbroth dilution method with Mueller-Hinton II cation-adjusted broth (Becton, Dickinson and Company, Sparks, USA), an inoculum of $5\times10^5$ cfu/ml and overnight incubation at 37°C. The MIC plates were custom made and contained freeze dried antibiotics provided by MCS Diagnostics (Swalmen, The Netherlands). The following antibiotics (range in mg/l) were tested: amoxicillin (0.06-128), co-amoxiclav (0.06-128), trimethoprim (0.03-64), co-trimoxazole (0.03-64), norfloxacin (0.03-64), ciprofloxacin (0.003-16) and nitrofurantoin (0.5-512). *Escherichia coli* ATCC 25922 and 35218 were used as control strains. The breakpoints for resistance were according to the EUCAST guidelines. The susceptibility to fosfomycin was determined with Neo-Sensitabs, Rosco Diagnositca, Denmark and read according to the CLSI guidelines.
*Escherichia coli* isolates resistant to co-amoxyclav were assessed for the presence of ESBL production using the combination disc diffusion test with ceftazidime and cefotaxime with and without clavulanic acid according to the guidelines of the NVMM. Confirmation was done by PCR.

*7.2.1.2 Neisseria gonorrhoeae*
In 2006, the project entitled Gonococcal Resistance to Antimicrobials Surveillance (GRAS) has been implemented in the Netherlands. This surveillance project systematically collects data on gonorrhoea using standardised measurements of resistance patterns by using an E-test, linked with epidemiological data. Participants are STI clinics and associated laboratories that identify the majority of STI in high risk populations. Isolates are sent to the RIVM/CIb for further analysis. From July 2006 through December 2009, the susceptibility of *N. gonorrhoeae* from 3117 patients was determined. Resistance levels were calculated using both the breakpoints for resistance according to the EUCAST guidelines and the CLSI guidelines, which were previously (2006-2008) used for interpretation of GRAS data.

*7.2.1.3 Neisseria meningitidis*
From 1993-2009 the Netherlands Reference Laboratory for Bacterial Meningitis received isolates from CSF and/or blood of patients with meningococcal disease. These strains were submitted by 75 bacteriological laboratories distributed over the country. The susceptibility to penicillin was determined by the E-test method. Strains with MIC < 0.125 mg/l were recorded susceptible, with MIC 0.125-0.38 mg/l intermediate and with MIC >0.5 mg/l resistant.

*7.2.1.4 Mycobacterium tuberculosis*
The first isolate of *M. tuberculosis* of each patient with tuberculosis in the Netherlands is routinely sent to the RIVM for susceptibility testing and confirmation of identification. Isolates obtained after more than six months from the same patient, are judged a new isolate. The susceptibility of the strains is tested quantitatively with a standard agar dilution assay according to the recommendations of the CLSI. The antibiotics chosen for reporting are INH, rifampicin, streptomycin and ethambutol. Resistance rates represent the proportion of moderately and fully resistant strains. The susceptibility data of 10916 strains, isolated from 1998-2009 are presented in this report.

### 7.2.2 Hospitals
Isolates of major pathogenic species were derived from different sources of hospital departments.

*7.2.2.1 Data reported to ISIS-AR*
The overall prevalence of antibiotic resistance in hospitals was estimated from the Infectious Disease Surveillance Information System for Antibiotic Resistance (ISIS-AR) dataset, based on routine antimicrobial susceptibility data obtained from laboratories in the Netherlands. ISIS-AR is coordinated by the Centre for Infectious Disease Control, at the National Institute for Public Health and the Environment (RIVM) in Bilthoven, the Netherlands, and collaborates with the Society of Medical Microbiology (NVMM). In 2007, the new surveillance system ISIS-AR replaced the old ISIS system that started in 1998 with collecting data. The new ISIS-AR collects next to antibiotic resistance data all epidemiological data present in the laboratory information systems. Furthermore, there is strong focus on the quality of data by national standardisation, structural quality control, and confirmation of unusual resistance data. The change to the new system also resulted in a change of the participating laboratories. In 2009, 14 laboratories reported results to ISIS-AR, two laboratories in academic hospitals and 12 laboratories serving non-academic hospitals and public health institutions.

The susceptibility of the isolates reported to ISIS-AR was routinely determined according to the standard techniques used in the individual laboratories. The majority of participating laboratories used automated systems for susceptibility testing, and used CLSI breakpoints, except for two laboratories using CRG (Dutch) breakpoints. The S-I-R interpretation as reported by the local laboratory was used for calculating resistance percentages. We took the number of intermediate and resistant isolates for *E. coli*, *P. mirabilis*, *K. pneumoniae*, *E. cloacae*, *P. aeruginosa*, *S. aureus*, and *S. epidermidis*, as these are identical to the R breakpoint of EUCAST for most antibiotics. This made it possible to compare the data of ISIS-AR with the results obtained from other databases, SERIN and SIRIN. Resistance percentages of *H. influenzae*, *M. catarrhalis*, *S. pneumoniae*, and



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Table 1. First isolates per clinical sample of patients in Unselected Hospital Departments in 2009.

| | Blood | Lower respiratory tract | CSF | Urine | Wound | Total |
|---|---|---|---|---|---|---|
| Number | 5967 | 10134 | 184 | 18294 | 10151 | 44799 |
| | | 838 | | | | |
| **Gram-positive cocci** | | | | | | |
| *Staphylococcus aureus* | 622 | 1491 | 17 | 610 | 2986 | 5726 |
| Coag neg Staphylococci | 2409 | 58 | 101 | 621 | 1178 | 4367 |
| *Enterococcus spp* | 228 | 73 | 8 | 1695 | 585 | 2589 |
| *Streptococcus pneumoniae* | 398 | 1083 | 30 | 6 | 84 | 1601 |
| *Streptococcus agalactiae* | 103 | 62 | 1 | 642 | 253 | 1061 |
| *Streptococcus pyogenes* | 88 | 39 | 2 | 12 | 245 | 386 |
| Subtotal | 3848 | 2806 | 159 | 3586 | 5331 | 15730 |
| | | | | | | |
| **Enterobacteriaceae** | | | | | | |
| *Enterobacter cloacae* | 98 | 526 | 3 | 469 | 424 | 1520 |
| *Escherichia coli* | 1330 | 1124 | 5 | 9364 | 2184 | 14007 |
| *Klebsiella oxytoca* | 98 | 324 | 1 | 528 | 242 | 1193 |
| *Klebsiella pneumoniae* | 270 | 576 | 1 | 1378 | 407 | 2632 |
| *Proteus mirabilis* | 98 | 298 | 0 | 1756 | 478 | 2630 |
| Subtotal | 1894 | 2848 | 10 | 13495 | 3735 | 21982 |
| | | | | | | |
| **Respiratory pathogens** | | | | | | |
| *Haemophilus influenzae* | 36 | 2199 | 6 | 2 | 93 | 2336 |
| *Moraxella catarrhalis* | 4 | 563 | 0 | 0 | 19 | 586 |
| *Neisseria meningitidis* | 19 | 13 | 9 | 0 | 2 | 43 |
| *Subtotal* | 59 | 2775 | 15 | 2 | 114 | 2965 |
| | | | | | | |
| **Non-fermentors** | | | | | | |
| *Acinetobacter baumannii* | 13 | 88 | | 68 | 64 | 233 |
| *Pseudomonas aeruginosa* | 137 | 1185 | | 1102 | 831 | 3255 |
| | | | | | | |
| **Other** | | | | | | |
| *Stenotrophomonas maltophilia* | 16 | 432 | | 41 | 76 | 565 |
| *Helicobacter pylori* | | | | | | 506 |

*H. Pylori* also included strains that showed intermediate and resistant isolates according to CLSI guidelines.

For analyses, the first isolate per species per patient in 2009 was included, selected from blood, wound, the lower respiratory tract and urine, except for *H. influenza* and *M. catarrhalis*, from which only isolates from the (higher and lower) respiratory tract were analyzed. Only positive cultures were included. Isolates for screening and inventory purposes were excluded.

In chapter 4.3.1 more detailed results from ISIS-AR, restricted to *E.coli*, are presented. For these analyses, we included bug/drug combinations if at least eight (from 14) laboratories provided data and if 50% or more of first isolates was tested. For unusual susceptibility results, the laboratory was specifically asked for confirmation. To ISIS-AR reported resistance percentages for 2009 were presented with 95% Wilson's confidence interval. Differences in the total number of isolates in the different paragraphs can be explained by i) selection of first isolates (per patient, per population), and ii) the number of antibiotics for which is tested.



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Table 2. Number of indicator strains (N=21.232) isolated from patients admitted to specified hospital wards and tested for their susceptibility to antibiotics in the period 1998-2008.

| Species | Intensive Care Units | Urology Services | Pulmonology Services |
|---|---|---|---|
| *E. coli* | 2223 | 6769 | |
| *K. pneumoniae* | 687 | 838 | |
| *E. cloacae* | 579 | 218 | |
| *P. mirabilis* | 450 | 949 | |
| *P. aeruginosa* | 1270 | 505 | |
| *E. faecalis* | 897 | 1325 | |
| *S. aureus* | 1148 | 406 | |
| *S. epidermidis* | 566 | 253 | |
| *S. pneumoniae* | | | 1858 |
| *H. influenzae* | | | 2870 |
| *M. catarrhalis* | | | 1230 |

The susceptibility results in hospitals over the years are presented as graphics (chapter 4.3.3), where the change between ISIS and ISIS-AR (2007 to 2008) is displayed by a break in the trend line. For comparability over the years, results from non-ICU as well as from ICU were included. For *H. pylori*, isolates were selected from clinical samples, and also from outpatient clinics and general practice. As the participating laboratories are not all identical to those participating in previous years, small differences in resistance rates as reported in Nethmap 2009 may appear.

*7.2.2.2 Specific Hospital Departments*

Unique unrelated consecutive isolates isolated from various clinical materials of patients admitted to Intensive Care Units, from urine of patients admitted to Urology Services and from respiratory specimens of patients admitted to Pulmonology Services were yearly collected from March 1st to October 1st. A maximum of 100 isolates per ward were collected each year. The strains were identified at the local laboratory for medical microbiology, stored at -200°C and then sent to a single laboratory (department of Medical Microbiology of the UMC St Radboud, Nijmegen from 1995-2001, and the department of Medical Microbiology of the University Hospital Maastricht from 2002 on) for quantitative susceptibility testing. A total of 28,500 strains were collected from 1996-2008, the results of 21,232 indicator strains, obtained from 1998-2008 (table 2) are presented in this report.

The susceptibility of the strains from the specific wards was determined quantitatively, i.e. by MIC determinations by broth micro-dilution assays using breakpoints for resistance according to the recommendations of EUCAST (December 2009) for *E. coli*, *P. mirabilis*, *K. pneumoniae*, *E. cloacae*, *P. aeruginosa*, *S. aureus*, *S. epidermidis*, *H. influenzae*, *S pneumoniae* and *M. catarrhalis*. *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *H. influenzae* ATCC 49247 and *S. aureus* ATCC 25923 were used as control strains in the MIC tests performed in the central laboratory. The antibiotics chosen for reporting were the antibiotics indicated by the Resistance Surveillance Standard of the SWAB published in 1999. This SWAB Resistance Surveillance Standard was also the guideline used for the presentation of these data. The guideline provides criteria for indicator-organisms, indicator-antibiotics, methods and breakpoints to be used.

### 7.2.3 EUCAST criteria

EUCAST criteria for both MIC testing as well as disk diffusion can be found on the website of EUCAST (www.eucast.org). The criteria are freely available as a downloadable pdf file for printing and reference as well as an excel file to be adapted for personal use. The excel file contains active links to rational documents that describe the rationale behind the breakpoints.



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## 7.3 List of abbreviations

| | |
|---|---|
| ABPA | acute bronchopulmonary aspergillosis |
| ALL | Lymphoblastic Leukemia |
| APUA | Alliance for the Prudent Use of Antibiotics |
| ATC | Anatomical Therapeutic Chemical Classification System |
| ATCC | American Type Culture Collection |
| BLNAR | Beta Lactamase Negative Amoxicillin Resistant |
| BSL-3 | biosafety level 3 |
| CBS | Statistics Netherlands |
| CDDT | combination disk diffusion test |
| cfu | colony forming unit |
| CIb | Centre for Infectious Disease Control Netherlands |
| CLSI | Clinical and Laboratory Standards Institute |
| COPD | Chronic Obstructive Pulmonary Disease |
| CRG | Committe on Guidelines for Susceptibility Testing |
| CSF | cerebrospinal fluid |
| CT | Computed tomography |
| DDD | defined daily dosage |
| DNA | Deoxyribonucleic acid |
| EARSS | European Antimicrobial Resistance Surveillance System |
| ECDC | European Centre for Disease Prevention and Control |
| ESBL | Extended-spectrum beta lactamase |
| EUCAST | European Committee on Antiicrobial Susceptibility Testing |
| GGD | Municipal Health Services |
| GP | general practice |
| GRAS | Gonococcal Resistance to Antimicrobials Surveillance |
| HSCT | hematopoietic stem cell transplantation |
| I | intermediate |
| ICAAC | Interscience Conference on Antimicrobial Agents and Chemotherapy |
| ICM | Intersectoral Coordinating Mechanisms |
| ICU | Intensive Care Unit |
| ISIS-AR | Infectious Disease Surveillance Information System on Antibiotic Resistance |
| M2B | M2 ion-channel blocker |
| MARAN | Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in the Netherlands |
| MIC | minimum inhibitory concentration |
| MRSA | methicillin resistant Staphylococcus aureus |
| NAI | neuraminidase inhibitor |
| NHG | Dutch College of General Practitioners |
| NIVEL | Netherlands Institute for Health Services research |
| NVDV | Netherlands Dermatological and Venereological Society |
| NVMM | Netherlands Society for Medical Microbiology |
| NVZA | Netherlands Association of Hospital Pharmacists |
| PCR | polymerase chain reaction |
| R | resistant |
| RIVM | National Institute for Public Health and the Environment |
| RTI | respiratory tract infection |
| S | sensitive |
| SERIN | Surveillance of Extramural Resistance in the Netherlands |
| SFK | Foundation for Pharmaceutical Statistics |
| SIRIN | Surveillance of Intramural Resistance in the Netherlands |
| STD | sexually transmitted disease |
| STI | sexually transmitted infection |
| SWAB | Dutch Working Party on Antibiotic Policy |
| UMC | University Medical Center |



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| | |
|---|---|
| UTI | urinary tract infection |
| VANTURES | Antibiotic Usage and Resistance Surveillance Working Group |
| VIZ | Netherlands Society for Infectious Diseases |
| WHO | World Health Organization |
| WIP | Dutch Working Party on Infection Prevention |



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NETHMAP 2010

## 7.4 Demographics and numerator data

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

| Year | Number of inhabitants (1 January) |
|---|---|
| 1997 | 15 567 107 |
| 1998 | 15 654 192 |
| 1999 | 15 760 225 |
| 2000 | 15 863 950 |
| 2001 | 15 987 075 |
| 2002 | 16 105 285 |
| 2003 | 16 192 572 |
| 2004 | 16 258 032 |
| 2005 | 16 305 526 |
| 2006 | 16 334 210 |
| 2007 | 16 357 992 |
| 2008 | 16 407 619 |
| 2009 | 16 485 787 |

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

| Year | Hospitals | Admissions (x 1000) | Bed-days (x 1000) | Length of stay (mean in days) |
|---|---|---|---|---|
| 1998 | 115 | 1551 | 14790 | 9.0 |
| 1999 | 109 | 1522 | 13940 | 8.7 |
| 2000 | 104 | 1485 | 13332 | 8.4 |
| 2001 | 101 | 1479 | 12778 | 8.2 |
| 2002 | 98 | 1544 | 12946 | 7.8 |
| 2003 | 97 | 1602 | 12651 | 7.5 |
| 2004 | 97 | 1681 | 12557 | 7.0 |
| 2005 | 96 | 1711 | 12396 | 6.8 |
| 2006 | 90 | 1749 | 11564 | 6.6 |
| 2007 | 89 | 1780 | 11271 | 6.3 |
| 2008 | 87 | 1873 | 11172 | 6.1 |

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

| Year | Hospitals | Admissions (x 1000) | Bed-days (x 1000) | Length of stay (mean in days) |
|---|---|---|---|---|
| 1998 | 8 | 200 | 2032 | 10.2 |
| 1999 | 8 | 201 | 1914 | 9.5 |
| 2000 | 8 | 197 | 1842 | 9.4 |
| 2001 | 8 | 193 | 1805 | 9.4 |
| 2002 | 8 | 193 | 1820 | 9.4 |
| 2003 | 8 | 200 | 1837 | 9.2 |
| 2004 | 8 | 210 | 1830 | 8.7 |
| 2005 | 8 | 214 | 1825 | 8.5 |
| 2006 | 8 | 218 | 1806 | 8.3 |
| 2007 | 8 | na | na | na |
| 2008 | 8 | na | na | na |

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

| Year | Hospitals | Admissions (x 1000) | Bed-days (x 1000) | Length of stay (mean in days) |
|---|---|---|---|---|
| 1998 | 107 | 1323 | 11768 | 8.9 |
| 1999 | 101 | 1300 | 11071 | 8.5 |
| 2000 | 96 | 1263 | 10544 | 8.3 |
| 2001 | 93 | 1265 | 10107 | 8.0 |
| 2002 | 90 | 1308 | 10266 | 7.8 |
| 2003 | 89 | 1374 | 9963 | 7.3 |
| 2004 | 89 | 1446 | 9929 | 6.9 |
| 2005 | 88 | 1467 | 9690 | 6.6 |
| 2006 | 82 | 1507 | 9641 | 6.4 |
| 2007 | 81 | na | na | na |
| 2008 | 79 | na | na | na |

*na: not available*



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