2 Extensive summary

In the Netherlands, several surveillance programs have been developed to monitor antimicrobial resistance in important pathogens in different settings (SERIN, SIRIN, ISIS-AR). In addition, a number of specific surveillance programs exist that focus on the monitoring of specific pathogens, or even specific resistance mechanisms. These programs often include susceptibility testing, including conformation of important resistance mechanisms and molecular typing. For instance, all MRSA isolates cultured in the Netherlands are submitted to a reference laboratory for further analysis. In table 2.01 an overview is provided of surveillance programs that are included in Nethmap 2013.

Table 2.01 Overview of Surveillance programs in the Netherlands.

Surveillance program[1]	**Origin of isolates**	**available since**	**Sources 2012**	**Central or decentral susceptibility testing**	**Method of susceptibility testing**
Surveillance program aimed at resistance surveillance in major pathogens					
SERIN	GP	1996	20 GP practices from NIVEL	Central testing	Microdilution
SIRIN	Hospital	1996	14 hospitals	Central testing	Microdilution
ISIS-AR	GP, Hospital, Nursing homes	2008	32 laboratories	Decentral testing	Various methods used in routine susceptibility testing
Specific surveillance program aimed at resistance surveillance in specific pathogens					
CPE	community, GP, nursing home, hospital	2010	Nationwide	Central testing	Phenotypic and genotypic (PCR) confirmation of carbapenemases
VRE	Hospital	2011	Nationwide	Central testing	PCR confirmation of VAN genes en genotyping
MRSA	community, GP, nursing home, hospital	1989	Nationwide	Central testing	PCR confirmation of MecAgene, Spa typing, MLVA

Neisseria meningitidis	Hospital	1994	Nationwide	Central testing	E-test
Neisseria gonorrhoeae	STI centers	2006	89% (of STI center attendees)	Decentral testing	E-test
Mycobacterium tuberculosis	General population	1993	Nationwide	Primarily central testing	Agar dilution and BACTEC-Mgit 960 (liquid breakpoint)
Influenza antiviral drugs	community, GP, nursing home, hospital	2005	NIVEL GP sentinels, SNIV nursing home sentinels, hospital/regional laboratories	central testing (RIVM, NIC-ErasmusMC, WHO-CC London)	Neuraminidase enzym inhibition assay; for established molecular markers sequencing and/or single nucleotide polymorphism (SNP) PCR
Resistance among anaerobic pathogens	Hospital	2010	1 lab	Central testing	E-test
Clostridium difficile	Hospital, nursing homes	2005	18 hospitals	(de)central testing	E-test and ribotyping
azole resistance in *Aspergillus fumigatus*	Hospital	2011	8 University hospitals	Central testing	EUCAST methodology

*SERIN= Surveillance of Extramural Resistance in The Netherlands; SIRIN= Surveillance of Intramural Resistance in The Netherlands; ISIS-AR= Infectious Disease Surveillance Information System on Antibiotic Resistance; GP=general practitioner ; CPE= Carbapenemase producing Enterobacteriaceae; VRE= vancomycin-resistant *Enterococcus faecium*; STI = sexually transmitted infections ; MGIT=Mycobacteria Growth Indicator Tube; EUCAST=European Committee on Antimicrobial Susceptibility Testing; NIVEL=Netherlands institute for health services research; NIC=National influenza center; WHO-CC = WHO Collaborating Centre

2.1 Most important trends in antimicrobial use

In GPs

- Compared to 2011, antibiotic use remains stable at 11.34 DDD/1000 inhabitants per day (vs 11.37). Over the past ten years the use gradually increased with 15% from 9.86 in 2003 to 11.34 DDD/1000 inhabitants per day.
- The continuing rise of azithromycin use to 0.70 DDD/1000 inhabitants per day has resulted in a use above that of clarithromycin.
- Use of nitrofurantoin keeps increasing.

In nursing homes

- Specific antibiotic consumption data in nursing homes are provided for the first time. The mean use in 55 nursing homes was 67 DDD/1000 residents/day but varied widely between 3.11 and 175 DDD/1000 residents/day.
- The high use of broad spectrum antibiotics is worrisome.

In hospitals

- After an increase in antibiotic use from 50 to 70.9 DDD/100 patient-days from 2002 to 2009, use seems to have stabilized with a value of 71.3 DDD/100 patient-days in 2011.
- Although overall use has stabilized there is general trend of more broadspectrum antibiotic use, in particular carbapenems. This should be a point of attention in the coming years.
- If use is expressed in DDD/100 admissions, use fluctuated between 306.8 and 344.7 between 2002 and 2008 but now has decreased to 306.4 in 2011. The reasons for this trend need to be explored.
- For the first time, extrapolated data of the use of systemic antibiotics expressed in DDD/1000 inhabitants/day are presented. Use in 2011 was 0.971 DDD/1000 inhabitants/day. This is the lowest level of antibiotic use in hospitals compared with other European countries.
- The point prevalence study in 32 hospitals by the PREZIES network showed that 32% of all admitted patients (N=9599) received antibiotics. Antibiotics most often prescribed were amoxicillin with clavulanic acid (20%), ciprofloxacin (12%) and cefuroxim (7%).

2.2 Most important trends in antimicrobial resistance

In GPs

- Resistance levels in selected GP patients are higher than in GP patients with uncomplicated UTI reported in 2012: trimethoprim 27% versus 22%, co-trimoxazole 25% versus 20%, norfloxacin 15% versus 4% and ciprofloxacin 10% versus 4% when comparing susceptibility for *E. coli* isolates. This difference in resistance underlines the importance of surveillance of resistance in populations and infections that are not routinely sampled in patient care, such as patients in primary care.
- The increase in resistance to third generation cephalosporins is likely to reflect the increase in ESBL-producing Enterobacteriaceae in the community, in particular becoming more prevalent in community onset infections with *E. coli*.

In nursing homes

- High resistance levels among *E. coli*.
- Ciprofloxacin resistance in *S. aureus* was high (25%).

In hospitals

- There is a general increase in resistance for almost all compound-pathogen combinations. For many of these this has been preceded by MIC creeps and shifts from the wild-type population to non-wild type.
- The strong increase in resistance to third generation cephalosporines and multi-drug resistance is likely to reflect the increase in ESBL-producing Enterobacteriaceae that is increasingly seen in patients with health-care associated infections.
- The prevalence of MRSA remains low.
- Resistance of *E. coli* to all tested agents has increased at ICUs. This trend is similar as seen in other patient groups, such as GP patients, OPD patients and patients from other hospital departments and reflects a general trend in the Dutch community and patient groups.
- Resistance of *K. pneumoniae* to all tested agents has increased although resistance levels are in general lower in 2012 than in 2011. Resistance in patients from urology services is higher than in patients from unselected hospital departments and outpatient clinics.

2.3 Antibiotic use and resistance in veterinary sector

In the years 2007-2012 the total sales of antibiotics licensed for therapeutic usage in animals in The Netherlands decreased by nearly 50%, from 495 tonnes in 2009 to 249 tonnes in 2012. This means that the policy objective for 2013, a 50% reduction in 2013, compared to 2009, is already accomplished in 2012. Compared to 2007 as the year with the highest antibiotic usage (565 tonnes), the decrease in usage up to 2012 was 56%. The use of fluoroquinolones and 3rd/4th generation cephalosporins has been reduced to a minimum. This is a major success of the activities implemented by the private parties involved in animal production, the independent control institute SDa and the authorities.

- In 2012 the resistance levels have decreased in the commensal *E. coli*, used as an indicator organism for the Gram-negative intestinal flora. This includes the occurrence of cefotaxime resistance in *E. coli* from broilers, which decreased from 20% in 2007 to 5.8% in 2012. For all *E. coli* from food-producing animals 37% were resistant to amoxicillin and 4.9% to ciprofloxacin based on EUCAST MIC-breakpoints. This compares to 47% amoxicillin resistance and 14% ciprofloxacin resistance in *E. coli* isolates from unselected hospital departments.
- *Campylobacter* spp. from humans and poultry showed very similar resistance levels, 56 – 62% of *C. jejuni* from poultry meat products and poultry feces, respectively, were resistant to ciprofloxacin, compared to 55% of human clinical isolates. Resistant to the macrolides was low in both populations.
- In food-producing animals MRSA occurred frequently in calves and pigs. However, almost isolates examined from pigs and calves belonged to the Livestock Associated MRSA CC398 (N = 179), the two remaining were ST9. Typical human Community-, or Hospital-Associated MRSA variants were not detected in these animals, nor newly acquired resistance and virulence genes of relevance.
- ESBL/AmpC-producing *E. coli* and to a lesser extend also *Salmonella* were frequently detected in poultry, pigs, cattle and meat thereof. The dominant enzymes detected in *E. coli* were CTX-M-1 (55%), CTX-M-2 (7.5%), CMY-2 (8.2%) and a variety of incidental others enzymes. The dominant human ESBL variant CTX-M-15 was only detected incidentally (3.8%) in animal faecal sources. In meat products 167 ESBL/AmpC producing *E. coli* were identified. The enzymes detected were CTX-M-1 (30%), CTX-M-2 (17%), CMY-2 (13%) and CTX-M-15 (1%).

2.4 Implications for therapy

The general picture that emerges from trends in resistance rates is not very encouraging. Resistance rates are increasing and MIC creeps for many antimicrobial-microorganism combinations indicate that this will continue in the near future. For many of the antibiotics that were long considered as first line of treatment, resistance has already become alarmingly high, and empiric (mono) therapy for some of these agents is now unjustified in the severely ill patient. Alternatively, antimicrobials long used in general practice have resistance rates of up to 30 % or more (e.g. trimethoprim) preventing its use as a first choice even in patients with uncomplicated UTI. Routine culturing with antibiograms becomes increasingly important to tailor therapy to the individual patient, and if broad spectrum therapy was chosen initially antibiograms should be used to narrow down antimicrobial therapy given to prevent even further emergence of resistance. In the summary below, some of the most important implications for therapy are provided, based on the general trends of resistance. As implications differ by category of patient and indication of use, the summary is organized as such. It should be borne in mind that the majority of conclusions below are based on agents used as intravenous therapy, except for agents that are available as oral drugs only or have a specific indication such as UTI. Non-susceptible rates can be higher than resistance rates in some cases.

In GPs

Urinary tract infections

- Approximately 75% of Gram-negatives cultured were *E. coli.* Other important pathogens were *K. pneumoniae* and *P. mirabilis.* High levels of resistance to amoxicillin, trimethoprim (up to 36%) and co-trimoxazole (up to 30%) make these agents less suitable for empirical treatment in UTI.
- The best suitable treatment options for uncomplicated UTI are nitrofurantoin (2% resistance in *E. coli* but increasing) and fosfomycin (1% resistance in *E. coli*, but 25% in *K. pneumoniae* and 14% in *P. mirabilis*). However, care must be taken with nitrofurantoin in the elderly.
- Resistance of co-amoxiclav was 15% in *E. coli* indicating that care should be taken with empirical treatment without further diagnostic work-up. Resistance was also over 10% for the fluoroquinolones (being over 11% for ciprofloxacin) leading to a similar conclusion.
- Multi-drug resistance, defined as resistance to all oral treatment agents for complicated UTI is increasing in selected GP patients complicating the oral treatment of complicated UTI among GP patients.

- The results indicate sampling for antimicrobial susceptibility testing becomes increasingly important in the treatment of UTI.

Pulmonary tract infections

- Penicillin resistance in pneumococci is still very low. In case of a respiratory tract infection with a high a priori chance of *S. pneumoniae* as the causative pathogen, penicillin/amoxicillin remains first choice for empirical treatment. Macrolides resistance exceeds 10%.
- The increase in co-amoxiclav resistant *H. influenzae* strains suggests an increase in BLNAR. In ISIS-AR this was 4% and in SIRIN up to 15%. These finding indicate limited usefulness of co-amoxiclav. Doxycyline may serve as a valid alternative empirical treatment choice or as the choice of therapy in case of no response to previous treatment.

In nursing homes

- Similar to specimens from GP patients, the majority of isolates cultured were *E. coli* (67%). All resistance levels except for nitrofurantoin were higher than 16% and 5% were multidrug-resistant. These values have become too high to warrant empiric treatment of complicated UTI without further diagnostics.

In hospitals

Outpatient departments

- Resistance rates against virtually all antimicrobials have increased in Gram-negatives.
- Except for nitrofurantoin and fosfomycin, high levels of resistance preclude empirical treatment with oral agents for UTI and culture and antibiograms and tailored therapy are necessary.
- Resistance rates are comparable to, or slightly higher than in GP, thus the treatment strategies will be largely similar

Unselected hospital patient departments

- High levels of resistance to amoxicillin, co-amoxiclav, cefuroxime, co-trimoxazole and ciprofloxacin, make these agents less suitable for empirical treatment in serious infections. The ciprofloxacin resistance rate of 14% in *E.coli* is especially worrisome.
- Piperacillin/tazobatam, cefotaxime/ceftriaxone, ceftazidime and aminoglycoside resistance rates are all between 5 and 10% and in the range that is generally considered to be acceptable for patients not severely ill.

- Combination therapy of a beta-lactam with an aminoglycoside are the best suitable options for empirical treatment in serious infections.

Intensive care patients

- High levels of resistance to amoxicillin, co-amoxiclav, cefuroxime, co-trimoxazole and ciprofloxacin, make these agents less suitable for empirical treatment in serious infections. The ciprofloxacin resistance rate of 15% in *E.coli* is especially worrisome, but compares well with the values in unselected hospital patients.
- There are significant differences in resistant rates between hospitals as well as over time. This clearly indicates that empiric therapy should be based on the local epidemiology of resistance.
- Piperacillin/tazobatam, cefotaxime/ceftriaxone, ceftazidime and aminoglycoside resistance rates are all between 5 and 10% . This is in a range that warrants combination therapy or at least close monitoring for the severely ill. However, resistance to combinations of a beta-lactam and an aminoglycoside is between 1 and 5%. It should be realized however, that resistance to combinations is based on the effect of the drug alone and does not take into account any synergistic effects that may be present.

2.5 Implications for public health and health policy

Antibiotic resistance is a major European and global public health problem and is, for a large part, driven by (mis) use of antibiotics. As a consequence, patients who are infected with resistant bacteria, that are often resistant to multiple antibiotics (multi-drug resistance), have limited options for treatment. Over the last years there has been a significant increasing trend of combined resistance/multidrug resistance, defined as resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides, in *E. coli* (ECDC) in many European countries. In the Netherlands, there is a general increase in resistance for almost all compound-pathogen combinations and multi-drug resistance in *E. coli* in all patient groups including GPs. This reflects a general trend, suggesting an increase in ESBL-producing Enterobacteriaceae in community onset and health care associated infections. The increasing trend of combined resistance means that, for patients who are infected with these multidrug-resistant bacteria, only few therapeutic options remain available, such as the carbapenems.

To control the increase in antibiotic resistance, trends in resistance and antibiotic use should be carefully monitored to allow intervention if necessary. To ensure and enhance the validity of resistance surveillance nationwide it would be useful to include a number of standard antibiotics in test panels in each laboratory. For interventions in antibiotic use, the SWAB recently published a guidance document (‘visiedocument’). In the document, endorsed by the Health Care Inspectorate, a number of measures are recommended including antibiotic stewardship, restricted use of some broadspectrum antibiotics and more diagnostic interventions to allow individualizing therapy and narrow down when culture results and antibiograms become known.

Primary care

Since GPs only send in isolates for culture and susceptibility testing in case of complicated infection or when there is no response to antimicrobial therapy, the data on GP patients will generally over-estimate resistance levels in GP patients. Thus, the patient who is first treated will likely respond much better to therapy as the present figures suggest.

The steady increase in the use of broader spectrum antibiotics like amoxicillin/clavulanic acid, azithromycin and ciprofloxacin in primary care, and the increase in resistance to third generation cephalosporines, underlines the importance of a good surveillance system of resistance and antibiotic use in populations and infections that are not routinely sampled in patient care, such as patients in primary care.

Nursing homes

The large variety in antibiotic use and the high use of broad spectrum antibiotics in nursing homes demonstrates that antibiotic prescription in nursing homes is mostly empirically and not always based on well-defined guidelines or actual resistance prevalence. The choice is usually based either on the resistance data from hospitals or from general practitioners. This will result in an antibiotic choice with a too broad spectrum, when the choice is based on hospital data, or a too small spectrum, when data from general practitioners are used. To control the emergence of resistance in nursing homes, prudent use of AB is essential. Additionally, since patients in nursing homes are not routinely sampled in case of infection this requires a change in local policies by performing more diagnostics. Another tool that may help here, is setting up a surveillance network in nursing homes that should give insight in the prevalence and spread of resistant micro-organisms as well as the use of antibiotics. Such a surveillance system will help to identify related factors and options for interventions and will play an important role in controlling the prevalence and spread of resistant bacteria among patients in nursing homes. Finally, surveillance in nursing homes helps to set up antibiotic therapy guidelines.

Hospitals

Surveillance data on resistance in patients attending outpatient and hospital departments is available from (1) the Surveillance of Intramural Resistance in The Netherlands (SIRIN) and (2) the Infectious Disease Surveillance Information System for Antibiotic Resistance (ISIS-AR) database. Data from

SIRIN is limited by the small number of isolates collected, but isolates are tested for susceptibility by a central laboratory and therefore a standardised methodology for susceptibility testing. In contrast, data from ISIS-AR is robust due to its large sample size and nation-wide collection sites, but the system uses data from on-site routine susceptibility testing in different laboratories, and testing methodology is therefore more heterogeneous. The now almost universal use of standard methodology and interpretation through EUCAST guidelines increasingly endorse the use of ISIS-AR data and conclusions derived there-from. This therefore is the last year SIRIN data are collected and reported.

Conclusions

We conclude that the data presented in NethMap 2013 show continuing increases in antibiotic resistance in the Netherlands. The overall rise in resistance requires a rethinking of antimicrobial use and policy, including restricted use of some classes of antibiotics, in particular those that are employed as a last line of defense. Diagnostic cultures and in particular susceptibility testing are becoming increasingly important to guide antimicrobial treatment choices.