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Pristup problemu antimikrobne rezistencije – iskustvo nizozemske Radne grupe za antimikrobnu strategiju

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Stručni rad

Zadnjih nekoliko desetljeća svjedoci smo konstantno rastućeg problema antimikrobne rezistencije zbog kojeg je Vijeće Europske Unije donijelo rezoluciju te preporuke o razumnoj uporabi antibiotika u humanoj medicini. Naglasak u preporukama je stavljen na uspostavljanje mreže praćenja antimikrobne rezistencije te implementiranje mjera za doprinos razumnoj potrošnji antibiotika kroz razvijanje nacionalnih smjernica o upotrebi antibiotika. Uspostava interdisciplinarnog nacionalnog tijela (ICM, od engl. *interdisciplinary coordinating mechanism*) za koordiniranje svih aktivnosti na području rezistencije bakterija na antibiotike predložena je kao glavni instrument implementacije preporuka. Kao ICM u Nizozemskoj je osnovana Radna grupa za antimikrobnu strategiju (SWAB), a u Hrvatskoj Interdisciplinarna sekcija za kontrolu rezistencije na antibiotike (ISKRA). Dobra suradnja između SWAB-a i ISKRA-e započeta je kroz Matra (Matra Pre-Accession Programme, MPAP) projekt "Praćenje antimikrobne rezistencije u humanoj medicini" nizozemskog Ministarstva vanjskih poslova. Nizozemska je zemlja s najnižom potrošnjom antibiotika u Europi te niskim udjelom antibiotske rezistencije kod većine bakterija. Rezistencija na neke antibiotike, ipak, raste.

Management of the antibiotic resistance problem – approach of the Dutch Working Party on Antibiotic Policy

Professional paper

In the past decades we are witnessing an increasing antibiotic resistance problem to which the EU Ministers of Health responded by issuing a "Council Recommendation on the prudent use of antimicrobial agents in human medicine" with the recommendation of establishing antimicrobial resistance surveillance systems and implementing measures to support the prudent use of antibiotics by setting evidence based guidelines. *Intersectoral Coordinating Mechanisms* (ICM) at national levels have been suggested as instruments of implementation. Consequently the Working Party on Antibiotic Policy (SWAB) was founded in the Netherlands, and the Interdisciplinary Section for Antibiotic Resistance Control (ISKRA) in Croatia. Good colaboration between the SWAB and the ISKRA started through the Matra Pre-Accession Programme (MPAP) project "Antimicrobial resistance surveillance in human medicine" of the Dutch Ministry of Foreign Affairs. The Netherlands is the country with the lowest antibiotic consumption in Europe and with low antibiotic resistance rates in the majority of pathogens. However, resistance to some antibiotics is rising.

Introduction

In the past decades we are witnessing an increasing resistance problem in the field of public health, in general practice and in hospitals. To name a few examples of high impact, multiple resistance in *Neisseria gonorrhoea*, *Mycobacterium tuberculosis*, *Staphylococcus aureus*, *Escherichia coli* and *Klebsiella pneumoniae* are an important threat for our ability to treat serious infections. Following a conference on the recommendation of the EU Ministers of Health and on the initiative of the Danish Ministry of Health and the Ministry of Food, Agriculture and Fisheries, the Council of the European Union issued a "Council Recommendation on the prudent use of antimicrobial agents in human medicine" [1]. This action must be considered a milestone in the European commitment to fight antimicrobial resistance. In the Council Recommendations an EU resolution from 1999 is quoted, which states that antimicrobial resistance increases morbidity and mortality due to communicable disease and leads not

only to a diminution of quality of life but also to additional health and medical care costs, and that action needs to be taken at community level.

In the aim to contain the increase of resistance it is recommended to establish antimicrobial resistance surveillance systems, to implement measures to support the prudent use of antibiotics by setting evidence based guidelines, to promote and design educational activities for health providers and to make relevant data available to the public. In order to create instruments for the implementation of the EU recommendations, Intersectoral Coordination Mechanisms at national level have been suggested.

Approach of the Dutch Working Party on Antibiotic Policy (SWAB)

In the Netherlands a multidisciplinary Working Party on Antibiotic Policy (Stichting Werkgroep Antibiotica Beleid, SWAB) was founded in 1996, as an initiative of the Society for Infectious Diseases, the Dutch Society for Medical Microbiology and the Dutch Association of Hospital Pharmacists. In the board of SWAB, in addition to members of the societies above-mentioned, a veterinarian, a general practitioner and a paediatrician are represented. Presently the SWAB is the ECDC (ECDC – European Centre for Disease Prevention and Control) National Antimicrobial Resistance Focal Point. SWAB strives after the aims as recommended by the EU Commission by optimizing the use of antimicrobial agents through guideline development, education and surveillance of resistance and antibiotic use. Following advice by the Dutch Advisory Council on Health Research in 2000 on the containment of resistance, in 2001 SWAB was appointed by the Dutch Ministry of Health, Welfare and Sports to coordinate the surveillance of resistance in collaboration with the National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu, RIVM), currently with the Center for Infectious Disease Control (CiB) in the same institute. The surveillance of the use of antibiotics and the development of antibiotic guidelines is funded structurally by the CiB.

Because of the emerging resistance against medically relevant antibiotics in the veterinary field in a departmental platform between the Ministry of Agriculture, Nature and Food Quality and the Ministry of Health, Welfare and Sport experts discuss with the politicians the actions to be undertaken. Counterpart of the SWAB in this platform is the Veterinary Antibiotic Resistance Surveillance Working group (VANTURES).

The SWAB, the ISKRA and the MATRA project

SWAB is comparable to the Interdisciplinary Section for Antibiotic Resistance Control (ISKRA) of the Croatian Ministry of Health and Social Welfare. Both organizations were founded as national Intersectoral Coordination Mechanisms (ICM) based on the EU recommendations [1] and have similar tasks. Apart from the representatives of the societies for clinical microbiology, infectious diseases and clinical pharmacology ISKRA includes representatives of a wider range of interested parties like representatives of the Ministry for Agriculture, Fisheries and Rural Development and the Ministry of Science, Education and Sports as well as the representative of the National Infection Control Committee. When constituting the Croatian ICM the Croatian Ministry of Health and Social Welfare took the advantage of collaboration with the Dutch Ministry of Foreign Affairs through the MATRA Pre-Accession Programme (MPAP) project "Antimicrobial resistance surveillance in human medicine". The name of the Matra Programme derives from the Dutch for social transformation, "maatschappelijke transformatie". The beneficiary of the project was the Croatian Reference Center for Antibiotic Resistance Surveillance and from the Dutch side project partners were the Dutch Ministry of Health, Welfare and Sports, the SWAB, the RIVM and the Working Party for Infection Prevention (WIP). As the SWAB is oriented towards international collaboration the members of SWAB gladly took part in the MATRA project mostly contributing to the area of guidelines development and implementation. In a number of visits to Croatia the Dutch clinical microbiology and infectious disease doctors took part in workshops on guideline development. At the first workshop the methodology of guideline writing was discussed and the two most important topics for primary health care (sore throat and urinary tract infections) and the two most important hospital topics (MRSA control and surgical prophylaxis) were selected. After the working groups for each topic were set up by the Croatian Ministry of Health the SWAB members were involved in draft guideline analysis and implementation policy. A good collaboration between the SWAB and the ISKRA continued after the ending of the MATRA project.

Antimicrobial drug use in the Netherlands

Surveillance of antimicrobial use consists of two parts: primary health care antimicrobial use and antibiotic use in hospitals. The Foundation for Pharmaceutical Statistics (SFK) is in charge for collecting and analysing primary health care antibiotic consumption data and SWAB is collecting and analyzing hospital antimicrobial consumption data obtained from hospital pharmacists. Data on antibiotic use are expressed in defined daily doses (DDD) per hundred patient days and per hundred admissions, because trends over time in both units of measurement do not always correlate. These data are published in NethMap. Over the past decade, outpatient consumption of antibiotics has risen only slightly, from 9.9 to 11.1 DDD/1,000 inhabitants/day in 2008 [2]. However, the use of antibiotics is still low if compared with other European countries [2, 3]. In the primary health care consumption of co-amoxiclav gradually replaced amoxicillin and the use of quinolones increased. Nitrofurantoin use increased while

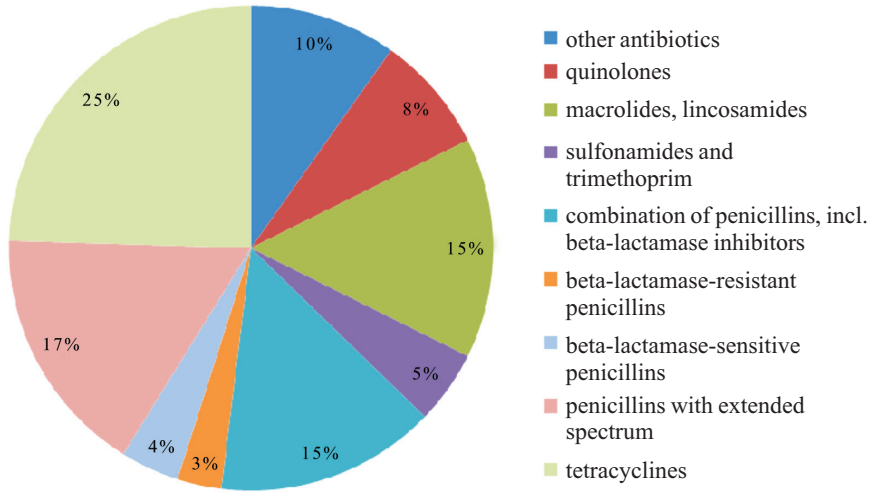


Figure 1. Distribution of antibiotic consumption for systemic use in primary health care in the Netherlands, 2008, adapted from data published on NethMap [2]
Slika 1. Raspodjela potrošnje antibiotika za sistemnu uporabu u primarnoj zdravstvenoj zaštiti u Nizozemskoj, 2008., izrađeno prema podacima objavljenima na NethMap [2]

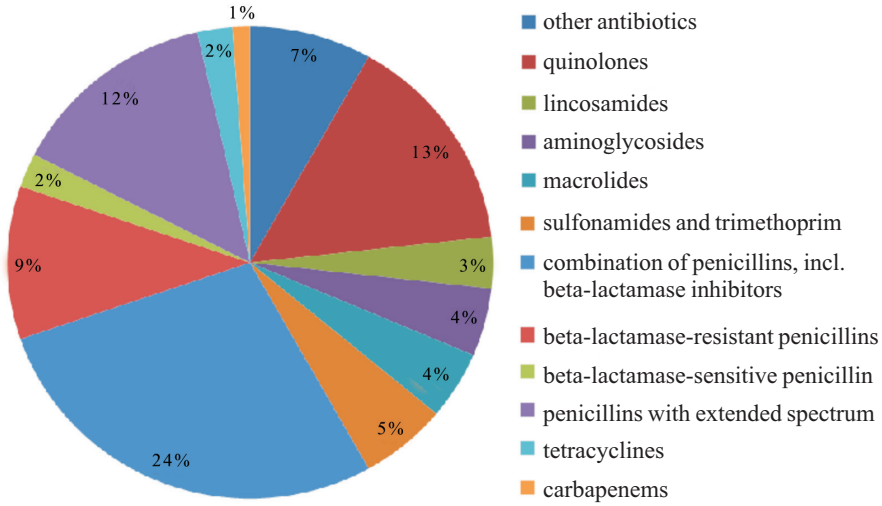


Figure 2. Distribution of hospital consumption of antibiotics for systemic use in The Netherlands, 2007, adapted from data published on NethMap [4]
Slika 2. Raspodjela bolničke potrošnje antibiotika za sistemsku uporabu u Nizozemskoj, 2007., izrađeno prema podacima objavljenima na NethMap [4]

trimethoprim use decreased which is in accordance with the revised guidelines for the treatment of cystitis. Tetracyclines (mainly doxycycline) represented 25 % of total antibiotic use in primary health care. Distribution of the use of antibiotics for systemic use in primary health care in 2008 is shown in Figure 1.

In hospitals the overall antibiotic use increased significantly from 47.8 to 61 DDD per 100 patient days in 2007, but this increase was due to the steady reduction in the average length of patient hospital stays while an increase of around 20 % in the number of admissions was seen over the past five years evidently leading to more medical interventions and more antibiotic use in hospitals in general. Overall antibiotic use per 100 admitted patients has remained partically the same, 336.2 DDD/100 admissions in 2003 and 335.0 DDD/100 admissions in 2007. Exceptions are the use of quinolones and glycopeptides. The consumption of ciprofloxacin in 2007 has significantly in-

creased since 1999 (2.5 to 5.5 DDD/100 patient days, 20 to 35 DDD/100 admissions) and this may be explained by an increase in the incidence of gram-negative resistant microorganisms. Vancomycin use has also increased (0.35 to 0.7 DDD/100 patient-days, 2.3 to 4.8 DDD/100 admissions) [2]. This might be due either to an increased focus on staphylococcal infections or an increased incidence of serious staphylococcal infections in the community and in health care settings. Distribution of the use of antibiotics for systemic use in 2007 is shown in Figure 2.

Resistance Surveillance in the Netherlands

Similary to the surveillance of antimicrobial usage, antibiotic resistance surveillance in the Netherlands is divided in two branches: primary health care and hospital resistance surveillance.

Primary health care surveillance is based on several studies ongoing in various parts of the Netherlands, coordinated by the national project Surveillance of Extramural Resistance in the Netherlands (SERIN). Ongoing surveillance systems on resistance rates in primary health care include:

- Resistance data for *Staphylococcus aureus* as part of the indigenous flora of healthy persons as to determine the basic level of resistance in the human reservoir
- Resistance rate of indicator organisms (*S. aureus* and *Escherichia coli*) in patients visiting their general practitioner
- Carrier state and level of resistance of *Streptococcus pneumoniae* in healthy children and healthy adults
- In 2006 the RIVM started a surveillance of resistance of *Neisseria gonorrhoeae* among patients from outpatient – sexually transmited infections (STI) clinics (the GRAS project)
- Since 1993 the Netherlands Reference Laboratory for Bacterial Meningitis has been determining the resistance level of *Neisseria meningitidis* from patients admitted to 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.

The overall prevalence of antibiotic resistance in hospitals is estimated by using resistance data generated in routine clinical care. These data are divided in two major

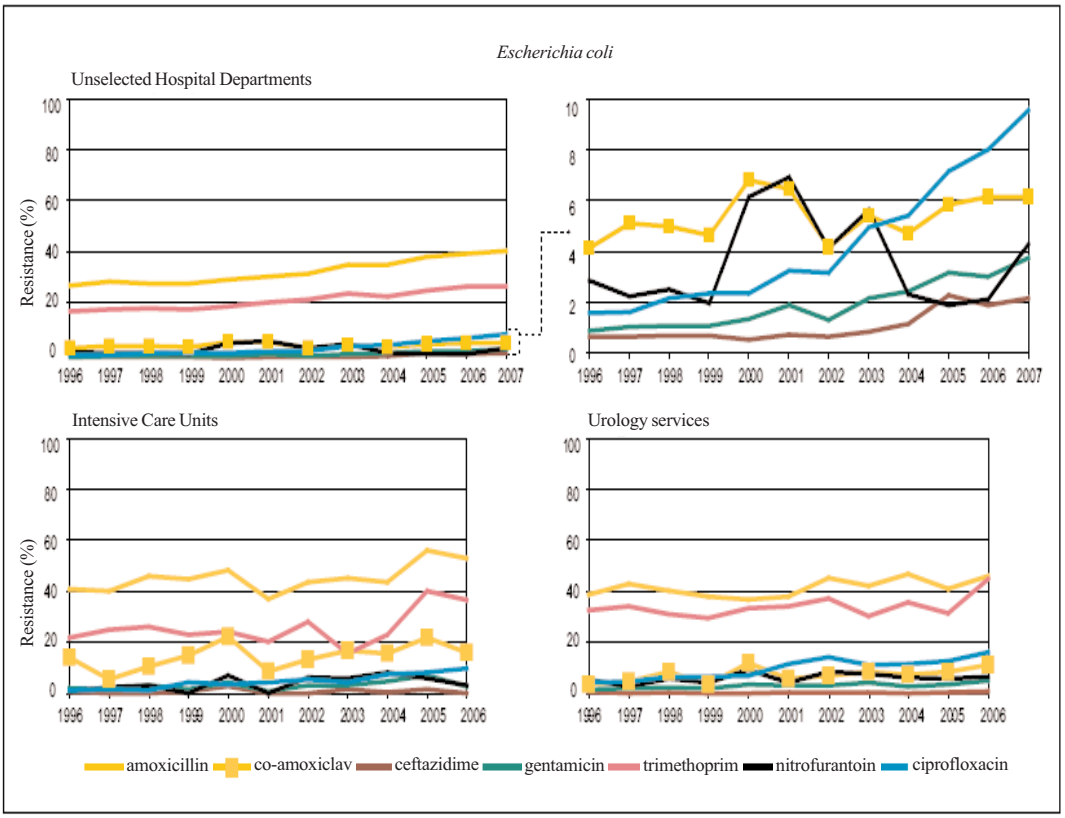
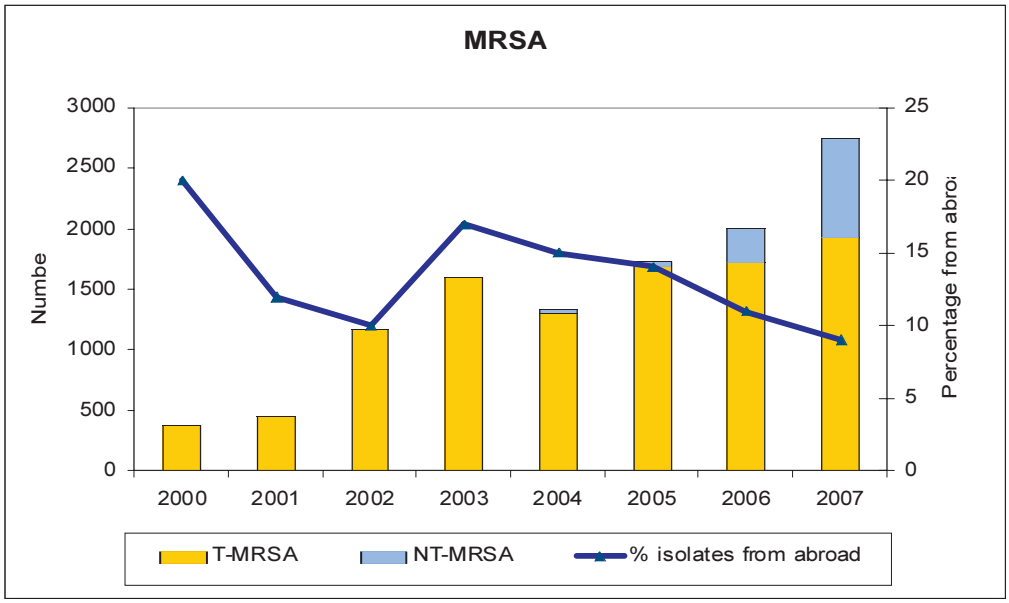


Figure 3. Resistance trends of *E. coli* to amoxicillin, trimethoprim, ceftazidime, aminoglycosides and ciprofloxacin in unselected hospital departments, Intensive Care Units and Urology Services in The Netherlands. NethMap 2008 [2]

Slika 3. Trendovi u rezistenciji *E. coli* na amoksicilin, trimetoprim, ceftazidim, aminoglikozide i ciprofloksacin na bolničkim odjelima, u jedinicama intenzivne njege i na urološkim odjelima u Nizozemskoj. NethMap 2008. [2]



Legend/Legenda:
T-MRSA = typable/tipabilni MRSA
NT-MRSA = non-typable/ne-tipabilni MRSA

Figure 4. Distribution of MRSA isolates in the Netherlands. Nethmap 2008 [2]
Slika 4. Distribucija MRSA izolata u Nizozemskoj. NethMap 2008. [2]

categories: unselected and selected hospital departments data. Unselected hospital departments and outpatient clinics data are collected from local laboratories by RIVM. Strains from selected hospital departments are collected by the Laboratory of Medical Microbiology of Maastricht University. These activities are covered by the national project for Surveillance of Intramural Resistance in the Netherlands (SIRIN). The population coverage for the hospital resistance surveillance is approximately 30 %.

In outpatient setting the resistance rates in *E. coli* are >30 % for amoxicillin and >20 % for co-trimoxazole whereas resistance to other antibiotics is low. In intensive care units co-amoxiclav resistance rate in *E. coli* in 2007 was 25 % with most strains showing MIC of intermediate category. These strains were not found among the community isolates. Ceftazidime-resistance level in the intensive care units and urology services was less than 1 % and showed no increase. Ciprofloxacin-resistance increased steadily among *E. coli* from unselected hospital departments, slowly during the first six years from 1–3 %, then more rapidly during the next six years: from 3 % in 2001 to 9 % in 2007, (Figure 3). This trend was also observed in the intensive care units. Co-amoxiclav-resistance in *K. pneumoniae* in intensive care units fluctuated at a high level (4–19 %) and resistance to cefotaxime and ceftazidime was sporadic. Ceftazidime and carbapenem resistance among *P. aeruginosa* isolated in intensive care units remained below 2 % [4]. Yearly a small number of MRSA were isolated from the intensive care units (N = 24 from 1996–2006) in the SWAB surveillance network. However, the incidence of MRSA increased 42 % since 2006 mostly due to the rise of the new non-typeable NT-MRSA [3], (Figure 4). The rate of penicillin non-susceptible pneumococci (PNS) is 2 % and macrolide resistance is 10 %.

Resistance in the Netherlands compared to other EU countries

The Netherlands together with Norway and Sweden are representing the countries with very low MRSA rates (<1 %). The proportion of invasive isolates of *E. coli* with resistance to third generation cephalosporins is still low and was reported less than 5 %. However, the resistance to fluoroquinolones follows the same trend as in the other parts of Europe and has been increasing throughout the years, with the current resistance of 10–25 %. The Netherlands is one of very few countries with low incidence of invasive *K. pneumoniae* isolates resistant to the 3rd generation cephalosporins (5–10 %). The proportion of *P. aeruginosa* invasive isolates resistant to ceftazidime, fluoroquinolones or carbapenems is 5–10 % which is low compared to other European countries [5].

Surveillance in the veterinary field

Therapeutic usage of antibiotics in food animals steadily increases, and it is followed by simultaneous increase of resistance levels in animal bacteria [6]. This fact and its direct influence on humans made surveillance of antibiotic resistance in animal bacteria and antibiotic usage in animals as imperative. In the Netherlands the Royal Veterinary Association's Antibiotic Policy Working Party published its policy in 1994 [6]. Rational and restrictive use of antibiotics was one of the foundations of this policy. Guidelines for therapy called "formularia" have been developed and their use promoted since the mid nineties of the last century. The data on monitoring of antimicrobial resistance and antibiotic usage in animals in the Netherlands is published every year in MARAN

(Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in the Netherlands) by VANTURES. The information presented in MARAN is based on a collation of data from ongoing surveillance systems on the use of antimicrobial agents in animal husbandry and the development of antimicrobial resistance in bacteria of animal origin and of relevance to public health. This study was primarily financed by the Ministry of Agriculture, Nature and Food Quality, through project 'Antimicrobial Resistance Research in Animals'. As an ICM, SWAB is in tight connection with VANTURES.

Antibiotic policy, therapeutic guidelines

Guideline programmes have a long tradition among the Dutch. It was started in the late 1980s by the Dutch College for General Practitioners, and was continued by SWAB.

Since its conception, the SWAB has developed national guidelines for the use of antibiotics. Guidelines are published in a Dutch medical journal (Nederlands Tijdschrift voor Geneeskunde) and in English on the SWAB website www.swab.nl. First guidelines aimed only at the hospitalized adult patients. They were based on the AGREE methodology (Appraisal of Guidelines, Research and Evaluation) [7, 8]. In 2006 SWAB introduced the electronic national antibiotic guide "SWAB-ID" for the antibiotic treatment and prophylaxis of common infectious diseases in hospitals. This guide also contains information on the most important characteristics of antimicrobial drugs. Advice on antibiotic treatment is based on existing evidence- based guidelines, where available. Where no guideline is available, the advice is based on an inventory of the antibiotic policies of the 12 Dutch centers with an infectious disease or medical microbiology training programme.

Disscusion

Increasing antibiotic resistance is a European and a world wide problem that is addressed by the various European professional societies and the EU Ministers of Health. Both the Netherlands and Croatia have good antibiotic resistance and antibiotic consumption surveillance systems in place and both countries are taking part in the European surveillance projects, the EARSS (EARSS-European Antimicrobial Resistance Surveillance System) and the ESAC (ESAC-European Surveillance of Antimicrobial Consumption). Consumption of antibiotics in the Netherlands is low as compared with other European countries and resistance rates are low for the majority of pathogens. However, some trends in community acquired pathogens like high amoxicillin and co-trimoxazole and increasing quinolone resistance in *E. coli* seem to be similar in the Netherlands as in other European countries. Analysis of antibiotic consumption surveillance data show that some changes in antibiotic consumption of different antibiotic classes can be explained by the change in guidelines on antibiotic use. The Netherlands has a long tradition in guideline writing [9] and this may be the clue to the rational antibiotic prescribing habits among the Dutch doctors. However, the control of guideline adherence is one of the weak points of antibiotic policy in general. Antibiotic treatment in hospitalized patients with a variety of underlying conditions and in the era of resistant pathogens is a very challenging task and should be guided by a team of infectious diseases and clinical microbiology professionals. Antibiotic prescribing auditing is an important tool in estimating a degree of compliance to antibiotic guidelines. One of the new actions to be taken by SWAB is to start a nation wide project on antibiotic prescribing auditing in order to study the adherence to SWAB guidelines. The SWAB is always open for the international collaboration and is looking forward to the future collaboration with the Croatian ISKRA as these two ICMs have similar tasks and goals.

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