Experiences in prevention and control of antibiotic resistance in Slovenia

M Čižman (milan.cizman@mf.uni-lj.si)[1]
1. Department of Infectious Diseases, University Medical Center Ljubljana, Slovenia

During 1991-1999 a significant increase of consumption of macrolides and fluoroquinolones was observed in Slovenia, and this was associated with significant increase of resistance of *Streptococcus pneumoniae* and *Streptococcus pyogenes* to macrolides and *Escherichia coli* to fluoroquinolones, respectively. Between 1999 and 2007 the prevalence of *S. pneumoniae* resistant to erythromycin increased from 3.7% to 16.8% even though the use of macrolides in the same period decreased from 3.81 to 2.43 defined daily doses (DDD) per 1,000 inhabitants and per day. The co-resistance and the spread of resistant clones were the reason for constant increase in macrolide resistance. Slovenia is one of the few European countries with decreasing prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in hospital care during the last years. As a result of control measures introduced in 1999, the MRSA prevalence rates decreased from 21.4% in 2000 to 8.3% in 2007.

Background

Slovenia is a small central European country with over two million inhabitants [1]. The country has a centralised compulsory Bismarck-style* health insurance system, which is administered by the Health Insurance Institute of Slovenia and includes almost all inhabitants (>99%). However, approximately 1.4 million residents also have supplementary health insurance provided by three private insurance providers. Prescription is needed for every antibiotic purchase, and in human medicine antibiotics may only be prescribed by physicians. The consumption of antibiotics in ambulatory care has been monitored in Slovenia since 1974, and the consumption of antibiotics in hospital care has been monitored since 1985. Since 2000 Slovenia has participated in EARSS (European Antibiotic Resistance Surveillance System) and since 2001 in ESAC (European Surveillance of Antibiotic Consumption) projects.

Resistance to antibiotics is a global public health problem. Selective antibiotic pressure and transferable resistance (clonal spread or horizontal resistance genes transfer) are major determinants of resistance development. It is irrefutable that the use of antibiotics promotes resistance. In this paper we describe the experiences in prevention and control of antibiotic resistance in ambulatory care, focusing on methicillin-resistant *Staphylococcus aureus* (MRSA) in hospital care.

Ambulatory care

In Slovenia the increased use of antibiotics in ambulatory care during the 1990s was associated with increased resistance of some respiratory infection pathogens. An increase in macrolide prescriptions by 3.5 between 1991 and 1996 was associated with significant increase in macrolide resistance in *Streptococcus pyogenes* and non-invasive *Streptococcus pneumoniae* between 1994 and 1997 [2]. Between 1994 and 1999, the macrolide consumption increased twofold, from 1.89 to 3.84 defined daily doses (DDD) per 1,000 inhabitants and per day, and at the same time the macrolide resistance in *S. pyogenes* increased from 0 to 7.4% and of non-invasive strains of *S. pneumoniae* from 0 to 9% [3]. The outpatient consumption of fluoroquinolones increased by 2.5, from 0.59 DDD per 1,000 inhabitants and per day in 1992 to 1.50 DDD per 1,000 inhabitants and per day in 1999 and this was paralleled by an increase of resistance of *Escherichia coli* to ciprofloxacin in adult patients from 3.6% in 1996 to 9.2% in 1999 [4].

Seeing that the resistance of some pathogens (*S. pneumoniae*, *S. pyogenes*, *E. coli*) had been increasing constantly, interventions were introduced to decrease their prevalence in the community. In June 2000, based on suggestions from infectious disease specialists, the Health Insurance Institute of Slovenia introduced administrative restrictive measures for the prescription of amoxicillin and clavulanic acid (co-amoxiclav) and fluoroquinolones [5]. Co-amoxiclav could no longer be prescribed for patients with *S. pyogenes* infections diagnosed clinically or documented microbiologically. Fluoroquinolones could only be prescribed as an alternative treatment for therapy of acute respiratory and urinary tract infections after clinical failure of first-choice antibiotics, or on the basis of tests showing susceptibility to fluoroquinolones and resistance to first-choice antibiotics [5]. In May 2004, the prescription of respiratory fluoroquinolones (moxifloxacin, levofloxacin) was modified. They could be prescribed in an unrestrictive manner only for severe community-acquired pneumonia and chronic obstructive pulmonary disease and when respiratory infection with resistant pathogens was expected. The staff of Health Insurance Institute of Slovenia checked the implementation of restrictive interventions by controlling individual prescriptions of physicians.

In Slovenia the overall consumption of antibiotics in outpatients decreased during the period between 2000 and 2007 by 20.32% [unpublished data]. However a greater decrease was observed for restricted than for non-restricted antibiotics (27.7% vs. 16.1%) [unpublished data]. This result shows that restrictive intervention can be efficient. To date a focused campaign directed at public and health care professionals has not been organised.

A detailed analysis of the causes and consequences of decreased antibiotic consumption over five years (1999-2003) showed a positive correlation between antibiotic consumption and repeated media reports and a negative correlation with the number of rapid diagnostic tests (C-reactive protein test (CRP), streptococcal antigen tests) [5]. Professional communication (scientific articles) and media reports for general public (lay articles) showed small negative correlation with antibiotic consumption. No increase in mastoiditis cases was observed in spite of reduced antibiotic consumption [5]. Reduced antibiotic consumption was paralleled by a decrease in penicillin resistance among invasive pneumococci and lower costs of antibacterials for systemic use. In contrast, reduced macrolide resistance rates of *S. pneumoniae* and *S. pyogenes* was not observed despite the 21.3% decline of total macrolide use during the period 1999 – 2004 [6].

A recent analysis showed that the prevalence of erythromycin resistance among invasive *S. pneumoniae* isolates increased from 3.7% in 1999 to 16.8% in 2007 in spite of a decrease of consumption of macrolides by 36.3% in the same period (from 3.81 to 2.43 DDD per 1,000 inhabitants and per day) [7]. The resistance increased almost eightfold among isolates from children (from 3.1% in 1999 to 24.6% in 2007). The most likely explanation for the continuous increase in macrolide resistance was co-resistance and the spread of resistant clones. The most frequent co-resistance pattern in the erythromycin-resistant strains of invasive *S. pneumoniae* isolates with erm(B) gene was resistance to penicillin, tetracycline and trimethoprim-sulfametoxazole.

To decrease the resistance of respiratory infection pathogens to macrolides, measures to reduce the use of macrolides especially new ones (by educational and/or restrictive interventions) and/or the introduction of conjugated pneumococcal vaccine are being discussed.

In addition, according to EARSS data the prevalence of resistance of *E. coli* to quinolones doubled (from 8.5% to 17.4%) between 2001 and 2007 in spite of reduced (15%) use of fluoroquinolones in the community (from 1.3 to 1.11 DDD per 1,000 inhabitants and per day) [8]. This data shows the complex correlation between antibiotic use and antibiotic resistance and indicates that the reduction of antibiotic use alone does not guarantee that lower prevalence of resistance can be achieved.

Hospital care

In 2008 Slovenia has 29 hospitals including two teaching hospitals, 10 general hospitals and 14 specialised hospitals providing orthopedic (1), pulmonary (2), gynecological (2), psychiatric (5), nursing (1), rehabilitation (2) and oncology (1) care, and three hospitals providing diagnostic or surgical procedures. All but three hospitals providing diagnostic or surgical procedures are state owned. In this section we focus exclusively on MRSA as an example to control antibiotic resistant bacteria. Slovenia is one of the few European countries which succeeded to reduce the prevalence of MRSA. In the period from 2000 to 2007 the prevalence decreased from 21.4% to 8.3% (by 61.3%).

In 1997 and 2001 two point prevalence studies showed high (75% and 60%) prevalence of MRSA in the adult intensive care units (ICU) in Slovenia [9]. Also a national point prevalence study of hospital-acquired infections in acute care hospitals in 2001 showed high (61.8%) prevalence of MRSA [10]. After the high prevalence of MRSA in Slovenia had been recognised two studies showed that with the comprehensive infection control program the number of MRSA cases could be decreased. In the first study the proportion of MRSA cases acquired in the hospital decreased from 50% to 6.1% during 1999 – 2002, and in the second the incidence of ICU-acquired MRSA decreased from 7.8% to 1.9% [11,12]. The legislation and regulation of the infection control program in health care institutions published in 1999 and the audit of infection control implementations in health care institutions published in 2006 also had an impact on the decline of the prevalence of MRSA in Slovenia [13,14].

Currently, the components of Slovenian strategy for MRSA control are:

- active surveillance – selective screening for MRSA in patients at risk of carrying MRSA on admission;
- contact isolation of patients with MRSA (not always possible because of single bedroom shortage);
- promotion of hand hygiene – use of alcohol-based hand rub;
- selective decolonisation;
- improved communication (reporting) about patients with MRSA within and between health care facilities;
- continuous education of health care workers (HCW) on appropriate hygiene procedures in health care institutions (hospitals, nursing homes);
- use of hospital computer system to record MRSA carriers;
- education of professionals (postgraduate educational courses have been organised by the Medical Faculty in Ljubljana since 1984 (162 physicians and 290 nurses have participated till 2008), national scientific meetings;
- education of patients (newspapers, magazines, TV, leaflets);
- spread of information to media and politicians.

The greatest obstacle for a further decrease in the prevalence of MRSA is the shortage of single-bed rooms and staff.

Notwithstanding the success in decreasing the prevalence of MRSA, a new resistant pathogen has emerged recently, the vancomycin-resistant enterococcus (VRE). Before the year 2005 according to EARSS data all invasive strains of *Enterococcus faecium* isolates had been susceptible to vancomycin [8]. In 2006, 6% and in 2007, 4.6 % of *E. faecium* invasive isolates were found to be resistant to vancomycin. The main source of resistant isolates are patients hospitalised in one haematological department in a tertiary care centre. In this department not enough single- or double-bed rooms are available, so the contact precautions are not possible to be provided.

In recent years higher use of linezolid was followed by the emergence of linezolid resistant enterococci (LRE) [unpublished data].

Conclusion

In Slovenia, antibiotic resistance is a problem in outpatient as well as hospital settings [8]. In order to combat antibiotic resistance, antibiotic policy and infection control are needed. Despite reduced use of all antibiotics including macrolides and fluoroquinolones in outpatient care, resistance of *S. pneumoniae* to macrolides and *E. coli* to fluoroquinolones is still increasing. Hospital consumption of antibiotics in Slovenia is moderate and stable and we have observed a decrease in MRSA prevalence probably due to better infection control [8,15]. However the emergence of VRE isolates has become an increasing problem in the last three years. Reducing prevalence of resistance is a difficult task; apart from prudent antibiotic use and better infection control it requires many other sustained interventions.

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*Note: Bismarck model healthcare systems are systems based on social insurance, where there is a multitude of insurance organisations (e.g. Krankenkassen) that are organisationally independent of healthcare providers.

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