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Short Communication

The long-term effects of restrictive interventions on consumption and costs of antibiotics

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ABSTRACT

In the last decade, Slovenia introduced restrictive measures for some antibiotic classes in ambulatory care as well as regulatory interventions to reduce costs. The aim of this study was to analyse the effects of these interventions on consumption and costs of antibiotics in ambulatory care. Consumption data were expressed in defined daily doses/1000 inhabitants per day (DID), number of packages/1000 inhabitants per day and number of prescriptions/1000 inhabitants per year. In 2000, Slovenia introduced restrictive measures for prescription of amoxicillin/clavulanic acid (AMC) and fluoroquinolones, in 2005 for oral third-generation cephalosporins and in 2009 for macrolides. Segmented regression analysis of interrupted time series was used to estimate the effects of restrictive interventions on antibiotic consumption. Total outpatient consumption of antibacterial drugs decreased by 29.65% from 20.27 DID in 1999 to 14.26 DID in 2012. Three years after the introduction of restrictions, consumption of AMC, fluoroquinolones and macrolides decreased by 29.3%, 23.8% and 28.8%, respectively, compared with the year before the intervention, and of non-restricted antibiotics by 3.3% (in 2003). Twelve years after the introduction of restrictive interventions, use of AMC and fluoroquinolones decreased by 28.1% and 28.5%, respectively, and use of non-restricted antibiotics by 18.8% (in 2012). In the same time period, the costs of AMC and fluoroquinolones were reduced by 63.3% and 52.4%, respectively, and of non-restricted antibiotics by 46.9%. Restrictive interventions in ambulatory care are effective in reducing antibiotic consumption and costs. Restrictive interventions had a significantly greater impact on consumption 3 years post-intervention than after 12 years.

1. Introduction

A wide variety of interventions have been successful in changing antibiotic prescribing both in the community and hospital settings [1,2]. Restrictive interventions are commonly used in hospitals but less commonly in outpatient services [2,3]. Restricted outpatient antibiotics usually include expensive antibiotics and/or new alternative antibiotics [3]. In previous research, we have shown that reduced consumption during the period 1999–2003 was higher for restricted antibiotics than for non-restricted antibiotics (27.9% vs. 8.4%). Also, cost reduction was higher for restricted than non-restricted antibiotics [4]. The aim of the present study was to analyse the effects of restrictive interventions on antibiotic use and costs in ambulatory care in Slovenia between 1999 and 2012.

2. Materials and methods

Slovenia is a small country with a population of ca. 2.06 million inhabitants according to the 2012 census [5]. Almost all inhabitants (>99%) have compulsory basic health insurance. A prescription is needed for every drug purchase. In addition, physicians prescribe antibiotics for humans only. Data on the number of packages, the costs of antibiotics, the age and sex of patients, and the identity number of the physicians and healthcare

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institutions prescribing antibiotics are collected every 3 months and are published annually. In the period 1999–2012, data on outpatient antibiotic consumption were collected using the Anatomical Therapeutic Chemical (ATC) classification system using defined daily doses (DDD) (WHO version 2012) [6]. Consumption was also expressed in number of packages/1000 inhabitants per day (PID) and number of prescriptions/1000 inhabitants per year RIY. The number of prescriptions and packages and the costs of antibiotics for insured persons and out-of-pocket paid antibiotics ('white' prescriptions for uninsured persons, prescriptions before travelling) were provided by the National Institute of Public Health of Slovenia and the Health Insurance Institute of Slovenia (HIIS).

2.1. Restrictive interventions

The pattern of restrictive interventions started in June 2000, when HIIS implemented prescribing limitations for drugs such as amoxicillin/clavulanic acid (AMC) and all fluoroquinolones (FQs) [4]. AMC can no longer be prescribed for infections caused by *Streptococcus pyogenes.* FQs can only be prescribed for urinary and respiratory tract infections as a second line of defence or if susceptibility is proved by susceptibility tests. The second step was taken in June 2005 when oral third-generation cephalosporins (ceftibuten) were limited only to continuation of hospital treatment, according to susceptibility test results or if the antibiotic of choice was not effective. Thereafter in June 2009, a prescribing limitation for macrolides was introduced because of the increasing resistance of *Streptococcus pneumoniae* to macrolides. Macrolides can be prescribed for the treatment of acute otitis media, acute bacterial rhinosinusitis and *Streptococcus* throat infections only when the patient is allergic to penicillin. In addition, clarithromycin has been allowed for treatment of *Helicobacter pylori* infection.

Since 2002, HIIS regularly audits physicians, checking for type of prescriptions, especially those that have limitations. Physicians are fined for non-compliance. In 2002, the recommendations for prescription of antimicrobials in ambulatory care were published and were then used by the majority of primary care physicians [7]. In addition, other educational activities for professionals and the public were published [4]. From 2008 to 2012, yearly events were held to promote European Antibiotic Awareness Day [8].

2.2. Costs of antibiotics

The prices of drugs in Slovenia are regulated. Maximum prices are set based on benchmark countries. In addition, for clusters of interchangeable drugs including antibiotics, HIIS sets the highest reimbursement price (so called 'reference price').

2.3. Statistical methods

Descriptive statistics are given as percentage change in mean consumption before and after restrictive intervention. Segmented regression analysis of interrupted time series was used to estimate the effect of guideline dissemination on antibiotic consumption [9]. Two segments were defined: the pre-intervention period (quarterly consumption in the time period before the intervention) and the post-intervention period (quarterly consumption in the time period after the intervention). A least-squares model was used to test for any significant changes in level or trend in the time series following implementation of the guidelines, controlling for any pre-intervention differences in level and trend. To correct for seasonal changes in the series, terms to indicate each season were included in the model, which decreases confounding by seasonality. Non-significant terms were then eliminated in a stepwise manner to obtain the most parsimonious model. The Durbin–Watson test was used to test for the presence of autocorrelation. In the case of a significant test result, the Prais–Winsten method was used to adjust for autocorrelation. The assumption of normally distributed residuals was verified with the Shapiro–Wilk test. A *P*-value of <0.05 was considered statistically significant. Analysis was performed using SPSS for Windows v.19.0 (IBM Corp., Armonk, NY) and R language for statistical computing (R version 3.0.0) [10].

3. Results

3.1. Total outpatient consumption of antibiotics in Slovenia

Total consumption of antibiotics decreased by 29.65% from 20.27 DDD/1000 inhabitants per day (DID) in 1999 to 14.26 DID in 2012 (Table 1).

During the same time period, the number of packages decreased by 37.2% from 3.12 PID in 1999 to 1.96 PID in 2012, and the number of prescriptions decreased by 33.5% from 791 RID to 526 RID.

3.2. Effect of restrictive interventions

Three years after the introduction of restrictive interventions, the consumption of AMC decreased by 29.3% from 5.81 DID in 1999 to 4.11 DID in 2003. Twelve years after the intervention, consumption decreased by 28.1% (5.81 DID vs. 4.18 DID) (Table 1).

Three years after the introduction of restrictive interventions, the consumption of FQs decreased by 23.8% from 1.51 DID to 1.15 DID, and 12 years after the intervention it decreased by 28.5% from 1.51 DID to 1.08 DID (Table 1). Quarterly outpatient consumption of FQs is shown in Fig. 1.

Consumption of non-restricted antibiotics decreased after 3 years (in 2003) and after 12 years (in 2012) following the introduction of restrictive interventions by 3.3% and 18.8%, respectively.

As shown in Table 2, quarterly consumption of AMC and FQs before the restriction was increasing significantly by 0.0581 DID ($P < 0.0001$) and 0.0044 DID ($P = 0.02$) per quarter, respectively. Consumption of non-restricted antibiotics was increasing by 0.0107 DID per quarter, but this increase was not statistically significant ($P = 0.583$). Following the restrictions, the mean quarterly consumption of AMC and FQs dropped significantly by 0.5333 DID ($P < 0.0001$) and 0.0666 DID ($P < 0.0001$), respectively, and continued to decline significantly ($P < 0.0001$ and $P = 0.0057$, respectively). Consumption of non-restricted antibiotics has also dropped during the same time period but the change was not significant ($P = 0.2506$).

Three years after the introduction of restrictive interventions, the consumption of macrolides decreased by 28.8% from 2.22 DID to 1.58 DID (2008 vs. 2012). However, the time series did not show a significant reduction because the quarterly consumption was decreasing significantly ($P < 0.0001$) even before the intervention. Quarterly consumption of non-restricted antibiotics was decreasing significantly before the restriction of macrolides ($P = 0.0001$). After that intervention, the trend reversed but the increase in quarterly consumption was not significant ($P = 0.2767$).

Pre- and post-intervention consumption of the third-generation oral cephalosporins (ceftibuten and cefixime) showed reduced use of ceftibuten by 83.3% (from 0.06 DID in 2004 to 0.01 DID in 2012) post-intervention. Cefixime was launched 1 year post-intervention in 2006. Consumption of cefixime increased from 0.03 DID in 2006 to 0.08 in 2008–2010 and decreased to 0.06 DID in 2012.