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The influence of a sustained multifaceted approach to improve antibiotic prescribing in Slovenia during the past decade; findings and implications

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Abstract

Introduction: Rising antibiotic resistance has become an increasing public health problem. There is a well-established correlation between antibiotic consumption and antimicrobial resistance. Consequently, measures to rationalise antibiotic prescribing should reduce resistant strains. Following a 24% increase in antibiotic consumption at the end of the 1990s, multiple activities were designed and introduced by the Health Insurance Institute of Slovenia (ZZZS) and other organisations in Slovenia at the end of 1999. These activities reduced antibiotic consumption by 18.7% by 2002. These measures have continued.
Objective: To study changes in antibiotic utilisation from 1995 to 2012, alongside the multiple interventions and their consequences including changes in resistance patterns.
Methods: Retrospective observational study involving all patients dispensed at least one ZZZS prescription for an antibiotic in Slovenia. Utilisation expressed in defined daily doses per one thousand inhabitants per day. Multifaceted interventions conducted over time involving all key stakeholder groups, i.e. Ministry of Health, ZZZS, physician groups and patients. These included comprehensive communication programmes as well as prescribing restrictions for a number of antibiotics and classes.
Results: From 1999 – 2012, antibiotic consumption decreased by 2% to 9% per year, overall by 31%. There were also appreciable structural changes. Overall antibiotic utilisation and the utilisation of 7 out of 10 antibiotics significantly decreased after multiple interventions. *S. pneumoniae* resistance to penicillin decreased in line with decreased utilisation. However, *S. pneumoniae* resistance to macrolides increased from 5.4 to 21 % despite utilisation halving. *E. coli* resistance to fluoroquinolones doubled from 10 % to 21 % despite utilisation decreasing by a third. Expenditures on antibiotics decreased by 53%.
Conclusion: Multiple demand-side measures introduced following increased utilisation significantly decreased subsequent antibiotic utilisation and associated costs. However, there was variable impact

on antibiotic resistance. Additional targeted activities are planned to further reduce antibiotic prescribing and resistance.

Introduction

Rising antibiotic resistance rates have become an increasing patient-safety and public-health problem across continents, exacerbated by a decline in antibiotic research and drug development programs (1-9). The World Health Organisation (WHO) considers continued rising resistance rates a threat to global stability (10).

There is a well-known correlation between antimicrobial resistance and the consumption of antibiotics (1, 4, 11, 12), as countries with higher antibiotic consumption typically have higher resistance to pathogens including community pathogens (11, 13, 14). Consequently, improving the rational prescribing of antibiotics should help reduce or prevent the development of resistance to pathogens and lower overall costs. Ecological pressures linked to resistance include the duration of treatment, prescribing of broad-spectrum versus narrow-spectrum antibiotics and, in the case of macrolides, prescribing long-acting instead of short-acting ones, which can increase resistance development (11). These concerns have resulted in multiple activities carried out by health professionals, public health institutions, health authorities and public foundations across countries to improve antibiotic prescribing in ambulatory care (5). These include a Pan-European campaign – Antibiotic Awareness Days, the development of 12 valid and specific indicators, as well as specific campaigns among individual European countries (4, 5, 7, 15-19).

Various studies have shown that multifaceted programs can reduce antibiotic consumption. In France, the multifaceted national programme ‘Keep Antibiotics Working’, targeting all key stakeholders, was launched in 2001. This programme was coupled with the public service campaign ‘Antibiotics are not automatic’ every winter since 2002. Compared to the pre-intervention period (2000–2002), the total number of antibiotic prescriptions per 100 inhabitants, adjusted for the frequency of flu-like symptoms during the winter season, decreased by 26.5% in the 2003-2007 period. The greatest reduction in antibiotic use (-36%) was seen among children (4). The IMPAC3T study showed that training physicians in advanced communication skills through seminar role-playing and peer feedback on consultation transcripts reduced antibiotic prescribing rates by 20% (20). More recently, the Genomics to Combat Resistance Against Antibiotics in Community-acquired LRTI in Europe (GRACE) consortium developed an Internet-based training tool for lower-respiratory-tract infections, coupled with training on C-reactive protein (CRP). These combined interventions led to an important reduction in antibiotic prescribing (21).

In Slovenia, multiple activities were instigated by the Health Insurance Institute (ZZZS) between 1999 and 2002 in response to an appreciable increase in antibiotic consumption (22). Antibiotic utilisation increased from 16.4 defined daily doses (DDDs) per one thousand inhabitants per day (DID) in 1995 to 20.4 in 1999.The multiple interventions resulted in an 18.7 % reduction of antibiotic use in 2002 compared to 1999 (22). ZZZS is the only provider of compulsory health insurance in Slovenia. The costs of antibiotics are mostly completely covered by ZZZS; consequently, there is limited patient co-payment. Primary health-care physicians issue approximately 45 % of all prescriptions for antibiotics. In Slovenia, antibiotics always require a prescription. By contrast, in Serbia and Spain an appreciable quantity of antibiotics have been self-purchased (23). In 2005, the National committee for the rational use of antibiotics was established at the Ministry of Health as a national coordinating body responsible for enhancing the prudent use of antimicrobials in Slovenia. Other measures have also been implemented to lower antibiotic utilisation.

The principal aim of this study was to analyse changes in the utilisation of antibiotics from 1995, i.e. before undertaking any intervention, to the end of 2012 alongside mapping the different interventions undertaken. Secondly, assess changes in resistance patterns and associated costs. As a result, potentially provide examples to other countries wishing to further improve their utilisation of antibiotics. This study builds on our earlier findings, which only considered the pre-2003 period (22). Overall, we believe that our study represents one of the longest follow-up periods of continual interventions on antibiotics instigated by a single health authority for its entire population.

Materials and methods

Study design (excluding interventions)

This is a retrospective non-randomised observational study with a before-and-after design (24) involving all physicians in Slovenia between 1995 and 2012. There were 1.99 million inhabitants in Slovenia in 1995 and 2.06 million in 2012. The percentage of uninsured was 1.7 % and 0.5% in 1999 in 2012, respectively.

All patients dispensed at least one antibiotic prescribed on a ZZZS prescription form in Slovenia (Anatomical Therapeutic Chemical – ATC - group J01) (25) were included in the study. Antibiotic utilisation is expressed in terms of Defined daily doses per thousand Inhabitants per Day (DID), in line with other publications comparing antibiotic use across countries (26, 27). Antibiotic utilisation is also expressed in the number of prescriptions per 1000 inhabitants to ensure the consistency and robustness of the utilisation data. The utilisation data was obtained from the regularly audited ZZZS Prescription Database, which contains the data on all prescription medications dispensed by all the pharmacies throughout Slovenia. All ZZZS prescriptions for oral antibiotics issued to ambulatory patients were included in the analysis. Prescriptions paid out of pocket (1 – 2 % of prescriptions for antibiotics) as well as parenteral antibiotics administered in nursing homes and in ambulatory care were not included.

The dynamics of antibiotic utilisation were quantified by linear regression using the open-source software package *R (28)* . The periods 1995 – 1999 and 1999 – 2012 were considered separately. For both periods, the consumption of antibiotics in DIDs was modelled as a linear function of time, i.e., consumption = a * year + b, where a (slope) and b (y-intercept) are the parameters to be estimated by linear regression. The results for the period 1995 – 1999 and for the period 1999 – 2012 were analysed separately. The *Index* was calculated depicting the relative change in antibiotic utilisation over the entire period, with the *Estimated slope* depicting the best-fit estimate for the slope of the regression line (i.e., of the linear function estimated by linear regression). A positive slope indicates an increase, a negative slope indicates a decrease, and the absolute value of the slope measures the steepness of the regression line. The *Standard error* is a measure of the difference between the actual utilisation and the utilisation predicted by the regression line, with value R^2, between 0 and 1, indicating how well the linear function models the dynamics of utilisation. The p value is the probability that the slope of the regression line is equal to zero, i.e., that the true line neither increases nor decreases. The utilisation in the observed period is statistically significantly increased or decreased if the p value is less than the predefined level of 0.05.

The pathogens that cause most infections in the community were subsequently chosen for further analysis to determine changes in antibiotic resistance patterns over time using standard methods, e.g. *S. pneumoniae* using haemocultures. *S. pneumoniae* is mostly found in the community and only rarely in hospitals and *Escherichia coli* is in 80 % of cases acquired in ambulatory care/ home environment and only 20 % in hospitals.

Reimbursed expenditure for antibiotics dispensed during the study period was also calculated and subsequently compared to total drug costs. The expenditures for the campaigns was also calculated based on the available data. Expenditure data is expressed in Euros with no allowance for inflation. This mirrors other studies, especially since the tendency of authorities in Europe is to reduce the prices of pharmaceuticals when budgets are being exceeded (29-31).

Interventions

Since 1995, there have been a number of activities involving the Ministry of Health, the National Committee for the rational use of antimicrobials and academic units to reduce antibiotic consumption. ZZZS became involved from 2000 onwards with introducing prescribing restrictions as well as additional activities, intensifying the various demand-side measures. These have been collated under the 4Es – Education, Engineering, Economics and Enforcement (32). The 4Es is a recognised methodology for collating and comparing the multiple demand-side measures that could potentially be introduced across classes and countries (30, 33-39). These interventions are shown in Table 1.

Table 1. Activities in the field of rational prescribing of antibiotics in Slovenia

Activity	Institution (organizer)	Targeted public	Introduction / frequency
2-day symposium on antibiotics once a year	Dept. of Infectious Diseases of the UMC Ljubljana	GPs	1995 every year
Prescribing restrictions for amoxicillin/ clavulanic acid and the fluoroquinolones	ZZZS	All physicians	2000/ permanent
Workshops in Primary health centres	Primary health centres, ZZZS	GPs	2001/ sporadically
Informative budget targets for prescribed drugs	ZZZS	All physicians	2001/ permanent
Guidelines on treatment of infectious diseases	Medical professionals	GPs	2002
Audits	ZZZS	All physicians	2002/ regularly
The drug Bulletin "Recept"	ZZZS	All physicians	2003/ twice a year
Workshop on rational prescribing of antibiotics	Faculty of Medicine University of Ljubljana	Specializing GPs	2004/ every year
Prescribing restrictions for cephalosporins	ZZZS	All physicians	2005/ permanent
Flyer “Safe use of drugs”	ZZZS, medical professionals	Lay public	2006/ always available
Booklet "My child has a fever"	ZZZS, medical professionals	Parents	2007/ always available
Workshop in a region with the highest use of antibiotics	National Committee for the Rational Use of Antimicrobials	GPs	2007/ once a year
Antibiotic Awareness Day	MoH and National Committee for the Rational Use of Antimicrobials	Lay public and GPs	2008/ every year
Prescribing restrictions for the macrolides	ZZZS	All physicians	2009/ permanent
Workshop on rational prescribing of antibiotics	Slovenian society of chemotherapy	Young physicians	2010/ every year
Flyer "Get well without antibiotics"	ZZZS, medical professionals	Lay public	2010/ always available
Flyer “Interactions of drugs”	ZZZS, medical professionals	Lay public	2010/ always available
Quality indicators including antibiotics	ZZZS	GPs	2011

NB: ZZZS = the Health Insurance Institute of Slovenia

In more detail:

- **Education -** includes educational programmes that influence prescribing such as (i) distribution of guidelines, guidance and formularies, (ii) academic detailing, (iii) monitoring or benchmarking of physician prescribing and (iv) encouraging international non-proprietary name (INN) prescribing (32, 40, 41). Evidence-based therapeutic guidelines were published in 2002 (42) and distributed to all GPs in Slovenia. Lectures, workshops and monitoring of prescribing habits were also organized.

In addition, since 1995 the Department of Infectious Diseases of the University Medical Centre Ljubljana has undertaken annual two-day symposia discussing ways to enhance the appropriate use of antibiotics. Since 2010, there is also a yearly workshop on the rational prescribing of antibiotics devoted to young doctors caring for outpatients and inpatients. This workshop is organised by the Slovenian Society of Chemotherapy. Once a year on November 18, there is also an ‘Antibiotic Awareness Day’ as part of the European Antibiotic Awareness Day programme (43). This event is organised by the Ministry of Health and the National Committee for the rational use of antimicrobials. Members of the public are informed on the subjects related to the rational use of antibiotics by media, posters and flyers.

In the region(s) with the highest consumption of antibiotics, the National Committee for the rational use of antimicrobials organises meetings for GPs. This programme is based on the European Council recommendation of 15 November 2001 on the prudent use of antimicrobial agents in human medicine (2002/77/EC).

Throughout the country, physician groups and ZZZS have organised multiple meetings in Primary health centres, focusing on rational prescribing with a particular emphasis on antibiotics. This includes comparisons of drug utilisation (including antibiotics) among physician groups and, since 2011, prescribing quality indicators on a regional and local level (engineering – see below). All education and workshops are clinically orientated and are well attended by general practitioners.

ZZZS also promotes rational prescribing through the drug bulletin ‘Recept’, which is published twice a year (44). In 2007, ZZZS has published a booklet for parents on the appropriate care of children with fever, which is widely distributed in all paediatric centres. For adults, there is a flyer on the responsible use of antibiotics, which is always available to health providers and public. These and other materials supporting the safe use of drugs are regularly sent to providers and are also available on ZZZS’s web page (45). The Ministry of Health also publishes flyers on the rational use of antibiotics for the lay public.

- **Engineering activities** - are concerned with organisational or managerial interventions (32). They include, for instance, prescribing targets and quality targets (32, 41, 46). In 2011, ZZZS developed a range of Quality indicators (QIs) for GPs (45, 47). The Quality indicator for antibiotics measures the intensity of antibiotic treatment in the number of DDDs of antibiotics per recipient. This was not as specific as the ESAC-recommended indicators, which reviewed antibiotic prescribing for specific infections (18). In the on-line application, every GP may view his or her own results and his or her relative position among peers. The purpose of this information is to influence the quality of future prescribing. There is no financial or other stimulation for improving the scores.

- **Economics** - includes both positive and negative financial interventions (32, 41). Examples include (i) patients covering the additional cost themselves for a drug that is more expensive than the current reference-priced drug (molecule or class), (ii) financial incentives to physicians for reaching the agreed prescribing targets or (iii) financial penalties for continued high-cost prescribing (32, 40). In Slovenia, there are budget targets for GPs for the prescription drugs. However, physicians are not given financial incentives for achieving the targets or fined in case of over-budget situations. They are, however, fined if they prescribe antibiotics outside of the agreed criteria (see below).

Co-payments for the drugs whose price exceeds the current reference price for the interchangeable drugs (Anatomic Therapeutic Chemical [ATC] Level 5 – molecule (25)) have been in effect since 2003.

- **Enforcement** - refers to regulations by law (32). Examples include (i) compulsory generic substitution in Sweden, (ii) compulsory international non-proprietary name (INN) prescribing (Lithuania), (iii) prescribing restrictions such as those for patented statins in Austria, Finland, Norway and Sweden as well as angiotensin receptor blockers in Austria, Croatia and Sweden (33, 41, 48-52). In Slovenia, there is no obligatory generic (INN) prescribing or substitution with INN prescribing the exception.

Since 2000, ZZZS has instigated prescribing restrictions for a number of antibiotics and classes including amoxicillin/ clavulanic acid, third-generation cephalosporins, fluoroquinolones and the macrolides. Their indications are defined together with their place in treatment, i.e., first, second or third line, as well as potentially other conditions for prescribing. Prescribing restrictions for amoxicillin/ clavulanic acid and the fluoroquinolones were instigated in 2000, for third-generation cephalosporins in 2005 and for macrolides in 2009 (22). Both types of "respiratory" fluoroquinolones, namely levofloxacin and moxifloxacin (53), have additional restrictions.

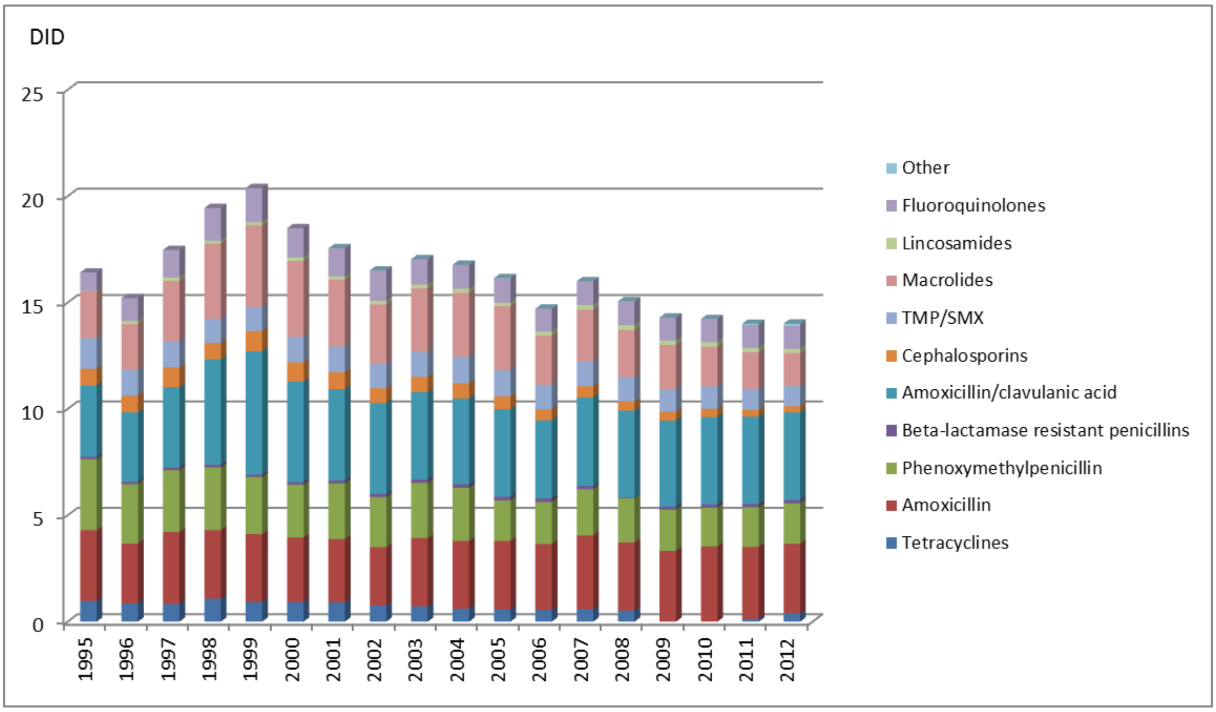
ZZZS has the authority to audit prescribing in accordance with the regulations and rules of the compulsory health insurance. A Health care provider may be fined in case its physician fails to observe the prescribing restrictions. If a prescription is not recognized by an auditor, the provider has to repay the total costs in question to ZZZS.

Results

Antibiotic utilisation

In the period from 1995 to 1999, there was a rapid increase in outpatient antibiotic utilisation (Figure 1), namely by 3.97 DID or 24% (from 16.41 DID to 20.38 DID). Since 2000, there has been a reduction in the utilisation of antibiotics (Figure 1), typically averaging 2 to 9 % per year. There were only two exceptions: in 2003 and 2007, the consumption increased by 3% and 9 %, respectively. Since no epidemics of influenza or acute respiratory tract infections were observed in these two years, this may just reflect fluctuations in the linear datasets. Antibiotic utilisation has stabilised at approximately 14 DIDs in recent years, i.e., between 2009 and 2012. From 1999 to 2012, antibiotic utilisation decreased by 31% (DID basis), following a 24 % increase in the preceding four years (1995 – 1999).

Figure 1. Antibiotic utilisation (ATC group J01) in defined daily doses per thousand inhabitants per day (DID) 1995 – 2012 in Slovenia



Within the time period 1999 to 2012, there were appreciable structural changes among the various antibiotic classes (Table 2). For example, the prescribing of cephalosporins was reduced by 77% (prescriptions) and 69% (DIDs), macrolides by 59% (both prescriptions and DIDs), tetracyclines by 78% (prescriptions) and 59% (DIDs), fluoroquinolones by 16% (prescriptions) and 34% (DIDs) and amoxicillin/ clavulanic acid by 31% (prescriptions) and 29% (DIDs). Amoxicillin utilisation has been stable since 1999. The fall in the utilisation of tetracyclines (e.g. doxycycline, others were not available) to zero in 2009 was a consequence of their disappearance from the market for more than a year. However, they were subsequently re-introduced leading to some use (Table 2). Among the "other" antibiotics (ATC J01X), nitrofurantoin was absent from the market for a number of years, but was re-introduced in 2010.

Table 2. Antibiotic utilisation in DIDs and in prescriptions/1000 inhabitants in 1999 and 2012 with corresponding indices.

Group	1999	2012	Index: (2012)/(1999) x 100	1999	2012	Index: (2012)/(1999) x 100
	Prescriptions/1000 inhabitants			**DIDs**		
Tetracyclines	22.55	4.95	22	0.92	0.37	41
Amoxicillin	118.52	111.36	94	3.19	3.29	103
Phenoxymethylpenicillin	91.78	70.23	77	2.68	1.90	71
Beta-lactamase resistant penicillins	8.65	6.38	74	0.12	0.16	139
Amoxicillin/clavulanic acid	193.19	132.77	69	5.80	4.11	71
Cephalosporins	49.37	11.24	23	0.96	0.30	31
TMP/SMX	60.72	49.90	82	1.14	0.94	82
Macrolides	183.63	75.88	41	3.82	1.56	41
Lincosamides	8.89	12.97	146	0.15	0.21	142
Fluoroquinolones	53.98	45.59	84	1.61	1.07	66
Other	0.00	4.69	/	0.00	0.11	
Sum	**791.29**	**525.97**	**66**	**20.38**	**14.01**	**69**

NB A score less than 100 represents a decrease

The results for the statistical analysis for periods 1995 – 1999 and 1999 – 2012 are presented in Tables 3 and 4, respectively. The first two columns in both tables show the consumption in DID for the first and the last year of the period under consideration. As mentioned, the column *Index* presents the relative change in consumption over the entire period. The column *Estimated slope* shows the best-fit estimate for the slope of the regression line. The column *Std. error* shows a measure of the difference between the actual consumption and the consumption predicted by the regression line. The R^2 value indicates how well a linear function models the dynamics of consumption. We can conclude that between 1995 to 1999, the overall antibiotic utilisation significantly increased and the utilisation of amoxicillin/clavulanic acid, macrolides, and fluoroquinolones also significantly increased. Between 1999 to 2012, utilisation of 7 out of 10 antibiotic classes significantly decreased. The only exceptions were amoxicillin and the lincosamides, whose utilisation significantly increased, and the beta-lactamase resistant penicillins, where the change was not statistically significant. The total utilisation of antibiotics also significantly decreased during this period (Tables 3 and 4, Figure 2).

Table 3. Linear regression analysis of the antibiotic utilisation in DIDs between 1995 and 1999

Group	1995	1999	Index: (1999)/(1995) x 100	Estimated slope	Std. error	R^2	p
Tetracyclines	0.96	0.92	96	0.014	0.035	0.05	0.71
Amoxicillin	3.34	3.19	96	0.011	0.082	< 0.01	0.90
Phenoxymethylpenicillin	3.33	2.68	81	-0.11	0.061	0.53	0.16
Beta-lactamase resistant penicillins	0.11	0.12	105	0.0020	0.0014	0.41	0.24
Amoxicillin/clavulanic acid	3.35	5.80	173	0.66	0.14	0.88	0.017
Cephalosporins	0.79	0.96	121	0.031	0.028	0.30	0.34
TMP/SMX	1.45	1.14	78	-0.073	0.024	0.76	0.054
Macrolides	2.20	3.82	174	0.46	0.076	0.93	0.0088
Lincosamides	0.02	0.15	734	0.025	0.016	0.46	0.21
Fluoroquinolones	0.86	1.61	187	0.20	0.016	0.98	0.0011
Other	**0.00**	**0.00**					
Total	**16.41**	**20.38**	**124**	**1.22**	**0.33**	**0.82**	**0.035**

Table 4. Linear regression analysis of antibiotic utilisation in DIDs between 1999 and 2012

Group	**1999**	**2012**	**Index: (2012)/(1999) x 100**	**Estimated slope**	**Std. error**	**R^2**	**p**
Tetracyclines	0.92	0.38	41	-0.066	0.010	0.78	< 0.0001
Amoxicillin	3.19	3.29	103	0.032	0.010	0.45	0.0090
Phenoxymethylpenicillin	2.68	1.90	71	-0.067	0.010	0.78	< 0.0001
Beta-lactamase resistant penicillins	0.12	0.16	139	0.0014	0.0024	0.026	0.58
Amoxicillin/clavulanic acid	5.80	4.11	71	-0.071	0.027	0.36	0.023
Cephalosporins	0.96	0.30	31	-0.050	0.0025	0.97	< 0.0001
TMP/SMX	1.14	0.94	82	-0.016	0.0040	0.58	0.0016
Macrolides	3.82	1.56	41	-0.16	0.012	0.94	< 0.0001
Lincosamides	0.15	0.21	142	0.0057	0.0010	0.72	0.00014
Fluoroquinolones	1.61	1.07	66	-0.034	0.0062	0.72	0.00013
Other	**0.00**	**0.11**					
Total	**20.38**	**14.01**	**69**	**-0.42**	**0.047**	**0.87**	**< 0.0001**

Figure 2: Total utilisation of antibiotics between 1995 and 2012 together with estimated regression lines.

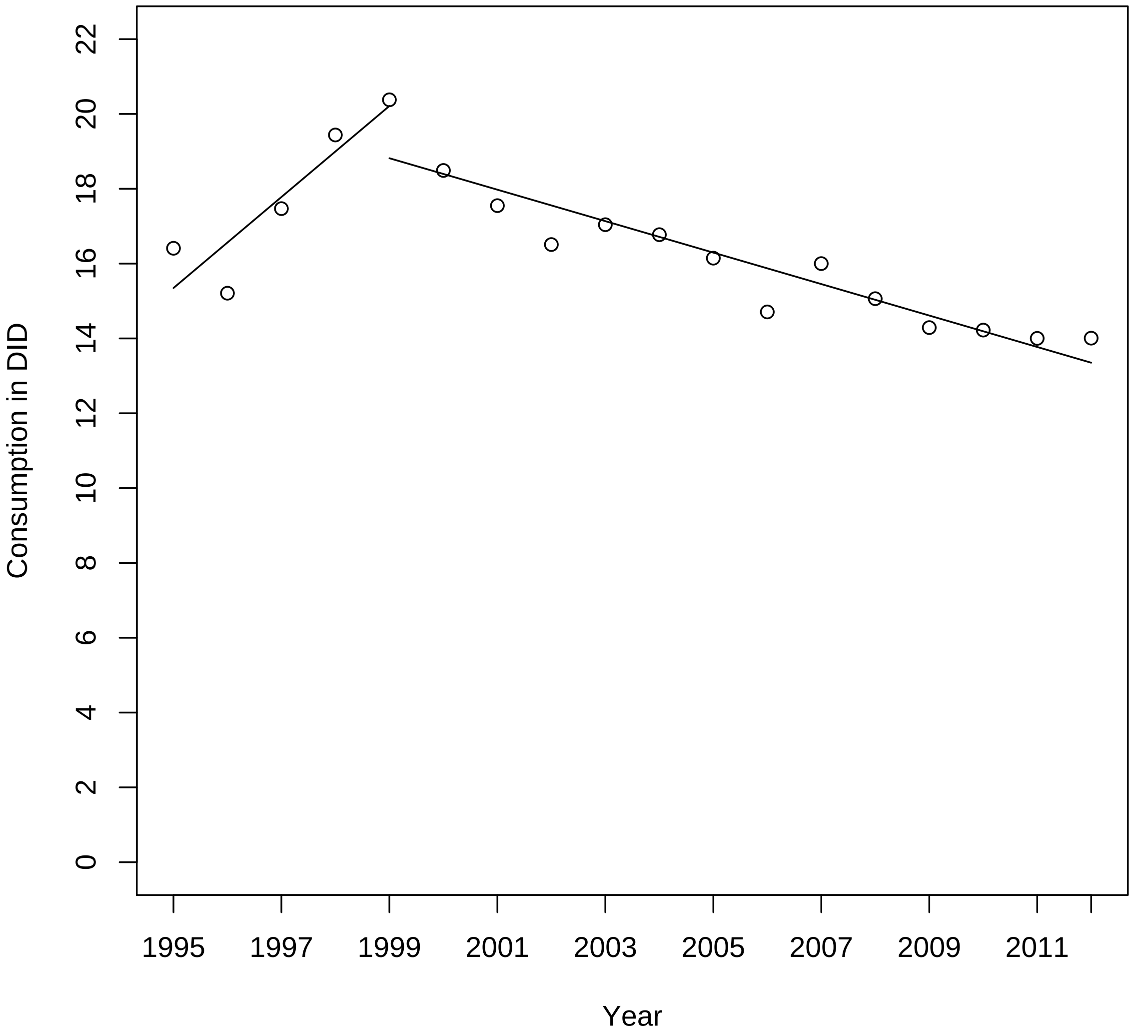


Figure 3 shows the consumption of restricted antibiotics between 1995 and 2012, with arrows indicating the year of the introduction of prescribing restrictions for individual antibiotics. Within the time period 1999 to 2012, the consumption of antibiotics with prescribing restrictions was reduced on average by 42%, and of non-restricted ones by 15% (Table 5, Figure 3). Individual classes where prescribing restrictions have been introduced are presented in Table 6.

Table 5. Consumption of restricted and non-restricted antibiotics in DID in 1999 and 2012 with the corresponding indices and linear regression analysis.

Antibiotics	1999	2012	Index: (2012)/(1999) x 100	Estimated slope	Std. error	R2	p
Restricted	12.19	7.03	58	-0.32	0.040	0.84	< 0.0001
Non-restricted	8.19	6.98	85	-0.11	0.020	0.70	0.00018

NB A score less than 100 represents a decrease

Figure 3. Utilisation of restricted antibiotics in DIDs 995 – 2012. Arrows denote the year of the introduction of the respective prescribing restrictions.

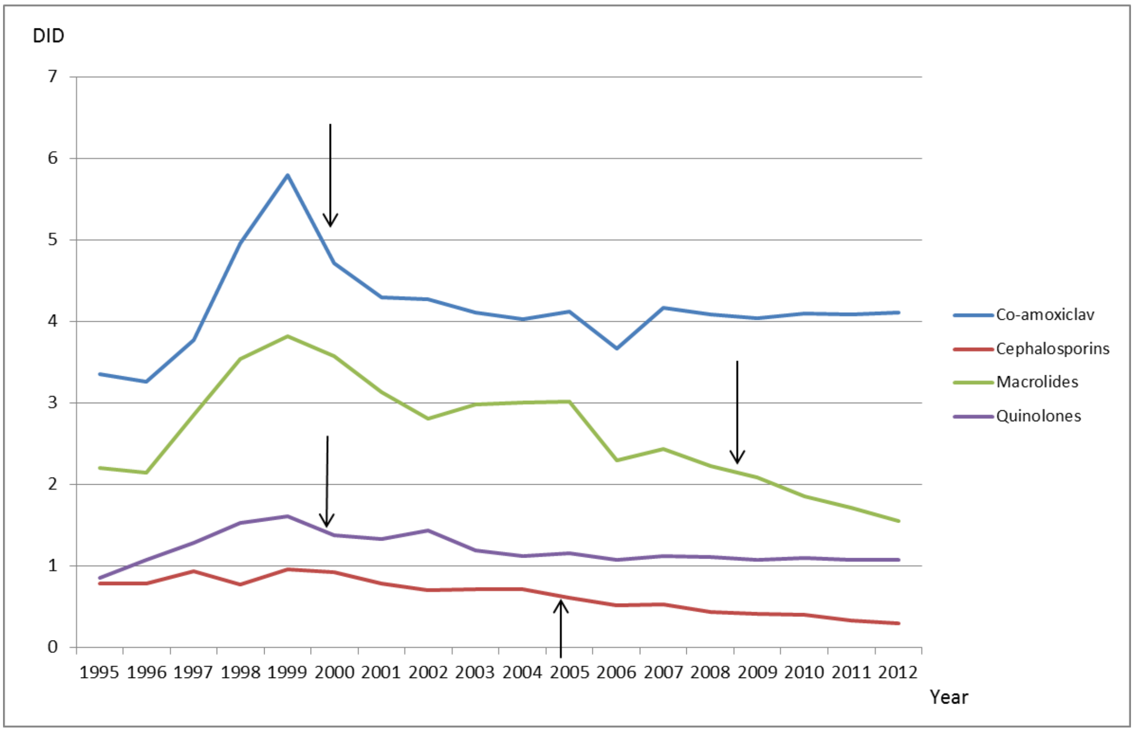


Table 6. Linear regression analysis of the consumption of individual restricted antibiotics with respect to the year of the introduction of the respective prescribing restrictions.

	YIR[1]	DID in YIR	DID in 2012	Index (2012)/(YIR) x 100	Estimated slope	Std. error	R^2	p
Amoxicillin/clavulanic acid	2000	4.71	4.11	87	-0.030	0.015	0.26	0.076
Cephalosporins	2005	0.61	0.30	49	-0.043	3.3×10^{-3}	0.97	1.2×10^{-5}
Macrolides	2009	2.08	1.56	75	-0.17	0.013	0.99	5.5×10^{-3}
Fluoroquinolones	2000	1.38	1.07	78	-0.027	5.3×10^{-3}	0.70	3.6×10^{-4}

[1]YIR: the year of the introduction of the respective prescribing restrictions

Antibiotic Resistance

Between 1999 and 2012, the penicillin resistance in invasive *Streptococcus pneumoniae* isolates decreased from 14.5 % to 10 %, i.e., by 31 %. The *S. pneumoniae* resistance to macrolides increased from 5.4 % to 21 %, an almost 4-fold increase. The peak was reached in 2011 with 24.3 % resistant isolates. The *Escherichia coli* resistance to fluoroquinolones continuously increased from 10 % to 21%, a twofold increase (59).

Economic considerations

Between 1999 and 2012, the overall costs of antibiotic prescriptions in Slovenia decreased by 53%, leading to cumulative savings of Euro 13.1 million in absolute terms. By contrast, the costs for all prescription drugs increased by 63 % in the same period. In 2001, 7.7 % of prescription drug expenditure was spent for antibiotics. In 2012, this figure dropped to just 2.6%. In 1999, amoxicillin/ clavulanic acid was second highest expenditure drug in the list of top-expenditure drugs in Slovenia in ambulatory care. In 2012, it dropped to 26th place, mostly due to the lower prices of amoxicillin/ clavulanic acid and the increasing utilisation of new higher-priced medicines.

Between 2004 and 2012, ZZZS spent Euro 325,000 on its various campaigns to encourage the rational and safe use of antibiotics through publications, posters and flyers (activities documented in Table 1). Before 2004, there were no ZZZS investments in this field. Investments of other institutions, mainly the Ministry of Health, are thought to be in the range of Euro500, 000 for the whole of the observation period.

Discussion

Between 1995 to 1999, there was a rapid and significant increase in total ambulatory care antibiotic utilisation (Table 3, Figure 1) by 3.97 DID. Since there appears to be no epidemiological explanation for this increase, which was due to the increased prescribing of amoxicillin/ clavulanic acid, macrolides and fluoroquinolones (Table 3), we believe that it can be explained by successful marketing activities to key stakeholder groups. However, we cannot say this with certainty.

The 1995 to 1999 increase was reversed following multiple demand-side activities initiated during the past 13 years (Tables 1, 2 and 4)resulting in a significant (31%) long-term reduction in antibiotic prescribing (Tables 2 and 4). Changes in prescribing may generally be seen as positive, with the exception of oral penicillins in terms of DIDs (Table 2). This may reflect a kind of "collateral damage" of "anti - antibiotics" activities. In addition, potentially either doses increased or the percentage of children as a percentage of all prescriptions for amoxicillin and beta-lactamase resistant penicillins decreased (54, 55).The consumption of non-restricted antibiotics also significantly decreased, although to a lesser degree than that of restricted antibiotics (Table 5). We believe this favourable result is strongly associated with our multifaceted approach among all key stakeholder groups, knowing how difficult it is to change the behaviour of key stakeholders through national projects (56, 57). All activities were based on the national guidelines for the treatment of infectious diseases. These activities were supported by medical societies and engaged medical professionals, members of national bodies at Ministry of Health and ZZZS' Committee for the reimbursement of medicines.

We believe it is impossible to point to anyone single measure as the one being the most influential given the plethora of interventions and initiatives undertaken (Table 1). However, we believe that prescribing restrictions and audits were probably the most influential measure, leading to a greater reduction in the utilisation of restricted antibiotics compared to non-restricted antibiotics (Table 5). The prescribing and utilisation of macrolides had been falling for 9 years (Figure 3, Table 2) before prescribing restrictions were introduced with activities to enhance the rational prescribing of all antibiotics (Table 1). However, the prescribing restrictions for the macrolides further limited their utilisation (Figure 2). We also believe that, in addition to the restrictions, clinically oriented education through symposia, workshops and focused meetings at the regional and local (primary health-care centre) level was crucial to encouraging more rational prescribing of antibiotics by interacting with all key stakeholder groups. National guidelines in the form of a practical booklet were used as an obligatory reference for education and audits during these interactions. We also believe that educational booklets for parents and flyers in physician offices and other locations were also beneficial in helping to reduce antibiotic prescribing. In the last 4 years (2009 – 2012), antibiotics utilisation has stabilized at 14.1+/-0.2 DID. Consequently, we believe that audits and intensification of all previous activities have reached their limits of effectiveness, and new activities are needed to further enhance the appropriate use of antibiotics. We believe that this new multifaceted approach, which involves local pharmacotherapeutic groups and emphasis on the quality of care, will be effective and will further enhance the quality of care. However, this approach has only been in operation for a short time, and it is still too early to analyse the results. Consequently, this will be the subject of further research activities.

As a result of these multifaceted initiatives, in 2011 Slovenia was among the 6 European countries out of 29 with the lowest consumption of antibiotics (58). This was a considerable improvement on the situation in 1999, when Slovenia was 11^{th} place out of 22 European countries.

The findings are similar to those seen in France with their national multiple interventions over a number of years (4). The initial reduction in the use of antibiotics of nearly 20% in during 1998-2002 was similar to the findings from the IMPAC3T study from Netherlands (20). However, the IMPAC3T study was not a national campaign instigated by health authorities aimed at all key stakeholder groups, unlike the campaigns in France and Slovenia.

The resistance data correlates with the changes of the consumption of antibiotics only for *Streptococci* and penicillins, where the decrease of resistance was greater than the decrease in utilisation (-31% vs -18%, respectively). In the case of *S. pneumoniae* resistance to macrolides, this increased fourfold despite a 59% decrease in their utilisation. Similarly, resistance of *E. coli* to fluoroquinolones increased twofold despite decreased utilisation (Tables 2 and 4). A possible reason for increasing *S. pneumoniae* resistance to macrolides is a relatively high consumption of long-acting azithromycin. In 2012, its consumption was 0.9 DID or 58% of all macrolides. The peak of this resistance was reached in 2011, and it seems that this negative trend has been converted. However, it is too early to make any firmer conclusions from our study and an in-depth analysis of resistance data is beyond the scope of this work.

Expenditure on antibiotics was appreciably reduced, i.e. by 54 % between 1999 to 2012, overall by an accumulated Euro13.1million. Alongside this, we estimate that only Euro825,000 was spent on advertising and campaigns since 2004. However, we acknowledge that the expenditure reduction has been assisted by a number of antibiotics losing their patent during the past decade, the reference pricing system in Slovenia and the general regulation of drug prices in Slovenia. Overall though, we believe that the Slovenian multi-faceted approach is both effective in reducing antibiotic consumption as well as appreciably cost-effective.

We acknowledge that the weakness of the surveillance system in ambulatory care in Slovenia is that the consumption of parenteral antibiotics in nursing homes and ambulatory care is not being monitored. However, according to the report of Lejko and colleagues, the national consumption of antibiotics in 2006 and 2007 in nursing homes was a maximum of 0.61 % of the total consumption of antibiotics for systemic use in ambulatory care in Slovenia (59). Consequently, we do not believe that including parenteral antibiotics in our analysis would have altered our findings. In addition, prescriptions paid for out of pocket represented only 1 – 2 % of prescriptions for antibiotics. We excluded them to improve the robustness of our data; however, again we do not believe excluding these prescriptions influenced our findings.

In conclusion, we believe that we have shown multiple demand-side measures during the past decade have been successful in not only stopping the increase in antibiotic utilisation seen at the end of the 1990s in Slovenia but also appreciably reducing it (by 31%). This confirms previous studies that multifaceted approaches are needed to positively influence the prescribing habits of physicians and that without these, there will be limited change in prescribing habits (41, 60, 61). We have also shown that the multifaceted approach in Slovenia has been cost-effective, with the cost of the various programmes appreciably outweighed by the savings. Additional intensive and localised approaches are now needed to reduce antibiotic resistance as well as further lower utilisation. We will report on these in due course. We believe that the findings will provide further guidance to other countries as they seek to further enhance their rational prescribing of antibiotics. This adds to the published knowledge base, some of which has already been described.

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Transparency

Jurij Fürst, Jana Mrak and Damjan Kos are employed by the Health Insurance Institute of Slovenia. Otherwise, the authors have no other relevant conflicts of interest to declare.

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