Improving antimicrobial prescription in primary care: a multi-dimensional approach to antimicrobial resistance

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Chapter 2

Trends in antibiotic selection pressure generated in primary care and their association with sentinel antibiotic resistance patterns in Europe

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Abstract

Objectives

We studied trends in antibiotic prescribing by primary care and assessed the associations between generated antibiotic selection pressure (ASP) and the prevalence of sentinel drug-resistant micro organisms (SDRMs).

Methods

The volume of antibiotic prescribing in primary and hospital care expressed in DDD/1000 inhabitants per day and the prevalences of SDRMs in European countries where GPs act as gatekeepers were obtained from the European Centre for Disease Control ESAC-NET. Associations were tested between (i) DDD and (ii) the Antibiotic Spectrum Index (ASI) as a proxy indicator for ASP, and the prevalences of three SDRMs: MRSA, MDR *Escherichia coli* and *Streptococcus pneumoniae* resistant to macrolides.

Results

Fourteen European countries were included. Italy, Poland and Spain had the highest prevalence of SDRMs and prescribed the highest volume of antibiotics in primary care (average 17 DDD per 1000 inhabitants per day), approximately twice that of countries with the lowest volumes. Moreover, the ASIs of these high antibiotic volume countries were approximately three times higher than those of the low-volume countries. Cumulative ASI showed the strongest association with a country's prevalence of SDRMs. The cumulative ASI generated from primary care was about four to five times higher than the cumulative ASI generated by hospital care.

Conclusions

Prevalences of SDRMs are associated with the volume of antimicrobial prescribing and in particular broad-spectrum antibiotics in European countries where GPs act as gatekeepers. The impact of ASP generated from primary care on increasing antimicrobial resistance may be much larger than currently assumed.

Introduction

Antimicrobial resistance (AMR) is increasing worldwide and represents a major threat to global healthcare (1). The major driver of the rise in AMR is the use of antibiotics (2). Worldwide, efforts are now being undertaken to decrease antibiotic prescribing and consequently reduce the rate of AMR development (1). Given that GPs are responsible for the majority of antibiotic prescriptions in a country, they potentially have an important role to play in reducing AMR (3). However, the extent to which antibiotic prescribing in primary care contributes to increasing AMR is still unclear (4). For varied reasons, not all GPs consider their antibiotic prescribing practices to be part of the process eventually leading to increasing AMR (5,6).

Part of the process leading to AMR is referred to as 'antibiotic selection pressure' (ASP), defined as the extent to which the use of antibiotics enhances the selective process increasing the growth of resistant microorganisms (7). According to the One Health concept, all antibiotic prescriptions contribute to ASP (8). The relative contribution to the ASP of an antibiotic most likely depends on the dosage, duration of use, and type and spectrum of an antibiotic.

The aim of this study was to inventory types and volumes of antibiotics prescribed by primary care practitioners in European countries where they act as gatekeepers. Importantly, this study investigates the correlation between a country's AMR and the overall level of antibiotic prescribing, and resultant antibiotic pressure, in that country. Testing associations between prescription data and the AMR levels in a country provides insight into the role primary care has compared with hospital care in increasing AMR.

Methods

In this study, we collected and analysed open source data on the volume of antibiotic prescriptions and on the prevalence of three drug-resistant micro organisms. The volume of antibiotic prescriptions was used to calculate ASP. The volume of antibiotic prescriptions and ASP were then correlated to the prevalence of a sentinel drug-resistant micro organism (SDRM).

The study was performed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidance for reporting observational studies (9), and the STROBE-AMS recommendations for reporting epidemiological studies of AMR and informing improvement in antimicrobial stewardship (S1) (10)

Country selection

We analysed data on antibiotic prescriptions from European countries because they collect and report their data in a standardized format through the European Centre for Disease Prevention and Control (ECDC) (11). For a country to be included in the study, GPs had to act as a 'gatekeeper' in the healthcare system, defined as a compulsory GP referral to access most types of specialist care except in case of emergency (S2) (12). These countries generally have lower levels of antibiotic prescriptions (13).

Data extraction

Antibiotic prescriptions

The volume of antibiotic prescriptions per country was extracted from the ECDC open source antimicrobial consumption database (ESAC-NET) on 15 March 2022 (11). The volumes were represented in DDD per 1000 inhabitants per day for the years 2011 through 2020. DDD is defined as the assumed average maintenance dose per day for a drug used for its main indication in adults (14). To translate absolute volumes of prescribed antibiotics to a value representing the ASP in a country, we calculate and present the Antibiotic Spectrum Index (ASI) as a proxy indicator for ASP (15). The ASI incorporates the volume of used antibiotics and their activity against micro organisms, expressing these through an index number representing the spectrum of micro organisms that are susceptible to that drug (S3a). The ASI assigns numerical values for an antibiotic that has activity against 1 or more of 13 categories of pathogens, with lower values indicating narrow-spectrum agents and higher values broader-spectrum agents.

The ECDC website does not provide data on individual antibiotics, instead providing information per Anatomical Therapeutic Chemical Classification System (ATC) fourth-level chemical subgroup. Antibiotics in a subgroup are effective against the same micro organisms and have an equal index number (15). Only antibiotics in ATC subgroups macrolides and quinolones have different index numbers. Hence, a mean ASI had to be calculated for these subgroups. For antibiotics lacking a reported ASI, one was calculated using the method proposed by Gerber et al. on the basis of their activity against microorganisms (15). In total, 13 antibiotics were not indexed in the ASI (S3b) and were indexed instead by our research group. The ATC subgroup J01RA, combinations of antibacterials, was excluded from the ASI analysis because it was not possible to calculate an average.

The cumulative ASI per ATC subgroup was calculated by multiplying the volume of antibiotic prescriptions in DDD per 1000 inhabitants by the ASI number for that

subgroup. The cumulative ASI (i.e. cumulative antibiotic spectrum index per 1000 inhabitants) in a country was calculated by adding up the ASIs of each subgroup. For each country, this was calculated for (i) primary care, (ii) hospital care and (iii) primary and hospital care combined (i.e. the combined cumulative ASI).

AMR of sentinel micro organisms

AMR surveillance systems can use a set of drug-resistant micro organisms rather than a complete overview of micro organisms to monitor trends in AMR (16). This approach was taken and three so-called SDRMs relevant for primary care were selected: *Staphylococcus aureus, Escherichia coli* and *Streptococcus pneumoniae* are often used to monitor AMR (16). MRSA was used because *S. aureus* is the leading cause of skin and soft tissue infections. From the order Enterobacterales, *E. coli* resistant to third-generation cephalosporins and fluoroquinolones and aminoglycosides was selected, because *E. coli* is the leading pathogen causing urinary tract infections. *S. pneumoniae* is the most common cause of community-acquired bacterial pneumonia and was considered resistant if non-susceptible to macrolides. We chose to select non-susceptibility to macrolides instead of resistance to penicillin. Macrolides are regularly second-choice antibiotics for the treatment of community-acquired pneumonia in primary care guidelines, making it a reserved antibiotic only used where other antibiotics are not effective or administrable (17).

Country-level prevalences of the three SDRMs were obtained from the ECDC open source database, Surveillance Atlas Antimicrobial resistance, on 2 March 2022 for the years 2011–2020 (11). The ECDC uses the EUCAST guidelines for detecting and reporting specific resistant micro organisms. Treatment of infections in primary care is most often empirical, and obtaining cultures is therefore not part of standard care and not always feasible due to practical reasons. Anticipating a lack of SDRM cultures available from primary care, we combined primary and hospital care data to characterize AMR in each country because, according to the One Health concept, all antibiotic prescriptions contribute to ASP and eventually to AMR (8).

Descriptive statistics were used to describe and compare antibiotic volumes between countries and periods, as well as the trends in the volume of antibiotic prescriptions, and the prevalences of SDRMs. The combined cumulative ASI and combined DDD were plotted against the prevalence of each SDRM per country for the year 2020, because it is the most recent year with available data. Univariate linear regression was used to calculate associations between (i) ASI and (ii) DDD and each SDRM prevalence.

Results

Statistical analysis

Fourteen European countries (Denmark, Estonia, Finland, Ireland, Italy, Latvia, Lithuania, The Netherlands, Norway, Poland, Slovenia, Spain, Sweden and the UK) were identified in which the GPs act as gatekeepers and from which data on antibiotic prescriptions and SDRMs could be obtained.

Volumes of antibiotic use in primary care and hospital care

The volume of antibiotic prescriptions in primary care decreased over the course of our observation period (2011–2020) in seven countries (Denmark, Finland, Italy, The Netherlands, Norway, Sweden and the UK—see Figure 1). Ireland, Italy, Poland and Spain had the highest volumes of antibiotic prescriptions in primary care in 2020, with DDDs between 16 and 17 per 1000 inhabitants per day. The volume of antibiotic prescriptions was in all countries at its lowest in the year 2020. The proportion of antibiotic prescriptions in hospital care compared with the total volume of antibiotic prescriptions ranged from a low of 7.4% in Poland to a high of 16.6% in Latvia.

Prevalence of resistant micro organisms

MDR *E. coli* was the SDRM with the lowest prevalence in most countries (Figure 2). The prevalence ranged from 1.2% (Norway) to 14.6% (Italy). The prevalence of MRSA was stable over the period 2011–2020 in most countries. Four countries (Ireland, Italy, Poland and Spain) had a prevalence above 10% for MRSA. The prevalence decreased over the observation period only in Ireland and the UK. Macrolide-resistant *S. pneumoniae* had the highest prevalence of the three SDRMs, with seven countries reporting a mean prevalence above 10% during the period 2011–2020.

Patterns of antimicrobial selection pressure

The cumulative primary care ASI in Italy and Spain was about three times higher than in the Netherlands and Sweden, whereas the volume of antibiotic prescribing in primary care in DDD was twice as high in Italy and Spain as The Netherlands and Sweden (Figure 3). Tetracyclines and penicillin were the largest contributors to the cumulative primary care ASI in all countries, respectively ranging from 3.6% (Italy) to 39.8% (Sweden) and from 22.9% (Norway) to 50.7% (Spain). Within the penicillin antibiotic group, penicillin combinations (ATC code J01CR) (e.g. amoxicillin/clavulanate) were the largest contributor to the cumulative primary care ASI in eight countries.

The contribution of primary care to the cumulative combined ASI (primary and hospital care) ranged from 80.4% (Finland) to 91.1% (Spain) (Figure 4).

Association of ASP and AMR in a country

The combined volumes of antibiotic prescribing in primary and hospital care, expressed both as DDD and the combined cumulative ASI, are shown plotted against the prevalence of the three SDRMs in Figure 5, and the standardized coefficients of association (beta) are presented in S4. The betas representing associations between SDRMs and combined cumulative ASI were all higher than those representing associations between SDRMs and combined total DDD.

Discussion

We studied the trends in volume of antibiotic prescribing in primary care, the prevalences of SDRMs, and the ASP using proxy indicators ASI and DDD in European countries where GPs act as gatekeepers. The volumes of antibiotic prescriptions in primary care and the prevalences of SDRMs varied significantly between countries. DDD and ASI were associated with SDRM prevalence. Primary care was a larger contributor to ASP than hospital care.

Total number of antibiotic prescriptions

We found a large variation in volume of antibiotic prescriptions between countries in primary care. This may be due to cultural effects on the prescription of antibiotics. Borg and Camilleri showed a high association between a high degree of uncertainty avoidance and the prescribing of more broad-spectrum antibiotics (18), and Fletcher-Lartey et al. showed uncertainty avoidance to be associated with inappropriate antibiotic prescribing (5). Italy, Poland and Spain had high uncertainty avoidance scores (19). In 2020, the volume of antibiotic prescriptions in primary care was lower in all countries than in preceding years. This is likely due to the trend of decreasing antibiotic prescriptions and the severe acute respiratory syndrome coronavirus-2 pandemic. During the pandemic, there were fewer non-coronaviral disease respiratory tract infections (20), leading subsequently to fewer antibiotic prescriptions.

SDRMs

The percentage of invasive isolates with MRSA declined in both Ireland and the UK between 2011 and 2020. The decline in Ireland and the UK is likely a result of the introduction of guidelines on the prevention and control of MRSA in 2007 and of multiple interventions including hygiene protocols and mandatory reporting of MRSA, respectively (21,22).

For all three SDRMs, Italy, Poland and Spain have the highest prevalences among the countries in our study. These three countries also have a higher volume of antibiotic prescribing as expressed in DDD, and a higher ASP as represented by ASI. The higher prevalence of an SDRM is a likely consequence of the high volume of antibiotic prescribing and will lead to prescribing of more broad-spectrum antibiotics. Physicians often assume drug-resistant micro organisms are at play when treating bacterial infections in locations where drug-resistant micro organisms are known to be an issue. This encourages prescribing broad-spectrum antibiotics, often supported by guidelines advising this course. The resulting evolutionary pressure on the microbiome leads to increased selection of antimicrobial resistance. This vicious circle of prescribing more and broader spectrum antibiotics can lead to a point of no return when few antibiotics suitable for empirical use remain.

Proxy indicators of ASP

The levels of DDD and ASI varied between countries. Primary care practitioners in Italy and Spain prescribed twice the volume of antibiotics compared with their colleagues in Denmark, The Netherlands and Sweden, but the cumulative ASI was three times higher in Italy and Spain. Furthermore, the DDD in Spain and Italy was comparable to those of Ireland and Poland for the year 2020, whereas the ASI in 2020 was 1.5 times higher in Spain and Italy. These differences may be largely explained by the very high number of prescriptions for penicillin combinations and quinolones in Italy and Spain in primary care. Both groups are broad-spectrum antibiotics and have high ASIs of 6 and 8, respectively.

The cumulative ASI seems to correlate better with the prevalence of a SDRM than does total antibiotic consumption expressed in DDD, as illustrated by data from Ireland and Italy. The DDD of Italy was only slightly higher than that of Ireland, but the prevalence of the selected SDRMs in Italy was significantly higher (Figure 2). Further, the ASI in Italy was much higher than that of Ireland and more strongly correlated with the prevalence of an SDRM (Figure 5 and S4). MRSA and *S. pneumoniae* showed the strongest associations with ASI, with standardized coefficients of 0.94 and 0.91,

respectively. Particularly relevant for primary care is the strong association with *S. pneumoniae* because this is a very common cause of respiratory tract infections in primary care, even more so than skin infections caused by *S. aureus* (23).

Comparison with existing literature

Although ASI has been examined in institutes such as hospitals and nursing homes (24–30), we found no studies exploring this at a national level. The studies who examined ASI in hospitals and nursing homes showed that ASI gives additional insight into antibiotic prescribing patterns compared with other proxy indicators such as DDD or days of therapy, and may be useful for internal and external comparisons of institutions (24,28,29). Monitoring antibiotic consumption combined with surveillance of resistant micro organisms is advised as part of the One Health strategy (31). Most healthcare systems still use DDD as the only measure to represent the volume of antibiotic use.

Strengths and limitations

A strength of our study is using absolute volumes of antibiotic prescriptions in primary and hospital care when calculating the proxy indicator cumulative ASI. The proxy indicator is in this way a better representation of the ASP in a country than, for example, weighted mean volumes. The applied method of calculating the ASP is relatively simple, which makes it easily implemented in almost every country or region as a proxy indicator.

A limitation of this study is that some of the prescribed antibiotics may not be directly related to increasing resistance found in a specific SDRM. However, exposure to antibiotics in general is sufficient to generate community-acquired resistant infections in members of the same community. Further, the cumulative ASI is a proxy indicator representing the level of implementation of antimicrobial stewardship and the prevalence of already existing AMR in a country. The ratio between antimicrobial stewardship and already existing AMR contributing to ASI is not deducible from our study.

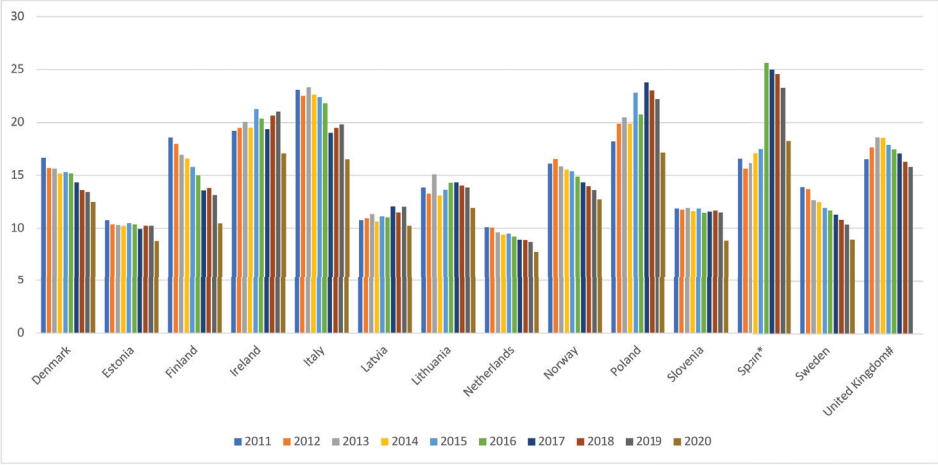
We used only three specific SDRMs in our study. Although using other SDRMs may lead to slightly different results, the expected trend would be similar. Because only European countries in which GPs act as gatekeepers were included in this study, the results may be less generalizable to countries with differently organized healthcare systems.

Conclusions

We found substantial variation in both the volume of antibiotic prescriptions in primary care and the prevalence of SDRMs between countries. There is, however, a clear association between the volume of antibiotic prescribing and the prevalence of SDRMs. Approximately 90% of the ASP expressed in the ASI originated from primary care, which is even more associated with the prevalence of SDRMs, compared with the volume of antibiotic prescribing. This emphasizes that the role of primary care in the development of AMR may be much larger than previously assumed by some GPs. This is an important insight, because some GPs may believe that antibiotic prescribing in their practice does not contribute to the development of AMR, but that instead AMR is driven by antibiotic prescriptions in hospitals or those used in veterinary care. The societal and medical impacts of this phenomenon warrant further investigation into mechanisms for improvement and implementation of antibiotic stewardship in primary care.

Figures

Figure 1. Volume of antibiotic prescription in Defined Daily Doses per 1000 inhabitans per day from primary care



*Spain saw a strong ostensible increase in prescription from 2016 onwards. However, this was due to the reporting of only reimbursement data until 2015, whereas figures from 2016 on were based on sales data (11)

#Data from primary care in the United Kingdom for the year 2020 was missing in the open source database of the ECDC.

Figure 2

Figure 2a. Meticillin-resistant *Staphyloccocus aureus*: percentage resistant isloates

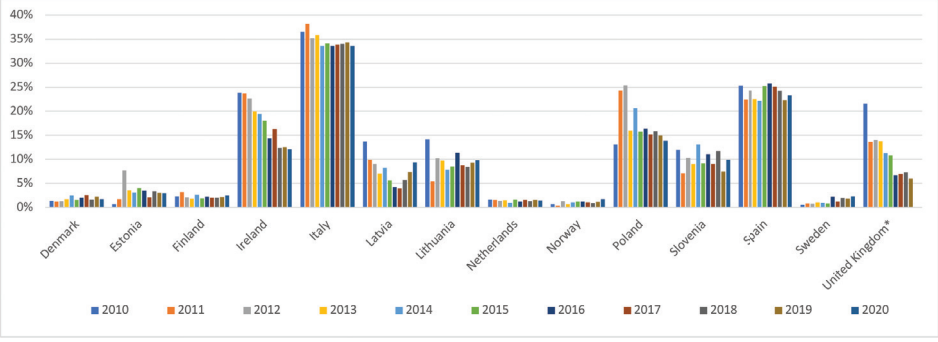


Figure 2b. *E.coli*, multidrugresistant*, percentage resistant isloates

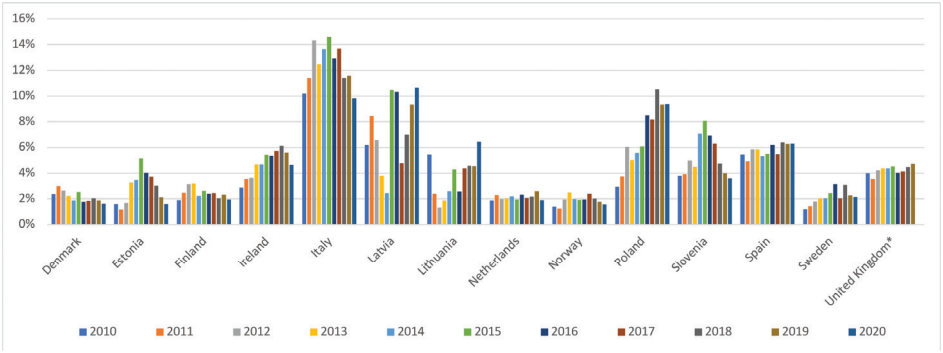
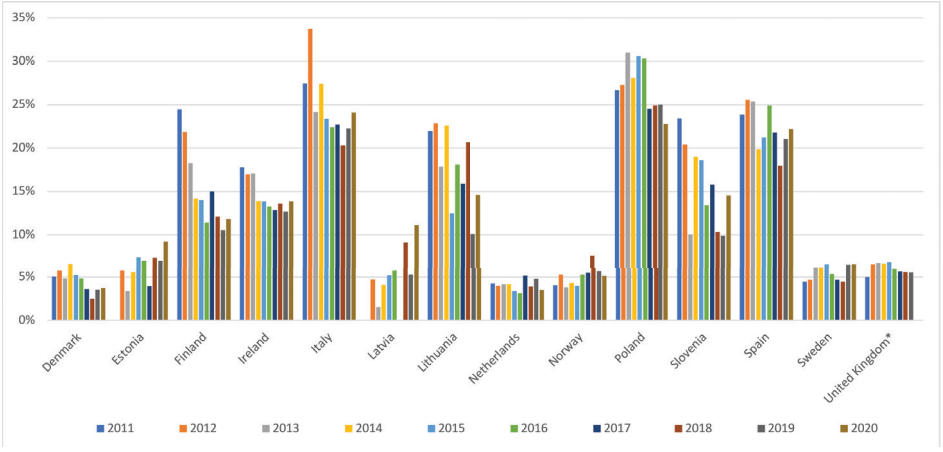
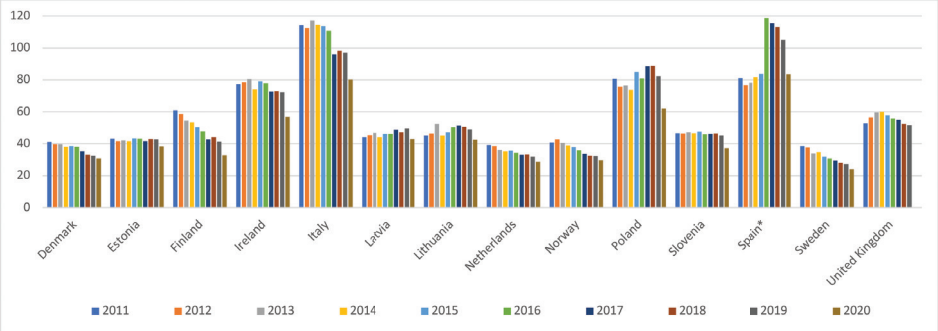


Figure 2c. *S.pneumoniae* non-susceptible to macrolides, percentage resistant isolates



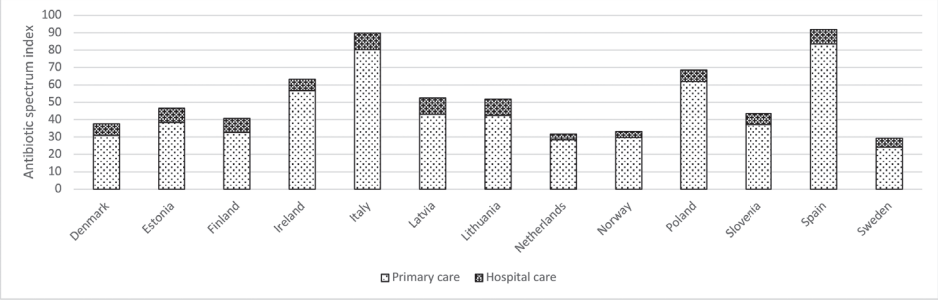
*Data from primary care in the United Kingdom for the year 2020 was missing in the open source database of the ECDC.

Figure 3. Antibiotic spectrum index for primary care



*Spain saw a strong ostensible increase in prescription from 2016 onwards. However, this was due to the reporting of only reimbursement data until 2015, whereas figures from 2016 on were based on sales data (11).

Figure 4. Antibiotic Spectrum Index for primary care and hospital care for the year 2020



*United Kingdom is not included due to missing data on the year 2020.

Figure 5. Antibiotic Spectrum Index and Daily Defined Doses plotted against prevalence Sentinel Multidrug Resistant Microorganisms

Figure 5a. Combined cumulative Antibiotic Spectrum Index plotted against prevalence Methicillin Resistant *S. Aureus* in 2020

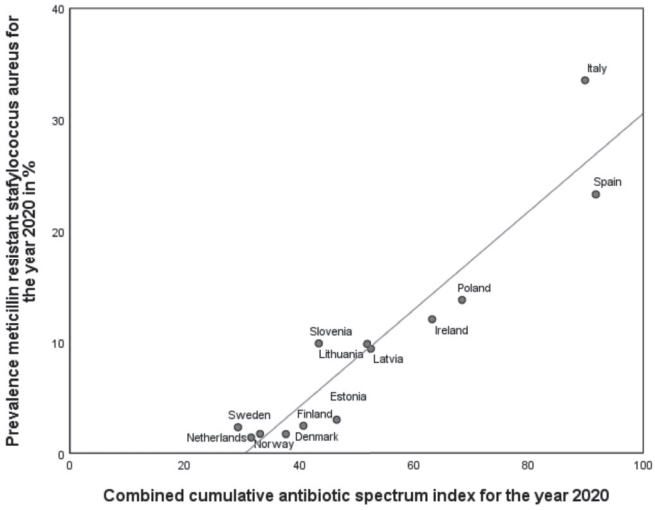


Figure 5b. Combined cumulative Antibiotic Spectrum Index plotted against prevalence *E. coli* in 2020

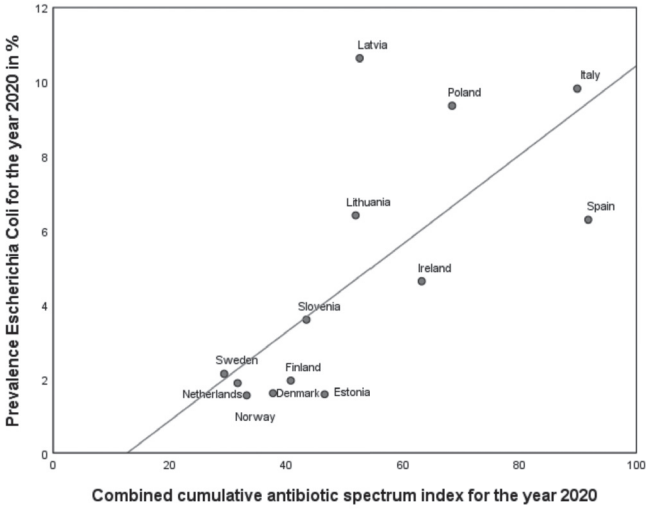


Figure 5c. Combined cumulative Antibiotic Spectrum Index plotted against prevalence *S. pneumoniae* in 2020

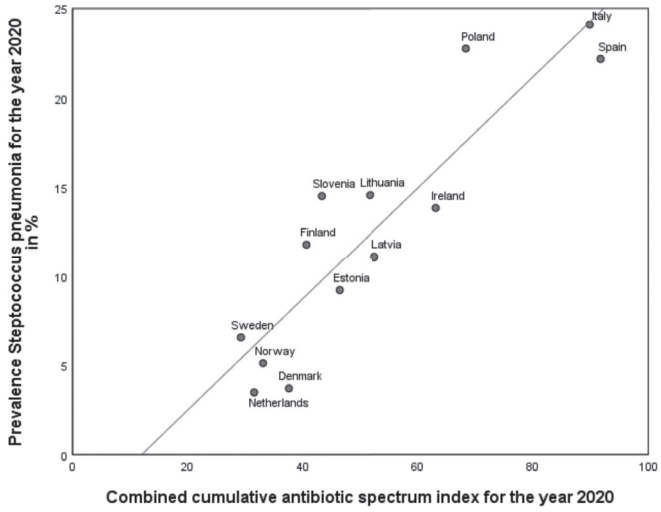


Figure 5d. Combined cumulative Daily Defined Doses plotted against prevalence MRSA in 2020

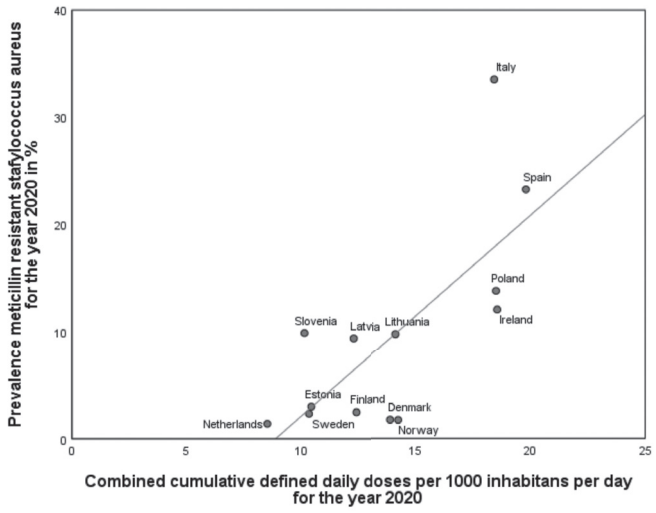


Figure 5e. Combined cumulative Daily Defined Doses plotted against prevalence *E. coli* in 2020

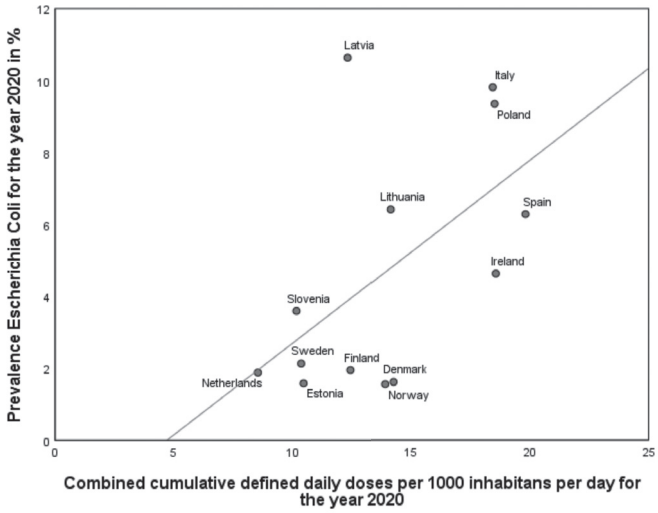
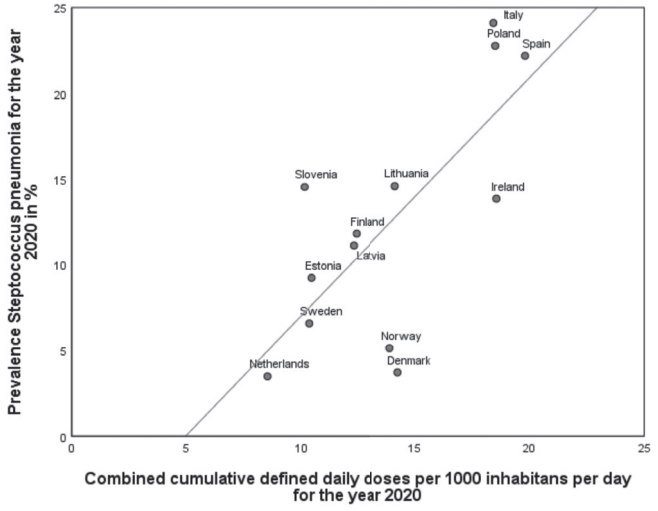


Figure 5f. Combined cumulative Daily Defined Doses plotted against prevalence *S. pneumoniae* in 2020.



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Supplements

Supplement 1. STROBE-AMS checklist

Item	Item number	STROBE recommendation	Pag	STROBE-AMS new items	Pag
Introduction					
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes	2.1 Report previous clinical in vivo and in vitro studies	4
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes		4
Methods					
Setting	5	Describe the setting, locations, relevant dates, including periods of recruitment, exposure, follow-up and data collection		5.1 Describe if setting is epidemic or endemic (high, low, medium) for the study outcome 5.2 Specify type of hospital or unit and characteristics of population served by the healthcare setting 5.3 Describe antimicrobial formulary in use at the study location related to the analysed antibiotics 5.4 Describe infection control measures dedicated to the target resistant bacteria applied at the study location	5
Participants	6	(a) *Cohort study*—Give the eligibility criteria, the sources and methods of selection of participants. Describe methods of follow-up *Case–control study*—Give the eligibility criteria, the sources, methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, the sources and methods of selection of participants (b) *Cohort study*—For matched studies, give matching criteria, the number of exposed and unexposed *Case–control study*—For matched studies, give matching criteria and the number of controls per case		6.1 Define unit analysed (person, department or other) 6.2 Provide reasons (epidemiological and clinical) for choosing matching criteria	NA NA

Item	Item number	STROBE recommendation	Pag	STROBE-AMS new items	Pag
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders and effect modifiers. Give diagnostic criteria, if applicable		7.1 Specify antimicrobial usage according to: type, dosage, duration and route of administration 7.2 Provide information using defined daily dosages (DDDs) and, in addition, other definitions closer to local reality (packages, prescriptions). Provide justification for the measurement presented 7.3 Address antimicrobial combinations 7.4 Explain rationale for grouping of antimicrobials 7.5 Define time at risk for antimicrobial exposure and for resistance development 7.6 Include description of potential confounders (other than epidemiological variables) 7.7 Provide definition of resistance, multidrug resistance, including pattern of co-resistance; whether studies performed to identify location or resistance eg, plasmid, chromosome, integrin, transposon 7.8 Definition of infection and/or colonisation. If not a validated reference, provide evidence of robustness of the new definition	5-7
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		8.1 Describe how antimicrobial consumption data were obtained (pharmacy, patients' charts, etc) and if it was actually used or purchased/dispensed	5-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why		11.1 Provide subgroup analyses for immunocompromised, surgical/ medical patients and patients in intensive care units, if applicable	5-7
Results					
Descriptive data	14	(a) Give characteristics of study participants (eg, demographic, clinical, social) and information on exposures and potential confounders		14.1 Specify among the exposure: previous stay in long-term care facilities, nursing home and other healthcare settings	8-9

Item	Item number	STROBE recommendation	Pag	STROBE-AMS new items	Pag
		(b) Indicate number of participants with missing data for each variable of interest			NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)			NA
Other analyses	17	Report other analyses performed—eg, analyses of subgroups and interactions, and sensitivity analyses		17.1 Report subgroup analysis by type of patients and type of microorganism, if applicable	9
Discussion					
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		19.1 Provide description of sources of selection bias, including infection control measures, audit and confounding	11
Generalis-ability	21	Discuss the generalisability (external validity) of the study results		21.1 Discuss study setting, type of hospital, local epidemiology for the generalisability	11-12
Other information					
Funding	22	Give the source of funding, the role of the funders for the present study and, if applicable, for the original study on which the present article is based			13

Bold typeface indicates main variables included in the STROBE tool.
STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; STROBE-AMS, STROBE for antimicrobial stewardship.
NA: Not applicable

Supplement 2: List of countries with a health care system where the general practitioner act as s gatekeeper

Gatekeeper is defined as a compulsory GP referral to access most types of specialist care except in case of emergency (1).

- Australia
- Canada
- Chile
- Costa Rica
- Denmark
- Estonia
- Finland
- Ireland
- Italy
- Latvia
- Lithuania
- Netherlands
- New Zealand
- Norway
- Poland
- Slovenia
- Spain
- Sweden
- United Kingdom

1. Organisation for Economic Co-operation and Development (OECD): OECD Health System characteristics Survey [Available from: http://www.oecd.org/.

Supplement 3a. List of antibiotics in Antibiotic Spectrum Index

Antibiotic	Antibiotic Spectrum Index	ATC code
Amikacin sulfate	6	J01GB
Amoxicillin	2	J01CA
Amoxicillin-clavulanate	6	J01CR
Ampicillin	2	J01CA
Ampicillin-sulbactam	6	J01CR
Azithromycin	4	J01FA
Aztreonam	3	J01DF
Cefazolin	3	J01DB
Cefdinir	3	J01DD
Cefepime	6	J01DE
Cefixime	3	J01DD
Cefotaxime	5	J01DD
Cefoxitin	5	J01DC
Cefpodoxime	3	J01DD
Cefprozil	4	J01DC
Ceftaroline	8	J01DI
Ceftazidime	4	J01DD
Ceftriaxone	5	J01DD
Cefuroxime	4	J01DC
Cephalexin	2	J01DB
Chloramphenicol	4	J01BA
Ciprofloxacin	8	J01MA
Clarithromycin	4	J01FA
Clindamycin	4	J01FF
Colistimethate	5	J01XB
Daptomycin	5	J01XX
Dicloxacillin	1	J01CF
Doxycycline	5	J01AA
Ertapenem	9	J01DH
Erythromycin	2	J01FA
Gentamicin	5	J01GB
Imipenem-cilastatin	11	J01DH
Levofloxacin	9	J01MA
Linezolid	6	J01XX
Meropenem	10	J01DH
Metronidazole	2	J01XD
Minocycline	5	J01AA
Moxifloxacin	10	J01MA
Oxacillin	1	J01CF

Antibiotic	Antibiotic Spectrum Index	ATC code
Piperacillin	4	J01CA
Piperacillin-tazobactam	8	J01CR
Rifampin	3	J04AB
Telavancin	5	J01XA
Ticarcillin-clavulanate	6	J01CR
Tigecycline	13	J01AA
Tobramycin	5	J01GB
Trimethoprimsulfamethoxazole	4	J01EE
Vancomycin	5	J01XA

Supplement 3b. Missing antibiotic in antibiotic spectrum index.

Antibiotic	Antibiotic Spectrum Index	ATC code
Amphenicols*	4	J01BA
Beta-lactamase inhibitors*	6	J01CG
Flucloxacillin*	1	J01CF
Fosfomycin*	1	J01XX
Macrolides**	3.5	J01FA
Nitrofurantoin*	1	J01XE
Norfloxacin*	8	J01MA
Other quinolones	8	J01MB
Quinolones**	8.5	J01MA
Streptogramins*	5	J01FG
Streptomycins*	5	J01GA
Tetracyclines*	5	J01AA
Trimethoprim*	1	J01EA

* In incidental cases that was no index number in the ASI for an antibiotic, an index number was calculated based on activity against micro organisms. If this was not possible, the antibiotic(group) was excluded from the analysis.
** Average ASI had to be calculated for the ATC subgroups macrolides and quinolones, as the different antibiotics within these ATC subgroups showed different ASIs. For each subgroup, the ASI was calculated based on a weighted average level of antibiotic prescriptions.

Supplement 4. Slope coefficients of plotting antibiotic spectrum index and volume of antibiotic prescriptions against sentinel multidrug resistant microorganisms

	Combined cumulative ASI in 2020		Combined total DDD / 1000 inhabitants per day in 2020	
	Slope coefficient (Beta)	p-value*	Slope coefficient (Beta)	p-value*
MRSA	0.94	<0.001	0.73	0.004
E. Coli	0.72	0.006	0.56	0.047
S. Pneumoniae	0.91	<0.001	0.74	0.004

* A p-value less than 0.05 was considered clinically significant.

MRSA: Methicillin resistant *S. Aureus*