



Universiteit
Leiden
The Netherlands

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

Sijbom, M.; Buchner, F.L.; Saadah, N.H.; Numans, M.E.; Boer, M.G.J. de

Citation

Sijbom, M., Buchner, F. L., Saadah, N. H., Numans, M. E., & Boer, M. G. J. de. (2023). Trends in antibiotic selection pressure generated in primary care and their association with sentinel antimicrobial resistance patterns in Europe. *Journal Of Antimicrobial Chemotherapy*, 78(5), 1245-1252. doi:10.1093/jac/dkad082


Version: Publisher's Version

License: [Creative Commons CC BY-NC 4.0 license](https://creativecommons.org/licenses/by-nc/4.0/)

Downloaded from: <https://hdl.handle.net/1887/3618698>

Note: To cite this publication please use the final published version (if applicable).

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

Martijn Sijbom ^{1*}, Frederike L. Büchner¹, Nicholas H. Saadah¹, Mattijs E. Numans¹ and Mark G.J. De Boer^{2,3}

¹Health Campus, The Hague/Department of Public Health and Primary Care, Leiden University Medical Center, The Hague, The Netherlands; ²Department of Infectious Diseases, Leiden University Medical Center, The Hague, The Netherlands; ³Department of Clinical Epidemiology, Leiden University Medical Center, The Hague, The Netherlands

*Corresponding author. E-mail: m.sijbom@lumc.nl

Received 19 September 2022; accepted 6 March 2023

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 microorganisms (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 inventorize 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 microorganisms. 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 microorganism (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, available as [Supplementary data](#) at JAC Online).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 microorganisms, expressing these through an index number representing the spectrum of microorganisms 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 microorganisms 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.*¹⁵ on the basis of their activity against microorganisms. 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 microorganisms

AMR surveillance systems can use a set of drug-resistant microorganisms rather than a complete overview of microorganisms 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 microorganisms. 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

Statistical analysis

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

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

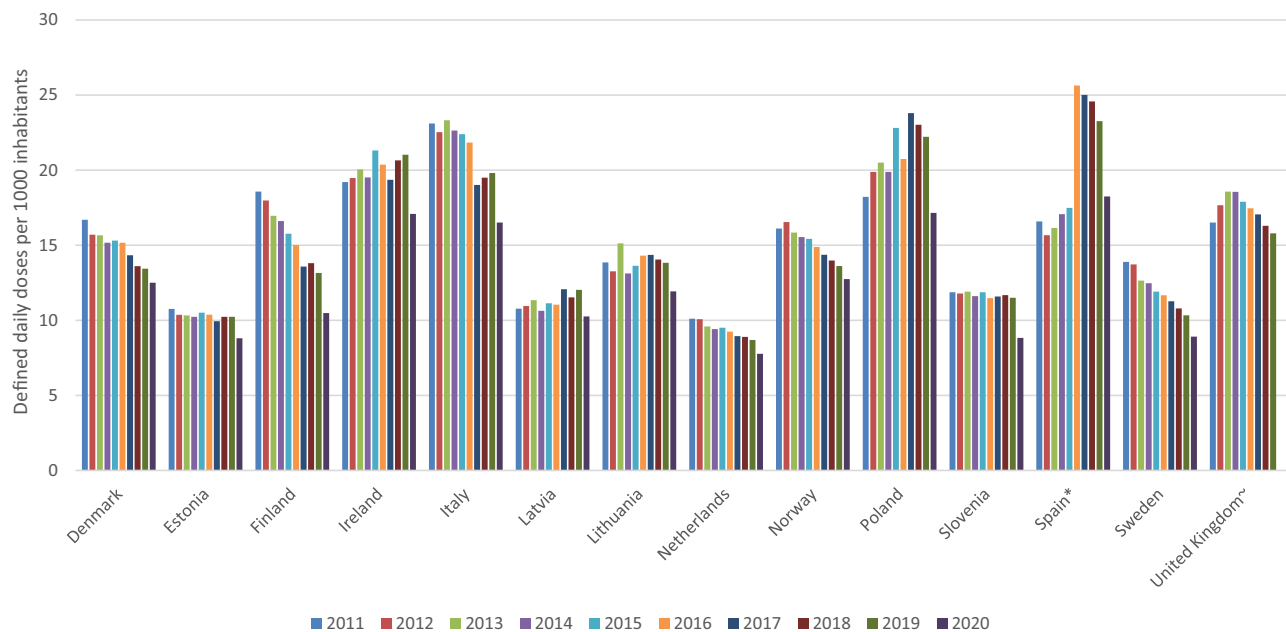


Figure 1. Volume of antibiotic prescriptions in defined daily doses per 1000 inhabitants per day from primary care. *Spain had an increase in prescription from 2016 onwards. This was due to the reporting of only reimbursement data until 2015, whereas figures from 2016 on were based on sales data.¹¹ ~Data from primary care in the UK for the year 2020 were not available in the open source database of the ECDC.

volume of antibiotic prescriptions ranged from a low of 7.4% in Poland to a high of 16.6% in Latvia.

Prevalence of resistant microorganisms

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 Camilleri¹⁸ showed a high association between a high degree of uncertainty avoidance and the prescribing of more broad-spectrum antibiotics, and Fletcher-Lartey *et al.*⁵ showed uncertainty avoidance to be associated with inappropriate antibiotic prescribing. Italy, Poland and Spain had high uncertainty avoidance scores.¹⁹ In 2020, the volume of antibiotic prescriptions in primary care was

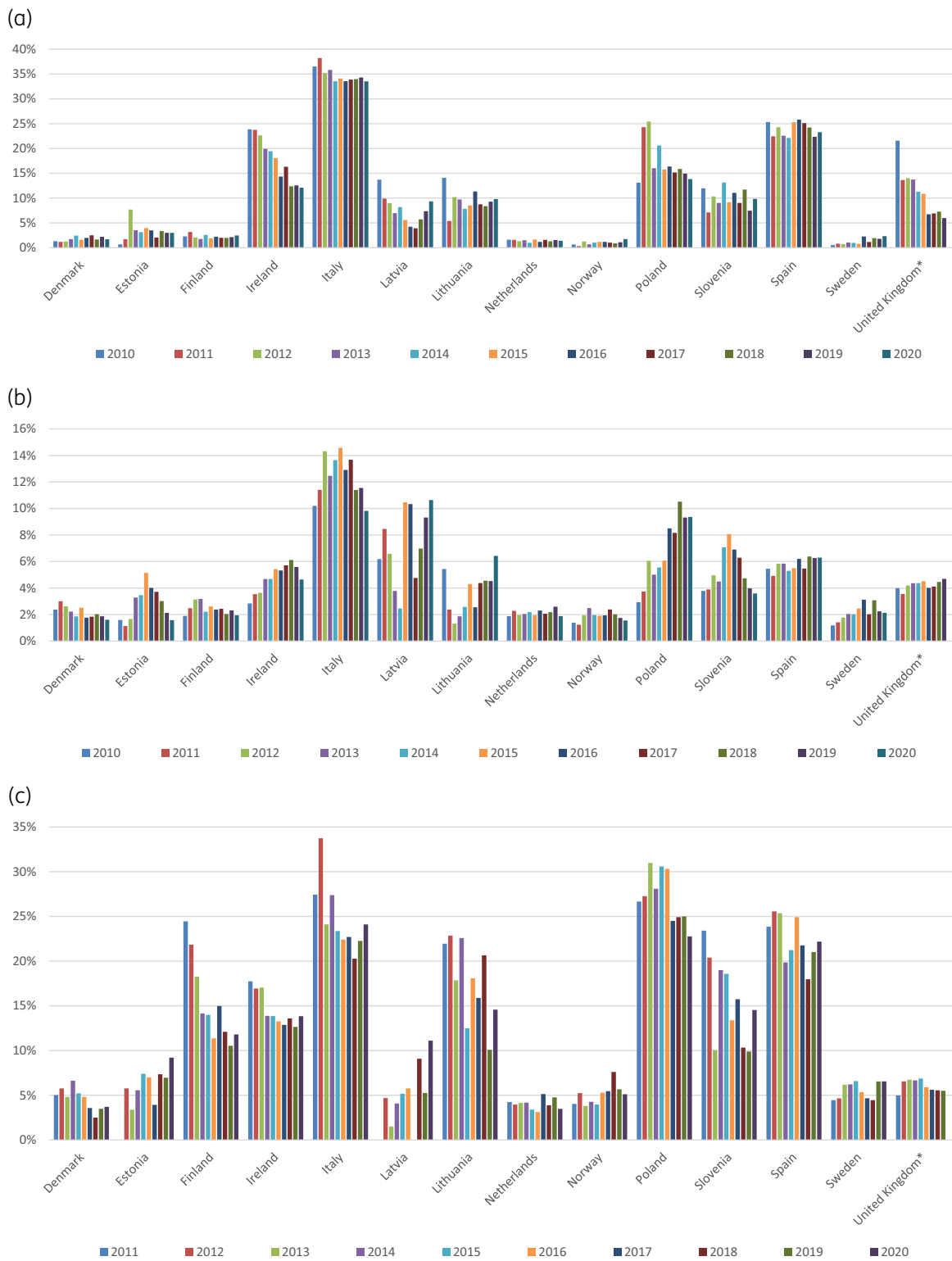


Figure 2. (a) MRSA, percentage resistant isolates. (b) MDR *E. coli*, percentage resistant isolates. (c) *S. pneumoniae* non-susceptible to macrolides, percentage resistant isolates. *Data from primary care in the UK for the year 2020 were not available in the open source database of the ECDC. MDR *E. coli* is resistant to third-generation cephalosporins and fluoroquinolones and aminoglycosides.

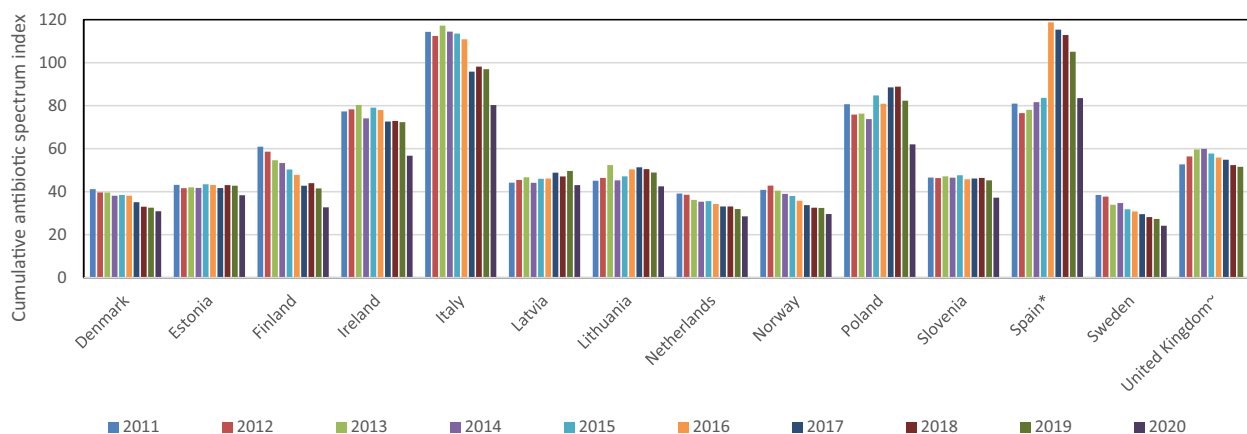


Figure 3. Cumulative antibiotic spectrum index for primary care. *Spain had an increase in prescription from 2016 onwards. This was due to the reporting of only reimbursement data until 2015, whereas figures from 2016 on were based on sales data.¹¹ ~Data from primary care in the UK for the year 2020 were not available in the open source database of the ECDC.

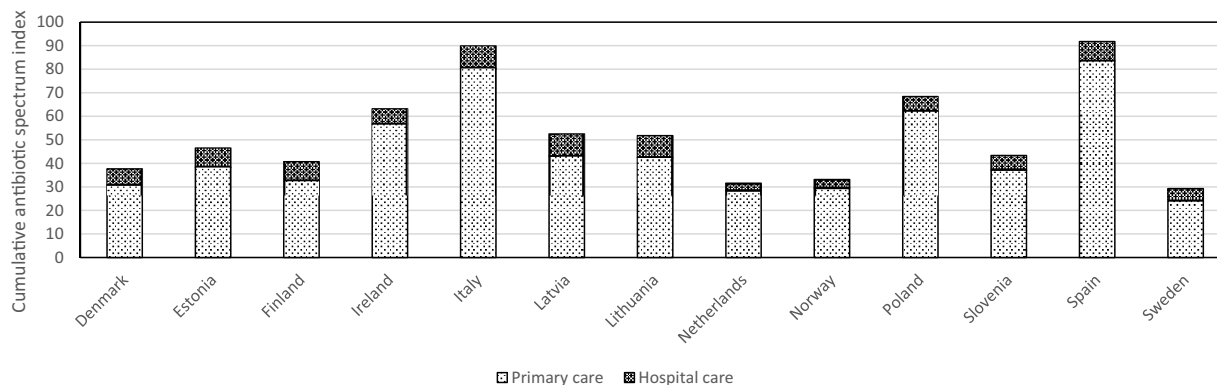


Figure 4. Antibiotic spectrum index for primary care and hospital care for the year 2020. The UK is not included due to missing data for the year 2020.

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 microorganisms are at play when treating bacterial infections in locations where drug-resistant microorganisms 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

Downloaded from https://academic.oup.com/jac/article/78/5/1245/7099685 by Jacob Heeren user on 02 June 2023

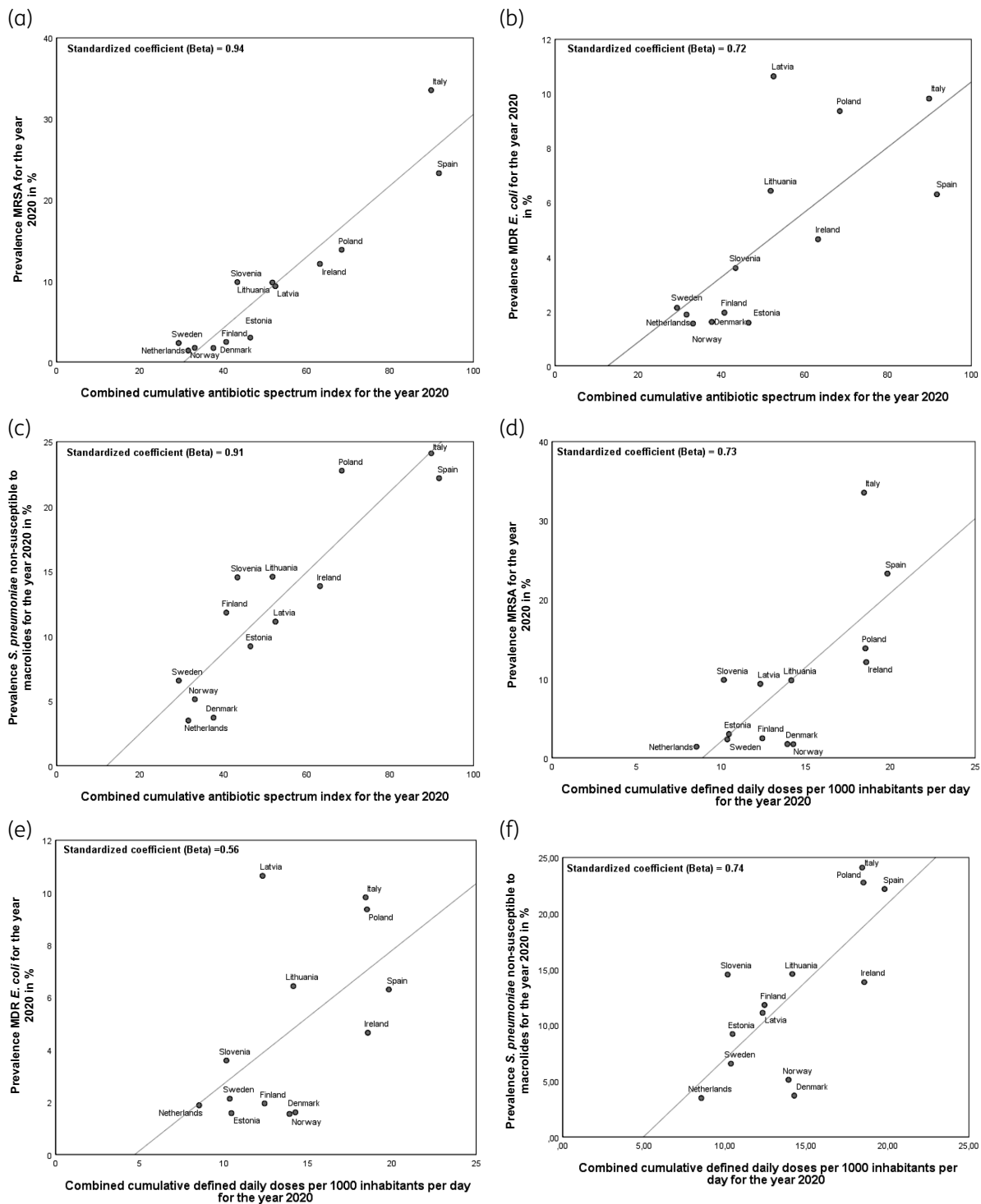


Figure 5. Antibiotic spectrum index and DDDs plotted against prevalence sentinel MDR microorganisms. (a) Combined cumulative antibiotic spectrum index plotted against prevalence of MRSA in 2020. The UK is not included due to missing data for the year 2020. Combined cumulative antibiotic spectrum index is primary and hospital care combined. (b) Combined cumulative antibiotic spectrum index plotted against prevalence of MDR *E. coli* in 2020. (c) Combined cumulative antibiotic spectrum index plotted against prevalence of *S. pneumoniae* non-susceptible to macrolides in 2020. (d) Combined cumulative DDDs plotted against prevalence of MRSA in 2020. (e) Combined cumulative DDDs plotted against prevalence of MDR *E. coli* in 2020. (f) Combined cumulative DDDs plotted against prevalence of *S. pneumoniae* non-susceptible to macrolides in 2020. Source: European Centre for Disease Prevention and Control: Antimicrobial consumption dashboard (ESAC-Net). <https://www.ecdc.europa.eu/en/antimicrobial-consumption/surveillance-and-disease-data/database>.

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 an 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 microorganisms 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.

Acknowledgements

The datasets were derived from the following public domain resources: European Centre for Disease Prevention and Control, antimicrobial consumption database (<https://www.ecdc.europa.eu/en/antimicrobial-consumption/surveillance-and-disease-data/database>) and European Centre for Disease Prevention and Control, ECDC surveillance atlas—Antimicrobial resistance (<https://www.ecdc.europa.eu/en/antimicrobial-resistance/surveillance-and-disease-data/data-ecdc>).

Funding

This study was supported by internal funding.

Transparency declarations

All authors declare no conflicts of interest.

Author contributions

All authors read, commented on and approved the final manuscript. M.S.: conception and design, review, data extraction and analysis, first draft of the manuscript and revisions. F.L.B.: data analysis, manuscript revisions. N.H.S.: data analysis, manuscript revisions. M.E.N.: data analysis, manuscript revisions. M.G.J.D.B.: conception and design, data analysis, manuscript revisions.

Supplementary data

S1–S4 are available as [Supplementary data](#) at JAC Online.

References

- 1 World Health Organization. Worldwide country situation analysis: response to antimicrobial resistance. 2015. www.who.int/news/item/29-04-2015-who-report-finds-systems-to-combat-antibiotic-resistance-lacking
- 2 Bell BG, Schellevis F, Stobberingh E *et al*. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic

- resistance. *BMC Infect Dis* 2014; **14**: 13. <https://doi.org/10.1186/1471-2334-14-13>
- 3** European Centre for Disease Prevention and Control. Antimicrobial consumption in the EU/EEA. Annual epidemiological report for 2019. <https://www.ecdc.europa.eu/sites/default/files/documents/Antimicrobial-consumption-in-the-EU-Annual-Epidemiological-Report-2019.pdf>
- 4** Costelloe C, Metcalfe C, Lovering A et al. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ* 2010; **340**: c2096. <https://doi.org/10.1136/bmj.c2096>
- 5** Fletcher-Lartey S, Yee M, Gaarslev C et al. Why do general practitioners prescribe antibiotics for upper respiratory tract infections to meet patient expectations: a mixed methods study. *BMJ Open* 2016; **6**: e012244. <https://doi.org/10.1136/bmjopen-2016-012244>
- 6** European Centre for Disease Prevention and Control. Survey of health-care workers' knowledge, attitudes and behaviours on antibiotics, antibiotic use and antibiotic resistance in the EU/EEA. 2019. <https://www.ecdc.europa.eu/en/publications-data/survey-healthcare-workers-knowledge-attitudes-and-behaviours-antibiotics>
- 7** Hughes D, Andersson DI. Evolutionary trajectories to antibiotic resistance. *Annu Rev Microbiol* 2017; **71**: 579–96. <https://doi.org/10.1146/annurev-micro-090816-093813>
- 8** World Health Organization. One Health. 2017. <https://www.who.int/news-room/questions-and-answers/item/one-health>
- 9** von Elm E, Altman DG, Egger M et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* 2007; **335**: 806–8. <https://doi.org/10.1136/bmj.39335.541782.AD>
- 10** Tacconelli E, Cataldo MA, Paul M et al. STROBE-AMS: recommendations to optimise reporting of epidemiological studies on antimicrobial resistance and informing improvement in antimicrobial stewardship. *BMJ Open* 2016; **6**: e010134. <https://doi.org/10.1136/bmjopen-2015-010134>
- 11** European Centre for Disease Prevention and Control. Antimicrobial consumption dashboard (ESAC-Net). <https://ecdc.europa.eu/en/antimicrobial-consumption/surveillance-and-disease-data/database>
- 12** Organisation for Economic Co-operation and Development. OECD health system characteristics survey. Report 2019. <https://www.oecd.org/health/characteristics.htm>
- 13** Blommaert A, Marais C, Hens N et al. Determinants of between-country differences in ambulatory antibiotic use and antibiotic resistance in Europe: a longitudinal observational study. *J Antimicrob Chemother* 2014; **69**: 535–47. <https://doi.org/10.1093/jac/dkt377>
- 14** World Health Organization. Defined daily dose (DDD). Definition and general considerations. <https://www.who.int/tools/atc-ddd-toolkit/about-ddd#:~:text=Who%20is%20who%3F,in%20middle%2Flow%20income%20countries>
- 15** Gerber JS, Hersh AL, Kronman MP et al. Development and application of an antibiotic spectrum index for benchmarking antibiotic selection patterns across hospitals. *Infect Control Hosp Epidemiol* 2017; **38**: 993–7. <https://doi.org/10.1017/ice.2017.94>
- 16** Diallo OO, Baron SA, Abat C et al. Antibiotic resistance surveillance systems: a review. *J Glob Antimicrob Resist* 2020; **23**: 430–8. <https://doi.org/10.1016/j.jgar.2020.10.009>
- 17** Dutch Society of General Practitioners. Acute coughing. Guideline 2011 [in Dutch]. <https://richtlijnen.nhg.org/standaarden/acute-hoesten>
- 18** Borg MA, Camilleri L. Broad-spectrum antibiotic use in Europe: more evidence of cultural influences on prescribing behaviour. *J Antimicrob Chemother* 2019; **74**: 3379–83.
- 19** Hofstede Insights. Compare countries tool. <https://www.hofstede-insights.com/product/compare-countries/>
- 20** Nivel. Actuele weekcijfers aandoeningen—surveillance [in Dutch]. <https://www.nivel.nl/nl/nivel-zorgregistraties-eerste-lijn/actuele-weekcijfers-aandoeningen-surveillance>
- 21** Health Protection Surveillance Centre. Prevention and control methicillin-resistant *Staphylococcus aureus*. 2013. <https://www.hpsc.ie/a-z/microbiologyantimicrobialresistance/europeanantimicrobialresistanceurveillancessystemearss/referenceandeducationalresourcematier/saureusmrsa/guidance/>
- 22** Stone SP, Fuller C, Savage J et al. Evaluation of the national clean your hands campaign to reduce *Staphylococcus aureus* bacteraemia and *Clostridium difficile* infection in hospitals in England and Wales by improved hand hygiene: four year, prospective, ecological, interrupted time series study. *Br Med J* 2012; **344**: e3005. <https://doi.org/10.1136/bmj.e3005>
- 23** Nivel. Zorg door de huisarts 2022. Nivel Zorgregistraties Eerste Lijn: jaarcijfers 2021 en trendcijfers 2017–2021 [in Dutch]. <https://www.nivel.nl/nl/publicatie/zorg-door-de-huisarts-nivel-zorgregistraties-eerste-lijn-jaarcijfers-2021-en-0>
- 24** Sullivan BA, Panda A, Wallman-Stokes A et al. Antibiotic spectrum index: a new tool comparing antibiotic use in three NICUs. *Infect Control Hosp Epidemiol* 2022; **43**: 1553–7. <https://doi.org/10.1017/ice.2021.467>
- 25** Leung V, Li M, Wu JH et al. Evaluating antimicrobial use and spectrum of activity in Ontario hospitals: feasibility of a multicentered point prevalence study. *Open Forum Infect Dis* 2018; **5**: 110. <https://doi.org/10.1093/ofid/ofy110>
- 26** Singh P, Steurer MA, Cantey JB et al. Hospital-level antibiotic use and complexity of care among neonates. *J Pediatr Infect Dis Soc* 2020; **9**: 656–63. <https://doi.org/10.1093/jpids/piz091>
- 27** Yarrington ME, Wrenn RH, Spivey J et al. Measuring empiric antibiotic spectrum—a journey through space and time. *Infect Control Hosp Epidemiol* 2022; <https://doi.org/10.1017/ice.2022.151>
- 28** Song S, Wilson BM, Marek J et al. Use of electronic pharmacy transaction data and website development to assess antibiotic use in nursing homes. *BMC Med Inform Decis Mak* 2021; **21**: 148. <https://doi.org/10.1186/s12911-021-01509-7>
- 29** Thampi N, Shah PS, Nelson S et al. Prospective audit and feedback on antibiotic use in neonatal intensive care: a retrospective cohort study. *BMC Pediatr* 2019; **19**: 105. <https://doi.org/10.1186/s12887-019-1481-z>
- 30** Savage TJ, Rao S, Joerger J et al. Predictive value of direct disk diffusion testing from positive blood cultures in a children's hospital and its utility in antimicrobial stewardship. *J Clin Microbiol* 2021; **59**: e02445-20. <https://doi.org/10.1128/JCM.02445-20>
- 31** Queenan K, Häslér B, Rushton J. A one health approach to antimicrobial resistance surveillance: is there a business case for it? *Int J Antimicrob Agents* 2016; **48**: 422–7. <https://doi.org/10.1016/j.ijantimicag.2016.06.014>