Variability in the community consumption of antibiotics: a problem in Europe, Spain and Asturias

Maria Luisa Sanchez[1], Manuel Javier Vallina-Victorero[2], Maria Rosario Bachiller[3], Ricardo Arbizu[1], Eugenia Llaneza[4], Shura Rozada[1], Jose Maria Eiros[5]

[1]Health Services Management Department, Health Service of the Principality of Asturias, Oviedo, Spain;
[2]Angiology and Vascular Surgery Department. Hospital of Cabueñes, Gijón, Spain;
[3]Faculty of Medicine, University of Valladolid, Spain;
[4]Microbiology Department, University Central Hospital of Asturias, Asturias, Spain;
[5]Microbiology Department, University Hospital "Rio Hortega", Valladolid, Spain

SUMMARY

Increasing bacterial resistance is strictly correlated to the increasing use of antibiotics, currently constituting a public health problem. The aim of this study was to describe the consumption of antibiotics in Asturias, an autonomous community in northwestern Spain, and compare the results obtained with data from elsewhere in Spain and other European countries. A descriptive study was carried out on the use of antibacterial drugs for systemic use, ATC code J01 [5, 6] in Asturias in 2011-2015. Data were obtained from the prescription-billing information system charged to the Health Service of Asturias. The consumption data are expressed in daily doses per 1,000 inhabitants and day (DHD), and number of packages per thousand inhabitants per day. The average weighted consumption of antibiotics for systemic use in the Asturian community was 26.23 daily doses per 1000 inhabitants per day (DHD) in 2015. This figure was higher than that of the EU/EEA population, which was 22.4 DHD, and that of the whole of Spain at 22.2 DHD. There is a wide variability in consumption among the different areas of the Asturian region. This variability is common to the rest of the country and Europe. It can be explained by the influence of the data used in the indicators and by the variability in medical practice. Priority should be given to homologating consumer-monitoring information systems and implementing national strategies aimed at providing more information to medical practitioners, encouraging the appropriate use of antibiotics so as to reduce variability, consumption and resistance.

Keywords: antibiotic resistance, antibiotic use in the community, practical medical variability.

INTRODUCTION

The increasing bacterial resistance is strictly correlated to the increasing use of antibiotics, currently constituting a first-order public health problem according to the World Health Organization (WHO), the Organisation for Economic Co-operation and Development (OECD) and the European Centre for Disease Prevention and Control (ECDC) [1-3]. The data available for Europe in the ESAC-Net show us a great variability of consumption between communities, placing the whole of Spain in position 2 of 27 countries in the last report (Antimicrobial consumption, Annual Epidemiological Report for 2017) [4].

Spain has devised a strategic action plan to reduce the risk of selection and dissemination of resistance to antibiotics that encompasses both human and veterinary medicine, with effect from 2014-2018 [5]. This plan establishes as a first measure the monitoring of the consumption of antibiotics as an indispensable tool to know the selective pressure exerted in the appearance of resistance.

Corresponding author
Maria Luisa Sanchez
E-mail: luisasn@gmail.com

The greatest share for the consumption of antibiotics is attributed to the outpatient setting, which accounts for approximately 92% of prescriptions in Spain and 80% internationally [5, 6].
The aim of this study is to describe the consumption of antibiotics in Asturias, an autonomous community in the north-west of Spain (or a province of Spain), and compare the results obtained with data from Spain and other European countries.

MATERIALS AND METHODS

We conducted a descriptive, retrospective study in Asturias, a province of Spain located in the north of the country that occupies a total area of 10,603.57 km² with a population of 1,051,229 people.
It is structured territorially in eight health administrative areas with the following population (Figure 1): Area 1: 43,744; Area 2: 27,960; Area 3: 151,059; Area 4: 336,273; Area 5: 299,654; Area 6: 50,942; Area 7: 63,547; Area 8: 75,020.
Data on the consumption of antibiotics was obtained from the billing data of the containers dispensed in the pharmacy offices run by the National Health System. In-hospital use, use from private prescription or mutual insurance companies, or antibiotics obtained without medical prescription was excluded from the study. We specifically looked at the use of systemic antibiotics, subgroup J01 of the ATC code classification, between 2011 and 2015. Demographic data were obtained from the Spanish National Institute of Statistics [7].

The results are expressed in defined daily doses per 1,000 inhabitants/day (DHD). The defined daily dose (DDD) is a technical unit of measurement established by the WHO Collaborating Centre for Drug Statistics and Methodology, which is used by the ESAC-Net (formerly ESAC), a Europe-wide network of national surveillance systems, providing European reference data on antimicrobial consumption, and is defined as the usual maintenance dose in adults for their main indication per day [8, 9]. The use of DHD allows the comparison of the use of medicines in different regions and over time without being influenced by market differences regarding the number of pharmaceutical forms or the concentration of active ingredient of the containers. As such, DHD is an indicator of the prevalence of use of a particular drug in the population. The number of containers per 1,000 inhabitants per day has also been used, being an indicator also used by ESAC in its comparisons [4].

RESULTS

The weighted average consumption of antibiotics for systemic use in the Asturian community was 26.23 DHD for 2015, that ranged from a maximum of 30.29 DHD in area 7 to a minimum of 22.49 DHD recorded in the area 5. The rest of the areas show the following values: Area 1: 25.48 DHD, Area 2: 28.77 DHD, Area 3: 26.31 DHD, Area 4: 22.61 DHD, Area 6:25.14 DHD and Area 8: 28.72 DHD (Table 1).
This number was higher than the previously reg-

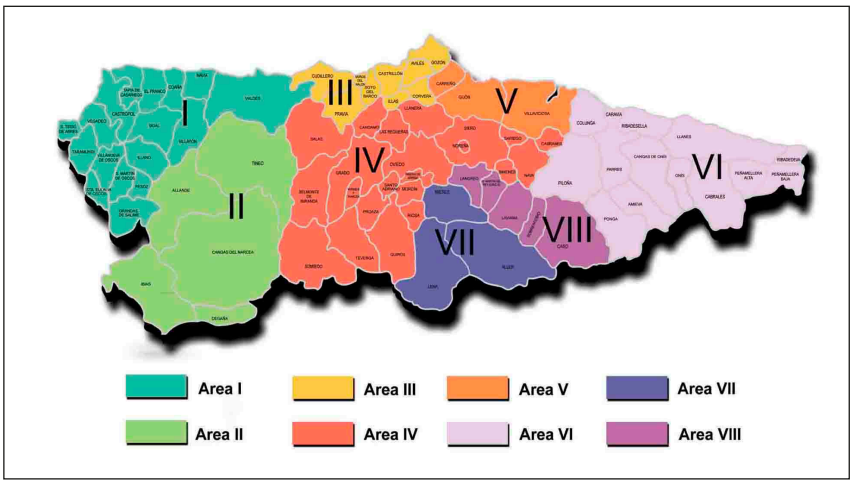


Figure 1 - Health Areas of Asturias.

istered amount for the weighted average consumption of systemic antibiotics of 22.4 DHD of the EU/EEA population, and higher than that of Spain overall, which is 22.24 (Figure 2).

The consumption tendency (Figure 3) shows that the average in Europe, although higher than in previous years, did not change significantly during 2011-2015. However, in Asturias and Spain

Table 1 - Community consumption of antibiotics in Asturias by Area, 2015 (expressed in DHD, that is DDD per 1000 inhabitants per day).

	Area 1	*Area2*	*Area 3*	*Area 4*	*Area 5*	*Area 6*	*Area 7*	*Area 8*
DHD	25.48	28.77	26.31	22.61	22.49	25.14	30.29	28.72

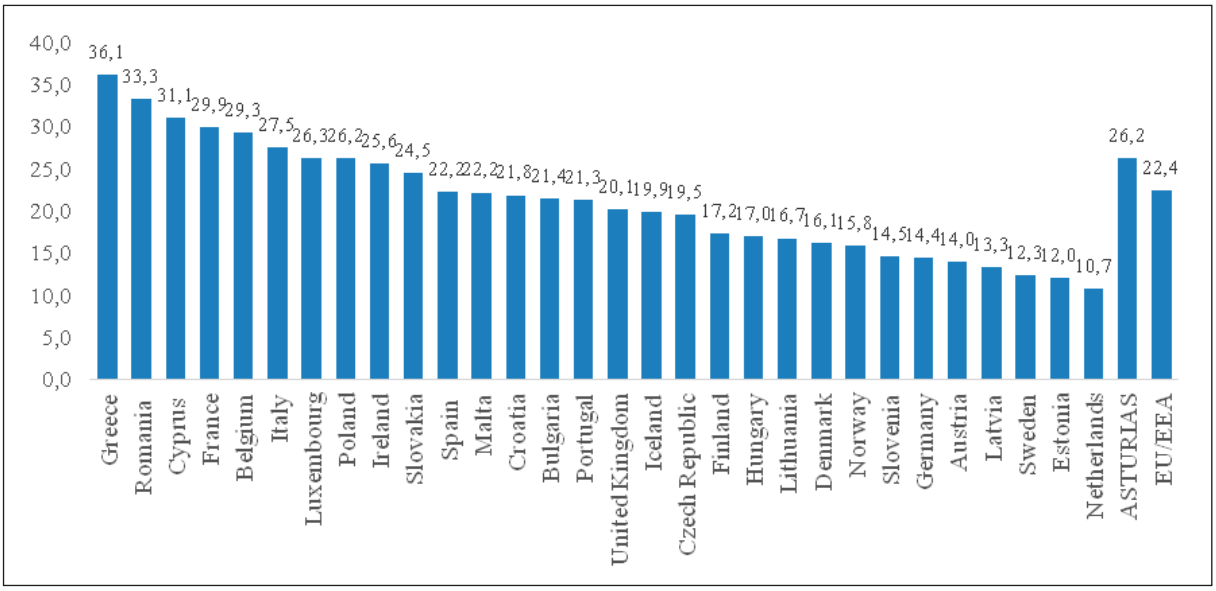
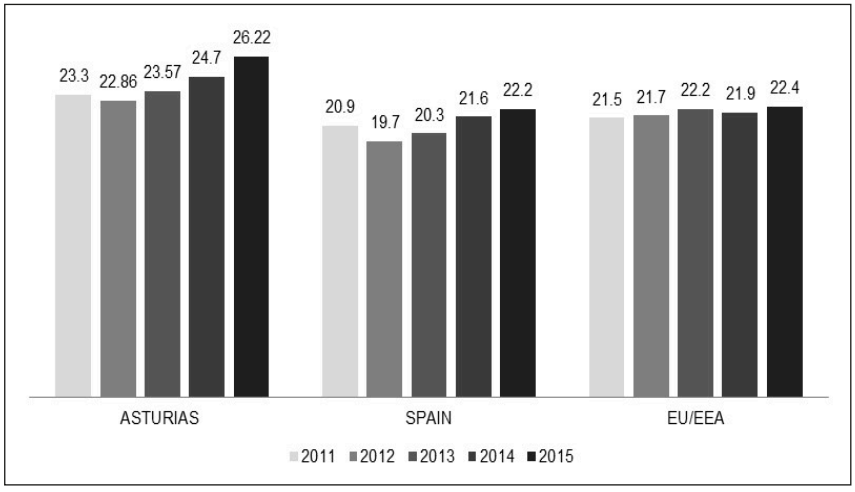


Figure 2 - Community consumption of antibiotics for systemic use by antibiotic group, Asturias, Spain, EU/EEA 2015 (expressed in DHD, that is DDD per 1000 inhabitants per day).

Figure 3 - Tendencies in antibiotic consumption for systemic use within the community, Asturias, Spain and EU/EEA countries, 2011-2015 (expressed as DDD per 1000 inhabitants and per day)



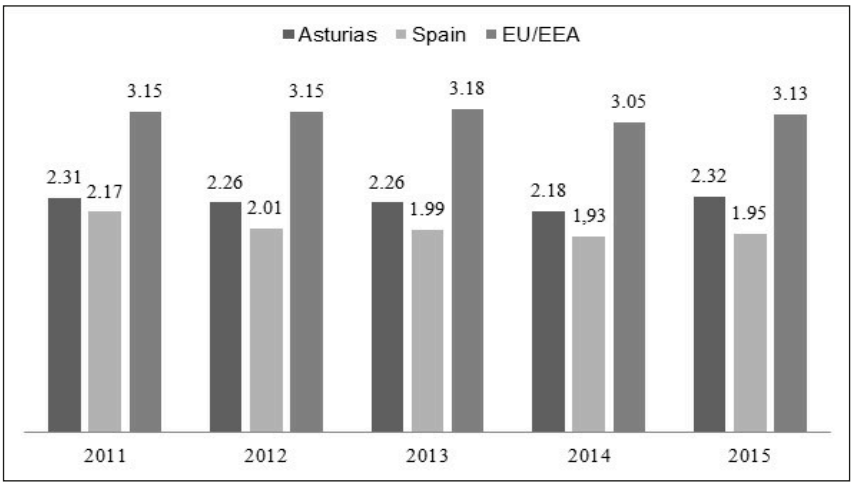


Figure 4 - Tendencies in community consumption of antibiotics for systemic use, Asturias, Spain, EU/EEA countries, 2011-2015 (expressed as packages per 1000 inhabitants and per day).

the tendency has been upward in the last three years.

When analysing the consumption tendency on the basis of packages per 1000 inhabitants per day (used by ESAC-Net as the best substitute available for prescriptions), the weighted average consumption of the EU/EEA was 3.1 packages per 1,000 inhabitants per day during the period of 2011-2015 showing no significant tendency [4].

In Asturias and Spain, the consumption was significantly lower with 2.32 and 1.95 packages per 1000 inhabitants and per day, respectively, with a downward tendency from 2012 to 2014, but picking up again in 2015 (Figure 4).

Antibiotics prescription (Table 2) was concentrated on four therapeutic subgroups: penicillins, quinolones, macrolides and cephalosporins, which together represented 92% of the community consumption of antibiotics for systemic use in 2015. Penicillins were the most used subgroup with 60%, followed by macrolides with 12%, quinolones with 11%, and cephalosporins with 9%.

DISCUSSION

The Spanish consumption of antibacterial agents for systemic use, in terms of daily dose defined per thousand inhabitants and day, has been among the highest in Europe for years and occupying now the second position of 27 countries, according to the latest report of ESAC-Net [4, 10, 11]. The data available in ESAC-Net for Europe show us a great variability of consumption both globally as well as in community and hospital set-

Table 2 - Community consumption of antibacterial agents for systemic use (ATC group J01) (primary care sector) expressed in DDD per 1000 inhabitants per day in Asturias in 2015

ATC group J01	*Community (primary care sector) in DHD*
Beta-lactam antibacterials, penicillins (J01C)	15.80
Quinolone antibacterials (J01M)	2.91
Macrolides, lincosamides and streptogramins (J01F)	3.08
Other J01 substances	0.71
Other beta-lactam antibacterials (J01D)	2.51
Sulfonamides and trimethoprim (J01E)	0.46
Tetracliclynes (J01 A)	0.75
Total	*26.23*

ting. Countries in the Mediterranean side, among which we find ourselves, present a greater consumption compared to the Nordic countries that present significantly lower consumption figures.

Our main finding was that the average community consumption of antibacterial agents for systemic use in Asturias charged to the public health service at the ambulant level in 2015 was 26.23 DHD. This means that more than 26 people out of 1,000 are receiving antibiotic treatment every day in Asturias. These data indicate a consumption higher than that found in countries around us, in Spain and in regions with a population structure similar to ours in demographic and dispersion indicators.

If we perform the analysis from the perspective of the health care systems, we find that in Asturias using the Beveridge model (The Beveridge Model is a nationalized health care system, similar to how public libraries and police forces are financed by the government being health care controlled through citizen tax money. Citizens of countries who use this health care plan do not directly pay for their medical or other health-related bills. The goal of this plan is to provide quality health care regardless of people's ability to pay for their care) antimicrobials were prescribed more than in other countries with a similar system such as Sweden (12.3 DHD), Denmark (16.1 DHD), Finland (17.2 DHD), and the United Kingdom (20.1 DHD) in 2015. Consumption in Asturias was also higher than in countries with a Bismarck type system, such as the Netherlands (10.7 DHD), Austria (14.0 DHD) or Germany (14.3 DHD). Consumption was lower than that observed in France (29.9 DHD) or Belgium (29.2 DHD), so the provision model does not seem to influence the use of this type of medicine.

It is striking that Mediterranean countries such as Greece, Romania, Cyprus, France and Italy have a higher level of antibiotic consumption than the Nordic and Central European countries and present a clearly differentiated pattern of use. None of these differences seems to be justified in an epidemiological pattern and must, therefore, respond to other causes. It is surprising, for example, that Belgium with 29.2 DHD almost triples the consumption of antibiotics in the Netherlands with 10.7 DHD [4].

Unfortunately, we observed not only a high consumption in Asturias in comparison to that observed in neighbouring countries, but when comparing the data with the complete Spanish National health Service for the same study period, the average consumption of Asturias was 15.14% higher than the average for Spain being 22.24 DHD. This variability is also observed in other regions, such as Galicia with a consumption of 23.54 or Andalusia with consumption of 20.3 DHD in 2015 [12, 13]. We found variability consumption among different areas, in agreement with data from other countries [9, 14, 15]. Specifically, in Switzerland in 2007 with a population similar to Asturias (in that year 1,074,862 inhabitants), DHD ranged from 7.28 for the northwest of Switzerland to 11.33 DHD in the Lake Leman region (variability of 4.05 DHD), with variations in consumption of 7.13 DHD in Asturias for the same year. This data is interesting, because the consumption in Asturias is double than that of Switzerland for a similar population [16].

This variability between different administrative areas is also observed in other regions, such as Galicia with a consumption of 23.54 or Andalusia with a consumption of 20.3 DHD in 2015. Pastor García et al. show differences in consumption of up to 6 DHD within Castilla y León [12, 13, 17].

Analysing evolutionary tendency by subgroup, it is observed that penicillins stably maintain the majority throughout the period; use of quinolones and macrolides decreases slightly, whereas use of cephalosporins increases.

Our data are similar in tendency and percentage of consumption to those described in other autonomous communities; the representativeness is similar to that of the whole country and other regions such as Andalusia or Galicia, but they differ in the consumption values [10-13].

However, when we compare with Europe, variability is greater, the use of penicillins (60%) being lower than in Denmark and Slovenia (66%), and almost twice than that of Germany (32%). Use of macrolides with 12% occupied an intermediate position between 5% (Sweden) and 25% (Slovakia), similar to quinolones with 11% (intermediate figure between 2% of the United Kingdom and 16% of Hungary). Cephalosporins with 9% have a representativeness that contrasts with those found between 0.2% (Denmark) and the 22% (Germany) [4].

As we have previously indicated, the geographical differences of antibiotic consumption are

well established in several studies, which point out that they do not correspond to a specific geographic or epidemic pattern in the different countries, autonomous communities and provinces of our country. It is even possible to observe this variability within the same province or health administrative area. Variability in consumption affects countries, regions within each country, both in tendency and in distribution [18-20].

CONCLUSIONS

One of the most striking aspects of the study has been to verify not only that the expenditure is higher than the average for Europe, Spain and other regions with similar demographic, geographical and structural characteristics, but that the evolutionary tendency has been growing and constant with a rebound in recent years when measured through DHD. The use of this indicator has allowed us to quantify the consumption of our community, compare it with other countries and other autonomous communities, monitor it during that period, describe the prescription profile by health administrative area and by therapeutic subgroup.

In accordance with the above, the DHD can be considered a hard indicator, independently of its limitations that can be minimised through a homogeneous construction. Together with this indicator, the monitoring of the number of containers per thousand inhabitants per day should be taken into consideration, since it is the other indicator used by ESAC-Net, which allows the comparison with Europe through the data provided.

Asturias presents an average community consumption of antibiotics for systemic use above the average of Spain and of Europe; it would be necessary to analyse if there are epidemiological factors that justify this pattern of use. At least in those areas of greatest consumption, interventions should be implemented to establish criteria for a more rational use of antibiotics as well as to document the local prevalence of resistance.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES

[1] World Health Organization. Global action plan on antimicrobial resistance. 2015 Retrieved from http://www.who.int/antimicrobial-resistance/publications/global-action-plan/en/ Last accessed May 5, 2019.

[2] Michael A., Charles C., Kai S., et al. Averting the AMR crisis: What are the avenues for policy action for countries in Europe? Policy Brief (1 March 2019), produced to inform the EU Ministerial Meeting on "Next steps towards making the EU a best practice region in combating AMR" held by the Romanian Presidency of the Council of the European Union in Bucharest on March 1, 2019. Retrieved from https://www.oecd.org/health/health-systems/Averting-the-AMR-crisis-Policy-Brief-32-March-2019.PDF Last accessed May 5, 2019.

[3] European Centre for Disease Prevention and Control. Who we are. Retrieved from http://ecdc.europa.eu/en/aboutus/who-we-are/Pages/who-we-are.aspx. /Last accessed May 5, 2019.

[4] European Centre for Disease Prevention and Control. Antimicrobial consumption. In: ECDC. Annual epidemiological report 2017. Stockholm: ECDC; 2018.: Retrieved from https://ecdc.europa.eu/sites/portal/files/documents/ESAC-NET-reportAER-2017-updated.pdf / Last accessed Jan 18, 2019.

[5] Plan estratégico y de acción para reducir el riesgo de selección y diseminación de la resistencia a los antibióticos. Segunda edición 2015. Retrieved from https://www.aemps.gob.es/./ Last accessed Nov 15, 2018.

[6] Malo S., Bjerrum L., Feja C., Lallana M.J., Abad J.M., Rabanaque-Hernández M.J. The quality of outpatient antimicrobial prescribing: a comparison between two areas of northern and southern Europe. *Eur. J. Clin. Pharmacol*. 70, 3, 347-353, 2014.

[7] Baquero Mochales F., Baraibar Castelló R., Campos Marqués J., et al. Resistenncia microbiana.¿ Qué hacer? Informe del panel de expertos. *Rev. Esp. Salud Pública*. 69, 445-461, 2008.

[8] WHOCC - ATC/DDD. Retrieved from http://www.whocc.no/atc_ddd_index/./ Last accessed Nov 15, 2018.

[9] WHO Collaborating Centre for Drug Statistics Methodology. Retrieved from http://www.whocc.no/./ Last accessed Nov 15, 2018.

[10] Lázaro Bengoa E., Madurga Sanz M., de Abajo Iglesias F.J. Tendencies in antibiotic consumption in Spain, 1985-2000. *Med. Clin. (Barc.)* 118, 561-568, 2002.

[11] Lázaro-Bengoa E., de Abajo Iglesias F.J., López-Navas A., Fernández-Cortizo M.J. Use of antibiotics in

Spain and regulatory framework for clinical development in the European Union. *Enferm. Infecc. Microbiol. Clin*. 28, 101-106, 2010.
[12] Uso ambulatorio de antibióticos en Galicia de 2007 a 2015. *Boletín Epidemiológico de Galicia*. 28, 18-31, 2016.
[13] Consumo de antimicrobianos en Andalucía - Consumo de antimicrobianos en Andalucía.pdf. Retrieved from: http://ws140.juntadeandalucia.es/pirasoa/. Last accessed Nov 15, 2017.
[14] Cars O., Mölstad S., Melander A. Variation in antibiotic use in the European Union. *The Lancet*. 357, 1851-1853, 2001.
[15] Kern W.V., de With K., Nink K., Steib-Bauert M., Schröder H. Regional Variation in Outpatient Antibiotic Prescribing in Germany. *Infection.* 34, 269-273, 2006.
[16] Achermann R., Suter K., Kronenberg A., et al. Antibiotic use in adult outpatients in Switzerland in relation to regions, seasonality and point of care tests. *Clin. Microbiol. Infect*. 17, 855-861, 2011.
[17] Pastor García E., Eiros Bouza .JM., Mayo Iscar A. Influencia de la estructura de la población en el consumo de antibióticos sistémicos en la provincia de Valladolid. *Rev Esp Salud Pública*. 76, 4, 2002.
[18] Dezileaux B., Martinez F. Comparaison des prescriptions de médicaments en ambulatoire: France, Danemark, Norvège, Suède. *Thérapie*. 71, 297-305, 2016.
[19] Kern W.V., de With K., Nink K., Steib-Bauert M., Schröder H. Regional Variation in Outpatient Antibiotic Prescribing in Germany. *Infection*. 34, 269-273, 2006.
[20] Kourlaba G., Gkrania-Klotsas E., Kourkouni E., Mavrogeorgos G., Zaoutis T.E. Antibiotic prescribing and expenditures in outpatient adults in Greece, 2010 to 2013: evidence from real-world practice. *Euro Surveill*. 21, 1-9, 2016.