**Introduction**

Antimicrobial resistance (AMR) is one of the most serious threats to public health worldwide [1-2] being the cause of severe health complications for patients, including longer illnesses, increased morbidity and mortality, prolonged stays in hospital, loss of protection for patients undergoing surgical operations and other medical procedures, and consequently increased healthcare costs [3-4]. A correlation has been demonstrated between the use of antibiotics, especially if they are broad-spectrum, and a high proportion of AMR, both in the hospital and community settings [5-6]. In response to antimicrobial resistance threatens in May 2015 the World Health Assembly adopted the so-called “One Health Approach”, a global action plan involving the coordination among countries and international agencies, different sectors and actors, including both human and veterinary medicines, to globally address AMR problem [7-8].

In Italy the resistance to antibiotics for all pathogens under surveillance remains high, generally above the European average [9-10]. The Italian antibiotics’ consumption, both in the community and hospital setting, is steadily higher than the average consumption in EU Member States and EEA countries (+6.5%), with high levels of inappropriate use, although with a decreasing trend in the last decade [11]. In such a context, in 2017 the first National Action Plan on Antimicrobial Resistance (*PNCAR,* *Piano Nazionale per il Contrasto dell’Antimicrobico-Resistenza*) was adopted in Italy [12]. In agreement with the WHO Action Plan, the Italian PNCAR applies the “one health approach” through the synergy of the antibiotic stewardship interventions between national, regional, and local levels, both in human and in veterinary field. Since antibiotic overuse in humans, especially in the outpatient setting, is one of the most important modifiable drivers of AMR [13], the PNCAR provides specific objectives and actions to promote a more rational use of antibiotics for human use, including the monitoring of the national consumption and trying to improve their appropriate use, particularly where they are used in high volumes. Among the indicators proposed, there was the reduction of the use of fluoroquinolones both in community and hospital setting. This objective seems to be even more urgent after the communication of the European Medicines Agency (EMA) in November 2018 requesting the suspension of the marketing authorisation of quinolones and the restriction of the indications for the prescription of fluoroquinolones due to potential serious toxic effects [14].

Since the PNCAR came into force, two dedicated annual National Report on Antibiotics’ use in humans have been published by the Medicines Utilisation Monitoring Centre (*OsMed – Osservatorio Nazionale sull’impiego dei Medicinali*) of the Italian Medicines Agency (*AIFA, Agenzia Italiana del Farmaco*) [15-16], although a previous one was published in 2009 [17]. Other studies were recently published on antibiotics ‘use in Italy but they reported data only for some Italian regions 18-19], with scant or incomplete information on regional variability. The aim of this article is to describe the pattern of antibiotic consumption in the community setting in Italy, both at national and regional level, from 2013 to 2018., including some indicators on appropriateness of use.

**Sources and Methods**

The consumption data for reimbursed antibiotics dispensed by community pharmacies were considered. Different data sources were used: 1. OsMed database, collecting data regarding the consumption of medicines dispensed by community pharmacies and reimbursed by the Italian National Health Care Service (NHCS); 2. Pharmaceutical Prescriptions database (also named “Italian Health Insurance Card database”) collecting patient level data on medicines dispensed by community pharmacies and reimbursed by Italian NHCS, used to evaluate the use of antibiotics in the Italian population by age and gender; 3. Diagnosis and prescription database (Health Search-IQVIA LPD) of a sentinel network of 800 general practitioners (GPs) related to 1.006.424 patients aged 14 years or over, representative of the adult primary care service at the national level, used to evaluate the appropriate use of antibiotics.

Data from influ*Net* surveillance system, a network coordinated by National Institute of Health of sentinel physicians made up of general practitioners and paediatricians who report cases of flu-like syndromes, were used to analyse the correlation between the antibiotics’ consumption and the incidence of flu syndromes in the October 2014-April 2019 period.

Data were arranged according to the Anatomical Therapeutic Chemical (ATC) classification established by the World Health Organization Collaborating Centre (WHOCC) for Drug Statistics Methodology as following: antibacterials for systemic use (J01), fluoroquinolones (J01MA), broad-spectrum penicillins (J01CA-CE-CF), combinations of penicillins, incl. beta-lactamase inhibitors (J01CR) cephalosporins (J01DB-DC-DD-DE), macrolides (J01FA).

Drug consumption was measured as number of Defined Daily Dose (DDD), which is the assumed average maintenance dose per day for a drug used for its main indication in adults [20]. It represents a standard in performing valid and reliable cross-national or longitudinal studies on drug consumption. Since DDD values of some medicines may change over time because of alterations in the main indication, or regulatory amendments for the recommended or prescribed daily dose, all historical data were retrospectively adjusted to the latest version of the DDD/ATC index.

The indicator calculated as “number of DDD per 1,000 inhabitants per day” was used. To make regional comparisons a weighted population was applied in the indicator calculation, in order to take into account age and gender differences across Italian regions [21]. Since it is not possible to analyse medicines use in children by using DDDs owing to the variability of children’s doses and to fact that the WHO DDD/ATC index reports DDD referred to adult subjects only, the indicators used to report antibiotic use in the paediatric population (aged between 0 and 13 years) were the prescription rate (expressed as number of prescriptions per 1,000 children) and prevalence of use (the proportion of the paediatric population that uses antibiotics) [22] calculated by using the patient level data from Pharmaceutical Prescriptions database.

**Results**

In 2018 the consumption of reimbursed antibiotics and dispensed by community pharmacies in Italy amounted to 16.1 DDD per 1,000 inhabitants per day (geographical variations are presented in detail in **Table 1)**. The differences between geographical areas and regions showed a spatial trend of growth in antibiotic consumption going from the North to the South of Italy. The 2018 rates of antibiotic consumption by areas were 12.7 DDD per 1,000 inhabitants per day in the North, 16.9 in the Centre and 20.4 in the South of the country (**Table 1).** The growing consumption trend from North to South is maintained even when evaluating the specific antibiotic classes; differences by geographical area are particularly evident for third-generation cephalosporins, fluoroquinolones, macrolides and penicillins associated with beta-lactamase inhibitors (**Figure 1**). The use of antibiotics was greater in extreme age groups than in the population aged between 20 and 64 years. However, in the latter group, there was a greater exposure to antibiotics in women than in men, probably for the treatment of urinary tract infections. In contrast, in the population aged 80 and older, men received more antibiotics’ prescriptions than women (**Figure 2**). The consumption of antibiotics showed a clear seasonality in all the years considered (**Figure 3**); moreover, the antibiotic consumption is higher in winter season with particularly high peaks in the incidence of flu syndromes (**Figure 4**). Data from a sentinel network of general practitioners showed that, in 2018, an antibiotic for systemic use was prescribed in 33.1% of patients diagnosed with flu, cold or acute laryngotracheitis and the fluoroquinolones were prescribed in 34.2% of women with not complicated cystitis (**Table 2**).

Considering the period 2013-2018, the consumption rates of antibiotics showed a significant reduction trend both at the national level (Compound annual growth rate-CAGR: -2.6%) and in the three geographical areas (North, Centre and South, CAGR: -2.6%, -3.1% and -2.5% respectively) (**Table 1**; **Figure 3**).

The consumption of fluoroquinolones, equal to 2.6 DDD per 1,000 inhabitants per day in the general population in 2018, showed a significantly decreasing trend in the period considered (January 2013-May 2019). The reduction in the use of fluoroquinolones (24%) was more accentuated than expected based on data from previous years starting from the end of 2018, after the EMA communication. In 2018 the consumption rates at the national level was equal to 1.9 DDD in women aged between 20 to 59 year and equal to 6.9 DDD per 1,000 inhabitants per day in the elderly aged 75 or over. The prevalence of use was 8.4% in women between 20 and 59 years while it reached 22.5% in the elderly 75 or over (**Table 3).** An incremental gradient from the North to the South of Italy was also observable for fluoroquinolone use. In 2018 the prevalence of use for women aged between 20 and 59 varied from 6.8% in the North to 10.2% in the South while, for the population aged 75 or older, it varied from 16.7% in the North to 30.5% in the South (**Table 3**). According to the data collected in 2018 through the sentinel network of general practitioners, the fluoroquinolones were inappropriately prescribed in 34.2% of women under 65 years diagnosed with uncomplicated cystitis.

Considering the paediatric population aged between 0 and 13 years, the antibiotic utilization rate in 2018 was 1,010 prescriptions per 1,000 children, while the prevalence of use was 40.8%. It was observed, also in this age group, an incremental spatial trend from North to South for both prescription rate and prevalence of use (36.6% in the North, 41.6% in the Centre and 45.9% in the South**) (Table 4a).**

For the children, there was a lower overall antibiotic prescription rate in the North, where penicillins are preferred to cephalosporins and macrolides. In the North penicillins showed higher prescription rates compared to other geographical areas, while for cephalosporins and macrolides, the opposite trend can be observed (**Table 4b**). Regarding the type of penicillins, in the North the broad-spectrum penicillins (e.g. amoxicillin) were prescribed more than in the rest of the country both in absolute and relative terms: the ratio between amoxicillin alone and the combination with clavulanic acid was 0.7 in the North and 0.3 both in the Centre and in the South.

**Discussion**

Antibiotic consumption data in the Italian community setting showed significant differences by geographical and regional area. A progressive increase in the consumption of antibiotics from the North to the South of the country was observed. The potential contributing factors to variability in antibiotics’ consumption were investigated and include the physician–patient (parents) relationship, socio-economic status, clinical microbiology and the difficulties faced by physicians in differentiating viral from bacterial infections [23] as well physician characteristics [24]. Relevant differences were also found in the type of prescribed antibiotics: the broad-spectrum antibiotics were more frequently prescribed in the South than in the North. Considering the general population, cephalosporins, penicillins associated with beta-lactamase inhibitors, fluoroquinolones and macrolides were more frequently prescribed in the South than in the Centre and in the North, both in absolute and relative terms. A similar South-North spatial trend was also observed in the paediatric population both in quantitative terms (prescription rate) and in qualitative terms (type of prescribed antibiotics).

In particular, the data from Medicines Utilisation Monitoring Centre highlighted the following main results: a marked seasonality in the antibiotic consumption with a higher than expected increase during the winter season; comparing the different calendar years, the occurrence of evident increases in consumption during the winter months when there were higher rates of flu syndromes; according to the data from the GPs’ sentinel network one-third of patients evaluated with symptoms related to the flu syndrome or to viral infections of the upper airways received an antibiotic prescription and a third of women who were diagnosed with uncomplicated cystitis received a prescription of a fluoroquinolone.

These results complement those from The European Surveillance System (TESSy) which show that Italy has high antibiotic consumption (with preference for broad spectrum ones) and high prevalence of bacterial resistance compared to other countries [11-25].

The results of our analyses indicate the need to quantitatively reduce unnecessary antibiotic prescriptions and the use of broad-spectrum antibiotics in Italy, in order to improve the appropriateness of antibiotic prescriptions, with a particular attention to specific population subgroups (i.e. paediatric population, women and elderly). These interventions, according to the available evidence, should be based on a multilevel and multifaceted approach that includes elements such as clinical-based education, patient leaflets and posters, pharmacist advice, feedback to prescribers and clinician training in communication skills [26-27-7]. A recent systematic review found that that strategies to reduce inappropriate demand and access to antibiotics appear to have a quantifiable impact primarily on antibiotic consumption, although the long-term sustained impact of these policies should be evaluated [28].

A clear result on the reduction of fluoroquinolones consumption was determined by an EMA regulatory intervention on the restriction of use of these drugs [14]. Other interventions based on different strategies should be added to the restrictive actions on specific classes of antibiotics, to avoid that consumption simply moves from one type of antibiotic to another one rather than obtaining a real overall reduction [27].

*Ad hoc* communication campaigns (as already done in the past) aimed at informing and raising awareness among the general population on the problem of excessive use of antibiotics and bacterial resistance, are interventions with proven efficacy [26-27-7]. Another fundamental field of action concerns physicians, with particular attention to GPs for the adult population and children. The actions directed at physicians, as well as information, training and the production of guidelines, include the collection and the timely feedback of surveillance results on antibiotic use and antimicrobial resistance [26-27]. The coordination activities at central national level are necessary but it is also essential to involve the local health services and stakeholders that allow the implementation of the necessary actions, considering the peculiarities of each operating context [26-27].

The data included in the present study can provide useful information to guide decision makers in the different settings in applying the tailored interventions and to monitor the impact of the PNCAR. Other countries, within the strategies to counter the rise in AMR, have published national report to monitor the antibiotics’ consumption [29]. Data included in the present study refers to the consumption in the whole Italian population, in the different geographic areas and regions and in specific sub-populations and, finally, allow the monitoring of the consumption in the medium-long term. Nevertheless, the study presents some limitations: the first one refers to the lack of consumption data related to the private purchase. Moreover, the study doesn’t report data according to the diagnosis on a general population basis; in fact, the presented diagnosis data are limited to a network of 800 general practitioners. This limitation could be overcome by implementing the systematic collection of diagnosis data (e.g. DRGs - Diagnosis-Related Groups) for outpatient prescriptions, as already planned in some areas of the country. Finally, data on consumption in the animal setting, that are not currently included in the national report, will be provided starting since 2020, as indicated in the objectives of the PNCAR.

**Conclusion**

In conclusion, although the situation regarding the use of antibiotics in Italy in 2018 indicates an excessive use of these drugs with considerable geographical differences, there is a significant downward trend in the various areas of the country and age groups that affects all classes of antibiotics. This result shows that there is an effort at central and local level, albeit with differences between regions, which must be valued and intensified. In this perspective it could be useful to identify the activities and the best practice implemented locally that could be exported to other areas of the country.

**Conflict of interest statement:**

The work reported in this manuscript did not receive any sponsorship or funding.

**Disclaimer:**

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the respective authors’ organisations.

**Acknowledgements:**

The Authors thank the “Working group of the National Observatory for Medicines Use Monitoring”: **Italian Medicines Agency (AIFA):** L. Li bassi, F. Trotta, M.P. Trotta, S.M. Cammarata, A. Cangini, A. Di Filippo, F. Fortinguerra, R. Frulio, M.A. Guerrizio, R. Marini, F. Milozzi, A. Pierantozzi, L. Pierattini, E. Pieroni, C. Rosiello, M. Sacconi, D. Settesoldi, F. Villa, A. Fabrizi, M. Fontanella, S. Perna, G. Pistolesi, M. Trapanese, C. Santini, I. Comessatti, F. Mazzeo, F. Pomponi, S. Vasta. **National Institute of Health (ISS):** R. Da Cas, P. Ruggeri. **Regional Social Health Agency Emilia Romagna:** C. Gagliotti, M.L. Moro. **For the analysis on the prescribing appropriateness, Italian College of General Practitioners and Primary Care:** C. Cricelli, A. Rossi, P. Lora Aprile, G. Medea, E. Marconi, F. Lapi, I. Cricelli. **Other Contributions:** Minister of Health for the data on Hospital Discharge Form (S. Carbone), the data of Drug Traceability, Hospital Consumption, and Direct Distribution databases (C. Biffoli e G. Viggiano); Farmadati for its contribution to listing medical products; National Institute of Health (ISS) for having provided data from influNet surveillance system (A. Bella) and from AR-ISS Group for the antibiotic resistance surveillance data (A. Pantosti, S. Bellino, S. Iacchini, M. Monaco, P.F. D’Ancona e P. Pezzotti).

**Data availability statement:**

The data that support the findings of this study are available from the corresponding author, [author initials], upon reasonable request.

**Figures legends:**

**Figure 1.** Regional variability in the consumption of antibiotics (DDD/1000 inhab. *die*) by ATC IIIlevel in 2018

**Figure 2.** Consumption and prevalence of use of antibiotics (J01) in community setting by age and gender in Italy in 2018

**Figure 3.** Trend on monthly basis of the consumption of antibiotics (J01) in Italy in the period 2014-2018

**Figure 4.** Correlation between consumption (DDD/1,000 inhab. *die*) of antibiotics (J01) and incidence of flu syndrome in the period 2014-2018

**References**

1. Laxminarayan R, Duse A, WattalCetal. Antibiotic resistance—the need for global solutions. Lancet Infect Dis 2013; 13: 1057–98.
2. Holmes AH, Moore LS, Sundsfjord A et al. Understanding the mechanisms and drivers of antimicrobial resistance. Lancet 2016; 387: 176–87.
3. Prestinaci F, Pezzotti P, Pantosti A. Antimicrobial resistance: a global multifaceted phenomenon. [Pathog Glob Health](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4768623/). October, 2015; 109(7): 309–318.
4. Wozniak TM, Barnsbee L, Lee XJ, Pacella RE. Using the best available data to estimate the cost of antimicrobial resistance: a systematic review. Antimicrob Resist Infect Control. 2019;8:26.
5. Goessens H. Ferech M. Stichele RV. Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross National database study. Lancet. 2005 Febr 12; 365(9459):579-87.
6. Castro-Sánchez. E.; Moore. L.S.; Husson. F.; Holmes. A.H. What are the factors driving antimicrobial resistance? *Perspectives from a public event in London. England. BMC Infect. Dis.* 2016. *16*. 465
7. World Health Organization (2015). Global Action Plan on Antimicrobial Resistance. WHO: Antimicrobial resistance (<https://www.who.int/antimicrobial-resistance/global-action-plan/en/>).
8. Collignon PJ, McEwen SA. One Health-Its Importance in Helping to Better Control Antimicrobial Resistance. [Trop Med Infect Dis.](https://www.ncbi.nlm.nih.gov/pubmed/30700019) 2019;4(1).
9. European Centre for Disease Prevention and Control. Surveillance of antimicrobial resistance in Europe 2018. Stockholm: ECDC; 2019.
10. Istituto Superiore di Sanità. AR-ISS: antibiotic resistance surveillance in Italy. Report for five-year period 2012-2016. Stefania Bellino, Simone Iacchini, Monica Monaco, Francesca Prestinaci, Claudia Lucarelli, Maria Del Grosso, Romina Camilli, Giulia Errico, Fortunato D’Ancona, Patrizio Pezzotti, Annalisa Pantosti and AR-ISS c 2018, vi, 98 p. Rapporti ISTISAN 18/22 (in Italian).
11. European Centre for Disease Prevention and Control (ECDC). Antimicrobial consumption. In: ECDC Annual Epidemiological Report for 2018”. Stockholm: ECDC; 2019a
12. Ministero della Salute. Piano Nazionale di Contrasto dell'Antimicrobico-Resistenza (PNCAR) 2017- 2020. Anno 2017. (<http://www.salute.gov.it/imgs/C_17_pubblicazioni_2660_allegato.pdf>)
13. Chatterjee A, Modarai M, Naylor NR, Boyd SE, Atun R, Barlow J, Holmes AH, Johnson A, Robotham JV. Quantifying drivers of antibiotic resistance in humans: a systematic review. [Lancet Infect Dis.](https://www.ncbi.nlm.nih.gov/pubmed/30172580) 2018;18(12):e368-e378.
14. European Medicines Agency (EMA). Disabling and potentially permanent side effects lead to suspension or restrictions of quinolone and fluoroquinolone antibiotics (EMA/795349/2018), 16 November 2018 (https://www.ema.europa.eu/documents/pressrelease/disabling-potentiallypermanent-side-effects-lead-suspension-restrictionsquinolone-fluoroquinolone\_en.pdf).
15. The Medicines Utilisation Monitoring Centre. National Report on antibiotics use in Italy. Year 2017. Rome: Italian Medicines Agency. 2019.
16. The Medicines Utilisation Monitoring Centre. National Report on antibiotics use in Italy. Year 2018. Rome: Italian Medicines Agency. 2019
17. The Medicines Utilisation Monitoring Centre. National Report on antibiotics use. Rome: Italian Medicines Agency. 2009
18. Barchitta M, Quattrocchi A, Maugeri A, La Rosa MC, La Mastra C, Sessa L, Cananzi P, Murolo G, Oteri A, Basile G, Agodi A. Antibiotic Consumption and Resistance during a 3-Year Period in Sicily, Southern Italy. Int J Environ Res Public Health. 2019;16(13).
19. Bonaldo G, Bianchi S, Ancona D, Procacci C, Natalini N, Motola D, Vaccheri A. The prescription of antimicrobials by general practitioners: the differences between north and south Italian provinces. [Expert Rev Anti Infect Ther.](https://www.ncbi.nlm.nih.gov/pubmed/31914829) 2020;18(2):165-170.
20. WHO Collaborating Centre for Drug Statistics Methodology, Guidelines for ATC classification and DDD assignment 2020. Oslo, Norway, 2019.
21. The Medicines Utilisation Monitoring Centre National report on medicines use in Italy. year. Italian Med. Agency 2018. 2019. [Internet]. 2019. Available from http://www.aifa.gov.it/content/rapporti- osmed- luso- dei- farmaci- italia.
22. Liem TB. Heerdink ER. Egberts AC. Rademaker CM. Quantifying antibiotic use in paediatrics: a proposal for neonatal DDDs. Eur J Clin Microbiol Infect Dis. 20
23. Avorn J, Solomon DH (2000) Cultural and economic factors that (mis)shape antibiotic use: the nonpharmacologic basis of therapeutics. Ann Intern Med 133:128–13510;29(10):1301–1303. doi:10.1007/s10096-010-0990-3
24. Mazzaglia G, Caputi AP, Rossi A, Bettoncelli G, Stefanini G, Ventriglia G, et al. Exploring patient- and doctor-related variables associated with antibiotic prescribing for respiratory infections in primary care. Eur J Clin Pharmacol. 2003;59:651–7.
25. European Centre for Disease Prevention and Control (ECDC). Surveillance of antimicrobial resistance in Europe 2018. Stockholm: ECDC; 2019b
26. European Commission. EU Guidelines for the prudent use of antimicrobials in human health. Luxembourg: European Commission; 2017. (<https://ec.europa.eu/health/amr/sites/amr/files/amr_guidelines_prudent_use_en.pdf>)
27. Public Health England. Department of Health. Behaviour change and antibiotic prescribing in healthcare settings Literature review and behavioural analysis. 2015.

(<https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/405031/Behaviour_Change_for_Antibiotic_Prescribing_-_FINAL.pdf>

1. Jane Mingjie Lim, Shweta Rajkumar Singh, Minh Cam Duong, Helena Legido-Quigley, Li Yang Hsu, Clarence C Tam, Impact of national interventions to promote responsible antibiotic use: a systematic review, Journal of Antimicrobial Chemotherapy
2. Veterinary Medicines Directorate (2019). UK One Health Report - Joint report on antibiotic use and antibiotic resistance, 2013–2017. New Haw, Addlestone: Veterinary Medicines Directorate.