Cangini Agnese (Orcid ID: 0000-0002-1640-3993)
Fortinguerra Filomena (Orcid ID: 0000-0002-6587-9808)

Title: Monitoring the community use of antibiotics in Italy within the National Action Plan on Antimicrobial Resistance

Authors: Agnese Cangini*, Filomena Fortinguerra*, Aurora Di Filippo*, Andrea Pierantozzi*, Roberto Da Cas°, Federico Villa§, Francesco Trotta*, Maria Luisa Moro^, Carlo Gagliotti^
* Agenzia Italiana del Farmaco (AIFA), Via del Tritone, 181-00187, Rome, Italy
§ Università del Piemonte Orientale "Amedeo Avogadro", Department of Pharmaceutical Sciences, Largo Guido Donegani 2, 28100, Novara, Italy
^Agenzia Sanitaria e Sociale Regionale Emilia-Romagna, Viale Aldo Moro 21, 40127 Bologna, Italy
° Istituto Superiore di Sanità, Viale Regina Elena, 299 – 00161 Rome, Italy

Corresponding author contact information: Agnese Cangini, Via del Tritone, 181-00187, Rome, Italy, a.cangini@aifa.gov.it

Principal Investigator statement: This manuscript is not a report on primary research performed with human subjects/patients; thus, there is no Principal Investigator for this paper.

Running Head: Community use of antibiotics in Italy

Keywords: Antibiotics; antimicrobial resistance; antimicrobial stewardship; prescriptions; drug utilization

Word count, table count, figure count: 2613 words, 5 tables and 4 figures

What is already known about this subject:

- Antimicrobial resistance (AMR), which is considered a serious threat to public health worldwide, is correlated to the use of antibiotics.
- Antimicrobial stewardship programs need to be adapted to specific settings taking into account consumption patterns and prescription determinants. The assessment of geographical variability, patient characteristics and the possibility of linking prescriptions to clinical diagnoses enables intervention models to be adapted to the context making them more effective.
- In Italy both the community consumption of antibiotics and the prevalence of bacterial resistance are higher than in other European countries.

What this study adds

- This study provides a model of analysis and presentation of antibiotic consumption data that can be replicated in other countries: different information sources and indicators are used (for example, prescriptions and prevalence of use are used for children); there is a strong focus on the informative value of data with disaggregation based on geographic areas and type of patients; information on diagnoses from a sentinel network of general practitioners is also provided; the seasonality of prescriptions is shown in parallel with the trend of flu syndromes.
- The analysis and presentation of these data (partly already used in national reports) is not only a surveillance activity but also acts as an implementation tool within the National Action Plan on Antimicrobial Resistance (PNCAR, 2017-2020) to allow the comparison between regions and promote the improvement actions already adopted in those settings that have better prescriptive profiles.
- This study fills an information gap on Italy's consumption and prescribing patterns which are presented in aggregate form in European reports, not highlighting the profound differences between areas both in terms of quantity and type of antibiotics used. In addition, the articles published so far are often in Italian and concern only some regions of the country.

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. In 2018 the resistance in Escherichia coli to fluoroquinolones was 41.7% in Italy *versus* 25.3% in Europe; while the resistance in Escherichia coli to third-generation cephalosporins was 28.7% in Italy *versus* 15.1% in Europe [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. In Italy, the NHS is organised into three levels: national, regional (19 Regions and 2 Autonomous Provinces) and local. The coverage, prices and mode of dispensation of antibiotics reimbursed by INHS, similarly to other medicines, are centrally defined by AIFA with the support of two Committees: Technical Scientific Committee (Commissione Tecnico Scientifica - CTS) and Prices and Reimbursement Committee (Comitato Prezzi e Rimborso - CPR), after the submission of the price and reimbursement dossier by the Marketing Authorisation Holders (MAHs). According to the current reimbursement classification, medicines are categorised in two groups: Class A comprises medicines covered by INHS which require a medical prescription. This class also includes the

subgroup H, that is medicines requiring specialist supervision and which are eligible for reimbursement only when used in an inpatient setting; Class C includes medicines not reimbursed by the INHS (with the exception of subjects with a lifetime war pension). Systemic antibiotics not reimbursed by INHS are dispensed only on the presentation of the medical prescription [20]. Regions, which are responsible for organizing the delivery, taking into account the population health needs, and for promoting the quality, appropriateness and efficiency of the services provided, have been issuing specific interventions, including guidelines, educational interventions for patients and physicians and consumption monitoring, to promote appropriateness of antibiotics use [21-22-23-24] and to contain the inefficient expenditure.

Sources and Methods

The consumption data for reimbursed (Class A) 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 [25]. 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 [26].

Regions are grouped in three geographic areas according to the Italian National Statistics Institute's classification; in the North group the following regions were included: Piemonte, Valle d'Aosta, Liguria, Lombardia, Provincia Autonoma di Trento e Provincia Autonoma di Bolzano, Veneto, Friuli-Venezia Giulia and Emilia-Romagna. In the Centre group the following regions were comprised: Toscana, Umbria, Marche and Lazio. In the South group Abruzzo, Molise, Campania, Puglia, Basilicata, Calabria, Sicilia and Sardegna were included [27].

Since it is not possible to analyse medicines use in children by using DDDs owing to the variability of children's doses (according to weight and age) and to fact that the WHO DDD/ATC index reports DDD referred to adult subjects only [28], 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) 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 other beta-lactam antibacterials, quinolones, macrolides and penicillins (**Figure 1**). The use of antibiotics was greater in extreme age groups than in the population aged between 20 and 64 years. In the paediatric population, aged between 0 and 4 years, the prevalence of use was 54.6% in males and 52.0% in females and in the elderly, after 75 years, 50.7% in men and 50.4% in women; in the population aged 85 and over the prevalence of use reached a percentage of 64.3% in men and 58.1% in women; while, in the population aged between 20 and 64 years, the prevalence of use was 29.8% in men and 38.7% in women. In this group there was a greater exposure to antibiotics in women than in men. 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**); in 2018 the consumption observed in January (24.5 DDD per 1,000 inhabitants per day) was over twice the consumption registered in August (11.4 DDD per 1,000 inhabitants per day); moreover, the antibiotic consumption was higher in winter season with particularly high peaks in the incidence of flu syndromes (**Figure 4**). In the years with minor incidence of flu syndromes, corresponding to the periods 2013-2014 and 2015-2016, the highest consumption was, respectively, 23.5 and 22.0 DDD per 1,000 inhabitants per day; on the other hand, in periods

2017-2018 and 2018-2019, with a major incidence of flu syndromes, the highest consumption was 25.5 and 22.4 DDD per 1,000 inhabitants per day, respectively. 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: -2.2%) and in the three geographical areas (North, Centre and South, CAGR: -2.2%, -2.6% and -2.1% respectively) (**Table 1**; **Figure 3**). The same decreasing trend was observed also when considering the consumption of the different antibiotic groups, with major reductions for broad spectrum penicillins (CAGR: -5.9%) and parenteral cephalosporins (CAGR -3.8%). (**Figure 5**)

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 (**Figure 6**). 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 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 (prescriptions rate) and relative terms (as a percentage of the entire ATC group J01): 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. A ratio higher than one would be the expected situation where the treatment with amoxicillin is preferred to that with amoxicillin associated with clavulanate. The latter should be used with caution because: it has a greater impact on resistance, has a lower intestinal tolerability and does not add anything to amoxicillin alone for the treatment of pneumococcal infections which is the most relevant pathogen in children's respiratory bacterial infections [29-30].

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. Published studies investigated the potential contributing factors to variability in antibiotics' consumption which include the physician–patient (parents) relationship, patient socio-economic status, clinical microbiology and the difficulties faced by physicians in differentiating viral from bacterial infections [31-32] as well physician characteristics [33]. 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 [9-11].

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 [34-35-7]. 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 [36].

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 [35].

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 [34-35-7]. 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 [34-35]. 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 [34-35].

Other countries, within the strategies to counter the rise in AMR, have published national report to monitor the antibiotics' consumption [37]. 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 allow the monitoring of the consumption in the medium-long term. Nevertheless, the analysis presents limitations typically characterising the studies relying on the administrative reimbursement databases of dispensed medicines [38]: these data, although they could not represent the true medication intake, can provide an adequate estimate since they refer to all prescribed antibiotics in Italy and allow the comparison between regions and the evaluation of temporal trends. The database lacks 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. The lack of systematic diagnostic test could lead to a misclassification between bacterial and viral infections. However, the detected level of antibiotics use is much higher than the expected, particularly in areas of the south of the country. 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 food-producing animals, 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. This study describes Italian consumption and prescribing patterns in the different geographical areas both in terms of quantity and type of antibiotics used, providing useful information to guide decision makers in the different settings in applying the tailored interventions and to monitor the impact of the PNCAR.

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.

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. 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 Available from 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. 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. Available from 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. 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 Available from https://www.ema.europa.eu/en/documents/press-release/disabling-potentially-permanent-side-effects-lead-suspension-restrictions-quinolone-fluoroquinolone_en.pdf
15. The Medicines Utilisation Monitoring Centre. National Report on antibiotics use in Italy. Year 2017. Rome: Italian Medicines Agency. 2019. Available from https://www.aifa.gov.it/sites/default/files/Rapporto-L%27uso_degli_antibiotici_in_Italia_2017_0.pdf
16. The Medicines Utilisation Monitoring Centre. National Report on antibiotics use in Italy. Year 2018. Rome: Italian Medicines Agency. 2019. Available from

https://www.aifa.gov.it/documents/20142/1074882/Rapporto_Antibiotici_2018.pdf/755967e7-575f-ca86-9aeb-7c557b612e03
17. The Medicines Utilisation Monitoring Centre. National Report on antibiotics use. Rome: Italian Medicines Agency. 2009. Available from http://www.agenziafarmaco.gov.it/content/rapporto-sulluso-dei-farmaci-antibiotici-analisi-del-consumo-territoriale-nelle-regioni-ital
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. 2020;18(2):165-170.
20. A. Cangini, F. Villa and F. Mammarella et al., How medicines are used in Italy: Data from the National Report 2018, Health Policy and Technology, https://doi.org/10.1016/j.hlpt.2019.12.002
21. Agenzia sanitaria e sociale regionale dell'Emilia-Romagna. Faringotonsillite in età pediatrica. Linea Guida Regionale, Marzo 2015
22. –Agenzia sanitaria e sociale regionale dell'Emilia-Romagna. Otite media acuta in età pediatrica. Linea Guida Regionale. Marzo 2015
23. Regione Campania. Deliberazione Giunta Regionale (DRG) n. 767 del 28/12/2016 "Linee di indirizzo e coordinamento per le aziende sanitarie ed ospedaliere della Campania sull'uso appropriato degli antibiotici e sul controllo delle infezioni da organismi multi resistenti per l'attuazione delle Azioni specifiche previste dal Piano Regionale della Prevenzione 2014-2018".
24. Regione Puglia. Deliberazione della Giunta Regionale (DGR) n. 177 del 14 febbraio 2017 "Misure urgenti per la razionalizzazione della spesa farmaceutica territoriale - Interventi volti ad incrementare l'appropriatezza prescrittiva dei farmaci Antibiotici." Bollettino Ufficiale della Regione Puglia - n. 25 del 24-2-2017
25. WHO Collaborating Centre for Drug Statistics Methodology, Guidelines for ATC classification and DDD assignment 2020. Oslo, Norway, 2019.
26. The Medicines Utilisation Monitoring Centre National report on medicines use in Italy. Year 2018. Italian Med. Agency 2019. [Internet]. 2019. Available from https://www.aifa.gov.it/documents/20142/0/Rapporto_OsMed_2018.pdf/c9eb79f9-b791-2759-4a9e-e56e1348a976
27. Istat. Annuario Statistico Italiano 2019. Available from https://www.istat.it/it/files/2019/12/Asi-2019.pdf
28. WHO Collaborating Centre for Drug Statistics Methodology, Guidelines for ATC classification and DDD assignment 2020. Oslo, Norway, 2019. Available from https://www.whocc.no/filearchive/publications/2020_guidelines_web.pdf
29. Cosgrove SE, Qi Y, Kaye KS, Harbarth S, Karchmer AW, Carmeli Y. The impact of methicillin resistance in Staphylococcus aureus bacteremia on patient outcomes: mortality, length of stay, and hospital charges. Infect Control Hosp Epidemiol. 2005;26:166–174. doi: 10.1086/502522

30. Salvo F, Polimeni G, Moretti U, Conforti A, Leone R, Leoni O. Adverse drug reactions related to amoxicillin alone and in association with clavulanic acid: data from spontaneous reporting in Italy. J Antimicrob Chemother. 2007;60:121–126. doi: 10.1093/jac/dkm111
31. 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
32. . Russo V, Monetti VM, Guerriero F, Trama U, Guida A, Menditto E, Orlando V. Prevalence of antibiotic prescription in southern Italian outpatients: real-world data analysis of socioeconomic and sociodemographic variables at a municipality level. Clinicoecon Outcomes Res. 2018;10:251-258.
33. 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.
34. European Commission. EU Guidelines for the prudent use of antimicrobials in human health. Luxembourg: European Commission; 2017. Available from (https://ec.europa.eu/health/amr/sites/amr/files/amr_guidelines_prudent_use_en.pdf)
35. Public Health England. Department of Health. Behaviour change and antibiotic prescribing in healthcare settings Literature review and behavioural analysis. 2015. Available from (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/405031/Behaviour_Change_for_Antibiotic_Prescribing_-_FINAL.pdf)
36. 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
37. Veterinary Medicines Directorate (2019). UK One Health Report - Joint report on antibiotic use and antibiotic resistance, 2013–2017. New Haw, Addlestone: Veterinary Medicines Directorate.
38. Piovani D, Clavenna A, Bonati M; Interregional Italian Drug Utilisation Group. Drug use profile in outpatient children and adolescents in different Italian regions. BMC Pediatr. 2013;13:46.

Table 1. Consumption (DDD per 1,000 inhabitants per day) of reimbursed antibiotics (J01) dispensed by community pharmacies in Italy in 2018

Region	2013	2014	2015	2016	2017	2018	Δ % 18-17	CAGR 13-18
Piemonte	14.8	14.2	13.9	12.9	12.7	12.7	0.4	-2,52
Valle d'Aosta	14.6	14.1	14.1	12.3	12.5	12.8	2.4	-2,17
Lombardia	15.1	14.6	14.5	13.8	13.6	13.7	0.3	-1,61
PA Bolzano	10.4	9.9	9.8	9.1	8.7	8.9	2.8	-2,56
PA Trento	14.4	14.4	14.2	13.3	13.7	13.5	-1.1	-1,07
Veneto	13.5	13.2	12.5	11.8	11.8	11.7	-0.5	-2,36
Friuli VG	13.1	12.5	12.4	11.6	11.9	11.8	-1.3	-1,73
Liguria	13.0	12.1	11.9	11.0	11.2	11.3	1.0	-2,31
Emilia R.	15.1	14.7	14.0	13.4	12.7	13.0	1.8	-2,46
Toscana	17.5	16.5	16.3	15.4	15.0	14.6	-2.8	-2,97
Umbria	20.5	19.6	19.1	18.6	18.2	18.1	-0.5	-2,05
Marche	19.7	19.3	18.6	18.3	17.7	17.8	0.5	-1,68
Lazio	21.4	20.0	19.5	18.5	18.2	18.1	-0.5	-2,75
Abruzzo	20.9	20.8	20.4	20.1	19.6	20.4	3.8	-0,40
Molise	20.7	21.1	20.2	18.7	18.0	18.5	2.9	-1,86
Campania	26.3	26.1	25.4	24.8	23.4	23.4	0.2	-1,93
Puglia	24.6	24.7	24.0	23.2	21.5	20.5	-4.5	-2,99
Basilicata	21.1	20.8	19.8	18.8	18.6	18.5	-0.5	-2,17
Calabria	23.1	23.1	22.4	21.4	21.4	20.6	-3.3	-1,89
Sicilia	22.1	20.9	20.0	19.3	19.3	19.2	-0.5	-2,32
Sardegna	16.6	16.3	16.0	14.7	15.1	14.9	-1.4	-1,78
Italy	**18.4**	**17.9**	**17.4**	**16.6**	**16.2**	**16.1**	**-0.5**	-2,20
North	14.5	13.9	13.6	12.9	12.7	12.7	0.4	-2,18
Centre	19.8	18.8	18.3	17.5	17.1	16.9	-1.0	-2,60
South	23.2	22.9	22.2	21.4	20.6	20.4	-1.1	-2,12

CAGR=compound annual growth rate

Table 2. Prevalence of inappropriate use of antibiotics by condition and geographic areas

Prevalence of use%				
Geographic areas	**Any antibiotic Flu, cold or acute laryngotracheitis**	**Fluoroquinolones, cephalosporins and macrolides Pharyngitis and Tonsillitis**	**Intravenous Cephalosporins and fluoroquinolones Acute bronchitis**	**Fluoroquinolones Not complicated Cystitis**
Italy	33,1	30,9	29,8	34,2
North	27,6	28,6	19,8	32,6
Centre	35,1	29,2	29,2	36,8
South	40,7	34,5	42,1	34,3

Table 3. Prevalence of community use of fluoroquinolones (J01MA) by Italian regions in 2018

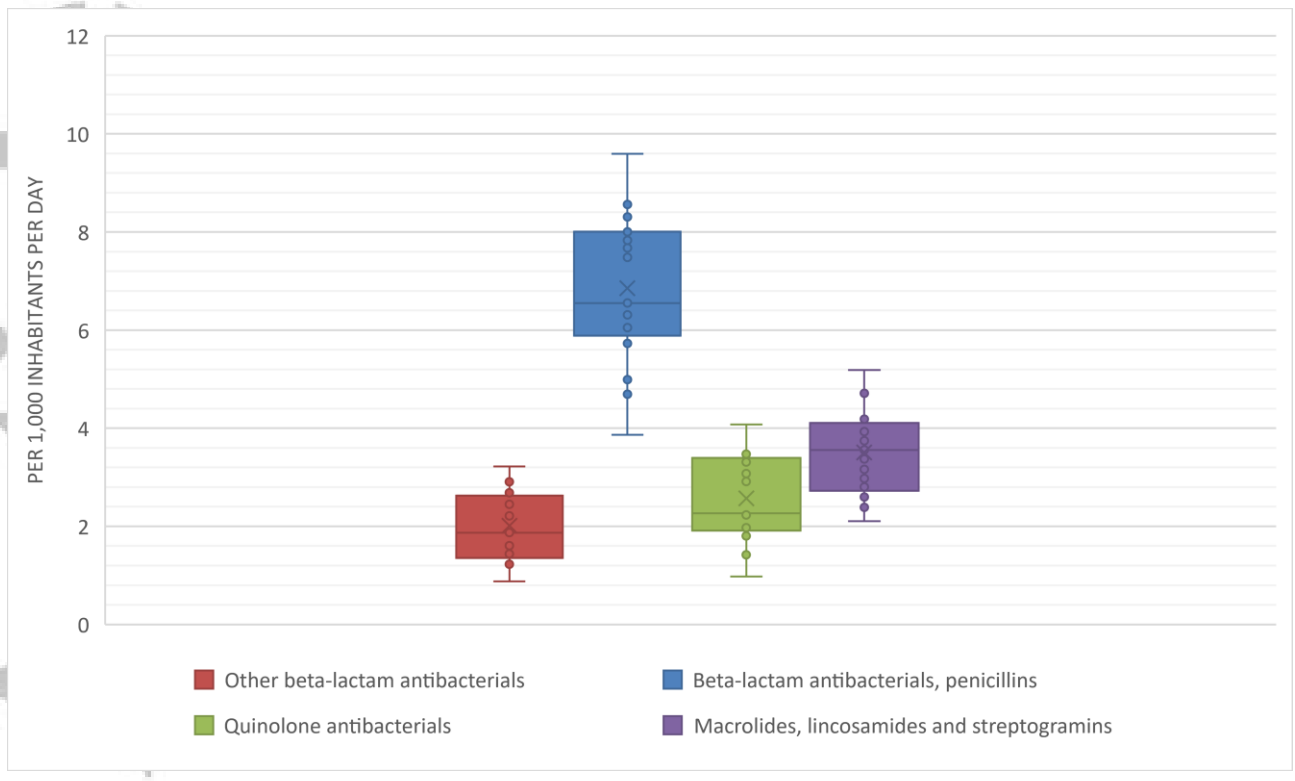
	Prevalence (%) Women 20-59 years	**Prevalence (%) Elderly ≥75 years**
Piemonte	7.4	18.3
Val d'Aosta	7.6	18.2
Lombardia	7.1	17.4
Bolzano	3.9	9.3
Trento	7.8	19.6
Veneto	7.1	17.7
Friuli VG	5.1	12.1
Liguria	6.6	17.3
Emilia R.	5.6	14.2
Toscana	7.4	21.6
Umbria	10.7	30.0
Marche	9.7	24.4
Lazio	9.1	25.6
Abruzzo	10.3	25.3
Molise	10.2	27.7
Campania	11.8	35.3
Puglia	10.6	29.6
Basilicata	10.1	28.9
Calabria	9.1	32.0
Sicilia	9.5	33.8
Italy	**8.4**	**22.5**
North	6.8	16.7
Centre	8.8	24.4
South	10.2	30.5

Table 4a. Prevalence of antibiotics use in paediatric population (0-13 years) by geographic area and ATC group in 2018

Geographic area	J01	J01CA	J01CR	J01DB	J01FA	Others
Italy	40,8	9,1	21,6	11,8	12,1	1,1
North	36,6	11,8	18,6	8,5	9,1	0,8
Centre	41,6	6,9	25,1	12,3	11,3	1,0
South	45,9	6,8	23,6	15,9	16,3	1,5

Table 4b. Prescription of antibiotics in paediatric population (0-13 years) by geographic area and therapeutic group in 2018

Therapeutic group	**Prescriptions per 1,000 children**			
	North	**Centre**	**South**	**Italy**
Broad-spectrum penicillins (J01CA-CE-CF)	245	124	113	175
Combinations of penicillins, incl. beta-lactamase inhibitors (J01CR)	359	471	412	399
Cephalosporins (J01DB-DC-DD-DE)	163	233	311	228
Macrolides (J01FA)	138	171	260	187
Other	14	21	28	20
Total	**920**	**1,020**	**1,122**	**1,010**



Legenda

The line inside the box represents the median of the regional distribution values; the ends of the box represent the first and third quartiles; the "whiskers" indicate the upper and lower values.

Only groups with a consumption major than 1 DDD per 1.000 inhabitants were reported

Figure 1. Regional variability in the consumption of antibiotics (DDD per 1,000 inhabitants per day) by ATC III level in 2018

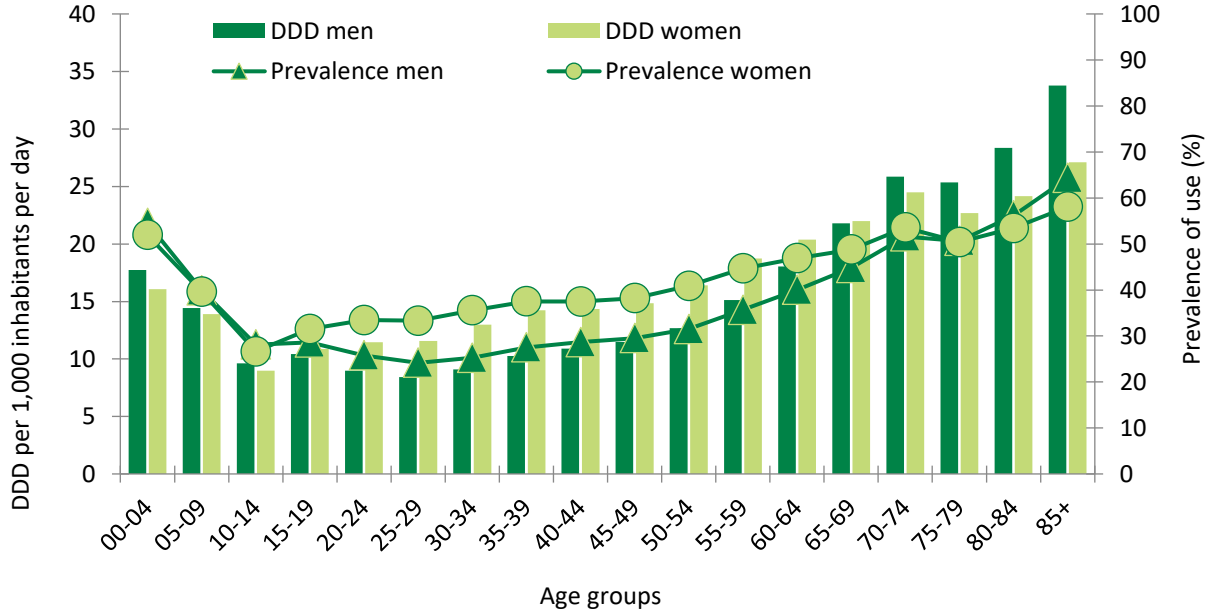
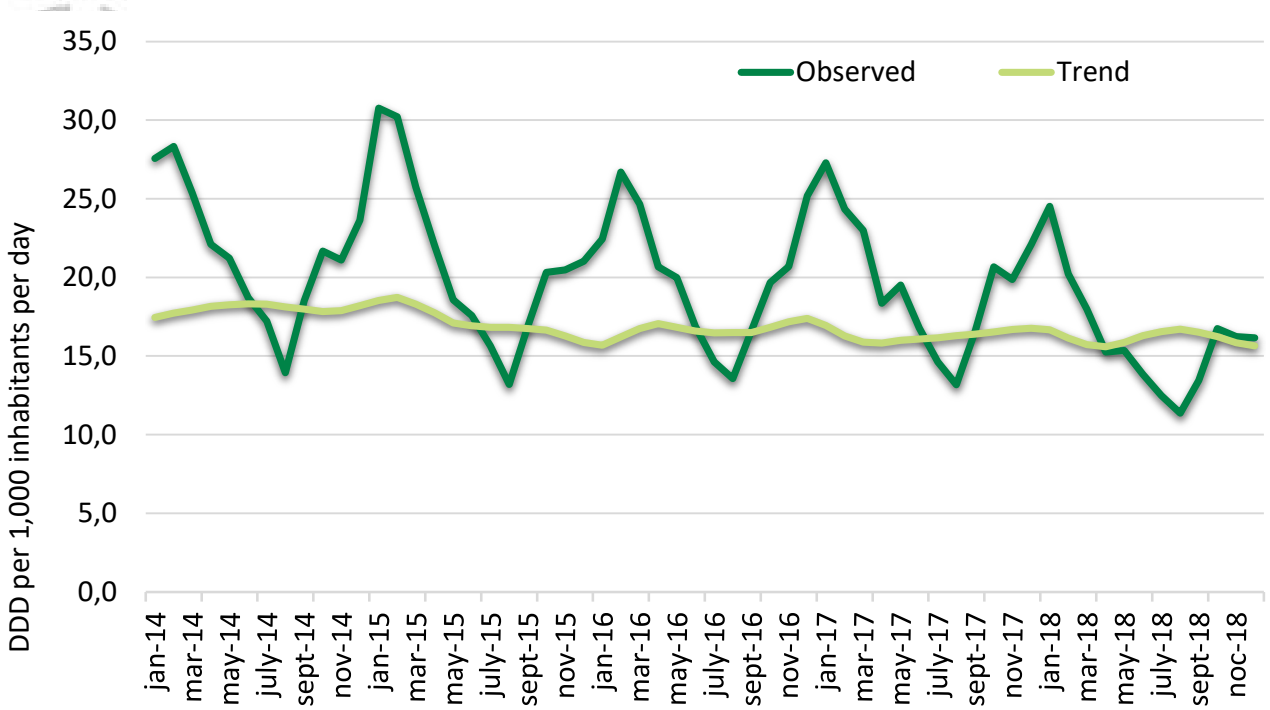


Figure 2. Consumption (DDD per 1,000 inhabitants per day) and prevalence of use of antibiotics (J01) in community setting by age and gender in Italy in 2018



The average monthly consumption (DDD/1000 inhabitants per day) was computed to assess the change in consumption during the study period. To eliminate seasonal components related to drug consumption, we conducted seasonal decomposition of the series. The Seasonal Decomposition procedure decomposes a series into a seasonal component, a combined trend and cycle component, and an "error" component. The procedure is an implementation of the Census Method I, otherwise known as the ratio-to-moving-average method. The approach used for the modeling of seasonal factors is multiplicative: the seasonal component is a factor by which the seasonally adjusted series is multiplied to yield the original series. Trends in antibiotics consumption were plotted over time.

Figure 3. Trend on monthly basis of the consumption (DDD per 1,000 inhabitants per day) of antibiotics (J01) in Italy in the period 2014-2018

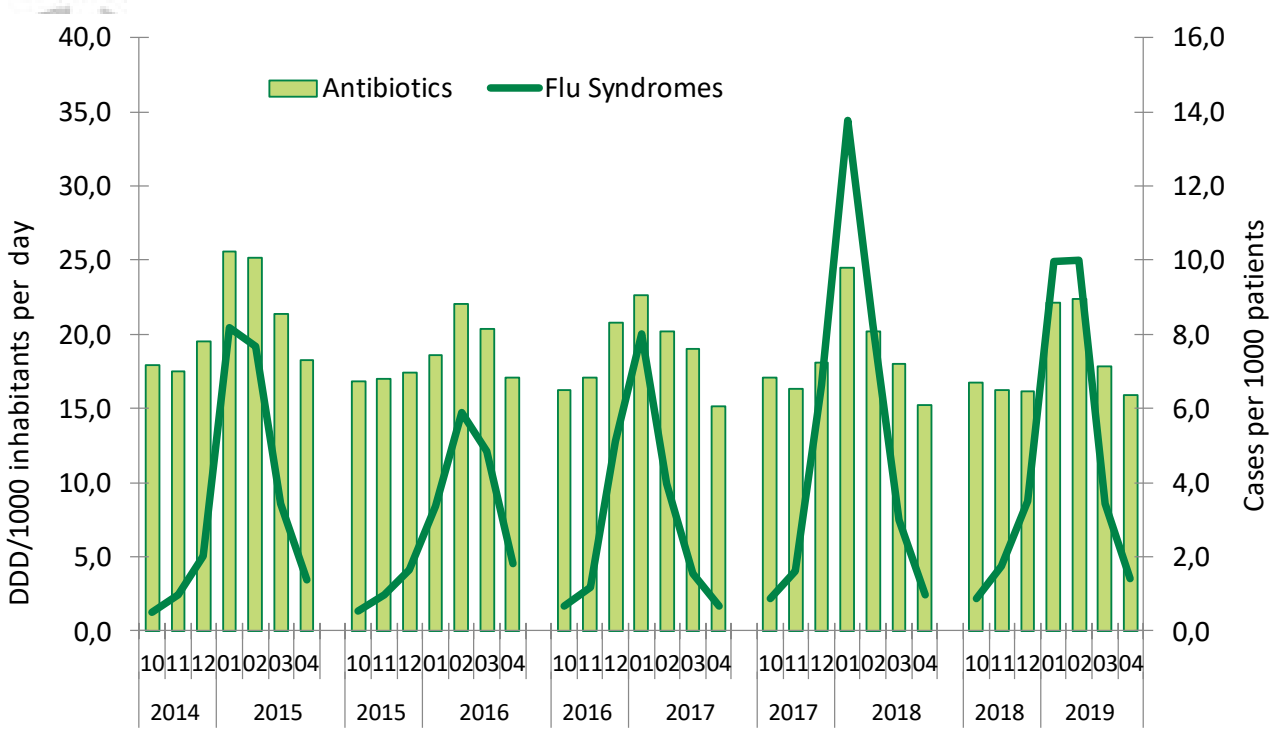


Figure 4. Correlation between consumption (DDD per 1,000 inhabitants per day) of antibiotics (J01) and incidence of flu syndrome in the period 2014-2018

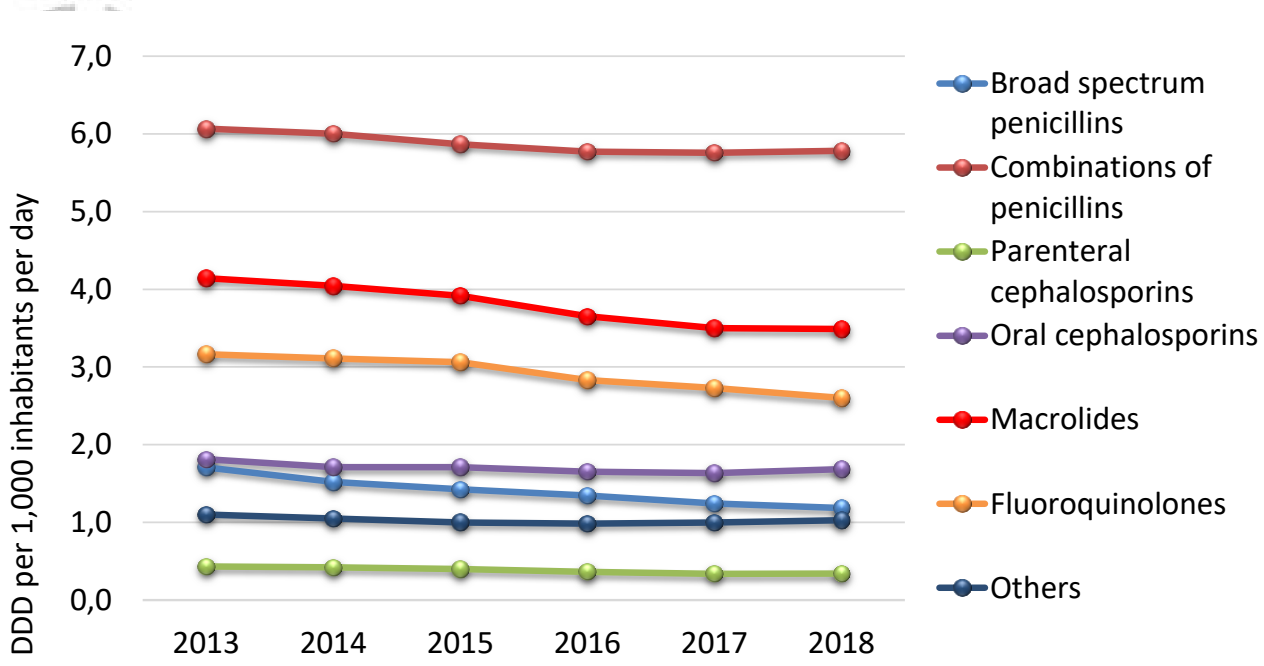
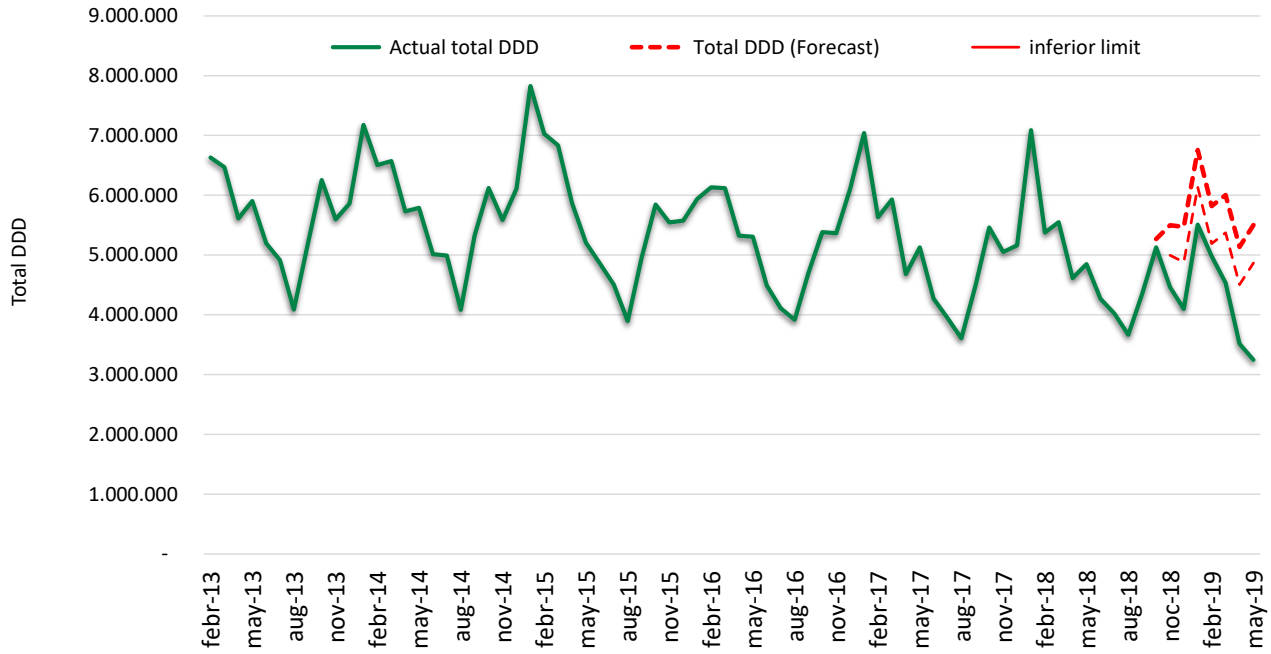


Figure 5. Trend on yearly basis of the consumption (DDD per 1,000 inhabitants per day) of antibiotics (J01) in Italy in the period 2013-2018 by antibiotic group



*EMA communication on fluoroquinolones and quinolones released on 16th November 2018.16/11/2018 (https://www.ema.europa.eu/en/documents/press-release/disabling-potentially-permanent-side-effects-lead-suspension-restrictions-quinolone-fluoroquinolone_en.pdf)

Figure 6. EMA communication effect on the fluoroquinolones consumption