Broad Spectrum project: factors determining the quality of antibiotic use in primary care: an observational study protocol from Italy

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ABSTRACT

Introduction: The overuse of antibiotics is causing worldwide spread of antimicrobial resistance (AMR). Compared with other countries, Italy has both high antibiotic consumption rates and high rates of AMR. Due to the fact that around 90% of antibiotics are prescribed by general practitioner (GPs), this study aims to measure the impact of knowledge, attitudes and sociodemographic and workplace-related factors on the quality of antibiotic prescriptions filled by GPs in the Italian Region of Sardinia.

Methods and analysis: Knowledge, attitude, sociodemographic and workplace-related factors deemed to influence physicians prescribing behaviour will be evaluated in a cross-sectional study conducted among all GPs of the Italian Region of Sardinia (n=1200). A knowledge and attitudes questionnaire (Knowledge and Attitudes on Antibiotics and Resistance - Italian version: KAAR) accompanied by a sociodemographic form will be linked to drug prescription data reimbursed by the National Health System. European Surveillance of Antibiotic Consumption quality indicators for outpatient antibiotic use will be calculated from drug prescription records. Every GP will be deemed to have demonstrated an adequate quality of prescriptions if half of the indicator score plus one is better than the median of the region. A multivariate Poisson regression model with robust variance estimation will be used to evaluate the impact of the determinants of antibiotic prescriptions on the actual prescribing quality of each physician.

Ethics and dissemination: The project has been approved by the ethics committee of the Regional Health Trust of Sardinia (176/2019/CE, 24 September 2019). The results will be useful to inform evidence-based interventions to tackle irrational antibiotic use in the community.

INTRODUCTION

Antimicrobial resistance (AMR) has emerged, alongside climate change, as a global threat to public health and wealth. Every year in Europe 33,000 people die due to infections caused by resistant bacteria and, globally approximately 700,000 cases of such infections occur every year. According to current estimates, AMR is causing an excess of healthcare system costs up to US$1 billion and a loss of gross domestic product (GDP) of US$3 trillion per year. By 2050, antimicrobial resistant bacteria will cause more than 10 million deaths each year and a global loss of GDP of more than US$100 trillion.

The overuse of antibiotics is one of the main drivers of AMR, but on a global scale antibiotic use is still rising. Italy has a higher...
consumption rate of antibiotics compared with many other European countries. In 2018, the annual consumption rate of Italian hospital and primary care sectors combined was 21.4 defined daily doses (DDDs)/1000 inhabitants/day (DIDs) and the vast majority of antibiotic prescriptions (ie, 90%, 19 DIDs) are filled by general practitioners (GPs). Aggregated level data show that there is a high variability of antibiotic prescription rates among different regions of the country and a high variability of antibiotic prescription rates in different seasons of the year, with highest rates occurring in influenza season. The finding of a strong seasonal variability seems to be consistent with previous studies that showed that, in general practice, the majority of antibiotics are prescribed for acute respiratory infections, such as acute bronchitis, otitis media, sinusitis or pharyngitis. In these conditions, according to guidelines, antibiotics are not routinely recommended and often inappropriately prescribed.

Moreover, the consumption of broad-spectrum antibiotics is approximately twice as high as in other European countries like Norway, Sweden or the UK.

For all these reasons it seems to be very likely that the majority of antibiotic prescriptions in Italy could be avoided. Both, qualitative and quantitative methodologies have been used in different settings of low-income, middle-income and high-income countries to understand the determinants of antibiotic overuse. Prescribing, especially antibiotic prescribing, is a complex behaviour, with intrinsic factors (sociodemographic variables, knowledge, attitudes) and extrinsic factors (signs and symptoms at presentation, comorbidity, sociodemographic variables, workload, influence of pharmaceutical companies, cost saving) that impact the healthcare professional decision. Therefore, to inform stakeholders (GPs, European and national agencies, scientific societies) in the development of effective interventions to tackle irrational antibiotic use, an understanding of the context specific determinants of antibiotic prescription is needed.

GPs have a key role in Italy’s National Health System (NHS). Virtually all of the resident population is compulsorily registered on a GP list and a pharmaceutical prescription can be charged to the NHS only if filled by a GP or a specialist consultant working directly for the NHS. Consequently, taking into consideration that in public healthcare systems GPs act as pharmaceutical gatekeepers, they could play an active role in tackling the phenomenon of antibiotic overuse and non-evidence-based prescription habits.

At the best of our knowledge, there are no published studies that measure, with validated tools, the knowledge and attitudes of GPs on AMR and antibiotic prescriptions in Italy. Moreover, we were not able to retrieve any study that evaluated the influence of knowledge and attitudes of GPs on their prescriptions of antibiotics in our settings.

Findings of this study will be useful to develop evidence-based physician-targeted interventions to improve the quality of antibiotic prescriptions among Italian GPs. Moreover, this study could serve as a generalisable methodological framework to gain an understanding of GPs prescription practices and, therefore, to develop effective interventions to foster good clinical practice in primary care.

**AIMS AND OBJECTIVES**

The study will be divided into two distinct but related parts: study axis A and study axis B.

**Study axis A**

**Aim**

To describe the attitudes and knowledge of GPs regarding AMR and antibiotic prescriptions by administering a questionnaire adapted from Spanish to Italian language, namely the Knowledge and Attitudes on Antibiotics and Resistance questionnaire (KAAR-11) for primary care physicians, adapted to Italian language and culture (ITA-KAAR).

**Objectives**

1. Measure the attitudes and knowledge of GPs through the administration of the ITA-KAAR questionnaire.
2. Describe the characteristics and working context of GPs by filling a sociodemographic form.
3. Evaluate the reliability and validity of the ITA-KAAR questionnaire.

**Study axis B**

**Aim**

To describe the quantity, pharmacological classes, appropriateness and interindividual variability of GPs prescriptions of antibiotics in the Italian region of Sardinia and to investigate the determinants of inappropriate prescriptions.

**Objectives**

1. Evaluate GPs antibiotic prescribing behaviour (quantity, pharmacological class, appropriateness, interindividual variability) through the analysis of prescription data of antibiotics for systemic use recorded in the administrative database of the Regional Health Trust of Sardinia (Azienda Tutela Salute, Sardegna).
2. Evaluate the association between the determinants of GPs prescribing behaviour (demographic factors, work environment, territorial context, attitudes and knowledge regarding antibiotics and resistance, resulting from the objectives A1 and A2) and the appropriateness of antibiotic prescriptions (resulting from the objective B1).

**METHODS AND ANALYSIS**

**Study design**

A cross-sectional study will be carried out for both study axis A and study axis B.
Study axis A
An attitudes and knowledge questionnaire (ITA-KAAR) and a sociodemographic form will be administered to all GPs working in the Italian region of Sardinia, to measure attitudes, knowledge and sociodemographic and work-context related factors deemed to be associated with AMR and antibiotic prescriptions.

Study axis B
A drug utilisation study will be conducted to evaluate the prescriptions and the appropriateness of antibiotic choice for systemic use of all Sardinian GPs and to investigate the influence of determinants of inappropriate prescription.

Study population and setting
All residents of the Sardinia Region are covered by the NHS, which provides comprehensive hospital and outpatient care for those registered with a GP. The GPs provide primary care for the whole temporarily or permanently resident population and a pharmaceutical prescription must be filled by a GP or a specialist consultant to be charged to the NHS.24

Study axis A
The entire Sardinian GP workforce (n=1200), providing care to 1 639 591 Sardinian inhabitants at the date of 1 January 2019, will be recruited.25 The ITA-KAAR questionnaire and a sociodemographic form will be filled by all GPs included in the study through an online platform.

Study axis B
All prescriptions of antibiotics for systemic use (Anatomical Therapeutic Classification—ATC J01) filled by Sardinian GPs will be extracted from the pharmaceutical database of the Regional Health Trust of Sardinia during the period 2017–2019. The database contains all prescriptions covered by the NHS and is regularly updated.

Outcome and covariates assessment
Study axis A
The knowledge and attitudes section of ITA-KAAR measures, by means of a Visual Analogue Scale (VAS), some of the GPs attitudes on AMR and antibiotic prescriptions, namely lack of knowledge, fear, external responsibility and complaisance to patient’s demands and expectations. The 7-item accessorial section of the questionnaire focuses on some of the main information sources for good clinical practice deemed to be relevant for GPs.

The questionnaire, including an additional section assessing sociodemographic and work-context related factors potentially associated with the appropriateness of antibiotic use, will be sent through an online platform via email to all GPs of the region of Sardinia. Reminders will be sent to non-responders every 10–14 days. The first 100 responders will be asked to complete the questionnaire a second time after 10–14 days (test–retest reliability). After this first phase of data collection, in case of low response rate, a comprehensive stepwise approach (including phone calls, postal reminders, reminders at continuous medical education events, involvement of locally known network leaders, professional associations and the state medical boards) will be used to achieve an acceptable response rate (see the Sample size section).26

The KAAR-11 questionnaire has shown to be a reliable and valid instrument to assess attitudes and knowledge of GPs on AMR and antibiotic prescriptions. The questionnaire was developed taking into account the findings of a literature review and a qualitative focus group study.20 27

The ITA-KAAR (KAAR-11 adapted to Italian language and culture, box 1) has been produced using the cross-cultural adaptation methodology described by Beaton and colleagues.28

Four professional translators and two bilingual physicians performed independently three forward and three backward translations of the original Spanish questionnaire. All the translators were naive to the aims and scopes of the study. An expert committee, composed by primary care physicians, research methodologists, a mental health expert, a university professor for pharmacology, a university professor for microbiology, two university professors for Italian and Spanish language and all the involved translators, reviewed the translations and produced a prefinal version of the questionnaire. A pilot study was carried out by administering the prefinal version of ITA-KAAR to an convenience sample of the target population (45 GPs working in different regions of Italy). Among these, two GPs from the Sardinian region participated in the pilot study of the cross-cultural adaptation process and will be therefore excluded from the study (axis A). Comments and suggestions of the responders were registered and the necessary amendments to the prefinal version were...
made to produce the final version of the ITA-KAAR. The detailed process of cross-cultural adaptation and preliminary validation are described elsewhere.29

An English version of ITA-KAAR and the sociodemographic form is provided in online supplementary file 1.

Study axis B
The Regional Health Trust of Sardinia will provide the data of all prescriptions of antibiotics for systemic use (ATC J01) filled by GPs between 1 January 2017 and 31 December 2019. For each GP and for each year of the study, DDDs and DID of the prescribed antibiotics and European Surveillance of antibiotic Consumption (ESAC) quality indicators for outpatient antibiotic use 30 will be calculated.

The following ESAC quality indicators will be considered:
1. J01_DID: consumption of antibiotics for systemic use (ATC J01) expressed in DDD.
2. J01C_DID: consumption of penicillins (ATC J01C) expressed in DDD.
3. J01D_DID: consumption of cephalosporins (ATC J01D) expressed in DDD.
4. J01F_DID: consumption of macrolides, lincosamides and streptogramins (ATC J01F) expressed in DDD.
5. J01M_DID: consumption of quinolones (ATC J01M) expressed in DDD.
6. J01CE_%: consumption of b-lactamase-sensitive penicillins (ATC J01CE) expressed as a percentage.
7. J01CR_%: consumption of combinations of penicillins, including b-lactamase inhibitors (ATC J01CR) expressed as a percentage.
8. J01DD+DE_%: consumption of third and fourth generation cephalosporins (ATC J01DD+J01DE) expressed as a percentage.
9. J01MA_%: consumption of fluoroquinolones (ATC J01MA) expressed as a percentage.
10. J01_B/N: ratio of the consumption of broad-spectrum (ATC J01CR+J01DC+J01DD+J01F excluded J01FA01) to the consumption of narrow spectrum penicillins, cephalosporins and macrolides (ATC J01CE+J01DB+J01FA01).
11. J01_SV: seasonal variation in total antibiotic consumption (ATC J01).
12. J01M_SV: seasonal variation in quinolone consumption (ATC J01M).

To take into account the different prevalence of consumption of antibiotics by patient’s age and gender, all the indicators will be calculated on the weighted population (based on the weights set up by the Department of Programming of the Italian Ministry of Health, online supplementary file 2) of the patients registered in the list of each physician. In particular, patients will be classified in age and gender classes; the number of subjects in each age and gender class will be multiplied by the corresponding weight; the sum of the values obtained will be proportionally reported to the regional population.

For each physician, a better performance in half plus one of the ESAC quality indicators compared with the median of the region, will be considered as an indicator of adequate quality of prescriptions of antibiotics (AQPA).

In order to better describe the variability of antibiotic prescribing behaviour of the study subjects in terms of use of first and second line drugs, for each GP and for each year of the study, prescriptions of antibiotics for systemic use (ATC J01) will be classified in the three groups of the WHO Essential Medicines List Access, Watch, and Reserve (AWaRe) classification.31

For the correspondence between ATC and WHO Essential Medicines List AWaRe classification see the online supplementary file 3.

Statistical analysis
All statistical analysis will be performed using R or MPLUS.32,33 Continuous variables will be described by mean and SD and, in case of asymmetric distributions, the median and IQR will be used. Categorical variables will be represented through frequency distributions (absolute and percentage values). Comparisons between groups will be made, for continuous variables through the t test (Mann-Whitney U test where necessary), while for categorical variables through the χ² test (Fisher’s exact test where necessary). Statistical significance will be expressed in terms of p values (p ≤ 0.05) and the 95% CIs will be added to the point estimates.

Study axis A
Handling of missing data will be dealt by imputation methods if the percentage of missing values is low (<3% for each item). Otherwise, observations with missing values will be excluded from the analysis.

Cronbach’s alpha will be used to assess the internal consistency of the total scale. The correlations between the items of the questionnaire will also be examined: items with a correlation lower than 0.30 will be considered for removal from the questionnaire, as well as items whose exclusion leads to an improvement in Cronbach’s alpha value of 0.001 or more. To evaluate the test–retest reliability, the Pearson correlation coefficients will be calculated between the scores at the first and second administration. Furthermore, the intraclass correlation coefficients will be calculated.

The factorial structure of the ITA-KAAR will be evaluated through an exploratory factor analysis (EFA), using the maximum likelihood estimation (MLE). The number of factors to be included in the EFA will be decided after (1) evaluation of the number of eigenvalues ≥1, (2) the screeplot and (3) the parallel analysis. The following goodness of fit indexes will be used to evaluate the different models: Tucker-Lewis Index ≥ 0.95 and ≥ 0.90 indicating a good or sufficient fit, respectively and the root mean square error of approximation ≤ 0.05 or ≤ 0.08 indicating good or sufficient fit, respectively. The correlation between factors will be estimated using the Pearson coefficient. Indicators with loadings less than 0.30 will be
considered for the removal from the questionnaire. Path diagrams will be used to compare the loadings of each factor. To evaluate the known-group validity, the medians of the questionnaire as a whole, for groups of items that explore the same domains and for the single items of the ITA-KAAR for the two groups of opposing doctors will be compared. These groups will be identified as the first and last decile of the percentage of ESAC indicators that, for each doctor, are greater than the reference value (median of the region).

To determine the ability of the ITA-KAAR in discriminating the prescribers with (AQPA=1) from those with inadequate quality of prescriptions (AQPA=0), a Receiver operating characteristic (ROC) analysis will be performed with evaluation of the area under the curve (AUC). The following scheme will be used for the interpretation of the AUC values: AUC=0.5: no discriminative ability; 0.5<AUC<0.7: inaccurate discriminative ability; 0.7< AUC<0.9: moderately accurate discriminative ability; 0.9< AUC<1.0: highly accurate discriminative ability; AUC=1.0: perfect discriminative ability.

Study axis B

The analysis of the association between ESAC quality indicators (dependent variable), sociodemographic factors and the answers to the ITA-KAAR questionnaire (explanatory variables) will be conducted through a Poisson regression model with a robust estimator of variance and will be expressed in terms of prevalence risk ratio. Prescribing is a complex process and, as highlighted by Teixeira in a systematic review of qualitative studies, antibiotic prescribing is influenced by multiple determinants. Our study is intended to uncover the relationship between some of the most important hypothesised determinants of antibiotic prescriptions and the quality of prescription itself by using a theoretical framework of antibiotic prescribing behaviour. This model considers both, intrinsic and external factors to the healthcare professional that influences antibiotic prescription habits of primary care physicians (figure 1).

Sample size

The calculation of the sample size (number of GPs to be interviewed) was performed on the basis of the results of a previous study and a literature review. Assuming a log-normal distribution, a difference in the medians of each item between the compared groups (AQPA=1 vs AQPA=0) of 0.25 points on the VAS and an SD of 0.83 (corresponding to a range of variability of 99% of the values per single item equal to half of the VAS), a population of 1200 GPs, a response rate equal to or greater than 40% (n=480) guarantees a power of the association study greater than 80%.

Patient and public involvement

GPs developed the research questions, the overall conception of the project and the present research protocol in collaboration with epidemiologists and public health professionals, in order to gain a better understanding of their own prescribing behaviours. Local medical boards are involved in the dissemination of the ITA-KAAR questionnaire and in a peer-led dissemination of the results of this study.

ETHICS AND DISSEMINATION

This project has been approved by the Ethics committee of the Regional Health Trust of Sardinia (protocol number 176/2019/CE, 24 September 2019). The results of this study will be disseminated through publications in peer reviewed journals, relevant meetings, congresses and teaching sessions addressed to GPs and the public.

DISCUSSION

There are few doubts that AMR is strongly related to antibiotic consumption. Prescribing is a complex process and, as highlighted by Teixeira in a systematic review of qualitative studies, antibiotic prescribing is influenced by multiple determinants. Our study is intended to uncover the relationship between some of the most important hypothesised determinants of antibiotic prescriptions and the quality of prescription itself by using a theoretical framework of antibiotic prescribing behaviour. This model considers both, intrinsic and external factors to the healthcare professional that influences antibiotic prescription habits of primary care physicians (figure 1).

Despite the comprehensiveness of the proposed theoretical model, few studies tested it in practice. Therefore, we have designed a study to fill this lack of knowledge using the widely accepted knowledge, attitudes and practice survey methodology to assess the educational needs of GPs on AMR and antibiotic prescriptions. The chosen study design has a number of strengths. First, the ITA-KAAR, Italian version of the KAAR-11 questionnaire, which is the only fully validated scale developed to assess knowledge and attitudes of GPs regarding AMR and antibiotic prescriptions, was translated and adapted to Italian using a methodology aimed to maintain the psychometric properties of the original version of the scale and will undergo a full validation study. Second, in order to fully validate the ITA-KAAR against an external ‘gold standard’ (known-group validity) and to measure the magnitude of the association between each explanatory variable and the quality of antibiotic
prescription, we will use a set of valid, reliable and internationally accepted indicators, calculated using data from clinical practice. This leads to further strengths of our study design: (1) they allow comparability to similar studies performed across Europe; (2) their use excludes any opportunistic selection of indicators for the purpose to meet the study objectives.

Third, the categorisation of the prescriptions of antibiotics for systemic use (ATC J01 subclasses) according to the WHO AWaRe classification, will enhance the comparability of the results of the present study to these of similar studies performed globally and will be useful to shape an appropriate communication strategy in the context of antibiotic stewardship interventions targeted to GPs in the Sardinia region and nationally.

Fourth, the data source of the drug utilisation study (study axis B) is an administrative database containing any antibiotic prescription covered by the NHS, filled by every single GP in the examined period of time. This completeness is a well-known strength of drug utilisation studies performed on large administrative databases, that have been widely used as reliable data sources among European countries to inform policy.

A further strength of the study refers to the estimation methodology that will be used to measure the magnitude of the association between the hypothesised determinants of antibiotic prescriptions and the real prescription data used in this study, namely a multivariate Poisson model with robust estimation of variance. This model is generally preferred to the traditional logistic model in cross-sectional studies when the dependent variable is not rare. In fact, in the case of frequent outcomes, typical in cross-sectional studies, the OR, obtained from the application of the traditional logistic model, can lead to a strong overestimation of the prevalence ratio and therefore of the magnitude of the association. Moreover, similarly to the multivariate logistic model, the Poisson model produces association measures that are adjusted with respect to the other confounding factors.

Some potential limitations need to be mentioned. First, the response rate to a questionnaire could be low even if a comprehensive data collection strategy is planned. To minimise non-response bias (a type of selection bias) and exclude the risk that responders differ in meaningful ways from non-responders, a subgroup analysis of responders and non-responders to the questionnaire will be performed in relation to each ESAC indicator. In particular, for both subgroups the percentages of GPs who have shown an AQPA=1 or an AQPA=0 as defined above, will be calculated. In case of differences that do not reach statistical significance between the two subgroups, non-response bias could be reasonably excluded.

A second limitation could be that the ESAC quality indicators used in our study are not developed to consider the underlying reason of the prescription (ie, the diagnosis). The choice of these indicators above others that take into account the clinical reason for encounter was made because data regarding the underlying diagnosis are not available in our setting (GP health records that could be used for research purpose does not exist in the region of Sardinia). Nevertheless, we feel that the ESAC quality indicators without the underlying clinical diagnosis are appropriate indicators for the purposes of our study. In fact, after adjustment for patients age and gender, we have no reason to believe that the population of patients registered in the list of any single GP differ from each other significantly with respect of the occurrence neither of diseases for which antibiotics are currently prescribed in general practice, nor for other conditions that could act as relevant confounding factors.
Future perspectives

Considering that 90% of antibiotic prescriptions in human health are filled by GPs, the results of this study will be useful to inform stakeholders on the educational needs and the context specific determinants of antibiotic use and will serve the development and implementation of further targeted interventions to reduce antibiotic consumption and prescriptions in the community, namely:

1. The design, administration and implementation of a multifaceted intervention targeted to the needs of physicians, as revealed in the first phase of the study.

2. The assessment, in a prospective design, of the impact of this intervention on reducing antibiotic prescriptions.

Due to the fact that determinants of inappropriate use of antibiotics are context-specific, the overall aim of the ‘Broad Spectrum’ project is to create a methodological framework to be applied in other Italian and European regions to tackle inappropriate antibiotic use, thereby reducing and preventing the spread of antibiotic resistance.

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