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Economic analysis of drug policies on antibiotics and risk-sharing contracts

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DOCTORATE PROGRAM IN BUSINESS ECONOMICS

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List of abbreviations

AMR	Antimicrobial Resistance
ARIMA	Autoregressive Integrated Moving Average
BHZ	Basic Health Zone
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
COVID-19	Coronavirus-19
DDD	Defined Daily Dose
ESAC	Surveillance of Antimicrobial Consumption
GDP	Gross Domestic Product
IBM	International Business Machines
JCR	Journal of Citation Report
MINECO	Ministry of Economic Affairs and Digital Transformation
NHS	National Health System
PM	Personalized Medicine
PRAN	National Plan against Antibiotic Resistance
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
RDL	Royal Decree-Law 16/2012
RSC	Risk Sharing Contract
SJR	Scimago Journal Rank
SPSS	Statistical Package for the Social Sciences
TPR	Therapeutic Positioning Report
WHO	World Health Organization

Index

Statement

A compendium of published works is presented, in compliance with the regulations for the defence of doctoral thesis in the University of La Rioja, approved by the Government Council on November 3, 2016, which in Chapter V article 13, regulates the defence of doctoral thesis as a compendium of publications [1].

The works have been published as original articles in scientific journals whose impact index is included in the Journal Citation Report (JCR) or the Scimago Journal Rank (SJR). In all publications, the doctoral student appears as the main author. The full references of the publications that constitute the thesis are listed below:

Publication 1: Rojas García P, Antoñanzas Villar F. Risk Sharing Contracts in the national health care system: Perceptions of health care professionals. *Revista Española de Salud Pública*. 2018; 92: e201807041. Impact factor JCR (2018): 0,635 (Q4) [2]

Publication 2: Rojas García P, Antoñanzas Villar F. Assessment of the quality of antibiotics prescription in a regional health system. *Revista Clínica Española*. 2021; 221: 497-508. https://doi.org/10.1016/j.rce.2020.04.015. Impact factor JCR (2019): 1,304 (Q3) [3]

Publication 3: Rojas García P, Antoñanzas Villar F. Effects of economic and health policies on the consumption of antibiotics in a Spanish region. *Expert Review of Pharmacoeconomics & Outcomes Research*. 2019. doi: 10.1080/14737167.2019.1647105. Impact factor JCR (2019): 2,032 (Q2) [4]

Publication 4: Rojas García P, Antoñanzas Villar F. Policies to Reduce Antibiotic Consumption: The Impact in the Basque Country. Antibiotics. 2020; 9, 423: doi:10.3390/antibiotics9070423. Impact factor JCR (2019): 3,893 (Q1) [5]

Publication 5: Rojas García P, Antoñanzas Villar F. Analysis of the prescription of antibiotics during the implementation of COVID-19 personal protection measures in a regional health system. ClinicoEconomics and Outcomes Research. 2021; 13 (927-36) Impact factor SJR (2020): 0,59 (Q1) [6]

Chapter 1. Introduction

Health Economics is a branch of Applied Economics that studies the economic and health effects of health policy decisions [7]. The contributions of this field of study are characterised by applying the approaches of economic theory to the field of health, such as the allocation of goods and services to patients while maintaining the efficiency and equity of health systems [8].

The Spanish health spending in public budgets is increasing. In 2019, they amounted to 75.025 billion euros, which is equivalent to 1,593 euros per inhabitant and 6.1% of the Gross Domestic Product (GDP) [9]. In 2020, it increased to represent 7.6% of GDP and accounted for 14.4% of Public Administration spending [10].

Within healthcare spending, hospital and specialised services (estimated at 44.001 billion euros in 2019, with an increase of 6.3% compared to the previous year) and pharmaceutical spending (estimated at 11.265 billion euros in 2019, with an increase of 2.5% compared to the previous year) stand out [9]. The contributions that emerge from research in Health Economics attempt to issue recommendations to achieve an efficient allocation of health resources while managing to provide the best clinical results.

This thesis, entitled *Economic analysis of drug policies on antibiotics and risk-sharing contracts*, is part of the research line in Health Economics of the Doctoral Programme in Business Economics of the University of La Rioja. The development of this thesis has been carried out within the Research Group in Health Economics of the Faculty of Business Sciences during the academic period 2017-2022.

Likely, drugs constitute the most regulated economic good subject to an uncountable number of policies addressing every step of their development: trials in animals and humans, patent protection of the molecule,

plants, international approval (e.g. Food and Drug Administration -USA-, European Medicines Agency -EU-), package and handling, marketing authorisation by national authorities, price decision and public funding, prescription and administration, international trade, regional, national and international surveillance systems for safety purposes, health outcomes analysis, etc. These policies have important economic consequences in the chain of participants in addition to other health and equity implications.

This thesis has focused the attention towards the analysis of two sets of policies: the new type of agreements that pursue to guarantee the health outcomes of the drug linking its payment by the public health system to the benefits obtained by patients, and those regulations that have consequences in the prescription of antibiotics. The reasons behind this selection are mostly derived from the importance of these agreements to facilitate the prescription of new advanced therapies, whose unitary costs are over one million euros, with high uncertainties about the durability of their health outcomes (namely, gene and cell therapies), and also due to the growing consciousness and acknowledgement that infectious diseases have big impacts in society´s welfare. Furthermore, the practical reason that the research group of health economics was conducting two projects on these two topics also contributed to their selection.

The first publication included in the thesis was elaborated along the development of the National Project entitled *Personalized Medicine and Shared Risk Contracts as new paradigms of healthcare management: theoretical economic models and applications* (MINECO ECO2016-78685-R, 2016-2019), carried out by the Research Group in Health Economics of the University of La Rioja. One of the objectives of the project was to perform a descriptive study on the use of shared risk contracts and, in the case of personalised medicine, to determine if the introduction of these contracts into clinical practice might be desirable.

As a precedent to this publication, it should be noted that in the academic year 2016-2017, the work entitled *Personalized medicine and shared risk contracts: new paradigms of health management* was presented as the final project of the Master's Degree in Business Management at the University of La Rioja. The Research Group in Health Economics also participates in academic activities of this degree [11]. This work laid the foundations for the first publication presented in this thesis, the starting point of which was the medical advance that the complete sequencing of the human genome represented in 2003.

This achievement of medical research allowed the development of new diagnostic and treatment strategies such as gene therapies [12]. Although these therapies offer great hope, they also present challenges for healthcare system administrators, as there is little scientific evidence of their efficacy and the duration of long-term clinical outcomes [13]. In addition, the cost of these therapies is high, which puts significant pressure on health budgets [14].

An important part of the contributions of Health Economics focuses on economic evaluation studies of new technologies, as well as the analysis of the financing of the health system and efficient budget management [15]. In this sense, the first drug which includes an economic evaluation in its Therapeutic Positioning Report (TPR) has recently been approved in Spain: Talazoparib, indicated for patients with breast cancer. TPRs improve decision-making on the inclusion of the drug in the pharmaceutical service of the National Health System (NHS) and the setting of its price, taking into account the drugs indicated for the same pathology [16].

The drug Luxturna is an example of the high cost that gene therapies can entail. It is indicated for patients with vision loss due to hereditary retinal dystrophy [17,18]. In 2020, the Interministerial Drug Price Commission announced that an agreement had been signed for the financing of this drug through a payment-by-results agreement with strict inclusion and exclusion

criteria for patients [19]. This type of agreement, together with price-volume agreements (which adjusts the price to the prescription volume), is part of the so-called Risk-Sharing Contracts (hereinafter RSC) [20]. RSC is an alternative payment model that links drug reimbursement to specific clinical outcomes [21,22]. In the case of Luxturna, the health administrations and the pharmaceutical company are in charge of checking that the agreed payment conditions are met and the revision of the initial price set at 345,000 euros per dose [19].

Since the first RSC was signed in Spain in 2011, several agreements have been reached between Autonomous Communities and pharmaceutical companies [24]. However, no evidence exists that proves that the NHS has profited from the clinical or economic benefits expected from signing RSCs. In the first publication of this thesis, this research question has been delved upon, and some barriers were pointed out which prove that RSCs could not be having the boom that had theoretically been attributed to them [23–25].

The following publications included in the thesis are related to the implications of different policies and regulations in the antibiotic use. In this occasion, the research was elaborated along the development of the European Project entitled *The value of diagnostics to combat antimicrobial resistance by optimizing antibiotic use* (European Commission: 820755 Call: H2020-JTI-IMI2-2017-13-two-stage. 2019-2023), in which the Health Economics Research Group participates, and the doctoral student collaborates since the 2018-2019 academic year, coinciding with the attainment of a predoctoral contract funded by the Autonomous Community of La Rioja. Doctors, microbiologists, health economists and scientists participate in this European Project to develop a new clinical management model that would allow reducing antimicrobial resistance (AMR) through the use of rapid diagnostic tests in patients with symptoms compatible with respiratory infections [26]. The contributions presented in this thesis are framed in this project but have

rather addressed the economic implications of national policies on co-payment and prescription, as they will be presented in the following lines.

While in Spain the prevalence of diseases treatable with gene therapies is estimated at less than 5 cases per 100,000 inhabitants [27,28], infectious diseases present a prevalence of more than 1,000 cases per 100,000 inhabitants [29]. Although it was thought that infectious diseases would disappear (antibiotics would kill bacteria and vaccines viruses), the truth is that these diseases present challenges for prescribers and a strong threat to public health [30,31]. In some cases, it is difficult to determine whether the infection is caused by a bacterium or a virus, so there is a tendency to overestimate bacterial infections and prescribe antibiotics unnecessarily [32].

Irrational use of drugs leads to a reduction in the quality and effectiveness of treatments, the appearance of problems in the supply chain, an increase in the hospitalisation rates, second-line treatments and mortality rates, issues that also translate into increased costs [33]. The case of antibiotics is especially sensitive since their irrational use contributes to the appearance of AMR, a warning already made by Alexander Fleming in 1945, in his speech at the reception of the Nobel Prize for the discovery of penicillin [34,35]. AMR has been estimated to cause more than 25,000 deaths annually in the European Union and carries a cost of € 1.5 billion [36].

In 2014, the National Plan against Antibiotic Resistance (PRAN) launched a "strategic and action plan whose objective is to reduce the risk of selection and dissemination of resistance to antibiotics and, consequently, reduce the impact of this problem on human and animal health, sustainably preserving the efficacy of existing antibiotics" [37,38]. In addition, since 2013, awareness and rational use of antibiotics campaigns have been carried out annually in November, coinciding with the European Antibiotic Awareness Day [39].

In 2012, and as a response to the budgetary impact of the 2008 crisis, an economic regulation was introduced to modify the pharmaceutical copayment rates, the Royal Decree-Law (RDL) 16/2012, by which the

copayment rate was linked to the patient's income level [40]. For the specific case of antibiotics, this RDL also included an additional provision [41] to adjust the doses contained in the antibiotic packages to the actual duration of treatment in order to prevent unnecessary consumption of these drugs and the generation of AMR, following the most recent clinical recommendations [41].

This thesis includes publications that have studied the effect of different health and economic measures on the prescription of antibiotics. These contributions complement the results obtained in the framework of the European Project. In addition, following the PRAN's recommendations to “elaborate regional consumption studies that provide information that facilitates the creation of policies that better adjust to the characteristics of the population” [37], the articles included in this thesis analyse and disaggregate by epidemiological (age, sex and month of the year) and economic variables (price of active principle and copayment rate, established by income level) the prescription of antibiotics [38].

During the third academic year of the completion of this thesis (2019-2020), the coronavirus-19 (COVID-19) pandemic was declared [42]. This health crisis had a budgetary impact and an attempt was made to deal with it with the approval of an exceptional loan of 140 million euros [43]. As a complementary study to the European Project, it was analysed whether personal protection measures against COVID-19 affected the prescription of antibiotics. The analysis was carried out considering clinical variables (active principle, age and sex of the patient) and socioeconomic variables (Basic Health Zone, BHZ and copayment rate determined by income level).

The following chapter presents a results memory, in which the main contributions of each publication are introduced and discussed. A full copy of the papers is also included.

Chapter 2. Results memory

2.1. First publication

2.1.1. Introduction to the first publication

Medical advances allow for more effective therapies but with a greater budgetary impact [44,45]. Those responsible for health systems try to control the increase in the costs of pharmaceutical products in different ways [46]. In the last decade, new instruments for health management and reimbursement have been established [22]. Among them, the so-called risk-sharing contracts (RSC), that present an alternative payment model, have lately received some attention. These contracts can reduce financial risk or also link the reimbursement of certain innovations to their clinical results (payment by results) [21].

Traditionally, these RSCs have been linked to financial results, with price-volume agreements predominating. In these cases, the contracts establish a discount or refund by the pharmaceutical company to the healthcare managers if the estimated budget under negotiation is exceeded [20]. However, RSCs have recently been introduced where the payment from healthcare facilities to the pharmaceutical company is contingent on health outcomes [22]. These health management instruments reduce the risks and costs of treating patients who do not respond adequately to a certain treatment, since the payment for this treatment only occurs if it is successfully concluded [47].

RSCs allow healthcare managers and the pharmaceutical industry to obtain a series of advantages that could not be obtained through the traditional reimbursement schemes. For pharmaceutical companies, signing an RSC allows them to demand a higher price because they assume the risk involved in accepting this type of contract. In addition, they generate a

signalling effect for the product, since only pharmaceutical companies that are sufficiently sure about the usefulness of their treatment will enter a market regulated in this way [48,49]. Also, RSCs facilitate the entry into the market of new technologies that would have greater difficulties without this management instrument [20,50].

For health managers, signing an RSC reduces the uncertainty inherent in purchasing new drugs and links the reimbursement of the product to its correct use [20]. In addition, health managers have the interest of the pharmaceutical company to achieve the objectives established in the contract, so they have their support when designing protocols and so that more objective and studied information on new treatments is achieved [51].

Competitiveness is created in the pharmaceutical sector based on the degree of product innovation while pharmaceutical manufacturers have different incentives to improve their profits. With the traditional reimbursement scheme, better economic results were achieved by increasing the number of treatments sold, while with RSCs the incentive is the continuous improvement of the efficiency of their medicines. Such improvements can be achieved by modifying the chemical components used or through better implementation and monitoring of the treatment process [50].

Despite the fact that RSCs are internationally recognised as health management instruments, their signature involves a considerable series of administrative efforts [52]. An example of this effort is the two years of failed negotiations before achieving the first RSC in Spain in 2011 [53]. In addition, RSCs involve a series of modifications in the reimbursement system that can generate disadvantages for both agents.

For pharmaceutical companies, RSC means assuming a risk because if they are not successful, they must return or stop receiving the agreed amount [49]. Another disadvantage is that pharmaceutical companies do not know if protocols are being followed or if treatment resources are being used under

optimal conditions. Variations in clinical practice from the recommendations made by the pharmaceutical company can lead to poor results [51].

For healthcare managers, even though RSCs present an attractive reimbursement system, these models can encourage the application of a certain treatment to many patients, a fact that is not without risks or costs, since resources would be consumed by patients for whom treatment has no effect [48]. Also, there are follow-up costs incurred by healthcare managers to conclude that the patient has indeed been cured, which in many cases may not outweigh the benefits of risk-sharing [48,54].

The first publication included in this thesis is entitled *Risk-Sharing Contracts in the national health care system: Perceptions of health care professionals,* which was published in Revista Española de Salud Pública in 2018.

The research question of this work is to better understand the issues and barriers related to the signing and application of these contracts in the clinical practice and the potential synergies of RSC with personalised medicine (PM). PM, which implies that drugs are directed to specific patient subgroups [55], has been included in this study as it is a relatively new practice and is especially implemented in cancer treatments, a research area with a tendency to develop new therapies with a great budgetary impact [56,57].

As there are no quantitative results of the economic and health effects achieved with the signing of RSCs, this first publication of this thesis analyses by means of a qualitative method if RSCs are appreciated as instruments that allow for the improvement of economic and administrative management. For the calculations the software for qualitative analysis NUD * IST Vivo (Nvivo) [58] was used.

2.1.2. Full copy of the first publication

Rojas García P, Antoñanzas Villar F. Risk Sharing Contracts in the national health care system: Perceptions of health care professionals. *Revista Española de Salud Pública*. 2018; 92: e201807041. Impact factor (2018): 0,635 (Q4) [2]

2.1.3. Comments to the first publication

The objective of this work was to study the perceptions of health professionals on the use of RSC through qualitative analysis. Qualitative research should be carried out when there is no scientific evidence on the phenomenon under study and questions related to human experience (set of individuals who are experiencing the phenomenon under study) are required [59]. It is also advisable to use qualitative methodology when the variables that could approximate the phenomenon under study cannot be easily identified [60]. The above criteria are met in the case of RSC, a phenomenon studied in this publication.

Some studies have approximated the analysis from a theoretical perspective based on certain assumptions such as that the follow-up costs are borne only by health managers, that the treatment is always effective, or that the costs of untreated patients are not included [50,54].

In relation to these limitations, in this work, the main impediments to the signing of RSCs were the need to increase laboratory tests to confirm some of the health outcomes on which the contracts are established. In addition, the staff must be increased to take care of bureaucratic tasks, such as the preparation of registries, and a great dependence on central services such as genetics laboratories is generated.

As the main result, it was concluded that RSCs allow for the improvement of the economic and administrative management of the hospital, highlighting budget control, the attainment of financing and the possibility of savings. In addition, it was perceived that RSCs favoured the introduction of PM since both PM and RSC promote and depend on the development of diagnostic tests, either for screening reasons (PM) or to increase clinical evidence to improve economic results (RSC).

Although it has recently been pointed out that RSCs are one of the five recommended mechanisms for regulating drug prices [61], it can be concluded that in Spain they have not had the boom that was expected. As has been found in this work, the signing of an RSC implies many administrative efforts and the information resulting from them has, unfortunately, not been published, hindering the possibility to learn and to obtain more benefits and savings for the NHS.

2.2. Second publication

2.2.1. Introduction to the second publication

The discovery of antibiotics was one of the greatest medical advances of the 20th century. However, the bacteria and pathogens that antibiotics fight have been evolving for more than 3.5 billion years and, more recently, have learned to resist the drugs that try to fight against them, to which they were previously susceptible [62,63]. Although it is a consequence of natural selection, the inappropriate and indiscriminate use of these drugs accelerates the process of generation of AMR, one of the ten main threats to global health declared by the World Health Organization (WHO) in 2019 [31,64].

Faced with the possibility of entering a post-antibiotic era, in which infections treatable for years can become fatal, a coordinated global policy response is required [65]. Otherwise, AMR will not only involve clinical problems but also economic ones, health costs will increase and labour productivity will be reduced, estimating losses of 85 billion dollars between the years 2015 to 2050 [66].

Several national and international organisations have carried out plans that establish strategies to face this threat [63,67]. The WHO Global Plan of Action on Antimicrobial Resistance establishes five objectives, two of which stand out for the purpose of this thesis: that of strengthening the knowledge of AMR through research and that of improving awareness through communication and education of the society [67].

The European Global Health Action Plan against AMR establishes, among other strategies, the development of guidelines for the prudent use of antimicrobials and research on the development of interventions that prevent the spread of AMR in different settings, such as hospitals [63]. At the end of 2020, the European Pharmaceutical Strategy was adopted to support

the research and technologies offered to patients to meet their therapeutic needs. New developments include the prioritisation of research in rare diseases and pediatric cancer, as well as in the fight against AMR [68].

In the national context, the National Plan against Antibiotic Resistance establishes six lines to address the threat of AMR: surveillance of the consumption of antibiotics, control of AMR, prevention with alternative treatment measures, research to improve knowledge about resistance, training for health professionals and communication with campaigns for the general population [69]. In addition, the monitoring of antibiotic consumption and the exploitation and analysis of data in the local, regional and national context is established as a key objective. This information allows comparisons to be made in order to detect good prescription practices [70].

Several regional studies have analysed the use of antibiotics. One of these studies describes the community consumption of the pediatric population in the Principality of Asturias between 2005 and 2018, finding an improvement in the pattern of use of these drugs [71]. Similarly, the consumption of antibiotics in the Basque Country between 2006 and 2011 was analysed and an upward trend was found until 2007, followed by a period of stability until 2010 when it reached its lowest level [72]. In another study, the consumption of antibiotics among different health areas of Aragon was described, concluding that the greatest variability in the prescription of antibiotics between health areas occurred in cephalosporins and quinolones [73]. Another study analysed the prescription of antibiotics in the pediatric population of Castilla y León between 2001 and 2010, as a result, a better adaptation to the therapeutic guidelines was found in the last years analysed [74]. A study of the antibiotics dispensed during the 2006-2011 period in the Valencian Community indicated that more measures and institutional campaigns were necessary to improve the rationalisation of these drugs [75].

All these regional studies have in common that they analyse the consumption of antibiotics according to one clinical variable, mainly the

active principle, the age of the population or the geographical demarcation. However, in order to detect the population groups in which the action plans against AMR could have an effect, it is necessary to carry out an analysis based on several clinical and economic variables.

The second publication included in this thesis is entitled *Assessment of the quality of antibiotics prescription in a regional health system* and was published in the Revista Clínica Española in 2020.

The research question of this work is based on the fact that many antibiotics are prescribed in the outpatient setting but there are no evaluations available to review whether these prescriptions are adequate. Therefore, this work tries to assess the quality of antibiotic prescription in the autonomous community of La Rioja, taking into account epidemiological (age, sex and month of the year) and economic variables (price of active principle and copayment rate, determined by income level).

To answer this research question a comparative method was followed, which considers nine quality indicators defined by the Surveillance of Antimicrobial Consumption (ESAC). Statistical analysis of differences with data analysis software IBM SPSS [76] was used for the calculations.

2.2.2. Full copy of the second publication

Rojas García P, Antoñanzas Villar F. Assessment of the quality of antibiotics prescription in a regional health system. *Revista Clínica Española*. 2021; 221: 497-508. https://doi.org/10.1016/j.rce.2020.04.015. Impact factor (2019): 1,304 (Q3) [3]

2.2.3. Comments to the second publication

In the second publication of this thesis, the quality of the prescription of antibiotics in the Autonomous Community of La Rioja was analysed, taking into account epidemiological (age, sex and month of the year) and economic (price of active principle and copayment rate, established by income level) variables. The study was part of the PRAN's recommendations on “the implementation of regional consumption studies that provide information that facilitates the creation of policies that better adjust to the characteristics of the population” [37,38].

The method was based on a retrospective study based on the dispensing records of ordinary official prescriptions of the Autonomous Community of La Rioja. To establish the existence of significant differences in the prescription of antibiotics by age, sex and type of contribution, the Chi-square test with a 95% confidence interval was used. Predictive analysis software International Business Machines (IBM) Corporation Statistical Package for the Social Sciences (SPSS) 20, 2011 (Armonk, New York) [76] was used.

As the main result, it was concluded that the quality of antibiotic prescription is determined not only by epidemiological variables, such as age or sex, but also by economic variables, such as the patient's income and the price of the antibiotic.

A “price effect” was detected in the prescription of antibiotics, since as the cost of the active principle increased, the number of antibiotics prescribed decreased. Also, an “income effect” was found since high-income patients were prescribed a greater number of fluoroquinolones, macrolides, third-generation cephalosporins, and fosfomycins (active principles with higher cost) than middle- or low-income groups. This phenomenon may be the object of further investigation in other Autonomous Communities, as it is a surprising finding. In this sense, we believe that some other variable (namely,

age and time since market authorisation of the antibiotic) will have to be considered to deeply disentangle this “income effect” that was initially found.

2.3. Third publication

2.3.1. Introduction to the third publication

The development of new antibiotics that control resistant bacteria is one of the possible solutions to this global threat to public health. However, the low price of these drugs (as cheap as 60 euro cents) discourages research by the pharmaceutical industry in this area [77]. Furthermore, it is estimated that a development period of between 10 and 20 years is necessary to obtain a new antimicrobial [78].

Although action plans that target the moderate use of antibiotics to maintain their effectiveness present another disincentive to the commercialisation of these drugs, they appear to be the only possible solution to the challenge posed by AMR [78]. In this sense, health policies, whose objective has been to improve the consumption of antibiotics, are carried out. One of the PRAN lines of action is to develop awareness campaigns on the rational use of antibiotics for the general population [69]. The last of these campaigns, which was awarded a value of more than 300,000 euros to a media agency and was part of the World Week of Awareness on the Use of Antibiotics, was issued in November 2020 and had as its main message “Antibiotics are NOT good for everything” [79,80]. Some authors have pointed out that it is necessary to know the effect of such awareness campaigns on drug use and to check whether they actually achieve the desired effect [81,82].

Although the set of economic policies that were established in Spain in response to the budgetary impact of the 2008 crises (specifically the modification of the pharmaceutical copayment rates introduced by RDL 16/2012 [40]) had no intention of affecting the consumption of antibiotics [40], some authors detected an effect of such policies on drug dispensing [83,84]. For example, it was found that the change in copayment rates led to a

12% reduction in the number of prescriptions and pharmaceutical spending [83].

The third publication included in this thesis is entitled *Effects of economic and health policies on the consumption of antibiotics in a Spanish region* and was published in the Expert Review Magazine of Pharmacoeconomics & Outcomes Research in 2019.

The research question of this work is to analyse if one economic policy (modification of the copayment rates introduced by the RDL) and health policies (broadcast of awareness and rational use of antibiotics campaigns) reduce the prescription of these drugs. Furthermore, the study compares the relative importance of both types of policy.

To answer this research question, the Box-Jenkins time series methodology was applied. The autoregressive integrated moving average model (ARIMA) identified was used to elaborate the forecast and the counterfactual analysis. The software IBM SPSS [85] was used for the calculations.

2.3.2. Full copy of the third publication

Rojas García P, Antoñanzas Villar F. Effects of economic and health policies on the consumption of antibiotics in a Spanish region. *Expert Review of Pharmacoeconomics & Outcomes Research*. 2019. doi: 10.1080/14737167.2019.1647105. Impact factor (2019): 2,032 (Q2) [4]

2.3.3. Comments to the third publication

In the third publication of this thesis, the effect of modifying a copayment measure and awareness campaigns and rational use in the consumption of antibiotics were studied.

On the one hand, the main objective of the copayment is, in theory, to control unnecessary consumption and pharmaceutical expenditure [86]. Previously, some works have been presented that have studied the effect of a copayment measure on drug consumption, finding a reduction in all the series analysed [83,87]. However, discrepancies were detected in their effect on the use of drugs such as antibiotics. While some authors have pointed out that this reduction also occurs in the case of antibiotic use, other authors indicated that no significant results were found [88,89].

On the other hand, although awareness campaigns and rational use of antibiotics have been carried out since 2013 [90], no studies have been found that have previously quantified its effect, despite the recommendations to assess these communications [81,82].

In order to quantify the effects of the RDL and the awareness and rational use campaigns, intervention analyses were carried out. As a method, the Box-Jenkins methodology was followed, using the IBM SPSS Statistics 24 analysis software [85]. Several variables were created to capture the effects of the policies. Also, counterfactual analyses were carried out to obtain the potential savings of the different policies, comparing the values predicted by the model with the actual values.

It was decided to study not only the total series of antibiotics but also to analyse by active principles, selecting three due to their high price (moxifloxacin, levofloxacin, clarithromycin) and another three due to their high frequency of prescription (azithromycin, amoxicillin and amoxicillin in combination with a beta-lactamase inhibitor). Thanks to this disaggregation

of the total series, it was found that the effect of the pharmaceutical copayment was greater in active principles with a higher price.

As a main result, it was concluded that the previous policies helped to reduce the consumption of antibiotics. However, each policy had different effects, the co-payment reduced consumption through a price effect, while awareness campaigns depended on other elements for their success, such as the means used and access to the target audience, among others.

2.4. Fourth publication

2.4.1. Introduction to the fourth publication

In line with the previous publication, the economic regulation introduced in 2012 in response to the budgetary impact of the 2008 crisis (RDL 16/2012 [40]) also included an additional provision (RDL 16/2012, fourth provision [41]), for which the doses in the antibiotic packages had to be adjusted to the actual duration of treatments. Given the recommendations of the health authorities to carry out this review to prevent the generation of AMR, antibiotics were the first drugs to undergo review and improvement of the doses included in the packages [91]. Thus, an attempt was made to prevent unnecessary use of these drugs by following the most recent clinical recommendations [41].

The aforementioned studies [83,84], which analysed the effect of RDL 16/2012 on the series of drug use in Spain, also concluded that copayment caused a sharp change in the mean level of the time series with reductions of between 10% and 20% in the number of prescriptions dispensed [84]. However, one of the limitations recognised by the authors is that the reduction in drug use could not be estimated using a more homogeneous measure of consumption such as defined daily doses (DDD) [84]. Having studied in the previous publication the time series of dispensed packages and expenditure in euros, it was decided to add the time series of DDD dispensed to the analysis of the Basque Country.

The fourth publication of this thesis is entitled *Policies to Reduce Antibiotic Consumption: The Impact in the Basque Country* and was published in the journal Antibiotics in 2020.

The research question of this work is to analyse if the economic policy of modification of copayment rates, introduced by the RDL, reduces the prescription of antibiotics, as seen in the previous publication. However, in

this work the analyse is performed in another region of Spain, the Basque Country, where the introduction of this standard was applied one year later than in the rest of the country. In addition, the effect of another policy (adjusting drug packaging) is also analysed.

To answer this research question, the Box-Jenkins time series methodology was applied. The autoregressive integrated moving average model (ARIMA) identified was used to elaborate the forecast and the counterfactual analysis. The software for statistical computing R was used [92] for the calculations.

2.4.2. Full copy of the fourth publication

Rojas García P, Antoñanzas Villar F. Policies to Reduce Antibiotic Consumption: The Impact in the Basque Country. Antibiotics. 2020; 9, 423: doi:10.3390/antibiotics9070423. Impact factor (2019): 3,893 (Q1) [5]

2.4.3. Comments to the fourth publication

The objective of this study was to analyse the impact of the modification of copayment rates, the adjustment of the doses contained in the packages and the approval of the PRAN in the consumption of antibiotics in the Autonomous Community of the Basque Country. This region was chosen because said Autonomous Community managed to delay the application of RDL 16/2012 [40] one year (until July 2013) through Decree 114/2012 [93], when the Constitutional Court annulled it in December 2012.

A Box-Jenkins analysis was performed using different R packages [92], statistical computing software and graphics. Counterfactual and intervention analyses were conducted to estimate the impact of previous policies. The analyses were carried out by disaggregating by active principle: higher and lower cost, as well as the frequency of its prescription.

As a contribution to this study, it can be pointed out that studies on the adjustment of the doses contained in the packages are usually carried out in a hospital setting. Along these lines, a study established that the personalised dosage of antibiotics in hospitalised patients reduces the inappropriate use of these drugs [94].

In the fourth publication included in this thesis, it was concluded that adjusting the doses to the packages significantly reduced the number of packages dispensed. Fewer packages were prescribed, but with a higher burden and price of the drug. Furthermore, despite the delay in the implementation of the modification of the copayment rates, an "accumulation effect" was found prior to the entry into force of the rule, a result found in other studies [83,87].

2.5. Fifth publication

2.5.1. Introduction to the fifth publication

On March 11, 2020, the WHO "deeply concerned by the alarming levels of the spread of the disease, its severity and the alarming levels of inaction" determined that COVID-19 could be characterised as a pandemic [42]. In the absence of therapeutic options, the antibiotic azithromycin with hydroxychloroquine was used as first-line treatment [95]. However, no evidence was found on the effectiveness of this treatment [96].

During the COVID-19 crisis, there was evidence of a problem in the capacity of the NHS to manage the pandemic, since with the crisis of 2008 there were cuts in personnel, beds and ICU rooms [97]. To deal with this health crisis, individual personal protection measures such as the use of the mask, the maintenance of interpersonal distance and the increase of hygiene were implemented [42]. In addition, in several countries, compulsory house confinements were decreed, as happened in Spain [98].

These individual protection measures could have had positive consequences in reducing the incidence of other respiratory infections. Considering that a large part of inappropriate prescribing occurs when treating viral respiratory diseases with antibiotics, these measures could have helped reduce the unnecessary use of these drugs [99].

The fifth publication of this thesis is entitled *Analysis of the prescription of antibiotics during the implementation of personal protection measures COVID-19 in a regional health service* and was published in the journal ClinicoEconomics and Outcomes Research in 2021.

The research question of this work is to assess the effect of the COVID-19 pandemic on the prescription of antibiotics in the outpatient setting. The objective of this study is to analyse the official monthly dispensations of antibacterials for systemic use (J01) disaggregated by clinical variables (active

ingredient, age and sex of the patient) and socioeconomic (basic health area and income level) and detect if the measures of personal protection by COVID-19 had some effect on the dispensing of antibiotics.

To answer this research question, the prescription of antibiotics of 2020 was compared to the prescription of 2019. The statistical analysis of differences with data analysis software IBM SPSS [85] was used for the calculations.

2.5.2. Full copy of the fifth publication

Rojas García P, Antoñanzas Villar F. Analysis of the prescription of antibiotics during the implementation of COVID-19 personal protection measures in a regional health system. ClinicoEconomics and Outcomes Research. 2021; 13 (927-36) Impact factor SJR (2020): 0,59 (Q1) [6]

2.5.3. Comments to the fifth publication

The objective of this study was to analyse the prescription of antibiotics during the implementation of COVID-19 protection measures in primary care in a Spanish region. The analysis was performed considering clinical variables (active principle, age and sex of the patient) and socio-economic variables (Basic Health Zone, BHZ, and copayment rate determined by level of income).

The prescription of antibiotics of 2020 was compared to the prescription of 2019. Furthermore, the DID prescribed in February, March, April and May 2020 were compared with the prescription of the same months in 2019 using the Chi-square test with a significance level of 0.05. The analyses were performed using IBM SPSS Statistics 24 software [85].

As the main conclusion of the fifth study presented in the thesis, it was found that the prescription of antibiotics in 2020 (period of implementation of the COVID-19 protection measures) was significantly lower (-23.73%) than in previous year. Despite being difficult to measure the effect of personal protection measures, that is, to quantify individual use of masks, compliance with social distance or even increased hygiene, these measures could be an additional reason for the lockdown, that began in March 2020, in order to more comprehensibly explain the reduction in the dispensing of antibiotics.

Chapter 3. Discussion

It should be noted that each article included in this thesis has its own discussion section in which the main contributions of each study are presented, the results obtained with other scientific works are compared and the limitations of each analysis are pointed out. Therefore, in this section, a general assessment of the thesis is carried out.

The publications presented address issues of Health Economics in line with the two Research Projects in which the author has collaborated during their stay in the Doctoral Programme (study of payment models for high-cost drugs or analysis of health policies and economic in the consumption of medicines, among others). Conclusions such as “synergies are created between a payment model based on an RSC and the introduction of PM”, “the prescription of antibiotics seems to follow a similar pattern to that of the consumption of other goods: greater demand for lower-priced items and vice versa, typical demand curve” or “in economic terms, penicillin presents a consumption pattern of an inferior good concerning income” are some elements that have been contributed to the field of study of Health Economics. In any case, this last finding may be due to the influence of other confounding variables (epidemiological or clinical) that should be analysed in greater detail and ascertained if they occur in other places or time periods.

RSCs have recently been recognised as one of the five mechanisms for regulating drug prices [61]. Despite being used in the international context with relative frequency, in Spain, there is still no adequate evaluation of their impact. The first publication included in this thesis, the result of participation in the project *Personalized Medicine and Shared Risk Contracts as new paradigms of healthcare management: theoretical economic models and applications* (MINECO ECO2016-78685-R, 2016-2019), allowed the approach to RSC, a studied phenomenon with few available empirical results. This

publication has been cited in a study on theoretical and empirical evaluations of the use of joint venture contracts in healthcare [100].

At the drug's maturity stage, health managers must manage its appropriate use, especially in cases where indiscriminate prescribing can lead to drug ineffectiveness, such as antibiotics [36]. With good management and the use of control instruments, the threat of antibiotic resistance is reduced. Antibiotics present a broad and complex line of research, mainly due to their ability to develop resistances. These are drugs that have been in the NHS drug portfolio for many years, so at first, this doctoral research has sought to understand how the prescription of these drugs is oriented in an area in which there are multiple forms of choice (various active principles with different clinical and economic characteristics). Some of the conclusions of the second publication of this thesis were cited during the Conference of the European Day for the Prudent Use of Antibiotics in 2018, in the presentation “Economics of resistance: antibiotics and the social cost” of the professor of Health Economics Dr. David Cantarero [101,102].

After conducting a static analysis (observations from 2017), the database was expanded to include dispensations made between 2009 and 2017 in order to be able to quantify the health and economic policy effect on the antibiotic consumption series. The third publication of this thesis has been cited by three international studies [5,103,104].

Similarly, with the database of official dispensing of antibiotics prescriptions of the Basque Health Service, an analysis of time series was carried out in this new context. As a novelty, the introduction of a new unit for measuring consumption, the DDD, which allows for more homogeneous comparisons is worth highlighting. The fourth publication was included in the special issue of the journal *Antibiotics* (Special Issue on the Use of Antibiotics in Primary Care).

With the declaration of the COVID-19 pandemic and based on the hypothesis that the individual protection measures, which were implemented

to deal with the health crisis, could reduce the prescription of antibiotics by also decreasing the number of viral respiratory infections, the fifth study concluded the thesis. The fifth publication of this thesis was accepted in the journal *ClinicoEconomics and Outcomes Research*. Some previous results of this publication have been presented at the VIII Workshop of Young Researchers in Economics and Business (Teruel, 2021).

In this sense, the contributions obtained in these publications have been presented as oral communications, posters and symposia in National and International Congresses, specialised in Health Economics (XXXIX Conference on Health Economics - Albacete 2019, XL Conference on Health Economics - online 2021, and the International Congress ISPOR Europe 2019, online 2019) and of general dissemination (V Doctoral Conference of the Iberus Campus - Jaca 2018, VI Doctoral Conference of the Iberus Campus -Jaca 2020 and I Doctoral Conference of the University of La Rioja- Logroño 2020).

In addition, it is worth mentioning that the author has learned to apply different methodology: qualitative analysis, statistical analysis of differences and analysis of time series following the Box-Jenkins methodology. In the same way, different statistical and data analysis software have been used such as NUD * IST Vivo (Nvivo) [58], IBM SPSS [76,85] and the software for statistical computing R [92].

For the duration of the Doctoral Programme (academic year 2017-2018 to 2021-2022), work has been done to achieve the competencies in training researchers in the area of Health Economics. All the objectives of this thesis have been in line with the purpose of the World Health Organisation (WHO, 1985) [105] to achieve the rational use of drugs, a concept that was defined taking into account clinical and economic aspects: “patients receive the appropriate medication for their clinical needs, in the doses corresponding to their individual requirements, for an adequate period of time and at the lowest possible cost them and for the community".

As future lines of work, quantitative analysis of the effect of different health policies to better understand their clinical and economic effects will be developed. In particular in the field of the economics related to the drug sector.

Chapter 4. Conclusions

This section presents the conclusions of the publications that comprise the compendium of articles of the doctoral thesis. Having previously included a discussion section, in which the main contributions of the thesis are detailed, this section includes a list of conclusions.

First publication:

1) RSCs are appreciated as instruments that allow for the improvement of the economic and administrative management of the hospital, since the interviewees indicated that RSC allows for the improvement of the economic and administrative management of the hospital, the statements obtained in this category are, to a greater extent, of a positive nature (based on real-life situations in hospitals).

2) RSCs are valued as management tools with positive implications for the health of the patients. In this case, half of the statements were positive (based on the current situation of the hospitals) and the other half normative (based on the point of view, opinion or interest of the subjects interviewed).

3) RSCs are considered as means favouring the introduction of the new paradigm of PM. The responses confirmed that the interviewees understand the link between both, considering them interesting and beneficial; However, this statement does not seem to come from medical practice, possibly due to having little experience in both concepts, but rather based on personal opinions (24.4% positive statements and 75.6% normative).

4) RSCs had positive opinions about their application, although work must be done to improve the regulatory and organisational context so that the additional complexity they incorporate does not constitute an obstacle to extending their use.

Second publication:

5) The quality of the antibiotic prescription is determined not only by epidemiological variables, such as age and sex, but also by financial variables, such as the patient's income and the price of the antibiotic.

6) The total consumption of antibiotics, that is, the sum of DDD dispensed through official prescriptions (18.45 DDD taking the number of inhabitants as the population value and 18.55 DDD as the number of health cards), through mutual societies (0.99 DID) and by private prescription (6.58 DID), for adults in La Rioja in 2017 it was estimated between 26.02 DDD and 26.12 DDD. This result corresponds to a "very low" quality of prescription.

7) Differences were found in the quality of the prescription by type of copayment contribution, being "high" in the group of active workers and "low" in pensioners. A wide margin of improvement was found in the prescription of third-generation cephalosporins and, with the exception of patients with low and middle income, in the consumption of fluoroquinolones.

8) Regarding the month of the year, it was detected that fosfomycin did not comply with the characteristic seasonality of antibiotics (higher consumption in the winter months), since it increased by 12.15% in the summer months compared to the winter months.

9) Regarding the economic variables, a "price effect" was detected that could potentially indicate the choice of lower-priced active ingredients. The prescription of antibiotics seems to follow a pattern similar to that of the consumption of other goods: greater demand for lower-priced items and vice versa (typical demand curve).

10) Statistically significant differences were found in prescriptions for the subgroups of antibiotics with lower prices, penicillins (J01CA with 0.14 euros / DDD and J01CR with 1.22 euros / DDD) in high-income patients compared to other groups, thus showing an apparent “income effect” that could consider, in economic terms, that penicillins would be an inferior

good with respect to income. Although it could be other influential variables.

Third publication:

11) Economic and health policies helped to reduce the consumption of antibiotics, although each one has different effects: the copayment reduces the overall consumption of medicines through a price effect (increase in the cost of the medicine), while awareness campaigns and rational use depend on other elements for their success (means used, access to the target audience...)

12) The pharmaceutical copayment is the most effective measure to reduce the consumption of antibiotics, with a reduction of 8.52% in the amount prescribed and 8.61% in the series of expenses) and its effect was greater in higher priced active ingredients.

13) The month prior to the entry into force of RDL 16/2012 (June 2012) was characterised by presenting an “accumulation effect”.

14) Two of the four awareness and rational use campaigns analysed (2013 and 2016) significantly reduced the consumption of antibiotics (around -4.30% in quantity and -3.92% in spending). The campaigns had a greater effect on the prescription of antibiotics for low-income patients.

15) The effect of the campaigns lasted 6 months, from November to May of the following year, perhaps because the consumption of antibiotics during the summer is lower than in the winter.

Fourth publication:

16) Once again, it was detected that one month prior to the introduction of the copayment modification policy, an "accumulation effect" was generated, equivalent to 8% in the three-consumption series analysed (packaging, DDD and expenditure).

17) The adjustment of medicine packages significantly reduced the number of dispensed packages by 12.19%. However, with this measure, fewer packages were prescribed, but with a higher dose and price.

18) The approval of PRAN reduced consumption by 0.779 DID (-4.51%), which represents a significant decrease both for antibiotics in the “access group” (indicated for first-line treatments) and in the “surveillance group” (for second-line treatments).

Fifth publication:

19) In 2020, the prescription of antibiotics (11.37 DID) was significantly lower (-23.73%) than in 2019 (14.91 DID).

20) The main reduction in the amount prescribed was found in May (-42.64%). However, the prescription was significantly higher (71.34%) in February 2020 than in the same month in 2019 in nursing homes.

21) In March 2020, prescriptions were lower (-13.71%) than in the same month in 2019, except for the middle-income group, in which prescriptions were higher (9.67%) as well as azithromycin (10.11%).

22) In April and May 2020, prescriptions were significantly lower than in 2019 in all age groups and both women and men.

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This section presents only the references used in Chapters 1, 2, 3 and 4 of this thesis. Each publication has its own reference section.

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