Essays on Antibiotic Prescription and Pharmaceutical Regulation

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To my wife Giovanna,
for all her patience, love and support.
To my beloved family.
This work would not have been possible without you.

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Abstract

Recent years saw a sharp increase in antibiotic resistance world-wide. The increase in resistance poses a serious threat to society and health systems. Over-prescription of antibiotics in primary care represents one of the key reasons for the surge in resistance. This thesis analyses the effectiveness of EU-wide policies in reducing over-prescription. This work then explores spatial dependence in antibiotic prescription in England. Lastly, this thesis analyses the impact of pharmaceutical regulation on social welfare and innovation. Understanding the impact of pharmaceutical regulation on innovation is important in addressing antibiotic resistance as one of the reasons behind the surge in resistance consists of a lack of newly developed antibiotics.

Chapter 2 studies the effectiveness of stewardship programmes in reducing antibiotics consumption across European countries. Using data from the Eurobarometers 72.5 (Nov-Dec 2009), 79.4 (April 2013), 85.1 (April 2016), and 90.1 (September 2018), I estimate the impact of stewardship programmes on antibiotic consumption via difference-in-difference analysis, run on a representative sample of the European population. I identify a negative impact of stewardship programmes on antibiotic consumption by means of diff-in-diff analysis. The effect is significant across years, as well as for individual years of policy implementation. I identify inter-temporal effects of the policy, with significant lead effects following its introduction. The results on stewardship are confirmed, even when accounting for alternative national policies, such as National Action Plans (NAP). Stewardship programmes present an impact also on alternative dependent variables, such as receiving antibiotics from a doctor, patient's intention to consult a doctor for future use, as well as patients opinions on antibiotics.

Chapter 3 explores spatial dependence in antibiotic prescription across English GP practices, by means of a spatial panel analysis developed from presentation level data for the years 2013-2017. I link antibiotic prescription rates to the local characteristics of GP practices, considering demographics, quality of care, condition prevalence, access to services, and supply-side variables. I estimate the role of spatial dependence via SLX models. I test two alternative measures of distance across practices: institutional and geographical proximity. I explore different channels of spatial dependence by means of interaction effects, spatial error and spatial autoregressive models. This paper finds that local demographics, supply side factors, condition prevalence and proxies of access to services all influence antibiotic prescription. Lastly, this paper identifies evidence of spatial dependence in prescription rates for all antibiotics as well as for individual antibiotic classes across English GP practices.

Chapter 4 analyses the impact of price regulation and patent length in influencing social welfare in a dynamic pharmaceutical market with innovation. After introducing a dynamic two-period model with R & D, I explore the trade-off between static efficiency, in which the regulator optimizes for surplus in individual periods, and dynamic efficiency, in which the regulator optimizes welfare in both periods, accounting for the firm's investment decisions. I then explore the impact of Value-Based Pricing (VBP) regulation, by which the regulator sets prices proportional to expected health benefits. I find an inter-temporal trade-off between static and dynamic welfare. I study the price vs patent trade-off which the regulator might exploit to obtain desired policy results. I compare welfare in an alternative market where the firm is allowed to maximise profits, studying the impact on the amount of market innovation. Lastly, I identify that VBP policy influences consumer surplus and innovation decisions.

Chapter 1

Introduction

This thesis presents three selected health economics studies on antibiotic prescribing and pharmaceutical innovation.

Antibiotic resistance is a growing health threat world-wide. With a total number of 700,000 deaths a year globally, the number of deaths associated with antibiotic resistance is expected to increase to an estimated 10 million deaths per year by 2050 (O'Neill, 2014). Even when individuals are not at immediate risk of death, in most cases, antibiotic-resistant infections require prolonged and/or costlier use of healthcare resources (CDC, 2013). Antibiotic resistance thus constitutes a serious global health risk that needs to be addressed to avoid excessive societal costs (European Observatory on Health Systems and Policies, 2019).

Increased resistance translates into higher costs for national health systems. In the EU alone antibiotic resistance has caused 33 thousand deaths every year, with an estimated 1.5 billion euros of yearly healthcare and productivity costs (European Observatory on Health Systems and Policies, 2019). Global healthcare costs have been estimated to reach a maximum of 1 billion dollars a year, with an economic burden of 3 trillion dollars in GDP costs, although estimates vary across studies (Naylor et al., 2018).

Antibiotic resistance consists of the reduced effectiveness of antibiotics in treating infections following repeated consumption (Mera et al. (2006), Monroe and Polk (2000)). An indiscriminate exposure to antibiotics over time decreases the organism's ability to resist to infections, thus decreasing drug effectiveness. In turn reduced effectiveness translates into increased risk of serious infections (Major, 2018), particularly among immunosuppressed and fragile patients (Vincent, 2015).

The excessive provision of antibiotics to individuals is one of the key reasons for the global increase in antibiotic resistance (Fleming-Dutra et al. (2016), Smieszek et al. (2018)). Resistance is also influenced by indirect factors, such as exposure to individuals infected by mutated bacteria, potentially occurring in places such as hospitals or airports, or due to environmental factors such as the direct provision of antibiotics to animals in food production chains (Qiao et al., 2018). Such indirect factors generate negative externalities on the health of individual populations by increasing the risk of spreading antibiotic resistant infections. The complex interaction of both direct and indirect factors associated with resistance might contribute to increased costs for society. Policy makers need to account for such externalities to effectively address antibiotic resistance, thus reducing risks for society.

Several actions have been taken by the World Health Organisation (WHO), the European

Union and by individual states to address this phenomenon. The WHO developed a global action plan to address resistance which became a blue print for individual countries (World Health Organisation, 2015).[1] A specific policy initiative has been developed also at an European level, with the "One Health" action plan against resistance (European Commission, 2017).[2] At an individual country level, the UK developed a number of recommendations which culminated in a series of guidelines introduced by NICE, the English National Institute providing guidance on clinical practice, and targeted at reducing unnecessary prescription (Department of Health and Social Care (2011), NICE (2018)). In the UK additional policy commitments against resistance were taken forward by National Government (House of Commons, 2018), which, among other indications, highlighted the need to address market failure for the development of new antibiotic drugs.[3]

Despite these efforts, there still exists a wide heterogeneity in the approaches used to deal with antibiotic resistance across individual countries. Some National Action Plans, for instance, provide specific and measurable targets, while others, although presenting important principles, appear to be more vague in nature. Similarly, many countries are still lagging behind in the introduction of such policies (European Observatory on Health Systems and Policies, 2019).

Addressing the issues of antibiotic resistance requires economic thinking. This thesis, while certainly not exhausting the conversation on this complex issue, provides a contribution in addressing antibiotics provision through the lens of health economics.

This thesis serves the following purposes. First, I evaluate the effectiveness of stewardship programmes, a policy action aiming at minimising unnecessary prescribing by GPs, in influencing antibiotic consumption in European countries. The specific research question of the first chapter is "*what is the impact of stewardship programmes in affecting antibiotic prescribing in European Countries?*". This question is examined using Eurobarometer data for the years 2009, 2013, 2016 and 2018. This survey data is analysed via *difference-in-difference* analysis. By confronting the dynamics of different countries in the percentage of respondents who reported having used antibiotics in the last 12 months, I identify a reduction in antibiotic consumption following the introduction of stewardship programmes.

The second chapter provides an econometric analysis to identify the potential presence of spatial dependence in antibiotic prescription across English GP practices. The specific research question I answer is "*what is the role of spatial dependence in influencing GPs antibiotic prescription rates?*". This study uses NHS prescription data together with available data on individual practices. This data is analysed via techniques from the spatial econometrics literature, including spatial lag (SLX), spatial autoregression (SAR) and spatial error model (SLX).

Lastly, the third chapter addresses the issue of pharmaceutical regulation in a market with innovation following the introduction of value-based pricing regulation, a price policy aimed at linking prices to realised health benefits. The specific research question of the third chapter is "*what is the impact of value-based pricing in influencing social welfare in a dynamic market with innovation?*". This question is answered in a two-period dynamic model with innovation. This chapter also presents some simulations to gain additional insights on this type of price regulation using realistic model coefficients.

[1] This plan included five strategic objectives, namely: improving awareness, strengthening surveillance and research, improve sanitation, hygiene and prevention measures, optimise the use of antibiotics in human and animal health, and develop the economic case for sustainable investments in medicines, diagnostic tools, vaccines and other interventions.

[2] This approach was based on three pillars: making the EU a best practice region, boosting research and innovation, and intensifying EU efforts to shape the global agenda against resistance

[3] See BBC news for a discussion on why it is difficult to develop new antibiotics (BBC Health, 2017).

The consumption of antibiotic medication can be considered as an economic issue. Antibiotic overconsumption, in fact, gives rise to an increase in resistance, in turn reducing the effectiveness of such medication to the wider population. The generation of a social cost (or gain) following the consumption of a good is widely analysed in the economic field under the term of externality[4]. The reduced effectiveness of antibiotic medication introduced by resistance following overconsumption can therefore be interpreted as a negative externality on consumption affecting future use. Coast et al. (1996) and Elbasha (2002) provide some initial results concerning the economic implications of such externality on society. Coast et al. (1996) identify weak incentives from practitioners to internalise social costs as a result of difficulties in measuring the externality. Elbasha (2002) provides initial estimates of the deadweight loss arising from such externality to be an annual 225 million dollars in the US for outpatient prescription of amoxicillin alone. Hermann and Gaudet (2009) explore the dynamics of such externality identifying that antibiotics efficacy and infection rates affect social optimum intertemporally by means of the use of antibiotics being made in individual periods. Laxminarayan and Brown (2001) provide a theoretical framework for the development of antibiotic resistance, showing that resistance emerges from selective pressure on non-resistant strains due antibiotic consumption.

Economists have often addressed the issue of externalities, identifying potential ways to reduce social cost arising from consumption. One of the instruments identified by economists to reduce the social cost introduced by externalities is the concept of Pigou tax. A Pigouvian tax is an instrument that policy makers might use in order to tax goods who generate negative externalities on the wider society. The purpose of such instruments is to internalise the cost of externalities into consumers' decisions, thus reducing potential harm.

One of the main criticism to the application of a Pigouvian tax stands with the ability of the Government to effectively measure the cost of the externality produced, and therefore, in the estimation of the appropriate tax level required to reduce such externality. In the case of antibiotic resistance, it is certainly challenging to correctly estimate the amount of overconsumption leading to a negative externality originated from resistance. The use of a Pigouvian tax in the context of antibiotic prescription is therefore of difficult application.

Some commentators considered the information asymmetries and cost of administration to give rise to imperfection in optimal taxes and regulation Christiansen and Smith (2016). In the context of antimicrobial resistance, some commentators have explored whether a Pigouvian Tax would be useful in reducing externalities arising from resistance Vagsholm and Hojgard (2010). The optimal level of taxation, however, appeared to be linked to the uncertainty of the amount of time required for the development of a new antibiotic type.

Chapters 2 and 3 of this thesis provide additional economic perspectives on the difficulty of finding practical implementations of instruments such as a Pigouvian tax in the context of antibiotic consumption. Chapter 2 identifies significant differences in both policy implementation and baseline levels of antibiotic consumption, therefore highlighting practical limitations in identifying the degree of overconsumption leading to resistance. Chapter 3 provides evidence of the existence of spatial dependence in antibiotic consumption across practices, thus highlighting potential practical limitations in effectively measuring overconsumption.

The issues addressed in this thesis relate a number of topics which are central in health economics, a field of economic knowledge which has seen important developments in recent

[4]For an economic discussion on externalities see Varian (2010).

times.

One key element in the economic theory of policy evaluation is the concept of natural experiment. Natural experiments arise when a set of agents, or a set of administrative areas, are affected by a given intervention at random, thus mimicking the behaviour of randomised control trials experiments.[5] The random assignment of treatment among individuals, or administrative areas, allows for the identification of an effective treatment and control group. When the treatment and control group are balanced, we can identify the causal effect of the policy by means of a valid counter-factual. The presence of a valid counter-factual is at the basis of the difference-in-difference methodology (diff-in-diff), a regression technique allowing for policy estimation.[6] Diff-in-diff has been applied extensively in health economics.[7] Examples of application include the estimation of food stamp programmes (Hoynes et al., 2016) and tax reforms on infant health (Hoynes et al., 2015). The topic of antibiotic resistance has seen very little attention when it comes to the application of counter-factual analysis. To the best of the author's knowledge, the work presented in this thesis is the first attempt to apply this methodology at a EU level.

Spatial economics is a field of applied economics and econometrics which aims to address the identification issues arising when estimating models where spatial dependence plays a role in influencing either the dependent variable, its covariates, or where spatial dependence arises as a random component.[8] Starting with the work of Paelinck and Klaassen (1979) and Anselin (1988), this strand of literature first addressed the issue of spatial correlation and the ways to address it with model estimation. Spatial econometric techniques have been applied to the field of health economics (Lippi Bruni and Mammi, 2016), and to the topic of antibiotic prescription in primary care (Filippini et al. (2014), Gonzalez-Ortiz and Masiero (2013)). The review proposed by Gibbons et al. (2015) explains clearly three key different types of modelling allowing for spatial correlation. These include spatial autoregressive (SAR), spatial lag (SLX) and spatial error models (SEM). SAR models allow for spatial lags in the dependent variable, thus addressing spatial auto-correlation in the dependent variable. SLX models allow for direct effects of neighbours' characteristics on own outcomes. SEM models introduce a random spatial component in the estimated relation. Gibbons et al. (2015) also indicate the fundamental challenges with this strand of literature.[9] One key element behind spatial analysis is the definition of spatial weights. In health economics spatial weights have been defined both in terms of averages of administrative weights, as well as in terms of geographical weights. Identifying the appropriate definition of spatial weights is part of the art of spatial econometrics.

The third topic considered in this thesis is the interplay of pharmaceutical innovation and pricing regulation. One of the potential reasons why antimicrobial resistance is the lack of progress by drug developers to bring forward new antibiotics. The latest antibiotic substances invented in the last 30 years were variations of drugs discovered by 1984 (BBC Health, 2017). Understanding the dynamics of innovation in pharmaceutical markets, and developing regulation that does not negatively impact on innovation, are therefore key elements to be addressed to ensure that resistance is kept to a minimum in the long-run. The literature on pharmaceutical innovation has an established tradition in health economics. Early works date back to Arrow (1962), Nordhaus (1969) and Scherer (1972). These studies originally focused on patent protection and the appropriation of realised profits by innovating firms. The third chapter of

[5] see Meyer (1995) for a detailed explanation on this topic

[6] See Abadie (2005) for a discussion of the diff-in-diff methodology. See Bertrand et al. (2010) for a discussion of the limitations of such methodology

[7] See Wing et al. (2018) for an effective review of the applications od diff-in-diff methodology to health economics.

[8] See the work by Gibbons et al. (2015) for a through review of spatial methods in economics.

[9] The key limitations are: the reflection problem, the presence of omitted variables and problems caused by sorting.

this thesis addresses the issue of pharmaceutical innovation focusing on three key components. First, this chapter analyses static versus dynamic optimisation. In a nutshell, static optimisation aims to obtain the maximum possible welfare in the current period. Dynamic optimisation, on the contrary, requires welfare optimisation inter-temporally. Second, this chapter identifies the role of price and patent variation in influencing optimal welfare. Lastly, this chapter addresses price regulation. Price regulation is important to ensure price control and the affordability of new pharmaceuticals for the national health system. In line with existing literature (Ghislandi (2011), Bardey et al. (2010)), this thesis shows that pricing regulation might have an impact on innovation distorting the general market dynamics.

The analysis of antibiotic resistance could be subject to a number of counter-claims. For instance, commentators might say that resistance is a complex issue which cannot be effectively addressed from a single perspective only. Similarly, commentators might argue that resistance is an emerging phenomenon of a complex system, hence analysis based on assumption of linearity might not consider potential tipping points which are difficult to identify ex-ante. Similarly, counter-arguments might be that healthcare systems could be ill-prepared in addressing resistance, or that top-down policies might prove to be ineffective in addressing this problem. While these counter arguments may stand, the purpose of this thesis is not to provide a conclusive view on antibiotic resistance as a whole, but rather to focus on specific issues of this multi-faceted phenomenon.

This thesis aims to expand the existing knowledge on the introduced topics. More specifically, this thesis first aims to fill the gap on the analysis of the effectiveness of stewardship programmes in reducing antibiotic over-consumption. Despite the importance of the topic of controlling antibiotic consumption, very little has been said regarding the effectiveness of existing policies in reducing consumption. The first chapter of this paper aims to provide an answer to this question. Second, this thesis aims at providing additional evidence concerning the spatial effects of antibiotic consumption. While there have been few studies analysing spatial effects in health economics issues, the analysis of spatial dependence in antibiotic consumption are limited. Existing studies in this field mostly use cross-sectional analysis. This limited literature also did not reach a final agreement on the sources of those dependences. The second chapter of this contribution aims to shed some light on this issue by providing a spatial panel analysis for England and by providing additional model specifications to explain the potential sources of spatial dependence. Lastly, very little has been said on the impact of value-based pricing of pharmaceuticals in affecting welfare and the probability of innovation. The third chapter of this thesis provides an analysis of the impact of this pricing policy on the dynamics of the pharmaceutical market.

The analysis presented in this thesis contributes to additional strands of literature. For instance, the analysis of stewardship programmes fits in the literature centred on cross-country comparison of antibiotic consumption (Klein et al. (2018), Blommaert (2014)). This strand of literature aims at identifying patterns of antibiotic consumption across countries. The purpose of this literature is to understand how different health systems address the issue of antibiotic consumption. The first chapter complements the healthcare literature that uses econometric techniques to obtain plausible causal effects from observational data (Hoynes et al. (2015), Hoynes et al. (2016), Wing et al. (2018)). This literature, already established in applied economics and econometrics, aims to identify the impact of specific policies and interventions. Based on the concept of natural experiment, this strand of literature aims to identify the impact of interventions. The second paper fits with spatial modelling in healthcare systems (Anselin (1988), Gibbons et al. (2015), Lippi Bruni and Mammi (2016), Filippini et al. (2014), Gonzalez-Ortiz and Masiero (2013)). The spatial modelling literature in healthcare systems, and

in the field of antibiotic prescription more specifically, aims at identifying the sources of spatial dependence and its impact on a specific target measure. The third chapter fits across a number of literature strands. First this chapter looks at the issue of welfare maximisation considering the implications of static and dynamic optimisation (Arrow (1962), Nordhaus (1969), Scherer (1972)). This literature looked at how social planner might price pharmaceuticals either for the maximisation of welfare in individual periods, or inter-temporally. The paper also fits in the literature of innovation in pharmaceutical markets (Arrow (1962), Nordhaus (1969), Scherer (1972), Van Cayseele (1989), Billette de Villemeur et al. (2019)). More specifically, the modelling approach is based on a pseudo-deterministic innovation probability function. This papers also fits in the strand of literature analysing rent-seeking behaviour and innovation (Krueger (1974), Boldrin and Levine (2013)). Lastly, this paper fits in the literature analysing price regulation and its impact on welfare and innovation (Brekke (2007), Miraldo (2010), Ghislandi (2011)).

This thesis is organised as follows. Chapter 2 explores the effectiveness of EU-wide policies, such as stewardship programmes, in influencing the reduction of the provision of antibiotics. This analysis is performed adopting difference-in-difference analysis based on Eurobarometer survey data. Chapter 3 analyses GPs patterns of antibiotic provision in England for the years 2013-2017 adopting techniques from spatial econometrics. Chapter 4 explores the dynamics of pharmaceutical regulation and its impact on innovation. By introducing a dynamic two-period theoretical model, this analysis first focuses on static-versus-dynamic objectives of innovation, then introducing an focus on the impact of regulation such as value-based pricing. Section 5 provides the conclusions.

Chapter 2

Estimating the impact of stewardship programmes on antibiotic consumption in EU. Evidence from the Eurobarometer for the years 2009-2018.

I. Introduction

This paper estimates the impact of the introduction of stewardship programmes in reducing antibiotic consumption across European countries.

The use of antibiotics increased globally over the past few years (Klein et al., 2018). Over-prescription of antibiotics is associated with higher antibiotics resistance (Mera et al. (2006), Monroe and Polk (2000)). Antibiotic resistance leads to reduced health outcomes and to increased costs for the national health systems. According to O'Neill (2014), antibiotic-resistant infections currently claim at least 50,000 lives each year across Europe and the US alone, with a potential global rise close to 10 million expected deaths per year by 2050. In the EU, antimicrobial resistance is expected to lead to 33 thousand deaths every year, with an estimated 1.5 billion euros of yearly healthcare and productivity costs (European Observatory on Health Systems and Policies, 2019). Reducing overconsumption of antibiotics might thus reduce costs for national health systems worldwide and prevent unnecessary deaths.

O'Neill (2014) identifies considerable variation in the patterns of global antibiotics resistance, with country-specific differences in prescription rates being a key source of variation. The authors also identify overconsumption being facilitated by over-the-counter availability and provision without prescription. Significant variation on antibiotic consumption was identified also within Europe (Megraud et al. (2013), Goossens et al. (2005), ESAC (2007), ESAC (2011), Ferech et al. (2006)). Fleming-Dutra et al. (2016) and Smieszek et al. (2018B) state that a substantial fraction of antibiotic prescriptions in primary care are likely to be inappropriate. Some authors identify health inequalities and income per capita as factors associated with antibiotics misuses and regional variation in prescription rates (Llor and Bjerrum (2014), Filippini et al. (2006), Koller et al. (2013)). Antibiotic resistant infections, which are linked to over-prescription, have an increased risk of worse clinical outcomes and death, and consume more healthcare

resources, compared to infections with non-resistant bacteria (World Health Organization, 2014).

Currently, most EU countries have well-established national and international surveillance systems for Antimicrobial Resistance (AMR), whereas countries in other parts of the European Region require strengthening or establishing surveillance (World Health Organization, 2014).

Policy makers world-wide introduced policies targeted to the reduction of the risks associated with antibiotic resistance. These include, for instance, the application of Stewardship Programmes and National Action Plans (NAP) (World Health Organisation, 2015). Stewardship programmes are quality improvement initiatives aimed to optimise the use of antibiotics via evidence-based recommendations targeted to health professionals (Tamma and Cosgrove (2011), Charani and Holmes (2013)). According to World Health Organisation (2015) optimised antibiotic consumption for human health requires prescription decisions to be based upon effective diagnosis and evidence-based prescribing. Evidence-based prescribing can be achieved via stewardship programmes, which allow the monitoring and promotion of antimicrobial use at national and local levels.

National action plans are coordinated national policies aiming to develop specific action to address antibiotic resistance, ensuring accountability and civil society engagement (Bonk, 2015). Despite global efforts by the WHO, many countries lag behind on the introduction of national policies (European Observatory on Health Systems and Policies, 2019).

Concerning the effectiveness of individual policies, CDC (2013) identifies stewardship programmes as one key action against antibiotic resistance. Effective stewardship ensures that every patient gets the maximum benefit from antibiotics, while preserving the life-saving potential of these drugs for the future. Prudent prescribing, arising from evidence-based stewardship, has been identified as one way to reduce the potential for resistance (Goossens (2009), van de Sande-Bruinsma et al. (2008)).

Conversely, despite the World Health Organisation's (WHO) efforts for the harmonisation of NAPs (WHO et al., 2016), Bonk (2015) identifies considerable variation internationally concerning NAP's implementation, with differences holding both in terms of areas of action, as well as expressed goals.[1] In addition, while National Action Plans often mention the introduction of stewardship programmes as part of the national strategy European Commission (2017), they often lack the amount of detail provided by evidence-based guidelines reported in stewardship programmes.[2] Due to the variation in their implementation at a national level, we do not make assumptions on NAPs being either complement or substitute to stewardship programmes.

According to WHO, not all EU countries have implemented antibiotic stewardship programmes[3] and NAPs at the same time.[4] Different temporal patterns in the implementation of national policies across EU countries, create the conditions to analyse the impact of such

[1]For instance, the Italian NAP clearly indicates a goal for the reduction of systemic antibiotics prescription by more than 10% at a local level and more than 5% in hospitals (Ministero della Salute, 2017), while the UK NAP, although stating priorities and calls to action, focuses more on defining the policy framework for containing over-prescription, without providing a target goal for prescription reduction (Department of Health and Department for Environment and Rural Affairs, 2013).

[2]For instance, the UK 2013 NAP states the intention to introduce stewardship programmes (among other policy actions) (Department of Health and Department for Environment and Rural Affairs, 2013), while it is not until the 2015 National Institute of Care Excellence (NICE) that quantitative and evidence-based guidelines are provided in primary care (NICE, 2015).

[3]See `https://ecdc.europa.eu/en/publications-datadirectory-guidance-prevention-and-controlprudent-use-antibiotics/antimicrobial`

[4]`https://www.who.int/antimicrobial-resistance/national-action-plans/library/en/`

policies on antibiotic consumption as a natural experiment. Due to the important differences in NAPs implementations across individual countries, this paper will focus mostly on stewardship programmes. Information concerning NAPs will be used only for sensitivity analysis.

This paper estimates the impact of stewardship programmes in reducing antibiotic consumption via difference-in-difference (diff-in-diff) analysis. We estimate our results on a repeated cross-section of a representative sample of the European population, using Eurobarometer survey data for the years 2009, 2013, 2016 and 2018. Our key dependent variable is a survey question asking respondents whether they consumed antibiotics orally in the last 12 months. Our results are identified taking into consideration respondents' characteristics as well as national level covariates. We estimate the impact of stewardship programmes in reducing antibiotic consumption by pooling it across treated and control groups, as well as estimating its impact for individual years of introduction. We confirm the robustness of our results by estimating an alternative difference-in-difference model introducing NAPs as a control variable.

The provision of antibiotics can be linked to both demand- and supply-side factors. Demand-side factors might include a higher requests from consumers, possibly due to beliefs of antibiotics being effective in addressing their health needs. Supply-side factors, on the contrary, might be linked to healthcare professionals acting as gate-keepers to antibiotic provision.

This paper estimates the impact of the stewardship programmes on antibiotic consumption. This effect is estimated for all respondents, as well as individual respondents' groups. We then identify the presence of inter-temporal effects of the introduction of stewardship programmes, by identifying significant lead effects, confirming an impact of stewardship programmes on antibiotic consumption in the years following its introduction.

We provide a first intuition of whether stewardship programmes are effective in influencing supply-side factors by estimating whether such programmes have reduced the share of antibiotics received from doctors and identifying the share of respondents who reported the intention to consult a doctor for future antibiotic use. We interpret these effects as evidence for stewardship programmes in being effective in improving the gate-keeping role of health professionals when it comes to antibiotic prescription.

We analyse the impact on potential demand-side effects by estimating the impact of stewardship programmes on respondent's beliefs concerning antibiotics. More specifically, the respondent's beliefs which are captured by the survey questions are: a) whether antibiotics are effective against flu, b) whether antibiotics kill viruses, c) whether overuse of antibiotics reduces their effectiveness, and d) whether antibiotics have side effects. We interpret these beliefs as proxies for demand-side factors influencing antibiotics consumption.

The estimation of the impact of stewardship programmes on antibiotic consumption, and its impact on the demand- and supply-side factors defined above, forms the motivation of this paper.

This paper is organized as follows. Section 2 provides some background on institutional settings and on the literature. Section 3 provides a description of the available dataset. Section 4 presents the methodology. Section 5 illustrates the results. Section 6 concludes.

II. Literature review

The available literature on antibiotic consumption identifies a high heterogeneity in the daily consumption of antibiotics by outpatients across European countries (Elseviers et al., 2007). Pouwels et al. (2018) show that, among English GP practices, the majority of practice-level variation in antibiotic prescribing cannot be explained by variation in prevalence of co-morbidities. Factors such as high consultation rates for respiratory tract infections and high prescribing rates for corticosteroids could explain much of the variation.

Dolk et al. (2018) suggest that a practice with a higher proportion of young children or elderly patients would be expected to have higher prescription rates than a practice with mainly working-age adults. Solomon et al. (2016) state that family physicians have an important role in combating antibiotic resistance through carefully prescribing antibiotics, communicating with patients about antibiotic appropriateness, and identifying and reporting unexpected treatment failures and suspected resistance.

From an empirical perspective, Burkhard et al. (2015) estimate the effect of financial incentives for physicians to sell more drugs and to substitute towards more expensive drugs, finding evidence that physician dispensing increases drug costs by 25% for GPs. This indicates a potential role for the physician in affecting prescription volumes. Kaiser and Schmid (2016) extend the previous analysis by exploring regional variation in GP prescribing for the Swiss case, and identifying that dispensing leads to a drug price increase of 34%. Penthofner (2016) show that GPs respond to liability pressure by prescribing more antibiotics.

Gonzalez-Ortiz and Masiero (2013) link antibiotic consumption to demographic and socio-economic characteristics of the population, the supply of health care services in the community and antibiotic co-payments estimating an Ordinary Least Squares (OLS) model with Fixed Effects (FE). The authors find that antibiotic use is affected by the age structure of the population and the supply of community health care. The authors also find a positive effect on antibiotic consumption by income elasticity and negative effects of co-payments. Huttner et al. (2010) identify that public interventions might be effective in controlling antibiotic consumption.

When considering country-level phenomena associated with antibiotic consumption, European Observatory on Health Systems and Policies (2019) indicate that factors such as weak healthcare systems, lack of sustainable healthcare funding, prevalence of over-the-counter (OTC) sales of antimicrobials, plus unhygienic living conditions, might all contribute to a higher diffusion of infectious diseases, thus potentially contributing to higher resistance. The authors also identify a potential link between antibiotic resistance and GDP per capita, particularly when comparing low- and middle-income countries to more developed ones. Similarly to Rousham et al. (2018), the authors highlight the pathways for antimicrobial resistance to be an interplay between human, animal and environmental factors.

There exists a stream of literature analysing the diffusion of professional know-how on antibiotic prescription across practitioners. In particular, there are studies focusing on health education interventions and their impact on prescription behaviour. These studies identify that such interventions are effective in achieving better alignment to national prescription guidelines reducing the provision of broad spectrum antibiotics (Dyrkorn et al., 2016). Comparison and peer effects were also found to be effective in ensuring that practitioners follow national guidelines (see Meeker et al. (2016) and Clegg et al (2019)), in reducing inappropriate prescription (see Gjelstad et al. (2013) and Linder et al. (2017)) and in the adoption of new drugs (Donohue et al, 2018). These results are in line with other streams of behavioural literature identifying that practitioners expect peers to know if they are overprescribing (Pinder et al., 2015) and with the

results by Hallswort et al 2016, which indicate that social norm feedback to prescribers can be an effective method to reduce overall consumption in ambulatory care (Hallsworth et al., 2016). Additional studies identify the importance of opinion leaders in influencing antibiotic prescription of other practitioners Nair et al. (2010). Other authors, however, highlight limitations in implementing large scale peer-audit and feedback mechanisms on general prescription in primary care (Trietsch et al., 2017). The WHO recognises the importance of knowledge diffusion on influencing antibiotic prescription, however it also highlights the need to acknowledge local cultural contexts to ensure behavioural change is achieved (Ledingham, 2019). This result appears to highlight potential persistence of local patterns in prescription behaviour.

Mueller and Olofystergren (2016) provide evidence of an existing relationship between the degree of regulation and antibiotic consumption in European countries. In particular, the authors highlight the importance of implementing specific regulatory items, such as the presence of Standard Treatment Guidelines, non-availability of drugs without prescriptions and pharmacist training modules, on reducing antibiotic consumption. The authors also highlight the importance of contextual aspects, such as the quality of the country's healthcare system, the overall governmental structure, the amount of healthcare resources and specific health policies and legislation as factors influencing antibiotic consumption. A variation in such factors may therefore underline potential cross-country variation in consumption. McGowan (1994) provide a detailed literature review of articles highlighting a negative link between antibiotic control and monitoring and susceptibility patterns to resistance. Similarly, Baur et. al. (2017) provide a review of studies exploring stewardship programmes, finding evidence of such programmes to be effective in reducing antibiotic consumption and resistance in hospital settings. Arda et al. (2007) find antibiotic control to be cost-saving and effective in reducing resistance. Filippini et al. (2012) identify an effectiveness of public education campaigns in reducing antibiotic consumption. Horowitz and Mohering (2004) identify a potential negative link between patent expiration and antibiotic resistance. A broader review of studies analysing policies targeted at reducing antibiotic resistance is provided by Sipahi (2008) and Brown and Laxminarayan (1998).

A separate strand of policy interventions aimed at reducing antibiotic consumption are the pay-for-performance policies. Pay-for-performance policies aim to incentivize quality improvement by rewarding health-care providers who reach pre-defined targets (Ellegard et al., 2018). Ellegard et al. (2018) study the effectiveness of pay-for-performance policies in reducing inappropriate antibiotic prescription behaviour in Swedish primary care, identifying an effectiveness in such policies in favouring the diffusion of narrow-spectrum antibiotics, which contribute less to resistance. An example of pay-for-performance policies are provided by the English Quality Premium. These policies aim to provide incentives to CCGs, statutory bodies of the National Health System (NHS) responsible for the planning and commissioning of healthcare services in local areas, to reach specific antibiotic prescription targets. Among the considered areas of intervention, these policies introduce incentives for CCGs to reduce antibiotic prescription among GP practices. Such incentives occur for both all antibiotics as a whole and for broad-spectrum antibiotics which are highly related to resistance NHSE (2016). According to the available evidence, such policies proved to be effective, as their introduction in 2015 coincided with a 3% drop in antibiotic prescribing (see Bou-Antoun et al. (2018)). This reduction proved to be sustained over time, consistently with PHE (2017) findings showing that GP practices respond to variation in guidelines.

Antibiotic stewardship programmes are specific policies whose scope is to ensure that all patients are treated with the most effective and least costly drug for the appropriate amount of time, all while minimizing treatments' potential side effects (MacDougall and Polk, 2005). One of the specific implementations of stewardship programmes is the provision evidence-based

guidelines to healthcare practitioners, so as to preserve the effectiveness of antibiotics by reducing resistance while achieving satisfactory health outcomes (Dellit et al, 2007). More generally, the term stewardship programme is used as an umbrella term enclosing an overarching policy aiming at changing antibiotic provision and directing its use. When introducing stewardship programmes, healthcare organizations may use a plethora of individual practices (see MacDougall and Polk (2005) and Dellit et al (2007)). Specific practices considered under stewardship programmes might include: formulary restrictions and preauthorization requirements, the development of evidence-based guidelines, combination therapy, optimisation of antibiotic prescription based on patients' characteristics, conversion from parenteral to oral prescription (see Brown and Laxminarayan (1998) and Dellit et al (2007) for an in-depth discussion on this topic). Expert recommendation on antibiotic stewardship suggests the monitoring of both outcome and process measures (Dods Ashley et al, 2014). Allerberger et al (2009) explore the implementation of antibiotic stewardship programmes across European countries identifying significant differences in country-level implementation as a result of heterogeneity in organisational aspects of healthcare delivery, financing and insurance across member states. A similar result is obtained by Bruce et al. (2009). In addition, MacKenzie et al (2007) highlights differences in staffing and in educational level of medical specialists as a source of variation in the actual implementation of stewardship programmes across European countries. When analysing stewardship programmes at an European level, a significant cross-country variation is to be expected.

Elzinga and Mills (1997) develop a theoretical framework to show that antibiotics prescription is elastic to price discounts, identifying that discounts increase consumer welfare in the managed care sector. This result identifies a role for price in affecting the probability of antibiotic use. Filippini et al. (2014) investigate the role of dispensing physicians in influencing antibiotics consumption. The authors develop a theoretical framework to show that when introducing an interaction between competing physicians and patients exposed to bacterial infections, the spatial effect of consumption may generate ambiguous results. Trottmann et al. (2016), on the contrary, identify no immediate evidence of GP prescription to be leading to higher drug costs compared to other forms of prescribing. The Turkish Ministry of Finance, which is responsible for the majority of healthcare expenditures, adopted formulary restrictions n 2003, leading to a reduction of 19.6% in antibiotic costs following the introduction of such policy Arda et al. (2007). The application of guidelines appeared to reduce inappropriate prescribing in pedriatic care Goreki et al. (2002) and in teaching hospitals Carling et al. (2003), while MacDougall and Polk (2005) identify several cases of stewardship programmes reaching cost-effectiveness in secondary care.

Wing et al. (2018) provide a review of the diff-in-diff methodology in public health policy research. Examples of its application include the estimation of the impact of taxes on tobacco consumption (Simon, 2016), alcohol consumption (Marcus and Siedler, 2015), preventative care (Kolstad and Kowalski, 2012). Diff-in-diff has also been applied to the estimation of the impact of new health policies on drug prescription in the US (Ketcham and Simon, 2014). A methodology to estimate the effects of introducing a policy in separate years is reported in Stevenson and Wolfers (2006) who introduce the staggered diff-in-diff.

To the best of our knowledge there are no papers estimating the impact of national policies on antibiotic consumption at an EU level via the application of diff-in-diff methodology.

III. Data

The European Commission has an established tradition of using the Eurobarometer to survey Europeans' public opinion on matters related to society at large, economics and current affairs.[5] The Eurobarometer is often targeted to measure specific topics of interest for policy makers. This study uses the results of the Eurobarometer 72.5 (Nov-Dec 2009), 79.4 (April 2013), 85.1 (April 2016) and 90.1 (September 2018) which survey the use of and attitudes towards antibiotics across European countries.

The Eurobarometer provides a nationally representative sample of the population of individual EU countries. Sample size in each country consisted of 1000 individuals, with the exception of Luxemburg and Malta which both had 500 respondents. Two additional exceptions were included for specific regions, namely, Germany, which had 1000 respondents in west Germany and 500 in East Germany. The United Kingdom, also had 1000 observations for Great Britain, and 300 observations for Northern Ireland. Individuals included in the survey were those above 15 years of age. The survey allowed for post-stratification sample weighting and population size weighting.

For the Eurobarometer 72.5, 79.4, 85.1 and 90.1 the fieldwork was carried out respectively in November 13 2009 to December 09 2009, May 24 to June 9 2013, April 09 to April 18 in 2016, and September 08 2018 to September 26 2018. Interviews were conducted face-to-face in people's home in the respective national language[6]. Where the techniques were available, CAPI (Computer Assisted Personal Interview) was used.

Survey responses were checked for completeness, missing data, duplicated records, illegal codes, consistency in response patterns and questions routing. Potential errors were address at source.

In the survey, the use of antibiotics was measured by asking respondents whether they consumed any antibiotics orally in the last 12 months. Responses to this question formed the main dependent variable of this study.

The barometer also includes questions concerning the source of antibiotics and the intention to consult a doctor for future antibiotic consumption. We used these two questions as alternative dependent variables, focusing on doctors as a source of antibiotics. Lastly, we considered questions on antibiotic beliefs as additional dependent variables. Beliefs were measured by respondents opinions on statements such as whether antibiotics are effective against flu, whether antibiotics kill viruses, whether antibiotics overuse might reduce their effectiveness, and whether antibiotics have side effects. All these responses were turned into dummy variables.

The Eurobarometer provides information about respondents' demographics, including respondents' nationality, the country in which the survey was asked, respondents age, gender, educational level, marital status, occupational status, household composition, and whether respondents had financial difficulties.

The information contained in the survey was subject to a data cleaning process. For instance, information concerning the country in which the survey was asked, and respondent's nationality were turned into dummies.[7] Observations related to Croatia were removed from the analysis,

[5] See `http://ec.europa.eu/commfrontoffice/publicopinion/index.cfm`

[6] Notice that by carrying out interviews in people's homes some specific categories of antibiotic users, such as elderly individuals living in care homes, might have been left out of the analysis.

[7] Considered countries were: Belgium, Denmark, Germany, Greece, Spain, France, Ireland, Italy, Luxembourg,

as observations for this country were not available in the 2009 Eurobarometer. We computed a "foreign" dummy set equal to one when the nationality of the respondent was different from the country in which survey was held. We also included dummies for individual years.

The survey allowed for questions with dichotomous answers, that is questions allowing for "Yes or No" answers, or any variation of this sort. Two scale variables were: use of antibiotics in the last 12 months, opinion on antibiotics use against viruses, opinion on antibiotics use against flu, opinion on antibiotics overuse, opinion on antibiotics side effects. Responses to these questions were turned into dummy variables.

Respondents age was organised in a series of dummies, namely being a teenager (15 to 17), being an adult (18 to 64) and being elderly (above 65). Gender was coded as two separate dummy variables.

Regarding education, respondents were asked to indicate the year in which they finished full-time education. Education was organised into a series of dummies. Considered levels were: early childhood or no education, primary, secondary and above secondary education. Age bands were respectively: less than 6, between 6 and 12, between 13 and 18, above 18.[8]

Occupation was organised into three main categories: non active, self-employed and employed. We implemented a dummy variable for each occupational category.

Marital status was turned into a series of dummies. More specifically we considered the following categories: being single, being single living with partner, being divorced or separated, being widow and having an "other" relationship status.

We created a dummy variable to indicate whether the household had any kids (age below 10) or teenagers (age 10 to 14).

Financial status indicated whether the respondent experienced any financial difficulty in paying bills at the end of the month. This variable was organised as a dummy, with 1 indicating "most of the time" and "from time to time" responses, and 0 otherwise.

Respondents' trust on information sources was measured by asking the respondents to indicate up to three trusted source.[9] Answers to this question varied across years. For this reason, prior to 2013, we included in the "other" category the answers "Government Website", "National Public Health Institute", "EU Website", "Health Related Website", "Medical Encyclopedia", "National Health Body", "Health Related Magazine". For 2016 onwards the "other" category included "Official Website", "blog", "Other website", "social media", "TV", "Radio", "other". Respondents' level of trust on the sources of information concerning antibiotics was turned into a series of dummies.

In the data cleaning process, all "don't know" or "non applicable" answers were turned into NA.

We then considered a number of country-level covariates, namely: GDP per capita, population density, and unemployment rate. All these variables were time varying. Other national-level

Netherlands, Portugal, United Kingdom, Austria, Sweden, Finland, Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovakia, Slovenia, Bulgaria, Romania, Croatia, Other countries.

[8]Notice that setting those age bands could lead to an approximation as educational stages may vary across countries.

[9]Available sources were: "A doctor", "A nurse", "A pharmacy", "A hospital", "Another health care facility", "Family or friends", "TV", "Newspapers or magazines", "The radio", "The internet" and "Other".

indicators associated with weak healthcare systems, lack of sustainable healthcare funding, prevalence of over-the-counter (OTC) sales of antimicrobials, plus unhygienic living conditions were considered, however they were not included due data limitations.[10] All national-level indicators were obtained from Eurostat database.[11]

To account for the severity of antibiotic resistance, we included the percentage of invasive staphylococcus aureus isolates with resistance to meticillin (MRSA).[12] Due to the positive feedback loop between antibiotic over-prescription and antibiotic resistance (Mera et al. (2006), Monroe and Polk (2000)), including the rate of antibiotic resistance among the covariates might lead to "bad controls" due to endogeneity (Angrist and Pischke, 2009). For this reason, antibiotic resistance was used only as a compositional changes check; that is to verify whether the introduction of stewardship policy was associated with the severity of antibiotic resistance.

To estimate the impact of national policies in influencing antibiotics consumption, we collected information on the application of those policies at a country level. Information on the year of implementation of stewardship programmes in individual countries was obtained from ECDC's website.[13] Information on the introduction of national action plans was obtained from WHO's library on national action plans.[14]

Table 2.1 presents a summary of implemented national policies. This table indicates the country division in treatment groups (column 2), the year of introduction of stewardship programmes (column 3), and the year of the introduction of a national action plan (column 4). Reported years indicate the years in which the policy was implemented. Stewardship programmes and national action plans were turned in a series of dummies equal to one from the years in which the policy was first implemented.[15]

The final dataset included 105556 observations.

IV. Methodology

Our key dependent variable consists of a dummy variable indicating respondents' antibiotic oral consumption in the last 12 months.[16]

As alternative dependent variables we consider the percentage of respondents who reported receiving antibiotics from a doctor, respondents' intention of consulting a doctor for future

[10] These included: a) healthcare expenditure per capita, b) out-of-pocket expenditure, c) income inequality (missing for most countries in 2018), d) antibiotics provided to animals (which starts from 2010 and ends in 2016), e) health personnel per 1000 inhabitants, f) hospital beds (data ends in 2017), g) hospital days of in-patients (ends in 2017), h) long-term care beds in nursing and residential care facilities, i) the number of air transport passengers, and l) number of households with internet access.

[11] `https://ec.europa.eu/eurostat/data/database`

[12] While this indicator is not the only indicator associated with antibiotic resistance, it captures one of the most common causes of bacterial infections in Europe `https://ecdc.europa.eu/sites/portal/files/documents/EARS-Net-report-2017-update-jan-2019.pdf`.

[13] https://ecdc.europa.eu/en/publications-data/directory-guidance-prevention-and-control/prudent-use-antibiotics/antimicrobial

[14] http://www.who.int/drugresistance/action-plans/library/en/

[15] Notice that our measure of antibiotic consumption refers to antibiotics consumed in the last 12 months. Germany, whose stewardship guidelines were published in December 2013, was included in treatment 2 group, as the fieldwork of the Eurobarometer ended in June 2013. On the contrary, the Netherlands, were included in treatment group 2 as the guidelines explicitly mention that they refer to the "prevailing professional standard in March 2016", hence they were in place by the time of the survey fieldwork.

[16] The specific survey question was: "Have you taken any antibiotics orally such as tablets, powder or syrup in the last 12 months?". This question allowed for "yes" or "no" answers.

Table 2.1: *Summary of national policies. Country division across control and treatment groups is related to the year of introduction of the stewardship programme. Reported years indicate the year of implementation of individual policies.*

Country	Treatment group	Stewardship programme	National action plan
Austria	Control	-	2014
Belgium	Control	-	2014-2019
Bulgaria	Control	-	-
Croatia	Control	-	-
Cyprus	Control	-	2012
Czech Republic	Control	-	2011-2013
Estonia	Control	-	-
Finland	Control	-	2017-2021
Greece	Control	-	2008-2012
Hungary	Control	-	-
Italy	Control	-	2017 - 2020
Latvia	Control	-	-
Lithuania	Control	-	2017 - 2021
Luxembourg	Control	-	-
Malta	Control	-	-
Portugal	Control	-	2013
Romania	Control	-	-
Slovakia	Control	-	-
Slovenia	Control	-	-
Sweden	Control	-	2016 - 2020
France	Treatment 0	2008	2011-2016
Ireland	Treatment 0	2009	2017 - 2020
Denmark	Treatment 1	2012	2017
Poland	Treatment 1	2011	-
Spain	Treatment 1	2012	2014 - 2018
Germany	Treatment 2	2013	2015-2020
Great Britain	Treatment 2	2015	2013-2018
Northern Ireland	Treatment 2	2015	2013-2018
Netherlands	Treatment 2	2016	2015 - 2021

antibiotic use. these variables are interpreted as potential supply-side proxies for doctors acting as gate-keepers to drug provision in primary care.

In addition, we check whether the introduction of national policies changed respondents' beliefs on antibiotics, as measured by the percentage of respondents who provided a positive response to any of the following statements: antibiotics kill viruses, antibiotics are effective against cold and flu, unnecessary use of antibiotics makes them become ineffective and antibiotics have side effects. We interpret these variables as demand-side factors affecting the potential demand for antibiotics from patients.

We first provide descriptive statistics of the variables considered in this analysis. Variables with a high percentage of missing values were removed from the analysis. To avoid potential collinearity we remove highly correlated variables.

To understand whether countries with higher antibiotic consumption were also the ones not adopting the policy, we first grouped antibiotic consumption per capita in individual years. Antibiotic consumption per capita was defined as Defined Daily Doses (DDD) per 1000 inhabitants per day. In the analysis we considered antibiotics in the ATC group J01 in both the community sector. Data was downloaded from the ECDC website.[17] To ease interpretation prescription rates were grouped across treatment and control groups. We used the methodology proposed by the World Bank in computing per capita consumption rates across treated and control groups. More specifically, we used the denominator (total population) in single years as a weight when computing average rates.[18] Population estimates in single years by country were downloaded from the World Bank.[19][20]

We consider stewardship programmes as our policy of interest. Due to its variation in its implementation across countries, we consider national action plans only for sensitivity analysis.[21]

To estimate the impact of the implementation of stewardship programmes on antibiotic consumption, we adopt a difference-in-difference model (Imbens and Woolridge, 2007).

Diff-in-diff framework requires the dependent variable to present parallel trends between the treated and non-treated groups. We provide an initial test for the presence of parallel trends by means of descriptive statistics for pre-treatment and post-treatment periods for the control and treated groups (Ho et al. (2007), Imbens and Rubind (2015)). We also test parallel trends hypothesis by means of graphical analysis. More specifically, we plot the dependent variable averaged across control and treated groups in single years (Antwi et al., 2013). To ensure fair comparison we considered non-treated countries as a control group, and 2009, 2013 and 2016 treatments as individual treated groups.

[17] Data were downloaded from `https://www.ecdc.europa.eu/en/antimicrobial-consumption/database/rates-country`. Site accessed on 29th May 2020.

[18] See https://datahelpdesk.worldbank.org for a discussion on the approaches to use when computing average rates. Site accessed on 31st May 2020.

[19] See `https://databank.worldbank.org/reports.aspx?source=2&series=SP.POP.TOTL` Site accessed on 31st May 2020.

[20] Notice that in the computation of population-adjusted DDD rates Liechtenstein was removed as it was DDD rates were missing in the observation period.

[21] As stated in the introduction, we interpret NAPs as either complement or substitute to stewardship programmes due to their variability across countries.

Our baseline model for the difference-in-difference analysis is

$$y_{ijt} = \alpha_j + \delta_t + \beta_1 x'_{1,ijt} + \beta_2 x'_{2,jt} + \gamma D_{jt} + \epsilon_{ijt} \tag{2.1}$$

where y_{ijt} represents an outcome for individual i in country j in year t, α_j represents individual country dummies, δ_t represents year dummies, $x'_{1,ijt}$ represents a vector of respondent's characteristics, $x'_{2,jt}$ represents country-level covariates, and D_{jt} is a variable equal to 1 for country j adopting the policy at time t, and ϵ_{ijt} is an error term.

In our analysis countries have all been treated in different time periods. To estimate the impact of individual years of introduction, we develop a *staggered* version of difference-in-difference model as proposed by Stevenson and Wolfers (2006). Staggered models generalize the standard difference-in-difference analysis to allow treatments to occur in different time periods.

More specifically, the staggered model can be written as

$$y_{ijt} = \alpha_j + \delta_t + \beta_1 x'_{1,ijt} + \beta_2 x'_{2,jt} + \sum_k \gamma_k D_{jk} + \epsilon_{ijt} \tag{2.2}$$

In our case we have $t \in \{2009, 2013, 2016, 2018\}$. In model 2.2, D_{jk}, is a dummy variable indicating whether stewardship programmes were introduced in years 2013 or 2016 respectively.[22]

We estimate a number of different models based on the approach of equation 2.1. Model DiD_1 represents an empty model containing only year- and country-specific effects. Model DiD_2 contains respondents characteristics. Model DiD_3 includes trust on information sources. Model DiD_4 includes interaction effects. Model DiD_5 includes country-level covariates. Notice that by including respondent characteristics we ensure that the impact of the policy is not due to unobserved covariates (Bellou and Bhatt, 2013).

Models 2.1 and 2.2 present a model estimated at a respondent level, however the source of variation arising from stewardship is at a country-level. This might lead to potential estimation bias in the standard errors of the model coefficients arising from residuals being clustered at a country level (Donald and Lang (2007), Bertrand et al. (2010), Cameron and Miller (2015)). To overcome this potential bias we introduce clustered residuals (Donald and Lang (2007), Bertrand et al. (2010), Cameron and Miller (2015)). We compute cluster-robust standard errors via Huber-White method, thus correcting for heteroskedasticity occurring at a country-level. Cluster-robust standard errors are applied to all presented models. Robust standard errors were computed using the R package *car*, with the function *hccm* with option type set equal to *hco*.

Our identifying assumptions are as follows. We assume that the majority of the variability of our dependent variable stands at a respondent level. We assume that the respondent's characteristics are capable of identifying most of that variance. We assume that country-level differences can be effectively captured by country fixed effects and by country-level covariates. We also assume that the country decisions to introduce stewardship programmes are exogenous and not linked to our set of covariates. The data generating process is thus assumed such that patients might be less likely to receive antibiotics if their doctors receive clear guidelines on provision, ceteris paribus.

We run a series of alternative models to test the robustness of our results.

[22] Treatment occurring in year 2009 is removed from the staggered analysis as we do not have a pre-treatment period.

First we run a series of robustness checks related to our identifying assumptions. We estimate the impact of introducing a dummy related to the implementation of the National Action Plan (NAP) among the independent variables.

To avoid potential identification issues arising from the staggered approach, we estimate the difference-in-difference model for individual years, that is we compare the control groups with treated groups in separated equations.

We then run our reference model 2.1 estimated across different population groups, namely teenagers, elderly, females, individuals with financial difficulties and foreigners. The same model is run on their complements groups. This check allows us to verify whether estimated results are robust for individual respondents groups.

To test the common trend assumption, we run an F-test between our reference model 2.1 with group-specific time trends and the same model without group-specific time trends. Rejecting the null hypothesis of the F-test will imply the invalidity of the common trend assumption. Group-specific time trends have been verified for individual countries and for individual respondents groups, namely teenagers, elderly, female respondents, respondents with financial difficulties and foreign respondents.

The inclusion of multiple years allow us to verify the potential lasting of policy effects over time (Bellou and Bhatt (2013), Marcus and Siedler (2015), Paik et al. (2016), Kolstad and Kowalski (2012)).

To test for this hypothesis, we introduce the following model specification

$$y_{ijt} = \alpha_j + \beta_t + \beta_1 x'_{1,ijt} + \beta_2 x'_{2,jt} + \sum_k \gamma_k D_{jt} + \sum_{s=1}^{S} D_{j,t+s}\gamma_s + \sum_{m=1}^{M} D_{j,t-m}\lambda_m + \epsilon_{jt}, \tag{2.3}$$

where S are the maximum future period, and M are the maximum previous periods considered. Under strict exogeneity, we expect future policy changes not to be associated with current outcomes, hence we expect $\gamma_s = 0 \forall s \in \{1, ..., S\}$. The values of the parameter γ_s indicate the effect of the policy s periods after its introduction. We call this effect lead effect. The parameter λ_m refers to the effect of the policy m periods prior its introduction. We call this effect lag effect. A positive lead effect will indicate a reinforcement of the policy over time, while positive lag effect indicate potential policy anticipation effects. This model is developed in three separate formats: one with only lead effects, one with only lag effects and one with both lead and lag effects simultaneously.

Our identification strategy requires the absence of endogenous selection of stewardship programmes by different countries at different points of time. The absence of endogenous selection would imply that countries' decision to adhere to stewardship programmes is not influenced by antibiotic consumption or resistance levels. Policy exogeneity, in fact, is a key element in interpreting its implementation as a natural experiment (Angrist and Pischke, 2009). The endogenous introduction of policies might occur for a number of reasons, including states changing regulation in response to changes in outcome variables (Besley and Case, 2000). To test for the absence of endogenous introduction of stewardship policies, we verify whether treatment exposure is anticipated by outcomes measured in an earlier period (Wing et al., 2018). Similar checks on the exogeneity of policy introduction are standard in the difference-in-difference analysis in health policy research (see Bachhuber et al. (2014), Raifman et al. (2017), Alpert (2016), Brot-Goldberg et al. (2017)). To check for this exogeneity, Wing et al. (2018)

state that the entire sequence of past and future treatment exposures must be independent of unmeasured determinants of outcome variables. In other words, the timing of treatment exposures must be statistically independent of the potential outcome distribution, thus ensuring exogeneity in treatment application. The idea we test for is that, after conditioning for time and country-specific fixed effects, treatment exposure is not influenced by outcome in earlier periods.

To test for this assumption, we run an OLS model defined as follows

$$D_{jt} = \alpha_j + \delta_t + \beta_2 x'_{2,jt} + \phi \hat{y}_{j(t-1)} + \eta_{jt} \tag{2.4}$$

where α_j are country-specific effects, δ_t are year-specific effects, $x'_{2,jt}$ are country-level covariates, $\hat{y}_{j(t-1)}$ is the average outcome variable in country j in period $t-1$, and η_{jt} is an error term.

As an additional check, we test for the absence of compositional changes in potential covariates by running compositional balance regression. The idea behind covariate balance is to test whether potential covariates of the outcome change following the treatment introduction (Pimentel et al., 2015) . To test for this we run a separate difference-in-difference model defined as $C_{ijt} = \alpha_j + b_t + \beta_1 x_{1,ijt} + \beta_2 x_{2,jt} + D_{jt}\delta + \epsilon_{ijt}$, where C_{ijt} are separate potential covariates (see Wing et al. (2018)). The model will tell us whether there are no compositional changes, if the coefficient δ is not significantly different from zero.

We then run a second series of robustness tests related to potential heterogeneity in the results. More specifically, we check if diff-in-diff models are significant by age group. We do so by running separate diff-in-diff models for different respondents' age groups.

Lastly, we estimate the impact of stewardship programmes on demand- and supply-side factors related to antibiotic consumption. This is achieved by estimating model 2.1 based on the alternative dependent variables and on the beliefs variables on the left-hand side.

V. Results

i. Baseline results

Table 2.2 provides the descriptive statistics of the variables shortlisted in the analysis.

Figure 2.1 shows the country average of the percentage of respondents who reported using antibiotics in the last 12 months. The figure shows important variation across countries in the dependent variable.[23]

To test for the soundness of the difference-in-difference approach, we first tested for the robustness of the parallel trend hypothesis in two ways.

First we computed the descriptive statistics of potential covariates aggregated across treated and control groups. The descriptive statistics, reported in table 2.7 in the Appendix, indicate consistency in the independent variables across treated and control groups. The only minor exceptions were the percentage of married respondents, the percentage of single respondents, trust in information received from pharmacists, and trust in information received from hospi-

[23] A similar cross-country variation was identified for the alternative dependent variables and for the opinion variables. These results are not reported for simplicity.

Table 2.2: *Descriptive statistics*

Variable	mean	std.dev	nbr.na
Year 2009	0.25	0.44	0
Year 2013	0.25	0.44	0
Year 2016	0.25	0.44	0
Year 2018	0.24	0.43	0
Antibiotic use (in last 12 months)	0.35	0.48	0
Antibiotic source: Doctor	0.34	0.48	17,430
Intention to consult doctor a for future use	0.71	0.45	92,357
Opinion: antibiotics kill viruses	0.55	0.50	7,996
Opinion: antibiotics cure flu	0.41	0.49	5,881
Opinion: overuse of antibiotics reduce effectiveness	0.91	0.28	6,005
Opinion: antibiotics have side effects	0.80	0.40	14,474
Foreign patient	0.04	0.18	0
Female patient	0.55	0.50	0
Male patient	0.45	0.50	0
Education level: Before primary	0.02	0.13	0
Age band: adult	0.71	0.45	0
Age band: elderly	0.26	0.44	0
Relationship status: married	0.52	0.50	65
Relationship status: having a partner	0.11	0.31	65
Relationship status: single	0.17	0.38	65
Relationship status: divorced	0.09	0.27	65
Relationship status: widow	0.10	0.30	65
Occupation status: non-active	0.51	0.50	0
Occupation status: self-employed	0.07	0.26	0
Patient with kids	0.18	0.39	1
Patient with teenagers	0.12	0.32	2
Patient with financial difficulties	0.37	0.48	393
Trust in information received from doctors	0.87	0.34	515
Trust in information received from hospitals	0.20	0.39	515
Trust in information received from family members	0.06	0.24	515
Trust from no source of information	0.03	0.17	515
Real GDP per capita	25140.0	14444.0	0
Population density	142.1	163.52	2955
Unemployment	8.72	4.6	2005
Resistance (MRSA)	17.32	14.22	6057
Stewardship programme	0.21	0.41	0
National action plan	0.43	0.50	0

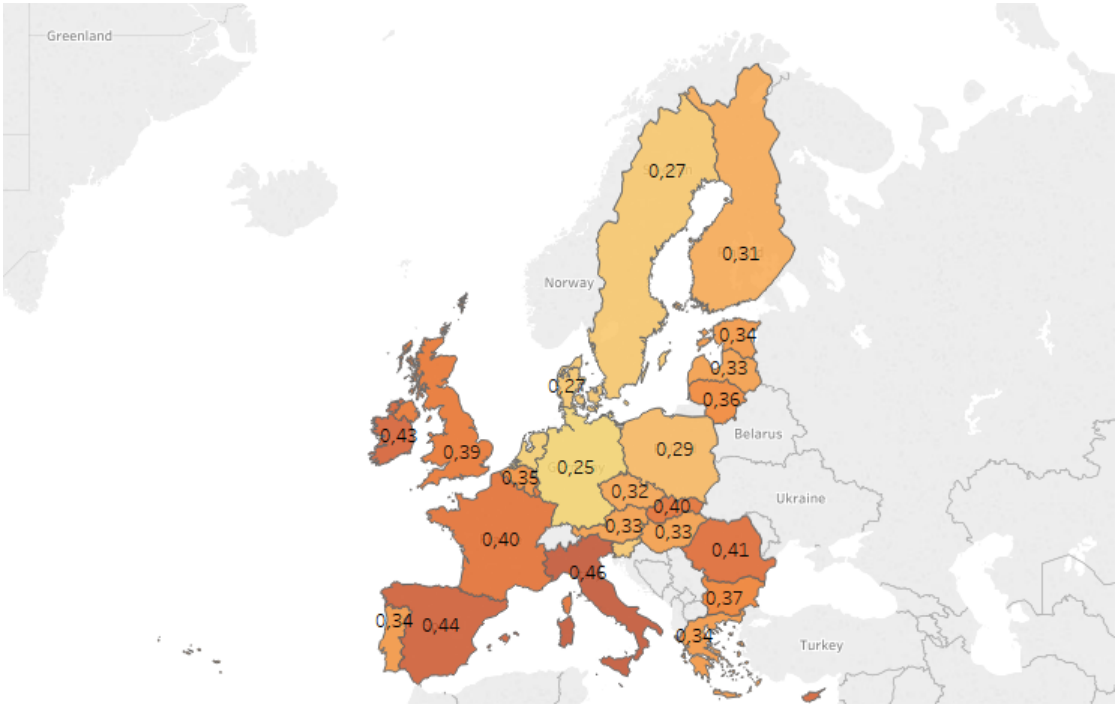


Figure 2.1: *Percentage of respondents who used antibiotics in the last 12 months - average by country (years 2009, 2013, 2016 and 2018).*

tals.[24] Financial difficulties saw the highest difference, with an average of 0.42 in the control group, and an average of 0.22 and 0.2 in the 2013 and 2016 treatment groups respectively. All country-level variables saw a change across treated and control groups (possibly because of country-level differences).

Figure 2.2 plots the averages of the dependent variable across treated and control groups. From this figure we can see that the observations treated in 2016 (in purple) appeared to present a parallel trend with the control group (in red) in the pre-treatment period. As we do not have observations prior 2009, it is not possible to check for parallel trends for observations treated in 2013. For these observations we rely on the differences for the covariates balance described at the previous point.

A similar graphical analysis was reported for the alternative dependent variables and for respondents beliefs. Results are reported in Figures 2.4 and 2.5 and 2.6 in the appendix. All figures appear to present a parallel trend across the control group and observations treated in 2016.

To verify whether there was a link between antibiotic consumption and the adoption of stewardship policy at a national level, we computed the amount of Defined Daily Doses (DDD) of antibiotics per 1000 antibiotics per day across single years by country. For simplicity, DDD rates are aggregated across treatment and control groups. Results are reported in Figure 2.3. The results appear to indicate an absence of clear relation between control and treatment groups. These figures show that the computed rate is always higher in treatment group zero compared to the control group. The opposite holds for the treatment two. The rate in the treatment

[24]These first two variables moved respectively from an average of 0.53 and 0.16 in the control group, to 0.47 and 0.25 in the 2016 treatment group. The trust variables changed respectively from an average of 0.43 in the control group, to 0.56 in the 2016 treatment group, and from 0.19 in the control group, to 0.24 in the 2016 treatment group.

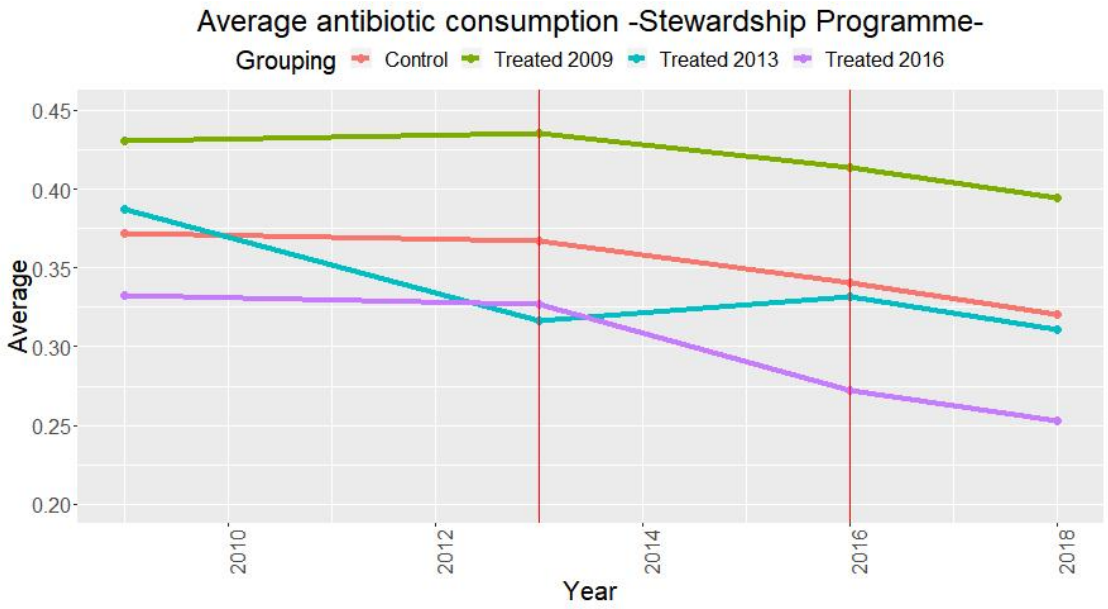


Figure 2.2: *Average of antibiotics consumption in last 12 months across control and treated groups. Red = control group, green = treatment group 0 (treated in 2009), blue = treatment group 1 (treated in 2013), purple = treatment group 2 (treated in 2016).*

one group appears to be lower than the control group at the beginning of the series, and it becomes higher than the control group at the end of the observed period. This result appears to indicate that the countries who adopt the policy are not necessarily the ones with the highest consumption rates.

Table 2.3 provides the estimation results for the difference-in-difference models. Results on top refer to the estimated coefficients for model (2.1). Results at the bottom represent the results for the staggered model (2.2).

Model DiD1 included only country and time dummies. Model DiD2 included patient characteristics. Model DiD3 included interaction effects. Model DiD4 included other questions from the Eurobarometer regarding the trustworthiness of information sources on antibiotics. Model DiD5 included country-level covariates.

Table 2.3 shows a negative and significant effect of antibiotic stewardship on antibiotic consumption in the last 12 months. This result is significant both when estimated across all years (top), as well as when estimated for individual years (bottom). Results of the estimated coefficients for the model covariates have not been reported for simplicity.

The table shows that the model including country-level covariates (model DiD5) presents the lower AIC. We therefore select the latter as our reference model

ii. Robustness checks

We verified the validity of our results via a number of robustness checks. The results of these checks are reported in table 2.8 in the appendix.

Table 2.8 shows that the estimated coefficient of stewardship programmes are negative and

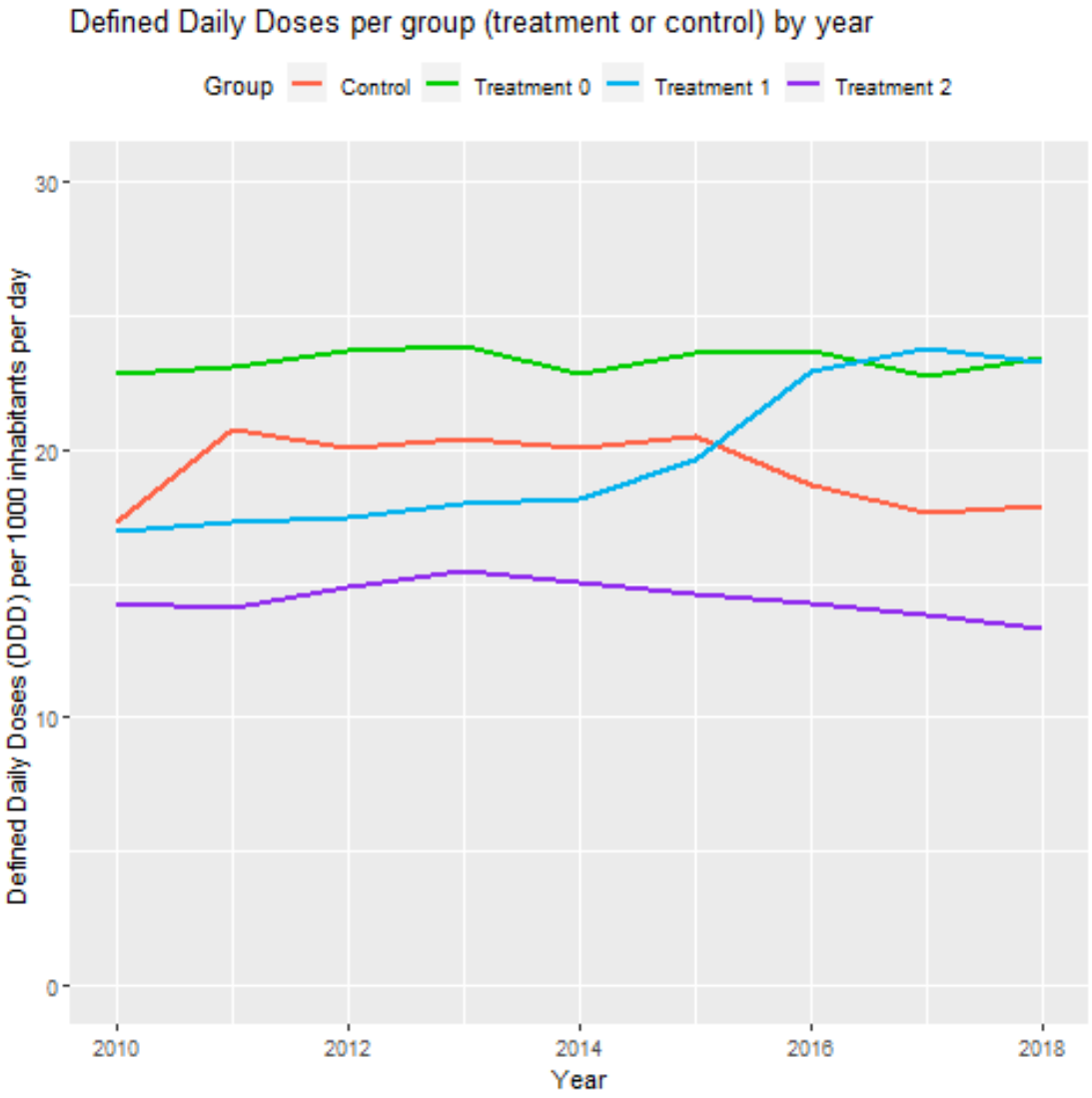


Figure 2.3: *Defined Daily Doses (DDD) of antibiotics per 1000 antibiotics per day across single years and averaged across control and treatment groups.*

Table 2.3: *Difference-in-difference baseline model. Above: stewardship pooled across years. Below: Stewardship estimated for individual years (stagered approach). DiD1 = model with time and country effects. DiD2 = model with patient characteristics. DiD3 = model with interaction effects. DiD4 = model with additional survey questions (trust in information sources on antibiotics). DiD5 = model with country-level covariates. Year refers to the year of the year of introduction of the policy. Estimated coefficients for covariates other than estimated effects variables have not been reported for simplicity (see main text for details).*

	Dependent variable:				
	Antibiotic consumption in last 12 months				
	DiD1	DiD2	DiD3	DiD4	DiD5
	(1)	(2)	(3)	(4)	(5)
Stewardship	-0.019^{***}	-0.019^{***}	-0.019^{***}	-0.019^{***}	-0.028^{***}
	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)
Observations	105,556	105,110	105,110	87,289	84,152
R^2	0.360	0.360	0.360	0.530	0.520
Akaike Inf. Crit.	140,975.000	139,706.000	139,492	105,702	101,630
Stewardship 2013	-0.040^{***}	-0.040^{***}	-0.041^{***}	-0.047^{***}	-0.046^{***}
	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)
Stewardship 2016	-0.028^{***}	-0.025^{***}	-0.025^{***}	-0.012^{***}	-0.032^{***}
	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)
Observations	105,556	105,110	105,110	87,289	84,152
R^2	0.360	0.360	0.360	0.530	0.520
Akaike Inf. Crit.	140,961	139,694	139,479	105,689	101,615
Note:					*p<0.1; **p<0.05; ***p<0.01

significant also when introducing a dummy indicating National Action Plan (NAP) among the covariates (see model "DiD5 with NAP"). The results holds both for the model (2.1) (on top) and for the staggered model 2.2 (at the bottom).

We then estimated diff-in-diff results of the staggered model 2.2 confronting individual treatment years with observations in the control group (see models "2013 only" and "2016 only" in Table 2.8). The estimated effect of stewardship is negative and significant for both treatment groups, however the magnitude of the estimated effect of stewardship in 2016 is reduced.

We then tested the inter-temporal effects of stewardship programmes described in model 2.3. We first estimated a model with leading variables only for the treatments in periods 2013 and 2016, thus setting $\lambda_m = 0$.[25] Results of this model are reported in Table 2.8 (see model "Lead"). The model presented negative and significant estimated effects of stewardship in both 2013 and 2016. Lead one effects were positive and significant for stewardship introduced in both 2013 and 2016, while they were positive but not significant for a lead two effect of stewardship introduced in 2013.

We checked for the effect of the common trend assumption on our regression results. The presence of common trends has been estimated for both individual respondents groups as well as for individual years. The results, non reported for simplicity, identify the presence of group-specific time trends present for elderly, female and respondents with financial difficulties. Although time trends are present for these groups, the estimated impact of stewardship policy is consistent in both sign and magnitude with results of DiD5 reported in table 2.3. The analysis identified the presence of a significant common trend being present at a country level. In this case the model with a country-level common trend identified a positive and significant effect for stewardship when considering it as pooled across all years, while the effect was negative and significant for stewardship introduced in 2016.

We checked for the independence of the timing of introduction of the dependent policy by estimating the value of single policies as a function of lagged outcome variables, as indicated in equation 2.4. To achieve that we first aggregated data at country level. We then regressed individual policy variables on lagged outcome (antibiotic use in last 12 months). Lagged outcomes resulted as non-significant in the OLS model.[26] These results, non-reported for simplicity, seem to suggest the exogeneity of policy treatment.

We checked for the absence of compositional changes. The purpose of this check was to verify whether individual policies had an impact on potential covariates of the outcome variables. We tested the impact of the policies on the following potential covariates: age teen, age elderly, financial difficulties, foreign. We also tested the potential impact of stewardship policy on national-level covariates. The results, non-reported for simplicity, were estimated including both the pre-treatment and post-treatment period as suggested in Wing et al. (2018). Stewardship 2013 treatment was negatively associated with being a teenager, having financial difficulties, being a foreigner and population density. The same variable was positively linked to being elderly and to unemployment. Stewardship 2016 was negatively linked to having financial difficulties and to unemployment, and positively linked to population density. These estimated effects may highlight a potential presence of compositional changes across treated and control groups.

[25] We tested also two alternative versions of the model: one with lagged treatment variable and one with both lagged and lead treatment variable. These models, however, presented non-identified lagged effects, hence they have not been considered in this analysis.

[26] The estimated coefficient for the average antibiotic use in last 12 months was equal to 0.17, with standard error equal to 0.64.

iii. Extensions: group-specific effects and demand- and supply-side factors

We checked the significance of difference-in-difference estimated for a version of models 2.1 and 2.2 estimated for different respondent groups. Results are reported in Table 2.4. Considered respondents groups were: teenager (and non-teenager), elderly (and non-elderly), female (and male), with financial difficulties (and without financial difficulties), foreign (and non-foreign). These models show that antibiotic stewardship were negative and significant for all respondents groups.

We tested a number of additional difference-in-difference models to identify whether the introduction of antibiotic stewardship programmes might impact either demand- or supply-side factors related to antibiotic consumption. For simplicity, this extension model has been computed only for the staggered version of the model (2.3).

First, we estimate the impact of stewardship programmes on supply-side factors. This is achieved by estimating whether such programmes influenced the provision of antibiotics from a doctor, and the intention of consulting a doctor for future antibiotics use.

The results, reported in table 2.5, indicate that stewardship had a negative and significant effect on receiving antibiotics from doctors in both 2013 and 2016 treatments (see model "Antibiotic source: doctor"). The two treatments had different lead effects, with stewardship in 2013 reporting a positive lead 1 and lead 2 effect, and with stewardship in 2016 reporting a negative lead effect. The model estimated with the alternative dependent variable indicating the intention to consult a doctor for future antibiotic use reported a positive and significant effect for both 2013 and 2016 stewardship. Stewardships introduced in the two years presented different lead one effects, with 2013 stewardship presenting a negative and significant lead one effect, and 2016 stewardship presenting a positive and significant lead one effect. 2013 stewardship presented a negative and significant lead 2 effect. These results appear to suggest that the introduction of stewardship programmes might have affected the provision of antibiotics by influencing gate-keepers behaviour.

We then estimated the impact of stewardship on variables associated with beliefs concerning antibiotics as a proxy for demand-side factors. Results are reported in Table 2.6. Stewardships programmes appeared to have reduced respondents beliefs on antibiotics being effective against flu and viruses. Stewardships introduced in 2013 appeared to have reduced the belief that overconsumption leads to a reduced effect of antibiotics and the opinion that antibiotics might have side effects, while the opposite might hold true for stewardships introduced in 2016. Stewardship programmes appeared to have a negative lead effect on opinion against flu. The opposite holds true for beliefs on antibiotics being effective against viruses, with the exception of 2013 stewardship lead two effect which is negative and significant. The belief on overconsumption reducing antibiotics effectiveness has a negative lead one effect for the 2013 treatment, while the opposite holds true for 2016 treatment. The lead 2 effect is not significant on this belief. The belief of antibiotics having side effects presents a a positive lead 1 effect for stewardship introduced in 2013, and a negative lead one effect for stewardship introduced in 2016. The lead 2 effect of stewardships introduced in 2013 is negative and significant. These results appear to indicate that stewardship programmes might have had an impact on demand-side factors by influencing respondents perceptions to such drugs.

Table 2.4: *Diff-in-diff model by respondent's groups.*

	Dependent variable:				
	Antibiotic use in last 12 months				
	Teenager	Elderly	Female	Fin. difficulty	Foreign
Stewardship	-0.110^{***}	-0.030^{***}	-0.022^{***}	-0.029^{***}	-0.240^{***}
	(0.003)	(0.001)	(0.001)	(0.001)	(0.001)
Observations	1,915	21,190	46,293	31,853	1,873
R^2	0.560	0.530	0.540	0.540	0.800
Akaike Inf. Crit.	2,467.000	25,491.000	57,557.000	39,800.000	1,569.000
Stewardship 2013	-0.140^{***}	-0.056^{***}	-0.032^{**}	-0.052^{***}	-0.800^{***}
	(0.005)	(0.001)	(0.001)	(0.001)	(0.025)
Stewardship 2016	-0.066^{***}	-0.029^{***}	-0.025^{***}	-0.044^{***}	-0.071^{***}
	(0.004)	(0.001)	(0.001)	(0.001)	(0.004)
Observations	1,915	21,190	46,293	31,853	1,873
R^2	0.560	0.530	0.540	0.540	0.800
Akaike Inf. Crit.	2,468.000	25,487.000	57,555.000	39,795.000	1,570.000
	No Teen	No Eld.	Male	Fin. stable	National
	-0.027^{***}	-0.028^{***}	-0.036^{***}	-0.025^{***}	-0.028^{***}
	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)
Observations	82,237	62,962	37,859	52,299	82,279
R^2	0.520	0.520	0.500	0.510	0.510
Akaike Inf. Crit.	99,193.000	76,139.000	44,003.000	61,772.000	99,894.000
Stewardship 2013	-0.044^{***}	-0.043^{***}	-0.062^{***}	-0.042^{***}	-0.045^{*}
	(0.005)	(0.001)	(0.001)	(0.001)	(0.025)
Stewardship 2016	-0.032^{***}	-0.033^{***}	-0.043^{***}	-0.026^{***}	-0.030^{***}
	(0.004)	(0.001)	(0.001)	(0.001)	(0.004)
Observations	82,237	62,962	37,859	52,299	82,279
R^2	0.520	0.520	0.500	0.510	0.510
Akaike Inf. Crit.	99,179.000	76,130.000	43,989.000	61,765.000	99,882.000

Table 2.5: *Diff-in-diff model: alternative dependent variables.*

	Dependent variable:		
	Antibiotic consumption In last 12 months	Antibiotic source: doctor	Consult doctor for future use
Stewardship 2013	-0.068^{***}	-0.067^{***}	0.033^{***}
	(0.001)	(0.001)	(0.001)
Stewardship 2016	-0.036^{***}	-0.037^{***}	0.170^{***}
	(0.001)	(0.001)	(0.001)
Stewardship 2013 Lead1	0.032^{***}	0.029^{***}	-0.041^{***}
	(0.001)	(0.002)	(0.001)
Stewardship 2013 Lead2	0.029^{***}	0.001^{***}	-0.065^{***}
	(0.001)	(0.003)	(0.001)
Stewardship 2016 Lead1	0.054^{**}	-0.130^{***}	0.140^{***}
	(0.001)	(0.003)	(0.001)
Observations	84,152	79,739	11,182
R^2	0.520	0.370	0.730
Akaike Inf. Crit.	101,602.000	103,032.000	13,391.000

VI. Conclusions

This paper analysed the impact of stewardship programmes in reducing antibiotic consumption in EU countries. The relationship between the introduction of this policy on consumption was explored by means of a difference-in-difference analysis estimated on Eurobarometer data, which provides a representative sample of the European population.

Our study identifies an effectiveness of stewardship programmes in reducing antibiotic consumption in EU countries. This result is consistent to a number of robustness checks, such as including alternative national policies such as National Action Plans among the covariates.

The presence of non-trivial inter-temporal effects on antibiotics consumption, with 2013 and 2016 treatment presenting positive lead one effect, and a positive lead 2 effect for stewardship in 2013, suggests a reduction of the effectiveness of such policy over time, thus highlighting the need for policy-makers to continuously assess the effectiveness of this policy.

Stewardship programmes appear to be effective also across individual respondents groups, suggesting an effectiveness of such policy in influencing antibiotics consumption of individual respondent groups. The magnitude of such effect, however, appears to be higher among teenagers and foreign respondents, while it appears to be comparatively lower for elderly and female respondents as well as respondents reporting financial difficulties. These variations in the magnitude of the estimated effect may suggest that policy makers should draw targeted communications aimed at specific segments of the national population to improve stewardship effectiveness.

Table 2.6: *Difference-in-difference: Respondent's beliefs.*

	Dependent variable:				
	Antibiotic consumpt. (12 months)	Opinion: flu	Opinion viruses	Opinion overcons.	Opinion side eff.
Stewardship 2013	-0.068^{***}	-0.012^{***}	-0.038^{***}	-0.007^{***}	-0.012^{***}
	(0.001)	(0.001)	(0.013)	(0.001)	(0.001)
Stewardship 2016	-0.036^{***}	-0.036^{***}	-0.045^{***}	0.019^{***}	0.012^{***}
	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)
Stewardship 2013 Lead 1	0.032^{***}	-0.018^{***}	0.018^{***}	-0.015^{**}	0.005^{***}
	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)
Stewardship 2013 Lead 2	0.029^{***}	-0.047^{***}	-0.038^{***}	0.001	-0.014^{***}
	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)
Stewardship 2016 Lead 1	0.054^{***}	-0.019^{***}	0.013^{***}	0.032^{***}	-0.027^{***}
	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)
Observations	84,152	76,610	78,648	78,481	70,460
R^2	0.520	0.620	0.520	0.920	0.830
Akaike Inf. Crit.	101,602.000	100,525.000	100,812.000	13,516.000	62,765.000

Note: *p<0.1; **p<0.05; ***p<0.01

The estimated effect of the introduction of stewardship policies is approximately a 2 to 3% decrease in the probability of consuming antibiotic orally in the last 12 months. This estimated effect appears to be consistent with other interventions aimed at the reduction of antibiotic consumption, such as the ones identified by Bou-Antoun et al. (2018) on the impact of Quality Premia on antibiotic prescriptions among English GP practices.

The introduction of such programmes appear to have influenced supply-side factors represented by doctors behaviour as gate-keepers to antibiotic provision and proxied in our study by two indicators, namely: receiving antibiotics from doctors and the intention to consult a doctor for future antibiotic use. These results appear to indicate that stewardship programmes were successful in improving the gate-keeping function of doctors in providing access to such drugs.

Stewardship programmes appear to have an influence also on demand-side factors related to antibiotic consumption, namely respondents' beliefs. More specifically, such policies appear to influence the share of respondents who believe that antibiotics are effective against flu or viruses. Such programmes, on the contrary, appeared to have obtained mixed results in influencing the beliefs of antibiotics overconsumption leading to reduced effectiveness or side effects. These result appear to indicate that stewardship programmes were, at least partially, effective in influencing also demand-side factors, with some limitations on beliefs related to overconsumption and awareness of side effects.

The results provided in this paper might be useful to policy-makers who wish to use evidence to improve the effectiveness of policies targeted at reducing antibiotic consumption. First, those countries who haven't yet introduced stewardship programmes might implement this policy to reduce consumption. Second, policy makers might develop policies which are targeted to specific segments of the population to increase effectiveness. Third, policy-makers might use the results presented in this paper to combine efforts to instruct doctors and at the same time develop campaigns aimed at improving awareness on antibiotics among the general public.

This paper has extended the literature on the estimation of the impact of policies aimed at reducing antibiotics consumption. We provide a novel analysis with a nationally-representative sample of the EU countries on a health matter of relevance. This study expands the current literature on difference-in-difference analysis applied to problems in healthcare and in policy evaluation. To the best of our knowledge this study is the first paper estimating the impact of antibiotic stewardship programmes European countries via difference-in-difference analysis.

The results presented in this paper shows a variety of implementations of both stewardship programmes and National Action Plan programmes. Some of the countries, such as Germany or the Netherlands, considered in the analysis have adopted both policies, sometimes during the same years (suggesting that those countries see the two policies as complementary), while other countries, such as Poland, adopted just one of the two policies (suggesting that they are seen as complementary). For this reason, the data sources analysed in this paper do not present enough variation to rigorously test for the substitutability or complementarity of the two policies, making it challenging to estimate individual effects. The adopted approach allowed for the inclusion of a NAP dummy as a sensitivity analysis. This sensitivity check aimed at controlling for the introduction of NAPS. The results do not seem to present considerable variation when NAP dummy is introduced. Due to the heterogeneity in NAPs goals and implementations across countries, it is possible that some National Action Plans include the introduction of stewardship programmes, thus playing as substitute to stewardship programmes. The analysis of whether stewardship programmes are complement or substitutes to NAPs would be an interesting question for future research. The analysis of the interplay of NAPs and stewardship

across countries is beyond the scope of this paper.

Our study is subject to a number of limitations. First, due to limitations in the survey, our study does not include reasons for antibiotic consumption among its covariates. Second, we do not include other potential covariates which may affect choices in antibiotics consumption, such as co-payments, again due to data limitations. Third, by comparing countries which are very different in nature, our study might be exposed to limitations in compositional balance across control and treated groups. Fourth, due to limitations in the number of observed periods, our study provided little evidence for the satisfaction of parallel trends hypothesis. Fifth, our study does not include other potentially relevant country-level covariates which might impact on antibiotic consumption, such as the amount of expenditure in healthcare of individual countries. Sixth, some specific categories of antibiotic users, such as elderly people in care homes, were not included in the analysis due to data limitations. Lastly, our study might be influenced by a potential link between antibiotic resistance levels and countries' decision to introduce stewardship programmes which might hamper the proposed identification strategy. Our analysis does not identify a link between lagged outcomes and the introduction of stewardship programmes, thus indicating a potential exogeneity in policy introduction. Considering the impact of resistance on antibiotic consumption, however, is beyond the scope of this paper and it would require additional research. The results of our study do not explicitly model the impact of issues potentially affecting antibiotic consumption, such as contamination effects in prescription behaviour across countries. The analysis of such contamination effect is beyond the scope of this paper.

VII. Appendix A: Data Tables and figures

Table 2.7: *Descriptive statistics across control and treated groups. Mean of single variables. Standard deviation in brackets.*

Variable	Control group	Stewardship: 2013	Stewardship 2016 2016
Antibiotic consumption in last 12 months	0.35 (0.48)	0.31 (0.46)	0.33 (0.47)
Antibiotic source: doctor	0.35 (0.48)	0.31 (0.46)	0.33 (0.47)
Intention to consult a doctor	0.71 (0.45)	0.72 (0.45)	0.67 (0.47)
Opinion: virus	0.59 (0.49)	0.53 (0.5)	0.41 (0.49)
Opinion: flu	0.45 (0.5)	0.44 (0.5)	0.23 (0.42)
Opinion: overuse	0.9 (0.3)	0.94 (0.24)	0.95 (0.22)
Opinion: side-effects	0.8 (0.4)	0.84 (0.37)	0.74 (0.44)
Foreign patient	0.04 (0.21)	0 (0.07)	0.04 (0.2)
Female patient	0.55 (0.5)	0.54 (0.5)	0.51 (0.5)
Edu: before primary	0.02 (0.13)	0.02 (0.15)	0.01 (0.11)
Age: adult	0.72 (0.45)	0.69 (0.46)	0.68 (0.47)
Age: elderly	0.25 (0.43)	0.29 (0.45)	0.29 (0.45)
Relationship: married	0.53 (0.5)	0.54 (0.5)	0.47 (0.5)
Relationship: partner	0.11 (0.31)	0.1 (0.3)	0.12 (0.32)
Relationship: single	0.16 (0.37)	0.17 (0.37)	0.25 (0.43)
Relationship: divorced	0.08 (0.27)	0.08 (0.27)	0.07 (0.26)
Relationship: widowed	0.11 (0.31)	0.1 (0.3)	0.07 (0.26)
Relationship: other	0.01 (0.1)	0.01 (0.08)	0.02 (0.12)
Occupation: non active	0.5 (0.5)	0.55 (0.5)	0.51 (0.5)
Occupation: self-employed	0.07 (0.26)	0.07 (0.25)	0.08 (0.27)
Family: with kids	0.18 (0.38)	0.17 (0.38)	0.18 (0.39)
Family: with teenagers	0.12 (0.32)	0.1 (0.31)	0.11 (0.32)
Financial difficulty	0.42 (0.49)	0.22 (0.41)	0.2 (0.4)
Trust: doctor	0.86 (0.34)	0.88 (0.33)	0.86 (0.35)
Trust: nurse	0.13 (0.34)	0.1 (0.3)	0.14 (0.35)
Trust: pharmacist	0.43 (0.5)	0.39 (0.49)	0.56 (0.5)
Trust: hospital	0.19 (0.39)	0.15 (0.36)	0.24 (0.43)
Trust: family	0.07 (0.25)	0.05 (0.22)	0.04 (0.21)
Trust: no interest	0.03 (0.17)	0.03 (0.17)	0.02 (0.12)
Resistance: MRSA	19.42 (16.14)	14 (8.15)	8.39 (9.15)
GDP per capita	21344.67 (14411.77)	28979.5 (12216.66)	34771.41 (4495.64)
Population density	117.41 (171.52)	147.28 (52.83)	372.33 (116.42)
Unemployment	8.93 (4.42)	9.05 (6.28)	5.79 (1.52)

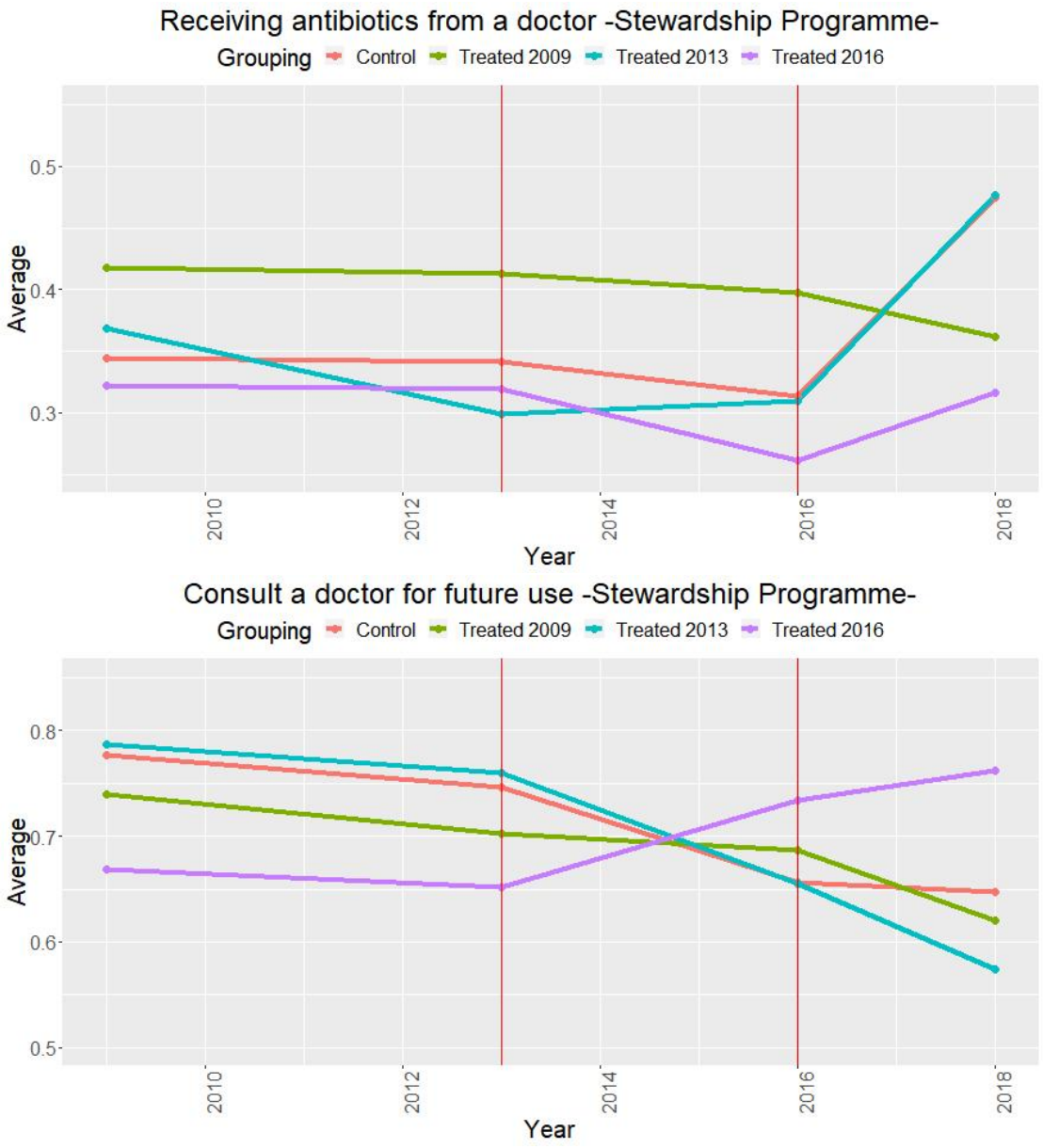


Figure 2.4: *Average of alternative dependent variables across control and treated groups. Top = receiving antibiotics from a doctor, bottom = intention to consult a doctor for future antibiotic use. Red = control group, green = treated in 2013, blue = treated in 2016, purple = treated in 2018.*

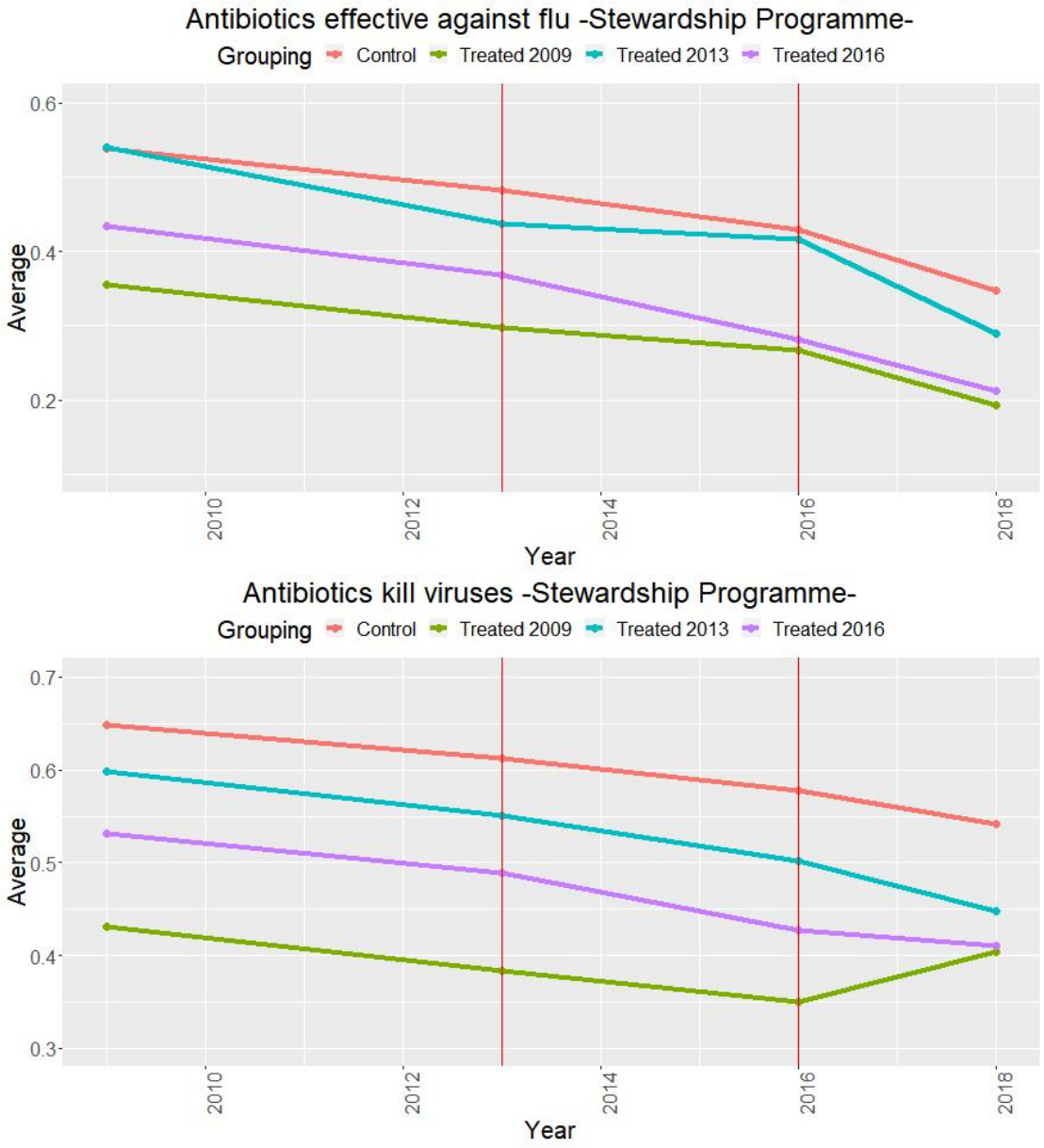


Figure 2.5: *Average of respondents beliefs across control and treated groups (1 of 2). Top = antibiotics are effective against flu; bottom: antibiotics kill viruses, bottom left: antibiotics overuse reduce effectiveness, bottom-right: antibiotics have side effects. Red = control group, green = treated in 2013, blue = treated in 2016, purple = treated in 2018.*

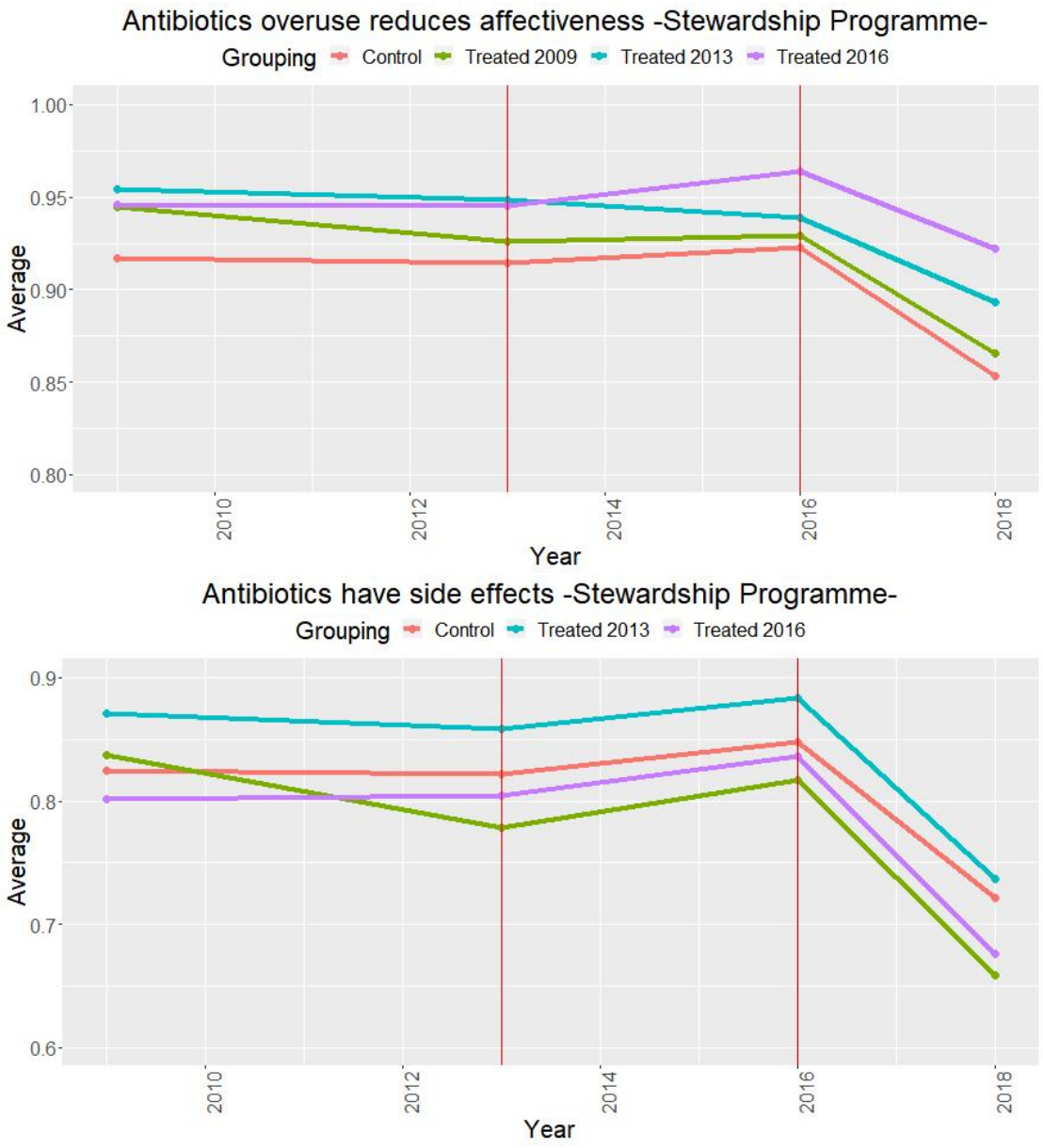


Figure 2.6: *Average of respondents beliefs across control and treated groups (2 of 2). Top: antibiotics overuse reduce effectiveness; bottom: antibiotics have side effects. Red = control group, green = treated in 2013, blue = treated in 2016, purple = treated in 2018.*

Table 2.8: *Diff-in-diff model. Robustness checks.*

	Dependent variable:				
	Antibiotic use in last 12 months				
	DiD5	DiD5 with NAP	2013 only	2016 only	Lead
Stewardship	-0.019^{***}	-0.030^{***}			
	(0.001)	(0.001)			
Observations	84,152	84,152			
R^2	0.521	0.521			
Akaike Inf. Crit.	101,615	101,631			
Stewardship 2013	-0.046^{***}	-0.046^{***}	-0.048^{***}		-0.068^{***}
	(0.001)	(0.001)	(0.001)		(0.001)
Stewardship 2016	-0.032^{***}	-0.041^{***}		-0.029^{***}	-0.036^{***}
	(0.001)	(0.001)		(0.001)	(0.001)
Stewardship 2013 L1					0.032^{***}
					(0.001)
Stewardship 2013 L2					0.029
					(0.001)
Stewardship 2016 L1					0.054^{**}
					(0.001)
Observations	84,152	84,152	66,327	68,463	84,152
R^2	0.521	0.520	0.530	0.510	0.520
Akaike Inf. Crit.	101,630	101,615	79,868	82,556	101,602
Note:					*p<0.1; **p<0.05; ***p<0.01

Chapter 3

Spatial dependence in antibiotics prescriptions in English GP practices: a panel analysis

This paper explores spatial dependence in antibiotics prescription rates among English GP practices by looking at presentation level data for the years 2013-17.

The use of antibiotics has increased globally over the past few years (Klein et al., 2018). Several authors identified that over prescribing is associated with increased antibiotics resistance (Mera et al. (2006), Monroe and Polk (2000)). Antibiotic resistance has already been identified as a major health threat worldwide, with 20% of neonatal deaths resulting from infections Li et al. (2015), and with deaths associated to antimicrobial resistance being approximately 700,000 a year, with an estimated 10 million deaths per year by 2050 (O'Neill, 2014). Even when individual lives are not at immediate risk, in most cases, antibiotic resistant infections require prolonged and/or costlier use of healthcare resources (CDC, 2013).

The majority of antibiotic prescriptions are provided in primary care settings, with 90% of all antibiotic prescriptions issued by general practitioners and with respiratory trait infections being among the leading reasons for prescribing (Llor and Bjerrum, 2014). In the UK, primary care accounts for approximately three-quarters of human antibiotic prescriptions (PHE, 2016). Fleming-Dutra et al. (2016) and Smieszek et al. (2018) state that a substantial fraction of antibiotic prescriptions in primary care are likely to be inappropriate. Prudent prescribing has been identified as one of the most effective ways to reduce resistance (Goossens (2009), CDC (2013)). Prudent prescribing, includes avoiding unnecessary prescriptions, delaying prescriptions if possible, favouring narrow-spectrum over broad-spectrum antibiotics, and optimizing treatment duration (Spivak et al., 2016). Antimicrobial stewardship programmes can facilitate reaching those goals (CDC, 2013).

Dolk et al. (2018) find that antibiotic prescription rates vary significantly across English GP practices, suggesting that there is potential to reduce prescribing in at least some practices. Pouwels et al. (2018) identify that variation in comorbidities prevalence alone cannot explain the variation in GPs' prescription patterns. The authors identify the role played by consultations on respiratory trait infections and prescriptions for corticosteroids as key factors in explaining variation of prescription rates in English primary care. LeSage and Dominguez (2012) suggest that in settings considering local behaviour, public choices might be affected by spatial dependence.

A limited number of studies analysing prescription identified evidence of spatial dependence in antibiotic prescription rates (Filippini et al. (2014), Gonzalez-Ortiz and Masiero (2013)). Spatial dependence is identified as spatial correlation in prescription rates resulting from two key channels, namely: a reduction in the risk of infections in neighbouring areas following antibiotic consumption (positive externality), a reduced effectiveness of antibiotics prescription in neighbouring areas arising from increased resistance following prescription (negative externality) (Gonzalez-Ortiz and Masiero, 2013).

The economic interpretation of these two effects is better understood when considering the practitioner's decision to prescribe antibiotics as a decision taken under imperfect information. When deciding whether to prescribe antibiotics, GPs, in fact, might be facing a trade-off between infection prevention, that is curing infections that might spread to other individuals in the community, and resistance prevention, that is the need to balance the use of antibiotics in order to avoid reducing their effectiveness and preventing higher treatment costs in the future.

As GPs might not have complete and timely information on the extent of infections occurring in the community, nor on the degree of antibiotic resistance, GPs might be reliant on informal (and unobserved) professional networks when deciding the amount of antibiotics to be used in treating symptoms presented by patients. Spatial dependence in prescription rates might thus arise from GPs learning from each other, via knowledge-sharing in their professional network. These informal networks might be affected by either institutional or spatial distances across practitioners. Institutional distance might influence peer effects by means of local efforts in reducing prescription, for example through local communication and education campaigns. Spatial distance might influence peer effects by means of direct sharing of best practices occurring between practitioners concerning the risks of infections and resistance.

The literature on antibiotic prescription has identified other potential channels for spatial dependence, such as individual administrative areas introducing specific targets related to antibiotic consumption. Spatial dependence might, therefore, be present also due to local programs promoting the achievement of specific health targets (Iezzi et al., 2014). This could be the case for antibiotic prescription in England where, following the introduction of Quality Premiums, which linked premiums to those Clinical Commissioning Groups (CCGS) who reached specific targets for average antibiotic prescription rates by GPs in their jurisdiction (NHSE, 2016). Spatial correlation in prescription rates might thus arise due to higher tier local authorities influencing prescription decisions of individual practices.

Lastly, according to Filippini et al. (2009) and Gonzalez-Ortiz and Masiero (2013) regional antibiotic consumption might be affected by heterogeneous attitudes towards antibiotics prescription in local areas. The identification of spatial dependence in antibiotic prescription is relevant in the fight against antibiotic resistance, as it allows policy makers to identify the correct ways to reduce such resistance, therefore avoiding unnecessary health costs. Understanding the impact of such channels in influencing spatial dependence in antibiotic prescription, forms the motivation of this paper.

Peer effects might influence practitioners' prescription decisions concerning not only the amount of antibiotics to be prescribed, but also the type of antibiotic provided to the community. The National Institute of Health Excellence (NICE) recommends practitioners to prescribe general spectrum antibiotics only when narrow spectrum antibiotics fail in treating infections(NICE, 2015a). The former type of antibiotics, in fact, is more subject to a risk of generating antibiotic resistance as it might potentially be effective against a broader type of bacteria, as compared to narrow spectrum antibiotics. The presence of peer effects might therefore be related also to the

practitioners decision to adhere to such advice, thus influencing practitioners' trade-off between infection and resistance prevention.

This paper expands the literature on spatial dependence in antibiotic prescription by proposing a spatial panel analysis of prescription rates among English GP practices across multiple years using a novel and nationally representative dataset. We use a spatially lagged independent variable model (SLX) as a baseline for the estimation of spatial dependence. Using an SLX model as a baseline allows to reduce the risk of misspecification when adjusting for spatial correlation (see Gibbons et al. (2015) and Halleck Vega and Elhorst (2015)). We estimate spatial dependence considering both institutional and geographical distances across GP practices, as well as a linear combination of the two. We use the percentage of antibiotic prescriptions over all practice prescriptions as an alternative dependent variable for robustness check.

We test for alternative channels of spatial dependence by considering different modeling approaches. First, we account for potential low-tier administrative effects arising from intervention introduced by low-tier commissioning bodies, namely Clinical Commissioning Groups (CCGs). In the English National Health System (NHS), CCGs are NHS bodies with the goal of organising the delivery of health and social care services. We account for potential interventions occurring at a commissioning level by introducing year and CCGs interactions. The presence of spatial dependence in the SLX model with interaction factors would indicate that spatial dependence is not arising from unobserved interventions occurring at a local level.

Our analysis aims to identify the role of individual channels of spatial dependence by estimating alternative spatial models. Starting from our SLX FE model as a point of departure for the analysis of spatial effects (Halleck Vega and Elhorst, 2015), we estimate alternative sources of spatial dependence by estimating a spatial autoregressive (SAR) and spatial error model (SEM), to account for externalities arising from antibiotic resistance and infection prevention respectively. To deepen our analysis of individual channels of spatial dependence, we introduce a number of fixed effect estimation strategies to isolate individual spatial effects, thus allowing us to explore the role of individual channels of spatial dependence. Second, following Filippini et al. (2009) and Gonzalez-Ortiz and Masiero (2013), we test for spatial dependence arising from random health shocks and from unobserved resistance rates by estimating respectively an spatial error model (SEM) and spatial autoregressive models (SAR).

Lastly, we test for the ability of spatial dependence, interpreted as the result of peer effects, in influencing practitioners' decision to prescribe narrow- versus broad-spectrum antibiotics. Narrow- and broad- spectrum antibiotics are identified by means of British National Formulary (BNF) codes, as reported by Open Prescribing (2020). Identifying spatial dependence in the use of broad spectrum antibiotics might be interpreted as a relevant sign of peer effects in influencing practitioners prescription behavior when it comes to prescribing antibiotics which are less linked to resistance, and ultimately, less likely to generate negative externalities on the healthcare system via resistance.

The presence of spatial dependence in antibiotic prescription might have policy implications as policies targeted at reducing prescription won't depend on individual rates only, but also on the externalities arising from institutional and physical proximity. Spatial dependence might imply that the consumption of antibiotics cannot be regarded as independently generated within regions (Gonzalez-Ortiz and Masiero, 2013). For this reason, if policy makers do not take such dependence into consideration, they may fail to identify the optimal antibiotic prescription rates (Filippini et al., 2014) thus leading to potential inefficiencies in local policies. The presence of spatial dependence leads therefore to the need of introducing regionally-coordinated policies when it comes to reducing antibiotics prescription (Filippini et al., 2014). This paper aims at

helping policy makers in achieving better policies related to the reduction of inappropriate prescription behaviour by means of identifying the correct channels of spatial dependence. Taking those channels into consideration when defining locally coordinated policies, in turn, might translate info reduced healthcare costs resulting from antibiotic resistance or the spread of infections in the community.

In addition, this study aims to provide more accurate estimates of the socio-economic determinants of antibiotic prescription by taking spatial dependence into account. Other studies focusing on explaining the socio-economic determinants of antibiotic consumption ignore the presence of spatial effects (Matuz et al. (2005), Filippini et al. (2006) and Nitzan et al. (2010)). Ignoring the effect of spatial autocorrelation in the residuals might lead to potentially inflated significance of estimated regression coefficients (Kelly, 2019).

This paper is organized as follows. Section 2 provides an introduction to the literature on antibiotics prescription. Section 3 provides a description of the available dataset. Section 4 provides a description of the methodology we used. Section 5 illustrates the results. Section 6 concludes.

I. Literature

The literature on antibiotics prescription suggests a link between consumption and a rise in antibiotic resistance (Monroe and Polk (2000), Mera et al. (2006)). Despite this evidence, UK outpatients are often prescribed antibiotics for self-limiting and/or non-bacterial infections (Gulliford et al., 2009).

Pouwels et al. (2018) show that, among English GP practices, the majority of practice-level variation in antibiotic prescribing cannot be explained by variation in the prevalence of co-morbidities. Factors such as high consultation rates for respiratory tract infections and high prescription rates for corticosteroids could explain much of the variation. Dolk et al. (2018) identified substantial variation in prescription rates across age groups, stating that a practice with higher proportion of young children or elderly patients would be expected to have higher prescription rates than a practice with mainly working-age adults. When considering the reason for antibiotic prescribing, the authors identify a majority of antibiotics being prescribed against infections of the respiratory and urinary tracts (Dolk et al., 2018).

Gonzalez-Ortiz and Masiero (2013) provide a thorough review of the determinants of antibiotic prescriptions. Age and demographic structure are key factors considered by several authors (Matuz et al. (2005), Nitzan et al. (2010), Filippini et al. (2006), Filippini et al. (2009), Kern et al. (2006), Gonzalez-Ortiz and Masiero (2013), Pouwels et al. (2018)). Pouwels et al. (2018) also include patient's gender among the covariates. Other authors, such as Matuz et al. (2005), Filippini et al. (2006), Filippini et al. (2009) and Kern et al. (2006), Gonzalez-Ortiz and Masiero (2013), consider individual income as a determinant of consumption.

Individual studies differ in the considered determinants. Matuz et al. (2005), Nitzan et al. (2010) and Pouwels et al. (2018) consider disease prevalence to be a key determinant of antibiotic prescription. Filippini et al. (2006) also include the share of foreigners on total population. Additional factors include education levels (Filippini et al., 2006), unemployment rates (Kern et al., 2006), drug prices (Filippini et al. (2006), Filippini et al. (2009)), and incidence of infections (Filippini et al., 2006). Matuz et al. (2005) also considers population density, number of individuals receiving free pharmaceuticals and social assistance, and yearly number of consultations.

Pouwels et al. (2018) allow for practice size, as proxied by the number of registered patients, as a relevant factor associated with prescription. Pouwels et al. (2018) also allow for the number of other prescribed drugs, such as immunosuppressive drugs and steroids, and consultations for other conditions.

Antibiotics consumption presents a high level of variations across regions within the same country (Kern et al., 2006). Looking at the UK, researchers identified significant variation in prescription patterns across the country (Hawker et al., 2014). As identified by Shallcross et al. (2017), antibiotic prescription appears to be uneven across the English population, with about half of such drugs prescribed in primary care being provided to less than 10% of patients. The presence of such an important geographical variation in antibiotic prescription suggests for the exploration of spatial dependence in antibiotic prescription rates.

There exists an extensive literature focusing on estimating the correlation of observations generated by the spatial structure of the data (Anselin (1988), LeSage and Pace (2010), Elhorst (2010)). Spatial econometrics methods have been used extensively to identify spatial dependence in health expenditures in secondary care (Revelli (2006), Lippi Bruni and Mammi (2016)) and in mental healthcare (Moscone et al., 2007). Gibbons et al. (2015) provide an extensive description of the econometric techniques necessary for the correct identification of spatial models. A review of spatial econometrics methods for health economics is provided by Moscone and Tosetti (2014).

The analysis of spatial dependence in antibiotic prescription received little attention. Filippini et al. (2014) investigate the role of the dispensing physician in influencing antibiotic consumption in 240 Swiss regions in the year 2002. The authors propose a spatial econometrics analysis combining both a spatial error and a spatial lag component (SARAR model). The authors find that dispensing practices induce higher rates of antibiotic consumption, even after controlling for patient characteristics, epidemiological variables, access to drug treatment, and spatial dependence. Gonzalez-Ortiz and Masiero (2013) apply spatial econometrics techniques to estimate spatial dependence in antibiotic consumption for the Italian case. The authors estimate the role of alternative channels of spatial dependence, namely resistance externalities due to prescriptions from neighbouring practices, and random health shocks by means of spatial lag (SAR) and spatial error (SEM) models respectively. The authors identify evidence of spatial dependence across regions, even when factors such as the demographic and socio-economic characteristics of the local population, the supply of health care services in the community and antibiotic co-payments are accounted for. Lippi Bruni and Mammi (2016), who analyse spatial dependence in hospital expenditures, provide a useful methodological reference in the specification of spatial weights matrices to model distance across districts, including institutional distance (indicating whether two practices were in the same administrative area), geographical distance and a convex combination of the two. The authors test the presence of dependence across districts by estimating both direct and indirect effects.

Compared to the work by Filippini et al. (2014) we allow for multiple years of observations. Our study differs from other studies analysing spatial dependence in antibiotic prescription in that we use a SLX model with practice-level fixed effects as our reference model, as this approach might prove more robust to misspecification arising from spatial autocorrelation in the residuals (Halleck Vega and Elhorst, 2015). Similarly to Gonzalez-Ortiz and Masiero (2013) we estimate a number of models to verify the presence of alternative channels of spatial dependence in antibiotic prescription. Compared to the studies by Gonzalez-Ortiz and Masiero (2013) we provide an additional analysis of potential channels of spatial dependence by introducing a model with CCG times year fixed effects. We follow the work by Lippi Bruni and Mammi (2016) in identifying an optimal definition of spatial weights based on a convex combination of

administrative and geographical weights. Lastly, we deepen the analysis by estimating spatial dependence on individual antibiotic classes.

Despite the importance in addressing spatial correlation to avoid biased estimation results (Kelly, 2019), care should be given in estimating spatial dependence. As suggested by Gibbons et al. (2015) an improper specification of the econometric model with spatial effects might lead to three main sources of bias: the reflection problem, the presence of omitted variables, and biases arising due to sorting issues.

Public interventions have been found to be effective in controlling antibiotic consumption (Huttner et al., 2010). In 2008 the National Institute for Health and Care Excellence (NICE) published guidelines on prescription recommending the avoidance of antibiotic treatment for self-limiting respiratory tract infections (RTIs), except if the patient is at high risk of serious complications because of pre-existing comorbidity (NICE, 2008). In 2015 NICE published a guideline introducing antibiotic stewardship programmes. The purpose of this guideline was to ensure that healthcare practitioners would reduce misuses to avoid a raise in antibiotic resistance (NICE, 2015).

In 2016 NHS England published a Quality Premium (QP) for Clinical Commissioning Groups (CCGs), providing financial incentives to those who reached set quality standards, including reaching a reduction in the number of antibiotics prescribed in primary care, as well as a reduction in the proportion of broad spectrum antibiotics (NHSE, 2016). Bou-Antoun et al. (2018) identify a 3% drop in antibiotic prescribing in April 2015, coinciding with the introduction of the Quality Premium. This reduction was sustained over time: 2 years after QP there was a 3% decrease in prescribing relative to that expected had the pre-intervention trend continued, there was also a concurrent 2% relative reduction in the rate of broad-spectrum antibiotic prescribing. This is consistent with the findings of PHE (2017) showing that GP practices respond to variation in guidelines.

In addition, 2016 saw the introduction of direct letters sent by the Chief Medical Officer (CMO) to over-prescribing practices. These letters were sent annually by the CMO to top 20% prescribing practices, informing them that they were in the top prescription quantile and including information on how to reduce prescription. This intervention was introduced following a trial period indicating that treated practices reduced overall prescription (Hallsworth et al., 2016). All of these policy efforts were in line with the commitment by the UK Government set up to halve inappropriate prescriptions of antibiotics by 2020 (AMR Policy Team, 2016).

II. Data

We computed GPs antibiotic prescription rates from presentation level data. Practice level prescription data for the years 2013 to 2017 were acquired from the Practice Level Prescribing Data datasets provided by NHS England.[1]

For each GP practice, prescription level data includes a list of all medicines, dressings and appliances that are prescribed and dispensed by GP practices each month. The data covers NHS prescriptions written in England. Included prescriptions are those written by GPs and other non-medical prescribers (such as nurses and pharmacists) who are linked to the single

[1]These open data are available at `https://digital.nhs.uk/data-and-information/publications/statistical/practice-level-prescribing-data`.

GP practices. Private prescriptions are excluded from presentation level data.[2]

We focus on the number of prescribed items, which are identified via British National Formulary (BNF) codes. Individual practices were identified by their practice code.

Antibiotics names and their respective BNF codes were obtained from section 5.1 of the BNF relating to antibacterial drugs, registered under chapter 5 who relates to infections.[3] Section 5.1 of the BNF is further divided into 13 subsections.[4]

We performed a number of data cleaning steps on prescription data.

First, we mapped prescription data to single antibiotic classes. This was done by linking prescribed items to BNF codes, using the first 6 digits of the reported items in the monthly prescription data. At the end of this process we obtained a version of the GP prescription level data including dummies for individual antibiotic categories (one for each subsection of section 5.1. of the BNF) as well as a dummy indicating whether the single prescription referred to an antibiotic or not. To ensure the robustness of the linkage, we checked whether all single antibiotics prescription codes were matched across tables.

Second, we computed a number of aggregated indicators for each prescription category. The prescription categories we considered are: a) single 6-digits BNF chapters, b) antibiotic class (aggregated), c) non antibiotic prescriptions, d) all prescribed items. For each aggregated class we focused on the number of prescribed items.

Third, we aggregated the number of prescribed items at an annual level (from monthly data).

All GP practices registered in England are included in the GP prescription data. To ensure homogeneity in the analysis we included only practices which are available in each of the months in the years 2013-2017. Practices which are not present in each one of the considered months were removed from the analysis.[5] At the end of this process our dataset included 9104 GP practices, for a total of 591605 records.

We considered a number of practice-level covariates for antibiotic prescription rates.[6] Unless otherwise specified, all data related to the characteristics of individual GP practices was available at annual level.

First we consider practice size, as measured by number of registered patients. To avoid scaling issues, we considered this variable in logs. The number of registered patients was down-

[2]More information is available here https://digital.nhs.uk/data-and-information/areas-of-interest/prescribing/practice-level-prescribing-in-england-a-summary/practice-level-prescribing-data-more-information

[3]BNF information can be obtained at `https://openprescribing.net/bnf/0501/`.

[4]These are: 1) penicillins, 2) cephalosporins and other beta-lactams, 3) tetracyclines, 4) aminoglycosides, 5) macrolides, 6) clindamycin and lycomycin, 7) some other antibacterials, 8) sulfonamides and trimethoprim, 9) antitubercolosis drugs, 10) metronidazole, tinidazolo andd ornidazole, 12) quinolones, 13) urinary-tract infections.

[5]The reasons for a GP practice for not being present in each single might include: a) opening of new practices, b) closure of single practices, c) merging, d) division into smaller practices. See `https://digital.nhs.uk/data-and-information/areas-of-interest/prescribing/practice-level-prescribing-in-england-a-summary/practice-level-prescribing-data-more-information`

[6]Confront Table 1 by Gonzalez-Ortiz and Masiero (2013) for a review of the main socio-economic determinants in antibiotic prescription in outpatient settings.

loaded from NHS Digital General Practice Data Hub [7] and from NHS Digital website.[8] Notice that the number of registered patients is available since 2013 with quarterly data. Annual data was computed by averaging quarterly data.[9] To account for differences in the population composition of individual practices, we computed the weighted composition of registered patients of individual practices by STAR-PU (Specific Therapeutic Group Age-sex weightings Related Prescribing Units) weights (cfr. Table 1 in Pouwels et al. (2018)). A summary of the weight associated to each age and gender band is reported in table 3.3 in the appendix. We also included information on the percentage of female patients and on the proportion of patients by age bands.

Second, we considered a number of measures related to the demographic composition of individual practices. All indicators related to practice composition were obtained from PHE Fingertips.[10] More specifically, we considered: a) percentage of over 65, b) percentage of children (under 18), c) percentage of female patients, d) percentage of patients with long-term conditions e) percentage of patients with caring responsibilities, f) percentage of unemployed patients, g) percentage of patients in nursing homes, h) life expectancy - MSOA based (male), i) life expectancy - MSOA based (female), l) deprivation score, m) income deprivation for older people (IDAOPI), n) income deprivation for children (IDACI).[11] In addition we included a number of indicators related to the prevalence of specific conditions[12]: a) total QOF points, b) QOF prevalence for hypertension (all ages), c) QOF prevalence for obesity (18+), d) QOF estimated smoking prevalence, e) blood pressure <= 150/90 mmHg in people with hypertension (HYP006). We also include a number of indicators related patient experience with their GP practice, namely: a) percentage of patients satisfied with phone access, b) percentage satisfied with practice appointment times, c) percentage reporting good overall experience of making appointment, d) percentage who would recommend the practice, e) percentage satisfied with opening hours, f) percentage who saw or spoke to a GP on the same day. Note that for the percentage of female patients in 2017 we used only the percentage of female patients in quarter 1, as this information was not available for other quarters.

We obtained quality outcome framework indicators for individual conditions. Data on specific conditions were obtained from NHS General Practice Data Hub.[13] Considered conditions were: a) cardiovascular group, b) respiratory group, c) lifestyle group, d) long-term conditions group, e) mental health group, f) muscoloskeletal group, g) fertility, h) quality and productivity, i) patient experience).

We considered supply-side information by looking at GP workforce statistics.[14] The information obtained on workforce included: a) GP density (head counts per 1000 patients), b) GP density computed as full-time equivalents per registered patient, c) percentage of GPs under 40 years of age, d) percentage of female GPs, e) proportion of GPs trained in the UK, f) nurses density (head counts per 1000 registered patients, g) administrative staff density (head counts per 1000 registered patients.

[7] https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/general-practice-data-hub

[8] See https://digital.nhs.uk/data-and-information/publications/statistical/patients-registered-at-a-gp-practice

[9] Note that for 2013, quarterly data was available only for Q2, Q3 and Q4.

[10] https://fingertips.phe.org.uk/profile/general-practice

[11] All deprivation scores were available for the year 2015 only.

[12] https://digital.nhs.uk/data-and-information/publications/statistical/quality-and-outcomes-framework-achievement-prevalence-and-exceptions-data

[13] https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/general-practice-data-hub

[14] These are available at https://digital.nhs.uk/data-and-information/publications/statistical/general-and-personal-medical-services/2005-2015-as-at-30-september-provisional-experimental-statistics

Workforce statistics also included GPs' contract type. These were general medical services (GMS), personal medical services (PMS), alternative provider medical services (APMDS), and primary care trust medical services contract (PCTMS). GMS contract types concern the delivery of a set of nationally agreed core medical services, with funding related to the number of registered patients. PMS contracts might include extra services compared to GMS ones, such as special clinics for the homeless or other local needs. APMS contracts allow for primary care organisations to contract non-NHS bodies such as commercial providers, or for general or personal medical services to provide additional primary care services. GMS contracts are contracted nationally, while PMS and APMDS contracts are contracted locally. Under PCTMS primary care trusts are allowed to provide services directly via the direct employment of staff.[15] Individual contract types were transformed into dummy variables, with GMS as a reference contract type.

We collected information concerning letters sent by the Chief Medical Officer (CMO) to GPs with high prescription rates.[16] These letters were submitted by the CMO to GPs in the top 20% based on antibacterial items per STAR-PU per 1000 population in the 12 months running from July 2014 to June 2015. The content of the letters reminded GPs of the threat of increasing antibiotic resistance and that their practice was among the highest percentiles of antibiotic prescriptions (at least top 20%). The letters also indicated a number of actions the GP could take to reduce antibiotic prescription .[17] A second round of letters was sent again in April 2017, and in the following years. We captured this information by setting a time-varying dummy equal to one from the year when the practice received a letter from the CMO.

We computed measures of spatial distance across GP practices. These were computed in two steps. First we computed spatial coordinates from GP addresses. Second we computed geographical distance across GPs using Harversine distance. Harversine distance was computed using the R package *geosphere* (Williams et al., 2016). We also created a dummy indicating whether practices were in the same CCG. Both these measures were used as alternative distance indicators to estimate spatial effects.

Compared to the indicators listed in Table 1 of Gonzalez-Ortiz and Masiero (2013), our study does not consider variables related to ethnicity, individual's choice of patient clinic, income, incidence of bacterial infections, and social assistance and number of consultations. While these indicators have been found to be associated with antibiotic prescription by other authors, they have not been included in this study due to data limitations.

At the end of the data cleaning process our dataset on antibiotics included 7168 GP practices for a total of 35840 records.[18]

[15] A description of what each contract type entails can be found at the following link (accessed on September 26th 2019) `https://practicebusiness.co.uk/gp-contracts-updates-to-gms-pms-and-apms/`. Additional details on PCTMS are described in Ellins et al. (2008)

[16] Information was obtained from this website `https://www.prescqipp.info/our-resources/webkits/antimicrobial-stewardship/`

[17] These included: a) give patients advice on self-care instead b) consider offering a back-up (delayed) prescription instead, c) talk to other prescribers in their practice to ensure they are also changing their antibiotic prescribing.

[18] The original prescription dataset presented 12476 unique practices. Of these, 9104 practices were contemporaneously present across all years. 8103 practices were present in the workforce dataset including information on practice patients. 7510 practices with workforce and patients information are also present across all years. A further 342 practices are removed because they lack patients' data.

III. Methodology

We estimate antibiotic prescription via regression analysis, considering the role of spatial dependence across GP practices.

Spatial dependence arises when agents are able to interact with each other across space (Gibbons et al., 2015). The result of such interaction is the presence of spatial correlation in agents' behaviour. Spatial dependence might affect the expression we aim to estimate in either the dependent variable, the covariates or the error term. The use of traditional OLS models might lead to misspecification in the presence of such dependence (Gibbons et al., 2015). The spatial econometrics literature provides a number of methods to estimate relationships across the dependent variable and its covariates in the presence of spatial dependence.

When analysing spatial dependence, Gibbons et al. (2015) warns against three potential identification issues: unobservable factors varying at the group level (reflection problem), omitted variables, endogenous group membership (sorting).

In the context of antibiotic prescription, Filippini et al. (2014) also highlight the following identification issues: endogeneity in antibiotic prescription and health needs of the local population, the presence of unobserved heterogeneity in local areas due to unobserved infection rates, and spatial correlation across different local areas (see Filippini et al. (2014).

To minimise the risk of potential misspecification we will first introduce a simple OLS model, linking antibiotic prescription rates to the characteristics of the areas served by the GP practice. We will then test for the presence of Practice-level Fixed Effects (FE) and Random Effects (RE). We will use a Hausman test to select between fixed- and random- effects.

We then introduce a set of models for the estimation of spatial dependence.

We start our analysis on spatial dependence by means of an Spatially Lagged Model (SLX), which represents our baseline for the analysis. The SLX model consists of a simple OLS model where the covariates are introduced as a spatially weighted average of the neighbouring areas. The type of spatial dependence captured by the SLX model is related to contextual (or exogenous) spatial correlation where practices respond to observable and exogenous characteristics of their group (Gibbons et al., 2015). Halleck Vega and Elhorst (2015) indicate that the SLX model is a useful baseline model as in this model spatial dependence coincides with the parameter estimates of the exogenous spatial lags, providing a simpler representation of spatial dependence and lower risks of identification issues compared to models allowing for spatial autoregression Gibbons et al. (2015). We will test the SLX model both in its simple form, as well as with extensions given by Fixed Effects (FE) and Random Effect (RE). We will use the Hausman test to select between the two.

Gibbons et al. (2015) indicate alternative types of spatial dependence, namely a spatial dependence generated by endogenous effects where individual behaviour responds to the anticipated behaviour and choices of other agents in the same reference group and an "correlated effect" where peer group specific unobservable factors influence individual and peer behaviour (common shocks) (Manski, 1993). These two effects are captured by the Spatial Autoregression Model (SAR) and the Spatial Error Model (SEM) respectively. SAR allows for a spatially lagged dependent variable among the set of covariates, while SER allows for spatial dependence in the error term. While these models provide useful representations of spatial dependence, Gibbons et al. (2015) indicate that the identification of the SAR model introduces the challenge of the reflection problem, that is only the overall effect of neighbourhood characteristics is identified

but not whether they are resulting from endogenous or exogenous effects. The SEM model, on the contrary, only requires no inter-group correlation. These models will be explored as a departure from the baseline SLX model. These expansions follow closely the approach proposed by Gonzalez-Ortiz and Masiero (2013) and Lippi Bruni and Mammi (2016).

Notice that we do not make explicit a-priori assumptions regarding the sign of spatial correlation. In principle, spatial correlation in antibiotic prescription might be either positive or negative. A positive spatial correlation might identify a positive feedback loop derived from practices prescribing more as a result of random health shocks in neighbouring areas or as a result of geographical clusters in high-prescribing prescription behavior, with the result of high-prescribing doctors being geographically close to each other. On the contrary, a negative spatial correlation might imply that doctors reduce their prescriptions following a random health shock as a result of neighbouring practices increasing their prescription in response to higher infection rates thus reducing the need for antibiotics in neighbouring areas, or by practices deciding to reduce prescription in order to mitigate resistance in case they are geographically close to a high prescribing practice.

We control for the presence of spatial by means of Moran I statistics (Moran (1950), Cliff and Ord (1981)). Moran I is a weighted correlation coefficient defined as the quadratic form of the variables considered for spatial correlation. The considered variables are standardised by subtracting the sample mean and adjusted by the variance (Anselin and Bera, 1998). One advantage of Moran I statistics is that it can be interpreted as a correlation coefficient, with absolute values of one representing perfect correlation and values of zero representing no spatial correlation. Similarly, Moran I statistics can be transformed into z-scores for hypothesis testing (Gonzalez-Ortiz and Masiero, 2013).

Our dependent variable is the log of the number of prescribed antibiotics per STARPU-patients. Computing logs allows us to avoid scaling issues in the model estimation.

Our baseline SLX model is defined as follows. Letting $\mathbf{Y_t}$ to indicate the vector of $N \times T$ observations of the dependent variable (number of prescribed antibiotics per 1000 STARPU-patient) prescription of antibiotic at time t, we have

$$\mathbf{Y_t} = \mathbf{X_t}\boldsymbol{\gamma} + \mathbf{W}\mathbf{X}_t\boldsymbol{\theta} + \boldsymbol{\mu} + \boldsymbol{\alpha_t} + \mathbf{u}_t \tag{3.1}$$

where $\mathbf{X}_t$ is a matrix of regressors, the $N \times N$ matrix $\mathbf{W}$ symbolises the pairwise spatial relationships between the individual practices, $\boldsymbol{\mu}$ is a vector of time-invariant GP-specific fixed effects, $\boldsymbol{\alpha_t}$ represents a vector of time fixed effects, and $\mathbf{u}_t$ is a vector of spatially and time uncorrelated disturbances[19].

We first consider a baseline OLS model, obtained by estimating model 3.1 without spatial effects and without GP-Fixed Effects, that is, we first set $\mathbf{W} = \mathbf{0}$ and $\boldsymbol{\mu} = \mathbf{0}$.

We perform a Shaphiro-Wilk test for the normality of the estimated residuals, and a Bresuch-Pagan test for heteroskedasticity. In case of absence of normality and heteroskedasticity in the residuals, we estimate a model with GP-clustered residuals.

As latent common factors might induce dependence leading to inconsistent estimations in case of correlation with such unobserved factors (Greene, 2012), we introduce a second version

[19]The notation used in equation (3.1) follows the standard notation for spatial econometrics as described in Gibbons et al. (2015). In the standard microeconometric notation the model could be written as $y_{it} = \gamma x_{it} + \phi \sum_j w_{i,j} x_{i,t} + \mu i + \alpha_t + u_{i,t}$

of the model accounting for GP-level Fixed Effects (FE) and Random Effects (RE).

We run a Hausman test to select between random or fixed effects represented by the parameter u_{zt} in equation 3.1.

We test for the presence of spatial autocorrelation in the residuals by applying Moran's I statistic (see Kelejian and Prucha (2001)). Having identified signs of cross-sectional dependence, we address spatial correlation across practices by means of spatial weights.

Following Lippi Bruni and Mammi (2016), we estimate two different versions of proximity: institutional and geographical proximity. We define institutional weights as

$$W_{(i,j),INST} = \begin{cases} 1, & \text{if GPs } i \text{ and } j \text{ are in the same CCGs,} \\ 0, & \text{otherwise.} \end{cases} \tag{3.2}$$

We define geographical weights across practices as

$$W_{(i,j),GEO} = \frac{1}{d_{i,j}}, \tag{3.3}$$

where $d_{i,j}$ represents the Haversine distance across coordinates of the two GP practices.[20] As standard in the literature, weights are row standardised, meaning that each neighbour weight is divided by the sum of all neighbour weights (Gibbons et al., 2015).

To ensure we capture the best weighting system of neighbouring dependent variables, we estimate an alternative model taking a linear combination of institutional and geographical distances. More specifically, this additional version of the spatial weights is defined as

$$W_{(i,j),CONV} = \phi W_{(i,j),INST} + (1 - \phi) W_{(i,j),GEO} \tag{3.4}$$

where $\phi > 0$. We first estimate the model with $\phi = 1$, hence estimating a purely geographical weight. We then reduce ϕ in steps of measure 0.1 by means of a gridding procedure, until obtaining a purely institutional weight ($\phi = 0$).

Administrative weights allow for the consideration of spatial dependence arising from an administrative grouping of GP practices. This approach, however, does not allow for dependence arising from geographical proximity. In addition, in this weighting system, all practices in the same administrative area are weighted equally. The geographical weight, on the contrary, allows for dependence arising from geographical distance, at the cost of ignoring administrative components. The weighted average of the two methods allow for a balance between these two components of spatial dependence. The literature on spatial methods provides additional details for the definition of alternative weight matrices (Gibbons et al., 2015), including time-varying weights. In particular, Halleck Vega and Elhorst (2015), allow for parametric spatial weights which can be useful to estimate the strength of connections from cross-sectional observation, rather than defining them in advance. Although this definition of spatial weights could prove useful, parametrized weights have not been included in the analysis to ensure model paucity.

We identify the best performing SLX model by selecting the model with the lowest Akaike Information Criterion (AIC).

[20] The distance of a practice with itself is set to zero.

To explore the role of different channels of spatial dependence described in the introduction, we introduce a number of alternative spatial dependence models. More specifically, to account for the role of the channel of common policies, we estimate an SLX defined as

$$\mathbf{Y_t} = \mathbf{X_t}\gamma + \mathbf{W}\mathbf{X}_t\boldsymbol{\theta} + \boldsymbol{\mu} + \boldsymbol{\alpha_t} + \boldsymbol{\gamma_t} + \mathbf{u}_t, \tag{3.5}$$

where γ_t represents the interaction of CCG fixed effects with year. The presence of spatial dependence in the SLX component of the model, even after introducing this interaction effect, will provide us with evidence for the presence of alternative channels for spatial dependence.

We test for the presence of spatial dependence arising from random health shocks by estimating a spatial error model similar to the one proposed by Gonzalez-Ortiz and Masiero (2013) and Lippi Bruni and Mammi (2016), namely

$$\begin{aligned} \mathbf{Y_t} &= \mathbf{X_t}\gamma + \boldsymbol{\mu} + \boldsymbol{\alpha_t} + \mathbf{u}_t, \\ \mathbf{u}_t &= \rho\mathbf{W}\mathbf{u}_t + \boldsymbol{\epsilon_t}, \end{aligned} \tag{3.6}$$

where $\boldsymbol{\epsilon_t}$ is a spatially non-correlated error term.

We test for the presence of spatial dependence arising from unobserved risk factors by estimating a spatial autoregressive model similar to the one proposed by Gonzalez-Ortiz and Masiero (2013) and Filippini et al. (2014), namely

$$\mathbf{Y_t} = \mathbf{W}\mathbf{Y_t}\boldsymbol{\beta} + \mathbf{X_t}\gamma + \boldsymbol{\mu} + \boldsymbol{\alpha_t} + \mathbf{u}_t \tag{3.7}$$

Lastly, we run a separate version of the model where we estimate spatial dependence for the prescription of broad-spectrum antibiotics as a percentage of total antibiotic prescription. Open Prescribing (2020) provides an indication of the antibiotics which can be considered as broad-spectrum, namely: co-amoxiclav, cephalosporins and quinolones. These antibiotics have to be prescribed sparingly to reduce the risk of resistance. This model allows us to verify for spatial dependence in prescription behaviour for this specific class of drugs. For simplicity, we report the results of this additional model in SLX format with FE (SLX RE model was estimated, however it reached singularity).

Notice that while a strand of literature suggests that antibiotic prescriptions are influenced by patients' expectations (Fletcher-Lartey et al., 2016), systematic reviews rejected the hypothesis of complacency (i.e. fulfilling patients expectations) playing a role in prescription behaviour, due to conflicting evidence among studies (Teixeira Rodrigues et al., 2013). Similar conclusions were found in other reviews (Lopez-Vazquez et al., 2011). It is therefore plausible that patients do not switch GP practices on the basis of prescription patterns. This is consistent with a different strand of literature stating that patients choice to switch GP practice is a multi-factorial one, and depending on issues such as: rudeness or attitude of the doctor, accessibility, and distance to the practice (Ghandi et al., 1997). We therefore consider the risk of sorting, as described by Gibbons et al. (2015) not to play a role when it comes to patients selecting GPs based on prescription patterns.

The OLS and SLX models are estimated with the R package *plm* (Croissant and Millo, 2008). The spatial error and the spatial autoregressive model are estimated with the R package *splm* (Millo and Piras, 2012).

IV. Results

i. Baseline analysis

Table 3.1 presents the descriptive statistics of shortlisted variables. We removed from the analysis those variables that presented a high number of missing observations (more than 5% of observations).[21]

Table 3.1: *Descriptive statistics*

	mean	std.dev	min	max
(Log of) STARPU-items per 1000 patients	6.933	0.291	0.538	11.704
(Log of) registered patients	8.780	0.603	2.708	11.020
Female patients (%)	49.915	2.254	13.799	63.347
Over 65 patients (%)	16.9	6.59	0	50.87
GP density (head counts)	0.700	0.758	0	100
Female GPs (%)	47.279	25.585	0	100
Under 40 GPs (%)	28.561	25.046	0	100
Foreign GPs (%)	33.820	35.124	0	100
Nurse density (head counts)	0.424	0.584	0	66.667
QOF points (%)	95.534	6.457	2.500	100
Unemployed patients (%)	5.710	5.001	0	62.180
Patients with caring responsibilities (%)	18.107	5.047	0	44.877
Prevalence: asthma	5.934	1.316	0	16.667
Prevalence: diabetes mellitus	6.553	2.045	0	25
GP contract: APMS	0.028	0.166	0	1
GP contract: GMS	0.628	0.483	0	1
GP contract: PMS	0.341	0.474	0	1
GP contract: PCTMS	0.003	0.057	0	1
Letters from CMO	0.073	0.260	0	1

Correlation analysis of independent variables identified high positive correlation across most prevalence groups. To avoid collinearity we focused on specific conditions. Dolk et al. (2018) found that cough was one of the main conditions, among the prescriptions that could be linked to a body part. Also, Nitzan et al. (2010), found that antibiotic prescriptions were linked to antibiotic mellitus prevalence. To account for these two factors, we considered prevalence of Asthma, as a proxy of cough, and prevalence of diabetes mellitus (the two conditions showed a low correlation (0.24).

We found mild correlation across the percentage of female patients, age and unemployment.[22] We found a mild correlation across patient age and asthma prevalence.[23] We found small negative correlation across asthma prevalence and working full-time (-0.33). We also found small negative correlation across working full-time and having caring responsibilities (-0.35). As correlation was mild across these variables we did not remove them from the analysis. GMS contracts were included as the reference category. The year 2013 has been included as the

[21] These variables are IMD2015, children's income deprivation (IDACI), and income deprivation for older people (IDAOPI).

[22] The correlation of the percentage of female patients with the percentage of over 85 was 0.37, and with percentage of unemployed was -0.4.

[23] Correlation across patients in the 65-74 age band and asthma was 0.4.

reference year.[24]

We explored time variation of the shortlisted covariates by means of graphical analysis. The following covariates reported a low-time variation (maximum absolute average year-on-year lower than 3%): (Log of) registered patients, Female patients (%), Over 65 patients (%), QOF points (%), Prevalence: asthma, Good appointment experience (%), Patients with caring responsibilities(%).

We first estimate an OLS model with no spatial effects, as defined in model 3.1 setting $w = 0$ and $u_j = 0$ for all j. Results of the baseline OLS model are reported in column 1 of table 3.2.

The preliminary OLS model provided an adjusted-R2 0.277. The F-test indicates that we can reject the null hypothesis of all regressors being equal to zero (p-value < 2.2e-16). Shapiro-wilk test indicates a rejection of the null hypothesis of normal residuals (p-value $<$ 2.22e-16).[25]. The Breusch-Pagan test indicates that we cannot accept the null hypothesis of residuals homoskedasticity (p-value $<$ 2.2e-16). To account for heteroskedasticity in the regression residuals we cluster residuals at a CCG level. All reported regression results thus present CCG-level clustered residuals.

Preliminary regression results indicate a positive coefficient for the year 2014, and a negative one for the years 2015 onwards. This is consistent with the introduction of the stewardship programme in 2015.[26] The following factors were positively associated with prescription: percentage of female patients, percentage of over 65 patients, percentage of patients with caring responsibilities, percentage of unemployed patients, percentage of foreign GPs, nurse density, APMS contracts, prevalence (both asthma and diabetes), having received a letter from CMO. The following factors were negatively associated with prescription: percentage of patients reporting a positive appointment experience, percentage of female GPs, percentage of under 40 GPs, QOF score, PCTMS contracts.

We run Hausman test to check for the significance of introducing alternatively CCG-level Fixed Effects (FE) or Random Effect (RE) (Wooldridge, 2010) to the model 3.1. The test indicated that we cannot accept the null hypothesis of RE being consistent, providing a p-value close to 0. For this reason the second column of table 3.2 provides the results of a regression model with practice-level Fixed Effects.

Compared to the simple OLS model, the OLS model with practice-FE provides a higher adjusted R2 (0.84).[27] The estimated coefficients were comparable across the OLS and OLS FE model, with a number of exceptions. The following regression coefficients changed sign from positive in the OLS to negative in the OLS FE: year 2014, diabetes mellitus prevalence, APMS and PMS contract. The following regression coefficients changed from negative to positive: percentage of patients reporting a positive appointment experience. The following regressors gained significance: log of registered patients (negative), GP density (positive), PMS contract (negative), while the following regressors lost significance: percentage of female GPS, percentage of patients with caring responsibilities, percentage of unemployed patients, PCTMS contract.

[24] We tried an alternative specification of the model with no intercept however the estimated model presented signs of strong collinearity.

[25] We perform Shapiro-Wilk test with the R function *shapiro.test* This function allows a maximum of 5000 observations, hence we run the test on a random sample of 5000 residuals.

[26] We attempted to report a policy dummy being equal to 1 for any observation registered from the year 2015 onwards. This variables, however, ended up being non identified when considered jointly with individual year effects.

[27] Notice that the OLS FE model is estimated using a *demeaned* equation (see Wooldridge (2010) and Croissant and Millo (2008) for details).

Before running a spatial model, we checked for evidence of spatial autocorrelation in dependent variable applying Moran's I test. This test provided an estimated value of 0.195, with a p-value lower than 2.2e-16, thus rejecting the null hypothesis of absence of spatial dependence in the log of antibiotic items per 1000 STARPU patients. Moran's I has been tested for each year and for two alternative spatial weight matrices (administrative and spatial). Each version of test confirmed the rejection of the null hypothesis of no spatial autocorrelation. Moran's I test was computed using the function *Moran.I* from the R package *ape* (Paradis et al., 2004).

Table 3.2: *Regression results. Dependent variable: (Log) prescribed antibiotics per 1000 STARPU patients*

	Dependent variable:					
	(Log of) prescribed antibiotics per 1000 STARTPU Patients.					
	OLS	OLS FE	OLS RE	SLX	SLX FE	SLX RE
	(1)	(2)	(3)	(4)	(5)	(6)
Year 2014	0.028***	−0.028***	−0.013**	0.230***	0.003	0.064***
	(0.008)	(0.006)	(0.005)	(0.029)	(0.020)	(0.017)
Year 2015	−0.097***	−0.067***	−0.079***	−0.052***	−0.039**	−0.041***
	(0.005)	(0.003)	(0.003)	(0.015)	(0.018)	(0.013)
Year 2016	−0.192***	−0.095***	−0.116***	−0.245***	−0.069***	−0.075***
	(0.005)	(0.004)	(0.003)	(0.024)	(0.024)	(0.016)
Year 2017	−0.178***	−0.140***	−0.160***	−0.121***	−0.130***	−0.119***
	(0.005)	(0.005)	(0.003)	(0.018)	(0.032)	(0.017)
(Log of) registered patients	−0.002	−0.244***	−0.061***	0.004	−0.223***	−0.043***
	(0.004)	(0.034)	(0.010)	(0.004)	(0.034)	(0.010)
Female patients (%)	0.009***	0.005	0.006***	0.010***	0.001	0.005**
	(0.001)	(0.004)	(0.002)	(0.001)	(0.005)	(0.002)
Over 65 patients (%)	0.005***	0.004*	0.005***	0.004***	0.002	0.004***
	(0.0003)	(0.003)	(0.001)	(0.0003)	(0.003)	(0.001)
GP density (Head counts)	0.001	0.011	0.014*	0.010**	0.013	0.018**
	(0.005)	(0.009)	(0.008)	(0.005)	(0.009)	(0.008)
Female GPs (%)	−0.001***	−0.0001	−0.0002***	−0.0004***	−0.0001	−0.0002***
	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)
Under 40s GPs (%)	−0.0003***	−0.0002***	−0.0002***	−0.0004***	−0.0003***	−0.0003***
	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)
Foreign GPs (%)	0.001***	0.0001*	0.0003***	0.001***	0.0001	0.0002***
	(0.00005)	(0.0001)	(0.00005)	(0.00005)	(0.0001)	(0.0001)
Nurse density (head counts)	0.080***	0.038***	0.053***	0.066***	0.036***	0.048***
	(0.008)	(0.010)	(0.008)	(0.007)	(0.011)	(0.009)
QOF points (%)	−0.002***	−0.0002	−0.002***	−0.002***	−0.0002	−0.001***
	(0.0002)	(0.0003)	(0.0002)	(0.0003)	(0.0003)	(0.0002)
Prevalence: asthma	0.051***	0.016***	0.038***	0.039***	0.016***	0.031***
	(0.001)	(0.004)	(0.002)	(0.002)	(0.004)	(0.003)
Prevalence: diabetes mellitus	0.008***	−0.004***	−0.0005	0.012***	−0.005***	−0.0001
	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)
Good appointment experience(%)	−0.001***	0.001***	0.00003	−0.001***	0.001***	0.00005
	(0.0002)	(0.0002)	(0.0001)	(0.0002)	(0.0002)	(0.0001)
Patients with caring responsibilities (%)	0.005***	−0.0001	0.001***	0.004***	−0.0001	0.001***
	(0.0003)	(0.0002)	(0.0002)	(0.0003)	(0.0002)	(0.0002)
Unemployed patients (%)	0.004***	0.0002	0.001***	0.003***	0.0002	0.001***
	(0.0004)	(0.0003)	(0.0003)	(0.0004)	(0.0003)	(0.0003)
GP contract: APMS	0.235***	−0.033	0.091***	0.068***	−0.047	0.004
	(0.019)	(0.038)	(0.028)	(0.018)	(0.038)	(0.026)
GP contract: PMS	0.002	−0.012***	−0.003	0.007**	−0.001	0.006*
	(0.003)	(0.005)	(0.003)	(0.003)	(0.005)	(0.004)
GP contract: PCTMS	−0.075**	0.003	0.004	−0.069**	0.019	−0.001
	(0.031)	(0.019)	(0.018)	(0.034)	(0.027)	(0.024)
Letters from CMO	0.293***	0.010***	0.038***	0.281***	0.008**	0.036***
	(0.006)	(0.004)	(0.003)	(0.006)	(0.004)	(0.004)
(Log of) registered patients W0.1				0.037	−1.462***	−0.459***
				(0.076)	(0.487)	(0.140)
Female patients (%) W0.1				−0.026	0.104**	0.081***
				(0.017)	(0.047)	(0.025)

Table 3.2: *Regression results. Dependent variable: (Log) prescribed antibiotics per 1000 STARPU patients*

Over 65 patients (%) W0.1				-0.021^{**}	0.091^{***}	0.012
				(0.008)	(0.034)	(0.011)
GP density (head counts) W0.1				-1.249^{***}	-0.241^{**}	-0.659^{***}
				(0.129)	(0.116)	(0.106)
Female GPs (%) W0.1				0.006^{***}	0.005^{*}	0.003^{*}
				(0.002)	(0.003)	(0.002)
Under 40 GPs (%) W0.1				-0.002	0.002	0.002
				(0.003)	(0.004)	(0.003)
Foreign GPs (%) W0.1				0.009^{***}	0.001	0.004^{***}
				(0.001)	(0.001)	(0.001)
Nurse density (%) W0.1				1.282^{***}	0.170	0.758^{***}
				(0.173)	(0.204)	(0.171)
QOF points (%) W0.1				-0.005	0.001	-0.010^{**}
				(0.004)	(0.006)	(0.004)
Prevalence: asthma W0.1				0.212^{***}	0.010	0.186^{***}
				(0.033)	(0.078)	(0.041)
Prevalence: diabetes mellitus W0.1				-0.042^{***}	-0.003	-0.014^{***}
				(0.007)	(0.004)	(0.004)
Good appointment (%) W0.1				0.004	-0.001	-0.003
				(0.004)	(0.007)	(0.005)
Caring responsibilities (%) W0.1				0.033^{***}	0.011	-0.001
				(0.011)	(0.011)	(0.009)
Unemployed patients (%) W0.1				-0.062^{***}	-0.006	-0.012
				(0.011)	(0.015)	(0.011)
GP contract: APMS W0.1				5.827^{***}	3.711^{***}	5.508^{***}
				(0.447)	(1.250)	(0.718)
GP contract: PMS W0.1				-0.327^{***}	-0.397^{***}	-0.512^{***}
				(0.065)	(0.100)	(0.079)
GP contract: PCTMS W0.1				0.650^{*}	-0.877^{**}	-0.300
				(0.383)	(0.364)	(0.283)
Letters from CMO W0.1				-0.563^{***}	-0.020	-0.070^{*}
				(0.073)	(0.040)	(0.036)
Constant	6.304^{***}		7.013^{***}	6.286^{***}		6.961^{***}
	(0.072)		(0.143)	(0.071)		(0.144)
Observations	35,840	35,840	35,840	35,840	35,840	35,840
R^2	0.278	0.348	0.288	0.321	0.355	0.310
Adjusted R^2	0.277	0.185	0.288	0.321	0.192	0.309
F Statistic	625^{***}	696^{***}	$14{,}491^{***}$	424^{***}	393^{***}	$16{,}088^{***}$
F Statistic	(df = 22; 35817)	(df = 22; 28650)		(df = 40; 35799)	(df = 40; 28632)	
Note:						*p<0.1; **p<0.05; ***p<0.01

Having identified the presence of spatial correlation, we estimate different versions of the SLX model 3.1, setting $w \neq 0$.

More specifically, we first estimate a simple version of the spatially lag (SLX) model. We then introduce an SLX model with alternatively GP-level Fixed Effects (SLX FE) and Random Effects (RE). We run a Hausman test to select between Fixed and Random Effects. The Hausman test rejects the null hypothesis of unique errors being correlated with the regressors, hence the FE should be preferred. Results of the spatial models are reported in columns 3 and 4 of Table 3.2. This table also presents the SLX RE model for comparison purposes.

Results of the spatial model have been obtained with a linear combination of administrative and spatial weights, as indicated in equation 3.4. The weights associated to ϕ, the administrative spatial component, was equal to 0.1. This value of ϕ has been obtained from the value that minimizes the Akaike Information Criterion (AIC) of the SLX model. Additional details on the optimal AIC associated to different combinations of spatial weights is reported in Figure 3.2 in the appendix.[28]

Compared to the OLS models, the spatial lag models presented regression coefficients with comparable sign and magnitude. Both the SLX and the SLX FE model presented a negative time trend, with the SLX presenting a positive coefficient for 2014 as in the baseline OLS model.

The key differences across the SLX and the OLS model were that GP density gained significance. The key differences across the SLX FE and the OLS FE model were that in the former the year 2014, the percentage of female patients, the percentage of over 65 patients, the percentage of foreign GPs, the percentage of QOF points, PMS contracts all lost significance, while the percentage of female patients became significant.

By looking of the averaged regressors of neighbouring practices (see regressors ending with $W0.1$ in Table 3.2) the SLX model identifies positive spatial dependence for the percentage of female GPs, the percentage of foreign GPs, nurse density, asthma prevalence, caring responsibilities, and GP contract type APMS and PCTMS. Similarly, the SLX identified negative spatial dependence for GP density, prevalence of diabetes mellitus, the percentage of unemployed patients, GP contract type PMS, and receiving letters from the CMO for over prescription.

The SLX FE model confirmed positive spatial dependence for the percentage of female GPs, and for GP APMS contract type (see last column of table 3.2). Similarly, negative spatial dependence was confirmed for GP density and PMS contract. Compared to the SLX results, in the SLX FE spatial average of the number of registered patients became negative and significant, as did PCTMS contract type. The percentage of female patients, the percentage of over 65 patients, became positive and significant. The percentage of foreign GPs, nurse density lost significance, percentage of patients with caring responsibilities, the percentage of unemployed patients and prevalence measures lost significance.

Among the estimated models, the SLX FE was the one minimising the Akaike Information Criterion (AIC), hence it should be the model to be preferred.[29]

Figure 3.1 provides a graphical representation of spatial dependence by presenting a map of the sum of the residuals grouped by individual practices and estimated for the OLS FE model (top) and the SLX FE model (bottom). The figure shows that for the simple OLS FE model there is a presence of spatial correlation in the residuals with clear spatial patterns appearing in the map. The same geographical clusters appear not to be present once spatial correlation is accounted for with the SLX FE model. This result appears to indicate that the presence of a spatial correlation of the residuals arising from the OLS FE model. This figure also shows that the SLX FE model captures the majority of such spatial correlation.

The spatial coefficients of the estimated SLX and SLX FE models might be capturing spatial dependence across GP practices. This spatial dependence might be arising from a number reasons, including institutional factors across different CCGS, different rates of bacterial resistance across local areas, area specific health shocks across areas or different prevention efforts in

[28] Notice that the optimal ϕ for the SLX FE was 0.2. Nonetheless we set ϕ to 0.1 for both models for simplicity.

[29] The AIC values of the estimated models were: OLS = 1530.53, OLS with FE = -60673.29, SLX = -676.97, SLX with FE = -60984.35.

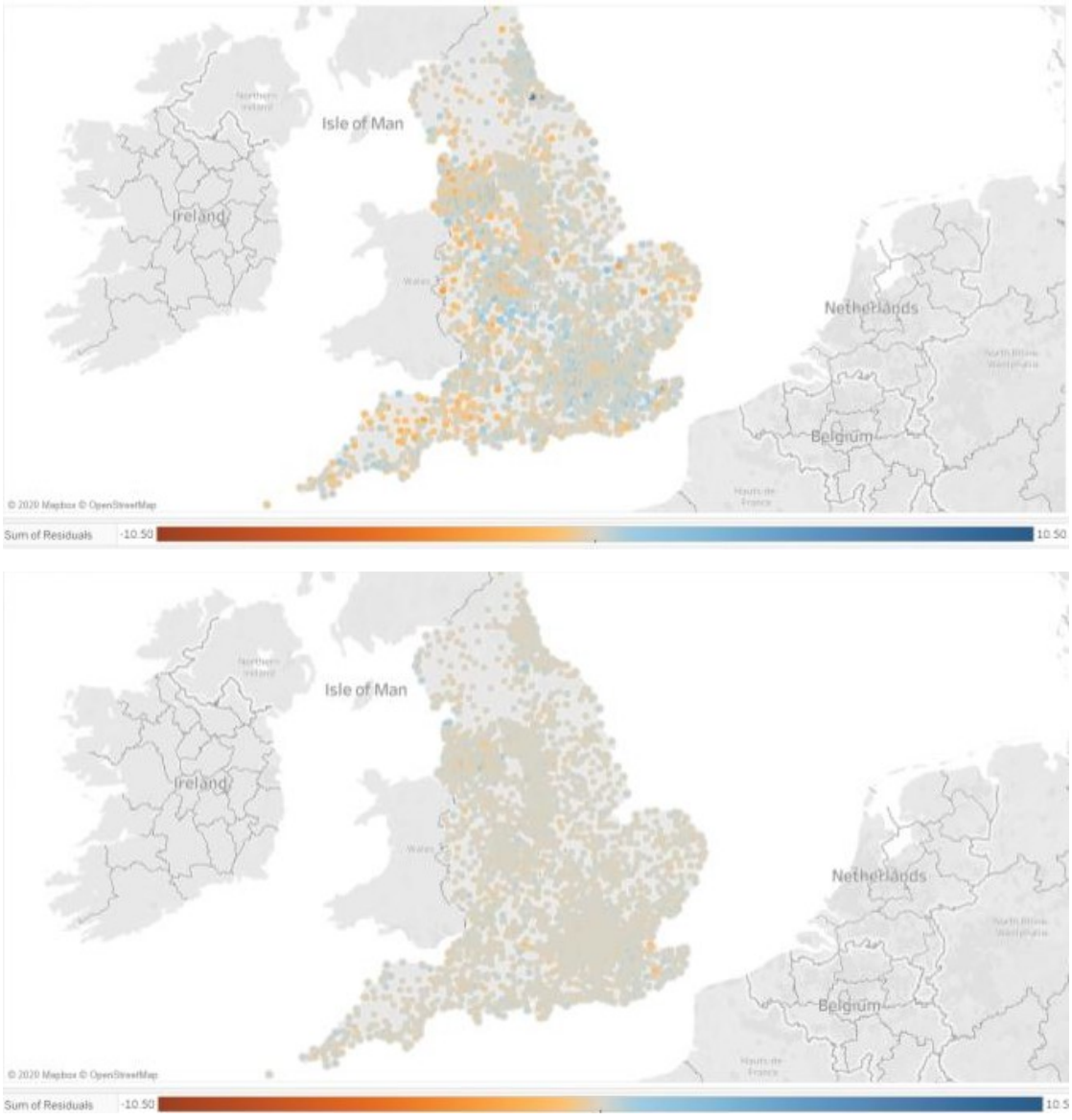


Figure 3.1: *Sum of residuals by GP practice, OLS FE model (top) and SLX FE model (Bottom). Blue = positive sum, Red = negative sum.*

bacterial resistance. We estimate a number of alternative models to verify the importance of different channels of spatial dependence.

Notice that in all estimated models, the dummy related to CMO letters was positive. This suggests that this dummy allows for the identification of high prescribers, and it provides no evidence that CMO letters had an effect in reducing prescription, while other covariates are accounted for.

ii. Exploring alternative channels of spatial dependence

We now report the estimated results of alternative spatial models used to explore alternative channels of spatial dependence. The results of these alternative models are reported in table 3.4 in the appendix.

First we estimate an alternative SLX FE model including CCG and year interaction effects, as defined in equation 3.5. These interactions are aimed to capture specific policy actions occurring at the CCG level in individual years. Results of this model are reported in the second column of Table 3.4 (see "SLX FE CCG*Year Interactions"). Compared to the SLX FE model, individual year dummies, except for 2016, became non-significant. The percentage of foreign GPs gained significance. Concerning spatially-weighted coefficients, the percentage of over 65 patients and GP density both lost significance, while nurse density and the percentage of unemployed patients both gained significance. These results seem to suggest that policy effects occurring at a CCG level had little impact on the nature of spatial dependence in antibiotic prescription.

We have then estimated an alternative form of spatial dependence, by introducing a spatial error model, as defined in equation 3.6. This model is used in Gonzalez-Ortiz and Masiero (2013) and Lippi Bruni and Mammi (2016) to estimate spatial dependence potentially arising from random health shocks in antibiotic prescription and in hospital expenditures respectively. In this case we can see that the parameter ρ, is equal to -0.961 and it is significant to the 0.01 level. This result indicates that the spatial component of the error model, is negative and significant, thus representing a negative spatial dependence across neighbouring practices in antibiotic prescription arising from random health shocks.

We've then considered an alternative channel of spatial dependence, by estimating a spatial dependence model as defined in equation 3.7. This model is used by Gonzalez-Ortiz and Masiero (2013) to estimate dependence arising from the prescription rates of neighbouring practices, and in and Lippi Bruni and Mammi (2016) to estimate spatial dependence in hospital expenditures. The estimated value of spatial dependence, indicated by the spatial autoregressive component β, reported in the last column of table 3.4, is equal to 0.133, however it fails to reach significance. This result indicates the absence of a significant spatial dependence (see model SAR).

The results of the analysis of the channels of spatial dependence appear to indicate that spatial dependence might be influenced by the characteristics of neighbouring practices (as captured by the SLX models). Spatial dependence appears to be only mildly influenced by CCG-specific policies (as indicated by the SLX model with CCG times year interactions). The estimated results in the SEM and SAR model appear to indicate that spatial dependence is more likely to occur via random health shocks, while it does not appear to be influenced by

the prescription rates of neighbouring practices ceteris-paribus.[30] [31] While care should be taken in interpreting the results of the SAR and SEM models due to the potential identification issues arising from potential endogeneity, these result might be interpreted as an indication of the absence of negative externalities due to antimicrobial resistance from over-prescribing. In addition, care should be given in the interpretation of these results on spatial correlation, as the estimated correlation is close to one, thus potentially identifying stationarity issues.

iii. Extensions

To deepen our analysis, we performed a second version of the SLX FE model estimated on broad-spectrum antibiotics. This additional model aims to identify whether spatial dependence is present also for this specific antibiotics class. Broad-spectrum antibiotics are of relevance for the analysis of antibiotic prescription as this specific class tends to be highly associated with increased antibiotic resistance. The results of this model are reported in table 3.5 in the appendix. For ease of comparison in each table we reported the results of the SLX and SLX FE on all antibiotic classes (left-most column). The SLX RE model is not reported as it reached singularity.

As indicated in the tables, spatial dependence appeared to be present also for broad-spectrum antibiotics, as indicated by the significance of the spatially lagged covariates. The sign of spatial dependence of individual covariates, where significant, was generally aligned with the sign of spatial dependence estimated for all antibiotics considered together, with the exception of the spatially-weighted letters from the CMO. Where significant, spatial dependence estimated on broad-spectrum antibiotics presented a higher magnitude compared to spatial dependence estimated on all antibiotics considered together.

Compared to the SLX FE model estimated on all antibiotics, the coefficient of the log of registered patients, GP density, GP contract PCTMS presented a higher negative magnitude in the broad-spectrum SLX FE model, while the coefficient on female GPs and GP contract APMS presented a higher positive magnitude. The coefficients on spatially weighted share of GPs under 40, nurse density, the percentage of patients reporting a good experience, and the letters all gained significance, while the same coefficients on the percentage of female patients and the percentage of over 65 patients lost significance. This result appears to indicate that spatial dependence on broad-spectrum antibiotics is affected more by supply side factors and policy interventions, compared to the demographics of the local population.

As a last robustness check, we compared the results of our SLX FE model with an alternative SLX FE model estimated on alternative dependent variables, namely the percentage of STARPU-adjusted antibiotics items (in logs) over all STARPU-adjusted prescribed items (in logs). Results are reported in Table 3.6 in the appendix. We found consistency in the presence of spatial dependence for the sign and significance of the following spatially weighted covariates: log of total patients (negative), percentage of female patients (positive), percentage of over 65 patients (positive), GP density (negative), percentage of female GPs (positive). In the alternative SLX FE

[30] Estimating the spatial error model (SEM) without practice fixed effects led to a positive and significant spatial error λ, with an estimated coefficient of 0.999 and standard error 0.172 (significant at 1% level). Similarly, the spatial autoregressive (SAR) model without practice fixed effects led to a positive and significant spatial autocorrelation ρ, with an estimated coefficient of 0.104 and standard error 0.012 (significant at 1% level).

[31] The estimated results have been obtained with a ML estimation of the spatial models. We estimated a separate version of the spatial models with GMM estimation. The GMM approach did not appear to influence the estimated results. The spatial error component coefficient rho is equal to 0.99, with variance equal to 0.01, hence significant. The estimated spatial autoregression component lambda is equal to 0.08 and it fails to reach significance (0.12 standard deviation).

model, the following spatially lagged covariates became significant: percentage of foreign GPs (positive). In the alternative models GP contracts presented the same sign and significance as the reference SLX FE model for all contract types.

V. Conclusions

This paper explores spatial dependence in antibiotic prescription rates among English GP practices by estimating a spatial panel analysis of presentation level data for the years 2013-17.

Several previous studies analysing socio-economic determinants of antibiotic prescription performed cross-sectional analysis of prescription data, hence not accounting for individual year effects (Matuz et al. (2005), Filippini et al. (2014), Kern et al. (2006)). Furthermore, studies reporting panel analysis were based on more limited number of observations compared to this paper (Gonzalez-Ortiz and Masiero (2013), Filippini et al. (2014)). In addition, several previous studies on the determinants of antibiotic prescription did not take into account spatial dependence (Matuz et al. (2005), Kern et al. (2006), Nitzan et al. (2010)), hence potentially overestimating coefficients significance (Kelly, 2019). Existing studies on antibiotic prescription adopting a spatial approach, such as Filippini et al. (2014) and Gonzalez-Ortiz and Masiero (2013) rely on estimated spatial models such as spatial error models (SEM) and spatial autoregressive models (SAR), which according to Gibbons et al. (2015) might pose higher identification challenges.

The study presented here is novel in a number of ways. First, by considering the data of over seven thousand GP practices for the years 2013-2017, we present a rich dataset, both in terms of explanatory variables, as in terms of number of available observations. Second, we estimate spatial dependence using an SLX approach as our baseline model, thus reducing the risk of misspecification. Third, we explore different channels of spatial dependence by confronting our SLX FE model, with SLX FE with CCG and year interaction effects, SEM and SAR models. Fourth, we estimate spatial models for overall antibiotic prescription, as well as broad-spectrum antibiotic prescriptions, thus allowing us to draw conclusions on GPs prescription behaviour. Lastly, the richness of our dataset allows us to analyse novel factors such as the introduction of relevant policy variables such as the effect of the introduction of letters from the Chief Medical Officer (CMO) to high-prescribing primary care practitioners.

This paper provides a contribution to the field of spatial methods applied to antibiotics prescription in primary care. This study does so by estimating a panel model over a dataset which is representative of antibiotics prescriptions in English primary care. To the best of our knowledge, this paper is also the first one to analyse spatial dependence in antibiotic prescribing among English GP practices.

This study confirms that antibiotic prescriptions are influenced by the demographics of the local population, supply-side factors connected to the provision of primary care services, condition prevalence and patients' experience in accessing services. The richness of our dataset allows us to study novel factors in antibiotic prescription in primary care. Our study allows us to identify differences in prescription rates across different GP contracts, thus identifying the effect of alternative contracts on prescription behaviour. In addition, we are able to control for relevant policy variables, such as receiving a letter from the CMO.

This study provides an in-depth exploration of the channels of spatial dependence in influencing antibiotic prescription rates. Our reference SLX model shows that a key source of such dependence is given by the characteristics of neighbouring practices, in particular practice

size, demographics of the local population and supply-side factors, such as GP density or the share of female GPs. This result appears to indicate that spatial dependence is affected by a combination of the specific needs of the local population and by the ability of the local health care system in addressing those needs. As infections tend to spread across the population, the identified spatial dependence from neighbouring characteristics is consistent with the presence of an externality arising from being close to a practice which is at lower risk of diffusion and which is better suited to address such infection. This effect of spatial dependence might be useful in identifying fragile nodes in the spatial network of primary care provision in its response to infections, thus providing a starting point for policy makers to identify weak points to address for the prevention of infection diffusion. Local decision makers, such as clinical commissioning groups might decide, for instance, to increase GP head counts in such areas that are more vulnerable to infections in terms of needs of the local population and that have weaker primary care, and that are closer to other practices with high risk and low capacity. Taking the spatial network of practices into account when planning prevention measures might thus maximise the effect of externalities arising from spatial dependence.

Our analysis has explored alternative channels of spatial dependence. In particular, we have explored the role of CCG-specific policies in influencing spatial dependence (as indicated by the SLX FE model with interaction effects). When taking into account the effect of specific CCG-level interventions, we see only a slight change in the spatial effects identified with our reference model. Although some spatially lagged covariates change significance (for example GP density becoming non-significant, or unemployed patients gaining significance), spatial dependence in practice size, demographics and supply-side factors seem to hold, thus highlighting a potential robustness to the identified spatial effect. This result might be useful to policy makers in understanding that year-specific interventions occurring at a local level might have little impact in addressing spatial differences across the country, which might require more long-term interventions to reach effectiveness. This result might be of particular importance for interventions targeted at preventing infections.

Lastly, our analysis on the channels of spatial dependence appears to indicate that such dependence is consistent with random health shocks, as identified by our spatial error model, while we find little evidence of prescription rates being influenced by externalities arising from resistance, as indicated from our spatial autoregressive model. This result might be indicating that the professional network of primary care practitioners is more responsive in sharing information on the local diffusion of infections than in sharing information on the local level of resistance and its implications on antibiotic effectiveness. The specific mechanics of this potential dynamics would require additional analysis, potentially including instruments related to antibiotic resistance.

The analysis on broad-spectrum antibiotics highlighted a different spatial pattern in the prescription of this antibiotic class compared to the dependence identified on all antibiotics. In particular, the spatial dependence for broad-spectrum antibiotics appeared to be less influenced by the demographics of the local population, and more by supply-side factors and policy intervention in neighbouring practices. This result is consistent with practices being influenced by higher standards of care and by the reception of a letter from CMO from a neighbouring practice. This result might be useful for policy makers as it indicates that a nudge to high-prescribing practices might induce a change in prescription behaviour in neighbouring areas concerning the provision of antibiotics which are highly related to an increase in resistance. This result is also consistent with an effective flow of information across the professional network of general practitioners when it comes to benchmarking of prescription behaviour. This result might be useful for policy makers as it indicates that a nudge to

a specific high-prescribing GP is effective in influencing the behaviour of neighbouring practices.

The results presented in this paper might be a useful starting point for policy makers who are interested in influencing antibiotic prescription taking the spatial structure of primary care provision into account. Stewardship programmes, in particular, have been identified as useful policy tools targeted to the optimisation of antibiotic prescriptions through the creation of evidence-based recommendations (Tamma and Cosgrove (2011) and Charani and Holmes (2013)). The results presented in this paper might be useful in identifying the influence of spatial dependence on such policies.

First, an analysis of such policies might take into consideration spatial dependence resulting from the characteristics of local areas and supply side factors related to primary care provision. Additional efforts on such policies might be targeted in those areas which are more affected by negative effects of spatial dependence. Second, this paper highlighted a role of information flows and professional benchmarking influencing prescription behaviour. Policy makers might increase the effectiveness of interventions such as stewardship programmes by facilitating the share of prescription best practices from the bottom-up via professional meetings and prescription benchmarking across practices. Third, this paper highlighted the importance of spatial dependence arising from nudges, such as receiving a letter from the CMO. Policy makers might consider providing the appropriate amount of visibility to such interventions to ensure the effectiveness of such letters on the prescription behaviour of neighbouring practices.

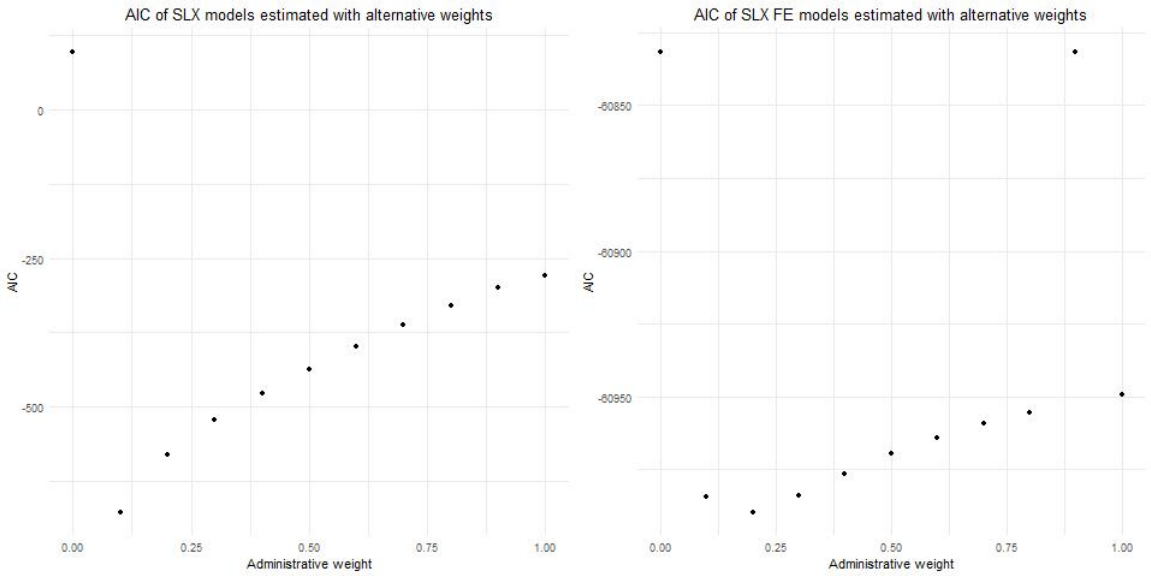
This study is subject to a number of limitations. First, this study does not include co-payment variables. Co-payments might have a relation to antibiotic provision as they might influence demand-side factors related to provision, hence they may represent an important factor related to prescription. Second, the analysis presents several interacting factors, such as prevalence, quality of local services and provision of primary care services. The interaction of these variables might lead to identification issues due to omitted variables. Third, this study does not consider time-varying weights when computing spatial dependence nor does it consider parametrized weights (for simplicity). It is possible that spatial dependence might have changed over time, particularly after the introduction of stewardship programmes. The impact of the introduction of stewardship programmes on spatial weights is beyond the scope of this paper. Future studies might explore the impact of different weights on the estimated results. Lastly, this study does not include antibiotic resistance variables, which nonetheless might be captured from individual practice fixed effects. Including instruments related to antibiotic provision might shed additional light on the effect of increased resistance of prescription. The analysis of the effect of resistance on antibiotic provision will require additional research.

VI. Appendix B

i. Data tables

Table 3.3: *Specific Therapeutic Group Age-sex weightings Related Prescribing Units*

Agend band (years)	Gender - male	Gender - female
0-4	0.8	0.8
5-14	0.3	0.4
15-24	0.3	0.6
25-34	0.2	0.6
35-44	0.3	0.6
45-54	0.3	0.6
55-64	0.4	0.7
65-74	0.7	1.0
75+	1.0	1.3



(a) *AIC SLX Model* **(b)** *AIC SLX FE Model*

Figure 3.2: *Akaike Information Criterion (AIC) estimated for different linear combinations of administrative and geographical weights. Indicated weights refers to the proportion of administrative weights. Left = SLX model. Right = SLX FE Model.*

ii. Additional estimated models

Table 3.4: *Regression results for alternative estimated channels. Dependent variable: (Log) prescribed antibiotics per 1000 STARPU patients*

	SLX FE	SLXFE	SEM FE	SAR FE
		CCG*Year Interactions		
Year 2014	0.003	-0.049	-0.028***	-0.056***
	(0.020)	(0.052)	(0.004)	(0.008)
Year 2015	-0.039**	-0.100.	-0.067***	-0.080***
	(0.013)	(0.053)	(0.002)	(0.011)
Year 2016	-0.069***	-0.118*	-0.094***	-0.118***
	(0.017)	(0.053)	(0.003)	(0.016)
Year 2017	-0.130***	-0.092.	-0.140***	-0.244***
	(0.019)	(0.053)	(0.003)	(0.007)
(Log of) total patients	-0.223***	-0.226***	-0.240***	0.005***
	(0.008)	(0.008)	(0.007)	(0.001)
Female patients	0.001	0.002	0.004**	0.004***
	(0.002)	(0.002)	(0.001)	(0.001)
Over 65 patients	0.002.	0.001	0.004***	0.011***
	(0.001)	(0.001)	(0.001)	(0.002)
GP density (head counts)	0.013***	0.015***	0.012***	0.011.
	(0.002)	(0.002)	(0.002)	(0.000)
Female GPs	0.001*	0.001**	0.001.	0.001***
	(0.000)	(0.000)	(0.000)	(0.000)
Under 40 GPs	0.001***	0.001***	0.001***	0.001**
	(0.000)	(0.000)	(0.000)	(0.000)
Foreign GPs	0.001.	0.001**	0.001**	0.038***
	(0.000)	(0.000)	(0.000)	(0.002)
Nurse density (head counts)	0.036***	0.034***	0.038***	0.001*
	(0.003)	(0.003)	(0.002)	(0.000)
QOF score	0.001	0.001	0.001*	0.016***
	(0.000)	(0.000)	(0.000)	(0.002)
Prevalence: asthma	0.016***	0.017***	0.016***	-0.004***
	(0.002)	(0.002)	(0.002)	(0.001)
Prevalence: diabetes mellitus	-0.005***	-0.003***	-0.004***	0.001***
	(0.001)	(0.001)	(0.001)	(0.000)
Good appointment experience	0.001***	0.001***	0.001***	0.001
	(0.000)	(0.000)	(0.000)	(0.000)
Caring responsibilities	0.001	0.001	0.001	0.001
	(0.000)	(0.000)	(0.000)	(0.000)
Unemployed patients	0.001	0.001	0.001	-0.033**
	(0.000)	(0.000)	(0.000)	(0.011)
GP contract: APMS	-0.047***	-0.049***	-0.036***	-0.012***
	(0.012)	(0.012)	(0.011)	(0.003)
GP contract: PMS	-0.001	0.004	-0.010**	0.004
	(0.004)	(0.004)	(0.003)	(0.011)
GP contract: PCTMS	0.019	-0.028		
	(0.015)	(0.020)		
Letters from CMO	0.008*	0.004		
	(0.004)	(0.004)		
(Log of) total patients W.01	-1.462***	-1.453***		
	(0.235)	(0.336)		
Female patients W.01	0.104**	0.256***		
	(0.034)	(0.074)		

Over 65 patients W.01	0.091***	-0.037		
	(0.025)	(0.041)		
GP density (head counts) W.01	-0.241*	-0.225·		
	(0.095)	(0.127)		
Female GPs W.01	0.005*	0.008**		
	(0.002)	(0.003)		
Under 40 GPs W.01	0.002	0.005		
	(0.002)	(0.003)		
Foreign GPs W.01	0.001	0.001		
	(0.001)	(0.002)		
Nurse density (head counts) W.01	0.170	0.412*		
	(0.125)	(0.165)		
QOF score W.01	0.001	0.012·		
	(0.004)	(0.006)		
Prevalence: asthma W.01	0.010	-0.165·		
	(0.061)	(0.094)		
Prevalence: diabetes mellitus W.01	-0.003	0.001		
	(0.004)	(0.004)		
Good appointment experience W.01	-0.001	0.003		
	(0.005)	(0.006)		
Caring responsibilities W.01	0.011	-0.009		
	(0.009)	(0.011)		
Unemployed patients W.01	-0.006	-0.046**		
	(0.012)	(0.015)		
GP contract: APMS W.01	3.711***	1.759*		
	(0.562)	(0.750)		
GP contract: PMS W.01	-0.397***	-0.468***		
	(0.077)	(0.138)		
GP contract: PCTMS W.01	-0.878***	-1.399***		
	(0.213)	(0.346)		
Letters from CMO W.01	-0.020	-0.028		
	(0.042)	(0.090)		
Constant	4.012·	8.547*	8.596***	-0.026***
	(2.195)	(4.238)	(0.098)	(0.004)
ρ	-	-	-0.961** (0.332)	-
λ	-	-	-	0.133 (0.097)
Observations	35,840	35,840	35,840	35,840
R^2	0.355	0.390		
Adjusted R^2	0.192	0.214		
F Statistic	27.53*** (df = 7207; 28632)	20.159 (df = 883; 27789)		

Note: *p<0.1; **p<0.05; ***p<0.01

Table 3.5: *Regression results. Antibiotics prescriptions vs broad spectrum antibiotics*

	Dependent variable:			
	(Log of) prescribed antibiotics per 1000 STARPU patients			
	All antibiotics		Broad spectrum antibiotics	
	SLX	SLX FE	SLX	SLX FE
Year 2014	0.230***	0.003	0.229***	0.003
	(0.029)	(0.020)	(0.060)	(0.038)
Year 2015	−0.052***	−0.039**	−0.099***	−0.096**
	(0.015)	(0.018)	(0.028)	(0.038)
Year 2016	−0.245***	−0.069***	−0.365***	−0.222***
	(0.024)	(0.024)	(0.046)	(0.050)
Year 2017	−0.121***	−0.130***	−0.257***	−0.368***
	(0.018)	(0.032)	(0.034)	(0.060)
(Log of) registered patients	0.004	−0.223***	0.051***	−0.116***
	(0.004)	(0.034)	(0.006)	(0.044)
Female patients (%)	0.010***	0.001	0.018***	−0.003
	(0.001)	(0.005)	(0.002)	(0.008)
Over 65 patients (%)	0.004***	0.002	0.013***	0.010**
	(0.0003)	(0.003)	(0.001)	(0.005)
GP density (Head counts)	0.010**	0.013	0.030***	0.029**
	(0.005)	(0.009)	(0.009)	(0.014)
Female GPs (%)	−0.0004***	−0.0001	−0.001***	−0.0004***
	(0.0001)	(0.0001)	(0.0001)	(0.0001)
Under 40s GPs (%)	−0.0004***	−0.0003***	−0.001***	−0.0005***
	(0.0001)	(0.0001)	(0.0001)	(0.0002)
Foreign GPs (%)	0.001***	0.0001	0.0002*	0.0001
	(0.00005)	(0.0001)	(0.0001)	(0.0001)
Nurse density (head counts)	0.066***	0.036***	0.043***	0.027*
	(0.007)	(0.011)	(0.010)	(0.015)
QOF points (%)	−0.002***	−0.0002	−0.002***	−0.001
	(0.0003)	(0.0003)	(0.0004)	(0.0005)
Prevalence: asthma	0.039***	0.016***	0.039***	0.013*
	(0.002)	(0.004)	(0.003)	(0.007)
Prevalence: diabetes mellitus	0.012***	−0.005***	0.002	−0.007***
	(0.001)	(0.001)	(0.002)	(0.002)
Good appointment experience(%)	−0.001***	0.001***	−0.002***	0.0005
	(0.0002)	(0.0002)	(0.0002)	(0.0003)
Patients with caring responsibilities (%)	0.004***	−0.0001	0.006***	−0.0003
	(0.0003)	(0.0002)	(0.001)	(0.0004)
Unemployed patients (%)	0.003***	0.0002	0.003***	0.001
	(0.0004)	(0.0003)	(0.001)	(0.001)
GP contract: APMS	0.068***	−0.047	0.076***	−0.091
	(0.018)	(0.038)	(0.021)	(0.056)
GP contract: PMS	0.007**	−0.001	0.010*	−0.019
	(0.003)	(0.005)	(0.006)	(0.012)
GP contract: PCTMS	−0.069**	0.019	−0.005	0.081*
	(0.034)	(0.027)	(0.057)	(0.043)
Letters from CMO	0.281***	0.008**	0.348***	−0.007
	(0.006)	(0.004)	(0.013)	(0.008)
(Log of) registered patients W0.1	0.037	−1.462***	0.090	−2.280***
	(0.076)	(0.487)	(0.145)	(0.758)
Female patients (%) W0.1	−0.026	0.104**	−0.161***	0.075
	(0.017)	(0.047)	(0.032)	(0.090)

Table 3.5: *Regression results. Antibiotics prescriptions vs broad spectrum antibiotics*

Over 65 patients (%) W0.1	−0.021**	0.091***	−0.128***	0.101
	(0.008)	(0.034)	(0.017)	(0.075)
GP density (head counts) W0.1	−1.249***	−0.241**	−0.598**	−1.019***
	(0.129)	(0.116)	(0.244)	(0.271)
Female GPs (%) W0.1	0.006***	0.005*	0.029***	0.015***
	(0.002)	(0.003)	(0.004)	(0.006)
Under 40 GPs (%) W0.1	−0.002	0.002	−0.057***	0.013*
	(0.003)	(0.004)	(0.006)	(0.007)
Foreign GPs (%) W0.1	0.009***	0.001	0.008***	0.001
	(0.001)	(0.001)	(0.002)	(0.002)
Nurse density (%) W0.1	1.282***	0.170	0.500	0.681**
	(0.173)	(0.204)	(0.328)	(0.336)
QOF points (%) W0.1	−0.005	0.001	0.073***	0.019
	(0.004)	(0.006)	(0.008)	(0.012)
Prevalence: asthma W0.1	0.212***	0.010	−0.232***	−0.264
	(0.033)	(0.078)	(0.061)	(0.169)
Prevalence: diabetes mellitus W0.1	−0.042***	−0.003	−0.067***	0.001
	(0.007)	(0.004)	(0.013)	(0.007)
Good appointment (%) W0.1	0.004	−0.001	0.046***	−0.031**
	(0.004)	(0.007)	(0.008)	(0.013)
Caring responsibilities (%) W0.1	0.033***	0.011	0.117***	−0.00002
	(0.011)	(0.011)	(0.022)	(0.021)
Unemployed patients (%) W0.1	−0.062***	−0.006	−0.173***	0.035
	(0.011)	(0.015)	(0.021)	(0.031)
GP contract: APMS W0.1	5.827***	3.711***	6.284***	8.532***
	(0.447)	(1.250)	(0.511)	(1.870)
GP contract: PMS W0.1	−0.327***	−0.397***	−0.579***	−0.118
	(0.065)	(0.100)	(0.129)	(0.234)
GP contract: PCTMS W0.1	0.650*	−0.877**	1.422**	−1.860***
	(0.383)	(0.364)	(0.692)	(0.597)
Letters from CMO W0.1	−0.563***	−0.020	−0.497***	0.176**
	(0.073)	(0.040)	(0.139)	(0.079)
Constant	6.286***		3.127***	
	(0.071)		(0.109)	
Observations	35,840	35,840	35,838	35,838
R^2	0.321	0.355	0.208	0.369
Adjusted R^2	0.321	0.192	0.207	0.210
F Statistic	424***	393***	234***	418***
F Statistic	df = 40; 35799)	(df = 40; 28632)	(df = 40; 35797)	(df = 40; 28630)

Note: *p<0.1; **p<0.05; ***p<0.01

Table 3.6: *Regression results: comparison of STARPU Items and percentage of antibiotics over all STARPU prescribed items.*

	Dependent variable: (Log of) prescribed items per 1000 STARPU patients (left) Percentage of prescribed antibiotic items (logs) over total prescribed items (logs) per 1000 STARPU patients (right)	
	SLX FE	SLX FE
	(1)	(2)
Year 2014	0.003	−0.003**
	(0.020)	(0.001)
Year 2015	−0.039**	−0.006***
	(0.018)	(0.001)
Year 2016	−0.069***	−0.010***
	(0.024)	(0.002)
Year 2017	−0.130***	−0.016***
	(0.032)	(0.002)
(Log of) registered patients	−0.223***	−0.007***
	(0.034)	(0.002)
Female patients (%)	0.001	0.0003
	(0.005)	(0.0003)
Over 65 patients (%)	0.002	−0.001***
	(0.003)	(0.0002)
GP density (Head counts)	0.013	0.001
	(0.009)	(0.001)
Female GPs (%)	−0.0001	−0.00000
	(0.0001)	(0.00001)
Under 40s GPs (%)	−0.0003***	−0.00001**
	(0.0001)	(0.00001)
Foreign GPs (%)	0.0001	0.00001
	(0.0001)	(0.00000)
Nurse density (head counts)	0.036***	0.0004
	(0.011)	(0.001)
QOF points (%)	−0.0002	−0.00000
	(0.0003)	(0.00002)
Prevalence: asthma	0.016***	0.001***
	(0.004)	(0.0002)
Prevalence: diabetes mellitus	−0.005***	−0.001***
	(0.001)	(0.0001)
Good appointment experience(%)	0.001***	0.0001***
	(0.0002)	(0.00001)
Patients with caring responsibilities (%)	−0.0001	−0.00001
	(0.0002)	(0.00001)
Unemployed patients (%)	0.0002	0.00003
	(0.0003)	(0.00003)
GP contract: APMS	−0.047	−0.002
	(0.038)	(0.002)
GP contract: PMS	−0.001	−0.001
	(0.005)	(0.0004)
GP contract: PCTMS	0.019	0.002
	(0.027)	(0.003)
Letters from CMO	0.008**	0.0002
	(0.004)	(0.0003)
(Log of) registered patients W0.1	−1.462***	−0.162***
	(0.487)	(0.038)
Female patients (%) W0.1	0.104**	0.011***

Table 3.6: *Regression results: comparison of STARPU Items and percentage of antibiotics over all STARPU prescribed items.*

	(0.047)	(0.004)
Over 65 patients (%) W0.1	0.091***	0.008***
	(0.034)	(0.003)
GP density (head counts) W0.1	−0.241**	−0.026***
	(0.116)	(0.009)
Female GPs (%) W0.1	0.005*	0.001***
	(0.003)	(0.0002)
Under 40 GPs (%) W0.1	0.002	0.0002
	(0.004)	(0.0003)
Foreign GPs (%) W0.1	0.001	0.0001**
	(0.001)	(0.0001)
Nurse density (%) W0.1	0.170	0.011
	(0.204)	(0.014)
QOF points (%) W0.1	0.001	0.0004
	(0.006)	(0.0004)
Prevalence: asthma W0.1	0.010	0.002
	(0.078)	(0.006)
Prevalence: diabetes mellitus W0.1	−0.003	0.0001
	(0.004)	(0.0003)
Good appointment (%) W0.1	−0.001	−0.0002
	(0.007)	(0.001)
Caring responsibilities (%) W0.1	0.011	0.0003
	(0.011)	(0.001)
Unemployed patients (%) W0.1	−0.006	0.001
	(0.015)	(0.001)
GP contract: APMS W0.1	3.711***	0.327***
	(1.250)	(0.095)
GP contract: PMS W0.1	−0.397***	−0.038***
	(0.100)	(0.008)
GP contract: PCTMS W0.1	−0.877**	−0.081**
	(0.364)	(0.033)
Letters from CMO W0.1	−0.020	−0.0004
	(0.040)	(0.003)
Observations	35,840	35,840
R^2	0.355	0.419
Adjusted R^2	0.192	0.273
F Statistic (df = 40; 28632)	393.278***	516.895***

Note: *p<0.1; **p<0.05; ***p<0.01

Chapter 4

A Dynamic Approach to Pharmaceutical Regulation: Value-based Pricing versus Welfare Maximisation

I. Introduction

This paper analyses the dynamic effects of price and patent regulation in a market with R&D. We analyse how market prices influence the trade-off between static and dynamics welfare optimisation, when an innovating firm is allowed to gain profits from its endogenous R&D activities. We explore the relationship between price and patent length, when the latter is allowed to vary. Lastly, we explore different policy schemes, including a Value-Based Pricing scenario (VBP) in which price is set as a fixed proportion of expected health benefits of the produced drugs.[1] [2]

Pharmaceuticals is a highly regulated market (Handoo et al., 2012). While the development of new drugs has provided high benefits for consumers in improving treatment and prevention of specific conditions (Weisfeldt and Zieman, 2007) and produced overall positive social benefits (Garthwaite (2012), Thanh et al. (2012), Lichtenberg (2007), Murphy and Topel (2006)), pharmaceutical prices have been rising steadily in several healthcare systems (Cameron et al. (2015), Cameron et al. (2015), Carone et al. (2012)). The steady increase in pharmaceutical costs raised the question of price containment to ensure drugs sustainability for healthcare systems (Zaprutko et al., 2017). At the same time, some authors indicated the need for a certain degree of market power by innovating firms to allow for the development of new drugs (Grabowski and Vernon, 1992). The achieved market power arising from patents and intellectual property rights, while allowing for innovation, might induce a certain degree of rent-seeking behaviour, where firms provide an innovation rate disproportionally low compared to the realised profits (Scherer, 2010). Balancing the need for innovation in pharmaceuticals, which leads to improved health outcomes for patients, with the potential for rent-seeking risks might be challenging in a market prone to moral hazard.

The regulation of pharmaceutical markets aims at maximising social welfare, in this paper we take into consideration two approaches to efficiency: static and dynamic. Static efficiency maximises social welfare in the current period. Dynamic efficiency, on the contrary, ensures that the optimal degree of innovation is achieved inter-temporally to maximise social welfare. Analysing the trade-off between static and dynamic efficiency is key when considering a market in which the regulator aims to optimise welfare, while at the same time requiring for innovation.

[1] This paper is a joint work with Prof. Alistair McGuire (LSE), Mireia Jofre-Bonet (City, University of London), and Sabine Grimm (Maastricht University Medical Centre).

[2] I am grateful to Shira Fano from Fondazione Nord Est for her useful comments on this chapter.

The study of the inter-play between the alternative goals of welfare maximisation and innovation originated with the analysis of patent protection, which dates back to the seminal work by Arrow (1962). The theory of patent protection analyses how the correct patent can be achieved, allowing innovators to be endowed with intellectual property rights, while at the same time avoiding the risks of dead-weight losses arising from monopolies (see Nordhaus (1969) and Scherer (1972) for an early formalisation of these concepts). Scherer (1972) later identified this optimal patent length to be finite and positive. Further contributions on the topic of patent protection were provided by Tirole (2002), who indicated that the definition of optimal R&D efforts were difficult to estimate in a setting with uncertain investment returns. The author, however, clearly indicated that the welfare effects of innovation depended on the degree of patent protection, with low patent protection leading to reduced R&D efforts, and viceversa.

The empirical literature on pharmaceutical markets appears to have identified a degree of overprotection when it comes from patent length. For example, Arora et al. (2008) found a 10% patent premium in pharmaceutical products compared to other patent protected markets. Alternative studies exploring the implications of patents on influencing the static versus dynamic trade-off identified that a no-patent scenario would increase immediate consumer surplus, while reducing the surplus of future consumers by three times (Hughes, Moore and Snyder). Similarly, Horowitz and Lai (1996) identified that the degree of patent protection that would optimise the amount of innovation exceeded the degree of patent protection required to optimise surplus. These studies thus highlight the need for the social planner to strike the right balance between innovation and welfare.

An alternative strand of empirical literature analysed how price regulation might negatively affect pricing of generics, influencing time to market and reducing patent protection (Danzon et al. (2000), Danzon et al. (2005), Kyle (2007)). While these studies provide useful indications on the implications of price regulation in pharmaceuticals, they provide no welfare considerations, nor conceptual frameworks for the analysis of such effects. When looking at the drivers of R&D decisions of innovating firms, Civan and Maloney (2007) identify that innovation is positively linked to the price of existing drugs treating similar conditions. Similarly, Dubois et al. (2015) found that elasticity of innovation positively depended on expected market size of the new drug. These studies thus show that price regulation might thus influence innovation dynamics.

There exists a small theoretical literature analysing optimal pricing under reference pricing, one of the most diffused price regulations of pharmaceuticals (see Merino (2000), Brekke (2007), Miraldo (2010) and Ghislandi (2011)). The key contribution of these studies stands in the understanding of the endogenous nature of reference pricing. Generally speaking, all of these models identify a reduction in consumer surplus following the introduction of price regulation. These studies thus identify the potential distortionary effects of price regulation (although patent length plays no role).

When analysing market innovation, it is important to identify the factors leading to the creation of new drugs. The small number of theoretical studies analysing pharmaceutical innovation propose a positive relationship between R&D investments and the development of new drugs (Camejo et al. (2011), Bardey et al. (2010) and Isaac and Reynolds (1988)). Investments are, in turn, influenced by expected revenues of new drugs, market uncertainty, revenue appropriability, market size, the degree of competition, demographic factors and intellectual property protection. The regulatory environment is generally found to have a negative impact on innovation. From an empirical perspective Grabowski and Vernon (1992), and later Vernon (2005), found that expected returns and firm's cashflows were important determinants of investments. Dubois et al. (2015) and Acemoglu and Linn (2004) identify a similar positive effect given by market size. Giaccotto et al. (2005) identifies that a 10% increase in pharmaceutical prices results in a 6% increase in R&D investment, thus highlighting an important relationship between price and investments. In line with this strand of literature, we find that price regulation in the pharmaceutical market might affect the amount of R&D investments and innovation via the impact on expected revenues and internal finance. Distortionary effects could potentially be offset by patent protection. The interplay between price and patent regulation has received little attention in the literature, thus the analysis of the endogenous dynamics of innovation stresses the need to explore this relationship more in detail.

All major European markets present a high degree of regulation (Panteli et al., 2016), with the majority of those markets being regulated via reimbursement schemes. Under this regulation product reimbursement affects innovative value, where the latter is determined by clinical evidence and the comparison of competing therapies (Bridges et al. (2009), Mossialos and Oliver (2005)). Alternatives based on value-based pricing, where pharmaceutical prices are based on drug's expected health benefits, have been proposed, however they have not been analysed in detail (Office of Health Economics (2007), Moise and Docteur (2007)). As stated by Claxton (2007), VBP might emphasize static welfare in order to compensate for firms' market power arising from patented pharmaceuticals. Although VBP aims at incentivising research in areas with high disease prevalence, the implementation of this policy might risk reducing welfare due to the long time between research and market entry of new drugs (McGuire et al., 2008). This may result in VBP jeopardising current welfare and reducing welfare outcomes in the long run. Determining welfare implications of VBP forms part of the motivation of this study.

Despite few efforts looking at the impact of VBP on demand elasticity (Yeung et al., 2018), to our knowledge, very little attention has been devoted to the analysis of the aforementioned topics. This paper aims at filling this gap by providing a dynamic two period model with R&D. Our analysis contributes to the literature by first identifying a trade-off between static and dynamic efficiency. We then provide an indication of the impact of price and patent regulation on overall welfare. We then show that VBP influences the market by altering price's impact on welfare. Our paper allows for an extension of the baseline model by comparing the results of welfare maximisation with an alternative framework where firm's profits are maximised. Our paper also provides some numerical illustrations based on realistic coefficients identified from the empirical literature.

This paper is organised as follows. Section 2 provides a brief literature review. Section 3 introduces the baseline model. Section 4 solves the model with a static and dynamic approach. Section 5 explores the trade-off between price and patent-length in terms of welfare. Section 6 introduces explores the implications of the introduction of a VBP regulation. Section 7 provides some modelling extensions. Section 8 reports numerical simulations. Section 9 concludes.

II. Literature review

Scherer (2010) provides an in-depth analysis of the empirical aspects of pharmaceutical innovation. In his review, the authors cites the work by DiMasi et al. (1991) and DiMasi et al. (2003) which identified an overall survival rate of new drugs (around 21%), with an indication of R&D costs being higher towards latter stages of drug development. The author also identified a link between gross margins and R&D investments, both presenting periodic fluctuations. Danzon et al. (2006) identified variation in success probabilities across therapeutic classes, with negative correlation with mean sales by category (consistently with dynamic competitive entry). DiMasi (2000) identifies a reduction in concentration of innovation in the pharmaceutical industry, with increased turnover in top producers and idiosyncratic differences in firm's innovation productivity. The importance of firm's characteristics was later confirmed by Kyle (2006). Cockburn (2006) identified a reduction in overall productivity of new drugs in the early 2000s, providing evidence of firms avoiding late stages of drug development on purely economic reasons. Highlighting the fragility of innovation in pharmaceutical markets, DiMasi and Paquette (2002) found a decrease in the time in which innovators enjoy the results of breakthroughs in new drug categories, following the diffusion of "me-too" drugs and suggesting a reduction in entry barriers. These specific types of drugs occur in those cases where an innovator develops a compound which is similar to existing ones to avoid huge research costs (Garattini, 1997). A similar increase in "addition to class" or "me too" drugs in the period 1987-2011 was found also by Lanthier et al. (2013). Harfhoff and Scherer (2000) showed that the distribution of the industry's portfolio is insufficiently diverse to eliminate significant variation in profits.

The earlier analyses on patent protection date back to the seminal work by Arrow (1962). Nordhaus (1969) then developed the idea further, explicitly modelling the trade-off between static and dynamic welfare, indicating that patent protection required a balance between social gains arising from innovation and cost reduction. In his analysis, the author identified an ambiguous effect of patent duration on welfare. Further work was developed by Nordhaus (1972) who extended the analysis to allow patent breadth in

influencing welfare results. With the introduction of patent breadth, the analysis was enriched by the degree to which innovation revenues can be appropriated by the innovator. The theory proposed by Nordhaus (1969) was later developed by Scherer (1972) who introduced an invention possibility function which linked innovation probability to R&D intensity. Under the new framework, welfare gains and losses due to variations in patent duration depended on price elasticity of demand, thus highlighting the link between price and patent.

Billette de Villemeur et al. (2019) develop a dynamic model of innovation with uncertainty, identifying that patents should be restrictive enough to provide sufficient incentive for innovation, however allowing for dynamic competition among innovators. Van Cayseele (1989) provides dynamic efficiency considerations introducing an analytical framework for optimal institutional arrangements for pharmaceutical patents. Frank and Salkever (1992) identify only limited variation in pharmaceutical prices following patent expiry. On the theoretical side, early works date back to the input by Dorfman and Steiner (1954), which indicates that profit maximising R&D investments should be increasing with price cost-margins (see Scherer (2010) for a simple explanation). More recent theories appeared to agree on the presence of rent-seeking behaviour, that is firms investing competitively in R&D to ensure monopoly gains. Early contributions on firm's rent-seeking behaviour date back to Krueger (1974). Boldrin and Levine (2013) argue against the need for patent, suggesting that patents lead to rent-seeking and sub-optimal innovation. The literature on innovation also looked at the optimal timing of innovation, with early studies highlighting the possibility of innovations being introduced prematurely in the market, when the latter were based on public knowledge (Barzel, 1968).

Puig-Junoy (2010) provides a detailed review of price regulation pharmaceuticals, identifying a levelling off of generic prices arising with price regulation. While tighter regulatory environments led to lower inflation in EU, the same regulatory environment appeared to have induced to a reduction in the number of new drugs developed in the same market (Golec and Vernon, 2010). Grabowski et al. (2017) identified that new regulatory environments might induce behavioural changes, with increased patent litigation from generic firms, following reduced branding periods. Cockburn et al. (2016) identify that patent and price protection affect the timing in which new drugs enter the market, with price regulation increasing the length of entrance of new drugs, and patent regulation reducing it. Jobjörnsson et al. (2016) find a non-monotonic relationship between willingness to pay and optimal pricing under reimbursement schemes. Using evidence from a natural experiment, Brekke et al. (2011) found a negative impact of reference pricing on the pricing of both branded and generic pharmaceuticals. Addressing the issue from a theoretical perspective, Brekke et al. (2016) found that reference pricing induces branded-name producers to price more aggressively, discouraging generic entry. Danzon et al. (2000b) found that strict price regulation tends to reduce prices for older and diffused molecules. Ekelund and Persson (2006) found a negative relation between price regulation and competition among branded drugs.

Value-Based Pricing (VBP) aims to achieve a balance between static and dynamic efficiency (Danzon, 2018). Sussex et al. (2010) show that VBP, when not intended as a simple function of realised Quality-Adjusted Life Years (QALY), requires to be considered as a multi-criteria assessment, including subjective considerations. Similarly, Garner et al. (2018) suggests that there is no clear definition of value associated to drugs. Pauly (2017) shows that there is not ordinarily a single VBP, but rather a schedule of different prices associated with varying volumes of buyers at each price. Levaggi (2014), while confirming that price regulation has distortionary effects on the market, identifies that value-based pricing is a preferable option compared to price bargaining when it comes to welfare maximisation.

III. The model

In this paper, we present a highly stylized welfare function associated to pharmaceutical innovation. Our benchmark model includes the determinants of innovation, R&D intensity and generic entry. We first provide the results for optimal prices with fixed patent length. We then introduce comparative static exercises to explore the trade-off in terms of welfare between applying a dynamic approach and applying a static one. Subsequently, we provide comparative static results when patent length is allowed to vary. We also introduce a number of policy considerations, including a model to explore the impact of VBP on

market dynamics. Lastly, we propose a number of model extensions.

i. The baseline model

We introduce a model whose social welfare baseline function is the result of the sum of the producer surplus (PS) generated by an innovating firm and the associated consumer surplus (CS) resulting from the drugs introduced in the market. Our model includes a social planner (interested in maximising social welfare), an innovating firm, a set of consumers consuming drugs, and a competitive fringe. The baseline model we propose is composed of two periods. In each period, an individual drug is launched. We use the index i to indicate individual drugs, hence $i = 1, 2$. To focus on the impact of price and patent regulation on R&D dynamics, we assume that each drug has a commercial life-span of $T > 0$. Each drug has a fixed launch date τ_i. For simplicity we assume that the first drug is available at the beginning of time, hence $\tau_1 = 0$. For the moment we assume a fixed patented length $s > 0$, which is equal for each drug. We incorporate the uncertainty surrounding R&D by including the term ρ_i, indicating the probability of successful innovation. For simplicity we assume that drug 1 is already available on the market at the start. We assume R&D costs to be a fixed amount R_1. This is in line with Camejo et al. (2011) who indicate that R&D costs are paid in the early stages of drug development. We assume fixed marginal costs mc_i for each product i. Each drug has a patented period followed by an out-of-patent period. We use the suffix g to indicate the non-patented sub-period, while we use no suffix to indicate the patented period. During the patented period all consumers use the branded version of the drug. During the patented period the firm sells quantity Q_i^m at a price p_i. After the patent expires generic entry occurs straight away (Hughes (Moore and Snyder)). Competition is represented by a competitive fringe entering the market.[3]. The competitive fringe has supply function equal to Q_i^f, with Q_i^f being twice differentiable and increasing in price. After patent expiration, the original firm is left with a fraction of the demand, defined as $Q_i^D = Q_i^M - Q_i^f$. In the baseline model, all the indicated parameters are assumed to be constant over time. For simplicity we assume a linear demand function of the form $p_i^m = a_i^m - b_i^m Q_i^m$. We assume Q_i^m and Q_i^d to be twice differentiable and decreasing with price. We assume Q_i^f to be twice differentiable and increasing with price. More specifically, we assume $q_i^f = a_i^f + b_i^f p_i$ The generic expression of CS and PS for a generic product $i = 1, 2, ...$, can thus be defined as

$$\begin{aligned} CS(p_i, s) &= \int_0^s e^{-rt} \tfrac{1}{2}(a_i^M - p_i) q_i^M dt + \int_s^T e^{-rt} \tfrac{1}{2} \left(\tfrac{b_i^f a_i^M + b_i^M a_i^f}{b_i^f + b_i^m} - p_i^g \right) q_i^d dt \\ &+ \int_s^T e^{-rt} [\tfrac{1}{2}(a_i^M + \tfrac{b_i^f a_i^M + b_i^M a_i^f}{b_i^f + b_i^M}) - p_i^g] q_i^f dt \end{aligned} \tag{4.1}$$

Similarly, PS for any drug i becomes

$$\begin{aligned} PS(p_i, s) &= \int_0^s e^{-rt} (p_i - mc_i) q_i^M dt + \int_s^T e^{-rt} (p_i^g - mc_i) q_i^d dt \\ &+ \int_s^T e^{-rt} \tfrac{1}{2} (p_i^g - a_i^f) q_i^f dt \end{aligned} \tag{4.2}$$

The social welfare associated to a drug over its lifetime can thus be written as:

$$\begin{aligned} W(p_i, s) &= \int_0^s e^{-rt} [\tfrac{1}{2}(a_i^M + p_i) - mc_i] q_i^M dt + \int_s^T e^{-rt} [\tfrac{1}{2} [(\tfrac{b_i^f a_i^M + b_i^m a_i^f}{b_i^m + b_i^f}) + p_i^g] - mc_i] q_i^d dt \\ &+ \int_s^T e^{-rt} \tfrac{1}{2} [(a_i^M - a_i^f + \tfrac{b_i^f a_i^M + b_i^M a_i^f}{b_i^f + b_i^M}) - p_i^g] q_i^f dt \end{aligned} \tag{4.3}$$

We present a version of the model with two products $i = 1, 2$ launched at different times whereas the R&D of product 2 depends on the profits made from the commercialisation of product 1. We assume that product 2 is launched at a time $t = \tau$, which we assume to be fixed. The launch occurs with a probability $\rho_2 > 0$ which is a function of R&D investments which are a fraction of the firm's period 1 profits. We also introduce a generic expression of R&D costs $R > 0$. The social welfare in a two period model is thus given by the social welfare from drug one plus the expected welfare from drug 2.

[3]Our model of competitive fringe is based on the model proposed by Church and Ware (2000) A graphical intuition of this model in a generic case is provided in Figure 4.3 in the appendix

The social welfare thus becomes

$$
\begin{aligned}
&W(p_1,p_2,s)=\int_0^s e^{-rt}[\tfrac{1}{2}(a_1^M+p_1)-mc_1]q_1^M dt+\int_s^T e^{-rt}[\tfrac{1}{2}[(\tfrac{b_1^f a_1^M+b_1^m a_1^f}{b_1^m+b_1^f})+p_1^g]-mc_1]q_1^d dt\\
&+\int_s^T e^{-rt}\tfrac{1}{2}[(a_1^M-a_1^f+\tfrac{b_1^f a_1^M+b_1^M a_1^f}{b_1^f+b_1^M})-p_1^g]q_1^f dt\\
&+\rho_2\int_\tau^{\tau+s} e^{-rt}[\tfrac{1}{2}(a_2^M+p_2)-mc_2]q_2^M dt+\int_{\tau+s}^{\tau+T} e^{-rt}[\tfrac{1}{2}[(\tfrac{b_2^f a_2^M+b_2^m a_2^f}{b_2^m+b_2^f})+p_2^g]-mc_2]q_2^d dt\\
&+\int_{\tau+s}^{\tau+T} e^{-rt}\tfrac{1}{2}[(a_2^M-a_2^f+\tfrac{b_2^f a_2^M+b_2^M a_2^f}{b_2^f+b_2^M})-p_2^g]q_2^f dt-R_2
\end{aligned}
\tag{4.4}
$$

We model innovation using an Innovation Probability Function (IPF). Our IPF incorporates 2 factors: R&D intensity, and the innovation production function. According to Grabowski and Vernon (1992) and Vernon (2005) firm's R&D decisions depend on the cash flow by profits or products currently in the market, and on the expected return to R&D obtained through future profits. We thus assume that R&D costs, R_2, to be a fraction m of the revenues generated in the previous patented period, with $0<m<1$.[4] Hence we define $\int_0^s ump_1q_1^m dt$, which simplifies to $\frac{1}{r}ump_1q_1^m(1-e^{rs})$. The literature on R&D expenditures and its relationship to innovation is limited. One strand of literature focused on a "low hanging fruit" scenario. Jensen (1987) found a correlation between R&D expenditures and the probability of drug discovery and that probability decreased over the examined time. Later studies have confirmed this (Pammolli et al., 2011). Everson (2003) stated that opportunities of drug discovery might be finite with easy targets exhausted first. This would lead to increasing efforts required to achieve a research success. These hypotheses encourage the use of an IPF with decreasing marginal productivity. As Baily (1972) noted, the IPF should not depend on R&D expenditure alone but if so, then the function should exhibit diminishing marginal returns. Further work on the IPF has been done by Arora et al. (2008) who modelled the number of innovations depending on R&D expenditure employing the elasticity of innovation as a main factor. A second strand of literature, namely the models analysing the relation between rent seeking behaviour and innovation, allowed for a deterministic innovation (see for example the work by Boldrin and Levine (2013)). For ease of analysis we follow this second strand of literature. More specifically, we assume a fixed cost K for innovation. We assume that the firm pays for this amount using its stream of profits generated during the patented part of period 1. We assume that prior to reaching this amount innovation might occur with a given probability. Upon reaching this amount, the innovation is certain[5]. We assume that the firm invests a fraction m of its profits into R&D activities, with $0<m<1$.

$$
h(p_1^s,s)=\frac{\rho_2}{K} \tag{4.5}
$$

The IPF simplifies to

$$
h(p_1^s,s)=\frac{\frac{1}{r}ump_1q_1^m(1-e^{rs})}{K} \tag{4.6}
$$

where u is a scaling parameter. The expression of the social welfare with the two drugs model thus becomes.[6]

$$
\begin{aligned}
&W(p_1,p_2,s)=[\tfrac{1}{2}(a_1^M+p_1)-mc_1]q_1^M(1-e^{-rs})\\
&+[\tfrac{1}{2}[(\tfrac{b_1^f a_1^M+b_1^m a_1^f}{b_1^m+b_1^f})+p_1^g]-mc_1]q_1^m(e^{-rs}-e^{-rT})+[\tfrac{1}{2}(a_1^m-a_1^f)+mc_1-p_1^g]q_1^f(e^{-rs}-e^{-rT})]\\
&+\tfrac{ump_1q_1^m(1-e^{-rs})}{rK}e^{-r\tau}\Big[[\tfrac{1}{2}(a_2^M+p_2)-mc_2]q_2^M(1-e^{-rs})+[\tfrac{1}{2}[(\tfrac{b_2^f a_2^M+b_2^m a_2^f}{b_2^m+b_2^f})+p_2^g]-mc_2]q_2^m(e^{-rs}-e^{-rT})\\
&+[\tfrac{1}{2}(a_2^m-a_2^f)+mc_2-p_2^g]q_2^f(e^{-rs}-e^{-rT})\Big]\\
&-\tfrac{1}{r}ump_1q_1^m(1-e^{-rs})
\end{aligned}
\tag{4.7}
$$

where we assume that $mc_i\leq p_i(1-um)$, so as to ensure that R&D costs are always lower than net profits.

[4] At this stage the fraction m of profits invested in R&D is assumed to be fixed. We will relax this assumption later on in the analysis.

[5] Note that reaching the amount K might induce strategic behaviour concerning the timing of the introduction of new drugs. For the moment we assume no strategic delay.

[6] Notice that as $um\leq 1$, we have that R&D costs are always lower or equal to the firm's profits.

IV. Results with fixed patent length

We now solve the two-period welfare maximisation problem defined in equation 4.7, assuming a fixed patent length s. We first identify the optimal prices. We then explore the static versus dynamic trade-off.

The comparative static results presented in the following pages aim to provide intuitions of the dependency of social welfare and prices on model parameters. As the expressions provided in this framework could not be solved analytically, illustrations of model solutions are provided via numerical simulations.

i. Optimal prices with fixed patent length

With a fixed patent length s, the prices maximising welfare is set by the social planner are:

$$\begin{aligned} p_1^* &= \tfrac{umK}{rK+um(W_2-K)}[(\tfrac{W_2-K}{K})a_1^m + \tfrac{r}{um}mc_1] \\ p_1^{s*} &= a_1^m + \tfrac{1}{2}(\tfrac{b_1^f a_1^m + b_1^m a_1^f}{b_1^m + b_1^f} + mc_1 - a_1^f) \\ p_2^* &= mc_2 \\ p_2^{s*} &= a_2^m + \tfrac{1}{2}(\tfrac{b_2^f a_2^m + b_2^m a_2^f}{b_2^m + b_2^f} + mc_2 - a_2^f) \end{aligned} \tag{4.8}$$

Proof: provided in the appendix.

Discussion: with the exception of the patented period of period 1, a welfare maximising social planner will always select prices that minimize the dead-weight loss arising from the firm's market power. The social planner will allow some market power for the firm in period 1 in order to allow for R&D activities. In this case prices during the patented part of period 1 will positively depend on marginal costs and the prices in period 2.

ii. Welfare and price

We now explore the impact of varying prices on consumer surplus, producer surplus and social welfare.

Starting from the generic expression of consumer surplus, an increase of the during-patent price of product 1 will directly affect CS in period 1 and producer surplus in period 1 associated to that product. The revenues during the patented life of product 1 will be higher and this will have a positive impact on the level of R&D invested in the development of a second period product and the probability that this investment is successful. All other components in the welfare function will not be affected by an increase in the first product price. We can therefore write

$$\begin{aligned} \tfrac{\partial CS}{\partial p_1} &= \tfrac{\partial CS_1}{\partial p1} + \tfrac{\partial \rho_2}{\partial p_1} CS_2 \\ \tfrac{\partial PS}{\partial p_1} &= \tfrac{\partial PS_1}{\partial p_1} + \tfrac{\partial \rho_2}{\partial p_1} PS_2 - \tfrac{R_2}{\partial p_1} \end{aligned} \tag{4.9}$$

Thus, $\frac{\partial W}{\partial p_1} > 0$ iff $|\frac{\partial CS_1}{\partial p_1} - \frac{\partial R_2}{\partial p_1}| < \frac{\partial PS_1}{\partial p_1} + \frac{\partial \rho_2}{\partial p_1}(CS_2 + PS_2)$ (a proof is provided in the appendix).

This expression tells us that welfare increases with price of product 1 only if the first period loss in terms of CS minus the loss in R&D (R_2) is smaller than the gain from increase in both periods PS plus the increase in the future product. R&D investment thus has an ambiguous effect on welfare: the larger R&D is, the smaller becomes the producer surplus, due to the increased R&D costs in period 1, and the larger becomes the future welfare due its impact on the innovation probability.

Given the specifications provided to social welfare, we have that the net effect of a patented period 1 price increase in social welfare is higher than zero provided that price is lower than a threshold price p_1^*,

indicated in expression 4.8.

A graphical intuition of this result is provided in the appendix.

Proof: provided in the appendix.

V. Results with varying patent length

We now consider the dynamics of model 4.7, when patent length s is allowed to vary.

i. Optimal patent length

The optimal patent length is the

$$\begin{aligned}
&\text{argmax}_s\, W = \text{argmax}_s[\tfrac{1}{2}(a_1^M + p_1) - mc_1]q_1^M(1-e^{-rs}) \\
&+[\tfrac{1}{2}[(\tfrac{b_1^f a_1^M + b_1^m a_1^f}{b_1^m + b_1^f}) + p_1^g] - mc_1]q_1^m(e^{-rs} - e^{-rT}) + [\tfrac{1}{2}(a_1^m - a_1^f) + mc_1 - p_1^g]q_1^f(e^{-rs} - e^{-rT})] \\
&+\tfrac{ump_1q_1^m(1-e^{-rs})}{rK}e^{-r\tau}\Big[[\tfrac{1}{2}(a_2^M + p_2) - mc_2]q_2^M(1-e^{-rs}) + [\tfrac{1}{2}[(\tfrac{b_2^f a_2^M + b_2^m a_2^f}{b_2^m + b_2^f}) + p_2^g] - mc_2]q_2^m(e^{-rs} - e^{-rT}) \\
&+[\tfrac{1}{2}(a_2^m - a_2^f) + mc_2 - p_2^g]q_2^f(e^{-rs} - e^{-rT})\Big] \\
&-\tfrac{1}{r}ump_1q_1^m(1-e^{-rs})
\end{aligned} \tag{4.10}$$

The expression of optimal patent length s^* is analytically complex.[7] An analysis of the optimal patent length is provided in the numerical simulation section.

ii. Impact on welfare from varying patent length

We explore the impact of a varying patent length on consumer surplus, producer surplus and social welfare.

The impact of a variation in patent length is defined by

$$\begin{aligned}
\tfrac{\partial CS}{\partial s} &= \tfrac{\partial CS_1}{\partial s} + \tfrac{\partial \rho_2}{\partial s}CS_2 + \rho_2\tfrac{\partial CS_2}{\partial s} \\
\tfrac{\partial PS}{\partial s} &= \tfrac{\partial PS_1}{\partial s} + \tfrac{\partial \rho 2}{\partial s}PS_2 + \rho_2\tfrac{\partial PS_2}{\partial s} - \tfrac{\partial \rho_2}{\partial s}
\end{aligned} \tag{4.11}$$

An extension of patent length s will directly affect CS and PS in both periods by extending the duration of the firm's monopoly. An extension of the firm's market power will impact R&D investments, as additional funds will be available, thus influencing the innovation probability.
The extension of the period will alter the consumer and producer surplus in the second period by altering the composition of the competitive and non-competitive portion of total drug's lifetime.

The expression of a variation of patent length on social welfare stems from solving:

$$\frac{\partial W}{\partial s} = \frac{\partial W_1}{\partial s} + \frac{\partial \rho_2}{\partial s}W_2 + \rho_2\frac{\partial W_2}{\partial s} - \frac{\partial R_2}{\partial s} \tag{4.12}$$

This expression gives the following intuition: the impact of varying patent length on social welfare is given by the variation in welfare in period one, which is altered due to the varying lengths of the patented and non-patented sub period, plus the variation in the innovation probability arising from the extended flux of patented profits, plus the variation in the expected welfare in period 2 arising from different patented sub-periods, minus the increased R&D investments.

The effect of a variation of patent length s on welfare W is positive provided that $|\tfrac{\partial W_1}{\partial s} - \tfrac{\partial R_2}{\partial s}| < |\tfrac{\partial \rho_2}{\partial s}W_2 + \rho_2\tfrac{\partial W_2}{\partial s}|$. This means that, in order for a variation in patent length s to have a positive effect on

[7] A description of the optimal patent length s^* is provided in the appendix.

social welfare over the two periods, the impact of the variation of patent length on welfare in period one minus the variation in the in R&D to develop the second drug must be less than the total effect of lengthening the patent time on the second period's welfare via the indirect effect of the patent length on the probability of successful innovation (rho 2) and the direct effect on the W2. A proof is provided in the appendix.

iii. Impact of varying patent length on prices

We now consider the impact that varying the patent length has on the welfare maximising price p_1^* indicated in equation 4.8.

The price of product one during the patent, p_1, and patent length s are intrinsically related. A variation in patent length will imply a variation in the price maximising welfare.

The relation between optimal patent price in period 1 and welfare maximising patent length is provided by:

$$\frac{\partial p_1^*}{\partial s} = re^{-rs}[(\frac{1}{2}(a_2^m + p_2) - mc_2)q_2^m - [\frac{1}{2}(\frac{b_2^f a_2^m + b_2^m a_2^f}{b_2^f + b_2^m} + p_2^g) - mc_2]q_2^m - [\frac{1}{2}(a_2^m - a_2^f) + mc_2 - p_2^g]q_2^f] + \frac{umK}{um(W_2-K)+rK}[\frac{a_1^m}{K} - \frac{um}{um(W_2-K)+rK}[(\frac{W_2-K}{K})a_1^m + \frac{r}{um}mc_1]] \tag{4.13}$$

Proof: provided in the appendix.

The expression above indicates that the effect of patent length on the optimal period one patent price will necessarily depend on the trade off between extending the period in which the innovative firms can charge higher price in period one and thus invest more on R&D for a second product and the reduction of the consumer surplus that having to pay a higher price for longer will entail.

In the given settings, the relationship between price p_1 and patent length s is not immediately intuitive and it cannot be solved analytically.

VI. Policy extensions

We now provide a number of policy extensions to the baseline model 4.7. The objective of this section is to identify how our results with alternative policy goals. In particular, we consider the case of firm's profit maximisation vis-a-vis a welfare maximising social planner, and value-based pricing.

Where analytically possible, we will compare the alternative policy options in terms of prices p_i, social welfare W_i and innovation probability h_i.

For simplicity, the results provided in the following sections have been obtained setting a fixed patent length s.

i. Welfare maximisation versus profits maximisation

We now confront the results obtained in equation 4.7 with an alternative framework where the firm is allowed to set prices to maximise profits.

The purpose of this section is to provide a comparative exercise where we confront optimal prices, welfare and the probability of innovation achieved under welfare maximisation with the ones achieved under profits maximisation.

The firm's profits maximisation problem is defined as:

$$\begin{aligned}&\Pi = (p_1 - mc_1)q_1^m(1-e^{-rs}) + \lambda(p_1^g - mc_1)(q_1^m - q_1^f)(e^{-rs} - e^{-rT}) \\ &+e^{-r\tau}\tfrac{ump_1q_1(1-e^{-rs})}{rK}[(p_2 - mc_2)q_2^m(1-e^{-rs}) + \lambda(p_2^g - mc_2)(q_2^m - q_2^f)(e^{-rs} - e^{-rT})] \\ &-ump_1q_1^m(1-e^{-rs})\end{aligned} \tag{4.14}$$

The set of prices maximising profits is defined as

$$\begin{aligned}p_1^* &= \tfrac{a_2^m}{2} + \tfrac{mc_1}{(1+\frac{um}{rK}A - um)} \\ p_1^{g,*} &= \tfrac{b_1^f(a_1^m - a_1^f) + (b_1^f + b_1^m)mc_1)}{3b_1^f - b_1^m} \\ p_2^* &= \tfrac{a_2^m + mc_2}{2} \\ p_2^{g,*} &= \tfrac{b_2^f(a_2^m - a_2^f) + (b_2^f + b_2^m)mc_2)}{3b_2^f - b_2^m}\end{aligned} \tag{4.15}$$

where $A = e^{-r\tau}[(p_2 - mc_2)q_2^m(1-e^{-rs}) + \lambda(p_2^g - mc_2)(q_2^m - q_2^f)(e^{-rs} - e^{-rT})]$.

Comparing the welfare and profit maximising prices, we can obtain the following proposition.

Proposition 1 provided that sales independent of price, a_1^m, are high enough, patented prices are higher under profit optimisation, than under welfare optimisation. Social welfare is lower under profit optimisation, but the probability of innovation is higher.

Proof: provided in the appendix.

Discussion: provided a high enough potential demand independent of prices, represented by the parameter a_1^m, compared to inter-temporal profits maximisation, the inter-temporal maximisation of social welfare comes at a cost of reduced investments in R&D activities.

Policy makers who are interested in optimising social welfare might thus be aware that achieving optimal welfare might imply a sub-optimal probability of innovation.

ii. Value-based pricing

We now explore the results of model 4.7 when Value Based Pricing (VBP) is applied. In this case price is set to $p_i = zh_i$, where h_i are the expected heath benefits associated to drug 1, and z is the fixed proportion of the health benefit that the regulator is willing to pay to the producer.

Notice that when the firm makes investments decisions, it makes decisions based on the expected benefits of the drug. There may be an expectation of this benefit when the drug is submitted for approval (based on clinical trials or other), but in a practical application, h_1 could be updated as new data appears.

Under VBP social welfare becomes

$$\begin{aligned}&W(zh_1, zh_2, s) = [\tfrac{1}{2}(a_1^M + zE(h_1)) - mc_1]q_1^M(1-e^{-rs}) \\ &+[\tfrac{1}{2}[(\tfrac{b_1^f a_1^M + b_1^m a_1^f}{b_1^m + b_1^f}) + zE(h_1)] - mc_1]q_1^m(e^{-rs} - e^{-rT}) + [\tfrac{1}{2}(a_1^m - a_1^f) + mc_1 - p_1^g]q_1^f(e^{-rs} - e^{-rT})] \\ &+\tfrac{umzE(h_1)q_1^m(1-e^{-rs})}{rK}e^{-r\tau}\Big[[\tfrac{1}{2}(a_2^M + zE(h_2)) - mc_2]q_2^M(1-e^{-rs}) + [\tfrac{1}{2}[(\tfrac{b_2^f a_2^M + b_2^m a_2^f}{b_2^m + b_2^f}) + zE(h_2)] - mc_2]q_2^m(e^{-rs} - e^{-rT}) \\ &+[\tfrac{1}{2}(a_2^m - a_2^f) + mc_2 - p_2^g]q_2^f(e^{-rs} - e^{-rT})\Big] \\ &-\tfrac{1}{r}umzE(h_1)q_1^m(1-e^{-rs})\end{aligned} \tag{4.16}$$

Defining the optimal proportion z resulting from equation 4.16 is analytically complex. An expression of the resulting First Order Conditions is reported in the appendix. The exact value of optimal fraction z

of realised health benefits h_i will be identified by numerical simulation.

We define the impact of a variation of the share z on CS, PS and Welfare. The impact of a variation of z on CS and PS is defined as

$$\begin{aligned} \frac{\partial CS}{\partial z} &= \frac{\partial CS_1}{\partial z} + \frac{\partial CS_1^g}{\partial z} + \frac{\partial \rho_2}{\partial z} CS_2 + \rho_2 \left(\frac{\partial CS_2}{\partial z} + \frac{\partial CS_2^g}{\partial z}\right) \\ \frac{\partial PS}{\partial z} &= \frac{\partial PS_1}{\partial z} + \frac{\partial PS_1^g}{\partial z} + \frac{\partial \rho_2}{\partial z} PS_2 + \rho_2 \left(\frac{\partial PS_2}{\partial z} + \frac{\partial PS_2^g}{\partial z}\right) - \frac{\partial R_1}{\partial z} \end{aligned} \tag{4.17}$$

From which, the derivative of social welfare with respect to z can be written as

$$\frac{\partial W}{\partial z} = \frac{\partial W_1}{\partial z} + \frac{\partial W_1^g}{\partial z} + \frac{\rho_2}{\partial z} W_2 + \rho_2 \left(\frac{\partial W_2}{\partial z} + \frac{\partial W_2^g}{\partial z}\right) - \frac{\partial R_2}{\partial z} \tag{4.18}$$

This expression illustrates the impact of a variation in the fixed proportion z of expected health benefits on social welfare. This expression indicates that by setting price to a fixed fraction of health gains, the consequences on welfare are complex. In this case, in fact, social welfare is influenced by the impact of price variation on R&D costs, on its impact on the innovation probability times period two welfare, and on the expected welfare in individual periods, which, under VBP, is given by the effect of price variation of the branded drug even after patent expiry. Social planners, therefore, when value-based pricing is introduced, need to consider the impact of a price variation on welfare during the whole life-time of the branded product, even after patent expiration.

VII. Numerical simulation

We now provide a numerical simulation of the results provided in model 4.7. The purpose of our simulation is two-fold. First we identify the optimal prices and patent length in a simple case. We then simulate varying degrees of z on social welfare under value-based pricing. Simulating these two results allow us to shed light on the optimal patent length and the optimal value of z, which are both analytically ambiguous.

i. Model calibration

For simplicity, we assume that the two drugs have the same price, that is $p_1 = p_2$ and equal health benefits, $h_1 = h_2$.

ii. Parameter values

To populate our model, we use plausible parameters extracted from the existing literature.

Probability of success, ρ_1 = 1: As product 1 already exists, we set the probability of successful R&D of product 1 to 1. No value is fixed for ρ_2 as it is defined by the IPF.

Discount rate, r = 0.035: The discount rate is 3.5%. For comparison purposes, the discount rate chosen is 3.5% as this is used for both costs and benefits in NICE guidance (2008).

Total useful product life, T = 30: The average life time of any product is 30 years, orientated at 25 years estimated by Hughes (Moore and Snyder).

Launch time of product 2, $\tau = 10$: The assumed time of launch of product 2 if successful is 10 years after launch of product 1.

Health benefit, h2 = h1 = 30,000: The health benefit of both products i = 1,2 expressed in monetary value is GBP 30,000. We assumed the health benefit to be 1 QALY. The literature on assigning a monetary value to a QALY is relatively sparse and issues such as the margin at which QALYs are bought rarely taken into account. Different approaches include using the existing WTP-based 'value of preventing a

statistical fatality' (Mason et al., 2009). Their results indicate a value range of approximately GBP 24,000 to GBP 70,000 per QALY. Other approaches found were direct valuation (cf. Gyrd-Hansen (2003)), and the use of statistical value of a life (cf. Murphy and Topel (2006)) and different approaches might yield different results. We therefore test two other values of health benefit, hi = 10,000 and hi = 50,000.

Marginal cost, mc_i = 4,000: The marginal cost per unit is assumed to be GBP 4,000. Camejo et al. (2011) stated that marginal cost of production was negligible compared with the large R&D costs. The value is chosen somewhat arbitrarily.

R&D expenditure, K = 800,000,000: We estimate that the amount required to make an innovation K is equal to GBP 0.8 billion. DiMasi et al. (2003) estimated drug development costs and found that they were at US$ 800 million at the time. Estimates from Congressional Budget Office (2006) suggest similarly that drug development costs were between US$ 800 million and 1 billion at the time and indicated that they were still rising. The R&D cost R2 of product 2 will be defined by the R&D intensity function.

R&D intensity, m = 0.2: Fraction of present value revenues invested in R&D. This is the R&D expenditure as percentage of present value of accumulated revenues. The value of 20% is a rounded estimate resulting from values retrieved from the OHE report on the pharmaceutical industry Office of Health Economics (2007) (between 17% to 31%) and the Congressional Budget Office (2006) that estimated 19%.

Innovation Production Function (IPF), u = 0.035: Constant scale parameter. This parameter has been set to a value such that the IPF in the baseline model is equal to 14%. This is the estimated rate of R&D innovation in pharmaceuticals found by Wong et al. (2019).

Prices, p2 = p1: The price of product 2 is equal to price of product 1, $p_i \geq mc_i > 0$ for $i = 1, 2, ..., n$. When looking for the optimal patent length, price is fixed at $p_i = 20,000$, a cost per QALY commonly used by NICE as a cost-effectiveness threshold.

Patent length, s = 10: The average patent life for all products is set at 10 when optimal prices are observed. Hughes (Moore and Snyder) found an average commercial patent life of eight to ten years.

Demand function, $q_i = 120,000 - 0.1p_i$: The demand function has parameters ai = 120,000 and bi = 10 for both products i = 1,2. The demand function was chosen such that it exhibited an elasticity of demand with respect to price of -20% at a point estimate of pi = 20,000. This was based on Costa-Font et al. (2013) who found that health care was a highly inelastic good, meaning that it is a necessity.

Competitive fringe supply function, $q^f(p_i) = 24000 + 0.5 * p1d$: With this we set that the branded quantity demanded after patent expiry is 20% of the demand during the patent period. Hughes (Moore and Snyder) found that market shares of incumbents fell to about 20% within one year after the patent expired.

iii. Results

We provide the results of social welfare simulated across the model parameters p_1 and s. The results of the simulation are reported in Figure 4.1.

The figure shows that social welfare is optimised for high values of patent length, and for average value of prices. Social welfare appears to be increasing with patent length, while it appears to present a concave relationship with price.

A graphical intuition of consumer surplus and producer surplus is provided in the appendix.

Figure 4.1 shows a concave relationship between price p_1 and welfare. Welfare increases with price p_1 up to a maximum to then decrease. For low values of patent length s, welfare presents an increasing relationship with price p_1. Welfare is generally increasing with patent length, expect for high price levels,

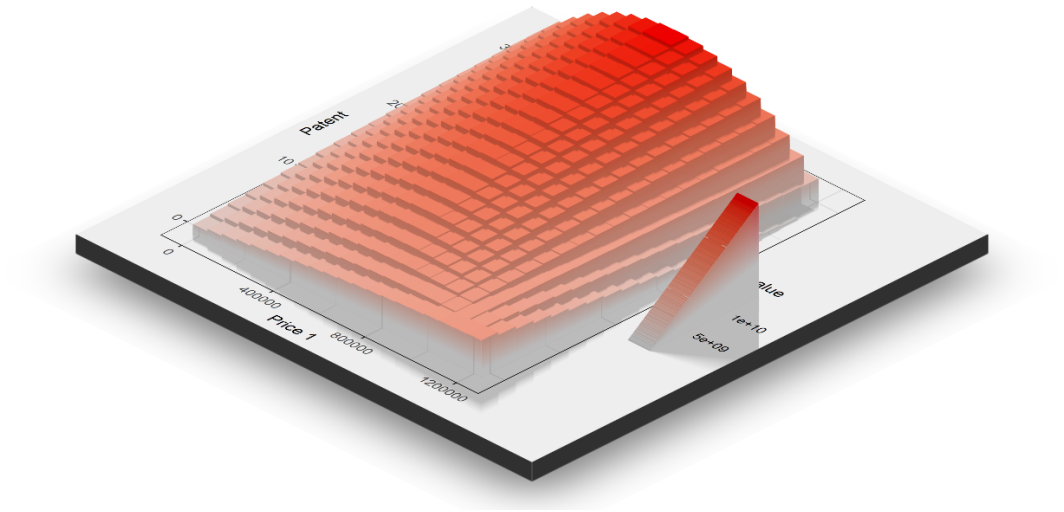


Figure 4.1: *Simulated social welfare for varying price 1 (x-axis) and patent length (y-axis).*

Table 4.1: *Optimal combination of price and patent for respectively social welfare, consumer surplus and producer surplus.*

Objective function	value	price	patent
Welfare	13964388773	570526.3	30
Consumer surplus	4509351822	4000	30
Producer surplus	23182091418	633473.7	30

for which welfare decreases with an increase in patent length.

Table 4.1 indicates the combinations of prices and patents that lead to a maximisation of the alternative objective functions. [8]

We then provide an estimation of optimal VBP parameter z, for different values of expected health benefits.

Figure 4.2 shows optimal value-based factor z as a function of expected health benefits h_1. The figure shows a negative relationship between the VBP factor z and health benefits. Value-based pricing parameter z varies with the realisation of the drug's health benefits.

Table 4.2 below provides a numerical example to illustrate the dynamics of the negative relation obtained between the health benefits parameter h_1 and the VBP proportion z.

For illustrative purposes, we will consider 3 cases: (a), (b) and (c). For case (a) we fix an arbitrary value of h_1 to 8000. From the numerical simulation, we know that the corresponding optimal value of z is 1. Case (a) is then represented by the vector $(h_{1,a} = 8000, z_a = 1)$. We then consider a second point (b) with an arbitrary value of h_1 set to 20000. For illustration purposes we leave the value of z unchanged to 1.

[8] The results on optimal prices appear to be highly sensitive to variations in other parameters. In particular, setting the demand function parameter a_{1m} to respectively 120000 (the original value), 60000 and 20000 introduced a dependence in the optimal patent and prices with respect to the discount rate r. The results of this sensitivity analysis are reported in Figure 4.6 in the appendix.

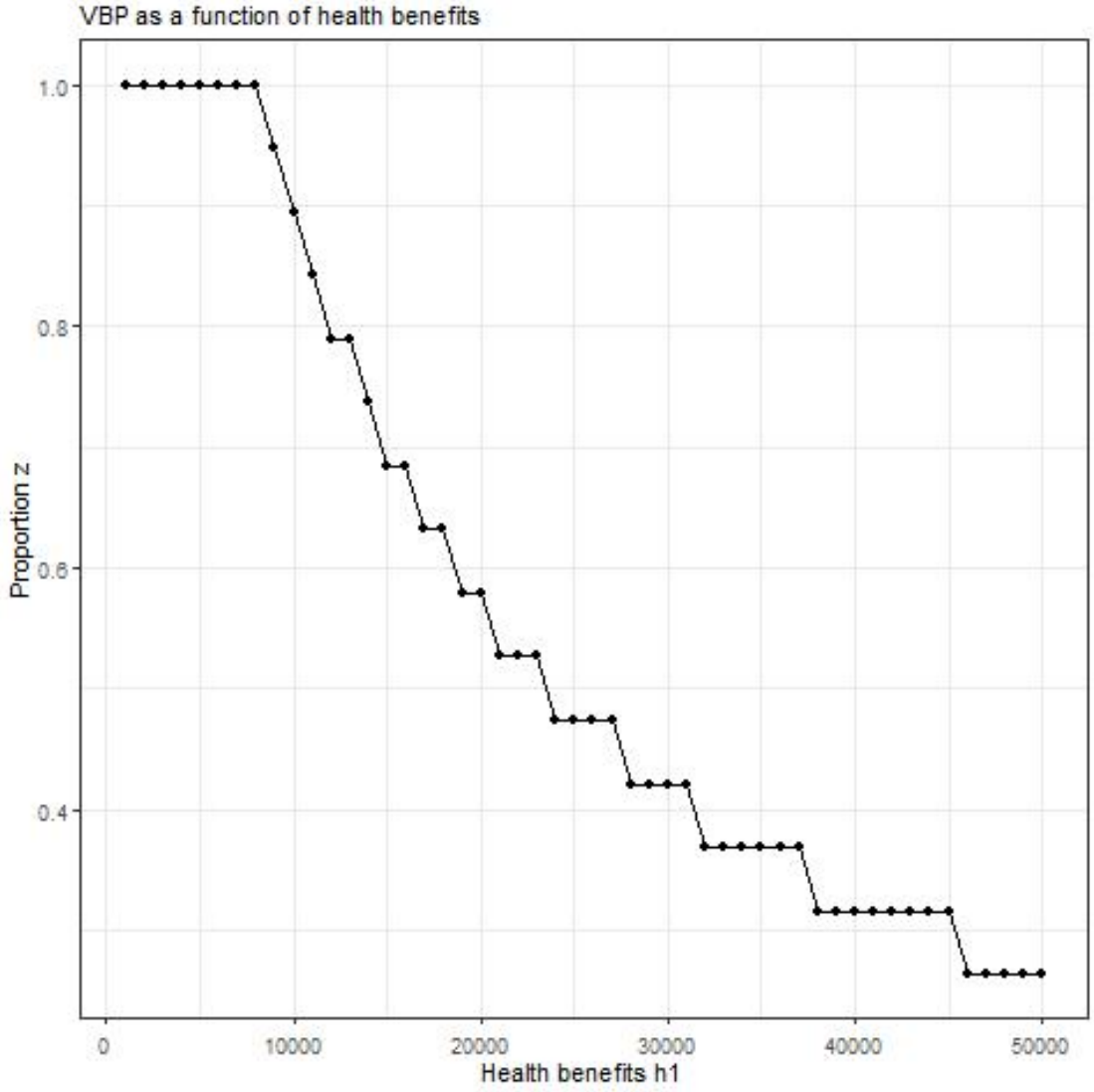


Figure 4.2: *VBP factor z as a function of health benefits* h_1.

Case (b) is then represented by the vector $(h_{1,a} = 20000, z_a = 1)$. We then consider a third case, case (c), where the parameter z is fixed to the optimal parameter resulting from the simulation and corresponding to the health benefits value of h_1. Case (c) is then represented by the vector $(h_{1,a} = 20000, z_a = 0.58)$. Table 4.2 decomposes the value of social welfare W into its individual components, allowing us to better understand its dynamics.

The table shows that, starting from point (a), an increase in health benefits does translate into an increase into the probability of innovation, with a subsequent increase in welfare in period 2. This increase in health benefits, however, is associated with a slight decrease in period 1 welfare. In turn, the trade-off between period 1 and period 2 welfare, leads to a reduction in z in order to achieve higher period 1 welfare to balance the higher period 2 welfare.

Table 4.2: *Worked example of optimal welfare as a function of varying health benefits h_1 and VBP proportion z.*

Case	h_1	z	W **(mln)**	W_1 **(mln)**	W_2 **(mln)**	ρ_2
(a)	8000	1	3246	3192	53	0.05
(b)	20000	1	3231	3113	1190	0.10
(c)	20000	0.58	3260	3175	84	0.07

VIII. Conclusions

This paper analysed the introduction of price regulation in a two-period dynamic model with innovation.

Our analysis explored the trade-off between static and dynamic optimisation of social welfare with R&D. We explored the impact of a variation in patent length, identifying a trade-off with optimal price. Lastly, we explore the introduction of value-based pricing, providing numerical simulations.

The results presented in this paper show that, by varying prices, the social planner might alter the composition of welfare in the first period to achieve optimal welfare inter-temporally via endogenous R&D.

Policy-makers can use this trade-off to ensure that welfare is maximised inter-temporally. Regulators might also exploit the relationship between price and patent length to ensure that welfare is optimised.

Our analysis shows that value based pricing alters market dynamics influencing the optimal price after patent expiration. Our numerical simulation provides indications of the negative relationship between the value based factor z and expected health benefits h_1. This shows that choosing the right VBP parameter z is risky when health benefits are not known ex-ante.

This paper has shown the impact of alternative pricing policies on social welfare. In particular, we saw the implications on social welfare from a pharmaceutical pricing resulting from a welfare-maximising social planner versus a value-based pricing policy. This analysis has shown that the two pricing policies lead to different dynamics of social welfare following a variation in price. In particular, compared to the welfare maximising price, value-based pricing introduces a dependence on the variation of expected welfare in period two following a variation in the VBP proportion. The variation of social welfare in the second period, following the variation in the VBP proportion, alters the value of social welfare achieved in period one as well as the optimal amount of innovation.

The inverse relationship between social welfare and the VBP proportion z has important implications when considering the link between VBP proportion, disease prevalence and innovation. For example, consider the case where the innovating firm operates under a VBP regime and it intends to invest its period one profits in the innovation towards a drug to cure a disease with high prevalence. In that case, a slight variation in the VBP proportion would alter the expected welfare arising from the expected health benefits of the period 2 drug, as its price would also depend on the VBP proportion. This variation in expected benefits in period 2 would alter the trade-off with welfare in period one, leading to an increase

in social welfare in period one and a lower innovation probability.

Policy makers should therefore be careful in considering a pricing policy linked to health benefits in individual periods, as it may alter the firm's investments decisions, leading to variations in the degree of innovation.

Our analysis is subject to a number of limitations. First it does not obtain complete determination of analytical solutions, hence the need to use numerical simulation. Second, our analysis does not account for extensions such as multiple innovating firms.

The presented model was developed to explore the theoretical implications of the introduction of a VBP policy on innovation and inter-temporal welfare. The features of the presented model did not aim to represent the specifics of some regulatory frameworks. In particular, the model accounted for a social welfare-maximising regulator. In some healthcare systems, such as the English NHS, drug prices are set between healthcare departments and the producer. The former, in particular might be interested in maximising achieved welfare for a given budget, hence not considering price implications on producer surplus. The difference with these specific regulations and the model may represent a limitation of this work.

Future research will allow for additional policy extensions and for a setting allowing for a portfolio of drugs developed by the innovating firm.

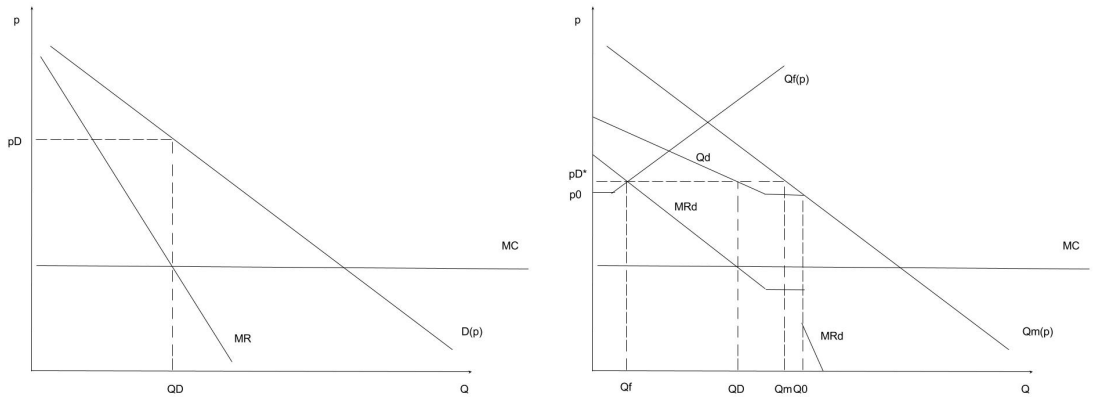


Figure 4.3: *Pricing models. Monopoly pricing (left). Competitive fringe pricing (right).*

IX. Appendix C - Proofs

i. Baseline model

Competitive fringe

Figure 4.3 provides a graphical intuition of the competitive fringe settings, in comparison to the monopoly pricing. The graph is derived from Church and Ware (2000).

Optimal prices, with fixed patent length

The First Order Conditions (FOC) of expression 4.7 are defined as

$$
\begin{aligned}
0 = \frac{\partial W}{\partial p_1} &= \tfrac{1}{2} q_1^m + [\tfrac{1}{2}(a_1^M + p_1) - mc_1]\frac{\partial q_1^m}{\partial p_1} + [\tfrac{um}{rK}(q_1 + p_1 \frac{\partial q_1^m}{\partial p_1})][[\tfrac{1}{2}(a_2^M + p_2) - mc_2] q_2^M (1 - e^{-rs}) \\
&+ [\tfrac{1}{2}[(\tfrac{b_2^f a_2^m + b_2^m a_2^f}{b_2^m + b_2^f}) + p_2^g] - mc_2] q_2^m (e^{-rs} - e^{-rT}) + [\tfrac{1}{2}(a_2^m - a_2^f) + mc_2 - p_2^g] q_2^f (e^{-rs} - e^{-rT})] \\
&- \tfrac{1}{r} um [q_1^m + p_1 \frac{\partial q_1^m}{\partial p_1}] \\
0 = \frac{\partial W}{\partial p_1^g} &= \tfrac{1}{2} q_1^m + [\tfrac{1}{2}[(\tfrac{b_1^f a_1^m + b_1^m a_1^f}{b_1^m + b_1^f}) + p_1^g] - mc_1]\frac{\partial q_1^m}{\partial p_1^g} + [\tfrac{1}{2}(a_1^m - a_1^f) + mc_1 - p_1^g]\frac{\partial q_1^f}{\partial p_1^g} - q_1^f \\
0 = \frac{\partial W}{\partial p_2} &= \tfrac{1}{2} q_2^m + [\tfrac{1}{2}(a_2^m + p_2) - mc_2]\frac{\partial q_2^m}{\partial p_2} \\
0 = \frac{\partial W}{\partial p_2^g} &= \tfrac{1}{2} q_2^m + [\tfrac{1}{2}[(\tfrac{b_2^f a_2^m + b_2^m a_2^f}{b_2^m + b_2^f}) + p_2^g] - mc_2]\frac{\partial q_2^m}{\partial p_2^g} + [\tfrac{1}{2}(a_2^m - a_2^f) + mc_2 - p_2^g]\frac{\partial q_2^f}{\partial p_2^g} - q_2^f
\end{aligned}
\tag{4.19}
$$

The optimal prices are found by inserting the expression of linear demand and supply functions in equation 4.19. More specifically, we assumed that $q_i^m = \frac{a_1^m - p_1^m}{b_1^m}$ and $q_i^f = a_1^f + b_i^f p_1$. Doing so, after some algebra, leads to the optimal prices defined in 4.8.

Considerations on model coefficients

Optimal prices: notice that the expression 4.8 provides some implications on model parameters. In particular, it would be reasonable to assume that $p_2 = p_2^g$, as otherwise we would have that either: a) the price of the generic is higher than the branded drug, b) the firm produces the drug at a price lower than marginal costs. Setting $p_2 = p_2^g$ implies that $mc_2 = (2b_2^m a_2^m + 3b_2^f a_2^m - b_2^f a_f)/(b_2^m + b_2^f)$. Also, it would be reasonable to assume that $|b_2^m| > |b_2^f|$, as otherwise the element on the RHS of the equality would be negative.

Innovation function: Inserting p_1^* into $h(x)$ leads to

$$\begin{array}{l} p_1^* = \frac{um(1-e^{-rs})}{rK}[\frac{umK}{rK+um(W_2-K)}[(\frac{W_2-K}{K})a_1^m + \frac{r}{um}mc_1]] \\ \frac{1}{b_1}[\frac{rK}{(rK+um(W_2-K))}(a_1^m - mc_1)] \end{array} \tag{4.20}$$

Having an IPF higher or equal to zero would then require setting $a_1^m \geq \frac{umK}{rK+um(W_2-K)}[(\frac{W_2-K}{K})a_1^m + \frac{r}{um}mc_1]$, and W_2, which is satisfied provided that $a_1^m - mc_1$.

Static versus dynamic welfare optimisation

Generic expression of consumer surplus

$$\begin{array}{l} CS = \frac{1}{2}(a_1^M - p_1)q_1^M(1-e^{-rs}) + \frac{1}{2}\Big(\frac{b_1^f a_1^M + b_1^M a_1^f}{b_1^f + b_1^m} - p_1^g\Big)q_1^d(e^{-rs} - e^{-rT}) \\ +[\frac{1}{2}(a_1^M + \frac{b_1^f a_1^M + b_1^M a_1^f}{b_1^f + b_1^M}) - p_1^g]q_1^f(e^{-rs} - e^{-rT}) \\ +\frac{mup_1q_1^m(1-e^{-rs})}{rK}e^{-r\tau}[\frac{1}{2}(a_2^M - p_2)q_2^M(1-e^{-rs}) + \frac{1}{2}\Big(\frac{b_2^f a_2^M + b_2^M a_2^f}{b_2^f + b_2^m} - p_2^g\Big)q_2^d(e^{-rs} - e^{-rT}) \\ +[\frac{1}{2}(a_2^M + \frac{b_2^f a_2^M + b_2^M a_2^f}{b_2^f + b_2^M}) - p_2^g]q_2^f(e^{-rs} - e^{-rT})] \end{array} \tag{4.21}$$

Consumer surplus in individual periods

$$\begin{array}{l} CS_1 = \frac{1}{2}(a_1^M - p_1)q_1^M(1-e^{-rs}) + \frac{1}{2}\Big(\frac{b_1^f a_1^M + b_1^M a_1^f}{b_1^f + b_1^m} - p_1^g\Big)q_1^d(e^{-rs} - e^{-rT}) \\ +[\frac{1}{2}(a_1^M + \frac{b_1^f a_1^M + b_1^M a_1^f}{b_1^f + b_1^M}) - p_1^g]q_1^f(e^{-rs} - e^{-rT}) \end{array} \tag{4.22}$$

$$\begin{array}{l} CS_2 = [\frac{1}{2}(a_2^M - p_2)q_2^M(1-e^{-rs}) + \frac{1}{2}\Big(\frac{b_2^f a_2^M + b_2^M a_2^f}{b_2^f + b_2^m} - p_2^g\Big)q_2^d(e^{-rs} - e^{-rT}) \\ +[\frac{1}{2}(a_2^M + \frac{b_2^f a_2^M + b_2^M a_2^f}{b_2^f + b_2^M}) - p_2^g]q_2^f(e^{-rs} - e^{-rT})] \end{array} \tag{4.23}$$

The derivative of CS with respect to price thus becomes

$$\frac{\partial CS}{\partial p_1} = (1-e^{-rs})[\frac{mu}{rK}(q_1^m - \frac{p_1^m}{b_1})e^{-r\tau}CS_2 - \frac{1}{2}(q_1^m + a_1^m - p_1)] \tag{4.24}$$

which is higher than zero provided that

$$p_1^m > \frac{\overbrace{\frac{1}{2} + \frac{1}{2b_1^m} - \frac{mu}{rK}\frac{1}{b_1^m}e^{-r\tau}CS_2}^{(a)}}{\underbrace{\frac{1}{2} + \frac{1}{2b_1^m} - 2\frac{mu}{rK}\frac{1}{b_1^m}e^{-r\tau}CS_2}_{(b)}}a_2^m \tag{4.25}$$

where conditions are
(a) as long as $\frac{1}{2} > \frac{1}{b_1^m}[\frac{mu}{rK}e^{-r\tau}CS_2 - \frac{1}{2}]$
(b) as long as $\frac{1}{2} > \frac{1}{b_1^m}[2\frac{mu}{rK}e^{-r\tau}CS_2 - \frac{1}{2}]$

The generic expression of producer surplus becomes

$$\begin{array}{l} PS(p,s) = (p_i - mc_i)q_i^M(1-e^{-rs}) + (p_i^g - mc_i)q_i^d(e^{-rs} - e^{-rT}) \\ +\frac{1}{2}(p_i^g - a_i^f)q_i^f(e^{-rs} - e^{-rT}) \\ \frac{mup_1q_1^m(1-e^{-rs})}{rK}e^{-r\tau}[(p_2 - mc_2)q_i^M(1-e^{-rs}) + (p_2^g - mc_2)q_2^d(e^{-rs} - e^{-rT}) \\ +\frac{1}{2}(p_2^g - a_2^f)q_2^f(e^{-rs} - e^{-rT})] \end{array} \tag{4.26}$$

Producer surplus in individual periods is

$$\begin{aligned} &PS_1(p,s) = (p_1 - mc_1)q_1^M(1-e^{-rs}) + (p_1^g - mc_1)q_1^d(e^{-rs} - e^{-rT}) \\ &+\tfrac{1}{2}(p_1^g - a_1^f)q_1^f(e^{-rs} - e^{-rT}) - \tfrac{1}{r}ump_1q_1^m(1-e^{-rs}) \\ &+e^{-r\tau}[(p_2 - mc_2)q_i^M(1-e^{-rs}) + (p_2^g - mc_2)q_2^d(e^{-rs} - e^{-rT}) \\ &+\tfrac{1}{2}(p_2^g - a_2^f)q_2^f(e^{-rs} - e^{-rT})] \end{aligned} \tag{4.27}$$

$$\begin{aligned} &PS_2(p,s) = e^{-r\tau}[(p_2 - mc_2)q_i^M(1-e^{-rs}) + (p_2^g - mc_2)q_2^d(e^{-rs} - e^{-rT}) \\ &+\tfrac{1}{2}(p_2^g - a_2^f)q_2^f(e^{-rs} - e^{-rT})] \end{aligned} \tag{4.28}$$

The derivative of PS with respect to price thus becomes

$$\frac{\partial PS}{\partial p_1} = (1-e^{-rs})[\frac{mc_1}{b_1} + (q_1^m - \frac{p_1}{b_1^m})(1 - muC_2)] \tag{4.29}$$

which is higher than zero provided that

$$\frac{\partial PS}{\partial p_1} = (1-e^{-rs})[\frac{mc_1}{b_1} + \overbrace{(q_1^m - \frac{p_1}{b_1^m})}^{(a)}\underbrace{(1 - muC_2)}_{(b)}] \tag{4.30}$$

where the conditions imply
(a) $q_1^m - \frac{p_1}{b_1^m} > 0$
(b) $1 - muC_2 > 0$

Expressing the condition for p_1 we have

$$p_1 < a_1^m + \frac{mc_1}{2(1 - muC_2)} \tag{4.31}$$

We now consider the derivative of W with respect to p_1.

$$\begin{aligned} &\tfrac{\partial W}{\partial p_1} = \tfrac{1}{2}q_1^m - \tfrac{1}{b_1}(\tfrac{1}{2}(a_1^M + p_1) - mc_1) + (\tfrac{um}{rK}(q_1 - \tfrac{\partial p_1}{b_1}))C_2 \\ &-\tfrac{1}{r}um(q_1^m - \tfrac{p_1}{b_1}) \end{aligned} \tag{4.32}$$

which simplifies to

$$\begin{aligned} &\tfrac{\partial W}{\partial p_1} = \tfrac{1}{r}\tfrac{um}{b_1^m}(\tfrac{C_2}{K} - um) + mc_1(\tfrac{1}{b_1^m} + \tfrac{1}{r}um) \\ &-p_1^m[\tfrac{1}{b_1^m} + \tfrac{1}{r}um(\tfrac{1}{b_1^m} + \tfrac{1}{2})] \end{aligned} \tag{4.33}$$

which is higher than zero provided that

$$p_1 < \frac{\frac{1}{r}\frac{um}{b_1^m}(\frac{C_2}{K} - um) + mc_1(\frac{1}{b_1^m} + \frac{1}{r}um)}{\frac{1}{b_1^m} + \frac{1}{r}um(\frac{1}{b_1^m} + \frac{1}{2})} \tag{4.34}$$

A graphical intuition of this results in provided in Figure 4.4.

ii. Proofs with varying patent length

Impact of patent length on prices

Starting from expression 4.52, the derivative of CS with respect to s becomes

$$\begin{aligned} &\tfrac{\partial CS}{\partial s} = re^{-rs}\Big[\tfrac{1}{2}(a_1^m - p_1)q_1^m - \tfrac{1}{2}(\tfrac{b_1^f a_1^m + b_1^m a_1^f}{b_1^f + b_1^m} - p_1^g)q_1^d - [\tfrac{1}{2}(a_1^m + \tfrac{b_1^f a_1^m + b_1^m a_1^f}{b_1^f + b_1^m}) - p_1^g]q_1^f \\ &+\tfrac{mup_1q_1^m}{rK}e^{-r\tau}[\tfrac{1}{2}(a_2^m - p_2)(1-e^{-rs}) + \tfrac{1}{2}(\tfrac{b_2^f a_2^m + b_2^m a_2^f}{b_2^f + b_2^m} - p_2^g)q_2^d(e^{-rs} - e^{-rT}) + [\tfrac{1}{2}(a_2^m + \tfrac{b_2^f a_2^m + b_2^m a_2^f}{b_2^f + b_2^m}) - p_2^g]q_2^f(e^{-rs} - e^{-rT})] \\ &+\tfrac{mup_1q_1^m}{rK}(1-e^{-rs})e^{-r\tau}[\tfrac{1}{2}(a_2^m - p_2)q_2^m - \tfrac{1}{2}(\tfrac{b_2^f a_2^m + b_2^m a_2^f}{b_2^f + b_2^m} - p_2^g)q_2^d - [\tfrac{1}{2}(a_2^m + \tfrac{b_2^f a_2^m + b_2^m a_2^f}{b_2^f + b_2^m}) - p_2^g]q_2^f]\Big] \end{aligned} \tag{4.35}$$

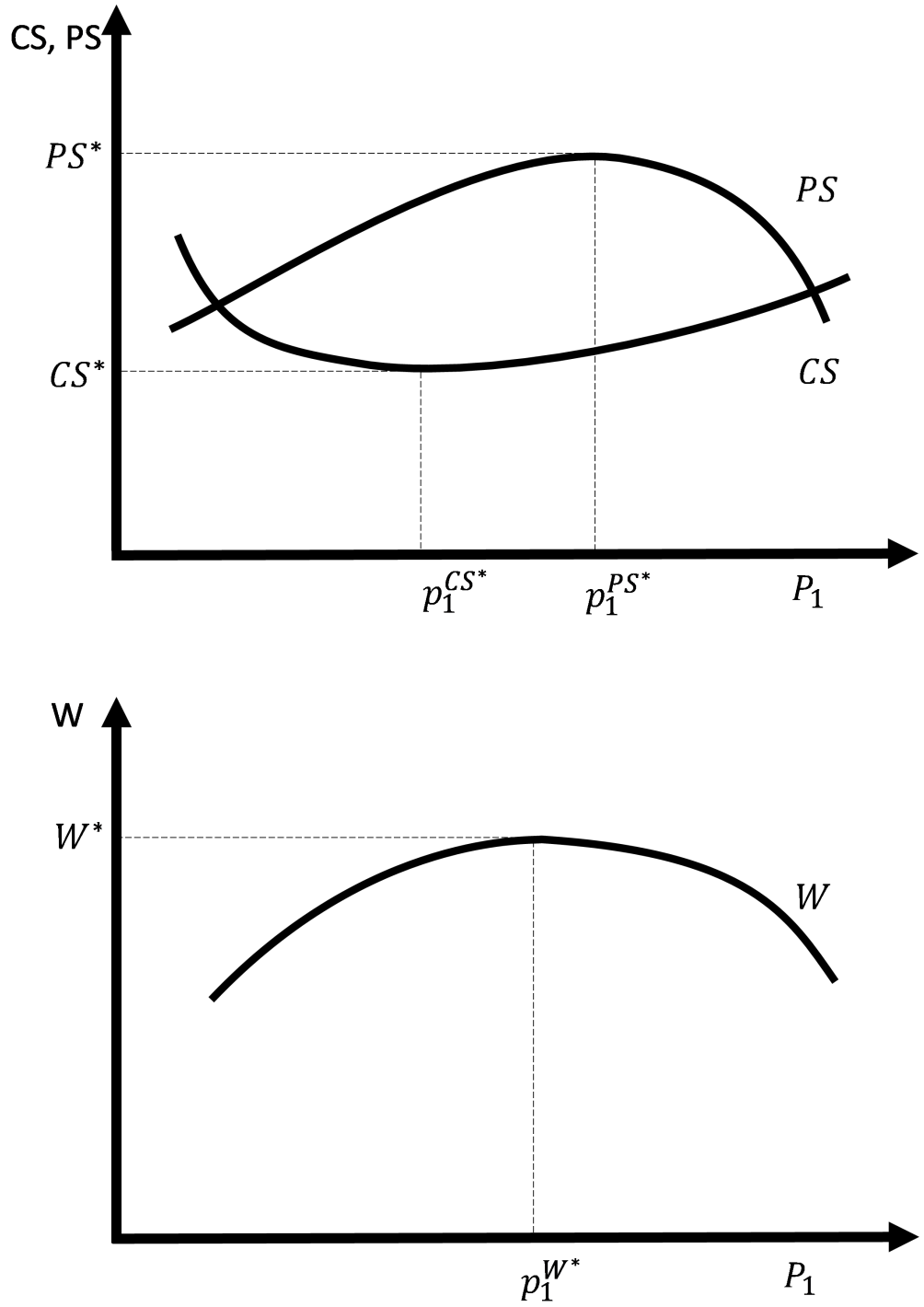


Figure 4.4: *Graphical intuitions for Consumer Surplus (CS), Producer Surplus (PS) and Social Welfare (W) for varying price.*

which is higher than zero provided that

$$s < \tau log(\frac{A}{B}) \tag{4.36}$$

where $A = \frac{mup_1q_1^m}{rk}e^{-r\tau}\Big[\frac{1}{2}(\frac{b_2^fa_2^m+b_2^ma_2^f}{b_2^f+b_2^m} - p_2^g)q_2^de^{-rT} + [\frac{1}{2}(a_2^m + \frac{b_2^fa_2^m+b_2^ma_2^f}{b_2^f+b_2^m}) - p_2^g]q_2^fe^{-rT} - \frac{1}{2}(a_2^m - p_2) + \frac{1}{2}(\frac{b_2^fa_2^m+b_2^ma_2^f}{b_2^f+b_2^m} - p_2^g)q_2^d + [\frac{1}{2}(a_2^m + \frac{b_2^fa_2^m+b_2^ma_2^f}{b_2^f+b_2^m}) - p_2^g]q_2^f - \frac{1}{2}(a_2^m - p_2)q_2^m\Big]$ and $B = r[\frac{1}{2}(a_1^m - p_1)q_1^m - \frac{1}{2}(\frac{b_1^fa_1^m+b_1^ma_1^f}{b_1^f+b_1^m}) - p_1^g)q_1^d - [\frac{1}{2}(a_1^m + \frac{b_1^fa_1^m+b_1^ma_1^f}{b_1^f+b_1^m}) - p_1^g]q_1^f + \frac{mup_1q_1^m}{rK}e^{-r\tau}[\frac{1}{2}(\frac{b_2^fa_2^m+b_2^ma_2^f}{b_2^f+b_2^m} - p_1^g)q_1^d + [\frac{1}{2}(a_2^m + \frac{b_2^fa_2^m+b_2^ma_2^f}{b_2^f+b_2^m}) - p_2^g]q_2^f] - \frac{1}{2}(a_2^m - p_2) - \frac{1}{2}(a_2^m - p_2)q_2^m + \frac{1}{2}(\frac{b_2^fa_2^m+b_2^ma_2^f}{b_2^f+b_2^m}) - p_2^g)q_2^d + [\frac{1}{2}(a_2^m + \frac{b_2^fa_2^m+b_2^ma_2^f}{b_2^fb_2^m}) - p_2^g]q_2^f]$.

Notice that the derivative of CS with respect to s can be positive provided that $\frac{A}{B} > 1$.

Similarly, starting from expression 4.26, the derivative of PS with respect to s becomes

$$\begin{aligned}\frac{\partial PS}{\partial s} &= re^{-rs}\Big[(p_1 - mc_1)q_1^m - (p_1^g - mc_1)q_1^d - \frac{1}{2}(p_1^g - a_1^f)q_1^f \\ &+ \frac{mup_1q_1^m}{rK}e^{-r\tau}[(p_2 - mc_2)q_2^m(2 - e^{-rs}) + (p_2^g - mc_2)q_2^d(e^{-rs} - e^{-rT} - 1) \\ &+ \frac{1}{2}(p_2^g - a_2^f)q_2^f(e^{-rs} - e^{-rT} - 1)]\Big]\end{aligned} \tag{4.37}$$

which is higher than or equal to zero provided that

$$s \leq -\frac{log(C)}{r} \tag{4.38}$$

where $C = \frac{1}{[(p_2^g - mc_2)q_2^d + \frac{1}{2}(p_2^g - a_2^f)q_2^f - (p_2 - mc_2)q_2^m]}\Big[\frac{[(p_1^g - mc_1)q_1^d + \frac{1}{2}(p_1^g - a_1^f)q_1^f - (p_1 - mc_1)q_1^m]}{mup_1q_1^me^{-r\tau}}rK + (p_2^g - mc_2)q_2^d(e^{-rT} + 1) + \frac{1}{2}(p_2^g - a_2^f)q_2^f(e^{-rT} + 1) - 2(p_2 - mc_2)q_2^m\Big]$. Notice that if C is higher than zero, then producer surplus is always increasing with s. If $0 < C < 1$, then producer surplus is first increasing and then decreasing with s. If $A < 0$ then the sign of the derivative of PS with respect to s is not defined.

The derivative of welfare W with respect to patent length s is defined as

$$\begin{aligned}\frac{\partial W}{\partial s} &= re^{-rs}\Big[\frac{1}{2}(a_1^m + p_1) - mc_1)q_1^m - [\frac{1}{2}[\frac{b_1^fa_1^m+b_1^ma_1^f}{b_1^m+b_1^f} + p_1^g] - mc_1]q_1^m - [\frac{1}{2}(a_1^m - a_1^f) + mc_1 - p_1^g]q_1^f \\ &+ \frac{ump_1q_1^m}{rK}e^{-r\tau}\big[[(\frac{1}{2}(a_2^m + p_2) - mc_2]q_2^m(1 - e^{-rs}) + [\frac{1}{2}(\frac{b_2^fa_2^m+b_2^ma_2^f}{b_2^m+b_2^f} + p_2^g) - mc_2]q_2(e^{-rs} - e^{-rT}) \\ &+ [\frac{1}{2}(a_2^m - a_2^f) + mc_2 - p_2^g]q_2^f(e^{-rs} - e^{-rT})] \\ &+ \frac{ump_1q_1^m(1-e^{-rs})}{rK}e^{-r\tau}[[\frac{1}{2}(a_2^m + p_2) - mc_2]q_2^m - [\frac{1}{2}[\frac{b_2^fa_2^m+b_2^ma_2^f}{b_2^m+b_2^f} + p_2^g] - mc_2]q_2^m - [\frac{1}{2}(a_2^m - a_2^f) + mc_2 - p_2^g]q_2^f] - ump_1q_1^m\Big]\end{aligned} \tag{4.39}$$

From which, after some algebra, the definition of optimal patent length becomes of the form

$$s^* = -\frac{1}{r}log(\frac{b}{a}) \tag{4.40}$$

where $a = -2\frac{ump_1q_1^m}{rK}e^{-r\tau}[[\frac{1}{2}(a_2^m + p_2) - mc_2]q_2^m - [\frac{1}{2}[\frac{b_2^fa_2^m+b_2^ma_2^f}{b_2^m+b_2^f} + p_2^g] - mc_2]q_2^m - [\frac{1}{2}(a_2^m - a_2^f) + mc_2 - p_2^g]q_2^f$

and where $b = -(\frac{1}{2}(a_1^m + p_1) - mc_1)q_1^m + [\frac{1}{2}[\frac{b_1^fa_1^m+b_1^ma_1^f}{b_1^m+b_1^f} + p_1^g] - mc_1]q_1^m + [\frac{1}{2}(a_1^m - a_1^f) + mc_1 - p_1^g]q_1^f - \frac{ump_1q_1^m}{rK}e^{-r\tau}(1 + e^{-rT})\Big[2[\frac{1}{2}(a_2^m + p_2) - mc_2]q_2^m - [\frac{1}{2}(\frac{b_2^fa_2^m+b_2^ma_2^f}{b_2^m+b_2^f} + p_2^g) - mc_2]q_2^m - [\frac{1}{2}(a_2^m - a_2^f) + mc_2 - p_2^g]q_2^f\Big]$.

Derivative of price with respect to patent length.

The derivative of price p_1 with respect to patent length s follows from the definition of optimal patent length provided in equation 4.8.

After some algebra, we can show that the derivative of p_1 with respect to s is higher or equal than zero provided that

$$s \leq -\frac{1}{r} log(-\frac{D}{rE}) \tag{4.41}$$

where $D = \frac{umK}{um(W_2-K)+rK}[\frac{a_1^m}{K} - \frac{um}{um(W_2-K)+rK}[(\frac{W_2-K}{K}a_1^m) + \frac{r}{um}mc_1]]$ and $E = (\frac{1}{2}(a_2^m + p_2) - mc_2)q_2^m - [\frac{1}{2}(\frac{b_2^f a_2^m + b_2^m a_2^f}{b_2^f + b_2^m} + p_2^g) - mc_2]q_2^m - [\frac{1}{2}(a_2^m - a_2^f) + mc_2 - p_2^g]q_2^f$.

iii. Proofs with policy extensions

The firm's profits in an individual period are defined as

$$\Pi_1(p_1, p_1^g) = (p_1 - mc_1)q_1^m(1 - e^{-rs}) + \lambda(p_1^g - mc_1)(q_1^m - q_1^f)(e^{-rs} - e^{-rT}) - ump_1q_1^m(1 - e^{-rs}) \tag{4.42}$$

Similarly,

$$\Pi_2(p_2, p_2^g) = e^{-r\tau}\frac{ump_1q_1(1 - e^{-rs})}{rK}[(p_2 - mc_2)q_2^m(1 - e^{-rs}) + \lambda(p_2^g - mc_2)(q_2^m - q_2^f)(e^{-rs} - e^{-rT})] \tag{4.43}$$

Therefore

$$\begin{array}{l}\Pi = (p_1 - mc_1)q_1^m(1 - e^{-rs}) + \lambda(p_1^g - mc_1)(q_1^m - q_1^f)(e^{-rs} - e^{-rT}) - ump_1q_1^m(1 - e^{-rs}) \\ e^{-r\tau}\frac{ump_1q_1(1-e^{-rs})}{rK}[(p_2 - mc_2)q_2^m(1 - e^{-rs}) + \lambda(p_2^g - mc_2)(q_2^m - q_2^f)(e^{-rs} - e^{-rT})]\end{array} \tag{4.44}$$

The FOC for equation 4.44 are

$$\begin{array}{l} 0 = \frac{\partial P}{\partial p_1} = (1 - e^{-rs})[\frac{a_1^m - 2p_1 + mc_1}{b_1^m} \\ + \frac{um}{rK}e^{-r\tau}[(p_2 - mc_2)q_2^m(1 - e^{-rs}) + \lambda(p_2^g - mc_2)(q_2^m - q_2^f)(e^{-rs} - e^{-rT})][\frac{a_1^m - 2p_1}{b_1^m}] - um(\frac{a_1^m - 2p_1}{b_1^m})] \\ 0 = \frac{\partial P}{\partial p_1^g} = \lambda[\frac{a_1^m - a_1^f}{b_1^m} - \frac{3b_1^f p_1^g - b_1^m p_1^g}{b_1^m b_1^f} + \frac{b_1^f mc_1 + b_1^m mc_1}{b_1^m b_1^f}] \\ 0 = \frac{\partial P}{\partial p_2} = \frac{e^{-r\tau}ump_1q_1(1-e^{-rs})^2}{rK}\frac{1}{b_2^m}(a_2^m - 2p_2 + mc_2) \\ 0 = \frac{\partial P}{\partial p_2^g} = \lambda\frac{e^{-r\tau}um(1-e^{-rs})(p_1q_1^m)}{rK}(e^{-rs} - e^{-rT})[\frac{a_2^m - a_2^f}{b_2^m} - \frac{3b_2^f p_2^g - b_2^m p_2^g}{b_2^m b_2^f} + \frac{b_2^f mc_2 + b_2^m mc_2}{b_2^m b_2^f}] \end{array} \tag{4.45}$$

From which optimal prices when firm's profits are optimized are

$$\begin{array}{l} p_1^* = \frac{a_2^m}{2} + \frac{mc_1}{(1+\frac{um}{rK}A - um)} \\ p_1^{g,*} = \frac{b_1^f(a_1^m - a_1^f) + (b_1^f + b_1^m)mc_1)}{3b_1^f - b_1^m} \\ p_2^* = \frac{a_2^m + mc_2}{2} \\ p_2^{g,*} = \frac{b_2^f(a_2^m - a_2^f) + (b_2^f + b_2^m)mc_2)}{3b_2^f - b_2^m} \end{array} \tag{4.46}$$

where $A = e^{-r\tau}[(p_2 - mc_2)q_2^m(1 - e^{-rs}) + \lambda(p_2^g - mc_2)(q_2^m - q_2^f)(e^{-rs} - e^{-rT})]$.

Proof of Proposition 1

Now, we let $p_1^{*,W}$ indicate the price optimizing welfare under patents in period 1, and $p_1^{*,\Pi}$ to indicate the price optimizing firm profits under during the period 1 patented period. We then check under which condition $p_1^{*,\Pi} > p_1^{*,W}$. Substituting the expressions 4.8 and 4.46 in, we obtain

$$\frac{a_1^m}{2} + \frac{mc_1}{(1 + \frac{um}{rK}A - um)} \geq \frac{umK}{rK + um(W_2 - K)}[(\frac{W_2 - K}{K})a_1^m + \frac{r}{um}mc_1] \tag{4.47}$$

which is satisfied when

$$a_1^m \geq \Big[\frac{\frac{rK}{rK+um(W_2-K)} - \frac{rK}{rK+umA-umrK}}{\frac{1}{2} - \frac{umK}{rK+um(W_2-K)}} \Big] mc_1 \tag{4.48}$$

Now, assuming that condition 4.48 and 4.25, we have that patented price in period 1 is higher when firm's profits are maximised, compared to when welfare is maximised, and the effect on welfare is negative.

When considering innovation probability, we have that $h(p_1^{*,\Pi}) \geq h(p_1^{*,W})$. Inserting optimal prices in the IPF expression 4.6, we have

$$\frac{ump_1^{*,\Pi} q_1^M(p_1^{*,\Pi})(1-e^{-rs})}{rK} \geq \frac{ump_1^{*,W} q_1^M(p_1^{*,W})(1-e^{-rs})}{rK} \tag{4.49}$$

which simplifies to

$$p_1^{*,\Pi} q_1^M \geq p_1^{*,W} q_1^M(p_1^{*,W}) \tag{4.50}$$

which is always satisfied, as $p_1^{*,\Pi}$ is by definition the price maximising firm's profits.

Value based pricing

With VBP we have that the innovation probability function becomes

$$\rho_2 = muzE(h_1)q_1(1-e^{-rs}) \tag{4.51}$$

Generic expression of consumer surplus

$$\begin{aligned}
CS &= \tfrac{1}{2}(a_1^M - zE(h_1))q_1^M(1-e^{-rs}) + \tfrac{1}{2}\Big(\tfrac{b_1^f a_1^M + b_1^M a_1^f}{b_1^f + b_1^m} - zE(h_1)\Big)q_1^d(e^{-rs}-e^{-rT}) \\
&+[\tfrac{1}{2}(a_1^M + \tfrac{b_1^f a_1^M + b_1^M a_1^f}{b_1^f + b_1^M}) - p_1^g]q_1^f(e^{-rs}-e^{-rT}) \\
&+\tfrac{muzE(h_1)q_1^m(1-e^{-rs})}{rK}e^{-r\tau}[\tfrac{1}{2}(a_2^M - zE(h_2))q_2^M(1-e^{-rs}) + \tfrac{1}{2}\Big(\tfrac{b_2^f a_2^M + b_2^M a_2^f}{b_2^f + b_2^m} - zE(h_2)\Big)q_2^d(e^{-rs}-e^{-rT}) \\
&+[\tfrac{1}{2}(a_2^M + \tfrac{b_2^f a_2^M + b_2^M a_2^f}{b_2^f + b_2^M}) - p_2^g]q_2^f(e^{-rs}-e^{-rT})]
\end{aligned} \tag{4.52}$$

Consumer surplus in individual periods

$$\begin{aligned}
CS_1 &= \tfrac{1}{2}(a_1^M - zE(h_1))q_1^M(1-e^{-rs}) + \tfrac{1}{2}\Big(\tfrac{b_1^f a_1^M + b_1^M a_1^f}{b_1^f + b_1^m} - zE(h_1)\Big)q_1^d(e^{-rs}-e^{-rT}) \\
&+[\tfrac{1}{2}(a_1^M + \tfrac{b_1^f a_1^M + b_1^M a_1^f}{b_1^f + b_1^M}) - p_1^g]q_1^f(e^{-rs}-e^{-rT})
\end{aligned} \tag{4.53}$$

$$\begin{aligned}
CS_2 &= [\tfrac{1}{2}(a_2^M - zE(h_2))q_2^M(1-e^{-rs}) + \tfrac{1}{2}\Big(\tfrac{b_2^f a_2^M + b_2^M a_2^f}{b_2^f + b_2^m} - zE(h_2)\Big)q_2^d(e^{-rs}-e^{-rT}) \\
&+[\tfrac{1}{2}(a_2^M + \tfrac{b_2^f a_2^M + b_2^M a_2^f}{b_2^f + b_2^M}) - p_2^g]q_2^f(e^{-rs}-e^{-rT})]
\end{aligned} \tag{4.54}$$

The derivative of CS with respect to price thus becomes

$$\begin{aligned}
&\tfrac{\partial CS}{\partial z} = -\tfrac{1}{2}E(h_1)q_1^M(1-e^{-rs}) - \tfrac{1}{2}(a_1^m - zE(h_1))\tfrac{1}{b_1^m}(1-e^{-rs}) - \tfrac{1}{2}E(h_1)(q_1^d)(e^{-rs}-e^{-rT}) \\
&+\tfrac{1}{2}(\tfrac{b_1^f a_1^m + b_1^m a_1^f}{b_1^f + b_1^m} - zE(h_1))\tfrac{\partial q_1^d}{\partial z}(e^{-rs}-e^{-rT}) \\
&\tfrac{mu(1-e^{-rs})}{rK}e^{-r\tau}(E(h_1)q_1^m - \tfrac{zE(h_1)}{b_1^m})[\tfrac{1}{2}(a_2^m - zE(h_1))q_2^m(1-e^{-rs}) + \tfrac{1}{2}(\tfrac{b_2^f a_2^m + b_2^m a_2^f}{b_2^f + b_2^m} - zE(h_2))q_2^d(e^{-rs}-e^{-rT}) \\
&+[\tfrac{1}{2}(a_2^m + \tfrac{b_2^f a_2^m + b_2^m a_2^f}{b_2^f + b_2^m}) - p_2^g]q_2^f(e^{-rs}-e^{-rT})] + \tfrac{muzE(h_1)q_1^m(1-e^{-rs})}{rK}e^{-r\tau}[-\tfrac{1}{2}E(h_2)q_2^m(1-e^{-rs}) \\
&-\tfrac{1}{2}(a_2^m - zE(h_2))\tfrac{1}{b_2^m}(1-e^{-rs}) \\
&-\tfrac{1}{2}zq_2^d(e^{-rs}-e^{-rT}) - \tfrac{1}{2}(\tfrac{b_2^f a_2^m + b_2^m a_2^f}{b_2^f + b_2^m} - zE(h_2))(\tfrac{1}{b_2^m} - \tfrac{1}{b_2^f})(e^{-rs}-e^{-rT})]
\end{aligned} \tag{4.55}$$

We can thus write that

$$\frac{\partial CS}{\partial z} = \frac{\partial CS_1}{\partial z} + \frac{\partial \rho_2}{\partial z} CS_2 + \rho_2 \frac{\partial CS}{\partial z} \tag{4.56}$$

Notice that the components $\partial CS_i/\partial z$ for $i = \{1, 2\}$ is now different to the previous expression, as it now includes the consumer surplus generated by drug i after patent expiration.

The generic expression of producer surplus becomes

$$\begin{array}{l} PS(p,s) = (zE(h_1) - mc_i)q_i^M(1-e^{-rs}) + (zE(h_1) - mc_i)q_i^d(e^{-rs} - e^{-rT}) \\ +\frac{1}{2}(p_i^g - a_i^f)q_i^f(e^{-rs} - e^{-rT}) \\ \frac{muzE(h_1)q_1^m(1-e^{-rs})}{rK}e^{-r\tau}[(zE(h_2) - mc_2)q_i^M(1-e^{-rs}) + (zE(h_2) - mc_2)q_2^d(e^{-rs} - e^{-rT}) \\ +\frac{1}{2}(p_2^g - a_2^f)q_2^f(e^{-rs} - e^{-rT})] \\ -muzE(h_1)q_1^m(1-e^{-rs}) \end{array} \tag{4.57}$$

Producer surplus in individual periods are

$$\begin{array}{l} PS_1(p,s) = (p_1 - mc_1)q_1^M(1-e^{-rs}) + (p_1^g - mc_1)q_1^d(e^{-rs} - e^{-rT}) \\ +\frac{1}{2}(p_1^g - a_1^f)q_1^f(e^{-rs} - e^{-rT}) - \frac{1}{r}ump_1q_1^m(1-e^{-rs}) \\ +e^{-r\tau}[(p_2 - mc_2)q_i^M(1-e^{-rs}) + (p_2^g - mc_2)q_2^d(e^{-rs} - e^{-rT}) \\ +\frac{1}{2}(p_2^g - a_2^f)q_2^f(e^{-rs} - e^{-rT})] \\ -muzE(h_1)q_1^m(1-e^{-rs}) \end{array} \tag{4.58}$$

and

$$\begin{array}{l} PS_2(p,s) = e^{-r\tau}[(p_2 - mc_2)q_i^M(1-e^{-rs}) + (p_2^g - mc_2)q_2^d(e^{-rs} - e^{-rT}) \\ +\frac{1}{2}(p_2^g - a_2^f)q_2^f(e^{-rs} - e^{-rT})] \end{array} \tag{4.59}$$

The derivative of PS with respect to z thus becomes

$$\begin{array}{l} \frac{\partial PS}{\partial z} = E(h_1)q_1^m(1-e^{-rs}) - (zE(h_1) - mc_1)\frac{1}{b_1^m}(1-e^{-rs}) + E(h_1)q_1^d(e^{-rs} - e^{-rT}) \\ -(zE(h_1) - mc_1)(\frac{1}{b_1^m} - \frac{1}{b_1^f})(e^{-rs} - e^{-rT}) \\ +\frac{mu(1-e^{-rs})}{rK}e^{-r\tau}(E(h_1) - \frac{1}{b_1^m zE(h_1)})[(zE(h_2) - mc_2)q_2^m(1-e^{-rs}) + (zE(h_2) - mc_2)q_2^d(e^{-rs} - e^{-rT}) \\ +\frac{1}{2}(p_2^g - a_2^f)q_2^f(e^{-rs} - e^{-rT})] \\ +\frac{muzE(h_1)q_1^m(1-e^{-rs})}{rK}e^{-r\tau}[E(h_2)q_2^m(1-e^{-rs}) - \frac{(zE(h_2)-mc_2)}{b_2^m}(1-e^{-rs}) + E(h_2)q_2^d(e^{-rs} - e^{-rT}) \\ -(\frac{1}{b_2^m} - \frac{1}{b_2^f})(zE(h_2) - mc_2)(e^{-rs} - e^{-rT})] \\ -mu(1-e^{-rs})(E(h_1)q_1^m - \frac{zE(h_1)}{b_1^m}) \end{array} \tag{4.60}$$

which can be written as

$$\frac{\partial PS}{\partial z} = \frac{\partial PS}{\partial z} + \frac{\partial \rho_2}{\partial z} PS_2 + \rho_2 \frac{\partial PS_2}{\partial z} - \frac{\partial \rho_2}{\partial z} \tag{4.61}$$

We now consider the derivative of W with respect to z.

$$\begin{array}{l} \frac{\partial W}{\partial z} = \frac{1}{2}E(h_1)q_1^m(1-e^{-rs}) - [\frac{1}{2}(a_1^m + zE(h_1)) - mc_1]\frac{E(h_1)}{b_1^m}(1-e^{-rs}) \\ +\frac{1}{2}E(h_1)q_1^m(e^{-rs} - e^{-rT}) - [\frac{1}{2}[\frac{b_1^f a_1^m + b_1^m a_1^f}{b_1^m + b_1^f} + zEH(h_1)] - mc_1](e^{-rs} - e^{-rT})\frac{E(h_1)}{b_1^m} \\ +\frac{umE(h_1)q_1^m(1-e^{-rs})}{rK}e^{-r\tau}[[\frac{1}{2}(a_2^m + zE(h_2)) - mc_2]q_2^m(1-e^{-rs}) \\ +[\frac{1}{2}[\frac{b_2^f a_2^m + b_2^m a_2^f}{b_2^m + b_2^f} + zE(h_2)] - mc_2]q_2^m(e^{-rs} - e^{-rT}) + [\frac{1}{2}(a_2^m - a_2^f) + mc_2 - p_2^g]q_2^f(e^{-rs} - e^{-rT})] \\ +umzE(h_1)q_1^m(1-e^{-rs})e^{-r\tau}[\frac{1}{2}E(h_2)q_2^m(1-e^{-rs}) - [\frac{1}{2}(a_2^m + zE(h_2)) - mc_1]\frac{E(h_2)}{b_2^m}(1-e^{-rs}) \\ \frac{1}{2}E(h_2)q_2^m(e^{-rs} - e^{-rT}) - [\frac{1}{2}[(\frac{b_2^f a_2^m + b_2^m a_2^f}{b_2^m + b_2^f}) + zE(h_2)] - mc_2](e^{-rs} - e^{-rT})\frac{E(h_2)}{b_2^m}] \\ -\frac{1}{r}um(1-e^{-rs})[E(h_1)q_1^m - \frac{zE(h_1)}{b_1^m}] \end{array} \tag{4.62}$$

Figure 4.5: *Numerical simulations for Consumer Surplus (in green to the left) and Producer Surplus (in blue to the right) for varying values of price (x-axis) and patent length (y-axis).*

which can be written as

$$\frac{\partial W}{\partial z} = \frac{\partial W_1}{\partial z} + \frac{\rho_2}{\partial z} W_2 + \rho_2 \frac{\partial W_2}{\partial z} \tag{4.63}$$

which is higher than zero iff $|\frac{\partial CS_1}{\partial z} \frac{\partial \rho_2}{\partial z}| < \frac{\partial \rho_2}{\partial z}(PS_2 + CS_2) + \rho_2(\frac{\partial CS_2}{\partial z} + \frac{\partial CS}{\partial z})$.

Equations concerning the sign of the derivatives of CS, PS and W with respect to z are not reported because of their analytical complexity.

iv. Proofs with modelling extensions

v. Numerical simulations

We provide the results for the numerical simulations of consumer and producer surplus for varying prices and patent length. Results are reported in Figure 4.5.

The figure shows that consumer surplus is defined as a convex curve in the price p_1 and patent length s space. The opposite relation holds for producer surplus, which is defined as a concave curve in the price and patent space.

Figure 4.6 provides the results for the sensitivity analysis exercise showing optimal price and optimal patent as a function of the discount rate r for different values of the parameter a_{1m}.

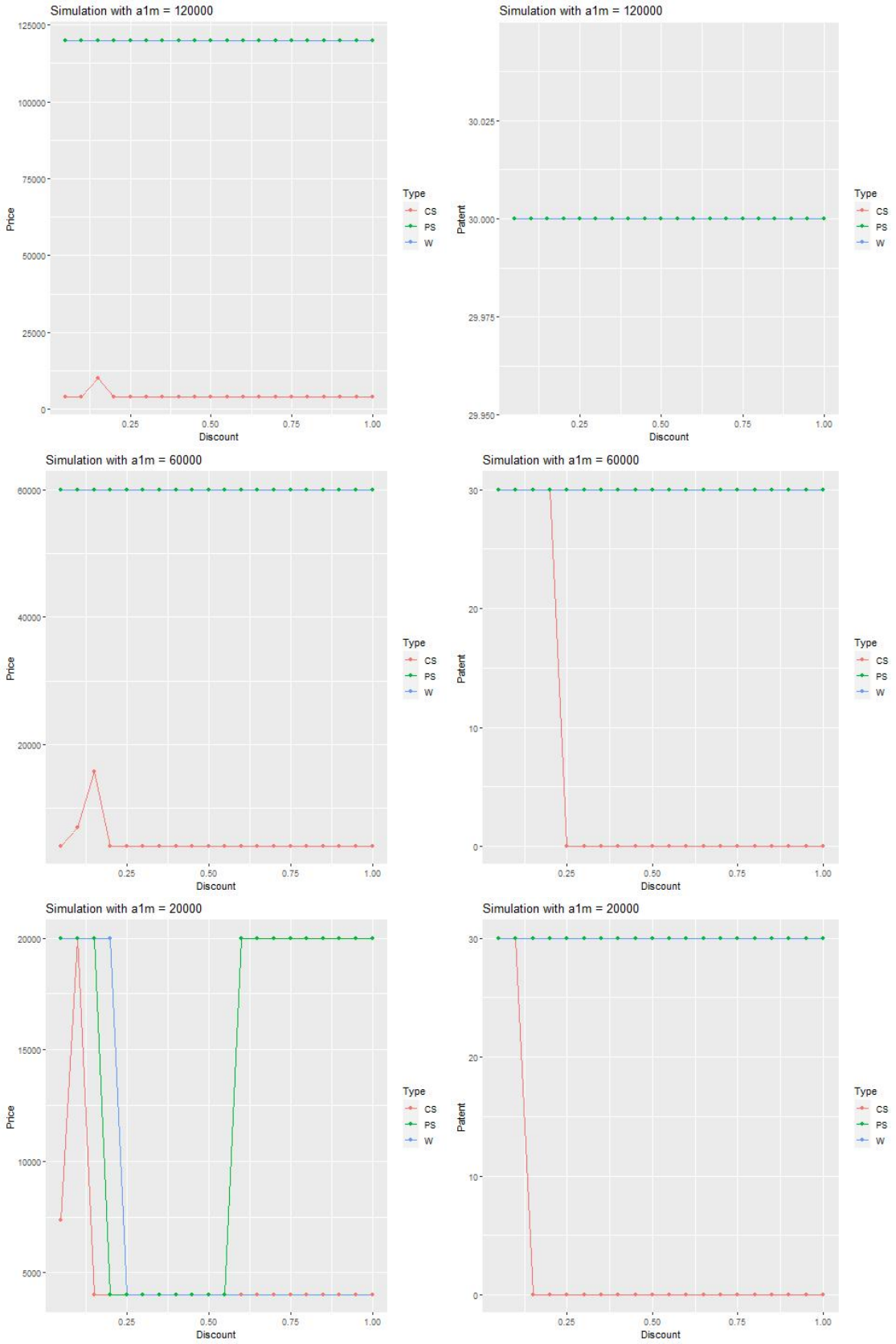


Figure 4.6: *Sensitivity analysis for optimal price (left) and patent (right) as a function of the discount rate r, computed for varying values of the demand function parameter* a_{1m}.

Chapter 5

Conclusions

The purpose of this thesis was to analyse the topic of antibiotic prescription and pharmaceutical innovation through the health economics lens.

The topic of antibiotic prescription is a relevant health issue worldwide due to its association with antibiotic resistance. Research has shown that higher antibiotic consumption leads to increased resistance (Monroe and Polk (2000), Mera et al. (2006)). Resistance, in turn, is associated with a reduced effectiveness of antibiotic drugs in curing infections (Major, 2018). The number of deaths attributed to antibiotic resistance are approximately 700,000 deaths a year globally, with an estimated increase to 10 million deaths worldwide by 2050 (O'Neill, 2014). Even when antibiotic resistance does not imply risk of death, resistant infections require prolonged and/or costlier use of healthcare resources(CDC, 2013). Higher antibiotic resistance, therefore, translates into increased costs for society and for national healthcare systems (European Observatory on Health Systems and Policies (2019), Naylor et al. (2018)). Estimates of healthcare and productivity costs in the EU, for example, amount to 1.5 billion euros per year (European Observatory on Health Systems and Policies, 2019), while the economic burden of antibiotic resistance worldwide has been estimated to a maximum of 3 trillion dollars in GDP costs, although estimates may vary(Naylor et al., 2018).

One of the reasons related to the increase in resistance is the relative lack of innovation in antibiotic drugs. Recent years have seen very little R&D efforts being invested by pharmaceutical companies in the development of new types of antibiotics. The latest versions of antibiotics were, in facts, variations of drugs developed in the early 1980s (BBC Health, 2017). The lack of new types of antibiotic drugs being introduced in the market limits the doctors' prescription possibilities available when treating infections, thus reducing healthcare effectiveness upon the increase of resistance. The fight against antibiotic resistance, therefore, requires a clear understanding of the dynamics of innovation in pharmaceutical products. One way to analyse the dynamics of pharmaceutical markets is to explore how price and patent length affect patients welfare and the probability of innovation. Identifying the impact of price and patent regulation on the development of new drugs, is relevant for the development of new antibiotics.

This thesis addressed the topics of antibiotic prescription and pharmaceutical innovation by introducing three related research questions.

The first research question asked "*what is the impact of stewardship programmes in affecting antibiotic prescribing in European Countries?*". Stewardship programmes are coordinated health interventions aimed at reducing antibiotic prescription via the selection of optimal drug regimens (Fishman, 2012). One of the purposes of this policy is to reduce unnecessary prescriptions which are one of the key factors related to the world-wide increase in resistance World Health Organization (2014). This first research question of this thesis was addressed using survey data from the Eurobarometer, a nationally representative EU-wide survey on citizens' perceptions, which provided data on antibiotic consumption for the years 2008, 2013, 2016 and 2018. The varying degree of implementation of stewardship programmes in European countries makes it important to estimate the impact of such policy in reducing prescription rates. [1] The

[1] See `https://www.who.int/antimicrobial-resistance/national-action-plans/library/en/` for an

asymmetric adoption of stewardship programmes across European countries allowed consideration of the introduction of such policies as a *natural experiment*. According to the definition provided by the UK Medical Research Council, natural experiments (NE) are events not under the control of the researcher and that divide the observed population into exposed and unexposed groups (Craig et al., 2012). The possibility to replicate some characteristics of Randomised Control Trials (RCTs) in situations where the researcher cannot replicate an experiment made NEs widely used for the estimation of the effects of public health interventions (Craig et al., 2017). This thesis addressed the first research question by adopting a *difference-in-difference* approach. Diff-in-diff analysis has been widely used in the healthcare literature to study causal relationship in public health settings (Wing et al., 2018). In proposed study treated countries were those in which stewardship programmes were introduced. The control group was composed of countries where stewardship programmes were still lacking. The analysis controlled for country-specific covariates and for the role of alternative policy measures. Sensitivity analysis exercises were performed to verify the robustness of the results.

The second research question of this thesis asked "*what is the role of spatial dependence in influencing GPs antibiotic prescription rates?*". The concept of spatial dependence has long been an important concept in the healthcare literature, with early contributions dating back to John Snow's pioneering studies in mapping cholera in the area of Soho in London (Snow, 1855). The concept of spatial dependence had its foundations in the econometrics literature with the work by Paelinck and Klaassen (1979) and Anselin (1988). In more recent years, the concept of spatial dependence in antibiotic prescriptions has been addressed by scholars, who identified a role of spatial dependence in influencing antibiotic prescription rates (Gonzalez-Ortiz and Masiero (2013), Filippini et al. (2014)). The third chapter of this thesis addressed the question of the role of spatial dependence in antibiotic prescription rates among English primary care practices using GP prescription data obtained from the English National Health System (NHS) for the years 2013-2017. This data, aggregated at individual practice level, was linked to a set of covariates describing the characteristics of local areas. Spatial dependencies were identified by means of spatial regression analysis, including Spatial Lag (SLX) models, Spatial Autoregressive Models (SAR) and Spatial Error Models (SEM). The use of alternative spatial dependence models allows us to explore the potential sources of spatial dependence to verify the role of random health shocks and resistance externalities from neighbouring areas as potential sources of spatial dependence (Gonzalez-Ortiz and Masiero (2013) and Filippini et al. (2014)). Among the set of confounders we also included a policy variable, namely a dummy indicating the letters received from the Chief Medical Officer (CMO) to over-prescribing GPs to account for the role of local interventions. The inclusion of such indicators allows this research to account for policy interventions occurring at an individual practice level. This study also introduced sensitivity analysis to verify the robustness of the analytical approach.

The third research question of this work was "*what is the impact of value-based pricing in influencing social welfare in a dynamic market with innovation?*". The study of the alternative goal of maximising social welfare while guaranteeing innovation traces back to the seminal work of Arrow (1962) on patent protection. Additional studies in this area looked at guaranteeing intellectual property rights, while at the same time minimising dead-weight losses arising from monopolies (Nordhaus (1969) and Scherer (1972)), although optimal degrees of patent protection were difficult to estimate (Tirole, 2002). In line with this literature, the third chapter looked at the dynamics of pharmaceutical innovation, considering both static and dynamic welfare optimisation, the impact of varying patent length on welfare, and the effect of Value-Based Pricing (VBP) on market dynamics. VBP is a specific pharmaceutical regulation were drug prices are set on drug's expected health benefits (Office of Health Economics (2007) and Moise and Docteur (2007)). The purpose of this regulation is to incentivise research in areas of higher unmet need, while at the same time guaranteeing price containment. Understanding the interplay of static and dynamic trade-off in a market with prices related to realised health benefits might shed new light on the effectiveness of VBP policy. The third research question of this thesis is related to the topic of antibiotics as one of the reasons why resistance is on the rise is thought to be the lack of newly developed antibiotic drugs (BBC Health, 2017). Analysing the conditions for pharmaceutical innovation is thus important to understand how to tackle antibiotic resistance.

Answering these three research questions provides a broad perspective on the topic of antibiotic

indication of the implementation of stewardship programmes in EU countries.

prescription. In this thesis the topic of antibiotics prescription is addressed by looking at the role played by policy interventions in reducing antibiotic consumption, the role of geographical and spatial linkages across practices in influencing prescription behaviour, and the role that pharmaceutical innovation and regulation might have on the development of new antibiotic drugs. These three perspectives, considered together, might provide policy makers with insights on different angles of antibiotic resistance.

The first paper provides a number of contributions to existing knowledge on the effectiveness of antibiotic policies in European countries. First, we identify that the introduction of stewardship programmes had an impact in reducing the provision of antibiotics across European countries. This result might prove useful for countries that have not yet adopted stewardship programmes. In addition, this study finds that stewardship programmes are effective in reducing prescription rates both for all antibiotic prescription as well as for individual antibiotic classes. This result appears to indicate that stewardship programmes are effective across the whole range of antibiotic prescriptions. The results identified in the second chapter of this thesis are robust to a number of alternative specification and robustness checks, such as introducing alternative policy variables such as National Action Plans (NAP). We interpret this result as an indication that stewardship programmes are effective in reducing prescription rates because they affect doctors' behaviour, while NAPs, which are certainly useful in the policy debate, might be less effective in immediately influencing prescription. Stewardship programmes are also found to impact patients' beliefs concerning antibiotics. This result is relevant because it indicates that stewardship programmes have the potential to change patients' perspective on antibiotics and the risk of resistance arising from over-prescription. The results found in the second chapter of this thesis expand the limited literature on the effectiveness of policy interventions in reducing antibiotic consumption (Bou-Antoun et al., 2018).

The analysis proposed in the second chapter of this thesis extends the existing literature on the comparison of antibiotic consumption across different nations, with a particular focus on European countries. The existing literature on cross-country comparison of antibiotic prescription rates has found a high degree of heterogeneity in prescription rates across different healthcare systems (see Elseviers et al. (2007) and O'Neill (2014)). In addition, the literature on cross-country comparison of antibiotic prescription rates highlights that healthcare systems might provide different incentives for the adoption of antibiotics (Blommaert (2014) and Klein et al. (2018)). Also, cross-national comparisons allow for benchmark in the performance of different healthcare systems. The analysis proposed in the third chapter of this thesis confirms the results proposed by the literature on cross-country comparison, confirming the results of significant differences across individual countries, once other factors are accounted for. Individual healthcare systems, therefore, appear to provide different prescription rates even when respondents', country and policy variables are introduced in the analysis.

Lastly, the second chapter of this thesis expands the existing literature concerned with applying difference-in-difference methodology to health economics problems, and to antibiotic consumption more specifically. The diff-in-diff methodology has been used extensively in the healthcare literature (see Wing et al. (2018) for a thorough review), however, to the best of our knowledge, it has not yet been used in the literature to estimate the impact of stewardship programmes on antibiotic prescription. This chapter shows the effectiveness of diff-in-diff in estimating the impact of policy interventions in reducing antibiotic consumption, via a repeated cross-section analysis. This analysis, therefore, provides an additional case highlighting the usefulness of such approach in helping policy-makers in estimating the impact of healthcare interventions.

The second paper of this thesis identifies the presence of spatial dependence in antibiotic prescription rates across English GP practices. Spatial dependence is found to be significant for varying definitions of spatial weights, namely administrative and geographical weights. This result confirms the approach proposed by Lippi Bruni and Mammi (2016), highlighting the usefulness of adopting a mixture of spatial and administrative weights in estimating spatial dependence in antibiotic prescription. In addition, dependence is found both when considering prescription rates of all antibiotics as well as for individual antibiotic classes. This result indicates that spatial dependence is therefore present across the whole spectrum of antibiotic prescriptions. Model results are robust to alternative specification of the dependent variable, such as the total prescribed antibiotics over all prescribed drugs of the individual practice. This chapter also highlights potential alternative explanations for spatial dependence. This is inferred by

identifying significant spatial effects in the SLX and SEM model, but not in the SAR model. This result appears to indicate that spatial dependence is driven mostly by random health shocks rather than by the direct consequence of antibiotic resistance in neighbouring areas. These results provide additional evidence in determining the reasons behind of spatial dependence in antibiotic prescription extending the type of results presented by Gonzalez-Ortiz and Masiero (2013) and Filippini et al. (2014) concerning the source of spatial dependence. Although these initial results are promising, an in-depth understanding of the mechanics behind spatial dependence in antibiotic prescribing will require additional research.

The analysis presented in the third chapter of this thesis expands the current knowledge on spatial dependence methods applied to health economics problems, and on antibiotic prescription more specifically. This is achieved by applying spatial dependence techniques to a new dataset for the English case. In addition, given the data availability for the years 2013 to 2017, the dataset allows for the development of a panel analysis, while other existing studies were based on cross-section analysis (Filippini et al., 2014). The richness of the dataset allows for the spatial analysis of individual antibiotic classes. To the best of our knowledge, an analysis of spatial dependence of individual antibiotic classes has not been attempted before. In addition, this study expands the strand of literature of spatial dependence by providing a more thorough analysis of the potential motivations of its presence in antibiotic prescriptions. Lastly, the identification of spatial dependence in antibiotic prescription rates might imply that quantitative studies on antibiotic prescription which did not account for spatial dependence may be subject to bias due to the lack of integration of the spatial dimension of the phenomenon.

The fourth chapter of this thesis identifies a number of results concerning innovation in the pharmaceutical market. First it identifies a trade-off between static and dynamic optimisation of social welfare in a two periods model of a pharmaceutical market with innovation. This trade-off highlights a balance between welfare optimisation in individual periods and the need for R&D investments to optimise welfare inter-temporally. Second, this paper provides insights concerning the impact of a variation of patent length on social welfare. Patent length is therefore found to influence social welfare, allowing various degrees of appropriation of intellectual property rights to the innovating firm. Third, this chapter identifies that VBP policy introduces distortions in the dynamics of pharmaceutical markets. By fixing prices to the expected health benefits of the newly introduced drug, price regulation alters market dynamics. Lastly, the numerical simulation proposed in this chapter identify a link between realised health benefits of newly discovered drugs and the optimal proportion used as pricing decided by the regulator. This result, therefore, highlights that policy makers would need to be careful in fixing prices to the right proportion of realised health benefits if their goal is to optimise realised welfare.

The fourth chapter of this thesis provides a contribution to different strands of the health economics literature. First, this chapter expands the literature on static versus dynamic optimisation of social welfare in pharmaceutical markets with R&D. This is achieved by exploring the impact that price variation has on single period welfare and on innovation. This work therefore is in line with the work introduced by Dorfman and Steiner (1954) and Arrow (1962) related to R&D investments and patent protection, which highlight a need of balance between patent protection and welfare. Second, this chapter expands the existing knowledge on the implications of patent length on welfare optimisation by estimating the impact of patent variation on optimal welfare. This second type of results fits in the strand of literature defined by the work by Tirole (2002) concerning the determination of optimal patent length. In our case the determination of optimal patent length is provided via numerical simulation. Third, this paper expands the literature on pharmaceutical regulation by providing an in-depth analysis of value-based pricing, expanding the still limited literature on VBP and its impact on static versus dynamic efficiency (Danzon, 2018).

The studies presented in this thesis have a number of policy implications.

The results of the second chapter of this thesis shows the effectiveness of stewardship programmes in reducing antibiotic consumption. The identified effectiveness of these programmes in reducing consumption appear to be robust to sensitivity analysis. The results presented in this chapter could provide a basis for further economic evaluation of stewardship programmes and their cost-effectiveness. Policy makers from countries that have not yet introduced such policies should consider developing stewardship

programmes to reduce antibiotic consumption. Similarly, stewardship programmes proved to be effective in influencing public opinion on antibiotics and their appropriate use. Policy makers should consider developing stewardship programmes together with targeted communication interventions to increase public awareness on the correct use of antibiotics. Lastly, over-national bodies should consider the presence of country-specific differences in antibiotic prescription rates when developing targeted policies, and in developing specific interventions aimed ad closing the gap between worst and best performing countries. While these result do not exhaust the possible evidence available on stewardship programmes, they provide a useful starting point for policy makers to evaluate the effectiveness of such policies.

The results of the third chapter of this thesis suggest that policy makers should take spatial dependence into account when developing new policies related to antibiotic consumption. Correctly identifying the mechanisms through which spatial dependence occurs, even via qualitative methods, is important to ensure effectiveness of future policies targeted at reducing antibiotic prescription. This chapter identifies that spatial dependence is clearly not only due to CCG-wide factors. On the contrary, the study presented in this chapter favours random health shocks as a source of spatial dependence, as opposed to dependence arising from resistance externalities from neighbouring practices. Policy makers who are interested in reducing antibiotic prescription rates should be careful in identifying effective ways to influence doctors' behaviour, even when random health shocks are at play. Future policies might also allow for a coordination of national and local interventions to address spatial dependence in prescription. Institutional and geographical considerations should be considered when developing policies targeted to the reduction of antibiotic prescription, thus requiring a higher coordination in the policy efforts of local bodies.

When it comes to pharmaceutical innovation, policy makers should take into consideration the inter-temporal aspects of R&D. The introduction of pharmaceutical pricing regulation aimed at welfare maximisation in individual periods might alter optimal welfare inter-temporally, therefore the development of new policies should consider their impact over time. Second, policy makers aiming for a specific goal such as welfare optimisation or cost containment should be aware of the impact of proposed policies on pharmaceutical innovation. To achieve a goal of cost containment without impacting innovation, policy makers might use additional regulatory levers such as the trade-off between price and patent length. Identifying the correct patent and price trade-off might guarantee the right amount of welfare and innovation, while achieving cost containment. Third, pharmaceutical regulators who are interested in considering value-based pricing regulation should be aware of its potential distortionary effects on market dynamics. In addition, as shown via simulation, regulators interested in introducing VBP should be aware that the introduction of such policy requires careful consideration concerning the appropriate proportion of realised health benefits as price of the new pharmaceuticals.

The studies presented in this thesis were subject to a number of limitations. The first chapter of this thesis, concerning the impact of stewardship programmes on antibiotic consumption, is subject to data limitations concerning potential confounders of antibiotics prescription. Including variables such as co-payments or the amount of healthcare expenditure per head might have an association with antibiotic prescription. Data associated to those variables, however, was not available for all countries in the considered years. Second, the studies on the impact of stewardship programmes and on spatial dependence in antibiotic prescription did not take into consideration the role of antibiotic resistance. While considering antibiotic resistance might introduce issues related to endogeneity, it is important to recognise that antibiotic consumption and antibiotic prescription might both be affected by resistance levels. The introduction of resistance was not possible because of data limitations and because of the lack of possible instruments to address endogeneity on antibiotic consumption and prescription rates. The chapter on value-based pricing regulation was subject to limitations related to the possibility of solving the model analytically, therefore numerical simulation was used. In addition, we allowed for VBP to be a fixed proportion of realised health benefits of newly developed drugs. Alternative specifications of value-based pricing could be conceived, such as considering different pricing proportions for different drug classes.

Future research might build on the results presented in this thesis. The analysis of stewardship programmes could be enriched by introducing the role of antibiotic resistance. Estimating the effectiveness of stewardship programmes on reducing antibiotic resistance might provide additional evidence of the usefulness of such programmes. A similar result could be explored for the analysis of spatial dependence

in antibiotic prescription rates. The inclusion of antibiotic resistance as a confounder would requires addressing the issue of endogeneity, resulting from the simultaneity of both consumption and prescription with resistance, by identified appropriate instruments. Nonetheless, the introduction of proxies of antibiotic resistance among the covariates of the analysis might provide further evidence on the sources of spatial dependence in antibiotic prescription rates allowing researcher to explore the sources of spatial dependence further. Lastly, researchers could use the results provided in value-based pricing paper to explore alternative specification of the VBP policy in a dynamic context. Alternative specifications of VBP might thus prove to reduce the potential distortionary effects of this pricing policy, while at the same time fulfilling its purposes, namely satisfying unmet needs while guaranteeing cost containment.

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