



**How do hospital characteristics and ties relate to the uptake of second-generation biosimilars? A longitudinal analysis of Portuguese NHS hospitals, 2015-2021.**

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**Title**

How do hospital characteristics and ties relate to the uptake of second-generation biosimilars?

A longitudinal analysis of Portuguese NHS hospitals, 2015-2021.

**Abstract (max. 200 words)*****Background***

There is limited evidence on within-country discrepancies in biosimilar uptake. This study analyzes differences in timing and diffusion of biosimilar uptake across Portuguese NHS hospitals and explores possible determinants.

***Research design and methods***

We analyzed publicly accessible consumption data of originator biologic and biosimilar drugs for adalimumab, etanercept, infliximab, rituximab, and trastuzumab, by hospital and month for the years 2015-2021 (N=9,467). We modeled the time to biosimilar adoption using survival regression models and the share of biosimilar consumption using generalized estimated equations with random hospital effects.

***Results***

Academic hospitals were characterized by a quicker uptake of adalimumab and infliximab biosimilars but lower shares for other drugs. A higher total consumption of biologics was related to a lower share of biosimilar uptake. A stronger participation in randomized controlled trials was linked to higher biosimilar shares and quicker uptake, except for rituximab. If all NHS hospitals had biosimilar shares equal to the highest ones, potential annual savings could reach 13.9 million euros.

***Conclusion***

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3 The findings suggest a need for capacity-building on biosimilar prescribing, including for  
4 doctors of academic hospitals and those working in settings where high biosimilar use would  
5  
6 be expected.  
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### 9 10 **Keywords**

11  
12 Biosimilar; uptake; diffusion; intra-country differences; hospital-related determinants; savings;  
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14 Portugal.  
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### 16 17 **1. Introduction**

18  
19 In the last decade, health systems have been challenged by the market entry of new drugs with  
20 high prices(1–4). This is the case mainly for biologics and specialty drugs with extremely high  
21 prices in some therapeutical areas, such as oncology and rare diseases (5–7). In a context of  
22 tight public budgets, especially constrained by a sluggish economic environment, improved  
23 efficiency is crucial. Promoting competition in off-patent markets may contribute to this  
24 efficiency, with increasing penetration of generics and biosimilars(8–11).  
25

26  
27 In 2021 biologic drugs accounted for 78.6 billion euros in spending, and 34% of drug  
28 expenditures in Europe(12). Among these, 80% of the main nine therapy classes were exposed  
29 to biosimilar competition. Biosimilars are highly similar to biological drugs and are approved  
30 with the “same high standards of quality, safety and efficacy” (13); their similar efficacy and  
31 safety outcomes have been shown in many observational and experimental studies (14–16).  
32 According to a joint statement published by the European Medicines Agency and the Head of  
33 Medicines Agencies in European Union Member States in September 2022, biosimilars  
34 approved in the EU are considered interchangeable(17). However, the savings potential appears  
35 not to have been fully exploited(18). There are some limitations on the supply side, such as  
36 patent litigation(19), but a major hindering factor for best exploiting the savings potential is  
37 limited uptake of biosimilars in practice, for several reasons. These include physicians’  
38 resistance to modify prescription choices based on economic arguments (20), while questioning  
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3 the similar efficacy and safety(21,22); by originator pharmaceutical companies threatening to  
4 withdraw rebates in the event of therapeutic switch (23); and by patients' reluctance to change  
5 well-functioning therapies, with the need, in some cases, to change the administration mode  
6 (24–26). Yet these behaviors are variable and strongly influenced by contextual factors, namely  
7 the policies favoring or not the uptake of biosimilars.

### 14 ***1.1. Cross-country variation and biosimilar policies***

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16 Substantial differences in the biosimilar market shares are observed across European countries,  
17 for instance in oncology, with biosimilar market shares ranging between 9% (Bulgaria) and  
18 94% (Denmark) in 2021(12). A major explanation for such discrepancies is the cross-country  
19 differences in policies related to biosimilar drugs, in terms of pricing policies (e.g., with or  
20 without linkage of biosimilar prices to originator ones; the specific design of external or  
21 internal reference pricing; and the use of tendering) and demand-side measures. Some countries  
22 have created incentives for biosimilar prescribing, based on quotas or prescription guidelines;  
23 direct replacement of the biologic originator with a biosimilar by pharmacists (allowed in a few  
24 countries); and the fact that the availability of educational programs directed to physicians,  
25 patients, and/or patients' associations varies(27,28).

26  
27 Recent contributions have highlighted the importance of coupling demand-side policies (e.g.,  
28 guidelines, quotas, INN prescribing) with pricing policies (e.g., tendering and price linkage),  
29 to enhance competition and savings (28,29). The recent example of Denmark was enlightening,  
30 with a large adoption of biosimilar adalimumab within a few weeks, based on a central multi-  
31 winner tendering on the supply side and specific guidelines before the biosimilar entry on the  
32 demand side (30). A survey for EU countries showed, also for the case of adalimumab, that  
33 tendering enhances competition and reduces prices, when coupled with early guidelines and  
34 physicians' and patients' education(31). Other policy dimensions are noticeable at an upper  
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3 regulatory level, such as differences in attributing the interchangeability designation or  
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5 differences in regulating patent litigation (32).  
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### 7 ***1.2 Within-country variation and biosimilar policies***

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10 Adding to the differences across countries, biosimilar uptake may also vary within-country,  
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12 across regions, or between health care facilities, as shown by a body of evidence (21,33–35)  
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14 that is, however, fairly limited.  
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17 Reasons for the intra-country differences have been examined by only a few studies. Three  
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19 recent studies may be highlighted, all based on mixed-method approaches. A study for  
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21 Germany observed substantial regional differences in biosimilar market shares; the  
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23 stakeholders who were interviewed attributed differences to the active use of quotas (i.e., with  
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25 or without clear monitoring and sanctioning processes), and to active communication strategies  
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27 by regional physician associations(20). A similar approach was used to examine the large  
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29 cross-county differences in biosimilar market shares in Sweden. Interviewees attributed  
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31 variations to price differences between biosimilars and originator drugs, to local guidelines and  
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33 their follow-up, and to the possibility of keeping savings to be reallocated to other therapeutic  
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35 areas, or to treat more patients (“gain sharing”)(34). In the same study a quantitative analysis  
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37 also showed that price differences between the biosimilar and originator drug accounted for  
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39 59% of cross-county variation in biosimilar market shares. Finally, large regional discrepancies  
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41 were observed in the UK. In interviews stakeholders highlighted the role of price differences,  
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43 gain sharing to providers prescribing biosimilars, and leadership by regional NHS offices(33).  
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### 49 ***1.3. The Portuguese case***

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51 The case of Portugal is of special interest because in the European Union it is among the bottom  
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53 third group of countries in GDP per capita, while the country has been facing tight public  
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55 budgets and recurring financial deficits. At the same time the National Health Service (NHS,  
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57 called *Serviço Nacional de Saúde / SNS*) guarantees universal coverage and charges low co-  
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3 payments for a considerable number of pharmaceuticals, while medicines delivered or  
4 administered in hospitals, such as biologic drugs, are free of charge for the patients. This makes  
5 Portugal comparable to many countries worldwide in which the public health service is  
6 struggling to reduce costs while guaranteeing quality and universal access.  
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12 In the Portuguese NHS, new biologic drugs are approved for reimbursement based on a health  
13 technology assessment mechanism including an economic evaluation, and prices are set based  
14 on external price referencing (this topic and the following are regulated by the Decree-Law  
15 97/2015, approved the 1<sup>st</sup> of June 2016). Biosimilar drugs can be financed provided that their  
16 price is at least 20% lower than that of the originator, similar to the linkage existing in other  
17 countries (e.g., Belgium, France, and Spain). Biosimilars are mainly provided in hospitals and  
18 are fully reimbursed. A centralized tendering is in place for inpatient biosimilars only, so most  
19 biosimilars are procured individually by hospitals, with the possibility of confidential discounts  
20 and ex-post rebates for the hospitals.  
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33 NHS hospitals are financed through global budgets, based on negotiated price-volume  
34 contracts. A small portion (5%) of the budget is attributed based on performance whereby the  
35 share of biosimilars is one indicator among several used to measure performance (high  
36 performance is attributed when the share is above 20%). Hospitals are residual claimants on  
37 potential profits, but this occurs very rarely in practice due to recurring deficits.  
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44 Close to what exists in most EU countries(28), guidelines recommend the prescription of the  
45 lowest-priced drug for naïve patients, but substitution by the pharmacist is not allowed. In this  
46 sense, the Portuguese NHS case may be considered as representative of several other EU  
47 countries in terms of biosimilar policies. Note, however, that Portuguese NHS hospitals have  
48 been facing severe financing constraints in the recent past, which may trigger a quick uptake  
49 of efficiency measures. Also, clinical guidelines suffer from severe limitations: they are rarely  
50 produced in a timely fashion, and never before the biosimilar has been approved for financing;  
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3 there is no systematic monitoring of the guidelines' application at hospitals; and there is no  
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5 management support to help hospitals implement the guidelines in practice.  
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#### 7 8 **1.4. Research questions**

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10 This study examines biosimilars' adoption across the Portuguese NHS hospitals, determinants  
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12 for possible differences, and the potential savings associated with adoption. In exploring the  
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14 impact of public hospital characteristics on biosimilar uptake, we seek to answer four main  
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16 questions, each of which is based on a hypothesis that may be contested. First, academic  
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18 hospitals and those with higher consumption of biologic drugs are expected to be more willing  
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20 to adopt biosimilars because of greater expected savings and more competences to  
21  
22 acknowledge interchangeability. Second, hospitals performing more randomized controlled  
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24 trials (RCT) related to originator drugs may be more reluctant to adopt biosimilars because of  
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26 marketing activities and rebates from pharmaceutical firms. Third, we assume that hospitals  
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28 with higher debts will be more inclined to adopt biosimilars in order to increase efficiency and  
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30 reduce spending. Fourth, it is expected that biosimilar adoption may increase over time.  
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## 35 **2. Methods**

### 36 **2.1 Data**

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38 We used data from the “Transparency Platform of the NHS”  
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40 (<https://www.sns.gov.pt/transparencia/>, accessed on 14 February 2022), which provides  
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42 publicly accessible monthly information, by hospital, on the consumption of originator biologic  
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44 and biosimilar drugs. The data refer only to the total consumption for the originator and  
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46 biosimilar drugs, without distinguishing which biosimilar of usually several available  
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48 biosimilar drugs was used. Therefore, we will refer hereinafter to “biosimilar drugs” in a  
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50 generic manner, without further details about brands or number of available presentations.  
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55 Data have been available since January 2015, meaning that we analyzed the biosimilars with a  
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57 positive NHS reimbursement decision only after that date (i.e., a decision that guarantees NHS  
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3 financing for the drug), and for which complete monthly data were available. We also excluded  
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5 molecules for which the observation period was too small or with too many missing  
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7 observations (sodic enoxaparine, epoietin), and one molecule for which the rate of biosimilar  
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9 was almost 100% over the complete period (filgrastim). This limited our sample to the  
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11 following five molecules: adalimumab (first consumption record in November 2018),  
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13 etanercept (October 2016), infliximab (January 2015), rituximab (January 2016), and  
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15 trastuzumab (May 2018). The last available month was July 2021, and our sample thus included  
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17 information for 5 molecules over 79 months, for 39 NHS hospitals. Indeed, we removed from  
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19 the sample hospitals with considerable missing data (data available for fewer than 100 of 345  
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21 per-hospital observations), all corresponding to small, specialized hospitals, and to public-  
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23 private partnerships for which data were available only from 2021 on. Our final sample  
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25 included 9,467 observations.  
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## 30 ***2.2 Explanatory factors***

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32 We used two groups of explanatory variables, namely, the general hospitals' characteristics,  
33  
34 and their ties to originator firms (variables are detailed in Table 1).  
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38 In the first dimension, we included as explanatory variable the academic vs. non-academic  
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40 hospital status. We also factored in the total monthly consumption of biological drugs  
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42 (volume), as proxy of the number of patients under treatment and to reflect the dimension of  
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44 potential savings. We also included information on each hospital case mix index (CMI), which  
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46 is the average complexity of inpatient stays and outpatient consultations, based on the relative  
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48 weights of Diagnosis Related Groups. This information was made available for the year 2015  
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50 only. In the absence of more recent data we applied this value to all years.  
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54 In the second dimension we included the total number of ongoing RCTs over the complete  
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56 period as proxy of the hospital relationship to the pharmaceutical industry supplying originator  
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58 products. We used the total number of RCTs for any drug, either biologic or not. This was used  
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3 in the absence of more specific factors regarding the relationship, such as the marketing  
4 expenses by pharmaceutical firms for the hospital or the number of visits by these firms to the  
5 hospital. The participation in RCTs primarily signals the hospital's interest in innovation and  
6 scientific activities and is accompanied by a close link to the manufacturer that developed the  
7 drug being evaluated, designed the study, influenced the selection of hospital sites, convinced  
8 their professionals to participate, financed the trial, and closely collaborated with professionals  
9 in the implementation of the study and interpretation of its results.

10 We also included the respective share per originator pharmaceutical firm in the expenditure  
11 data per hospital as a proxy of the firm portfolio in the hospital in order to gain an awareness  
12 of possible closer relationships. We retrieved contracts with pharmaceutical firms and  
13 eliminated all joint contracts, that is, those that involved various pharmaceutical firms, given  
14 that we could not identify the share related to the firm of interest. Overall, 1,478 Abbvie  
15 contracts were included, 3,525 MSD contracts, 3,136 Pfizer contracts, and 3,637 Roche  
16 contracts. This variable was divided by the total pharmaceutical expenditure by hospital/year,  
17 to obtain the share of each firm in each hospital portfolio, per year. Unfortunately, the same  
18 exercise could not be performed for biosimilar drugs, since we did not know which biosimilar  
19 was consumed, and which firm commercialized it. We also considered in the analysis of the  
20 biosimilar share, the time since the biosimilar was launched, in months.

21 Finally, an additional analysis was performed to investigate whether hospitals that are more  
22 indebted were more inclined to adopt biosimilars earlier and to a greater extent. To do so, we  
23 accessed data on overdue debt by the end of each year, which are publicly available through  
24 the Transparency Platform, and calculated its burden as the percentage of overdue debt on total  
25 annual expenditures. Unfortunately, we were able to obtain data on expenditures for only the  
26 years 2016 to 2019, so that this analysis was performed only for this shorter period.

### 27 ***2.3 Statistical analysis***

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3 We first performed a survival analysis on the time to adoption of the biosimilar. The month of  
4 adoption was defined as the earliest month with consumption of the biosimilar in any hospital.  
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6 We could have opted instead for the official date of approval for NHS financing, but we  
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8 rejected this option because time may elapse between approval and purchasing contracts and  
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10 their use can be implemented.  
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14 Survival regressions were performed on the time to adoption. We first tested the proportional  
15 hazard assumption by checking if the association with explanatory variables varied with time  
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17 (if this were the case, then the proportional hazard assumption would be rejected). We used  
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19 parametric models because the assumption was not fulfilled (Table A1, appendix). In cases for  
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21 which parametric models were adopted we selected the most appropriate distribution using the  
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23 Akaike Information Criterion (Table A2, appendix).  
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27 We then modeled the share of biosimilar consumption on the total consumption of biologic  
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29 drugs. Since we had repeated observations per hospital and month, we used panel data analysis  
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31 techniques, namely generalized estimated equations with random hospital effects. The choice  
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33 of random effects was determined by all explanatory variables that were hospital-fixed  
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35 characteristics. We modeled the share as function of the same explanatory variables used in the  
36  
37 survival analysis, adding however a variable for the time since the biosimilar approval. We  
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39 used negative binomial models, which were the most appropriate based on the AIC (Table A3,  
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41 appendix) and because it is appropriate when there are many zero values in the data. Both  
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43 survival and panel-data regressions were first performed by medicine (INN). The Stata13  
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45 software was used for all analyses.  
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#### 48 49 50 51 ***2.4 Estimate of savings potential***

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53 For modeling the savings potential in different scenarios, we developed a base case scenario  
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55 based on 2020 total hospital expenditure (latest year with complete data). The expenditure was  
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57 determined using the consumption data of each drug multiplied by its average price, for the  
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3 originator and the biosimilar drug, respectively. The price data of originator and biosimilar  
4 drugs were provided by APOGEN, for the year 2020 through data collected by IQVIA  
5 (confidential data on file). The prices are those that were effectively paid by hospitals,  
6 accounting for rebates in the case of originator drugs and for the biosimilar actually selected  
7 by the hospital. We calculated potential savings by measuring the total expenditures for each  
8 hospital for the year 2020, if they behaved as the hospital with the highest share of biosimilars  
9 during that year.

### 19 **3. Results**

21 For the five medicines under analysis, we observed an increasing consumption quota for  
22 biosimilars over time, while the originator share decreased (Figure 1). In July 2021 the  
23 biosimilar quota was more than 90% for infliximab and above 80% for rituximab. However,  
24 for adalimumab, etanercept, and trastuzumab, the shares of all their biosimilars used in  
25 hospitals was approximately the same as for the respective shares of the biological originator  
26 products. We observed a high inconsistency in the biosimilar consumption share by hospital,  
27 by June 2021 (the last month in our sample) (Figure 2). In the case of adalimumab, etanercept,  
28 infliximab, and trastuzumab, values go from zero to 100%, while they vary between 55% and  
29 100% in the case of rituximab.

31 The median time from first use (launch) to adoption was the lowest for adalimumab (22  
32 months), followed by trastuzumab (27 months), etanercept (37 months), and rituximab and  
33 infliximab (46 months) (Table 2). The uptake time was slightly quicker at academic hospitals,  
34 and at hospitals with more RCTs. Results were variable regarding the case mix, the  
35 consumption of biologics, and the originator firms' portfolio. The highest share over the period  
36 was observed for infliximab (54.2%) and rituximab (42.1%). Shares were generally larger at  
37 high-consuming hospitals, while no clear pattern emerges for the other variables.

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3 Survival analysis depicted a faster uptake at academic hospitals of adalimumab (HR=1.75) and  
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Survival analysis depicted a faster uptake at academic hospitals of adalimumab (HR=1.75) and  
infliximab (HR=1.27), but this status was not statistically associated with uptake for other  
medicines (Table 3). A greater consumption of biologic drugs was linked to a quicker uptake  
for trastuzumab (HR=1.37) and etanercept (HR=1.18), but to a slower uptake of infliximab  
(HR=0.77). The relationship with case mix was never significant, except for infliximab, for  
which a lower CMI was linked to a quicker uptake. A greater participation in RCTs was linked  
to a more rapid adoption of etanercept (HR=1.35) and infliximab (HR=1.14) biosimilars, while  
the link was weak for the other medicines. The highest relationship with originator firm was  
significantly positive for rituximab (HR=1.16) and not significant in the other cases.

For all drugs, we observed that the time after biosimilar first use was positively related to the  
share of biosimilars. A lower share among academic hospitals was observed for all drugs except  
adalimumab, but none of the links were significant. A lower consumption of biologic drugs, a  
higher number of RCTs, and a lower case mix index were related to a higher share of  
biosimilars, except for rituximab. The share of originator firm in the hospital portfolio was  
inversely related to the adalimumab (beta=-1.14) and etanercept (beta=-1.07) biosimilar  
quotas, but positively related to other biosimilar medicines (although results were not  
significant).

The additional analysis on the overdue debt burden on the restricted sample (2016-2019 period)  
showed that this factor was significantly related to earlier uptake of adalimumab and rituximab,  
to a higher share of rituximab, but to a lower share of adalimumab and etanercept (appendix,  
Table A4).

We then calculated the potential savings if all hospitals performed as those with the highest  
share of biosimilars, and we obtained potential savings of 20.796 million euros for  
adalimumab, 20.439 million euros for etanercept, 20.692 million euros for infliximab, 33,200  
euros for rituximab, and 12.915 million euros for trastuzumab (Table 4). Savings ranged from

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3 9% (etanercept) to 32% (trastuzumab) on total expenditures for the drug. In total, potential  
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5 annual savings would reach 13.9 million euros, only for the five drugs we evaluated (i.e., 1%  
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7 of total hospital drug expenditures for the year 2020).  
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## 10 **4. Discussion**

### 11 **4.1 Key findings**

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14 Overall, hospital biosimilar utilization shares reached 50% or more in the three years following  
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16 their first use, for the five molecules studied. Yet, these shares were characterized by high  
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18 heterogeneity, ranging from no use in some hospitals to exclusive use of biosimilars in others.  
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20 A longer delay in biosimilar adoption was observed for rituximab and infliximab, which  
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22 nevertheless experienced a greater biosimilar share throughout the period; although their  
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24 uptake was quicker, the lowest shares were observed for etanercept and adalimumab. Academic  
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26 hospitals were characterized by a quicker uptake of adalimumab and infliximab biosimilars but  
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28 lower shares of biosimilars for all except one drug. Except for rituximab, a higher consumption  
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30 of biologics was related to a lower share of biosimilar uptake. More RCTs were linked to a  
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32 greater biosimilar share except for rituximab, and a quicker uptake for all drugs; a greater share  
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34 of originator portfolio was linked to quicker uptake for all drugs, while the link with shares  
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36 was negative for adalimumab and infliximab but positive for the other drugs. A higher burden  
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38 of hospital overdue debt was related to an earlier uptake of adalimumab and rituximab, but the  
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40 link with biosimilar share was ambiguous. Finally, huge discrepancies across hospitals, ranging  
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42 from 0% to 100% biosimilar shares, suggest that substantial savings could be achieved if all  
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44 hospitals performed as the best.  
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### 50 **4.2 Interpretation**

#### 51 ***The high heterogeneity in biosimilar uptake***

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54 First and foremost, there are substantial differences in the uptake of biosimilars across public  
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56 hospitals in Portugal, for all the drugs investigated. These findings are in line with results from  
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3 other countries, where heterogeneity was also observed across regions in Germany, Sweden  
4 and, although to a lower extent, the UK (12)(34). Some of the causes of heterogeneity (e.g., the  
5 degree of quotas application) across German, Swedish, and UK regions is not comparable to  
6 those observed across Portuguese hospitals, which have no competence on setting quotas or  
7 defining guidelines. Portuguese hospitals can define local guidelines, may have drug  
8 formularies, or may adapt stricter rules and support policies to favor the biosimilar uptake. Yet,  
9 there are neither strong incentives (weak budget constraints) nor recommendations to do so by  
10 the central administration, so that these initiatives depend on the local commitment, interest,  
11 and power of hospital managers. Finally, findings from other countries highlight the key role  
12 of price differentials, discounts, and gainsharing (in Sweden, 59% of the variation was  
13 explained by differences in prices). These economic dimensions may also play an important  
14 role in Portuguese hospitals, but we could not analyze this issue. Note, however, that the  
15 absence of a relationship with hospital debts suggests that gainsharing, and more generally  
16 financial constraints, may have a low priority in prescription choices.

17  
18 The lower shares of etanercept and adalimumab biosimilars have several possible explanations.  
19 First, contrary to the other drugs, they are administered by the patient, using a subcutaneous  
20 injection, and they therefore require the patient's involvement to define the treatment option,  
21 which may be more difficult to obtain. In particular, the treatment switch always results from  
22 a shared decision between the practitioner and the patient, and thus requires a strong motivation  
23 on both sides when the switch is demanding in terms of administration. In comparison,  
24 rituximab and trastuzumab are administered through intermittent treatment by intravenous  
25 injection at the hospital, so that the decision resides more among practitioners, requiring a  
26 lower involvement of the patient. Second, a 2010 Ordinance mandates public hospitals to  
27 deliver biologic drugs for rheumatic diseases free of charge to patients of their catchment area  
28 upon any out-of-hospital prescription, including at private settings (Despacho 14919/2010, 2<sup>nd</sup>  
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3 of December 2010). It becomes virtually impossible for the hospital to opt for a biosimilar for  
4 naïve patients or to switch therapy since the prescription was issued in the outpatient setting.  
5  
6 Third, etanercept and adalimumab are prescribed for auto-immune disorders, which require  
7  
8 more complex treatments and whose outcomes are more difficult to measure. Outcome  
9  
10 measurement for rheumatic diseases is more difficult to assess and less consensual since it is  
11  
12 more related to quality of life (compared e.g., to cancer outcomes, which are related to  
13  
14 survival). This may lead to a greater reluctance to modify a well-functioning therapy, especially  
15  
16 by rheumatologists(21,36). Fourth, the literature mentions that originator companies have  
17  
18 adopted particularly aggressive competition strategies in the case of etanercept(20). In the  
19  
20 Netherlands, also on etanercept, the competition authority launched a preliminary investigation  
21  
22 on procurement practice of the originator firm to offer large discounts to hospitals, with the  
23  
24 aim of discouraging switch ([https://www.acm.nl/en/publications/drug-manufacturer-pfizer-](https://www.acm.nl/en/publications/drug-manufacturer-pfizer-discontinue-its-steering-pricing-structure-enbrel-following-discussions-acm)  
25  
26 [discontinue-its-steering-pricing-structure-enbrel-following-discussions-acm](https://www.acm.nl/en/publications/drug-manufacturer-pfizer-discontinue-its-steering-pricing-structure-enbrel-following-discussions-acm), accessed on 13  
27  
28 October 2022). Finally, this result cannot be related solely to the shorter observation period for  
29  
30 adalimumab (33 months) and etanercept (57 months), since the period was also shorter for  
31  
32 trastuzumab (38 months), which yielded different results.

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34 Noticeably, three years after its first use the share of etanercept was slightly below 40%, well  
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36 below the 56% observed in Germany after a similar period. By contrast, the share of infliximab  
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38 was around 70%, while 61% in Germany.

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40 In this paper, we sought to answer four main questions, each of which is based on a hypothesis  
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42 that may be contested. We next detail how we answer those questions.

### 43 44 45 **Academic and high-consuming hospitals**

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47 We initially postulated that academic hospitals and those with higher consumption of biologic  
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49 drugs would be more willing to adopt biosimilars because of greater expected savings and more  
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51 competences to acknowledge interchangeability.  
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3 The quicker uptake but lower shares of biosimilar at academic hospitals does not support this  
4 hypothesis; in this case, the adoption of biosimilar drugs was more likely to occur later, after  
5 months or years of treatment with the originator, which makes the switch more complex.  
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10 Another consideration is that there may be a stronger long-term fidelity to originator firms.  
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12 Another possible explanation is the 2010 Ordinance mentioned above, which obliges public  
13 hospitals to provide biologic drugs free of charge for rheumatic diseases prescribed at private  
14 facilities, without the possibility of modifying that prescription. Anecdotal evidence suggests  
15 that academic hospitals are the ones in greater demand, so they may be among those more  
16 subjected to external prescriptions that they cannot alter.  
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24 Surprisingly, a greater consumption of biologic drugs was not substantially linked to a quicker  
25 uptake or higher share of biosimilar drugs, despite the expected greater savings. We may  
26 hypothesize that greater consumption also permits larger rebates from originator firms, which  
27 we could not assess. A possible hypothesis would be that both academic and high-consuming  
28 hospitals may also be treating more complex patients, i.e., they may face a larger pool of  
29 patients for which biosimilar drugs are not recommended, either for clinical reasons or because  
30 switching may cause adherence problems. However, this hypothesis is challenged by the  
31 outcome on the case mix variable, which did not show significant relationships with uptake  
32 and shares.  
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44 That academic and high-consuming hospitals are not characterized by a greater and quicker  
45 uptake of biosimilars suggests a need for a stronger and earlier management, communication,  
46 and education effort at the national level and in academic hospitals before the originator is  
47 widely selected for most patients. In other words, such activities should consider the possible  
48 anticipation of the biosimilar arrival into the market, presenting this market entry and its  
49 potential economic gains at an early phase. The communication and education strategies,  
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3 coupled with the creation of guidelines, were demonstrated as effective policies in the three  
4 countries where these were evaluated (Germany, Sweden, and the UK(20,33,34)).  
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### 7 **Ties with firms commercializing originator drugs**

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10 We then postulated that hospitals performing more randomized controlled trials (RCT) related  
11 to originator drugs may be more reluctant to adopt biosimilars because of marketing activities  
12 and rebates from pharmaceutical firms. Yet our findings show that stronger links with the  
13 pharmaceutical industry in research and development did not seem to be detrimental to the  
14 consumption of biosimilars, even though in some cases it appeared to favor the rapid uptake  
15 and consumption. We may argue that links with originator firms are related to a greater interest  
16 in adopting new – potentially costly – therapies, prompting the need for savings with older  
17 molecules. This result is aligned with those for the UK showing the role of gainsharing as driver  
18 of biosimilar adoption(33). It may also be that these are the hospitals more oriented toward  
19 scientific innovation and research, which promotes interest and knowledge about new drugs  
20 and biosimilars.  
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### 35 **The role of financing constraints**

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37 We initially assumed that hospitals with higher debts would be more inclined to adopt  
38 biosimilars to increase efficiency and reduce spending. We found, though, that more-indebted  
39 hospitals were not clearly more likely to adopt biosimilars, contrary to expectations. However,  
40 the Portuguese hospital financing scheme explains this result; indeed, over the last decade there  
41 has been a dramatic under-budgeting of hospitals, which has provoked high debt compensated  
42 by regular bailouts. That is, due to these bailouts, debts have not been viewed by hospital  
43 managers as a major issue; in other words, the application of a soft budget constraint has not at  
44 all encouraged management practices seeking efficiency and cost containment.  
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3 This hesitancy of hospital managers to encourage biosimilar uptake suggests limited  
4 knowledge, or awareness of efficiency gains for the whole SNS, as highlighted by the savings  
5 potential analyzed in this study.  
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### 9 10 **The role of time**

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12 As expected, the share of biosimilars increases with time since their first use. This result  
13 confirms expectations, as physicians and patients gain experience about the use of biosimilars  
14 and their therapeutic equivalence, as more biosimilars enter the market, and guidelines about  
15 biosimilar use get more widely diffused and known.  
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### 20 21 **4.3 Strengths and limitations**

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23 The study stands out for its novelty. While differences across regions of a few European  
24 countries have been addressed (however, this has not been done for Portugal before), no  
25 quantitative analysis has measured how such differences were related to providers'  
26 characteristics. The major strength of this study is its use of a large dataset of biologic  
27 consumption over six years for the complete universe of Portuguese public hospitals, which  
28 supports the validity of the results.  
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37 The major limitation is the use of aggregate data at the hospital level. No information was  
38 available about the detailed clinical characteristics of the patients, nor about the exact  
39 indication for which the medicine was prescribed. It may well be that variations in uptake are  
40 related to patients' diseases and their severity. Also, we had no information on the prescribing  
41 physicians' characteristics, which would have allowed us to refine the analysis, relating the  
42 biosimilar consumption to the physician experience and practice, for instance. Although it is  
43 unlikely that patients' profiles for each hospital change substantially on a yearly basis, the use  
44 of a single case mix value from a single year might be a limitation, i.e., we might have under-  
45 estimated the case complexity in later years, which might make the biosimilar uptake more  
46 difficult.  
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3 We did not consider the official date of approval for financing because delays were observed  
4 between approval and launch to the market. Instead, we used the month in which the first  
5 adoptions were recorded, which may be later than when access was effectively guaranteed. As  
6 a result, we might have underestimated the median time of adoption. Nevertheless, the  
7 underestimation is equal for all providers, so that our findings on hospital determinants are not  
8 affected. Another limitation is that our dataset includes no data on the individual biosimilars  
9 consumed, but for the purpose of the study, we would not consider this as a limitation.

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19 Finally, we did not have access to the individual hospital policies and initiatives regarding  
20 biosimilars, or the relevance of efficiency consideration in hospital decisions and its  
21 consequences, such as the inclusion of biosimilars in drug formularies, the internal incentives  
22 to prescribers, the existence of training or discussions about rational prescribing, or the  
23 guidelines in terms of patients' involvement in treatment decisions. These issues could only be  
24 addressed through specific surveys at providers' level. While this is beyond the scope of this  
25 paper, such policies might be examined in future research that builds on this study.

## 36 **5. Conclusions**

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38 As expected, the longer the time following approval, the higher was the biosimilar uptake. Even  
39 so, half of the SNS hospitals in the cases we assessed took more than 2.5 years to adopt  
40 etanercept biosimilar, 3.5 years for rituximab biosimilar, and almost 2 years for trastuzumab  
41 biosimilar, despite the potential savings that reached 46% per dose in the case of trastuzumab.

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46 In contrast to what might be expected, the biosimilar potential was not fully exploited at  
47 academic and large hospitals, which would likely benefit most from the biosimilar use. This  
48 finding suggests a need for a stronger and earlier management, communication, and education  
49 effort before the originator is widely selected for most patients.

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56 Involvement in clinical trials does not hinder the biosimilar uptake, and even promotes it. Thus,  
57 it seems that involvement in scientific activities and interest in innovative drugs is not  
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3 incompatible with the search for efficiency in prescription, so that these activities could be  
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5 promoted.  
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### 7 **Author contribution**

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10 Concept and design: Perelman, Vogler, Mateus

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12 Analysis and interpretation of data: Perelman, Duarte-Ramos, Gouveia, Pinheiro, Ramos,  
13  
14 Vogler, Mateus

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17 Drafting of manuscript: Perelman

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20 Critical revision of the paper for important intellectual content: Duarte-Ramos, Vogler, Mateus

### 21 **Declaration of interest**

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23  
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25  
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27  
28 role in the design and conduct of the study; collection, management, analysis, and interpretation  
29  
30 of the data; preparation, review, or approval of the manuscript. The funder was informed that  
31  
32 the paper was submitted, and agreed with the submission. Authors not affiliated to the Nova  
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34 National School of Public Health did not receive any funding for participating in this study.  
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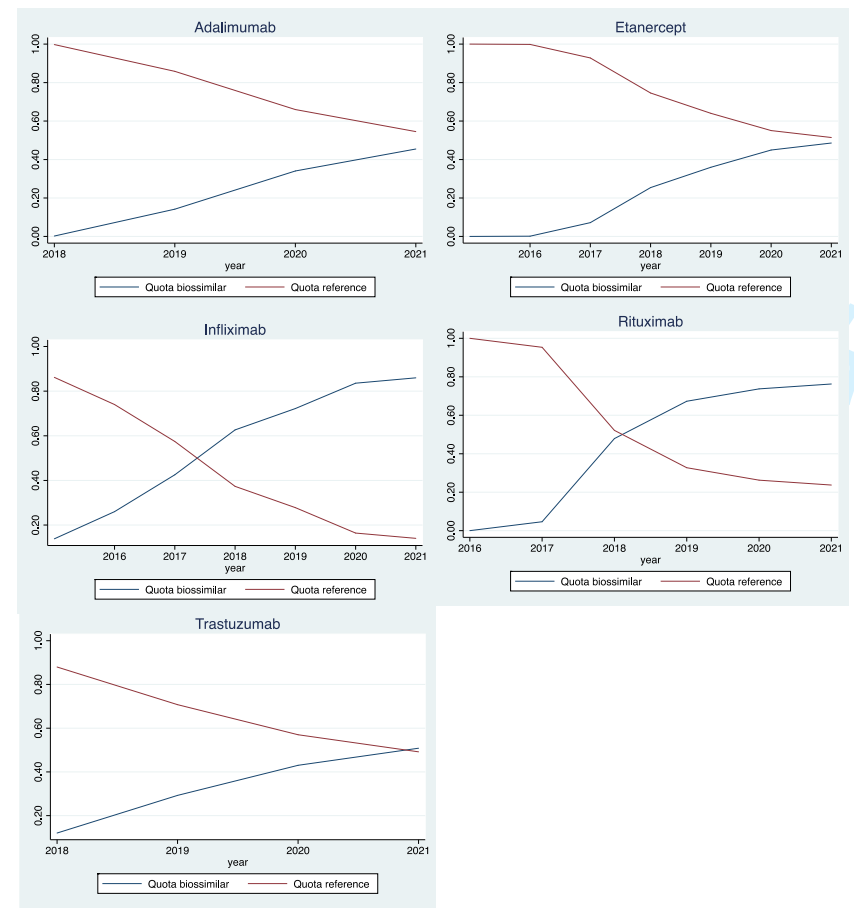
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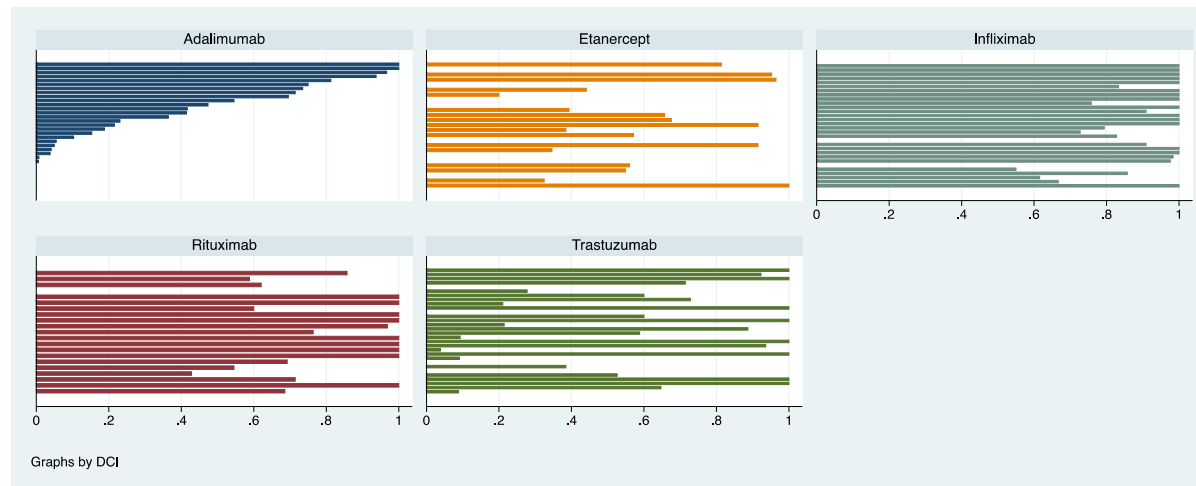
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FIGURES

Figure 1. Biosimilar quota, by year (own construction)



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Figure 2. Biosimilar share, by hospital, June 2021\* (own construction)

\*Each bar represents a hospital (its biosimilar share). Adalimumab biosimilar hospital decreasing shares, from 100% to zero %, are used to order shares for other drugs. The x-axis represents the biosimilar share, from 0 to 1 (100%).

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Table 1. List of variables

Variable	Categories	Source
Academic status	Academic Non-academic	Publicly available
Total monthly consumption of biological drugs	High (fourth quartile) Median-Low (quartiles 1-3)*	Transparency platform of the SNS, by hospital and month
Casemix index	Median-high (quartiles 2-4) Low (first quartile)	Central Administration of the Health System (ACSS), by hospital for the year 2015
Ongoing RCTs	High (fourth quartile) Median-Low (quartiles 1-3)	National Authority of Drugs and Health Products (Infarmed, IP), total for the 2015-2021 period, by hospital
Share of each pharmaceutical firm commercializing reference drugs in the hospital expenditures	High (fourth quartile) Median-Low (quartiles 1-3)	Platform of public contracts ( <a href="https://www.base.gov.pt/base4">https://www.base.gov.pt/base4</a> ), contracts with pharmaceutical firms, by hospital and year.
Rate of overdue debt on total expenditures	High (fourth quartile) Median-Low (quartiles 1-3)	Transparency platform of the SNS, by hospital and year, and ACSS data on total annual expenditures, by hospital and year (2016-2019)

\*For this variable the coding was the reverse of the one used for other variables, to avoid a multicollinearity problem.

Table 2. Median time to adoption and biosimilar quota, by hospital characteristic.

	Median time to adoption					Biosimilar quota (%)				
	Adalimumab	Etanercept	Infliximab	Rituximab	Trastuzumab	Adalimumab	Etanercept	Infliximab	Rituximab	Trastuzumab
	22	37	46	46	27	18.0	19.3	54.2	42.1	32.8
Academic hospital										
No	23	37	47	46	27	16.9	18.9	56.1	42.0	32.6
Yes	20	36	44	45	26	23.5	21.3	46.0	42.7	33.9
Biologics consumption										
Low-median	23	38	44	46	29	16.9	18.2	52.5	42.6	31.2
High	22	34	51	46	23	21.4	22.6	59.3	40.7	38.0
Casemix index										
Low	22	38	43	48	28	19.0	19.5	59.0	40.2	31.6
Median-High	22	37	47	45	26	17.6	19.2	53.2	42.5	33.1
Number of RCTs										
Low-median	23	38	46	46	28	16.7	17.4	54.1	44.5	31.2
High	21	33	44	46	23	23.2	28.6	54.3	35.8	38.1
Share of originator firm										
Low-median	22	37	47	44	27	13.6	15.8	54.9	41.6	31.1
High	22	39	43	46	28	18.8	20.1	50.9	44.3	38.5

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Table 3. Hazard ratios of time to biosimilar adoption (standard errors between brackets).

	Adalimumab	Etanercept	Infliximab	Rituximab	Trastuzumab
Academic hospital	1.75 (0.30)***	0.86 (0.09)	1.27 (0.10)***	1.10 (0.11)	1.01 (0.13)
Biologics consumption, high	0.82 (0.12)	1.18 (0.11)*	0.77 (0.06)***	1.03 (0.12)	1.37 (0.15)***
CMI, low	1.08 (0.13)	0.98 (0.08)	1.17 (0.08)**	0.82 (0.09)*	1.06 (0.13)
Number of RCTs, high	0.99 (0.15)	1.35 (0.14)***	1.14 (0.08)*	0.91 (0.09)	1.18 (0.15)
Share originator firm, high	0.89 (0.13)	0.94 (0.08)	1.08 (0.07)	1.16 (0.10)*	1.07 (0.12)
Distribution	Weibull	Gompertz	Weibull	Weibull	Weibull

\*10%, \*\*5%, \*\*\*1%

Table 4. Panel data analysis of biosimilar quota (coefficients and standard errors between brackets).

	Adalimumab	Etanercept	Infliximab	Rituximab	Trastuzumab
Time since first adoption (months)	0.17 (0.01)***	0.09 (0.01)***	0.03 (0.01)***	0.11 (0.01)***	0.06 (0.01)***
Academic	0.28 (0.24)	-0.32 (0.28)	-0.10 (0.30)	-0.17 (0.20)	-0.25 (0.28)
Biologics consumption, high (active substance)	-0.53 (0.11)***	-0.14 (0.08)*	-0.24 (0.07)***	0.14 (0.10)	-0.09 (0.10)
CMI, low	-0.04 (0.18)	0.39 (0.19)**	0.15 (0.25)	-0.43 (0.18)**	-0.08 (0.24)
Number of RCTs, high	0.47 (0.22)***	0.78 (0.27)***	0.14 (0.28)	-0.23 (0.19)	0.27 (0.26)
Share originator firm, high	-1.14 (0.19)***	-1.07 (0.20)***	0.05 (0.19)	0.28 (0.16)*	0.39 (0.23)*

\*10%, \*\*5%, \*\*\*1%

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Table 5. Association of uptake and shares with the burden of overdue debt.

Variable	Uptake	Shares
Adalimumab	6.71 (1.15)***	-0.38 (0.17)**
Etanercept	0.92 (0.08)	-0.37 (0.09)***
Infliximab	0.95 (0.07)	0.02 (0.07)
Rituximab	1.23 (0.12)**	0.34 (0.09)***
Trastuzumab	0.79 (0.12)	-0.07 (0.17)

\*10%, \*\*5%, \*\*\*1%

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Table 6. Potential savings associated to biosimilars

Variable	Relative and absolute price difference (biosimilar vs originator drug)	Potential savings (in million euros and in percentage of total expenditures for the drug)
Adalimumab	-24€ (-35%)	20.796 (26%)
Etanercept	-19€ (-13%)	20.439 (7%)
Infliximab	-151€ (-49%)	20.692 (13%)
Rituximab	-4€ (-33%)	0.332 (9%)
Trastuzumab	-170€ (-46%)	12.915 (32%)

**Appendix**

## A1. Test proportional hazard assumption, complete sample

	Etanercept	Rituximab	Trastuzumab
Chi square	20.98	16.36	6.89
p-value	<0.01	0.04	0.55

## A2. AIC results for various distributions for survival model, complete sample

	Etanercept	Rituximab	Trastuzumab
Gompertz	1,756	334	-276
Weibull	1,850	279	-286
Log-logistic	2,054	374	-310
Log-normal	2,200	337	-327

## A3. AIC results for various distributions for GEE, complete sample

	Etanercept	Rituximab	Trastuzumab
Normal	1,911,331	3,088,245	1,047,268
Poisson	49,105	32,650	17,586
Negative binomial	10,185	6,932	3,339
Gamma	18,658	15,607	7,741