R&D and market size: who benefits from orphan drug legislation?*

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September 13, 2021

Abstract

Since the early 80s, incentives have been introduced to stimulate R&D for rare diseases. We develop a theoretical model to study the impact of *push* and *pull* incentives on the intensive and extensive margin of optimal R&D investments. The model describes the mechanisms by which the type of incentives provided may favor R&D for orphan diseases with comparatively high prevalence. In our empirical analysis, we merge data on orphan drug designations by the Food and Drug Administration with Orphanet data on disease characteristics. In line with the theoretical results, we find evidence supporting the idea that the incentives adopted may have contributed substantially to widening the gap between more and less rare diseases classified as orphan. Our theoretical and empirical findings together suggest that, if providing some therapeutic option to patients with very rare diseases is a priority, a revision of the current system of incentives should be considered.

Keywords: pharmaceutical innovation; orphan drug regulation; Gumbel distribution; market size; health inequality

JEL: I14; I18; O31; O38; C35

*This is the accepted version of the article published in the Journal of Health Economics, with doi: 10.1016/j.jhealeco.2021.102522

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1 Introduction

Orphan diseases are those that affect a small number of individuals, with the exact definition varying from one institutional context to another. Despite the fact that each of these diseases usually affects very few people, currently 7,000 orphan diseases are described in the literature, and it is estimated that 25 to 30 million US citizens and 27 to 36 million EU residents suffer from an orphan disease (Health and Safety, 2015). However, treatment with a specific indication is available for less than 10% of known rare diseases (Melnikova, 2012; Tambuyzer, 2010).

The literature provides evidence of a positive correlation between innovation and market size.[1] As a result, the low prevalence of orphan diseases often provides insufficient incentive for the private sector to invest in R&D. This has led several countries to introduce special legislation, starting from the approval of the Orphan Drug Act (ODA) in 1983 in the US. The typical toolkit includes both *pull* incentives, such as market exclusivity, and *push* incentives, such as tax credits on R&D expenditure. Overall, there seems to be a general consensus that special regulations adopted around the world have contributed to closing the gap between orphan and non-orphan diseases. Braun et al. (2010), Lichtenberg and Waldfogel (2009) and Yin (2008) provide evidence of a positive impact of the ODA on R&D directed at orphan diseases. Similar evidence is provided by Westermark et al. (2011) for the EU.

Our study aims to go beyond the analysis of the aggregate impact of regulations on innovation for orphan versus non orphan diseases, and to investigate how they affect the distribution of additional R&D efforts within the class of orphan diseases. The main question we seek to answer is how the impact of incentives on R&D is affected by the prevalence of a disease. Indeed, some orphan diseases affect almost 100,000 individuals worldwide whilst others have recorded very few cases. We study theoretically how *pull* and *push* incentives interact with market size in affecting the distribution of additional R&D efforts across different diseases. In doing this, we separate the intensive and extensive margin of investment. Empirically, we use data from the Food and Drug Administration (FDA) to investigate how the allocation of R&D within the class of orphan diseases changed over time, as incentives were strengthened due to the adoption of special legislation in additional geographic areas. Based on theoretical and empirical results, we

[1] Acemoglu and Linn (2004) find that a 1% increase in potential market size is associated with a 6% increase in the total number of new drugs launched in the US. Similarly, Dubois et al. (2015) find that additional revenues of $2.5 billion are required to support the invention of one new chemical entity. Sources of expansion in market size that have been shown to have a positive impact on innovation include the extension of public insurance coverage (Blume-Kohout and Sood, 2013; Clemens, 2013), policies designed to increase the use of existing technologies (Finkelstein, 2004) and exogenous demand shocks (Clemens and Rogers, 2020). Symmetrically, unfavourable market conditions have been shown to reduce R&D investment. Budish et al. (2015) show that the combination of corporate short-termism and fixed patent duration diverts private R&D away from long-term projects. Stern (2017) investigates the impact of delays and uncertainty in the approval process on the propensity to invest in high risk projects. Agha et al. (2020) show that introducing a risk of exclusion from insurance coverage for some pharmaceuticals may shift investments towards areas facing lower risk.

draw policy implications suggesting possible directions for a revision of the incentive system aimed at addressing clinical needs that remain as yet unmet.

The disadvantage for rare diseases in terms of innovation has been studied both theoretically (Jobjörnsson et al., 2016) and empirically (Barrenho et al., 2019). Conti and Gruber (2020) present several motivations for the introduction of specific incentives aimed at addressing this scarcity of therapeutic options. Plausibly, one rationale is related to inequality aversion (McCabe et al., 2005), given the huge differences in the availability of treatments between rare and common diseases. The problem can also fit an equality of opportunity framework, given that disease prevalence is clearly beyond individual control (Roemer, 1998). Another possible rationale is related to a spillover effect: R&D for orphan diseases might generate scientific insights that are useful for the treatment of other diseases (Rodwell and Aymé, 2015).[2]

The possibly heterogeneous impact of the incentives on different orphan diseases is extremely relevant, given the huge number of orphan diseases and the large variability in the level of research; this variability can be ascribed to differences in therapeutic class, prevalence, number of scientific publications (Heemstra et al., 2009; Pammolli et al., 2009), and population affected, e.g. diseases with onset in childhood (Raïs Ali and Tubeuf, 2019). In the analysis by Yin (2008) on the effect of the ODA on the flow of clinical trials in the years immediately following its approval, differences in impact emerge when the prevalence of rare diseases is accounted for, with a smaller impact on most rare diseases.

Of the reasons to support R&D on orphan diseases at least two suggest that it is not only total effort that matters, but also how the effort is distributed across diseases. First, according to the 'fair innings' argument (Harris, 2006), all individuals should be allowed to achieve a minimum health status (e.g. in terms of life expectancy), meaning that gains by those who have not yet achieved this threshold should be valued more. This view is consistent with the objectives of European legislation[3] and with robust evidence on individual preferences (e.g. Nord et al., 1995). The second argument is based on the insurance value of innovation. Ex ante, a new treatment can reduce the uninsurable physical risk for individuals who might get sick, by raising utility in the bad state of the world (Philipson and Zanjani, 2014; Lakdawalla et al., 2017). This insurance value increases with disease severity (Lakdawalla and Phelps, 2020). This also means that, in a hypothetical situation with a number of diseases that are equally severe if untreated, the incremental value of an innovation providing a given health gain is largest if it targets a disease with no existing therapeutic option.

The existence of a variety of incentives within orphan drug legislation also raises the ques-

[2]For example, the finding that the alteration of the Niemann-Pick C1 protein responsible for the rare degenerative disorder called Niemann-Pick disease is also responsible for Ebola virus entry (Carette et al., 2011; Côté et al., 2011) suggested a possible strategy to fight the virus.

[3]The preamble to EU Regulation 141/2000 states that *'patients suffering from rare conditions should be entitled to the same quality of treatment as other patients'*.

tion of which of them is best suited to achieve the intended objectives. Concerning the possibly different impact of *pull* and *push* programs, the existing literature mainly focuses on the role of asymmetric information (see e.g., Kremer, 2002; Rietzke and Chen, 2020). Our analysis shows that there may also be verifiable dimensions worth considering. In particular, market size is an essentially observable variable that interacts differently with *pull* and *push* programs. Accounting for this may allow the two types of incentives to be balanced in line with policy goals or to incorporate this observable variable into the design of the incentive scheme.

Our article contributes theoretically and empirically to the literature in three ways. It is the first to characterize the heterogeneous impact of orphan regulations for diseases with different levels of prevalence over a long time-span (1983-2016). Second, we study the impact of orphan regulation on both the extensive and the intensive margin, by studying: *i*) the probability of obtaining an investment in R&D for a certain disease, *ii*) the intensity of the R&D effort. Third, we contribute to the literature investigating the different impacts of *pull* versus *push* R&D incentives. We show theoretically that in our framework both types of incentive have an unambiguously stronger effect on the extensive margin of investment for less rare diseases, meaning that the impact on the probability of obtaining an investment is greater for less rare orphan diseases. However, the mechanisms involved and hence the size of this difference are not the same for *pull* and *push* programs. In terms of investment intensity, it is not possible to conclude unambiguously whether more or less rare diseases benefit more from the incentives.

The empirical analysis exploits a dataset obtained by merging data on Orphan Drug Designations (ODDs), used as a proxy for R&D effort,[4] with Orphanet data providing information on disease characteristics (INSERM, 1999). We extend the theory-based distinction between the intensive and the extensive margin of R&D to the empirical analysis by means of a zero-inflated count data model, where the dependent variable is the yearly number of ODDs granted by the FDA at the disease level. For the sake of consistency with the theoretical model, the excess of zeros is modeled using the Gumbel distribution, to replace the standard Logit or Probit model. Our empirical approach exploits the fact that different countries (or geographical regions) introduced reforms at different points in time and, according to our theoretical results, diseases with different prevalence may have benefited differently from the regulations.

We find that, within the class of orphan diseases, the increase in R&D efforts is concentrated mainly on less rare diseases. According to our baseline specification, the difference between the predicted number of orphan designations per year for a disease in the highest and the lowest class of prevalence was 5.6 times larger after 2008 than in the period 1983-1992. The main conclusion remains valid even when controlling for a number of other factors potentially affecting the relative convenience of investing in less rather than more rare diseases. To the best

[4]Obtaining an ODD from the relevant regulatory authority is a necessary formal step to access the incentives.

of our knowledge, no evidence of this dynamic has previously been reported. Based on our theoretical analysis and the results of model calibration, we argue that how orphan incentives were designed may have contributed to widening this gap. By relying almost exclusively on *pull* incentives, European legislation may have exacerbated this tendency.

In terms of policy implications, our results suggest that, if reducing the number of diseases with no therapeutic option available is a priority, then a revision of the incentive tool-kit should be considered, with the aim of curbing the widening gap between less and more rare orphan diseases. One way of mitigating this tendency could be to shift the balance of incentives towards *push* tools. A more radical reform might be to consider abandoning the idea of setting an arbitrary threshold of prevalence, below which all diseases benefit from the same type of incentives, and to move towards prevalence-dependent incentives.

The structure of the article is as follows. Section 2 describes the various regulations that have been adopted over time. Section 3 describes the model, which is solved in Section 4. Section 5 presents the main results of a model calibration. Sections 6 and 7 describe, respectively, data and methodology for the empirical analysis, with results presented in Section 8. Section 9 concludes and discusses policy implications.

2 Institutional framework

Over the past 35 years, orphan drug regulations have been adopted in several countries around the world. The US was the first country to develop specific legislation. In 1983, Congress passed the ODA, according to which a drug is considered *orphan* if it treats a rare disease or condition affecting fewer than 200,000 people in the US (about 6.25 in 10 thousand persons) or if it is not expected to be profitable within seven years following approval by the FDA.[5] The incentives for drugs designated as orphan are (1) assistance from the Office of Orphan Product Development during the development process; (2) tax credits (up to 50% of clinical development costs); (3) exemption or waiver of application (filing) fees; (4) seven years of marketing exclusivity and (5) subsidies for clinical trials from the Orphan Products Grant Program. Although multiple orphan designations may be granted for a particular disease (Gibson and von Tigerstrom, 2015), for 7 years no marketing approval is given to a subsequent sponsor of a drug containing the same active moiety or principal molecular features as a previously approved drug intended for the same therapeutic indication unless this can be shown to be clinically superior.

Special regulations with the same objectives were subsequently introduced in several countries, such as Singapore (1991), Japan (1993), Australia (1998), South Korea (1998), the EU

[5]Originally, the ODA definition of orphan was any disease or condition occurring "infrequently" in the United States without reasonable expectations of profits. The Health Promotion and Disease Prevention Amendments of 1984 specified the prevalence requirement (Herder, 2017).

(2000) and Taiwan (2000). We focus on those approved in the areas with the largest markets: Japan and the EU.

In April 1993, Japan substantially revised its orphan medicinal product system, introduced in 1985, extending the tools used to incentivize research into orphan diseases. In addition to the existing (1) reductions in the data required for applications, and (2) the accelerated review process, the following incentives were introduced: (3) protocol assistance; (4) tax credits (up to 6% of clinical and non-clinical costs); (5) subsidies for clinical and nonclinical studies and (6) ten years of market exclusivity. To be designated as orphan, a drug has to treat a rare and serious disease or condition affecting less than 50,000 persons in Japan (about 4 in 10 thousand persons); no appropriate alternative treatment should be available on the market or the expected efficacy and safety must be higher than existing products. Because the incentives which are the main focus of our analysis were introduced in Japan in 1993, we refer to this as the date when special legislation was introduced.

In December 1999, the EU also introduced specific incentives for the development of orphan medicinal products through Regulation (EC) No 141/2000. The incentives include (1) protocol assistance; (2) access to a centralized procedure allowing immediate marketing authorization in all member states; (3) reduced fees for regulatory procedures and (4) ten years of market exclusivity. In order to benefit from the incentives, orphan drugs have to be designated as such before receiving marketing authorization. Moreover, when the application is made, the drug must treat a condition affecting no more than 5 in 10 thousand persons in the Community, or a life threatening or chronically debilitating condition for which it is unlikely, without incentives, that the marketing of the medicinal product in the Community would generate sufficient returns to justify the necessary investment;[6] finally, there should be no satisfactory alternative methods authorized in the Community or, if such a method exists, the medicinal product must be expected to bring significant benefit to those affected by the condition (article 3 of the Regulation). In addition to the incentives mentioned in the regulation, France and the Netherlands provide tax credits (Health and Safety, 2015).

The incentives provided by the US, Japan and the EU are summarized in Table 1, with the requirements for drugs to be considered as orphans.

Since November 2007, the European Medicines Agency (EMA) and the FDA have been collaborating to encourage joint applications for orphan drug status both in the EU and the US. A shared application form has been developed, in an effort to reduce the administrative burden on the orphan drug sponsor (Braun et al., 2010; Mariz et al., 2016). This has reduced the cost of eligibility for incentives in both geographical areas. Parallel applications in Japan and the EU are also encouraged, although a shared application form is not yet in place (Mariz et al., 2016).

[6] According to Tambuyzer (2010), more than 99.5% of orphan designations in the EU are granted because of the prevalence criteria.

	US (1983)	Japan (1993)	EU (2000)
Orphan disease:			
	$<$ 200,000 in US (6.25/10,000) or not profitable	$<$ 50,000 in Japan (4/10,000)	$<$ 5 in 10,000 in EU or both not profitable & life-threatening
Main incentives:			
Tax credit	Yes (50% clinical costs)	Yes (6% clinical and non-clinical costs)	Member state specific
Market exclusivity	Yes (7 years)	Yes (10 years)	Yes (10 years)
Reduced applic. fees	Yes (waved)	No	Yes (reduced)
Protocol assist.	Yes	Yes	Yes
Subsidies for clinical trials	Yes	Yes	No

Table 1: Comparison of orphan drugs regulations in the US, Japan and EU.

3 The model

Let N^f firms be free to decide on the size of an R&D investment, $I \geq 0$, targeting disease j, which affects n_j individuals. For an orphan drug, there are two key regulatory steps in the development process. In the first step, the firm developing the molecule applies for an ODD. If granted, the ODD provides the firm with eligibility for incentives related to the development of the orphan drug. If the development process is successfully completed, the firm goes on to the second regulatory stage: marketing authorization.[7] From the perspective of the firm, both stages entail uncertainty. Let $p_j^d(I)$ be the probability that the firm obtains an ODD, given the R&D investment I. For the function $p_j^d(I)$ we assume that $\frac{\partial p_j^d(I)}{\partial I} > 0$, $\frac{\partial^2 p_j^d(I)}{\partial I^2} < 0$ and $\lim_{I\to 0} \frac{\partial p_j^d(I)}{\partial I} = +\infty$. Moreover, $p_j^d(0) = 0$ and $\lim_{I\to\infty} p_j^d(I) = 1$.

Conditional on obtaining an ODD, the firm carries on with the development process. With probability p_j^m, assumed to be independent of I, this leads to the marketing approval of the product. Given disease specific per patient net revenue m_j, conditional on obtaining an ODD, the expected per patient net revenue is $p_j^m m_j$. To simplify the notation, we define $M_j(\Omega_j) = p_j^m m_j$. The parameter Ω_j is a vector of disease specific characteristics that may affect the probability p_j^m and/or the net revenue m_j. For example, some regulators grant a price premium to drugs targeting life threatening conditions.

[7] In principle, it is also possible that a drug reaches the market without having previously obtained an ODD. However, this occurs for only 2% of US marketing authorizations in our dataset. For the sake of simplicity, we assume that only drugs with an ODD receive marketing authorization.

The expected profit for firm i ($i = 1, 2, \ldots, N^f$) investing I to develop a drug for disease j is:

$$E\Pi_{ij} = p_j^d(I)[M_j\, n_j] - I + \delta_{ij}. \tag{1}$$

The term δ_{ij} is an idiosyncratic component that aims to capture any additional positive or negative component of the expected profit known only to the firm. This may be related, for example, to the impact on R&D costs of other projects undertaken by the firm, simultaneously or previously. It is assumed that δ_{ij} is known to the firm before deciding the investment strategy. From the perspective of the researcher, δ_{ij} is the realization of a random variable, with density $f(\Delta)$. According to Eq. 1, a new drug that obtains market authorization captures the entire market. This simplifying assumption is justified by the fact that, in our data, only for a small fraction of orphan diseases (6%) is more than one treatment authorized over the entire time span. We also introduce the simplifying assumption that firms make their investment decisions independently. However, in Appendix A we relax the assumption that a new drug captures the entire market and show that the quality of the relevant results is unchanged.

The aim of our analysis is to study the impact of the different forms of incentives introduced as part of the special legislation on: *i)* the probability of obtaining an investment in an orphan disease, *ii)* the probability of obtaining an orphan designation. Our analysis is carried out *within* the class of orphan diseases. In other words, we do not contrast rare versus non-rare diseases, but more versus less rare diseases within the class of orphan diseases. As a result, we assume that all diseases are eligible for incentives. Our focus is on how the impact of different types of incentives is affected by the prevalence of an orphan disease.

Our comparison of alternative incentives focuses on the usual distinction between *pull* and *push* programs. *Pull* incentives are those that aim to increase the net market revenue of investments made in orphan diseases. The best known instance is market exclusivity, to which all products with orphan designation are entitled. We model this as a mark-up, z ($z \geq 0$), on net revenues. This way of modeling *pull* incentives is sufficiently flexible to account for other types of incentives, such as a price premium to which all orphan drugs are equally entitled.

Push incentives reduce the cost of R&D investment in rare diseases. Examples of such incentives include tax credits, reduced application fees for market authorization and protocol assistance. We model this type of incentive as an allowance on investment costs, such that, conditional on obtaining an ODD, the investment cost borne by the firm is $I(1-\gamma)$, with $0 \leq \gamma \leq 1$.[8]

To take the role of these incentives into account, the expected profit function can be written

[8]Note that a pure form of *push* incentive would be conditional only on the decision to invest. The conditionality on the achievement of an ODD that we introduce is meant to make the model as consistent as possible with the legislation as outlined in Section 2.

as:

$$E\Pi_{ij} = p_j^d(I)[M_j\, n_j](1+z) - (1 - p_j^d(I)\,\gamma)I + \delta_{ij}. \tag{2}$$

Eq. 2 shows that access to *pull* incentives is conditional upon obtaining an ODD and reaching the market (recalling $M_j = p_j^m m_j$), whereas obtaining an ODD is sufficient for eligibility for *push* incentives.

4 Optimal investment policy

We start by characterizing optimal decisions from the perspective of a single firm and then move on to analyze of the outcome of these decisions at the market (disease) level.

4.1 The firm's decisions

The firm aims to maximize the expected profit in Eq. 2 with respect to I. The first order condition can be written as:

$$\frac{\partial p_j^d(I)}{\partial I}[M_j\, n_j(1+z)] + \gamma\left(\frac{\partial p_j^d(I)}{\partial I}\, I + p_j^d(I)\right) = 1. \tag{3}$$

The first order condition in Eq. 3 requires the marginal cost of investment on the right hand side to be equated with the marginal benefit, which has two components: *i)* the increased probability of reaching the market and its revenues, *ii)* the positive impact on the expected revenue provided by the *push* incentive. The assumption that $\lim_{I\to 0} \frac{\partial p_j^d(I)}{\partial I} = +\infty$ ensures the existence of a strictly positive value of I, solving the equation. We assume the marginal benefit to be strictly decreasing in I, meaning that Eq. 3 defines a unique optimum.[9] Eq. 3 also highlights the well known role of market size as an incentive for R&D investments: a reduction in n_j reduces the marginal benefit of investment and leads to a lower optimal level of investment. According to Eq. 3, the optimal investment level (I_j^*) depends only on characteristics at the disease level, but not on δ_{ij}.

[9]Note that this condition is directly implied by the assumption of the strict concavity of $p_j^d(I)$, for sufficiently small values of γ.

4.1.1 Impact of *pull* incentives

We can use the implicit function theorem to study the impact of an increase in z on the optimal level of investment:

$$\frac{dI_j^*}{dz} = -\frac{\frac{\partial p_j^d(I)}{\partial I} M_j n_j}{\frac{\partial^2 p_j^d(I)}{\partial I^2}[M_j n_j(1+z) + \gamma I] + 2\gamma \frac{\partial p_j^d(I)}{\partial I}} > 0. \tag{4}$$

From the perspective of our analysis, it is particularly interesting to investigate how the marginal impact on I_j^* of an increase in z varies with n_j. Differentiating Eq. 4 with respect to n_j obtains:

$$\begin{aligned}\frac{\partial^2 I_j^*}{\partial z \partial n_j} =& \frac{\frac{\partial p_j^d(I)}{\partial I} M_j n_j \left[\frac{\partial^3 p_j^d(I)}{\partial I^3}\frac{\partial I_j^*}{\partial n}[M_j n_j(1+z) + \gamma I_j^*] + \frac{\partial^2 p_j^d(I)}{\partial I^2}\left(M_j(1+z) + 2\gamma \frac{\partial I_j^*}{\partial n}\right)\right]}{\left[\frac{\partial^2 p_j^d(I)}{\partial I^2}[M_j n_j(1+z) + \gamma I_j^*] + 2\gamma \frac{\partial p_j^d(I)}{\partial I}\right]^2} + \\ &- \frac{M_j\left(\frac{\partial^2 p_j^d(I)}{\partial I^2}\frac{\partial I_j^*}{\partial n} n_j + \frac{\partial p_j^d(I)}{\partial I}\right)}{\frac{\partial^2 p_j^d(I)}{\partial I^2}[M_j n_j(1+z) + \gamma I_j^*] + 2\gamma \frac{\partial p_j^d(I)}{\partial I}}.\end{aligned} \tag{5}$$

Eq. 5 cannot be unambiguously signed, meaning that the size of the impact of a *pull* incentive on I_j^* may increase or decrease in n_j. The ambiguity is due to two impacts that go in opposite directions. There is a positive impact because, for a given level of I, the increase in expected revenues due to an increase in z is proportional to the market size. However, given z, I_j^* is higher when n_j is larger. As the marginal productivity of an increase in I, in terms of the increased probability of obtaining an ODD, is decreasing, this impact goes in the opposite direction.

Given $I_j^*(M_j, n_j)$, the firm invests only if the expected profit at the time of investment is non-negative, i.e.:

$$p_j^d(I_j^*)[M_j\, n_j](1+z) - (1 - p_j^d(I_j^*)\,\gamma) I_j^* + \delta_{ij} \geq 0. \tag{6}$$

The study of this condition is particularly important in the case of rare diseases, given that most of them have no ODD. It is therefore possible to define a minimum value of δ_{ij}, $\hat{\delta}_j$, such that the firm makes an investment in R&D for disease j:

$$\hat{\delta}_j = (1 - p_j^d(I_j^*)\,\gamma) I_j^* - p_j^d(I_j^*)[M_j\, n_j](1+z). \tag{7}$$

To investigate the impact of n_j on the decision whether or not to invest, we study the depen-

dency of $\hat{\delta}_j$ on n_j. Observing that

$$\hat{\delta}_j = -E\Pi_{ij}(I_j^*) + \delta_{ij}, \tag{8}$$

simplifies calculations through the application of the envelope theorem, therefore:

$$\frac{\partial \hat{\delta}_j}{\partial n_j} = -p_j^d(I_j^*) M_j (1+z) < 0. \tag{9}$$

Hence, other things being equal, for a comparatively rare disease the value of δ_{ij} must be larger for the firm to decide to undertake any investment (Eq. 9). Thus, it is less likely to observe R&D investment in comparatively rare diseases.

Using a similar approach, we can study the impact of an increase in z on $\hat{\delta}_j$. This leads to

$$\frac{\partial \hat{\delta}_j}{\partial z} = -p_j^d(I_j^*)\, M_j\, n_j < 0, \tag{10}$$

which shows the role of z in making it more likely that there is investment for disease j, by reducing the value of $\hat{\delta}_j$. Also in this case, we are interested in the heterogeneous impact of this incentive tool across different classes of prevalence. By differentiating Eq. 10 with respect to n_j, we obtain:

$$\frac{\partial^2 \hat{\delta}_j}{\partial z \partial n_j} = -M_j \left[\frac{\partial p_j^d(I)}{\partial I} \frac{\partial I_j^*}{\partial n_j} n_j + p_j^d(I_j^*) \right] < 0. \tag{11}$$

The negative sign of the expression means that the impact of an increase in z on the probability of a firm undertaking an investment is larger for less rare diseases.

4.1.2 Impact of *push* incentives

As for the *pull* program, we start by describing the impact on I_j^* of a marginal change in the incentive:

$$\frac{dI_j^*}{d\gamma} = -\frac{\frac{\partial p_j^d(I)}{\partial I} I + p_j^d(I)}{\frac{\partial^2 p_j^d(I)}{\partial I^2}[M_j n_j (1+z) + \gamma I] + 2\gamma \frac{\partial p_j^d(I)}{\partial I}} > 0. \tag{12}$$

We also use the same approach to investigate the heterogeneity of the impact:

$$\frac{\partial^2 I_j^*}{\partial \gamma \partial n_j} = \frac{\left(\frac{\partial p_j^d(I)}{\partial I} I_j^* + p_j^d(I)\right) \left[\frac{\partial^3 p_j^d(I)}{\partial I^3} \frac{\partial I_j^*}{\partial n}[M_j n_j (1+z) + \gamma I] + \frac{\partial^2 p_j^d(I)}{\partial I^2}\left(M_j (1+z) + \gamma \frac{\partial I_j^*}{\partial n}\right) + 2\gamma \frac{\partial^2 p_j^d(I)}{\partial I^2} \frac{\partial I_j^*}{\partial n}\right]}{\left[\frac{\partial^2 p_j^d(I)}{\partial I^2}[M_j n_j (1+z) + \gamma I] + 2\gamma \frac{\partial p_j^d(I)}{\partial I}\right]^2} -$$
$$- \frac{\frac{\partial^2 p_j^d(I)}{\partial I^2} \frac{\partial I_j^*}{\partial n} I_j^* + 2 \frac{\partial p_j^d(I)}{\partial I} \frac{\partial I_j^*}{\partial n}}{\frac{\partial^2 p_j^d(I)}{\partial I^2}[M_j n_j (1+z) + \gamma I] + 2\gamma \frac{\partial p_j^d(I)}{\partial I}}. \tag{13}$$

As for z, this term cannot be unambiguously signed, because two effects operate in opposite directions. Other things being equal, with a larger value of n_j, I_j^* is larger and so is the gain from an increase in γ. However, a higher value of I_j^* also implies a lower marginal productivity of additional investment, in terms of increased probability of obtaining an ODD. Therefore, also the impact of an increase in γ on I_j^* may increase or decrease in n_j.

Concerning the impact on the minimum value of the idiosyncratic term that makes an investment in disease j profitable, we obtain:

$$\frac{\partial \hat{\delta}_j}{\partial \gamma} = -p_j^d(I^*)\, I_j^* < 0 \tag{14}$$

and

$$\frac{\partial^2 \hat{\delta}_j}{\partial \gamma \partial n_j} = -\frac{\partial I_j^*}{\partial n_j}\left(\frac{\partial p_j^d(I)}{\partial I} I_j^* + p_j^d(I)\right) < 0. \tag{15}$$

In this case too, the impact is greater for less rare diseases.

Concerning the size of the impact on $\hat{\delta}_j$ and the dependency of this impact on n_j, note that a quantitative comparison between *pull* and *push* incentives cannot be based on a direct comparison of Eq. 10 with 14 and of Eq. 11 with 15. The reason is that the *pull* incentive is a fraction of expected revenues, whereas the *push* incentive is a fraction of investment costs. Concerning the role of n_j, the following proposition states an important qualitative difference between a *pull* and *push* incentive, based on the comparison between Eq. 11 and Eq. 15:

Proposition 1. *For both types of incentives, the reduction in $\hat{\delta}_j$ is greater for less rare diseases. However, while for a* push *incentive this is due only to an indirect effect, i.e. through the impact on I_j^*, for a* pull *incentive there is both a direct and an indirect effect.*

The calibration set out in Section 5 is used to investigate the quantitative implications of this result.

4.2 Market outcomes

We can now move on to study the impact of incentives at the disease level, assuming that the N^f firms make independent investment decisions, as characterized in the previous subsection. We focus on two outcomes:

1. the probability that at least one firm makes an R&D investment targeting disease j;
2. the expected number of ODDs for disease j.

Starting with the first, investment by at least one firm occurs if

$$\max_i \{\delta_{ij}\} > \hat{\delta}_j. \tag{16}$$

For the most common types of distributions $f(\Delta)$, including the normal and the exponential, the Gumbel distribution is the limiting distribution of $\max_i\{\delta_{ij}\}$ (Ahsanullah, 2016). We use $f^G(\tilde{\delta})$ and $F^G(\tilde{\delta})$ to denote the probability density function and the cumulative density function (CDF) of $\max_i\{\delta_{ij}\}$, respectively. The indicator function $\mathcal{I}_j^I$ can be used to define whether at least one firm invests in disease j ($\mathcal{I}_j^I = 1$) or not ($\mathcal{I}_j^I = 0$). We obtain

$$\mathcal{P}(\mathcal{I}_j^I = 1) = 1 - \int_{-\infty}^{\hat{\delta}_j} f^G(\tilde{\delta}) d\tilde{\delta}. \tag{17}$$

Following the analysis in the previous subsection, the focus is on how the impact of incentives changes with prevalence, i.e.:

$$\frac{\partial^2 \mathcal{P}(\mathcal{I}_j^I = 1)}{\partial z \partial n_j} = -\left[\frac{\partial^2 F^G(\tilde{\delta})}{\partial \tilde{\delta}^2} \frac{\partial \hat{\delta}_j}{\partial n} \frac{\partial \hat{\delta}_j}{\partial z} + \frac{\partial F^G(\tilde{\delta})}{\partial \tilde{\delta}} \frac{\partial^2 \hat{\delta}_j}{\partial z \partial n}\right] \tag{18}$$

and

$$\frac{\partial^2 \mathcal{P}(\mathcal{I}_j^I = 1)}{\partial \gamma \partial n_j} = -\left[\frac{\partial^2 F^G(\tilde{\delta})}{\partial \tilde{\delta}^2} \frac{\partial \hat{\delta}_j}{\partial n} \frac{\partial \hat{\delta}_j}{\partial \gamma} + \frac{\partial F^G(\tilde{\delta})}{\partial \tilde{\delta}} \frac{\partial^2 \hat{\delta}_j}{\partial \gamma \partial n}\right]. \tag{19}$$

Given the results of the previous subsection, the sign of the second term in brackets is negative for both expressions. As the derivatives of $\hat{\delta}_j$ with respect to n, z and γ are also negative, the following proposition holds.

Proposition 2. $\frac{\partial^2 F^G(\tilde{\delta})}{\partial \tilde{\delta}^2} \leq 0$ *is a sufficient condition for both a* pull *and a* push *incentive to increase the probability of having investment in disease j more for less rare diseases.*

According to Eq. 18 and 19 the condition is not necessary, since the two terms in brackets have opposite signs if the condition is not met. However, we argue that the condition is very likely to be satisfied for our market, because the relevant part of $F^G(\tilde{\delta})$ is likely to be concave. Investment in disease j occurs if $\tilde{\delta}_j \geq \hat{\delta}_j$. Given that most orphan diseases attract no investments, $\hat{\delta}_j$ is likely to be comparatively high, meaning that the relevant part of the Gumbel distribution is in the right tail, i.e. where the CDF is concave.

We can now move on to study the impact of incentives on the expected number of ODDs, conditional on $\mathcal{I}_j^I = 1$. Let $\tilde{N}^f(\hat{\delta}_j)$ be the number of firms that decide to invest in j, because $\delta_{ij} > \hat{\delta}_j$. For each of these firms, the investment decision has a Bernoulli outcome, with probability of obtaining an ODD equal to $p_j^d(I_j^*)$. From Eq. 3, the optimal investment level, and hence the probability of success, is the same for all firms for which it is convenient to invest in disease j. The sum of $\tilde{N}^f(\hat{\delta}_j)$ independent random variables with Bernoulli distribution has a *Binomial*$(\tilde{N}^f(\hat{\delta}_j), p_j^d(I_j^*))$ distribution, for which the limiting distribution is *Poisson*. If we take this approximation, the number of ODDs, conditional on investment, is distributed *Poisson*, with parameter $\lambda_j = \tilde{N}^f(\hat{\delta}_j) \cdot p_j^d(I_j^*)$.

	$\mathcal{P}(\mathcal{I}_j^I = 0)$	# ODD $\mid \mathcal{I}_j^I = 1$
$\uparrow z$	Negative; impact size increasing in n_j	Positive; role of n_j ambiguous
$\uparrow \gamma$	Negative; impact size increasing in n_j	Positive; role of n_j ambiguous

Table 2: Summary of theoretical results: impact of an increase in the policy parameters.

The following proposition summarizes the results of the theoretical analysis of the impact of incentives on the expected number of ODDs, conditional on $\mathcal{I}_j^I = 1$, for different classes of prevalence.

Proposition 3. *Conditional on at least one firm investing in disease j, the impact of incentives on the expected number of orphan designations may be greater or lower for less rare diseases.*

This ambiguity follows from the fact that the expected number of designations is $\lambda_j = \tilde{N}^f(\hat{\delta}_j)\, p_j^d(I_j^*)$. The impact on the probability that at least one firm invests in market j has been shown to be greater for less rare diseases. However, this does not necessarily imply that the impact on $\tilde{N}^f(\hat{\delta}_j)$ is also greater, as this depends on the distribution of δ_{ij}. Moreover, the impact on I_j^* is also ambiguous (Eq. 5 and Eq. 13).

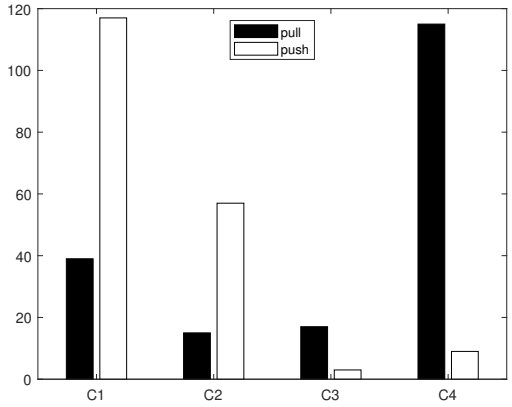
Table 2 summarizes our main theoretical results. Since in the empirical analysis we explicitly model $\mathcal{P}(\mathcal{I}_j^I = 0) = 1 - \mathcal{P}(\mathcal{I}_j^I = 1)$, as is common in zero-inflated models, Table 2 refers to this probability.

5 Calibration

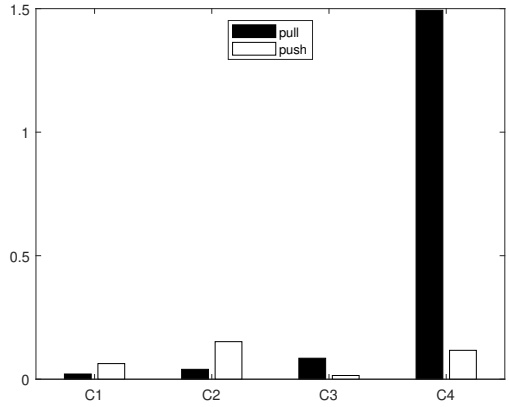
This section presents the main results of a calibration of the theoretical model.[10] The main aim is to explore the difference in the impact of *push* versus *pull* incentives, with an emphasis on whether the advantage for less rare diseases is larger with one type or other of incentive. Overall, the theoretical analysis carried out so far does not lead to a clear prediction on this point. The data used for the following empirical analysis are also not suitable to provide a conclusive answer. In terms of policy implications, the ability to compare the two types of incentives is important, because it may inform on whether a different mix of incentives can be used to influence the distribution of R&D efforts between less and more rare diseases.

To operationalize the model, the probability function of obtaining an ODD is defined as $p_j^d(I) = \sqrt{\frac{2\arctan(\epsilon I)}{\pi}}$, where ϵ is a parameter and π is the mathematical constant. The model is calibrated with the same data used in our empirical exercise, as described in detail in Section 6. Details of the calibration and additional output are presented in Appendix B.

[10] The calibration is implemented using the software MATLAB ®.



(a) Additional ODDs per class of prevalence ($z = 0.2$, $\gamma = 0.745$).



(b) Average number of additional ODDs per disease by class of prevalence ($z = 0.2$, $\gamma = 0.745$).

Figure 1: Distribution of additional ODDs due to the incentives, across classes of prevalence ($C1$: $< 1/1,000,000$; $C2$: 1-9/1,000,000; $C3$: 1-9/100,000; $C4$: 1-5/10,000).

We generate a sample of 2,553 diseases, the number for which the information on prevalence is not missing in our dataset (see Table 3). A prevalence value is associated with each disease, assuming a Log-Normal distribution for this parameter. Each disease is then assigned to a class of prevalence as defined in Orphanet: "<1/1,000,000" ($C1$), "1-9/1,000,000" ($C2$), "1-9/100,000" ($C3$), and "1-5/10,000" ($C4$). For the idiosyncratic term (δ_{ij}) a Normal distribution is assumed.

We are interested in how the additional ODDs obtained thanks to the incentives are distributed across classes of prevalence. The calibration exercise is based on three steps:

1. solution of the model with no incentive;
2. solution of the model with *pull* incentive (z) only;
3. iteration of the solution with *push* incentive (γ) only, to find the level of incentive such that the total number of ODDs gained is the same as in point 2.

For step 2, we set $z = 0.2$. Given the other parameter values, the iterated solution of the model shows that the condition defined in point 3 is satisfied with $\gamma = 0.745$.

Figure 1(a) shows the number of additional ODDs for each class of prevalence for the two types of incentive. By construction (step 3 of the calibration), the sum of the height of the bars for each type of incentive across the classes of prevalence is the same. More informative from the policy perspective, however, is the number of additional ODDs per disease (Figure 1(b)), which is strictly related to the probability that a patient suffering from a certain disease may benefit from new therapeutic options in the future. Figure 1(b) shows that there is a clear

difference in the distribution of additional R&D effort generated by *pull* and *push* incentives. With the *push* incentive, the increase in the number of ODDs per disease is higher in the two classes with lower prevalence, against the enormous advantage for the class of less rare diseases in the case of *pull* incentives. As shown in more detail in Appendix B, the calibration results suggest that the combination of direct and indirect mechanisms favoring less rare diseases in terms of extensive margin (Proposition 1) drives the overall impact on the number of ODDs, resulting from the combination of the intensive and extensive margin. As a result, there is much more advantage for less rare diseases than in the case of a *push* incentive, for which only an indirect mechanism favors these diseases in terms of the extensive margin.

6 Data and measures

We begin by identifying the full list of orphan diseases, i.e., those for which a drug may obtain an ODD. To do this, we rely on the Orphanet database (INSERM, 1999), the standard reference for information on rare diseases. The list used in the empirical analysis was downloaded in October 2017. After excluding some items, according to the criteria detailed in Appendix C, our list includes 5,132 diseases. Orphanet provides information on the class of prevalence of the disease, if already documented:[11] "<1/1,000,000", "1-9/1,000,000", "1-9/100,000", and "1-5/10,000".[12] We refer to worldwide prevalence; where this information is not provided, we consider prevalence in Europe or, failing that, in the US. Additional information at the disease level was retrieved from Orphanet, including the therapeutic class(es), the age at onset and age at death (the latter is available only for 28% of diseases). Ages are categorized as antenatal, neonatal, infancy, childhood, adolescence, adulthood and elderly.

In order to gather information on the existing knowledge of each disease, PubMed[13] was searched to retrieve the number of articles published over the period 1970-2016 which contain the name of each disease in the title, abstract or content. This information was used to construct a measure for the stock of publications (SP), following the perpetual inventory method:

$$SP_{jt} = P_{jt} + (1 - \rho)SP_{j,t-1},$$

where P_{jt} is the number of publications related to disease j at time t and $\rho = 0.1$ is the rate of obsolescence of knowledge, as generally applied in the empirical literature (Keller, 2002).

[11] In a few cases (6.7% of diseases), a numeric value for prevalence is also provided. However, the availability of this information is unevenly distributed across classes of prevalence. Given this limitation, the point estimate of prevalence is not used in the empirical analysis.

[12] Information on prevalence refers to year 2017. We are unable to track moves from one class to the other, which, however, are highly unlikely, given the width of the classes considered.

[13] See https://www.ncbi.nlm.nih.gov/pubmed/.

The list of rare diseases is systematically updated, as approximately 250 new diseases are described each year (Westermark et al., 2011; Wästfelt et al., 2006). Hence, the list downloaded in October 2017 may include diseases which were unknown earlier. A lack of ODDs for a disease as yet undiscovered cannot be interpreted as a lack of R&D targeting that disease. To account for this, our baseline analysis includes disease j only if its stock of publications in $t-5$ is positive (i.e., $SP_{j,t-5} > 0$).[14] The variable based on the number of publications is also used as a control to proxy the level of scientific information available on the disease.

A key decision concerns how to measure R&D efforts at the disease level. Our proxy of R&D efforts targeting rare diseases is the flow (number) of ODDs granted by the FDA per year between 1983 and 2016. An ODD represents the "successful translation of rare disease research into an orphan drug discovery and development program" (Heemstra et al., 2009). Obtaining an ODD is necessary for the project, and eventually for the drug, to be eligible for the incentives. Compared to the proxies for R&D used in previous contributions, such as the number of clinical trials (see, for example, Yin, 2008), ODDs have the advantage of providing information for a lengthy time span from a single administrative source. A potential limitation is that ODDs are only available for orphan diseases, meaning that they are not suitable for an analysis of the impact of the orphan legislation on orphan versus non-orphan diseases. Given that we focus on the heterogeneous impact *within* the class of orphan diseases, this concern is less relevant.

We focus on ODDs granted in the US, because the ODA passed in 1983 enables the dynamics in the number of designations over the selected time span to be studied. This includes 1993, when Japan significantly strengthened its orphan provisions, and 2000, when orphan legislation was introduced in the EU. As pharmaceuticals are a global industry, it is convenient for the inventors to apply for orphan drug status in several countries, in order to benefit from additional incentives. Together with the size of the US market, this means that FDA data provide a reliable picture of global R&D activity. For each drug, the FDA provides the date of orphan designation, marketing approval (if any), the designated indication, and the company sponsoring the request.

Every effort was made to match the indications of the FDA list of ODDs with the Orphanet list of diseases. Further details of assignment criteria and the exclusion of some of the 3,996 ODDs granted by the FDA between 1983 to 2016 are provided in Appendix C.

All in all, our data comprise 136,036 observations (5,132 diseases over – at most – 34 years). The distribution of diseases included in the analysis across prevalence classes is shown in Table 3. There is no information on the prevalence (or it has not yet been documented) in Orphanet for a large number of diseases: these are considered as a separate class. Among the classes with known prevalence, a significant majority of diseases are classified with a prevalence of under 1 in 1 million (36.89%), with only 2.98% in the class 1-5/10,000. Table 3 also shows that the

[14] Robustness of the results to this criteria is explored in Appendix D.

Prevalence	number of diseases	% total	avg. number of ODDs per disease (yearly)
$C1$: <1/1,000,000	1,893	36.89	0.03
$C2$: 1-9/1,000,000	205	3.99	0.13
$C3$: 1-9/100,000	302	5.88	0.17
$C4$: 1-5/10,000	153	2.98	0.22
$C0$: Missing prev.	2,579	50.25	0.13
Total	5,132	100	–

Table 3: Distribution of the diseases among prevalence classes.

average yearly number of ODDs per disease tends to increase substantially with prevalence.[15] While most diseases have no ODD, some have several ODDs and, in some cases, several approved treatments. These lucky exceptions are far more likely to occur when the market size is comparatively large: for example, only 0.53% of diseases in $C1$ have over two approved medicines, whereas the percentage is 13.07% in $C4$.

7 Empirical methods

Our theoretical analysis allows us to study *i*) the probability of no R&D for a certain disease ($\mathcal{I}_j^I = 0$), and *ii*) the expected number of ODDs conditional on $\mathcal{I}_j^I = 1$. Empirically, the two processes can be jointly modeled using a zero-inflated count data model. The unconditional expected number of ODDs is the result of the combination of the zero-inflated and count part of the model, which are jointly estimated via maximum likelihood.

The zero-inflated model indicates the determinants of the two different processes causing a zero outcome (Lambert, 1992): choice (the decision not to invest in R&D) and nature (the lack of innovative output, conditional on positive investment) (Winkelmann, 2008). R&D effort, proxied by the number of ODDs targeting disease j granted in year t, y_{jt}, is therefore modeled as:

$$y_{jt} = \begin{cases} 0, & \text{if } \mathcal{I}_{jt}^I = 0 \\ y_{jt}^*, & \text{if } \mathcal{I}_{jt}^I = 1 \end{cases} \tag{20}$$

where:

- $\mathcal{I}_{jt}^I$ is the binary variable introduced in Section 4. If $\mathcal{I}_{jt}^I = 0$, the outcome is a "certain zero", also referred to as "strategic" or "structural" zero (Staub and Winkelmann, 2013). For the sake of consistency with the analysis in Section 4, we depart from the standard

[15]The numbers of ODDs are calculated taking the average over the study years and over the diseases in each prevalence class.

assumption that the relevant probability distribution for the inflated part is either *Logistic* or *Normal* (hence, the estimated model is either Logit or Probit) and adjust the model for the *Gumbel* distribution;[16]

- y^*_{jt} is a count variable, representing the number of ODDs targeting disease j granted by FDA in year t. From the analysis in Section 4, under the assumptions of our model, its distribution can be approximated by a *Poisson*, with parameter $\lambda_j = \tilde{N}^f(\hat{\delta}_j) \cdot p^d_j(I^*_j)$. However, given that λ_j is disease-specific, when several diseases are considered, it is natural to refer to the Negative Binomial distribution, to account for over-dispersion.

The density for y_{jt} is:

$$f(y_{jt}) = \begin{cases} \mathcal{P}(\mathcal{I}^I_{jt} = 0) + [1 - \mathcal{P}(\mathcal{I}^I_{jt} = 0)] f^{nb}(0) & \text{if } y_{jt} = 0 \\ [1 - \mathcal{P}(\mathcal{I}^I_{jt} = 0)] f^{nb}(y^*_{jt}) & \text{if } y_{jt} \geq 1, \end{cases} \tag{21}$$

where $f^{nb}(\cdot)$ is the density function of the Negative Binomial distribution. The probability of being in the "certain zero" case ($\mathcal{I}^I_{jt} = 0$) is estimated using the Gumbel distribution:

$$\mathcal{P}(\mathcal{I}^I_{jt} = 0) = \exp(-\exp(-x'_{jt}\beta_1)). \tag{22}$$

Conditional on $\mathcal{I}^I_{jt} = 1$, the expected number of ODDs is:

$$\lambda_{jt} = \exp(x'_{jt}\beta_2). \tag{23}$$

Combining the two processes, the unconditional expected number of ODDs can be expressed as:

$$E(y_{jt}|x_{jt}) = (1 - \mathcal{P}(\mathcal{I}^I_{jt} = 0))\, \lambda_{jt} = (1 - \exp(-\exp(-x'_{jt}\beta_1)))\exp(x'_{jt}\beta_2). \tag{24}$$

For two reasons, our identification strategy cannot rely on the existence of a set of diseases to be used as a control group in the conventional way: (i) our measure of R&D effort is specific to orphan diseases, (ii) incentives are applied over the whole observation period. However, the incentives accumulated over time as new reforms were introduced, so the overall intensity of treatment (incentive) grew after each reform. Moreover, according to our theoretical analysis, disease prevalence affects the impact of incentives. We exploit these characteristics, in a difference-in-differences framework. Referring to equations 22 and 23, we specify:

$$x'_{jt}\beta = \alpha + \sum_i \zeta_i Ci_j + \sum_p \tau_p Dp_t + \sum_i \sum_p \kappa_{ip}(Ci_j \times Dp_t) + \theta W_{jt}, \tag{25}$$

[16]The STATA® code used for estimation is available from the authors upon request.

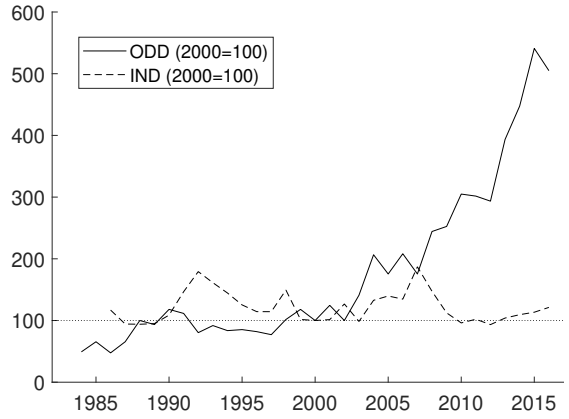
where β refers to both β_1 and β_2, which are separately estimated. Note that we normally use the same set of variables in the Gumbel and Negative Binomial part of the model. Ci denotes the class of prevalence, from the rarest ($C1$) to the least rare ($C4$) (see Table 3). To improve the readability of results, in estimating the model we aggregate classes $C2$ and $C3$ on the basis of statistical testing.[17] The new class is denoted as $C23$. Diseases where prevalence is missing are included as a separate class ($C0$). The binary variables Dp indicate relevant periods of time, related to the introduction of special legislation in the three geographical areas of interest, and to the joint application in the US and EU, which enhanced access to the incentives: 1983-1992 ($D1$, incentives available in the US only); 1993-1999 ($D2$, incentives available in the US and Japan); 2000-2007 ($D3$, incentives also available in Europe) and 2008-2016 ($D4$, possibility of joint application in Europe and the US). $C1$ and $D1$ are taken as reference categories.

The interaction coefficients κ_{ip} are the main parameters of interest, both in the Gumbel and Negative Binomial part of the model, representing the differential effect of the reforms for diseases in class of prevalence Ci, compared to those in the lowest class of prevalence, $C1$. The sign of κ_{ip} in the Gumbel part of the model is related to the signs of $\partial\mathcal{P}(\mathcal{I}_j^I = 0)/\partial z\partial n_j$ and $\partial\mathcal{P}(\mathcal{I}_j^I = 0)/\partial\gamma\partial n_j$; in the count part of the model, conditional on positive investments, it is related to the compound effect of $\partial I_j^*/\partial z\partial n_j$ and $\partial I_j^*/\partial\gamma\partial n_j$. Based on our theoretical analysis, we expect $\kappa_{ip} < 0$ for all i and all p in the Gumbel part of the model (Proposition 2), whereas the sign may be positive or negative in the count part of the model (Proposition 3). W is a vector including additional control variables which, according to the analysis in Section 4, may have an impact on R&D effort:

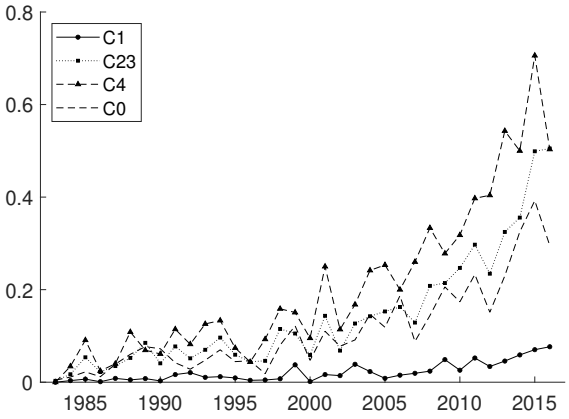
- a dummy variable ($EarlyD$) indicating whether the disease causes premature death (at pediatric age or in adulthood; 9% in our sample). This variable might affect the per patient net revenue, m_j, as some regulators grant a price premium to drugs targeting life-threatening conditions, and pediatric drugs are granted additional market exclusivity;

- the stock of publications (SP), given that inputs from science can play a relevant role in stimulating R&D efforts (Pavitt, 1984; Mansfield, 1995);

- dummy variables for 26 therapeutic classes (TC) and a dummy variable identifying genetic diseases (G), as assigned to diseases by Orphanet.



(a) Yearly number of ODDs (continuous line) and investigational new drugs (IND) applications (dashed line); year $2000 = 100$.



(b) Average number of new ODDs per disease among prevalence classes ($C1$:<1/1,000,000; $C23$: 1-99/1,000,000; $C4$: 1-5/10,000); $C0$: missing prevalence).

Figure 2: Trends of innovation over time.

8 Empirical Results

Figure 2 provides a descriptive illustration of the evolution of research efforts for orphan diseases. Figure 2(a) compares the yearly number of ODDs (solid line; year $2000 = 100$) with the number of investigational new drug (IND) applications for orphan and non-orphan diseases in the US (source: FDA; dashed line; year $2000 = 100$).[18] Although the comparison may not be fully homogeneous, it clearly suggests that the increase in R&D effort was much higher for orphan diseases. The existing literature shows that the availability of incentives for orphan drugs, accumulated over time, was a key determinant of the sharp increase in the number of ODDs (Yin, 2008; Westermark et al., 2011; Braun et al., 2010). More closely related to our research question, Figure 2(b) shows the evolution in the average number of new ODDs per disease for each class of prevalence. The graph shows that the growth documented in Figure 2(a) is driven mainly by ODDs for less rare diseases.

Our empirical strategy allows disentangling the contribution of the intensive and extensive margin to the observed dynamic. The main results of the model estimation are shown in Table 4. Note that, for each specification, Table 4 only shows the estimated coefficients of the interaction terms of interest (κ_{ip} in Eq. 25) for the zero-inflated (Gumbel) part (Eq. 22) and of the "count" part of the model (Eq. 23). The full table of results (Table 7) is set out in Appendix

[17] In the model estimated with all available classes of prevalence from Orphanet data (i.e., $C1$, $C2$, $C3$, $C4$, and $C0$) the null hypothesis of equality of the coefficients related to $C2$ and $C3$ cannot be rejected (p-value=0.8254).

[18] IND application is the regulatory step required in the US to commence clinical trials on humans for all drugs, including orphan drugs. Note that this measure would not be suitable to replace ODDs in our analysis, as the data available do not allow them to be linked to therapeutic indications.

	(1) $nodd_t$		(2) $nodd_t$		(3) $nodd_t$		(4) $nodd_{t+5}$	
	Gumbel $\mathcal{P}(\mathcal{I}_j^I = 0)$	count #ODD $\mid \mathcal{I}_j^I = 1$	Gumbel $\mathcal{P}(\mathcal{I}_j^I = 0)$	count #ODD $\mid \mathcal{I}_j^I = 1$	Gumbel $\mathcal{P}(\mathcal{I}_j^I = 0)$	count #ODD $\mid \mathcal{I}_j^I = 1$	Gumbel $\mathcal{P}(\mathcal{I}_j^I = 0)$	count #ODD $\mid \mathcal{I}_j^I = 1$
$C23 \times D2$	-2.856***	-1.423***	-2.782***	-1.387***	-2.614***	-1.403***	-3.563***	-1.873***
	(0.744)	(0.386)	(0.714)	(0.426)	(0.725)	(0.410)	(0.731)	(0.369)
$C23 \times D3$	-2.811***	-1.113***	-2.718***	-1.067***	-2.574***	-1.147***	-3.691***	-1.473***
	(0.712)	(0.343)	(0.681)	(0.362)	(0.652)	(0.378)	(0.736)	(0.390)
$C23 \times D4$	-3.129***	-1.195***	-3.045***	-1.161***	-2.938***	-1.317***	-3.633***	-1.363***
	(0.753)	(0.354)	(0.733)	(0.378)	(0.687)	(0.402)	(0.790)	(0.389)
$C4 \times D2$	-2.441	-1.249*	-2.300	-1.194*	-2.328	-1.279*	-4.328***	-2.163***
	(1.606)	(0.669)	(1.770)	(0.706)	(1.860)	(0.744)	(1.222)	(0.602)
$C4 \times D3$	-4.365***	-1.447**	-4.207**	-1.374**	-4.190**	-1.538*	-6.160***	-2.140***
	(1.615)	(0.673)	(1.750)	(0.690)	(1.896)	(0.791)	(1.281)	(0.631)
$C4 \times D4$	-4.587***	-1.616**	-4.484***	-1.564**	-4.488**	-1.803**	-6.243***	-2.035***
	(1.587)	(0.693)	(1.725)	(0.707)	(1.867)	(0.812)	(1.547)	(0.598)
$C0, C23, C4$	yes		yes		yes		yes	
$D2, D3, D4$	yes		yes		yes		yes	
$TC\&G$	yes		yes		yes		yes	
$EarlyD$	no		yes		yes		no	
$\ln(SP_{j,t-5})$	no		no		yes		no	
N	136036		136036		136036		111023	

$C1$: <1/1,000,000 (reference cat.); $C23$: 1/1,000,000-9/100,000; $C4$: 1-5/10,000; $C0$: missing prevalence.

$D1$: 1983-1992 (reference cat.); $D2$: 1993-1999; $D3$: 2000-2007; $D4$: 2008-2016.

TC: therapeutic class dummies; G: genetic disease dummy; $EarlyD$: early death dummy; SP: publication stock.

Standard errors (clustered by disease) in parentheses .

* $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$

Table 4: Selected estimation results: interaction effects (κ_{ip} in Eq. 25); results for the complete specification in Appendix D, Table 7.

D. Dummy variables for disease prevalence and time period, therapeutic class and genetic diseases are included in all specifications.[19] As a partial maximum likelihood framework is used, standard errors are clustered by disease in order to adjust for within-disease serial dependence (Wooldridge, 2010, Ch. 13).

Column (1) shows the results for our baseline specification. In the Gumbel part of the model, the coefficients associated with the interaction terms are negative and statistically significant, with the sole exception of $C4 \times D2$: in line with Proposition 2, the increase in incentives provided over time brings an advantage for less rare diseases compared to the most rare in terms of the extensive margin of R&D.

Complementary to these results, Figure 3(a) plots the predicted probability of a "certain zero" for the classes of prevalence $C1$, $C23$ and $C4$ conditional on the controls of Column (1). From the second (93-99) to the third period (00-07, when market exclusivity is additionally provided in the EU), a larger variation in probability is detected for $C4$ as compared to both $C23$ (difference: -33 percentage points; p-value $= 0.005$) and $C1$ (difference: -35 percentage points; p-value $= 0.003$).

The coefficients of the interaction terms are also significant in the count part of the model of

[19] Diseases with unknown prevalence are included, but interactions involving the corresponding dummy are not shown.

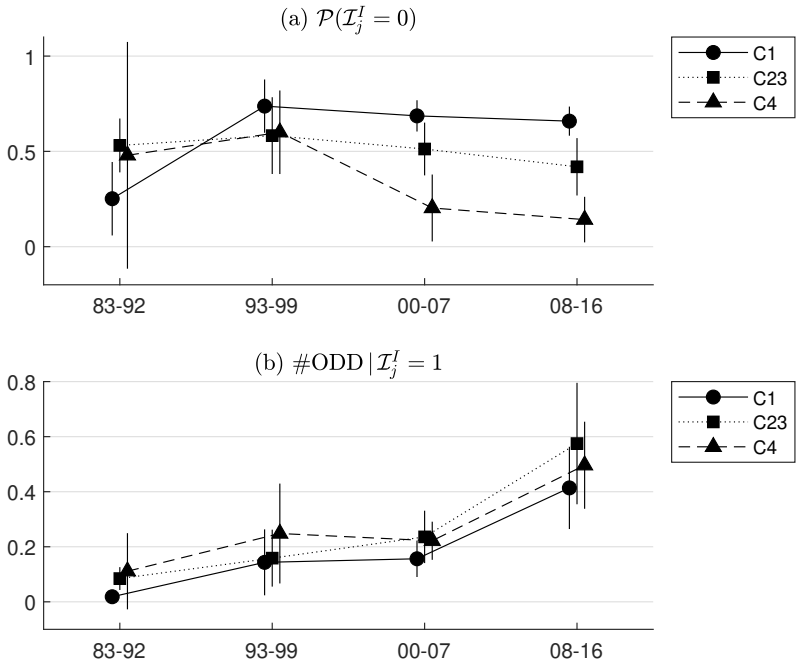


Figure 3: Predicted values for classes of prevalence $C1$, $C23$ and $C4$ in each period (with 95% confidence interval): (a) predicted probability that $\mathcal{I}_j = 0$ (Gumbel; Eq. 22); (b) predicted number of ODDs, conditional on $\mathcal{I}_j > 0$, computed as $\exp(x_{jt}\hat{\beta}_2)$ (count; Eq. 23).

Column (1), indicating the heterogeneous impact of the reforms according to prevalence. In this case, the sign of the difference, for which the theoretical prediction is ambiguous, is in favor of $C1$. In Figure 3(b) we plot the average of the exponential values of $x_{jt}\hat{\beta}_2$. This corresponds to the predicted number of ODDs per disease conditional on $\mathcal{I}_{jt}^I > 0$ (see Eq. 23).[20]

We combine the estimated coefficients in the Gumbel and count part of the model to calculate the predicted number of ODDs per year per disease (Eq. 24). Figure 4(a) shows this predicted number for each period, while Figure 4(b) shows the differences in the predicted number of ODDs ($C23$ *versus* $C1$ and $C4$ *versus* $C1$). Over time, there has been an increase in the number of ODDs for all classes of prevalence. This was led by a decrease in the probability of no positive investment for diseases belonging to $C4$ and by an increase in the intensity of investments, conditional on $\mathcal{I}_{jt}^I = 1$, for diseases in all classes. When comparing $C1$ and $C4$, the magnitude of the heterogeneous impact on the probability of making an investment (Gumbel part) outweighs the difference in terms of research intensity (count part) which goes in the opposite direction. Thus, over time, we observe a widening gap in the predicted number of ODDs for a disease in the lowest *versus* the highest class of prevalence. The difference in the

[20]Note that coefficients in the table represent semi-elasticities, whereas the figure shows the exponential of the linear combination corresponding to the predicted number of ODDs conditional on $\mathcal{I}_j > 0$.

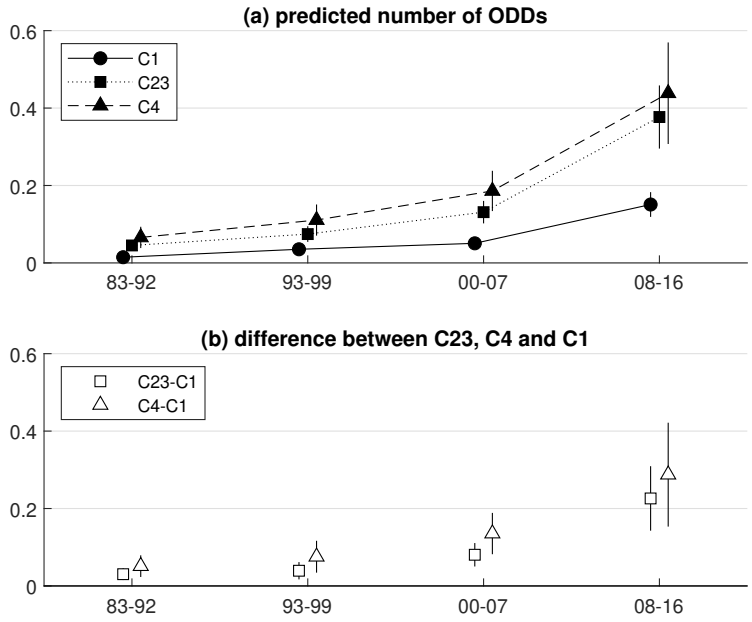


Figure 4: (a) Predicted number of ODDs (see Eq. 24) for $C1$, $C23$ and $C4$; (b) difference between $C23$, $C4$ and $C1$ (95% confidence interval reported in the graphs).

predicted number of ODDs is 5.6 times larger in the last period compared to the first.[21]

Columns (2) and (3) of Table 4 include additional control variables (respectively, $EarlyD$ and $\ln(SP_{j,t-5})$). Column (4) takes into account the possibility that, despite an immediate impact of the reform on R&D effort, the increase in the number of ODDs may be delayed. Therefore, the effect of independent variables at time t on the number of ODDs in $t+5$ is considered. A five-year lag has been selected, i.e., the average time span from the beginning of clinical trials to an ODD application.[22] Importantly, results for the heterogeneous effect of Orphan Regulations across classes of prevalence shown in Column (2)-(4) confirm the results of the baseline specification of Column (1). Moreover, when the time lag is taken into account, the estimated effect of the reforms is larger. This is in line with the idea that, when not accounting

[21] Since the Japanese law considers the lowest threshold for defining an orphan drug (about 4 in 10 thousand), a subset of diseases in $C4$ does not benefit from incentives in this country. Hence, starting from period $D2$, the estimated coefficients of $C4$ and its interactions may represent a lower bound.

[22] The length of the lag was estimated by combining our own calculations using FDA data with data on the length of drug development provided by DiMasi et al. (2016). According to these calculations, the *average* time lag between designation and marketing approval for drugs designated before 2005 is 68 months. The analysis does not extend beyond 2005 to avoid data censoring. DiMasi et al. (2016) indicate a time period of 126 months from synthesis to approval. In light of the difference between these two numbers, designations take place on average five years after the synthesis of the compound. This result is in line with Hay et al. (2014), who find that ODDs are most often given to a drug in phase 2, which, according to DiMasi et al. (2016), is roughly five years after synthesis.

for the lag, the impact of the reform is estimated in a period in which its effects are as yet partial. If this is the case, impacts estimated not accounting for the lag may be a lower bound.

The empirical analysis does not allow us to formally distinguish between the impact of *pull* versus *push* incentives, as both have been part of US and Japan regulations since their introduction. However, the European legislation provides solely *pull* incentives, and tax-related provisions are delegated to single countries. The results of Proposition 1, coupled with the fact that only two European countries provide tax incentives (see Section 2), suggest that the design of the European legislation may have contributed substantially to the widening of the gap between less and more rare diseases, as observed in Figure 4, after 2000.

There are clearly some challenges in the identification of a causal impact of orphan drug regulations adopted over time in our empirical analysis. One concern is that, due to the lenghty time span considered, other events, in addition to those for which we can control, may have impacted on the development of new orphan drugs. One example is the Human Genome Project completed in 2003: this may have increased R&D for genetic diseases, a large share of orphan diseases. However, in our data, 90% of diseases in $C1$ have a genetic origin against 67% in $C23$ and 41% in $C4$. If the Project increased R&D for genetic diseases, our estimate of the greater impact of the European legislation for $C4$ versus $C1$ would be biased downward. What may limit the validity of our conclusions is the presence of events other than orphan legislation, which had a stronger impact on diseases with a comparatively high level of prevalence. We are not aware of any relevant event with these characteristics during the period of analysis, and Appendix D (Table 9) shows that our results are robust to changes in the specification aiming to control for the impact of such events.

Additional robustness checks related to sample selection and the way in which we count the number of ODDs, are set out in Appendix D. The main results presented in this Section are confirmed.

9 Concluding remarks

There is ample evidence that the incentives provided through orphan regulations have increased investments in projects targeting rare diseases, with a potential reduction in inequality between orphan and common diseases. In this article, we study the impact of these incentives on the distribution of R&D efforts within the class of orphan diseases, with a focus on heterogeneity in relation to prevalence.

In a theoretical framework, we show that, under plausible assumptions, both *pull* and *push* programs increase the *probability of investment* more for a less rare disease. For *push* incentives the impact is only indirect, whereas it is both direct and indirect for *pull* incentives. In

terms of the *optimal level of R&D investment*, it is not possible to conclude unambiguously whether the impact of the incentives increases or decreases with the prevalence of the disease. A calibration exercise suggests that with *pull* incentives the combination of the extensive and intensive margin of investment leads to a large advantage for less over more rare diseases. Empirically, orphan designations, a condition for eligibility for incentives, are used as a proxy for R&D effort to investigate the impact of the introduction of incentives in different geographical areas over time. We utilize a Gumbel zero-inflated negative binomial model which, in line with the theoretical analysis, allows us to study the intensive and extensive margin of R&D effort separately. We find that the number of new designations per year has increased over time for all orphan diseases, but the concentration toward less rare diseases has also increased: the difference between the predicted number of new orphan designations per year for a disease in the highest and the lowest class of prevalence is 5.6 times larger in the last than in the first period of analysis. This result is driven by the extensive margin of R&D. Overall, our analysis suggests that the introduction of the European legislation, mainly providing *pull* incentives, contributed substantially to this outcome. Although it may be argued that the causal interpretation of our results can be challenged by the presence of events, other than the orphan legislation, which had a heterogeneous impact according to prevalence, our findings are supported by several robustness checks.

In line with our findings, a recent assessment of European orphan legislation concludes that *'the tools provided . . . have not done enough to direct the development in areas of greatest 'unmet clinical need'* (European Commission, 2020, p. 34). By showing that R&D efforts have been concentrated on less rare diseases, that the gap has been widening over time and that the type of incentives adopted may be important, our analysis has clear policy implications. If providing as many patients as possible with some therapeutic option is an objective, an increase in the relative weight of *push* incentives should be considered. The adoption of some of these incentives, such as tax credits, may be more challenging at the European level than in other regulatory frameworks, due to the fact that individual EU member states are still responsible for fiscal policies. An alternative approach might consider the introduction of provisions tailored to disease prevalence. For example, Jobjörnsson et al. (2016) explore the impact of changing the level of statistical significance required by regulatory authorities to grant marketing approval according to disease prevalence. Finally, the distribution of R&D efforts across diseases is important not only in terms of equity, but also in terms of efficiency, because the insurance value of innovation is a larger fraction of the overall value of innovation for very rare diseases (Lakdawalla et al., 2017). However, it is also worth mentioning that alternative efficiency considerations may lead to a more favorable evaluation of a concentration of R&D efforts on less rare diseases. This may occur, for instance, in the presence of significant economies of scale.

One challenge for future research is to explore the relationship between equity and efficiency in the provision of R&D incentives for orphan diseases.

Although the focus of the present article is the market of pharmaceuticals for rare diseases, we believe that some insights have more general implications. For example, the separation between the analysis of the extensive and intensive margin of R&D investment may be relevant for a wide range of research questions related to biomedical innovation, given that the industry constantly faces the dilemma of which therapeutic areas to invest in. Our analysis also shows that the relative impact of *push* versus *pull* programs changes according to the prevalence of the disease. In markets other than pharmaceuticals there may be other dimensions of heterogeneity worth considering in assessing how the distribution of benefits is affected by the specific type of incentive adopted.

Acknowledgments

We are grateful to the Editor and two anonymous Reviewers for valuable comments provided on an earlier version of the paper. We would like to thank participants at the Essen Health Conference 2020, the 4^{th} meeting of the American-European Health Economics Study Group (Vienna, 2019), the 12^{th} Annual Conference on Innovation Economics (Chicago, 2019), the 18^{th} Journées LAGV (Aix-en-Provence, 2019), the 8^{th} ZEW/MaCCI Conference on the Economics of Innovation and Patenting (Mannheim, 2019), the 10^{th} Annual Meeting of the Network on Economics of Regulation and Institutions (Rome, 2019), the 8^{th} Italian Congress of Econometrics and Empirical Economics (Lecce, 2019), the European Health Economics Association Conference (Maastricht, 2018), and at the seminar series of the University of Milan Bicocca (2019). We are particularly grateful to Marco Caliari, Giorgio Calzolari, Annika Herr, Giuseppe Moscelli, Mauro Sylos Labini and Van Ahn Vuong for their helpful suggestions. The usual disclaimer applies.

Funding

This work was supported by the University of Verona under the program 'Bando di Ateneo per la Ricerca di Base'.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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A The impact of incentives in a competitive model

Following Yin (2008), the market of an orphan disease j is modeled as a unit circle, with patients uniformly distributed along its length (Salop, 1979). Let F_j be the number of identical firms active in the market of disease j, supplying different drugs that are not vertically differentiated. Each firm supplies one drug, so that the number of firms active in the market equals the number of products. Quality is also assumed to be homogeneous, meaning that patient choices depend

only on their location in relation to suppliers. Each patient buys from the closest supplier, so that each firm serves n_j/F_j patients. For the sake of simplicity, we assume I to be exogenous[23] and $p_j^d = 1$. The profit function can be written as:

$$E\Pi_j = M_j(1+z)\frac{n_j}{F_j} - (1-\gamma)I. \tag{26}$$

Below, we study the impact of *pull* and *push* incentives on the equilibrium number of firms $\bar{F}_j$, and in particular how this impact changes with n_j.

A.1 *Pull* incentive

Assuming that firms are free to enter the market, the usual zero profit condition applies:[24]

$$E\Pi_j = M_j(1+z)\frac{n_j}{\bar{F}_j} - (1-\gamma)I = 0. \tag{27}$$

By applying the implicit function theorem, we find:

$$\frac{\partial \bar{F}_j}{\partial z} = \frac{\bar{F}_j}{1+z} > 0. \tag{28}$$

As expected, *pull* incentives increase the equilibrium number of firms. Regarding the most interesting question from our perspective, i.e. how this impact changes with n_j, we find that:

$$\frac{\partial^2 \bar{F}_j}{\partial z \partial n} = \left(\frac{1}{1+z}\right)\frac{\partial \bar{F}_j}{\partial n_j}. \tag{29}$$

Once more applying the implicit function theorem to Eq. 27, we obtain:

$$\frac{\partial \bar{F}_j}{\partial n_j} = \frac{\bar{F}_j}{n_j}, \tag{30}$$

which can be replaced in Eq. 29 to obtain:

$$\frac{\partial^2 \bar{F}_j}{\partial z \partial n} = \frac{\bar{F}_j}{n_j(1+z)} > 0. \tag{31}$$

Hence, in a model with several firms, an increase in the level of *pull* incentives has a greater impact on the number of firms / products for less rare diseases.

[23] This is equivalent to introducing the hypothesis that investment enhances drug quality, for which a minimum threshold is set, assumed to be binding for orphan diseases (see Yin, 2008).

[24] To be precise, $\bar{F}_j$ should be defined as the largest integer such that the expected profit is non negative. Given the aim of the analysis, and without loss of generality, we treat $\bar{F}_j$ as a continuous variable.

A.2 *Push* incentives

Referring to Eq. 27, the same methods are applied as for the *pull* incentive to determine:

$$\frac{\partial \bar{F}_j}{\partial \gamma} = \frac{I\,\bar{F}_j^2}{M_j\,n_j(1+z)} > 0. \tag{32}$$

In this case too, the impact on the equilibrium number of firms / products of the incentive is positive. Concerning the heterogeneous effect across diseases with different levels of prevalence, we find that:

$$\frac{\partial^2 \bar{F}_j}{\partial \gamma \partial n} = \frac{2n_j I \bar{F}_j \frac{\partial \bar{F}_j}{\partial n} - I\bar{F}_j^2}{M_j n_j^2(1+z)}. \tag{33}$$

Replacing $\frac{\partial \bar{F}_j}{\partial n}$ from Eq. 30 gives:

$$\frac{\partial^2 \bar{F}_j}{\partial \gamma \partial n} = \frac{\bar{F}_j^2 I}{M_j n_j^2(1+z)} > 0. \tag{34}$$

According to Eq. 34, with a *push* incentive too, the impact on the equilibrium number of firms / products is greater for less rare diseases.

B Calibration details

The calibration process is divided into two main parts. The first is the creation of a sample of diseases with different values of prevalence. Although prevalence is expressed in relative terms, what matters to a firm when shaping its optimal investment policy is the absolute size of the market. The thresholds separating classes of prevalence are transformed by assuming a total population size of 965.1 million, the sum of the populations (reference year: 2017) in the three main geographical areas where orphan legislation was introduced. These values (see Column 3 in Table 5) and the corresponding percentiles (Column 4) are used as a benchmark for the calibration of the distribution of prevalence among diseases in our simulated sample. Next, an iterative process is used to identify the combination of mean and standard deviation of the Log-Normal distribution that minimizes the sum of the distance, in percentage terms, between the value of prevalence corresponding to the switching percentiles (i.e. 74.17, 82.19 and 94.01; see Column (4) of Table 5) in the original distribution (Column 3) and its calibrated counterpart. Finally, given that the generated sample of diseases includes some whose prevalence exceeds the highest threshold (482,550), these are dropped (1.92% of the originally generated sample). The match between the calibrated sample of diseases in Column (5) and the original sample looks sufficiently close.

Class	Threshold		Prevalence: threshold percentile		# ODD: cumulative distribution	
	Relative	Absolute	Original	Calibrated	Original	Calibrated
(1)	(2)	(3)	(4)	(5)	(6)	(7)
$C1$	1/1,000,000	965.1	74.17	72.42	15.72	15.96
$C2$	9/1,000,000	8,685.9	82.19	87.17	45.49	42.38
$C3$	9/100,000	86,859	94.01	95.15	60.54	62.89
$C4$	5/10,000	482,550	100.00	100.00	100.00	100.00

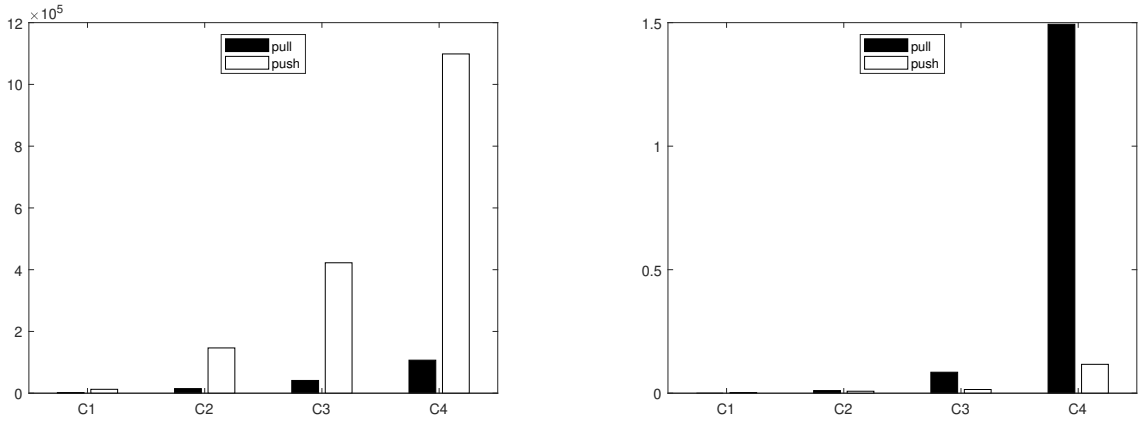
Table 5: Summary of information used to calibrate the model.

Parameter	Description	Value
mean prevalence	mean of the Log-Normal distribution	4.41
s.d. prevalence	s.d. of the Log-Normal distribution	4.2
M_j	expected net revenue per patient	300
ϵ	parameter of $p_j^d(I)$ function	1.4e-05
$E[\Delta]$	mean of the idiosyncratic term	-80e+06
s.d.$[\Delta]$	s.d. of the idiosyncratic term	49e+06
# diseases	number of diseases	2553
# firms	number of firms	20

Table 6: Calibrated parameter values.

The second part of the calibration relies on FDA data on granted ODDs, which we match to diseases, following the methods described in Section 6. Ideally, we would like to be able to identify a set of parameter values that allows to obtain a reliable distribution of ODDs across classes of prevalence in a situation without incentives. The fact that we have no data for the period before the introduction of incentives rules this out. To overcome this problem, the benchmark chosen was the distribution of ODDs across classes of prevalence cumulated over the 10 years after 1983, i.e., the period when only the US had orphan legislation. We are implicitly assuming that the impact of the incentives was still limited in this period compared to subsequent years. Column (6) of Table 5 reports the cumulative distribution of ODD for the four classes of prevalence. The remaining parameters in the model are set in order to obtain, for the simulation of the model with no incentives (step 1), a distribution of ODD across classes of prevalence which is reasonably similar to this benchmark. Table 6 shows the parameter values used in our calibration. Column (7) of Table 5 shows the calibrated cumulative distribution of ODDs for the situation without incentives.

As stated in Section 5, the model is solved: (1) without incentives, (2) with only a *pull* incentive ($z = 0.2$, $\gamma = 0$), (3) iterating the solution to find the value of a *push* incentive leading to the same number of ODDs as in the second step, with $z = 0$; this condition is satisfied with $\gamma = 0.745$.



(a) Change in optimal investment level per disease by class of prevalence ($z = 0.2, \gamma = 0.745$).

(b) Change in the number of firms that invest per disease by class of prevalence($z = 0.2, \gamma = 0.745$).

Figure 5: Change in optimal investment level and number of investors due to the incentives.

The most significant output, i.e. the distribution of the additional number of ODDs across classes of prevalence for the two types of incentive, is shown in the main text (Figure 1). Figure 5 shows how the two decisions considered in our theoretical analysis, i.e. investment intensity and whether or not to invest, contribute to this result. Given our parameter values, Figure 5(a) shows that the impact of both types of incentives on the optimal investment level, which was theoretically ambiguous, increases with the level of prevalence. For all classes of prevalence, the increase is larger for *push* incentives, due to the lower expected value of the marginal cost of the investment involved. On the other hand, the distribution of additional firms that decide to invest is greatly in favor of less rare diseases when the incentive is *pull* (Figure 5(b)). This is in line with the theoretical result that only for a *pull* incentive is a direct mechanism at work (Proposition 1). Therefore, the difference in terms of the probability of having positive investment (Figure 5(b)) seems to be driving the clear advantage for the class of less rare diseases in terms of additional ODDs, as shown in Figure 1.

C Additional information on the sample of diseases

Starting from the initial sample of 9,530 records available from the Orphanet database, we excluded 2,208 which do not refer to a specific disease, but to aggregations called "group of phenomes" (e.g., "rare pulmonary diseases"). Diseases emerging in the antenatal period or causing death before birth (323 diseases) were excluded. 568 records referring to surgical procedures were also dropped, and 192 items with obsolete nomenclature were updated and moved accordingly.

Concerning the FDA database of ODDs, this includes 3,996 designations granted between 1983 to 2016. Of these, 408 records referring to products for surgery, prevention, transplant, diagnostics and imaging procedures were excluded, and 199 records were dropped because information on the treated disease cannot be retrieved from Orphanet.

Where the FDA designated indication refers to a "group of phenomes", we rely on the hierarchical classification of orphan diseases provided by Orphanet to link the ODD with all relevant diseases, and we assign one ODD to each disease in the "group".[25]

D Detailed results and robustness checks

Table 7 shows the full set of estimated coefficients for the regression of Table 4. The results for the interactions of interest are commented on in the main text. The coefficients of time period dummies ($D2$, $D3$, $D4$) show that, for diseases in $C1$, both the probability of a "certain zero" and the expected number of ODDs (conditional on positive investment) increase with respect to first time period (1983-92).

In the Gumbel part of the model, the value of the coefficients for the prevalence dummies ($C23$, $C4$, $C0$) measures the difference in $\mathcal{P}(\mathcal{I}^I_{jt} = 0)$ between each class of prevalence and the reference category $C1$ in the period 1983-92. In the first time period (1983-92), in all models but the fourth, $C4$ is not statistically different from $C1$ in terms of probability of a "certain zero", whereas $C23$ is. In subsequent periods, both $C23$ (in all periods) and $C4$ (after year 2000) differ from $C1$, as highlighted by a test on the null hypothesis $Ci + Ci \times Dt = 0$,[26] indicating that the probability of a "certain zero" is lower for diseases in classes other than $C1$.

In the count part of the model, coefficients for Ci are positive and statistically significant: conditional on $\mathcal{I}^I_{jt} = 1$, less rare diseases experience larger investments (higher number of ODDs) in the first time period. However, the gap among classes of prevalence shrinks over time in percentage terms (see the negative sign of the interaction terms).

Column (2) of Table 7 takes into account the characteristics of the disease in terms of life expectancy, and includes a dummy variable that identifies diseases causing premature death ($EarlyD$). This variable is not significant either in the Gumbel or in the count part of the model, but its joint effect in the two equations is statistically different from zero (p-value=0.038

[25] For example, some drugs were designated for the treatment of hypereosinophilic syndrome, which is classified as a "group of phenomes" in Orphanet and comprises different diseases on the Orphanet list (i.e., idiopathic hypereosinophilic syndrome, primary hypereosinophilic syndrome, and secondary hypereosinophilic syndrome). The ODD assigned to this syndrome is therefore assigned to the three diseases comprising this "group". We believe that this way of counting ODDs is more appropriate than fractional counting that would assign 1/3 ODD to each disease, as we are interested in the availability of therapeutic options at the disease level.

[26] An exception being Model (4) in which the sums $C4 + C4 \times Dt$ are statistically different from zero at the 5% level for all time periods.

	(1) $nodd_t$		(2) $nodd_t$		(3) $nodd_t$		(4) $nodd_{t+5}$	
	Gumbel $\mathcal{P}(\mathcal{I}_j^I = 0)$	count #ODD $\mid \mathcal{I}_j^I = 1$	Gumbel $\mathcal{P}(\mathcal{I}_j^I = 0)$	count #ODD $\mid \mathcal{I}_j^I = 1$	Gumbel $\mathcal{P}(\mathcal{I}_j^I = 0)$	count #ODD $\mid \mathcal{I}_j^I = 1$	Gumbel $\mathcal{P}(\mathcal{I}_j^I = 0)$	count #ODD $\mid \mathcal{I}_j^I = 1$
$C23$	1.646***	1.524***	1.599***	1.488***	1.535**	1.463***	2.010***	1.743***
	(0.618)	(0.343)	(0.605)	(0.349)	(0.634)	(0.382)	(0.758)	(0.366)
$C4$	1.344	1.797***	1.210	1.757***	1.310	1.744**	2.466**	2.290***
	(1.650)	(0.647)	(1.782)	(0.658)	(1.935)	(0.774)	(1.119)	(0.561)
$C0$	2.498***	1.427***	2.439***	1.445***	2.387***	1.576***	2.386***	1.221***
	(0.480)	(0.421)	(0.544)	(0.438)	(0.557)	(0.389)	(0.485)	(0.287)
$D2$	3.172***	2.053***	3.124***	2.033***	3.019***	2.047***	3.463***	2.387***
	(0.617)	(0.426)	(0.677)	(0.470)	(0.688)	(0.405)	(0.557)	(0.309)
$D3$	2.701***	2.139***	2.622***	2.101***	2.523***	2.123***	3.484***	2.679***
	(0.663)	(0.308)	(0.672)	(0.337)	(0.631)	(0.352)	(0.520)	(0.285)
$D4$	2.483***	3.113***	2.421***	3.086***	2.342***	3.120***	2.610***	3.140***
	(0.617)	(0.296)	(0.627)	(0.320)	(0.606)	(0.344)	(0.496)	(0.259)
$C23 \times D2$	-2.856***	-1.423***	-2.782***	-1.387***	-2.614***	-1.403***	-3.563***	-1.873***
	(0.744)	(0.386)	(0.714)	(0.426)	(0.725)	(0.410)	(0.731)	(0.369)
$C23 \times D3$	-2.811***	-1.113***	-2.718***	-1.067***	-2.574***	-1.147***	-3.691***	-1.473***
	(0.712)	(0.343)	(0.681)	(0.362)	(0.652)	(0.378)	(0.736)	(0.390)
$C23 \times D4$	-3.129***	-1.195***	-3.045***	-1.161***	-2.938***	-1.317***	-3.633***	-1.363***
	(0.753)	(0.354)	(0.733)	(0.378)	(0.687)	(0.402)	(0.790)	(0.389)
$C4 \times D2$	-2.441	-1.249*	-2.300	-1.194*	-2.328	-1.279*	-4.328***	-2.163***
	(1.606)	(0.669)	(1.770)	(0.706)	(1.860)	(0.744)	(1.222)	(0.602)
$C4 \times D3$	-4.365***	-1.447**	-4.207**	-1.374**	-4.190**	-1.538*	-6.160***	-2.140***
	(1.615)	(0.673)	(1.750)	(0.690)	(1.896)	(0.791)	(1.281)	(0.631)
$C4 \times D4$	-4.587***	-1.616**	-4.484***	-1.564**	-4.488**	-1.803**	-6.243***	-2.035***
	(1.587)	(0.693)	(1.725)	(0.707)	(1.867)	(0.812)	(1.547)	(0.598)
$C0 \times D2$	-3.663***	-1.874***	-3.619***	-1.859***	-3.522***	-1.917***	-3.350***	-1.604***
	(0.636)	(0.553)	(0.739)	(0.604)	(0.696)	(0.464)	(0.578)	(0.331)
$C0 \times D3$	-3.047***	-1.312***	-2.989***	-1.287***	-2.886***	-1.381***	-2.968***	-1.246***
	(0.513)	(0.377)	(0.534)	(0.397)	(0.558)	(0.367)	(0.549)	(0.313)
$C0 \times D4$	-2.486***	-1.396***	-2.442***	-1.382***	-2.386***	-1.520***	-2.055***	-1.085***
	(0.488)	(0.376)	(0.535)	(0.392)	(0.558)	(0.367)	(0.517)	(0.289)
$EarlyD$			-0.285	0.203	-0.207	0.218		
			(0.370)	(0.154)	(0.357)	(0.150)		
$\ln(SP_{j,t-5})$					-0.033	0.078***		
					(0.026)	(0.018)		
Constant	-1.360*	-4.730***	-1.295*	-4.744***	-0.996*	-4.959***	-1.680***	-4.571***
	(0.708)	(0.299)	(0.678)	(0.301)	(0.605)	(0.330)	(0.527)	(0.274)
$\ln(\alpha)$	0.894***		0.894***		0.795***		0.842***	
	(0.201)		(0.196)		(0.161)		(0.159)	
N	136036		136036		136036		111023	
AIC	55999.94		55951.90		55692.84		50335.00	
BIC	56854.34		56825.94		56586.52		51171.73	

Standard errors (clustered by disease) in parentheses.
Therapeutic class and genetic dummy variables included in all specifications.
Column (1) also includes interactions between $TC\&G$ dummies and time period dummies in the count part of the model.
* $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$

Table 7: Full estimation results (Table 4).

in Model (3) and 0.046 in Model (4)).

Column (3) includes the stock of publications at time $t-5$ (in log) to proxy the level of scientific knowledge related to disease j: inputs from science play a relevant role in stimulating R&D efforts. Indeed, results highlight that a larger stock of publications increases the number of ODDs in the count part (it also reduces the probability of a "certain zero", although not significantly).

The results for the model of Column (4) are commented in the main text.

The following two subsections present two sets of robustness checks. First, different ways of measuring the dependent variable (Table 8) are considered. The sample is then modified and additional control variables are introduced (Table 9).

D.1 Counting the number of ODDs

Column (1) of Table 8 excludes the designations received after the drug obtained marketing approval for other indications from the count of ODDs.[27] In this case, the innovation can be considered less substantial. When excluding these designations from the count, results are qualitatively similar to those shown in Table 4.

Column (2) includes only ODDs assigned to private companies (96% of the ODDs in our sample), excluding ODDs assigned to universities, hospitals and medical centers, non-profit organizations and patient associations. Our main results are again unaffected.

D.2 Sample issues and control variables

In the count part of the model presented in Column (1) of Table 9, additional controls are added in the form of interactions between therapeutic class and genetic dummies ($TC\&G$) and period dummies.[28] These interaction terms aim to capture the effect of technological reforms at the therapeutic class level. Technological breakthroughs fostering the level of innovative effort in a specific therapeutic class might bias our results if correlated with the level of prevalence.

Column (2) includes a proxy for the per patient net revenue at the industry level (mg).[29] In particular, it includes the ratio between the producer price index of manufacturing pharmaceuticals and medicines, and the price index for private fixed investments in intellectual property

[27] The relevant information was retrieved from the list of orphan-designated products with at least one marketing approval for a common disease provided by the FDA and the Drugs@FDA database.

[28] The interaction terms are included only in the count part of the model as this specification has a lower Bayesian Information Criterion (BIC) compared to models where the interaction terms are also (or solely) included in the Gumbel part of the model.

[29] On the basis of the theoretical model, disease-specific per patient net revenues (m_j) should affect incentives to undertake R&D investments. Unfortunately, we are not aware of reliable proxies for net revenues, as well as price indices or dynamics in R&D costs, at the disease level.

	(1) excl.appr.		(2) firm only	
	Gumbel $\mathcal{P}(\mathcal{I}_j^I = 0)$	count #ODD $\mid \mathcal{I}_j^I = 1$	Gumbel $\mathcal{P}(\mathcal{I}_j^I = 0)$	count #ODD $\mid \mathcal{I}_j^I = 1$
$C23$	1.514**	1.488***	1.785***	1.415***
	(0.591)	(0.364)	(0.653)	(0.340)
$C4$	1.610	1.672**	1.061	1.657***
	(1.866)	(0.769)	(1.731)	(0.527)
$C0$	2.680***	1.551***	2.611***	1.344***
	(0.503)	(0.377)	(0.465)	(0.295)
$D2$	3.239***	2.151***	3.662***	1.986***
	(0.619)	(0.360)	(0.600)	(0.303)
$D3$	2.722***	2.168***	2.977***	2.173***
	(0.549)	(0.325)	(0.473)	(0.271)
$D4$	2.404***	3.090***	2.740***	3.143***
	(0.540)	(0.318)	(0.425)	(0.269)
$C23 \times D2$	-2.726***	-1.451***	-3.329***	-1.385***
	(0.692)	(0.381)	(0.837)	(0.365)
$C23 \times D3$	-2.653***	-1.107***	-3.064***	-1.022***
	(0.584)	(0.356)	(0.828)	(0.342)
$C23 \times D4$	-2.981***	-1.168***	-3.328***	-1.083***
	(0.589)	(0.374)	(0.589)	(0.346)
$C4 \times D2$	-2.571	-1.146	-2.512	-1.102**
	(1.817)	(0.736)	(1.714)	(0.523)
$C4 \times D3$	-4.687***	-1.420*	-4.498**	-1.310**
	(1.815)	(0.780)	(1.899)	(0.514)
$C4 \times D4$	-4.982***	-1.524*	-4.782**	-1.465***
	(1.819)	(0.803)	(1.915)	(0.535)
$C0 \times D2$	-3.854***	-2.037***	-4.093***	-1.776***
	(0.609)	(0.416)	(0.593)	(0.338)
$C0 \times D3$	-3.238***	-1.444***	-3.184***	-1.257***
	(0.499)	(0.354)	(0.493)	(0.302)
$C0 \times D4$	-2.604***	-1.486***	-2.546***	-1.330***
	(0.502)	(0.346)	(0.445)	(0.295)
Constant	-1.270**	-4.780***	-1.429**	-4.673***
	(0.543)	(0.321)	(0.686)	(0.358)
$\ln(\alpha)$	0.921***		1.029***	
	(0.157)		(0.150)	
N	136036		136036	
AIC	54359.26		54254.62	
BIC	55213.66		55109.02	

Standard errors (clustered by disease) in parentheses.
Therapeutic class and genetic dummy variables included in all specifications.
* $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$

Table 8: Results – Robustness checks on how the number of ODDs is measured.

	(1) $TC_j \times Dp_j$		(2) mg_t		(3) all obs.		(4) $SP_{83-5} > 0$	
	Gumbel $\mathcal{P}(\mathcal{I}_j^I = 0)$	count #ODD $\mid \mathcal{I}_j^I = 1$	Gumbel $\mathcal{P}(\mathcal{I}_j^I = 0)$	count #ODD $\mid \mathcal{I}_j^I = 1$	Gumbel $\mathcal{P}(\mathcal{I}_j^I = 0)$	count #ODD $\mid \mathcal{I}_j^I = 1$	Gumbel $\mathcal{P}(\mathcal{I}_j^I = 0)$	count #ODD $\mid \mathcal{I}_j^I = 1$
$C23$	0.474	1.471***	1.309**	1.417***	2.149***	1.265***	1.857**	1.844***
	(0.565)	(0.475)	(0.554)	(0.341)	(0.429)	(0.248)	(0.772)	(0.560)
$C4$	0.600	1.692***	1.025	1.712***	0.923	1.344***	1.643	2.036*
	(0.781)	(0.611)	(1.426)	(0.571)	(1.597)	(0.475)	(2.186)	(1.078)
$C0$	0.487	0.668	-0.266	0.730*	2.720***	1.137***	3.039***	1.938**
	(0.498)	(0.431)	(0.711)	(0.417)	(0.347)	(0.239)	(0.855)	(0.810)
$D2$	0.753	0.508	3.356***	1.671***	3.840***	1.930***	2.492***	1.931***
	(0.561)	(0.437)	(0.614)	(0.432)	(0.348)	(0.240)	(0.912)	(0.644)
$D3$	0.550	0.689	3.204***	1.511***	3.663***	2.197***	2.981***	2.554***
	(0.602)	(0.463)	(0.627)	(0.338)	(0.308)	(0.228)	(0.827)	(0.703)
$D4$	0.395	1.484***	3.913***	1.921***	3.073***	2.974***	2.614***	3.330***
	(0.548)	(0.451)	(0.612)	(0.372)	(0.323)	(0.227)	(0.910)	(0.733)
$C23 \times D2$	-1.528**	-1.213***	-2.498***	-1.323***	-3.324***	-1.155***	-2.371***	-1.358**
	(0.681)	(0.436)	(0.693)	(0.378)	(0.456)	(0.268)	(0.890)	(0.605)
$C23 \times D3$	-1.609**	-1.117**	-2.448***	-1.007***	-3.628***	-1.053***	-2.997***	-1.471**
	(0.639)	(0.466)	(0.629)	(0.336)	(0.447)	(0.270)	(0.708)	(0.648)
$C23 \times D4$	-1.997***	-1.148**	-2.861***	-1.096***	-3.480***	-0.899***	-3.207***	-1.385*
	(0.668)	(0.474)	(0.662)	(0.348)	(0.457)	(0.306)	(0.750)	(0.746)
$C4 \times D2$	-1.159	-0.741	-2.112	-1.173*	-2.554*	-1.005**	-1.697	-1.061
	(0.831)	(0.568)	(1.441)	(0.604)	(1.476)	(0.473)	(1.893)	(0.876)
$C4 \times D3$	-3.688***	-1.387**	-3.964***	-1.366**	-3.633***	-1.235***	-3.860***	-1.707**
	(0.912)	(0.601)	(1.426)	(0.587)	(1.373)	(0.452)	(1.311)	(0.838)
$C4 \times D4$	-3.887***	-1.460**	-4.327***	-1.521**	-2.551*	-0.981*	-3.539**	-1.719**
	(0.827)	(0.606)	(1.362)	(0.607)	(1.512)	(0.502)	(1.580)	(0.766)
$C0 \times D2$	-1.430**	-0.958**	-3.803***	-1.887***	-3.904***	-1.541***	-3.176***	-1.941**
	(0.555)	(0.423)	(0.622)	(0.518)	(0.400)	(0.284)	(0.947)	(0.757)
$C0 \times D3$	-1.028*	-0.653	-3.508***	-1.381***	-3.580***	-1.198***	-3.460***	-1.762**
	(0.583)	(0.428)	(0.543)	(0.376)	(0.367)	(0.272)	(0.811)	(0.761)
$C0 \times D4$	-0.504	-0.613	-3.919***	-1.660***	-2.759***	-1.081***	-2.822***	-1.649**
	(0.521)	(0.420)	(0.576)	(0.421)	(0.389)	(0.269)	(0.986)	(0.828)
mg			-2.010***	1.246***				
			(0.392)	(0.252)				
$mg \times C0$			2.073***	0.490**				
			(0.419)	(0.223)				
Constant	0.710	-3.366***	1.286	-6.034***	-1.026***	-4.012***	-0.752	-4.558***
	(0.638)	(0.487)	(0.927)	(0.476)	(0.397)	(0.205)	(0.667)	(0.441)
$\ln(\alpha)$	0.777***		0.816***		0.774***		0.613	
	(0.173)		(0.205)		(0.168)		(0.557)	
N	136036		133348		212092		91392	
AIC	55479.21		55469.14		71872.74		37299.61	
BIC	57129.08		56361.00		72765.78		38119.41	

Robust (clustered by disease) standard errors in parentheses.

Therapeutic class and genetic dummy variables included in all specifications.

* $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$

Table 9: Results – Robustness checks: sample issues and additional control variables.

products for firms operating in pharmaceutical and medicine manufacturing (as a proxy for R&D expenditure).[30] The ratio between the two indices grew substantially over the observation period. Also included is an interaction term between $C0$ (missing prevalence) and the ratio in the Gumbel and count part of the model.[31]

Column (3) includes the full set of diseases in all time periods, without the selection based on the stock of publications.

Finally, the estimation in Column (4) is based on the balanced panel of diseases known at the beginning of the observation period (i.e., with a positive value of SP_{t-5} in year 1983). By using a balanced set of observations in Column (3) and (4), we aim to investigate whether our results are driven by sample composition.

All in all, the robustness checks carried out in this section confirm the main results in Table 4 (and Table 7).

[30]Both indices were downloaded from Federal Reserve Economic Data. See: https://fred.stlouisfed.org. Data for the producer price index in 1983 are not available, so one observation for each disease was lost.

[31]Interaction terms between the classes with known prevalence and mg are not statistically different from zero either in the Gumbel or count part of the model. Note that, according to the theory, an increase in m_j works as an increase in z, meaning that the size of the impact depends on n_j.