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

Simona Gamba† Laura Magazzini‡ Paolo Pertile§

PRELIMINARY DRAFT

Abstract

Since the early 80s, orphan drug regulations have been introduced to stimulate R&D for rare diseases. We develop a theoretical model to study the heterogeneous impact on optimal R&D decisions of the incentives for diseases with different levels of prevalence. We show the mechanisms through which the type of incentives deployed by orphan drug regulations may stimulate R&D more for orphan diseases with comparatively high prevalence, thus increasing inequality within the class of orphan diseases. Using data from the Food and Drug Administration on the number of orphan designations, our empirical analysis shows that, while R&D has increased over time for all orphan diseases, the increase has been much greater for the less rare. According to our baseline specification, the difference between the predicted number of orphan designations for a disease belonging to the highest and the lowest class of prevalence is 5.6 times larger after 2008 than it was in 1983. Our findings support the idea that the type of incentives in place may be responsible for this increase in inequality within orphan diseases.

Keywords: pharmaceuticals, innovation, orphan regulations, market size, inequality
JEL: I14; I18; O31; O38; C35

*We would like to thank participants at the Eighth ZEW/MaCCI Conference on the Economics of Innovation and Patenting (Mannheim, 2019), the X Annual Meeting of the Network on Economics of Regulation and Institutions (Rome, 2019), the Eighth 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. We are particularly grateful to Van Ahn Vuong for her helpful comments. We acknowledge financial support from the program 'Bando di Ateneo per la Ricerca di Base' funded by the University of Verona. The authors declare no conflict of interest.

†Department of Economics, University of Verona, Verona, Italy. gamba.simona@gmail.com
‡Department of Economics, University of Verona, Verona, Italy. laura.magazzini@univr.it
§Department of Economics, University of Verona, Verona, Italy. paolo.pertile@univr.it

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 often affects only few people, there are currently 7,000 orphan diseases described in the literature, so that 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, less than 10% of rare diseases currently known have an available treatment (Melnikova, 2012; Tambuyzer, 2010).

Given that the pharmaceutical industry is mainly responsible for R&D investments for new drugs, the allocation of resources across diseases is affected by the expected return on investments. Hence, the market size is a critical dimension. The empirical and theoretical analysis of the effect of market size on innovation identifies a positive relationship. 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 market and with a 4% increase when only nongeneric drugs are taken into account. The result is confirmed by Dubois et al. (2015), who find that R&D efforts are directed towards larger markets, and estimate that, on average, additional revenues of $2.5 billion are required to support the invention of one new chemical entity. Jobjörnsson et al. (2016) propose a theoretical model to study how the interaction between the regulation of marketing approval by institutions such as FDA and EMA and reimbursement decisions by payers affects R&D investment, showing that R&D investments are less likely if a disease is rare. Barrenho et al. (2019) use data on marketing authorizations to obtain concentration curves and concentration indexes of innovation, according to the burden of disease and the market size. They find that innovation is concentrated toward diseases with a greater market size, i.e. those with higher prevalence or higher willingness to pay.

In addition to the limited size of the market, research efforts directed towards orphan diseases may be hindered by the difficulty in identifying patients with rare diseases for clinical trials, in the logistic organization of the trials themselves, by the poor understanding of the course of the disease, as well as by the low expertise in the medical community (Tambuyzer, 2010).

In order to address the lack of incentives to undertake research targeting rare pathologies, policy makers have introduced a number of tools to incentivize R&D for orphan diseases. The main tools are tax credits on R&D expenditure, market exclusivity for new products, protocol assistance and reduced marketing authorization fees. The necessary formal step to access these incentives is obtaining an *orphan drug designation* (ODD) from the competent regulatory authority. The first special legislation was introduced in the United States, with the Orphan Drug Act (ODA), approved in 1983. Since then, several other countries have established regulations

for the development of orphan drugs. The economic rationale for these incentives can be hardly related to efficiency: given that R&D costs are largely independent of the market size, other things being equal, the expected return per unit of investment in terms of population health is lower when the size of the market is smaller. On the other hand, inequality aversion provides a strong motivation, given the huge differences in the availability of treatments between rare and common diseases. The problem can also fit an equality of opportunity framework (Raïs Ali and Tubeuf, 2019), given that the disease prevalence is clearly beyond individual control (Roemer, 1998).

Overall, there seems to be a general consensus that special regulations adopted over 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) show evidence of a positive impact of the ODA on R&D directed to orphan diseases and Lichtenberg (2013) finds that an increased availability of drugs for orphan diseases reduced mortality. A positive impact on the number of designations and approvals for orphan drugs is also found in Europe (Westermark et al., 2011). On the other hand, concerns have been raised that part of the increase in the number of designations and approvals might not be the result of a really innovative effort, but rather due to strategic behaviour by the pharmaceutical industry. For example, Yin (2009) highlights that firms have incentives to develop drugs for rare subdivisions of more common diseases, pointing that as much as 10% of innovations for orphan diseases would have been developed even in absence of the policy. It is therefore important that incentive policies are efficiently designed, so to maximize the social return on expenditure.

While most of the literature has addressed the question whether special regulations are effective in reducing the gap between R&D for orphan and non orphan diseases, far less attention has been devoted to the possibly heterogeneous impact across different orphan diseases. However, this is an extremely relevant issue, given the huge number of orphan diseases and the large variability among them, along several dimensions. Among previous studies on this topic, Heemstra et al. (2009) take into account orphan designations in Europe and the US, and highlight a strong heterogeneity in the level of research effort across different diseases, the heterogeneity depending on the therapeutic class, prevalence and the number of scientific publications. Yin (2008) analyzes the impact of the ODA on R&D activity targeting rare diseases, proxied by the number of clinical trials, and shows that the rarest diseases have benefited less from the introduction of the special legislation in the United States.

The dimension of heterogeneity, on which this paper focuses, is prevalence. Among orphan diseases, there are some that affect almost 100,000 individuals worldwide and others that only

record few cases. We believe that, if an equity argument provides the rationale for incentivizing orphan versus non-orphan diseases, the equity implications of these incentives within the class of orphan diseases cannot be disregarded. Our analysis aims at characterizing the dynamic impact of orphan regulations introduced over time and across countries.

We use a simple theoretical model to study the impact of orphan regulation on two outcomes: i) the probability of having any investment in R&D for a certain disease ii) the intensity of the R&D effort, which affects the probability of obtaining an ODD. To account for the heterogeneity in the tool set used in different contexts, we separately consider *output-related* incentives (e.g., market exclusivity) and *input-related* incentives (e.g., tax credits). We show that both types of incentives have an unambiguously stronger effect on the first outcome for less rare diseases, meaning that the impact on the probability of having any investment is larger for less rare diseases among the orphan ones. This advantage of less rare diseases is greater when *output-related* incentives are in place. This means that the exposure to treatment (incentives) changes with the prevalence of the disease. 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 counterpart of our theoretical model is a Zero Inflated count data model, where the dependent variable is the yearly number of ODD at the disease level, as a proxy for R&D intensity. For the sake of consistency with the distributional assumptions that we make, the excess of zeros is modelled using the Gumbel distribution, to replace the standard Logit or Probit model. We adopt a difference-in-differences approach to exploit the fact that reforms have been introduced at different points in time in different geographic areas and that, according to our theoretical results, diseases with different prevalence might have benefited differently from the regulations.

We find that, over time, R&D efforts have increased substantially more for less rare diseases within the class of orphan diseases, thus increasing inequality within the class of orphan diseases. These conclusions remain valid even when controlling for a number of other factors potentially affecting the relative convenience of investing in less vis-a-vis more rare diseases. To the best of our knowledge, no evidence of this dynamics has been previously reported. Based on our theoretical results, we argue that the way in which orphan incentives were designed may have contributed to widening this gap. By relying almost exclusively on *output-related* incentives, the European legislation may have exacerbated this tendency.

In terms of policy implications, our results suggest that, if inequality aversion is a fundamental motivation for orphan legislation, then a revision of the incentive tool-kit should be considered, with the objective of curbing the widening of the gap between less and more rare orphan

diseases. One way of mitigating this tendency could be to shift the balance of incentives towards *input-related* tools. A more radical reform could consider abandoning the idea of setting an arbitrary threshold of prevalence, below which all diseases benefit from the same type of incentives, to move towards prevalence-dependent incentives.

The structure of the paper is as follows. Section 2 describes the different regulations that have been adopted over time. Section 3 describes the model, which is solved in Section 4. Section 5 ans 6 describe, respectively, data and methodology for the empirical analysis, whose results are presented in Section 7. Section 8 concludes and discusses the policy implications.

2 Institutional context

Over the last 35 years, orphan drug regulations have been adopted in several countries around the world (Pammolli et al., 2009). The US were the first country to develop a specific legislation. In 1983 the Congress signed the ODA, according to which a drug is considered *orphan* if it treats a rare disease or condition affecting fewer than 200,000 persons 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.[1] 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[2] and (5) subsidies for clinical trials from the Orphan Products Grant Program.

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

[1]This is the current definition of orphan drugs, that was introduced with the Health Promotion and Disease Prevention Amendments of 1984. Indeed, originally the Orphan Drug Act of 1983 defined a rare disease as one that "occurs so infrequently in the United States that there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from the sales in the United States of such drug". Other minor amendments of the ODA took place over the years to mitigate strategic behavior on the side of the firm (Herder, 2017).

[2]Market exclusivity represents a stronger protection for firms compared to patents. While patents prevent other companies from making, using, offering for sale, selling, and importing for these purposes the drug, market exclusivity implies that the regulatory agency cannot approve another drug for the same indication without the sponsor's consent. Moreover, patent protection is filed early in the development process, whereas market exclusivity is granted when the product is launched in the market. As the development process can last many years (DiMasi et al., 2016), empirical analysis has shown that market exclusivity, on average, extends patent protection by 0.8 years (Seoane-Vazquez et al., 2008). Furthermore, some orphan drugs contain natural products for which it is not possible to obtain patent protection (Pammolli et al., 2009). For these reasons, we believe the fact that several countries introduced or extended their patent coverage for pharmaceuticals during the analyzed period is not relevant for our analysis.

EU (2000) and Taiwan (2000).[3] In what follows we only consider the introduction of special regulations in the three areas with the largest markets: US, Japan and the EU.

In April 1993, Japan substantially revised its orphan medicinal product system, introduced in 1985, so as to extend the tools used to incentivize research on orphan diseases. So, in addition to the already existing (1) reductions in the required data for application, and (2) 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. Compared to those introduced in the US, incentives introduced in Japan entail a longer period of market exclusivity, but a lower percentage for the computation of the tax credit.[4] In order to be designated as orphan, the drug, which has to be proved highly effective and safe, has to treat a rare and serious disease or condition affecting less than 50,000 persons in Japan (about 4 in 10 thousand persons), and such disease should not have any other available treatment. Since in Japan the incentive tools which are the main focus of our analysis were introduced in 1993, we refer to this as the date when the special legislation was introduced.

In December 1999, also the European Union approved a regulation on orphan medicinal products: the Regulation (EC) No 141/2000.[5] The regulation establishes a procedure for designating orphan drugs and sets incentives for R&D. 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 the marketing authorization is granted. Moreover, the targeted drug has to treat a condition affecting no more than 5 in 10 thousand persons in the Community when the application is made, or it has to treat 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 return to justify the necessary investment;[6] finally, there should exist no satisfactory alternative methods authorized in the Community or the medicinal product has to bring significant benefit to those affected by that condition (article 3 of the Regulation). In addition to the incentives mentioned in the regulation, some member states have introduced other measures to support R&D, such as tax reductions (allowed in France and the Netherlands) (Health and Safety, 2015).

[3] With the exception of Australia, all these countries provide (extra) market exclusivity for orphan drugs (Sharma et al., 2010).

[4] Indeed, non-clinical costs per approved new compound are estimated to be lower than clinical costs (1 billion US$ versus 1.5 billion US$, according to DiMasi et al. 2016).

[5] As in the US, also in Europe several regulations took place after the first one. Also in this case, however, none of the following six regulations modified the incentives introduced with the first one and presented here.

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

	US (1983)	Japan (1993)	Europe (2000)
Disease:			
Prevalence	$<$ 200,000 in US (6.25/10,000)	$<$ 50,000 in Japan (4/10,000)	$<$ 5 in 10,000
Characteristics	Rare or not profitable	Rare	Rare or not profitable & life-threatening
		Serious	
		No other treatment available or clinically superior	No other treatment available or clinically superior
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.

Incentives provided by the US, Japan and Europe are summarized in Table 1, together with requirements for drugs to be considered as orphan.

Since November 2007, the European Medicines Agency (EMA) and the FDA are collaborating to encourage joint applications to the orphan drug status both in Europe and the US. A common 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). Parallel applications in Japan and Europe are also encouraged, although a common application form is not in place yet, due to administrative differences between the two offices (Mariz et al., 2016).

prevalence criteria.

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 that has developed a molecular entity applies for an ODD. If granted, the ODD makes the firm eligible for any incentive related to the development of an orphan drug. If the development process is successfully completed, the firm will approach the second regulatory stage: marketing authorization. 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 introduce the standard assumptions $\frac{\partial p_j^d}{\partial I} > 0$ and $\frac{\partial^2 p_j^d}{\partial I^2} < 0$. Moreover, given that p_j^d is a probability, $p_j^d(0) = 0$ and $\lim_{I\to\infty} p_j^d(I) = 1$.

Conditional on obtaining an ODD, the firm will carry on the development process. With probability p_j^m this will lead to the marketing approval of the product.[7] Given the disease specific per patient net revenue m_j, conditional on obtaining an ODD, the expected net revenue is $p_j^m \cdot m_j$. To simplify notation, we define the individual level expected net revenue, conditional on having obtained an ODD, as $M_j(\Omega_j) = p_j^m m_j$. 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.

The expected profit for firm i $(1, 2, \ldots, N^f)$ associated with an investment I targeting disease j is:

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

The term δ_{ij} is an idiosyncratic component aiming to capture any additional component of the expected profit that is only known to the firm. This may result, for example, from the possibility of exploiting knowledge acquired on other projects that the firm had previously undertaken. 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 takes the whole market. We believe that this simplifying assumption is reasonable. Indeed, market exclusivity, which is part of the set of incentives deployed for all regulations described in Section 2, prevents the authorization of a new drug unless it is shown to be more effective than the current standard of treatment. This suggests that, if a new drug is authorized while market exclusivity still holds, the new drug is likely to take the whole market.

The aim of our analysis is to study the impact of different forms of incentives among those that have been introduced as part of the special legislation on: *i)* the probability of having in-

[7] Without loss of generality, p_j^m is assumed independent of I.

vestment on a rare disease, *ii)* the probability of having 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 disease, 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.

Incentives can be distinguished into two categories: *output-related* and *input-related*. *Output-related* incentives are those that aim to increase the net market revenue of investments made on orphan diseases. The best known instance of such instrument is *market exclusivity*, to which all products with an orphan designation are entitled. This is part of the incentive package provided, for example, by the US, Japan and Europe. We model this as a mark-up, z ($z \geq 0$), on net revenues. This way of modeling *output-related* incentives is sufficiently flexible to account also for other types of incentives, such as a price premium to which all orphan drugs are equally entitled.

Input-related incentives reduce the cost of R&D investment for rare diseases. Examples of such incentives include tax credits, reduced fees for market authorization applications and protocol assistance. We model this type of incentive as an allowance on investment costs, such that the investment cost borne by the firm is $I(1-\gamma)$, with $0 \leq \gamma \leq 1$. To take the role of these incentives into account, the expected profit function can be written as:

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

4 Optimal investment policy

In this section, we study the firms' optimal investment policy and the impact of R&D incentives on the expected number of ODD, our proxy for R&D effort. The focus is on how this impact is affected by the size of the market (disease prevalence). Given that innovations are protected by market exclusivity and that only for a small fraction of orphan diseases (6%) more than one treatment is authorized, we believe that it is reasonable to introduce the simplifying assumption that firms make their investment decisions independently.

We start by characterizing the decision from the perspective of a single firm and then move to the analysis 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 is:

$$\frac{\partial p_j^d(I)}{\partial I} = \frac{1-\gamma}{M_j \cdot n_j(1+z)}. \tag{3}$$

The second order conditions are satisfied under the assumptions on the functional form of $p_j^d(I)$ that were introduced above. Eq. 3 implicitly defines the optimal investment level $I^*(M_j, n_j)$ and highlights the well known role of market size as an incentive for R&D investments: with n_j small, other things being equal, the optimal investment level is lower.

4.1.1 Impact of *output-related* incentives

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

$$\frac{dI^*}{dz} = -\frac{1-\gamma}{(\partial^2 p_j^d/\partial I^2) M_j n_j (1+z)^2}. \tag{4}$$

According to Eq. 4, an increase in z provides an incentive to invest more, by reducing the value on the right hand side of Eq. 3. From the perspective of our analysis, it is also interesting to investigate how the marginal impact on I^* of an increase in z varies with n_j. Differentiating the right hand side of Eq. 4 with respect to n_j obtains:

$$\frac{\partial^2 I^*}{\partial z \partial n_j} = \frac{(\partial p_j^d/\partial I)(\partial^3 p_j^d/\partial I^3) - (\partial^2 p_j^d/\partial I^2)^2}{(\partial^2 p_j^d/\partial I^2)^2 (1+z)^2} (1+z) \frac{\partial I^*}{\partial n_j}. \tag{5}$$

Given that $\partial I^*/\partial n_j > 0$ (see Eq. 3), the sign of Eq. 5 is the same as the sign of its first term. Since $\partial^3 p_j^d/\partial I^3$ may be positive,[8] the expression cannot be unambiguously signed. This means that, conditional on $I^* > 0$, we cannot unambiguously say whether the impact on the probability of obtaining a designation of strengthening an *output-related* incentive is greater for a more or a less rare disease.

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

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

It is then possible to define a minimum value of δ_{ij}, $\hat{\delta}_j$, such that the firm makes any investment

[8] Indeed, the sign is positive for the increasing and concave functional forms typically employed in economics.

in R&D for disease j:

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

To investigate the impact of n_j on the decision whether to invest or not, we study the dependency of $\hat{\delta}_j$ on n_j. Observing that

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

which allows to simplify calculations through the application of the Envelope Theorem, the following expression obtains:

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

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 the value of the stochastic variable above which a positive amount is invested. This leads to

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

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 the right hand side of Eq. 10 with respect to n_j, we obtain:

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

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

4.1.2 Impact of *input-related* incentives

As for z, the impact on I^* of an increase in γ is positive (see Eq. 3). Concerning the heterogeneity of the impact, using the same approach as above, we find that:

$$\frac{\partial^2 I^*}{\partial \gamma \partial n_j} = \frac{(\partial^3 p_j^d/\partial I^3)(\partial I^*/\partial n_j)n_j + \partial^2 p_j^d/\partial I^2}{(\partial^2 p_j^d/\partial I^2)^2 M_j \cdot n_j^2(1+z)}. \tag{12}$$

As for z, this term cannot be unambiguously signed, meaning that the impact of an increase in γ on I^*, and hence on the probability of having an ODD, conditional on investing, may be increasing or decreasing in the disease prevalence.

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

$$\frac{\partial \hat{\delta}_j}{\partial \gamma} = -I^*(M_j, n_j, z, \gamma) < 0 \tag{13}$$

and

$$\frac{\partial^2 \hat{\delta}_j}{\partial \gamma \partial n_j} = -\frac{\partial I^*}{\partial n_j} < 0. \tag{14}$$

Also in this case, the impact is greater for less rare diseases.

The following proposition states an important difference between an *input-related* and an *output-related* incentive:

Proposition 1. *For both types of incentives, the reduction in $\hat{\delta}_j$ is greater for less rare diseases. However, while for an* input-related *incentive this is due only to an indirect effect, for an* output-related *incentive there is both a direct and an indirect effect.*

The proposition follows immediately from the comparison between Eq. 11 and Eq. 14.

In terms of magnitude, a marginal increase in z can be interpreted as an increase by, e.g. 1% in expected revenues from commercialization. Similarly, for γ, it can be seen as a 1% reduction in the investment cost faced by the firm. As long as expected revenues and investment costs are sufficiently similar, the magnitudes of the two impacts can be compared by comparing $\frac{\partial^2 \hat{\delta}_j}{\partial z \partial n_j}$ with $\frac{\partial^2 \hat{\delta}_j}{\partial \gamma \partial n}$. This comparison shows that, starting from a situation with no incentive ($z = 0, \gamma = 0$), the introduction of an *output-related* incentive provides a greater comparative advantage for less rare disease, than the introduction of an *input-related* incentive.[9]

[9] To see this, substitute into Eq. 11, the expression for $M_j \cdot n_j$ from Eq. 3 and compare the resulting expression with Eq. 14.

4.2 Market outcomes

We can now move to the study of the impact of incentives at the disease level, under the assumption that the N^f firms make independent investment decisions, as characterized in the previous subsection. We will 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 ODD for disease j.

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

$$\max_i\{\delta_{ij}\} > \hat{\delta}_j. \tag{15}$$

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 denote by $f^G(\tilde{\delta})$ and $F^G(\tilde{\delta})$, respectively, the probability density function and the cumulative density function of $\max_i\{\delta_{ij}\}$. 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 ($\mathcal{I}_j^I = 0$). The probability that at least on firm invests in j is

$$\mathcal{P}(\mathcal{I}_j^I = 1) = 1 - \int_{-\infty}^{\hat{\delta}_j} f^G(\tilde{\delta}) d\tilde{\delta}. \tag{16}$$

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

$$\frac{\partial^2 \mathcal{P}(\mathcal{I}_j^I = 1)}{\partial z \partial n_j} = -\left[\frac{\partial^2 F^G(\tilde{\delta})}{\partial \tilde{\delta}^2}\frac{\partial \hat{\delta}_j}{\partial n}\frac{\partial \hat{\delta}_j}{\partial z} + \frac{\partial F^G(\tilde{\delta})}{\partial \tilde{\delta}}\frac{\partial^2 \hat{\delta}_j}{\partial z \partial n}\right] \tag{17}$$

and

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

According to the analysis presented in Section 4.1, the sign of the second term in brackets is negative for both expressions. Since 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 an* output-related *and an* input-related *incentive to increase the probability of observing investment in disease j more for less rare diseases.*

According to Eq. 17 and 18 the condition is not necessary, because if it is not satisfied, the two terms in brackets have opposite signs. However, for our market of interest, we argue that the condition is very likely to be satisfied. One may think, for example, of a situation where the distribution of Δ is symmetric. In this case, the condition of Proposition 2 requires that investing in disease j is optimal for less than half of the firms. Given the scarcity of investment in R&D for rare diseases, this is very likely to be satisfied.

We can now move to the study of the impact of incentives on the expected number of ODD, 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, whose limiting distribution is *Poisson*. If we take this approximation, the number of ODD, conditional on investment is distributed *Poisson*, with parameter $\lambda_j = \tilde{N}^f(\hat{\delta}_j) \cdot p_j^d(I_j^*)$.[10]

The following proposition summarizes the results of the theoretical analysis of the impact of incentives on the expected number of ODD across 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.*

The ambiguity of this impact follows from the fact that the expected number of designations is $\lambda_j = \tilde{N}^f(\hat{\delta}_j) \cdot p_j^d(I_j^*)$. The impact on the probability of having at least one firm investing 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. 12). This prevents us from signing the impact on λ_j theoretically.

Table 2 summarizes our theoretical results, separately for the two outcomes that have been considered: the probability that at least one firm invests and the expected number of ODD, conditional on investment. For consistency with the empirical analysis that follows, the table refers to $\mathcal{P}(\mathcal{I}_j^I = 0)$. Our main focus is on the lower part of the table, i.e. on how the impact on the two outcomes of interest changes with prevalence. The previous analysis has shown that both *input-related* and *output-related* incentives tend to favor less rare diseases in terms of probability

[10] Given that λ_j is disease specific, in the empirical analysis, where several diseases are considered, we refer to the *Negative Binomial* distribution, to account for over-dispersion.

	$\Pr(\mathcal{I}_j^I = 0)$	# ODD ($\mathcal{I}_j^I = 1$)
	$\hat{\delta}_j$	$\lambda_j = \tilde{N}^f(\hat{\delta}_j) \cdot p_j^d(I^*)$
$\uparrow n_j$	Negative	Positive
$\uparrow z$	Negative	Positive
$\uparrow \gamma$	Negative	Positive
prevalence and exposure to treatment		
$\uparrow z$	Larger for larger n_j	Ambiguous
$\uparrow \gamma$	Larger for larger n_j	Ambiguous

Table 2: Summary of theoretical results

that at least one firm invests. For the impact on the expected number of ODD, conditional on having investment, the impact is ambiguous.

5 Data and measures

The first step in our analysis is the identification of the full list of orphan diseases, i.e. those for which a drug is eligible to obtain an ODD. For this purpose, we rely on the Orphanet database (INSERM, 1999), which is the standard reference for information on rare diseases.[11] 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). The version used in the empirical analysis was downloaded in October 2017. The full list downloaded counts 9,530 records. However, 2,208 records do not refer to specific diseases, but to aggregations of them (e.g. "Rare Pulmonary Diseases"). For the purposes of the empirical analysis, only specific diseases will be considered, following the criteria detailed in this section.

Our proxy of R&D efforts targeting rare diseases is the number of ODD granted by the FDA 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). Having an ODD is a necessary condition for the project, and eventually for the drug, to be eligible for the incentives provided under the special legislation. In comparison with proxies of R&D used in previous contributions, such as the number of clinical trials (see, for example, Yin, 2008), ODD have the advantage of being retrievable from a single administrative source.

We focus on designations in the US as it is the largest pharmaceutical market in the world;

[11] Orphanet was established in 1997 in France, to expand knowledge on rare diseases and to improve their diagnosis, care and treatment. Since 2000 the initiative is a European endeavor. Further information is available at www.orpha.net.

moreover, the ODA establishment in 1983 allows us to study the dynamics in the number of designations over a long time span, including 1993, when Japan reviewed its orphan provisions, and 2000, when an orphan legislation was introduced in Europe. Since the pharmaceutical industry is a global one, it is convenient for the inventor to apply for the orphan drug status in several countries to benefit from additional incentives, meaning that FDA data provide a reliable picture of the 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.

A major effort was undertaken to match the indications of the FDA list of ODD with the Orphanet list of diseases. Out of 3,996 ODD granted by the FDA between 1983 to 2016, we exclude 408 records referring to products for surgery, prevention, transplant, diagnostics and imaging procedures, while 199 records are dropped because information on the treated disease cannot be retrieved from Orphanet. Moreover, in some cases, we were not able to match the designated indication to a single disease, but rather to an aggregation of diseases ("group of phenomes").[12] In this case, in order to be consistent in the definition of the market, we rely on the hierarchical classification of orphan diseases provided by Orphanet to link the aggregation with all relevant diseases belonging to it and match the FDA designation at the disease level. If more than one disease is included in the group, one orphan drug designation is attributed to each disease, i.e. a non-fractional count is adopted. In the robustness checks, we show results for the case of fractional counting.

Orphanet also provides information on the class of prevalence of each disease at the country level, as well as worldwide.[13] As a measure of market size, we refer to worldwide prevalence. When this information is missing, we consider prevalence in Europe or, if missing, in the US. Diseases belonging to the following prevalence classes are included in the analysis: "$<$1/1,000,000", "1-9/1,000,000", "1-9/100,000", and "1-5/10,000".[14] From Orphanet we also retrieve additional information at the disease level, including the therapeutic class(es) of each disease, information on the age of onset and age at death (however, the latter is available only for 28% of diseases). Ages are reported as antenatal, neonatal, infancy, childhood, adolescence, adulthood and elderly. We exclude from the analysis those diseases emerging in the antenatal

[12]For example, some drugs were designated for the treatment of the hypereosinophilic syndrome, which is classified as a "group of phenomes" in Orphanet and comprises different diseases included in the Orphanet list (i.e., idiopathic hypereosinophilic syndrome, primary hypereosinophilic syndrome, and secondary hypereosinophilic syndrome).

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

[14]Information on prevalence refers to year 2017 and we are unable to track moves from one class to the other. However, these are very unlikely to occur, given the width of the classes considered.

period or causing death before birth (323 diseases). We also removed 568 diseases referring to surgical procedures, and 192 items representing an old nomenclature (these were moved to an updated item).

Finally, we complement information provided by Orphanet with an ad hoc search into PubMed,[15] in order to gather information on the stock of knowledge for each disease. An automated search was conducted on PubMed for each disease in our list, retrieving the number of articles published over the period 1970-2016 and containing the name of the disease in the title, abstract or content. We use this information 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 typically applied in the empirical literature (Keller, 2002).

The information on publications is used both as a control variable to proxy the level of scientific information available about the disease, as well as to select those diseases that had already been discovered at a given point in time (Heemstra et al., 2009). New pathologies are constantly added to the list of orphan diseases, so that the list of known diseases in October 2017 (the basis of our analysis) might also include pathologies which were not known at an earlier time. Of course, a lack of ODD for a disease that has not been discovered yet, cannot be interpreted as a lack of R&D effort targeting that disease. To account for this, we include in our baseline analysis disease j only if its stock of publications in $t - 5$ is positive (i.e., $SP_{j,t-5} > 0$).

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 among prevalence classes is reported in Table 3. Information on the prevalence is missing (or not yet documented) in Orphanet for a large share of the diseases: these are considered as a separate class. Among the classes with known prevalence, the large majority of diseases is classified with a prevalence lower than 1 in 1 million (36.89%), with the "least rare" diseases ($N4$) only accounting for 2.98% of the total. Table 3 also shows how the average number of ODD per year changes from one class of prevalence to another. The reported numbers of ODD are calculated taking the average over years in the study period and over diseases in each class of prevalence. These descriptive statistics are coherent with our theoretical results and in line with the literature suggesting a positive correlation between market size and R&D effort (Acemoglu and Linn, 2004; Dubois et al., 2015).

[15]Pubmed is a web-search service maintained by the US National Libraty of Medicine. It comprises more than 28 million citations for biomedical literature from MEDLINE, life science journals, and online books. For more information, please visit https://www.ncbi.nlm.nih.gov/pubmed/.

Prevalence	number of diseases	% total	avg. number of ODD per disease (yearly)
$N1$: <1/1,000,000	1,893	36.89	0.03
$N2$: 1-9/1,000,000	208	3.99	0.13
$N3$: 1-9/100,000	302	5.88	0.17
$N4$: 1-5/10,000	153	2.98	0.22
$N0$: Missing prev.	2,579	50.25	0.13
Total	5,132	100	–

Table 3: Distribution of the diseases among prevalence classes

6 Empirical methods

The pharmaceutical market is characterized by the presence of multinational firms that serve several markets. Hence, the number of designations per disease granted in the US may be considered a reliable proxy for the global R&D effort. Over the whole period considered in the analysis, incentives were available in at least one geographic area. The incentives provided by the reforms of Japan and Europe added to those provided by the ODA in the US. The theoretical results presented in Section 4 show that the impact of both market exclusivity and tax credits on the probability of having investment is positive and, under reasonable assumptions, it is greater for less rare diseases (Proposition 2). This implies a different exposure to treatment (incentives). We exploit these differences in time and across classes of prevalence using a difference-in-differences approach.

In the empirical analysis we cannot distinguish between the impact of *output-related* versus *input-related* incentives, as both of these were part of the US and Japan regulations since their introduction. However, the European regulation provides uniquely *output-related* incentives, whereas tax-related provisions are delegated to single countries. The fact that only two European countries provide tax incentives (see Section 2) allows us to interpret the effect observed after 2000 as the result of a wider applicability of market exclusivity. Combined with the large size of the European market, this might have increased inequality between more and less rare orphan diseases (see Proposition 1).

The empirical counterpart of our theoretical model is a Zero Inflated Negative Binomial (ZINB) model: the inflated and the count part are respectively related to the probability of having no R&D for a certain disease ($\mathcal{I}_j^I = 0$) and to the expected number of ODD conditional on $\mathcal{I}_j^I = 1$. The unconditional expected number of ODD results from the combination of the two parts, which are jointly estimated via maximum likelihood.

The ZINB model allows us to understand the determinants of the two different processes determining a zero outcome (Lambert, 1992): choice (the decision not to invest in R&D) and nature (the lack of innovative output, conditional on the level of effort) (Winkelmann, 2008).

R&D effort, proxied by the number of ODD targeting disease j in year t, is therefore modeled as:

$$y_{jt} = \begin{cases} 0, & \text{if } \mathcal{I}_j^I = 0 \\ y_{jt}^*, & \text{if } \mathcal{I}_j^I = 1 \end{cases} \tag{19}$$

where:

- $\mathcal{I}_j^I$ is the binary variable introduced in Section 4.2.[16] If $\mathcal{I}_j^I = 0$, 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 of Section 4.2, we depart from the standard 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 to let the distribution be *Gumbel*;[17]

- y_{jt}^* is a count variable, representing the number of ODD targeting disease j in period t. From the analysis of Section 4.2, under the assumptions of our model, its distribution can be approximated by a *Poisson*, with parameter $\lambda_j = \tilde{N}^f(\hat{\delta}_j)) \cdot p_j^d(I_j^*)$. 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. When $y^* = 0$, zeros in the outcome are due to nature.

As a result, the density for y_{jt} is:

$$f(y_{jt}) = \begin{cases} \Pr(\mathcal{I}_j^I = 0) + [1 - \Pr(\mathcal{I}_j^I = 0)] \Pr(y_{jt}^* = 0) & \text{if } y_{jt} = 0 \\ [1 - \Pr(\mathcal{I}_j^I = 0)] \Pr(y_{jt}^* > 0) & \text{if } y_{jt} \geq 1. \end{cases} \tag{20}$$

The probability to be in the "certain zero" case ($\mathcal{I}_j^I = 0$) is estimated using the Gumbel distribution:

$$\Pr(\mathcal{I}_j^I = 0) = \exp(-\exp(-x'_{jt}\beta_1)).$$

[16] We do not make explicit reference to time here, as there might be lags between R&D investments and ODD. However, this does not affect our empirical strategy.

[17] The Stata code used for the estimation is available from the authors upon request.

Conditional on $\mathcal{I}_j^I = 1$, the expected number of ODD is:

$$\lambda_{jt} = \exp(x'_{jt}\beta_2) \tag{21}$$

The unconditional expected number of ODD is expressed as a combination of the two processes:

$$E(y_{jt}|x_{jt}) = (1 - \Pr(\mathcal{I}_j^I = 0)) \cdot \lambda_{jt} = (1 - \exp(-\exp(-x'_{jt}\beta_1)))\exp(x'_{jt}\beta_2), \tag{22}$$

where

$$x'_{jt}\beta = \alpha + \sum_{i=0}^{4} \zeta_i Ni_j + \sum_{p=1}^{4} \tau_p Dp_t + \sum_{i=0}^{4}\sum_{p=1}^{4} \kappa_{ip}(Ni_j \times Dp_t) + \theta C_{jt}. \tag{23}$$

Note that we normally use the same set of variables in the Gumbel and in the Negative Binomial part of the model. Ni represents the class of prevalence, from the rarest ($N1$: "<1/1,000,000") to the least rare ($N4$: "1-5/10,000"; see Table 3). The binary variables Dp indicate relevant periods of time, related to the introduction of special legislation in the three geographic areas of interest, and to the joint application for the US and Europe: 1983-1992; 1993-1999; 2000-2007 and 2008-2016.[18] The 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 each reform for diseases belonging to the class of prevalence Ni, with respect to those in the lowest class of prevalence. C is a vector including additional control variables which, according to the analysis presented in Section 4, may have an impact on R&D effort:

- a dummy variable indicating whether the disease causes premature death (in paediatric age or adulthood). 9% of diseases included in the analysis (and for which information on the age at death is available) causes premature death. 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 paediatric drugs are granted additional market exclusivity;[19]

- a proxy for the probability of obtaining marketing authorization, p_j^m. This variable is constructed as the ratio between the sum of marketing authorizations granted in the previous 5 years and the sum of designations received in the previous 5 to 9 years. We define the variable at the level of the therapeutic area to overcome the problem of zeros at the denominator, due to the large number of diseases with no ODD. We consider a time lag of up

[18]The first time period (1983-1992) and $N1$ are taken as reference categories.

[19]The extra market exclusivity for paediatric drugs lasts 2 years in Europe (Regulation (EC) No 1901/2006), and 6 months in US (Section 505(A) of the Food and Drug Administration Modernization Act of 1997).

to 4 years as, from FDA data, about 50% of all approvals take place within 4 years from designation;[20]

- the stock of publications, SP. This variable is meant to account for the fact that advances in scientific knowledge in one therapeutic area may increase the probability of obtaining an ODD. Indeed, the pharmaceutical research is the leading example of a science-based sector (Pavitt, 1984), because a large part of innovation builds on academic research (Mansfield, 1995). As a result, inputs from science can play a relevant role in stimulating R&D efforts at the market level.

Therapeutic class dummy variables, along with a dummy variable identifying genetic diseases, are also included.[21]

7 Results

In Column (1) of Table 4 we present the results of a simplified model in which we do not account for the heterogeneity in the effect of the regulations: we omit the interaction terms from Eq. 23. These are included in our baseline specification, whose results are reported in Column (2). In Columns (3)-(5) additional control variables are included in the analysis. For each specification we present the results of the zero inflated (Gumbel) part of the model (probability of a "certain zero"), and the "count" part (modeling the determinants of innovation output for diseases not included in the "certain zero" group).

Results in Column (1; Gumbel) show that it is more likely to have no R&D effort ($\mathcal{I}_j^I = 0$) for very rare diseases. Similarly, Column (1; count) shows that the expected number of ODD is higher for the group of least rare diseases, and that the introduction of special regulations over time is associated with an increase in the number of ODD.

Interactions between the classes of prevalence and the time periods are added both in the Gumbel and the count parts of the model presented in Column (2), in order to account for any heterogeneity in the impact of reforms across classes of prevalence. Results from Column (2; Gumbel) point out that, in the first time period, it is more likely to observe zero R&D investments

[20]This statistics is obtained by taking into account the designation-approval lag for designations that received a marketing authorization. We only considered designations obtained before the year 2005, as the designation-approval lag for more recent ODD would be censored. If also more recent designations are taken into account, we find that 60% of all approvals take place within 4 years from designation.

[21]We consider 26 therapeutic class dummy variables corresponding to the classification provided by Orphanet. These are not mutually exclusive, as a disease may belong to more than one classification. As an example, craniopharyngioma is classified as neurological, endocrine, and neoplastic disease. It is also a genetic disease.

for diseases belonging to $N3$ compared to the reference category ($N1$). In order to analyze what happens in subsequent time periods, we test the null hypothesis that $Ni + Ni \times Dt = 0$. We find that these sums are all negative and statistically significant, pointing out that in all periods but the first the probability of a "certain zero" is lower for diseases belonging to classes other than $N1$. As for the dynamics over time, the coefficients associated to the interaction terms are all negative and statistically significant: the reduction in the probability of observing a "certain zero" is greater for less rare diseases. As, in the context of nonlinear models, statistical tests about partial effects and interaction terms are not necessarily informative (Greene, 2010), Figure 1 shows the dynamics in the predicted values from Column (2) to better understand the role of the interactions. Figure 1(a) plots the predicted probability of having a "certain zero" as a function of time for the classes of prevalence $N1$ and $N4$.[22] From the second to the third period, when market exclusivity is introduced also in Europe, the larger variation in probability is detected for the largest class of prevalence: for $N4$ the variation is of -39 percentage points as compared to less than -10 for the other classes.[23]

In the count part of the model (Column 2; count), the negative sign of the interaction terms suggests that, for diseases not in the "certain zero" group, the extension of incentives favor more diseases belonging to the lowest class of prevalence ($N1$): conditional on having any R&D investment, the extension of incentives reduces the gap, in terms of ODD, between more and less rare diseases. Recall that this outcome is related to the optimal level of investment in the theoretical model (I^*) and that the results for the comparative statics of γ and z are ambiguous. The reduction in the gap highlighted by Column (2; count) is visible in Figure 1(b), plotting the dynamics in the linear combination $x_{jt}\hat{\beta}_2$ over time for $N1$ and $N4$. In Figure 1(c) we plot the exponential value of the linear combination presented in 1(b), as in Eq. 21.

Graph (d) of Figure 1 shows the combined effect of the Gumbel and the count parts, i.e. the predicted number of ODD per year per disease. Even when orphan regulation was in force only in the US (1983-1999), the predicted number of ODD was lower for diseases belonging to $N1$ compared to less rare diseases.[24] Over time, there has been an increase in the number of ODD for all classes of prevalence, but this has been greater for the less rare diseases. This means that the magnitude of the heterogeneous impact on the probability of undertaking any investment

[22]The plot including all classes of prevalence (Figure 3) is reported in Appendix A and shows that the classes of prevalence $N2$ and $N3$ behave very similarly to $N4$.

[23]Note that the lower threshold for the definition of an orphan disease in Japan (about 4 in 10 thousand) means that some of the diseases belonging to $N4$ do not benefit from incentives in this country. Hence, starting from period $D2$, the estimated coefficients of $N4$ and its interactions may represent a lower bound.

[24]A test on the predicted number of designations for diseases having a prevalence of "<1/1,000,000" ($N1$) and for those having a prevalence of "1-9 /1,000,000" ($N2$) rejects the null hypothesis of no difference (p-value=0.041).

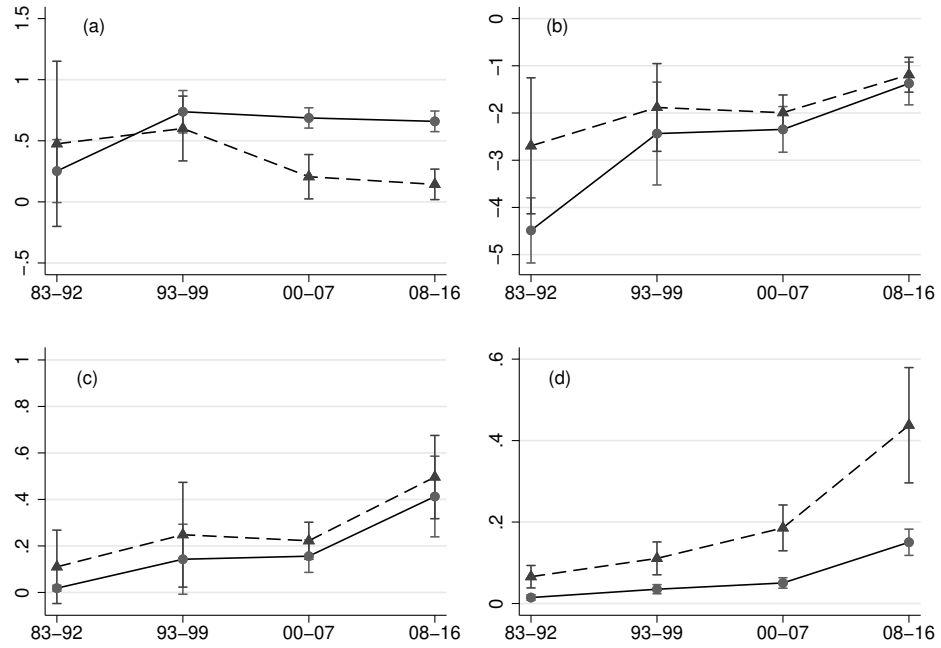

Figure 1: Predicted values for class of prevalence $N1$ (continuous line) and $N4$ (dashed line): (a) Predicted probability that $\mathcal{I}_j = 0$; (b) linear combination $x_{jt}\hat{\beta}_2$; (c) predicted number of ODD, conditional on $\mathcal{I}_j > 0$; (d) predicted number of ODD

(Gumbel part) outweighs the effects on research intensity (count part), which goes in the opposite direction. The difference between the predicted number of ODD for a disease belonging to the lowest class of prevalence and one in the highest class is 5.6 times larger in the last period than in the first one.

In Column (3) of Table 4 we take into account the characteristics of the disease in terms of life expectancy, and include 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= 0.033).

In Column (4) we include 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 at the market level. Indeed, results highlight that a larger stock of publications increases the number of ODD in the count part (it also reduces the probability of having a "certain zero", although not significantly).

Finally, in Column (5), we control for the average probability of receiving a marketing autho-

	(1)		(2)		(3)		(4)		(5)	
	Gumbel	count	Gumbel	count	Gumbel	count	Gumbel	count	Gumbel	count
$N2$	-1.264**	0.279	2.022	1.587***	1.931*	1.535***	1.801**	1.507***	-1.718*	-0.338
	(0.505)	(0.265)	(1.271)	(0.584)	(0.997)	(0.548)	(0.917)	(0.554)	(0.908)	(0.397)
$N3$	-1.330***	0.445**	1.392**	1.496***	1.374**	1.472***	1.363*	1.444***	-0.918	0.194
	(0.431)	(0.185)	(0.644)	(0.387)	(0.636)	(0.362)	(0.723)	(0.393)	(0.643)	(0.325)
$N4$	-3.025**	0.369**	1.318	1.792***	1.200	1.758***	1.317	1.749**	-1.010*	0.507
	(1.389)	(0.186)	(1.685)	(0.669)	(1.805)	(0.666)	(1.950)	(0.782)	(0.612)	(0.333)
$N0$	-0.112	0.114	2.496***	1.428***	2.450***	1.456***	2.392***	1.580***	-1.116***	-0.296
	(0.231)	(0.129)	(0.478)	(0.476)	(0.538)	(0.447)	(0.555)	(0.385)	(0.404)	(0.264)
$D2$	0.053	0.473***	3.172***	2.051***	3.134***	2.040***	3.018***	2.046***		
	(0.201)	(0.111)	(0.657)	(0.449)	(0.680)	(0.469)	(0.689)	(0.402)		
$D3$	0.101	1.038***	2.704***	2.140***	2.629***	2.105***	2.520***	2.120***	-0.453	0.111
	(0.289)	(0.149)	(0.907)	(0.322)	(0.759)	(0.344)	(0.648)	(0.356)	(0.506)	(0.310)
$D4$	0.265	1.947***	2.485***	3.112***	2.426***	3.090***	2.341***	3.119***	-0.623	1.130***
	(0.287)	(0.152)	(0.809)	(0.300)	(0.692)	(0.321)	(0.617)	(0.345)	(0.450)	(0.292)
$N2 \times D2$			-3.415***	-1.732***	-3.335***	-1.695***	-3.191***	-1.738***		
			(1.043)	(0.525)	(0.966)	(0.566)	(0.963)	(0.546)		
$N2 \times D3$			-3.139**	-1.325**	-3.010***	-1.269**	-2.846***	-1.321**	0.399	0.418
			(1.303)	(0.575)	(1.049)	(0.563)	(0.955)	(0.560)	(0.822)	(0.402)
$N2 \times D4$			-3.568***	-1.347**	-3.442***	-1.307**	-3.274***	-1.406**	0.126	0.390
			(1.329)	(0.584)	(1.088)	(0.586)	(0.993)	(0.591)	(0.733)	(0.335)
$N3 \times D2$			-2.549***	-1.286***	-2.478***	-1.253***	-2.324***	-1.251***		
			(0.733)	(0.407)	(0.724)	(0.461)	(0.751)	(0.421)		
$N3 \times D3$			-2.626***	-1.011***	-2.552***	-0.972***	-2.412***	-1.055***	-0.158	0.148
			(0.698)	(0.335)	(0.639)	(0.347)	(0.656)	(0.372)	(0.695)	(0.282)
$N3 \times D4$			-2.855***	-1.114***	-2.800***	-1.089***	-2.718***	-1.266***	-0.512	-0.069
			(0.781)	(0.354)	(0.722)	(0.361)	(0.712)	(0.396)	(0.656)	(0.266)
$N4 \times D2$			-2.416	-1.239*	-2.291	-1.193*	-2.326	-1.275*		
			(1.624)	(0.708)	(1.784)	(0.714)	(1.870)	(0.748)		
$N4 \times D3$			-4.327***	-1.438**	-4.183**	-1.372**	-4.187**	-1.535*	-1.896*	-0.294
			(1.636)	(0.688)	(1.774)	(0.686)	(1.917)	(0.793)	(1.123)	(0.332)
$N4 \times D4$			-4.561***	-1.607**	-4.475**	-1.565**	-4.495**	-1.803**	-2.281**	-0.575
			(1.612)	(0.718)	(1.747)	(0.706)	(1.881)	(0.815)	(0.989)	(0.351)
$N0 \times D2$			-3.660***	-1.870***	-3.631***	-1.869***	-3.524***	-1.918***		
			(0.631)	(0.640)	(0.732)	(0.624)	(0.691)	(0.460)		
$N0 \times D3$			-3.043***	-1.308***	-2.992***	-1.291***	-2.883***	-1.378***	0.659	0.531*
			(0.578)	(0.396)	(0.548)	(0.395)	(0.562)	(0.364)	(0.466)	(0.289)
$N0 \times D4$			-2.481***	-1.392***	-2.447***	-1.385***	-2.386***	-1.519***	1.078***	0.344
			(0.501)	(0.404)	(0.531)	(0.391)	(0.557)	(0.364)	(0.381)	(0.278)
$EarlyD$					-0.258	0.218	-0.187	0.230	-0.123	0.310**
					(0.363)	(0.153)	(0.350)	(0.147)	(0.318)	(0.143)
$\ln(SP_{j,t-5})$							-0.033	0.077***	-0.045	0.076***
							(0.028)	(0.018)	(0.038)	(0.025)
p_j^m									-0.267	0.079
									(0.489)	(0.269)
Constant	1.047	-3.590***	-1.351	-4.729***	-1.285*	-4.745***	-0.996*	-4.960***	2.098***	-3.050***
	(0.641)	(0.288)	(0.889)	(0.299)	(0.720)	(0.301)	(0.602)	(0.329)	(0.569)	(0.328)
$\ln(\alpha)$	1.014***		0.898***		0.893***		0.794***		0.711***	
	(0.176)		(0.250)		(0.202)		(0.160)		(0.264)	
N	136036		136036		136036		136036		105359	
AIC	56111.23		56006.45		55958.26		55702.65		48933.29	
BIC	56808.49		56939.41		56910.86		56674.90		49803.72	

Robust (clustered across pathologies) standard errors in parentheses.

Therapeutic class and genetic dummy variables included in all specifications.

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

Table 4: Results of model estimation

rization for drugs belonging to each therapeutic class. This, however, causes a sample reduction, since the probability of success cannot be computed for years 1983-1990. Given the large reduction in the number of observations for the first time period (comprising years 1983 to 1992), we omit this time period from the estimation. In comparing the results with those of the other columns, it is important to note that in Column (5) the reference time period is changed to 1993-1999. The coefficient for the probability of success (negative in the Gumbel part of the model and positive in the count part, as expected) is not statistically significant.

Importantly, results about the heterogeneous effect of Orphan Regulations across classes of prevalence reported in Column (3)-(5) confirm results of the baseline specification reported in Column (2).

Overall, these results show that moving from the period when only the ODA was effective in the US to periods when additional regulations were enforced, the probability of observing any R&D investment (zero inflated part of the model) has increased far more for less rare diseases. Although, conditional on investment taking place, the expected number of ODD (count part of the model) moves in the opposite direction, the net impact is still largely in favor of less rare diseases (see Figure 1(d)). This empirical evidence is consistent with the theoretical analysis of the impact of the incentives deployed, which shows a greater exposure to treatment for less rare diseases in terms of probability that at least one firm invests (Proposition 1). This suggests that the introduction of the incentives in Japan and Europe may have played a crucial role in widening the gap between more and less rare orphan diseases. In particular, the European legislation may have exacerbated this tendency, by relying mainly on *output-related* incentives, which favor less rare diseases both through an indirect and a direct mechanism (Proposition 1). This interpretation is robust to the addition of other variables that, according to the theory, may be responsible for determining the relative size of the incentives. The next section presents additional robustness checks.

7.1 Robustness checks

We organize our robustness checks along two dimensions. First, we consider different ways of measuring the dependent variable (the number of ODD at the disease level; see Table 5). Then, we modify the sample and introduce additional control variables (Table 6).

7.1.1 Counting the number of ODD

In Column (1) of Table 5 we exclude from the count of ODD those designations that are received after the drug has already received marketing approval for some other indications. In this case, the innovation can be considered less substantial.[25] When excluding these designations from the count, results are qualitatively similar to those reported in Table 4.

In Column (2) we take into account the possibility that, even with an immediate impact of the reform on the research effort, the increase in the number of ODD may be observed with delay. We therefore consider the effect of independent variables at time t on the number of ODD in $t + 5$. The five-year window has been selected as it is the average time span from the beginning of clinical trials to the ODD application.[26] When the time lag is taken into account, the estimated effect of the reforms is larger, as can be seen from the comparison of Figure 2(d) and Figure 1(d). This result is in line with the idea that, not taking into account the lag, the outcome is associated with a period when the last reform has not produced its effect yet. Therefore, the results that do not take into account the research designation lag may be a lower bound.

In Column (3) a different approach is adopted for the allocation of ODD originally assigned to multiple diseases: instead of counting one ODD for each matched disease, we use fractional counting. Estimated coefficients change and we no longer observe statistical significance for the interaction terms in the count part of the model. However, results in the Gumbel part are confirmed, with larger decrease in the probability of observing a "certain zero" for diseases in the largest class of prevalence ($N4$). In terms of the dynamics in the expected number of ODD, estimates of the interaction terms confirm the increasing effort directed towards less rare diseases (in class of prevalence $N2$, $N3$, and $N4$) as compared to more rare diseases (class $N1$).

Finally, in Column (4) only ODD assigned to private companies are included in the analysis (96% of the ODD in our sample), therefore excluding those ODD assigned to universities, hospitals or medical centers, not-profit organizations and patient associations. Our main results are again unaffected.

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

[26] The five-year window is estimated by combining our own computation on FDA data and data on drug development length provided by DiMasi et al. (2016). According to our computation, the *average* time lag between designation and marketing approval for drugs designated before 2005 is 68 months (again, we consider the 2005 limit to avoid data censoring that characterizes more recent years). DiMasi et al. (2016) reports a time period of 126 months from synthesis to approval. By taking the difference between these two numbers, we find that designations take place on average five years after synthesis of the compound. This result is in line with Hay et al. (2014), who find that ODD are most often received when a drug is in phase 2, that is roughly five years from synthesis (according to DiMasi et al., 2016).

	(1) excl.appr.		(2) $y_{j,t+5}$		(3) fractional		(4) firm only	
	Gumbel	count	Gumbel	count	Gumbel	count	Gumbel	count
$N2$	1.871*	1.544**	1.945**	1.643***	8.573***	1.643**	2.338**	1.449**
	(1.068)	(0.619)	(0.924)	(0.482)	(2.950)	(0.650)	(1.151)	(0.607)
$N3$	1.318**	1.483***	2.061	1.795***	7.705***	2.225***	1.435**	1.411***
	(0.643)	(0.369)	(1.323)	(0.500)	(2.263)	(0.527)	(0.598)	(0.310)
$N4$	1.587	1.667**	2.457**	2.280***	10.597***	2.802***	1.040	1.656***
	(1.820)	(0.752)	(1.174)	(0.577)	(3.593)	(0.523)	(1.764)	(0.530)
$N0$	2.672***	1.554***	2.397***	1.218***	4.848***	0.682	2.628***	1.346***
	(0.508)	(0.401)	(0.494)	(0.284)	(1.674)	(0.507)	(0.461)	(0.294)
$D2$	3.220***	2.148***	3.482***	2.381***	6.323***	0.330	3.686***	1.982***
	(0.687)	(0.360)	(0.582)	(0.309)	(1.992)	(0.523)	(0.593)	(0.303)
$D3$	2.702***	2.161***	3.507***	2.675***	6.014***	0.483	2.997***	2.169***
	(0.587)	(0.340)	(0.537)	(0.283)	(1.967)	(0.560)	(0.483)	(0.262)
$D4$	2.384***	3.082***	2.630***	3.137***	6.157***	1.392***	2.746***	3.133***
	(0.589)	(0.329)	(0.498)	(0.257)	(1.997)	(0.508)	(0.429)	(0.255)
$N2 \times D2$	-3.254***	-1.738***	-3.487***	-1.989***	-26.443***	-0.229	-3.825***	-1.590***
	(1.003)	(0.564)	(1.137)	(0.492)	(8.355)	(0.594)	(0.922)	(0.457)
$N2 \times D3$	-2.979***	-1.304**	-3.746***	-1.436***	-42.482**	0.060	-3.510**	-1.175*
	(1.017)	(0.610)	(0.966)	(0.497)	(17.204)	(0.706)	(1.515)	(0.643)
$N2 \times D4$	-3.427***	-1.339*	-3.258***	-1.285***	-56.202***	0.385	-3.725***	-1.148**
	(1.146)	(0.693)	(0.832)	(0.447)	(15.616)	(0.653)	(1.080)	(0.563)
$N3 \times D2$	-2.483***	-1.345***	-3.698***	-1.826***	-4.896**	0.049	-3.144***	-1.320***
	(0.786)	(0.391)	(0.881)	(0.432)	(2.204)	(0.551)	(0.864)	(0.365)
$N3 \times D3$	-2.499***	-1.023***	-3.675***	-1.480***	-5.995***	0.364	-2.876***	-0.961***
	(0.593)	(0.361)	(1.066)	(0.486)	(2.074)	(0.582)	(0.616)	(0.303)
$N3 \times D4$	-2.748***	-1.090***	-4.011***	-1.401***	-5.723***	0.564	-3.091***	-1.040***
	(0.653)	(0.374)	(1.305)	(0.531)	(2.023)	(0.542)	(0.582)	(0.321)
$N4 \times D2$	-2.539	-1.137	-4.332***	-2.148***	-3.878*	-0.016	-2.499	-1.091**
	(1.772)	(0.722)	(1.270)	(0.617)	(2.288)	(0.559)	(1.738)	(0.531)
$N4 \times D3$	-4.642**	-1.408*	-6.202***	-2.126***	-12.653***	0.460	-4.514**	-1.300**
	(1.804)	(0.771)	(1.322)	(0.646)	(4.346)	(0.603)	(1.800)	(0.514)
$N4 \times D4$	-4.950***	-1.513*	-6.265***	-2.020***	-12.963***	0.323	-4.800***	-1.448***
	(1.792)	(0.791)	(1.555)	(0.616)	(4.390)	(0.556)	(1.840)	(0.538)
$N0 \times D2$	-3.838***	-2.036***	-3.366***	-1.596***	-6.699***	-0.135	-4.105***	-1.765***
	(0.636)	(0.428)	(0.594)	(0.332)	(2.139)	(0.542)	(0.589)	(0.339)
$N0 \times D3$	-3.225***	-1.440***	-2.985***	-1.242***	-6.627***	0.265	-3.191***	-1.246***
	(0.504)	(0.380)	(0.562)	(0.311)	(2.153)	(0.580)	(0.495)	(0.297)
$N0 \times D4$	-2.588***	-1.480***	-2.067***	-1.081***	-6.906***	0.034	-2.544***	-1.317***
	(0.511)	(0.353)	(0.518)	(0.288)	(2.190)	(0.528)	(0.451)	(0.289)
Constant	-1.248**	-4.779***	-1.693***	-4.573***	-25.435***	-6.064***	-1.402**	-4.667***
	(0.611)	(0.334)	(0.524)	(0.268)	(7.812)	(0.507)	(0.600)	(0.319)
$\ln(\alpha)$	0.922***		0.849***		-0.429		1.038***	
	(0.187)		(0.160)		(0.311)		(0.128)	
N	136036		111023		136036		136036	
AIC	54366.23		50339.77		21282.44		54258.32	
BIC	55299.19		51253.43		22185.94		55191.29	

Robust (clustered across pathologies) standard errors in parentheses.

Therapeutic class and genetic dummy variables included in all specifications.

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

Table 5: Results – Robustness checks on the way the number of ODD is measured

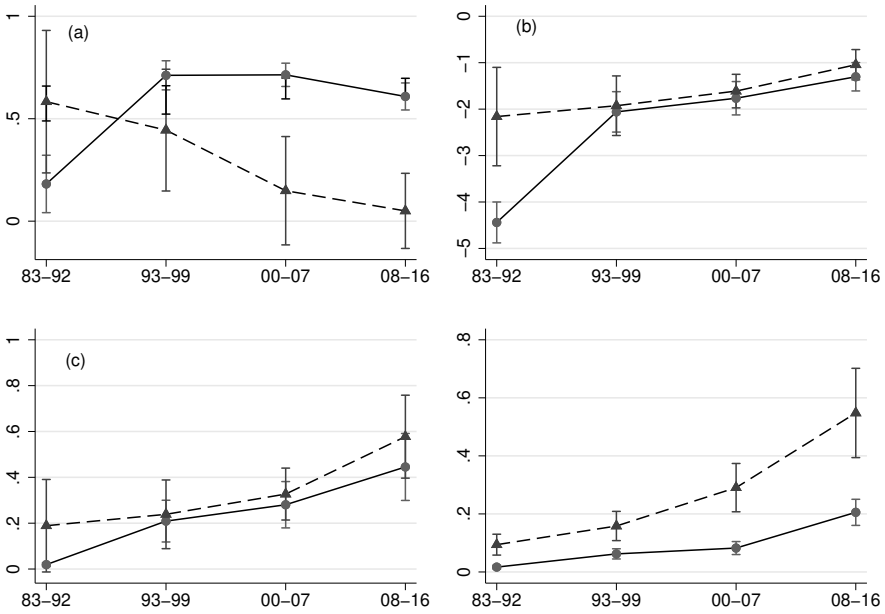

Figure 2: Predicted number of ODD when considering a five years lag in the regressors (see Column (2), Table 5).

7.1.2 Sample issues and control variables

In the count part of the model presented in Column (1) of Table 6, we add as additional controls the interactions between therapeutic class dummies (TC_j) and period dummies.[27] These interaction terms aim at capturing the effect of technological reforms at the therapeutic class level. In the case that technological breakthroughs, fostering the level of innovative effort in a specific therapeutic class, take place in the same years as the orphan regulations, the omission of therapeutic classes specific trends might bias our results in the presence of correlation with the level of prevalence. However, results confirm the negative and statistically significant effect of the interaction terms between class of prevalence and period dummies.

In Column (2) we include a proxy for the net revenue at the industry level.[28] In particular, we consider the ratio between the producer price index of pharmaceutical and medicine manufacturing, and the price index for private fixed investment in intellectual property products for firms

[27]The interaction terms are included only in the count part of the model due to a lower BIC with respect to models where the interaction terms are included also (or only) in the Gumbel part of the model.

[28]On the basis of our theoretical model, disease-specific 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 indexes or dynamics in R&D costs, at the disease-level.

	(1)		(2)		(3)		(4)	
	$TC_j \times Dp_j$		mg_t		all obs.		$SP_{83-5} > 0$	
	Gumbel	count	Gumbel	count	Gumbel	count	Gumbel	count
$N2$	0.834	1.521**	1.693*	1.484***	2.848***	1.439***	2.909***	2.300***
	(0.656)	(0.613)	(1.009)	(0.559)	(0.653)	(0.458)	(0.567)	(0.454)
$N3$	0.210	1.439***	1.127*	1.409***	1.690***	1.171***	0.775	1.588***
	(0.567)	(0.461)	(0.609)	(0.353)	(0.503)	(0.225)	(0.579)	(0.396)
$N4$	0.559	1.668***	1.024	1.715***	0.836	1.324***	1.418	1.904***
	(0.789)	(0.616)	(1.440)	(0.567)	(1.569)	(0.445)	(1.132)	(0.544)
$N0$	0.471	0.668	0.260	1.322***	2.695***	1.118***	3.715***	2.315***
	(0.489)	(0.426)	(0.635)	(0.393)	(0.381)	(0.245)	(1.205)	(0.780)
$D2$	0.722	0.487	3.318***	1.611***	3.824***	1.904***	2.624***	1.888***
	(0.559)	(0.434)	(0.627)	(0.424)	(0.366)	(0.244)	(0.837)	(0.643)
$D3$	0.518	0.675	3.135***	1.413***	3.658***	2.176***	3.417***	2.724***
	(0.621)	(0.468)	(0.742)	(0.339)	(0.329)	(0.233)	(0.806)	(0.475)
$D4$	0.366	1.475***	3.735***	1.706***	3.054***	2.952***	3.026***	3.481***
	(0.552)	(0.449)	(0.680)	(0.338)	(0.353)	(0.231)	(0.867)	(0.477)
$N2 \times D2$	-2.056**	-1.516***	-3.127***	-1.652***	-3.819***	-1.502***	-3.327***	-1.713*
	(0.864)	(0.564)	(0.959)	(0.521)	(0.738)	(0.450)	(1.228)	(0.942)
$N2 \times D3$	-1.928**	-1.206*	-2.780***	-1.219**	-4.309***	-1.408***	-3.656***	-1.925***
	(0.793)	(0.628)	(1.064)	(0.559)	(0.913)	(0.520)	(0.910)	(0.583)
$N2 \times D4$	-2.439***	-1.284**	-3.339***	-1.244**	-4.021***	-1.040*	-4.183***	-1.919***
	(0.724)	(0.620)	(1.067)	(0.569)	(0.857)	(0.543)	(0.771)	(0.621)
$N3 \times D2$	-1.238	-1.060**	-2.234***	-1.189***	-2.992***	-0.965***	-2.375***	-1.342**
	(0.764)	(0.446)	(0.666)	(0.393)	(0.494)	(0.253)	(0.895)	(0.636)
$N3 \times D3$	-1.378**	-1.062**	-2.328***	-0.915***	-3.246***	-0.864***	-3.004***	-1.521***
	(0.700)	(0.474)	(0.611)	(0.332)	(0.468)	(0.251)	(0.839)	(0.517)
$N3 \times D4$	-1.675**	-1.059**	-2.636***	-1.028***	-3.148***	-0.810***	-2.798***	-1.343**
	(0.812)	(0.494)	(0.674)	(0.344)	(0.483)	(0.283)	(0.751)	(0.551)
$N4 \times D2$	-1.112	-0.707	-2.099	-1.160*	-2.467*	-0.969**	-1.846	-1.057
	(0.842)	(0.572)	(1.446)	(0.602)	(1.468)	(0.457)	(1.134)	(0.695)
$N4 \times D3$	-3.642***	-1.359**	-3.968***	-1.354**	-3.590***	-1.208***	-3.617***	-1.633***
	(0.925)	(0.620)	(1.440)	(0.578)	(1.343)	(0.427)	(1.021)	(0.589)
$N4 \times D4$	-3.846***	-1.435**	-4.335***	-1.507**	-2.470*	-0.949**	-3.221***	-1.586***
	(0.831)	(0.620)	(1.379)	(0.599)	(1.482)	(0.476)	(1.030)	(0.576)
$N0 \times D2$	-1.411***	-0.947**	-3.730***	-1.782***	-3.877***	-1.509***	-3.381***	-1.986***
	(0.547)	(0.419)	(0.611)	(0.518)	(0.427)	(0.293)	(0.847)	(0.653)
$N0 \times D3$	-1.006*	-0.647	-3.372***	-1.197***	-3.561***	-1.171***	-4.012***	-2.024***
	(0.587)	(0.431)	(0.565)	(0.345)	(0.397)	(0.284)	(0.853)	(0.519)
$N0 \times D4$	-0.482	-0.608	-3.598***	-1.262***	-2.726***	-1.053***	-3.391***	-1.895***
	(0.517)	(0.417)	(0.550)	(0.345)	(0.428)	(0.278)	(0.959)	(0.531)
mg_t			-1.759***	1.511***				
			(0.325)	(0.180)				
$mg_t \times N0$			1.655***					
			(0.333)					
Constant	0.748	-3.355***	0.949	-6.367***	-1.035**	-4.025***	-0.616	-4.299***
	(0.611)	(0.477)	(0.890)	(0.404)	(0.416)	(0.207)	(0.669)	(0.375)
$\ln(\alpha)$	0.780***		0.825***		0.788***		0.581**	
	(0.171)		(0.209)		(0.163)		(0.231)	
N	136036		133348		212092		91392	
AIC	55485.69		55477.80		71869.02		37279.63	
BIC	57214.13		56438.27		72844.17		38174.81	

Robust (clustered across pathologies) standard errors in parentheses.

Therapeutic class and genetic dummy variables included in all specifications.

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

Table 6: Results – Robustness checks: sample issues and additional control variables

operating in pharmaceutical and medicine manufacturing (as a proxy for R&D expenditures).[29] The ratio between the two indexes has grown substantially over the observation period. We also include an interaction term between $N0$ (missing prevalence) and the ratio in the Gumbel part of the model.[30] In the count part of the model, the coefficients of $D2$, $D3$ and $D4$ are smaller compared to our baseline specification, as part of the effect is captured by the increasing trend in the ratio over time. However, the main result of our analysis is unaffected.

In Column (3) we consider the full set of diseases, removing the selection of the basis of the stock of publications. In this case, also $N2$ and $N4$ become significant in the first period, unlike in the models that disregard diseases that cannot be related to any publications, especially in the Gumbel part of the model. This may be due to the fact that most of the diseases that are added after the first year belong to $N1$.

Finally, in Column (4), we consider the balanced panel of diseases that were known at the beginning of our observation period (i.e., with a positive value of SP_{t-5} in year 1983). By using a balanced set of observations, we aim at investigating whether our results are driven by the composition of the sample.

All in all, the robustness checks performed in this section confirm the main results from Table 4.

8 Concluding remarks

Since the early 80s, regulators have started to address the lack of incentives to invest in innovation for rare diseases by means of specific provisions. As the pharmaceutical market is a global one, these incentives for the development of orphan drugs have cumulated over time as new countries have introduced them. There is ample evidence that this has increased investments in projects targeting rare diseases, meaning a potential reduction in inequality between orphan and common diseases. In this paper, we study the distribution of R&D efforts within the class of orphan diseases, with a focus on heterogeneity with respect to prevalence.

We developed a theoretical model to show that the type of incentive that is used may be

[29] Both indexes have been downloaded from the Federal Reserve Economic Data. See: https://fred.stlouisfed.org. Data are no available for the producer price index in 1983, so that one observation for each disease is lost.

[30] In unreported analyses we have considered the interaction between all classes of prevalence and the industry-wide margin both in the Gumbel and count part of the model. This is motivated by the fact that, theoretically, an increase in M_j works as an increase in z, meaning that the size of the impact depends on n_j. Only the interaction term between $N0$ and the ratio in the Gumbel part of the model is statistically different from zero, so only this interaction is retained in the estimated model in Column (2). This model has also to be preferred with respect to the model where all interactions are included according to the Bayesian Information Criterion (BIC).

crucial to define the relative convenience to invest across different classes of prevalence. In particular, we consider both *output-related* incentives, such as market exclusivity, and *input-related* incentives, such as tax credits. The model shows that both types of incentive increase more the *probability of observing investment* for a less rare disease. This is due to both a direct and an indirect impact for *output-related* incentives, whereas for *input-related* incentives the impact is only indirect. It is not possible to conclude unambiguously whether the impact of the incentives on the *optimal level of R&D investment* increases or decreases with the prevalence of the disease.

We use the number of orphan designations, a condition to become eligible for incentives, as a proxy of R&D effort, to investigate the impact of the introduction of incentives in different geographic areas over time. We find that the number of designations has increased over time for all orphan diseases, but inequality within orphan diseases has also increased: the difference between the predicted number of orphan designations for a disease belonging to the highest and the lowest class of prevalence is 5.6 times larger in the last than in the first period of the analysis. The gap between less and more rare diseases seems to have widened after 2000, when the orphan legislation was introduced in the EU. We argue that the large weight of *output-related* incentives embodied in this legislation, when compared for example with the US legislation, combined with the large size of the EU market, may have contributed substantially to this result. If the reduction of inequality in the distribution of R&D efforts is an objective of European policy makers, then the weight of *input-related* incentives should be increased. However, the adoption of some of these incentives, such as tax credits, may be more challenging than in other regulatory frameworks, due to the fact that single EU member countries are still responsible for the definition of fiscal policies. In this context, an extension of the incentive tool set to include provisions that can be tailored to the prevalence of a disease, should also be considered.

References

Acemoglu, D. and Linn, J. (2004). Market size in innovation: theory and evidence from the pharmaceutical industry. *The Quarterly journal of economics*, 119(3):1049–1090.

Ahsanullah, M. (2016). *Extreme Value Distributions*. Tsokos, C.P (ed.), Atlantis Studies in Probability and Statistics, Vol. 8.

Barrenho, E., Miraldo, M., and Smith, P. C. (2019). Does global drug innovation correspond to

burden of disease? the neglected diseases in developed and developing countries. *Health economics*, 28(1):123–143.

Braun, M. M., Farag-El-Massah, S., Xu, K., and Coté, T. R. (2010). Emergence of orphan drugs in the United States: a quantitative assessment of the first 25 years. *Nature Reviews Drug Discovery*, 9(7):519.

DiMasi, J. A., Grabowski, H. G., and Hansen, R. W. (2016). Innovation in the pharmaceutical industry: new estimates of R&D costs. *Journal of health economics*, 47:20–33.

Dubois, P., De Mouzon, O., Scott-Morton, F., and Seabright, P. (2015). Market size and pharmaceutical innovation. *The RAND Journal of Economics*, 46(4):844–871.

Greene, W. (2010). Testing hypotheses about interaction terms in nonlinear models. *Economics Letters*, 107(2):291–296.

Hay, M., Thomas, D. W., Craighead, J. L., Economides, C., and Rosenthal, J. (2014). Clinical development success rates for investigational drugs. *Nature biotechnology*, 32(1):40.

Health and Safety, F. (2015). *Inventory of Union and Member State incentives to support research into, and the development and availability of, orphan medicinal products*. European Commission.

Heemstra, H. E., van Weely, S., Büller, H. A., Leufkens, H. G., and de Vrueh, R. L. (2009). Translation of rare disease research into orphan drug development: disease matters. *Drug discovery today*, 14(23-24):1166–1173.

Herder, M. (2017). What is the purpose of the orphan drug act? *PLoS medicine*, 14(1):e1002191.

INSERM (1999). *Orphadata: Free access data from Orphanet*. available on http://www.orphadata.org (data version: 1.2.4/4.1.6).

Jobjörnsson, S., Forster, M., Pertile, P., and Burman, C.-F. (2016). Late-stage pharmaceutical r&d and pricing policies under two-stage regulation. *Journal of health economics*, 50:298–311.

Keller, W. (2002). Geographic localization of international technology diffusion. *American Economic Review*, 92(1):120–142.

Lambert, D. (1992). Zero-inflated Poisson regression, with an application to defects in manufacturing. *Technometrics*, 34(1):1–14.

Lichtenberg, F. R. (2013). The impact of new (orphan) drug approvals on premature mortality from rare diseases in the united states and france, 1999–2007. *The European Journal of Health Economics*, 14(1):41–56.

Lichtenberg, F. R. and Waldfogel, J. (2009). Does misery love company? evidence from pharmaceutical markets before and after the orphan drug act. *Michigan Telecommunications and Technology Law Review*, 15:335.

Mansfield, E. (1995). Academic research underlying industrial innovations: sources, characteristics, and financing. *The review of Economics and Statistics*, pages 55–65.

Mariz, S., Reese, J. H., Westermark, K., Greene, L., Goto, T., Hoshino, T., Llinares-Garcia, J., and Sepodes, B. (2016). Worldwide collaboration for orphan drug designation. *Nature reviews Drug discovery*, 15(6):440.

Melnikova, I. (2012). Rare diseases and orphan drugs. *Nature Reviews Drug Discovery*, 11:267–268.

Pammolli, F., Riccaboni, M., and Magazzini, L. (2009). Nuove politiche per l'innovazione nel settore delle scienze della vita. *Rapporto CERM*, pages 02–2009.

Pavitt, K. (1984). Sectoral patterns of technical change: towards a taxonomy and a theory. *Research policy*, 13(6):343–373.

Raïs Ali, S. and Tubeuf, S. (2019). (in)-equality in the allocation of r&d resources for rare diseases. *Social Justice Research*.

Roemer, J. (1998). *Equality of Opportunity*. Harvard University Press.

Seoane-Vazquez, E., Rodriguez-Monguio, R., Szeinbach, S. L., and Visaria, J. (2008). Incentives for orphan drug research and development in the united states. *Orphanet journal of rare diseases*, 3(1):33.

Sharma, A., Jacob, A., Tandon, M., and Kumar, D. (2010). Orphan drug: development trends and strategies. *Journal of Pharmacy and Bioallied Sciences*, 2(4):290.

Staub, K. E. and Winkelmann, R. (2013). Consistent estimation of zero-inflated count models. *Health economics*, 22(6):673–686.

Tambuyzer, E. (2010). Rare diseases, orphan drugs and their regulation: questions and misconceptions. *Nature Reviews Drug Discovery*, 9(12):921.

Wästfelt, M., Fadeel, B., and Henter, J.-I. (2006). A journey of hope: lessons learned from studies on rare diseases and orphan drugs. *Journal of internal medicine*, 260(1):1–10.

Westermark, K. et al. (2011). European regulation on orphan medicinal products: 10 years of experience and future perspectives. *Nature Reviews Drug Discovery*, 10(5):341.

Winkelmann, R. (2008). *Econometric analysis of count data*. Springer Science & Business Media.

Yin, W. (2008). Market incentives and pharmaceutical innovation. *Journal of Health Economics*, 27(4):1060–1077.

Yin, W. (2009). R&d policy, agency costs and innovation in personalized medicine. *Journal of health economics*, 28(5):950–962.

A Appendix

In Figure 3 we report the equivalent of Figure 1 with a line for each class of prevalence. The figure is obtained using the estimated coefficients of our baseline model, reported in Column (2) of Table 4.

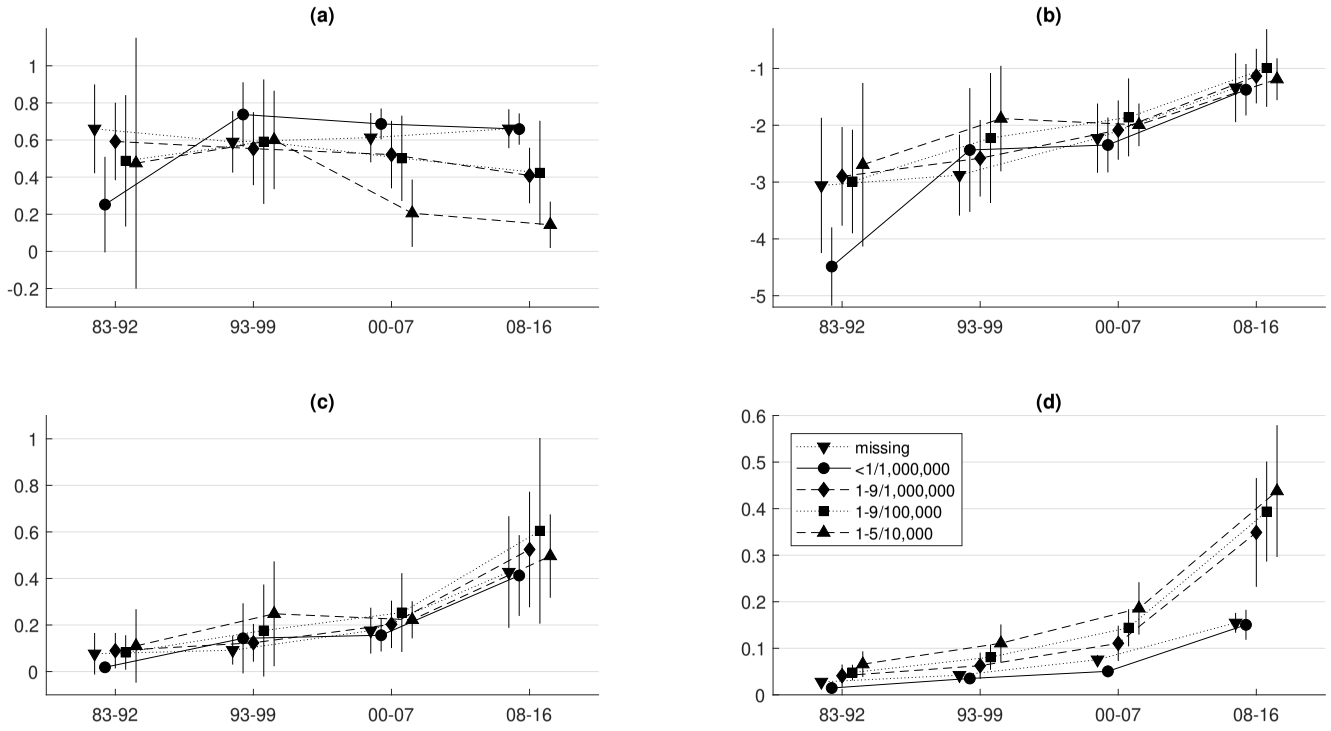

Figure 3: Predicted values for all classes of prevalence: (a) Predicted probability that $\mathcal{I}_j = 0$; (b) linear combination $x_{jt}\hat{\beta}_2$; (c) predicted number of ODD, conditional on $\mathcal{I}_j > 0$; (d) predicted number of ODD