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Promoting innovation in small markets: Evidence from the market for rare and intractable diseases☆

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ABSTRACT

In many medical care markets with limited profit potential, firms often have little incentive to innovate. These include the market for rare diseases, "neglected" tropical diseases, and personalized medicine. Governments and not-for-profit organizations promote innovation in such markets but empirical evidence on the policy effect is limited. We study this issue by analyzing the impact of a demand-side policy in Japan, which reduces the cost sharing of patients with some rare and intractable diseases and attempts to establish and promote the treatment of those diseases. Using clinical trials data taken from public registries, we identify the effect of the policy using a difference-in-difference approach. We find that the demand-side policy increased firms' incentive to innovate: firm-sponsored clinical trials increased 181% (0.16 per disease per year) when covered by the policy. This result indicates that the demand-side policy can be an important part of innovation policies in markets with limited profit potential.

1. Introduction

Innovation is less likely to occur when the corresponding economic return is expected to be small. This is an important policy issue in many medical care areas where, because of the limited market potential, firms have little incentive to develop treatment procedures. These include the market for rare diseases that have a small number of patients, "neglected" tropical diseases such as dengue fever and rabies that prevail in developing countries, and personalized medicine that tailors treatment to a specific patient group. To encourage innovation in these small markets, various demand-side and supply-side policies that increase revenue and reduce the cost of innovation, respectively, have been proposed and implemented by governments and not-for-profit organizations. A well-known example is the United States Orphan Drug Act (ODA) of 1983 that attempted to promote R&D for rare diseases. More recently, to promote drug development for "neglected" tropical diseases, the "priority review voucher" was introduced in the United States in 2007, which grants the developer of a treatment for these diseases an expedited review process that can be transferred to a third party.[1]

Regardless of the importance of the issue, empirical evidence on the effects of policies that aim to promote innovation in small markets is limited. This paper aims to fill this gap by analyzing the impact of a demand-side policy that reduces cost sharing of patients with rare and intractable diseases in Japan. By reducing

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[1] Please see Ridley et al. (2006) for more about the "priority review voucher."

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patient cost sharing, the government aims to establish and promote the treatment of rare and intractable diseases that are extremely difficult to treat and reduce the high medical expenses that patients incur.[2] Thus, one of the main objectives of the policy is to promote innovation using the demand-side instrument. Reducing the cost of medical treatments may encourage patients to seek more medical treatments, and the resulting increase in revenue may encourage firms to engage in more R&D activities on those diseases. If, on the other hand, receiving treatment of intractable diseases is not discretionary to the patient, then reducing cost sharing will affect neither the size of the market nor firm behavior.

We attempt to identify the effect of the government policy on R&D activities using a difference-in-difference (DID) approach. In 2009, as part of an economic stimulus package after the financial crisis in 2008, the Japanese government added 17 intractable diseases to the list of diseases eligible for reduced cost sharing.[3] Our basic idea of identification is to compare the number of new clinical trials over time for the diseases added to the list in 2009 with those of other similar intractable diseases that were not eligible for reduced cost sharing throughout the data period. To determine the control group, we exploit an institutional detail. Traditionally, the number of diseases eligible for reduced cost sharing has been small and, moreover, the choice of diseases has been criticized as being arbitrary and unfair. In 2015, the government redefined the eligibility for reduced cost sharing and expanded the coverage to more than 300 diseases. This implies that there were many other diseases that deserved the same benefit in 2009 but did not obtain it until 2015. We use the latter diseases as controls.

Although the market for disease treatment is global, part of drug development costs is country-specific and thus the decision to conduct clinical trials is likely to be affected by local innovation policies. In the current context, in order to sell pharmaceutical products in Japan, the Ministry of Health, Labour and Welfare (MHLW) requires companies to conduct phase I and II trials among the Japanese population,[4] because how a drug affects the human body (pharmacodynamics) and how the body affects the drug (pharmacokinetics) can differ depending on ethnic factors.[5] Because of this requirement, any domestic policy change that would improve local profitability of a product will encourage a global company to conduct additional clinical trials in Japan. Such a "home country bias" may be weaker for phase III trials, however, because unlike phase I and II trials, phase III trials specific to local population may not be needed if one can show that there is no significant difference in phase I and II trial results according to ethnic factors.[6] Our analysis examines such a possibility as well.

Our main data are from Japan's primary registries, which are public databases containing information on clinical trials. We carefully searched the registries using a number of keywords and identified clinical trials related to the intractable diseases we study. This original data set covers the period between October 2005 and September 2014 and contains the names of the drugs or devices in trial, trial start date, trial phase, and whether the trial was conducted by a sponsor firm or physician-led. We also collected additional data on the number of patients with the diseases.

Our findings can be summarized as follows. First, we find that reduced cost sharing for rare and intractable diseases increased the number of firm-sponsored clinical trials as much as 181% (0.16 per disease per year) when covered by the policy. This implies that even for intractable diseases for which patients seem to have little discretion to receive treatments, reduced cost sharing appears to increase the market size, which in turn encourages firms to increase R&D activities on those diseases. Second, we find that the estimated impact was large relative to the average number of clinical trials per disease before the policy was implemented. Thus, the demand-side policy can be an important part of innovation policies that aim to stimulate R&D on drug and medical devices with limited market potential. Third, the observed results were found in phase II, and not in phase I. One interpretation of this result is that the primary effect of the policy is to encourage firms to conduct additional trials for existing drugs and devices but not necessarily to initiate an entire new line of product development.

To our knowledge, few studies have examined the effects of innovation policy on markets with small profit potential. One notable exception is Yin (2008) who studied the impacts of the ODA in the United States. The ODA intended to increase pharmaceutical innovations for rare diseases that affected less than 200,000 patients by extending market exclusivity periods and by reducing R&D costs through tax credits. Yin found that by comparing with the diseases that affected just above 200,000 patients, the ODA increased the number of clinical trials for rare diseases that affected less than that number. Our study differs from his in two ways. First, the type of demand-side policy we examine (reduced cost sharing) differs from that used in the ODA. Moreover, while we focus on the impact of the demand-side policy, Yin's estimate captures the combined effect of the two policies that constitute the ODA. Thus, Yin's evidence may not be informative for policymakers who wish to understand the impact of either of the policies. Second, the Japanese policy targets rare and intractable diseases, while the ODA is only concerned with rarity. The results could be different if, for example, patients with intractable diseases have more inelastic demand for medical treatments. To our knowledge, no previous study has examined whether R&D activities for intractable diseases respond to government policies.

The studies by Finkelstein (2004) and Blume-Kohout and Sood (2013) are also closely related to ours. Finkelstein (2004) found that health policies that promote the utilization of existing vaccines, such as the 1991 CDC recommendation that all infants be vaccinated against Hepatitis B, also affects incentives to develop new vaccines. Blume-Kohout and Sood (2013) found that the introduction of Medicare Part D in the United States is associated with increases in pharmaceutical R&D for drug classes with higher Medicare market share. A notable difference between ours and their studies is that, while we focus on examining the effectiveness of a demand-side innovation policy, the above studies highlight that health policies that affect demand may also unintendedly affect R&D.[7]

[2] For the objectives of the policy, see http://www.nanbyou.or.jp/pdf/kousei21_1.pdf (In Japanese. Accessed March 17, 2016.)

[3] According to the government announcement, 11 diseases were added to this list. However, the government also subdivided one disease category, diencephalo-hypophysial dysfunction, into seven specific diseases and specified their names in the list. This makes the number of added diseases 17. We use the finer disease categories in this paper.

[4] Uesaka (2011). Worldwide simultaneous clinical drug development and multiregional clinical trials. Journal of the National Institute of Public Health, 60 (1), 18–26 (in Japanese)

[5] http://www.mhlw.go.jp/shingi/2007/03/dl/s0329-13i.pdf (pages.3–4) (in Japanese. Accessed December 16, 2016)

[6] In 1998, the MHLW issued a notice that if pharmaceutical companies could show that the dose-response relationship is not different between the Japanese and overseas populations, then they could extrapolate the results of phase III clinical trials in other countries instead of conducting a phase III clinical trial among the Japanese population. Even in this process, companies are required to do phase I and phase II clinical trials among the Japanese population. This is called a "bridging study." Please see the following for details: http://www.nihs.go.jp/mss/ICH-E5.pdf (page.8) (in Japanese. Accessed December 16, 2016)

[7] Kyle and McGahan (2012) also examined whether the passage of the TRIPS Agreement, which increased the levels of patent protection, increased R&D activities, finding that such effects were present in developed countries but not in developing countries.