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RESEARCH AND MARKET STRUCTURE: EVIDENCE FROM AN ANTIBIOTIC-RESISTANT PATHOGENIC OUTBREAK

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ABSTRACT

Do upstream research shocks impact unconnected downstream product markets? We explore this question using a natural experiment involving a publication that identified a pathogenic outbreak in India involving a carbapenem antibiotic resistant superbug. Consistent with theory, we find that this upstream research shock caused multinational firms selling carbapenem antibiotics in India to reduce their downstream market exposure. Rational antibiotic stewardship implies that we should observe a similar response by domestic Indian firms. Surprisingly, we observe the opposite; domestic Indian firms filled the void in the market left by multinational firms. We confirm this aggregate finding with prescription level data, Indian physicians prescribed fewer focal multinational products relative to domestic firm products. Results are robust to alternate control groups and placebo testing. Implications for antibiotic resistance, global health policy and innovation policy are discussed.

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1.0 Introduction

Research and development (R&D) is often viewed as a linear process. In the pharmaceutical industry, for example, university technologies are often commercialized by small, research-intensive firms and ultimately licensed or acquired by larger firms for development prior to being taken to market. This technology push view of innovation (*e.g.*, Mowery and Rosenberg, 1979) is long and expensive with high rates of failure (*e.g.*, DiMasi *et al,* 2016). Shocks to upstream research in this kind of system ripple, for example, through development before impacting downstream product markets.[1] But what if shocks occur elsewhere in the innovation ecosystem? Would this imply that shocks to one aspect of R&D could directly impact some other distantly connected part of the innovation ecosystem?

It is not surprising that shocks to research will impact future development activities or that development shocks will impact product markets (*e.g.*, Byrsiki *et al.,* 2021). Nor is it surprising that product market shocks impact development activities (*e.g.*, Agarwal and Gaule, 2021; Manso *et al*., 2019; Branstetter *et al*., 2014; Blume-Kohout and Sood, 2013; Dranove *et al.,* 2021; Dubois *et al*., 2013; Acemoglu and Linn, 2004; Finkelstein, 2004). In these literatures, however, events are occurring *between* connected parts of the R&D process.[2] Complementing this are studies that focus on events *within* one part of the R&D process. For example, a series of papers explore the impact of development shocks on future development activities (*e.g.*, Krieger *et al.*, 2018; Hermosilla and Wu, 2018; Higgins and Rodriguez, 2006). Missing from the literature, however, is a clear understanding whether a causal relationship exists between *unconnected* parts of the R&D process. That is, do upstream research shocks directly impact related but disconnected downstream product markets?

[1] We follow the standard use of "upstream" and "downstream" in the innovation literature. With specific reference to R&D, upstream commonly refers to research-related ("R") activities while downstream commonly refers to development-related ("D") activities and product markets.

[2] For our purposes we will assume that the R&D process is linear; research-related activities result in new development-related activities which translate into new products. When we refer to "connected" parts of this process we are referring to those activities located next to each other. Specifically, research and development are connected as are development and product markets. In contrast, research and product markets are considered "unconnected". When we refer to events "within" one part of the R&D process we mean those activities entirely contained within research, development, or product markets, respectively.

Using a natural experiment involving the publication of the discovery of the broad-spectrum antibiotic resistant *New Delhi Metallo-Beta-Lactamase* (NDM-1) superbug in India, we fill this gap in the literature. Prior to the publication in *Lancet Infectious Diseases* (Kumarasamy *et al.*, 2010) little attention was paid to this particular superbug (Figure 1). Using this event as an exogenous shock to research, coupled with unique and disaggregate data from the pharmaceutical industry, we are able to examine the impacts of this event on unconnected but related downstream antibiotic product markets. Importantly, we exploit variation across product markets (*i.e.*, broad spectrum and narrow spectrum antibiotics), firm types (*i.e.,* domestic, and multinational firms) and countries (*e.g.*, India and U.S.).

We adopt a duopoly model with differentiated goods and linear demand and apply a solution concept from Cournot competition in terms of quantity choice (Dixit, 1979) to explain *ex post* strategic behavior of multinational and domestic firms in reaction to the NDM-1 research shock. In doing so we make important contributions to the literature. First, we find that the effects of the NDM-1 research shock were dramatic in the downstream Indian antibiotic product market. More specifically, multinational firms withdrew drugs from the affected antibiotic market. Within the context of our model, this pivot away from the Indian market can be explained by increases in marginal costs driven by changes to reputational costs faced by multinational firms.

This reaction by multinational firms also aligns with the extant literature focused on the trade-offs firms face in deciding between ethics and profits, especially in the presence of negative market shocks and given risks to reputation (*e.g.*, Adbi *et al.,* 2018; Cheah *et al.,* 2007; Rhee and Haunschild, 2006). Past work also demonstrates how future reputation can ultimately become a source of market power allowing firms to charge premium pricing (Allen, 1984; Shapiro, 1983; Klein and Leffler, 1981). Building reputation, however, is costly and can have a bearing on firm entry and exit decisions (Bachmann *et al*., 2021; Strittmatter and Lechner, 2020). This, in turn, will affect market structure and industry evolution when there are negative shocks to reputation. Emerging empirical evidence from the Volkswagen emission scandal aligns with this postulate (Bachmann *et al*., 2021; Strittmatter and Lechner 2020).

These reputational costs may be more significant for larger, multinational firms facing a 'liability of foreignness' amidst calls for corporate social responsibility in host countries (*e.g.*,

Crilly *et al.,* 2016; Campbell *et al*., 2012; Zaheer and Mosakowski, 1997). This is especially pertinent in sectors that have public health implications. For example, reputational costs may be higher if multinationals sell 'dodgy' medicines in host markets. A negative shock may credibly reveal adverse information about a product, impacting the firm's ability to exercise market power not just locally but also globally. Thus if multinationals don't have the same local institutional backing as domestic firms, they will need a higher rate of responsiveness so as to avoid possible sanction by regulators (Kostova *et al.*, 2008).

This is precisely what we observe in our empirical setting. Not only do we see a multinational withdrawal from the market, but correspondingly we also document that prescriptions for multinational firm drugs in the affected markets also decline relative to domestic firm antibiotic prescriptions. This suggests that the change in physician behavior that we observe occurred through the intensive margin. We know from prior literature that pharmaceutical advertising and detailing impacts physician behavior (*e.g.*, Datta and Dave, 2017; Manchanda and Honka, 2005); this is no different in the Indian pharmaceutical market. Specifically, we track bonus doses or quantities that firms provide as a direct incentive to sellers (Bhaskarabhatla *et al*., 2016). In the post-treatment period, we find a significant reduction in bonus quantities by multinational firms compared to domestic firms.

Within affected markets, variation also exists in terms of drug age or vintage. Pharmaceutical innovation within antibiotics has been relatively sparse (*e.g.*, Spellberg and Gilbert, 2014). Thus, in the face of newly discovered resistance, firms should respond more rapidly to protect newer classes of drugs. Dividing drugs in affected markets by vintage (*e.g.*, Chahine *et al*., 2010; Papp-Wallace *et al.*, 2011), we find that multinational firms do react more sharply in pulling newer drugs from the Indian market. More broadly, this finding provides evidence of the *nature* of how an upstream research shock impacts downstream product markets. In our context, this suggests that newer innovations are impacted more severely than older innovations. This has significant implications for firms as newer innovations (*i.e.*, drugs) tend to be higher priced as they are still covered by some type of regulatory or patent protection versus older drugs that most likely already face generic competition. To the extent that current revenues are used to fund future R&D (*e.g.*, Branstetter *et al.,* 2016), our results suggest there could be implications for future innovation.

Next, we find that the void in the market left by multinational firms is filled by domestic firms who increase production. Within the context of our model, any reduction in one firm's output (*i.e.*, multinational firm), due to their strategic interaction, creates an opportunity for the other firm (*i.e*., domestic firm) to step in and increase their own output. Importantly, domestic firms are manufacturers and are not involved in novel R&D, so their business is driven primarily by quantity considerations. Domestic firms, therefore, do not face the same global reputational concerns as multinational firms. The important distinction here is that multinational firms are producing branded, novel drugs while domestic firms are producing generic versions of previously branded drugs. In most countries, branded drugs are held responsible for harm to patients, as long as generics versions were truly bioequivalent.[3]

This finding, worryingly, implies that downstream demand for drugs in affected markets does not wane. Antibiotic overuse is a global public health crisis (*e.g.*, Ackerman and Gonzales, 2012) and is even more acute in India (*e.g.*, Thakolkaran *et al.,* 2017) and thus market behavior in India may cause a significant negative externality in global antibiotic resistance (Coburn *et al*. 2021).[4] Our results suggest, however, that some combination of downstream actors, including physicians, pharmacists and/or patients are either choosing to act in a medically irrational manner or are oblivious to the shock.[5] Sadly, survey evidence appears to support both explanations. In one survey, 89 percent of physicians believed that providers were overprescribing antibiotics (Thakolkaran *et al.,* 2017). In the same survey, however, 80 percent of physicians stated that they did not receive periodic information on trends in bacterial resistance. Of those that did receive information, 8 percent reported receiving information from clinical laboratories, 2 percent from medical journals and 1 percent from the pharmaceutical industry. Combined with our core findings, this would imply that as multinational firms pulled

[3] For example, in 2011 the U.S. Supreme Court ruled in favor of protecting generic firms from being sued for failing to provide adequate label warning about side effects because federal law requires them to use the branded versions' labels.

[4] The WHO just recently (re-)sounded the alarm on drug-resistant bacteria in April 2021: https://www.ft.com/content/f04275a3-5095-4f9e-a711-6fe7d59216dc.

[5] To contrast with our focal analysis on the Indian market, we have estimated the market impact using data from the U.S.; the effects are not significant. This is in line with the explanation that such aggressive reorientation in market structure combined with overprescription of antibiotics is predicated on a weaker regulatory body. Results are described more fully in the main text.

out of the Indian market, they failed to sufficiently inform physicians as to *why* they were leaving.

The heterogeneous firm reaction between multinationals and domestic firms also relates to the broader literature on technology choice and product abandonment (*e.g.*, Bayus and Agarwal, 2007; Klepper and Simons, 1997). Much of this literature has focused on how technologies emerge and diffuse (Murmann and Frenken, 2006; Rogers, 2003) while usually finding they are welfare enhancing (*e.g.*, Trajtenberg, 1989). Less investigated is why firms reduce their commitment to existing technologies. Reducing market commitment to existing technologies is difficult because it entails foregoing sunk cost investments (Finkelstein and Gilbert, 1985) and conceding the product market to competitors (Younkin, 2016). Our results - increased reputational costs in the face of negative upstream research shocks - provide a new, plausible channel that may help explain why firms abandon a product or market.

Along with our core findings we conduct numerous robustness and placebo tests to ensure the validity of our results. First, using a placebo mid-point test our pre-trends do not violate the parallel trends assumption. Second, our findings are robust with respect to three different alternate control groups. Third, our results are robust to controlling for regional heterogeneity within India. Fourth, we consider whether this research shock spilled over into other markets that were not exposed to the levels of NDM-1 antibiotic resistance found in India. Using data from the U.S., we find no evidence of any impact on their antibiotic market.

Finally, our findings also have important policy implications given the *Red Queen Effect* in antibiotics resistance (Dieckmann *et al*., 1995). The *Red Queen Effect* depicts a situation where - *it takes all the running you can do, to keep in the same place*.[6] In the context of antibiotics, pharmaceutical firms are globally running a (difficult) R&D race to produce newer antibiotics, but at the same time, as more antibiotics are consumed (often indiscriminately prescribed) it increases the probability of resistance thereby destroying incentives for innovation. This horse race between economics and clinical externalities is at the heart of designing optimal health and innovation policies (Eswaran and Gallini, 2019), prompting infectious disease experts like Dr. Anthony Fauci to comment: "*Resistant microbes outstrip new antibiotics. It is an*

[6] The *Red Queen Effect* is aptly inspired from Lewis Carroll's *Through the Looking Glass*, a sequel to *Alice's Adventures in Wonderland*.

ongoing problem. It is not like we can fix it, and it is over. We have to fight continued resistance with a continual pipeline of new antibiotics and continue with the perpetual challenge."[7]

2.0 Institutional Background

2.1 Antibiotic discovery, consumption, and resistance

Alexander Fleming discovered penicillin in 1928. By 1940, scientists had already discovered the existence of resistant bacterial strains and acknowledged the fear of over-use (Spellberg and Gilbert, 2014).[8] By the mid-1940s, streptomycin, a successful drug for tuberculosis was introduced, but very soon after resistant bacteria were discovered. The 1950s saw the development of many classes of antibiotics that are still used today (*e.g.*, tetracyclines, macrolides/lincosamides/streptogramins, glycopeptides, rifamycins and nitroimidazoles). Besides the discovery of quinolones and trimethoprim in the 1960s there was a long development gap until the oxazolidinones in the early 2000s (*e.g.*, Conly and Johnston, 2005; Davies and Davies, 2010). The early triumphs of the global pharmaceutical industry over infectious diseases was captured by Nobel laureate M. Burnet's quip "…*the virtual elimination of the infectious diseases as a significant factor in social life…"* (Burnet *et al.*, 1972).

A large set of global pharmaceutical firms including Novartis, AstraZeneca, Sanofi, Allergen, Merck, Roche, GlaxoSmithKline, and Pfizer are active in antibiotics development and manufacturing. While antibiotics have been shown to positively impact long-run economic development (Acemoglu and Johnson, 2007), the supply of new antibiotics has slowly dried up. Unfortunately, bacteria continue to evolve (Spellberg and Gilbert, 2014). For example, from the World Health Organization's list of antibiotics in clinical development, only three of them can potentially target the NDM-1 bacteria. This bacterium is the focus of our analysis and has shown resistance towards carbapenems, the broad-spectrum antibiotic also known as the 'last line of defense' for bacterial infections.[9,10]

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[7] See: https://www.post-gazette.com/healthypgh/2014/05/25/Medical-marathon-Race-is-on-to-develop-new-antibiotics-Medical-marathon-U-S-Centers-for-Disease-Control-and-Prevention-employ-shotgun-approach-to-bring-antibiotic-resistance-under-control/stories/201405250015

[8] See: https://www.nytimes.com/1945/06/26/archives/penicillins-finder-assays-its-future-sir-alexander-fleming-says.html

[9] See: https://www.who.int/news-room/detail/17-01-2020-lack-of-new-antibiotics-threatens-global-efforts-to-contain-drug-resistant-infections

[10] See: https://www.theguardian.com/business/2020/jan/17/big-pharma-failing-to-invest-in-new-antibiotics-says-who

High levels of antibiotic consumption and the related rise in antibiotic resistance is a globally well-recognized problem (*e.g.*, Goff *et al*., 2016). Antibiotic resistance kills more than 700,000 people each year with projected deaths exceeding 10 million per year by 2050 (O'Neill, 2014). While the dangers have been recognized since the 1940s, it has proven difficult to reduce the use of the antibiotics. Between 2000 and 2015, global antibiotic consumption has increased by 65 percent (Klein *et al*., 2018). Much of this increase, and resulting rise in resistance, has occurred in low-and-middle income countries. India is an important contributor to this global rise in antibiotic resistance, including the presumed source of the broad spectrum antibiotic resistant NDM-1 superbug.[11] NDM-1 has now spread to more than 70 countries and the latest report of its outbreak has emerged from as far away as a remote Norwegian archipelago.[12] Important, however, for our analysis is the fact that during our sample period the spread of NDM-1 to the U.S. was extremely limited (and mostly as a result of patients having come into the U.S. from foreign countries).

With respect to India, antibiotic consumption has dramatically outpaced the growth in global consumption, expanding by 103 percent over the 2000 to 2015 time period (Klein *et al*., 2018). On a relative basis, India's share in the global antibiotics market increased from 15.1 percent in 2000 to 18.6 percent in 2015. While it is impossible to pin down a single reason to explain this trajectory in India, there are several demand-side culprits contributing to this problem. First, rising incomes and economic growth in India do not appear to have translated into improvements in water, sanitation, and public health (Laxminarayan and Heymann, 2012). Second, physicians continue to prescribe antibiotics for upper respiratory infections and diarrheal diseases for which they have limited value (Thakolkaran *et al.,* 2017; Chatterjee *et al.*, 2015; Laxminarayan and Heymann, 2012). Third, physicians routinely receive compensation in exchange for prescribing antibiotics (Roy *et al.*, 2007).[13] Fourth, some antibiotics are available over the counter allowing patients easy (and often uninformed) access to drugs (Laxminarayan

[11] See: https://www.downtoearth.org.in/blog/health/india-the-antibiotic-capital-of-the-world-63097
[12] See: https://www.wsj.com/articles/superbug-from-india-spread-far-and-fast-study-finds-11548633600 and http://outbreaknewstoday.com/italy-superbug-ndm-1-outbreak-reported-in-tuscany-24484/
[13] Competition between physicians also play a role. Physicians report feeling pressured by patients for a quick remedy otherwise they risk losing the patient to other physicians (Kotwani *et al.*, 2010). In conversations with physicians, they report to us that they believe it is better to err on the side of caution because they feel that a Type-I error is more acceptable both psychologically and socially.

and Chaudhury, 2016). Finally, there is increased use of antibiotics in the animal sector driven by demand for meat and poultry (Van Boeckel *et al*., 2015).

2.2 Indian pharmaceutical industry

From the supply side, the Indian pharmaceutical industry is marked by over-dependence on antibiotics as their main source of revenue. In 2006, most of the best selling drugs in India were antibiotics (Duggan *et al.*, 2016). Some of the highest selling brands in India includes products from both multinationals and domestic firms like GlaxoSmithKline's Augmentin and Alkem Laboratories' Clavam (both having the active ingredient amoxicillin and clavulanic acid), and Aristo Pharmaceuticals' Monocef (active ingredient being ceftriaxone, a cephalosporin).[14]

In developed countries, antibiotics account for around 8 percent of total pharmaceutical sales, however, in developing countries, such as India, their share is around 20 percent (Chaudhuri *et al.*, 2006).[15] Prior to the identification of the NDM-1 superbug in India, it would be safe to suggest that neither the demand nor the supply side were paying enough attention to the brewing problem of drug-resistance. Luckily, rationalizing drug usage globally has slowly started to take hold (Pulcini *et al*., 2012) and it seems India has taken the cue. In 2014, the Indian government instructed pharmacists to set up registers to maintain detailed record of drug sales and also implemented other community surveillance programs to monitor medically irrational prescribing behavior following some prior work that shows positive effects of these in European markets (Coburn *et al*., 2021).[16]

Adding to the complexity of the problem, the Indian pharmaceutical industry is highly fragmented with over 5,000 firms operating in the market (Adbi *et al.*, 2021; Chattopadhyay and Bercovitz 2020; Adbi *et al*., 2019). Traditionally, the market has been dominated by generic manufacturers due to India relaxing their intellectual property regime in the 1970s. The liberalization of the Indian economy in the 1990s led many of these generic manufacturers to begin to export to other developing economies (Hafner and Popp, 2011). Coupled with the passage in the U.S. of *The Drug Price Competition and Patent Term Restoration Act* (1984),

[14] See: https://www.livemint.com/news/india/dcgi-moves-to-curb-sales-of-antibiotics-without-prescriptions-11577380637918.html
[15] Based on AIOCD reports, we find that anti-infective accounts for 17 percent of sales in 2012.
[16] See: http://origin.searo.who.int/india/topics/antimicrobial_resistance/amr_containment.pdf

Indian generic manufacturers also began to export to the U.S. market (Branstetter *et al.*, 2016; Chatterjee, 2009; Chaudhuri, 2005). This dynamic shifted in 2005 with the implementation of the World Trade Organization's Trade Related Intellectual Property Rights (WTO-TRIPs) requirements which re-strengthened the intellectual property regime in India. One major implication of WTO-TRIPs has been the rise of multinational firms within the domestic Indian market (*e.g.*, Duggan *et al.*, 2016; Chatterjee *et al.*, 2015; Kapczynski, 2009).

2.3 Multinational reputational costs

Past work in industrial organization shows how the benefit of future reputation can induce firms to produce high quality goods whether in monopoly or competitive settings; reputation ultimately becomes a source of market power allowing firms to charge premium pricing (*e.g.*, Allen, 1984; Shapiro, 1983; Klein and Leffler, 1981). The intuition is straight forward, reputation serves as a signal to solve the adverse selection problem. Logically, building reputation involves costs that might have a bearing on firm entry and exit decisions. This, in turn, will affect market structure and industry evolution when there are negative shocks to reputation. Recent empirical evidence from the Volkswagen emission scandal supports this assertion (Bachmann *et al*., 2021; Strittmatter and Lechner, 2020).

More broadly, prior work has focused on the dynamics of seller reputation (*e.g.*, Cabral and Hortacsu, 2010) and the role of buying reputation in online markets (*e.g.*, Li *et al*., 2020). It has also examined the limits of reputation in online platform markets (*e.g.*, Nosko and Tadelis, 2015; Fan *et al*., 2016). Collectively, this strand of work clearly demonstrates the importance of reputation costs for a firm.

As discussed above, these reputational costs may be more significant for larger, multinational firms facing a liability of foreignness where they face calls for corporate social responsibility in host countries (*e.g.*, Crilly *et al.,* 2016; Campbell *et al*., 2012; Zaheer and Mosakowski, 1997). This is especially important in sectors with public health implications. For example, reputational costs may be higher if multinationals sell 'dodgy' medicines in host markets causing trust implications (Aivalli *et al*., 2018). A negative shock may credibly reveal adverse information about a product, impacting the firm's ability to exercise market power not just locally but also globally. Thus if multinationals don't have the same local institutional

support as domestic firms, they will need a higher rate of alertness so as to avoid possible sanction by regulators (Kostova *et al.*, 2008).

Recent empirical evidence suggests broader applicability of these intuitions across sectors. For example, Chinese toymakers were perceived as having lousy quality even when the mistake was by designers based in the U.S. (Beamish and Bapuji, 2008). Moreover, multinationals operating in emerging markets face higher reputational costs due to the risk of public crises (Zhao *et al*., 2014). Both Conoco Phillips failure to admit oil spill-related environmental damage in China and the Maggi controversy associated with Nestle in India (Pai, 2018; Dhanesh and Sriramesh, 2018) negatively impacted multinational firm reputation.[17] A related literature from marketing also extends these insights with work on country-of-origin effects. For example, European consumer response to a beef and horsemeat scandal was influenced by their perception of the brand's home country (Barbarossa *et al.,* 2016).

Another important aspect of reputational costs for multinational firms comes from the risk of potential negative spillover of brand damage from local to global markets. Firms attempt to insulate themselves from this kind of damage by outright avoiding markets where these kinds of spillover can occur. For example, prior work has shown that firms with higher corporate reputations are less likely to have a presence in the least developed countries due to institutional uncertainty and the likely risk of negative global spillover to their corporate reputation (Musteen *et al.*, 2013). Interestingly, there is now evidence of this same effect in more developed economies due to corporate scandals, for example, in the Swedish financial industry (Jonsson *et al.*, 2009), the U.S. toy (Freedman *et al.,* 2012) and oil industries (Barrage *et al.,* 2020) as well as the Chinese dairy industry (Bai *et al.,* 2021).

Finally, for pharmaceutical products these issues are particularly sensitive given their significant public health implications. For example, in the case of Dengvaxia, a dengue vaccine produced by Sanofi Pasteur, the vaccine was effective in reducing dengue cases, however, it led to several deaths in the Philippines. Ultimately, the vaccine program was suspended and arrest warrants issued for three Sanofi executives translating into significant reputational damages for

[17] https://edition.cnn.com/2012/04/27/world/asia/china-oil-spill/index.html

Sanofi.[18] Critically, the Dengvaxia episode led to an overall negative perception of vaccination in the Philippines (Larson *et al.*, 2019).

3.0 Theoretical Model

Our theoretical model helps explain and illustrate possible firm-level reactions in downstream product markets to upstream research shocks. Given the adverse nature of the shock one might expect both multinational firms (MNCs) and domestic firms to face higher reputational costs thereby leading them to withdraw from an impacted focal product market. However, such an equal likelihood to withdraw is predicated on the assumption that both types of firms face similar reputational consequence. Given our discussion in the previous section, this might not be the case and we present a simple strategic interaction model that concisely explains such behavior. The intuition is that even if the firms were facing identical reputational costs in the pre-shock period, a post-shock difference in relative reputational consequences can lead to differential responses.

Consider a duopoly model with linear demand where we will apply the solution concept from Cournot competition in terms of quantity choice. The baseline framework is built on Dixit (1979). For simplicity and to retain tractability, we treat the multinational and domestic firms as two separate sets of firms. This assumption not only simplifies the model considerably but also is consistent with our econometric approach as we detail in our empirical approach and identification strategy below. We denote the aggregate quantities produced by the multinational firms and domestic firms as q_f and q_d, respectively.

We start by defining the demand side and assume a continuum of consumers with a quasi-linear utility function (Singh and Vives, 1984) in terms of quantity supplied by multinationals (q_f) and domestic firms (q_d) as follows:

$$U(q_f, q_d, Z) = \alpha\,(q_f + q_d) - \frac{\beta}{2}\,(q_f + q_d)^2 + Z \qquad (1)$$

where α and β are shape parameters of the utility function. The parameter descriptions and restrictions in the current representation are standard (*e.g.*, Haraguchi and Matsumura, 2014). Z represents a bundle of outside consumption goods that are competitively provided. We

[18] https://www.manilatimes.net/2021/02/02/news/top-stories/3-dengvaxia-firm-execs-ordered-arrested/836166

assume that the price of commodity bundle Z is normalized to 1. We can generate the inverse demand functions for the multinational and domestic firms, respectively, by equating marginal utilities to prices:

$$p_f = \alpha - \beta\,(q_f + q_d) \qquad \text{and} \qquad p_d = \alpha - \beta\,(q_d + q_f). \qquad (2)$$

On the producer side, we assume that the marginal cost is constant for both the multinational and domestic firms. Note that marginal cost is derived from a firm's total cost function which includes *all* costs faced by the firm, including reputational costs. We denote these marginal costs by c_f and c_d, respectively. Assuming that $\alpha > c_{f,d}$, the profit functions of these firms are given by: [19]

$$\pi_f = (p_f - c_f)q_f \qquad \text{and} \qquad \pi_d = (p_d - c_d)q_d. \qquad (3)$$

By maximizing profits, we can write

$$\frac{\partial \pi_f}{\partial q_f} = \alpha_f - 2\beta q_f - \beta q_d = 0 \qquad \text{and} \qquad \frac{\partial \pi_d}{\partial q_d} = \alpha_d - 2\beta q_d - \beta q_f = 0, \qquad (4)$$

where $\alpha_f = \alpha - c_f$ and $\alpha_d = \alpha - c_d$.[20]

From (4) we can generate the reaction functions for the multinational and the domestic firms, respectively:

$$R_f(q_d) = \frac{\alpha_f - q_d\beta}{2\beta} \qquad \text{and} \qquad R_d(q_f) = \frac{\alpha_d - q_f\beta}{2\beta}\ . \qquad (5)$$

By solving the reaction functions, we can generate the equilibrium quantities in terms of exogenous parameters as:

$$q_f^* = \frac{2\alpha_f - \alpha_d}{3\beta} \qquad \text{and} \qquad q_d^* = \frac{2\alpha_d - \alpha_f}{3\beta}\,. \qquad (6)$$

This leads to the relative market shares as

[19] The autonomous component is greater than the marginal costs for both multinational and domestic firms. This is a necessary condition for ensuring an interior solution.
[20] The second-order conditions are satisfied.

$$s_f^* = \frac{2\alpha_f - \alpha_d}{\alpha_f + \alpha_d} \quad \text{and} \quad s_d^* = \frac{2\alpha_d - \alpha_f}{\alpha_f + \alpha_d}. \tag{7}$$

We posit that the NDM-1 research shock leads to differential changes for these firms' strategic choices due to differential changes in reputational costs. The reputational cost for multinational firms goes up for selling a potentially controversial product in a foreign market (the domestic market of India is a foreign market for multinational firms), reflected by an increase in marginal costs, c_f. Their counterpart (domestic firms), on the other hand, do not witness such an increase in cost. This may arise due to at least two reasons. First, as discussed above, MNCs have presence in many different markets across the globe while domestic firms are local in nature. Therefore, the spillover of potential damage to reputation may have larger pecuniary consequences for MNCs. Second, MNCs are also more actively engaged in R&D which is costly. Therefore, they should be on the margin more protective of their products in the face of future obsolescence (should there be deepening of antibiotic resistance) and reduce their presence.

Our model generates a clear prediction for such a differential change in the perceived cost. If c_f goes up, then α_f goes down (since $\alpha_f = \alpha - c_f$). Consequently, the market share of multinational firms, s_f^*, goes down and simultaneously the market share of the domestic firms, s_d^*, goes up. Mathematically, the derivative of the market share for MNCs with respect to their marginal cost, $\frac{\partial s_f^*}{\partial c_f}$, is negative while the derivative of the market share for domestic firms with respect to the MNC marginal cost, $\frac{\partial s_d^*}{\partial c_f}$, is positive.

This last effect of market share of domestic firms increasing is due to backfilling linked to the strategic response of domestic firms. The economic intuition is that given the fixed demand function, any reduction in one type of firms' presence, creates an opportunity for the other type of firms to step in to extract profit. Since we have combined all MNCs into one strategic player here for modelling purpose, reduction in market share and firm withdrawal is consistent with reducing market presence ultimately leading to exiting the market in an empirical sense. From the point of view of the model, both the reduction in share and withdrawal (intensive margin) and market exit (extensive margin) would induce effectively the same downward adjustment in equilibrium share, s_f^*. The opposite is true for domestic firms.

4.0 Data

We utilize three main sources of data. First, we use the Pharmatrac database maintained by the All India Organisation of Chemists and Druggists (AIOCD) for drug sales data at the molecule-region-time level in India. This data is collected from more than 500,000 retailers representing about 60 percent of drug sales in India. Sales are reported at the stock-keeping unit (SKU)-region-month level (aggregated at quarterly level for the purpose of analysis) and includes price at which drugs are supplied to the retailer, maximum retail price, bonus quantities to retailers and quantity sold. This dataset has become the standard source of sales data to study the Indian pharmaceutical market (*e.g.*, Adbi *et al*., 2021; Adbi *et al.*, 2019;). Our time frame covers the period from 2008 to 2012, with quarterly information consisting of a total of three carbapenems and sixteen narrow-spectrum antibiotics sold by more than one hundred firms.

In our baseline specification, the treatment group consists of the carbapenem antibiotics (ATC codes J01DH04, J01DH02 and J01DH51) and the control group consists of narrow-spectrum antibiotics.[21] Important for our identification strategy, narrow spectrum antibiotics are not an effective treatment for the NDM-1 superbug. To compile our control group of narrow spectrum antibiotics, we follow the medical literature. In particular, following Kristensen *et al.* (2019), narrow spectrum antibiotics consist of: (1) β-lactamase sensitive penicillin (J0CE01and J0CE02); (2) β-lactamase resistant penicillin (J01CF01 and J01CF02); (3) first-generation cephalosporins (J01DB01, J01DB04 and J01DB05; and, (4) macrolides (J01FA01). All molecules along with their corresponding ATC classification are given in Appendix Table A1.

Second, we are also interested in physician prescribing behaviour. For this purpose, we utilize a unique proprietary dataset drawn from the IQVIA Prescription Audit Database that consists of approximately three million physician prescriptions on a quarterly basis covering all of India. IQVIA is a well-recognized, global provider of pharmaceutical data. As before, this dataset has been used in prior work (*e.g.*, Adbi *et al.*, 2019; Bhaskarabhatla and Chatterjee, 2017; Dutta, 2011).

In our robustness analysis aiding also in enhancing our identification strategy, we examine whether the NDM-1 research shock impacted market structures outside India. For this

[21] Anatomical Therapeutic Code (ATC) is the standard therapeutic coding scheme developed by the World Health Organization. Importantly, drugs are approved by ATC code by the FDA. For details see: https://www.whocc.no/atc_ddd_index/

analysis we turn to data from IQVIA MIDAS for the U.S market, which has a low level of reported carbapenem-resistance (Figure 2). More specifically, we obtain sales data at the molecule-time level for the U.S. antibiotics market and conducted a placebo test with this sample for the first quarter in 2008 to the fourth quarter in 2012. The U.S. sample covers eight molecules; two of them are carbapenems and the remaining six are narrow spectrum antibiotics.

Finally, a detailed listing of all variables along with their source and a description of how they were constructed are given in Table 1. In Table 2 we present a detailed timeline of important events that took place after the NDM-1 paper was published in *Lancet Infectious Diseases*. The publication led to the formation of government committees within India as well as follow-up publications that were plausibly endogenous to the first publication.

5.0 Empirical Strategy and Identification

5.1 Multinational shares in the downstream carbapenem product market

Building on our theoretical arguments in Section 3.0 and to understand the causal effect of the upstream NDM-1 research shock on downstream multinational firm product markets, we first estimate the following base specification:

$$MNCshare_{mt} = \beta_0 + \beta_1 Carbapenem_m + \beta_2 NDM1_t + \beta_3 (NDM1_t \times Carbapenem_m) + \beta_4 Total\ Revenue_{mt} + \beta_5 Molecule_m + \beta_6 Time_t + \epsilon_{mt} \quad (8)$$

The dependent variable, $MNCshare_{mt}$, is defined as multinational firm market share for molecule (m) at time (t), where time is defined by quarters. The variable $Carbapenem_m$ is defined as a dummy variable equal to one if a molecule belongs to the treatment group, zero otherwise. $NDM1_t$ is defined as a time-varying dummy that differentiates between the pre- and post-*Lancet* publication (*i.e.*, research shock) periods. The coefficient of interest, β_3, provides the estimate for the impact of the NDM-1 research shock on downstream multinational firm market share in the carbapenem market (*i.e.*, treated group) relative to narrow spectrum antibiotics (*i.e.*, control group). As predicted from our model, we anticipate this coefficient of interest to be negative if multinational firms withdraw from the market and domestic firms engage in backfilling. Given

the nature of the dependent variable we include results from both OLS and Fractional Probit models across most specifications. For Equation (8) we cluster the standard errors by molecule.[22]

Second, to analyze possible inter-firm heterogeneity, we follow Dutta (2011) and estimate firm sales shifts based on Defined Daily Dosages (DDD).[23] For this analysis, our unit of observation changes to the firm-molecule-time level and we estimate the following triple differences specification:

$$\log(Sales_{fmt}) = \alpha_0 + \beta_1 \log(Price_{fmt}) + \beta_2 Carbapenem_m + \beta_3 NDM1_t + \beta_4 MNC_f + \beta_5(NDM1_t \times Carbapenem_m) + \beta_6(MNC_f \times Carbapenem_m) + \beta_7(MNC_f \times NDM1_t) + \beta_8(MNC_f \times NDM1_t \times Carbapenem_m) + \beta_9 Time_t + \beta_{10} Molecule_m + \beta_{11} Firm_f + \beta_{12}(Molecule_m \times Firm_f) + \epsilon_{mft} \quad (9)$$

where the dependent variable, $Sales_{fmt}$, corresponds to the sales of a particular firm, *f*, for molecule, *m*, in time *t*. Again, time is measured in quarters. The interpretations of the dummy variables remain identical to those in Equation (8), except MNC_f which is defined as a dummy equal to one if a firm is multinational, zero otherwise. The coefficient of interest in this specification, β_8, provides the estimate of change of multinational sales in carbapenems post-NDM-1 research shock.

In this specification we also control for the log of molecule prices, $Price_{fmt}$. To account for potential endogeneity of prices we utilize the richness of our data. The final cost paid by consumers is broken down into retail price plus margin. Retailer margin influences the profit of the manufacturer and their marketing expense (Sudhir, 2001; Lal and Narasimhan, 1996) and thus acts as a cost shifter (Nevo, 2001; Ellison *et al.*, 1997).[24] Hence, retail margin influences the

[22] As a robustness check, we re-estimate our baseline specification with cluster bootstrap standard errors. Results are reported in Appendix Table A2 and remain robust. Additionally, to account for the presence of zeroes and the bounded nature of the dependent variable (between 0 to 1), we use a fractional probit model (Papke & Wooldridge, 2008).

[23] While computing the Defined Daily Dosage (DDD) in the paper, we followed the recommendation of the World Health Organization (WHO). For example, using these recommendations, the DDD of Doripenem is 1500 mg per day for a person weighing 70 kg. Thus, for *Q* mg of Doripenem, the DDD units would be *Q*/1500. In the case of intravenous injections for antibiotics as well as oral administration, we convert the mg content into DDD counts following the above method. Thus, all medicines are comparable in terms of DDD.

[24] Quantity demand of a particular product is directly related to the price paid by a consumer. The final price consists of two factors, price at which the drug is procured by the retailer and retailer margin which includes profit along with marketing, distributional and other expenses borne by the retailer. This variable represents a cost shifter for the

price but not sales thereby plausibly satisfying the exclusion criteria. Building on this insight, we use it as an instrumental variable for prices.[25]

We also control for unobserved heterogeneity at the time, molecule, and firm level with respective fixed effects. To account for molecule-firm level idiosyncrasies, such as time-invariant heterogeneity in historical capabilities of some firms in producing some molecules over others, we also control for molecule-firm paired fixed effects. Standard errors in this specification are clustered at the molecule-firm level.

5.2 *Physician prescription behaviour*

To unpack the intensive margin mechanisms of our overall market structure effects, we explore the impact of the NDM-1 research shock on physician prescription behaviour. Physicians are a major stakeholder in this phenomenon as they directly influence patients (Guan *et al.*, 2019; Basu *et al.*, 2008). It is not unreasonable to suggest that they would understand the problem of over-prescription of antibiotics and the consequent growth of antibiotic resistant strains. Additionally, drug firms regularly engage in detailing by sending sales personnel to interface with physicians. This should, theoretically, create a clear channel for information to flow from firms to physicians. To understand if and how physicians prescribing behaviour changed in reaction to the NDM-1 research shock, we test the following specification:

$$MNC\_RXshare_{mt} = \beta_0 + \beta_1 Carbapenem_m + \beta_2 NDM1_t + \beta_3 (NDM1_t \times Carbapenem_m) + \beta_4 Molecule_m + \beta_5 Time_t + \epsilon_{mt} \quad (10)$$

Equation (10) is the same as Equation (8) except we replace the dependent variable with *MNC-RXshare*$_{mt}$, defined as share of prescriptions written for molecule (m) in quarter(t). As before, our coefficient of interest is β_3 which captures the impact of the treatment on the prescription share for multinationals in the post-treatment period. Here it will be useful to evaluate the possible mode of physician responses in the context of our model. There are two possible ways physicians can respond. One, they themselves reduce the prescription quantity (perhaps following scientific literature) thereby making MNCs pull back from the domestic market. Two, the MNCs themselves pull back from the market, decreasing incentives as they do

firm, as the consumer will be unaware of the mark-up, but the firm needs to incorporate this margin in their profit maximizing exercise as this represents a cost for them to distribute and sell their product.

[25] The first stage F-statistic in our instrumental variable estimation is 470 which is greater than the recommended value of 10 (Staiger and Stock, 1994).

so, leading physicians to prescribe fewer MNC-produced products. As we discuss below, our evidence points to this second mechanism.

5.3 Analysis of pre-trends

Our identification strategy relies on the fact that the control group is not exposed to treatment in either period. Importantly, the shock in question did not impact our control sample (*i.e.*, narrow spectrum antibiotics). In Figure 3, we can visually observe that our pre-trends do not appear to violate the parallel trends assumption. To quantitatively test the parallel assumption more formally we follow the approach adopted in (Higgins *et al.*, 2021) and take our pre-trend data and split it in half, defining the midpoint as an arbitrary treatment (*Placebotreatment*) event and estimating our main diff-in-diffs specification (Equation 8). If the parallel trend assumption is violated the coefficient β_3 will be statistically significant.

The results for this placebo test are reported in Table 3. Given the nature of our dependent variable we report two specifications, one for OLS (Model 1) and another for Fractional Probit (Model 2). In both specifications our coefficient of interest, β_3, is not statistically significant. Combined, the visual evidence in Figure 3 along with these placebo test results suggest that the parallel trends assumption is not violated.

This is consistent with the institutional evolution after the publication of the Lancet article (Table 2). Parliamentary discussions were held with a sequence of newspaper reports coming out over the following months. Almost one year after publication another article came out in Lancet which we view as endogenous to the first publication. All of this coincided with the emergence of a national policy to tackle antibiotic resistance in India and the identification of the first case in Canada. The cumulative effects of these events show up in firm-level responses, as seen in our empirical results.

6.0 Empirical Findings

6.1 Descriptive analysis

In Table 4, we provide descriptive summary statistics. We see that in terms of the narrow spectrum antibiotic market (Panels 1 and 2), the relative size of the market remained relatively stable in terms of multinational share. In contrast, in the carbapenem market (Panels 3 and 4), we see that the multinational share declined. A complementary analysis in terms of prescribing behavior of physicians, indicates a very similar scenario. In Panels 5 and 6, the multinational

market share for narrow spectrum antibiotics remained stable while in Panels 7 and 8, the multinational market share for carbapenems reduces after treatment. We examine this phenomenon more formally in regressions, specifically we quantify the causal impact of our shock controlling for unobserved heterogeneity in our models. In Panels 1 and 2 in Table 4, we also see that both multinational and local firms increased bonus doses in narrow spectrum antibiotics after the shock. In contrast, in Panels 3 and 4, we see that the average bonus doses of carbapenems for local firms increased while they decreased for multinational firms. This provides descriptive support for the assertion that multinational firms reduced incentives (through bonus doses) for carbapenems after the NDM-1 shock while we find local firms backfilling, potentially leveraging bonus doses as incentives to physicians.

6.2 Impact of the upstream research shock on downstream product markets

We start by estimating Equation (8). In Model 1, Table 5 we report OLS regression results with multinational market share (*MNCshare*) as the dependent variable. Model 2 reports results using a Fractional Probit specification. We find strong support across all the models that the market share of multinationals went down for carbapenems in the post-treatment period. Interpreting Model 1, we observe that the NDM-1 research shock led to a reduction of 16.9 percent in multinational firm market share for an average carbapenem molecule. Given average sales of 65.17 million DDD per quarter for an average carbapenem molecule, this 16.9 percent reduction in market share translates into a 11.03 million DDD reduction per quarter, per carbapenem molecule. Next, to test the effects at the intensive margin, we redefine the dependent variable as the multinational share of prescriptions by physicians (*MNC-RXshare*). These results are presented in Model 3 and the effect is even stronger.

Finally, to analyze possible inter-firm heterogeneity we use Equation (9) and redefine the dependent variable as firm level sales measured in DDD (*Log (Sales)*). Price is instrumented in this specification and results are presented in Model 1, Table 6. In this triple difference setting, we observe a sharp drop in the quantity of carbapenems sold by multinationals in the post-treatment period (*MNC x NDM-1 x Carbapenem*). A similar decline is also seen at the prescription-level for multinationals (*Log (RX per Doctor)*), Model 2, Table 6. In this specification, average MNC prescriptions per doctor decline. These results, along with those

from Model 3, Table 5, suggest that the shift in physician behaviour is occurring through the intensive margin, accompanying the sales withdraw we observed for multinational firms.

6.3 Unpacking underlying heterogeneous mechanisms

6.3.1 Supply-side responses to the NDM-1 research shock

Beyond firm choices and physician behaviour it is conceivable that the supply-side would also react to the NDM-1 research shock. As a mechanism of the average multinational firm's revealed preferences, we can analyze the level of bonus doses or quantities that firms provide as a direct way to incentivize sellers. This strategic use of bonus quantities has been highlighted earlier to be a pervasive phenomenon in Indian pharmaceutical markets (Bhaskarabhatla *et al.*, 2016). Bonus quantity represents the extra quantity provided to retailers to increase sales of a particular molecule. For example, a firm may give a retailer one extra strip of a drug for free for every one hundred strips of drugs they are able to sell within a fixed time period. We examine this issue using Equation (9) and present results in Model 3, Table 6. To estimate the effects on bonus quantities, we use an inverse hyperbolic sine transform (Bahar *et al.*, 2020; Bellemare and Wichman, 2020) which is well-defined for zeros. We find that in the post-treatment period, multinational firms reduced bonus quantities of carbapenems compared to domestic firms. This reduction in incentives is entirely consistent with a firm that is pulling a product out of a market.[26]

6.3.2 Vintage: Old versus new carbapenems

So far, we have considered carbapenems as one homogeneous group of molecules that belong to the same class. But there may be generational differences within carbapenems in terms of vintage of the active ingredient, underlying technology, safety or efficacy. It is also more likely that older drugs face generic alternatives; reputational costs for selling older vintage carbapenems should be muted, at least with respect to newer drugs. An examination of differential effects by vintage allows us to indirectly test the variation in reputational risks. Therefore, we broadly divide our treatment group of carbapenems into "old" versus "new" following prior work (*e.g.*, Chahine *et al.*, 2010; Papp-Wallace *et al.*, 2011) and examine

[26] In Appendix Table A3 we split carbapenems into "low" versus "high" MNC bonus doses or quantities as an indirect test for the reputational risks multinationals may face in these former cohort of molecules. We find there is larger reduction for higher bonus share molecules compared to lower bonus share molecules.

whether these subgroups experienced differential reductions in market shares for multinationals.[27]

To explore whether multinational firms react more aggressively with respect to their newer drugs we estimate Equation (8) with this split sample in Table 7. Models 1 and 2 present results for multinational sales share in newer carbapenems compared to older carbapenems using OLS, while Models 3 and 4 show the same using a Fractional Probit model. Across all models, the interaction term (*NDM-1 x Carbapenem*) is negative and significant. Importantly, we find that multinational firms reacted more sharply with respect to their newer carbapenems. In all cases, they actively reduced their sales in these new carbapenems consistent with our discussions on reputational risks being higher for newer vintage carbapenems suggest.

6.3.3 Accounting for regional heterogeneity

Previous studies (*e.g.*, Adbi *et al*., 2021; Dandona *et al*., 2017) identify the importance of regional heterogeneity in India. In order to account for this spatial component, we incorporate three sets of dummies into Equation (8): (1) *Geography*; (2) *Molecule x Geography*; and (3) *Geography x Time*. *Geography* is defined as 23 regions in India as per the AIOCD database and broadly correspond to state boundaries in India. Results are presented in Table 8. Across Models 1 to 3 we find that our OLS results are quantitatively consistent with our baseline model (Model 1, Table 5). Similarly, across Models 4 to 6 we find that our Fractional Probit results are also quantitatively consistent with their corresponding baseline model (Model 2, Table 5). Collectively, the results from Models 1 to 6, Table 8 demonstrate that, after controlling for regional heterogeneity, multinational market share of carbapenems declined in the post-treatment period.

6.4 Robustness

6.4.1. Alternative controls

Our benchmark control group consists of narrow spectrum antibiotics. To ensure that our results are not driven by this choice, we re-examine our core results using several alternate control groups. First, we create a control group comprised of all other broad-spectrum antibiotics, excluding carbapenems. The rationale for considering this alternate control group

[27] See Appendix Table A1 for the set of molecules along with the ATC classification.

comes from the *Lancet* publication itself. More specifically, the paper explicitly mentioned carbapenem in its abstract: "*Gram-negative Enterobacteriaceae with resistance to carbapenem conferred by New Delhi metallo-beta-lactamase 1 (NDM-1) are potentially a major global health problem*." (Kumarasamy *et al*., 2010). Thus, there is a possibility that physicians might consider carbapenems as a separate entity within the group of broad-spectrum antibiotics. We re-estimate Equation (8) this new control group and report results in Models 1 and 2, Table 9; results remain robust.

Next, to ensure we are not splitting controls in ways that may be biasing our results, we create a broad control group consisting of all antibiotics, excluding carbapenems. We again re-estimate Equation (8) with this new control and report results in Models 3 and 4. Results not only remain robust but are also quantitatively similar to Models 1 and 2 even though the sample size increased by over 50 percent.

Finally, we explore a third alternate control group based on the synthetic control method (Abadie *et al.*, 2010; Abadie and Gardeazabal, 2003). For our analysis, the outcome of interest is the mean multinational market share of carbapenems in the pre- and post-NDM-1 research shock time period. Using the synthetic control method, we assign weights to narrow-spectrum molecules to create an artificial matched sample of carbapenem molecules. This third control group along with our treatment group is plotted in Figure 4 and regression results from the estimation of Equation (7) are reported in Models 5 and 6, Table 9. As with our prior two set of controls, results remain robust.

6.4.2. Did the NDM-1 research shock spill over to overseas markets?

Given that antibiotics are globally available; one can reasonably ask whether the structural shift in the Indian market spilled over into other countries. If the answer to this question is "yes," it would be a rare example of such shocks spilling from the "Global South" to the "Global North." In addition, it may also raise global welfare concerns with negative externalities from carbapenem resistance. If the answer to this question is "no," that would align with the intuition that perhaps institutional monitoring mechanisms of antibiotics in the Global North are more well established. In this case, firms there may not be as concerned about a local upstream research shock emanating from the Global South. Importantly, it would also provide further support for our identification strategy.

To explore this question, we obtain additional data for the U.S. antibiotics market, a context which also represents a lower *ex ante* antibiotic resistant market (Figure 2). If our focal research shock was general in nature, then we would expect to see similar kinds of effects in lower antibiotic resistant markets. Physicians in the U.S., for example, may begin to proactively prescribe fewer carbapenems. Regulators and/or multinational firms may also begin to limit the sale of these 'last line of defense' drugs. If so, we would expect to see a negative impact at the aggregate level in the U.S. antibiotics markets.

Our treatment group for this analysis is a matched sample of carbapenem molecules sold both in India and the U.S.; the control group remains narrow spectrum molecules. These are plotted in Appendix Figure A1. From this plot there is no visual evidence of any impact from the NDM-1 research shock. There is a minor decline in sales but that seems to be happening both in carbapenem and narrow spectrum antibiotic markets. Regression results are reported in Table 10 and are consistent with this lack of visual evidence; the interaction term of interest is not significant. From a policy perspective, this non-response suggests that U.S. regulators did not (yet) appear concerned that this particular antibiotic resistance would spread to the U.S. or rise to a level of concern that warranted a response.

7.0 Conclusion and Discussion

The effects of market structure on R&D are well documented; however, the impacts of research directly on market structure are less established. We fill this gap by exploring the causal impacts of a shock to upstream research on related but unconnected downstream market structure. We use a natural experiment involving the publication of the discovery of the broad-spectrum antibiotic resistant *New Delhi Metallo-Beta-Lactamase* (NDM-1) superbug in India. The focal article was published in August 2010 in the highly prestigious *Lancet Infectious Diseases*, with little evidence that much attention was paid to NDM-1 prior to that event (Figure 1). This publication stirred an intense policy debate in India ranging from speculation about regional discrimination (similar to what was witnessed with the "Wuhan" coronavirus (Hu *et al*., 2020; Masters-Waage *et al.*, 2020; Wang *et al*., 2020)), the potential adverse impact on medical tourism in India (Saliba *et al*., 2016), and what this find meant for health policy in India – especially given that these particular drugs are the 'antibiotics of last resort'.

We start with a theoretical model to conjecture about *ex post* strategic behavior of multinational and domestic firms in reaction to this research shock and then empirically examine our theoretical propositions. In doing so, we make several contributions to the literature. First, we find that the upstream NDM-1 research shock caused multinational firms to withdraw products from the downstream domestic Indian market. We theorize that multinational firms suffer a reputational cost, due to factors such as to their liability of foreignness (Zaheer and Mosakowski, 1997). This, in turn, increased their marginal cost leading them to withdraw from the downstream product market. This result contributes to the abandonment literature by providing a new channel by which firms may choose to withdraw from a market. We bolster this finding by showing that, at the physician level, prescriptions for multinational firm drugs declined, relative to domestic drugs. Importantly, we show that these effects do not carry over into markets with low-antibiotic resistance.

While declining antibiotic use in the post-treatment period may be viewed positively for public health and antibiotic stewardship reasons, this was not how it ultimately turned out in the local Indian antibiotics market. Instead, the void created in the market by multinational firms was filled by domestic producers; antibiotic use did not wane. Again, these actions are consistent with our theoretical model. Domestic firms are manufacturers and not involved in novel R&D, so their business is driven primarily by quantity considerations. Domestic firms, therefore, do not face the same global reputation concerns as multinational firms. An important distinction here is that multinational firms produce branded, novel drugs while domestic firms are producing generics. In most countries, branded drug producers are held responsible for any harm to patients, even if generics are also being sold.

Our findings have profound public health & policy implications. Antibiotic overuse is a global public health crisis (Ackerman and Gonzales, 2012) and the resulting issues with resistance do not stop at national borders. While 89 percent of physicians believe antibiotics are overprescribed (Thakolkaran *et al*., 2017), in the face of this shock, our results suggest that the volume of prescriptions did not decline. The only change in physician behavior observed was the rotation from prescribing multinational firm products to domestic firm products. It would be easy to blame physicians, especially given some of the financial incentives to prescribe drugs, however this ignores the demand from patients (consumers) and the role of government. Patients

continually demand antibiotics, even in cases when they are not medically necessary (*e.g.*, most ear infections in children). Furthermore, governments could take more aggressive actions with respect to antibiotic stewardship and limit their use in other areas, such as farming. Lest we believe the implications of antibiotic resistance are not serious, in one study (CDC, 2016) 2 million illnesses and 23,000 deaths were attributed to antibiotic resistance in just the U.S. That same study assigned a direct cost of $20 billion plus an additional $35 billion in lost productivity; global costs are even higher.

Our results also have implications for innovation policy. To the extent that sales from current products fund future R&D (e.g., Branstetter *et al*, 2016), as multinational firms withdraw from India, this could dampen future innovation. Antibiotics also suffer from the *Red Queen Effect* – the innovation-resistance cycle is never ending. Multinational firms are globally running a (difficult) R&D race to produce newer antibiotics, while at the same time, as more antibiotics are consumed there is the probability of increased resistance. This creates the situation where the newest antibiotics may be held back in reserve, which may be appropriate from a stewardship perspective, but this limits revenues thereby creating disincentives for companies to undertake their development. Recent procurement policies from COVID-19 may offer a new path forward. In the COVID-19 response governments directly funded both push (*i.e.*, direct funding of R&D) and pull (*i.e.*, rewards for successful development of products) mechanisms instead of relying on traditional market mechanisms, such as patents (Sampat and Shadlen, 2021).

It is worth noting that the pathogenic outbreak we explore here is markedly different than the one caused by COVID-19. In our case, we were dealing with an established product market that experienced an upstream research shock. This upstream shock caused responses in downstream product markets. In the case of COVID-19, in contrast, there was no established market, this was a shock to the entire system. And while we now see new research ('R') taking place, the strongest initial response was in development ('D') as the underlying technologies used for the vaccines (*e.g.*, viral vectors and mRNA) were already developed for use in other areas (Agarwal and Gaule, 2021). But the greatest take-away from COVID-19, in terms of innovation policy, as Sampat and Shadlen (2021) point out are the extraordinary measures taken by governments. It is yet to be seen whether governments will use those bold measures to combat other problems, such as antibiotic resistance.

Our work is not without limitations and potentially offers avenues for future studies. First, while we test and find that there were no effects of the Indian NDM-1 shock in the U.S. antibiotics market, it would be worth investigating if there are variations in this result by the entirety of the "Global North" and "Global South". Data for such a study would be costly but a more complete analysis could help coordinate global policy responses. Second, the persistence (if any) of shocks to reputational costs are a worthy avenue of future work. Does performance return to some steady-state, why or why not? Third, our results suggest a more detailed analysis on upstream innovation is warranted. Given the public welfare importance of antibiotics, understanding possible disincentives for innovation is critical. Our results also point to the public value of scientific publications and global pathogenic outbreak databases for surveillance like the Berlin Outbreak Database (Vonberg *et al*., 2011) and the need to study in more detail their welfare effects. Fourth, future work should build on our findings and the emerging literature on reputation (for firm-level market power) to empirically validate measured reputation effects on market structure not just in antibiotics but other markets more generally. Finally, it may be worthwhile for future work to understand more nuanced exit distributions and the speed of exit between heterogeneous firms. As with all research, more is left to be done.

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Figure 1. Patterns in Google search: Cumulative frequency of Google searches within India for NDM-1 from Q1:2008 to Q4:2012. The vertical bar denotes the time of treatment (*i.e.*, publication of NDM-1 article in *The Lancet Infectious Diseases*) in August 2010. We utilize the search frequency for each month and aggregated them over quarters to match the frequency in the main analysis. Google search does not provide the absolute number of searches in a given month. It normalizes the maximum number of searches within a given time horizon (month 1, 2008 to month 12, 2012 in this case) to one hundred. On this normalized scale, searches for NDM1 in first quarter of treatment were at 100 and this moved beyond 100 in the post treatment periods, being zero in the pre-treatment periods but ultimately reaching beyond 250 in Q4 2012.

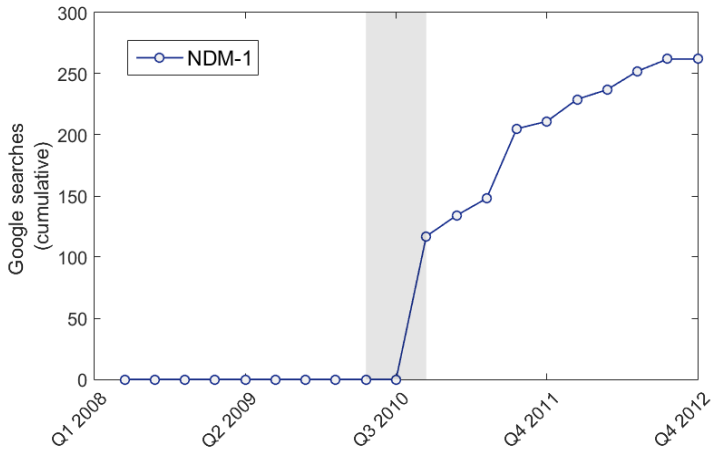

Figure 2. Resistance to carbapenems across countries: Resistance has been measured by randomly testing bacteria with respect to treatment in carbapenems and noting the frequency of resistant bacteria. India has the highest resistance while the United States is in the group of countries with the lowest resistance. Data source: The Center for Disease Dynamics, Economics & Policy. Resistance Map: Antibiotic resistance. 2012.

Figure 3. Multinational share in sales during pre- and post-treatment periods: Multinational market share in sales during pre- and post-treatment periods (separated by the vertical line) in the carbapenems (treated) and narrow-spectrum antibiotic markets. The y-axis denotes multinational market share while the x-axis denotes the number of quarters from Q1:2008 to Q4:2012. Source: AIOCD Pharmatrac.

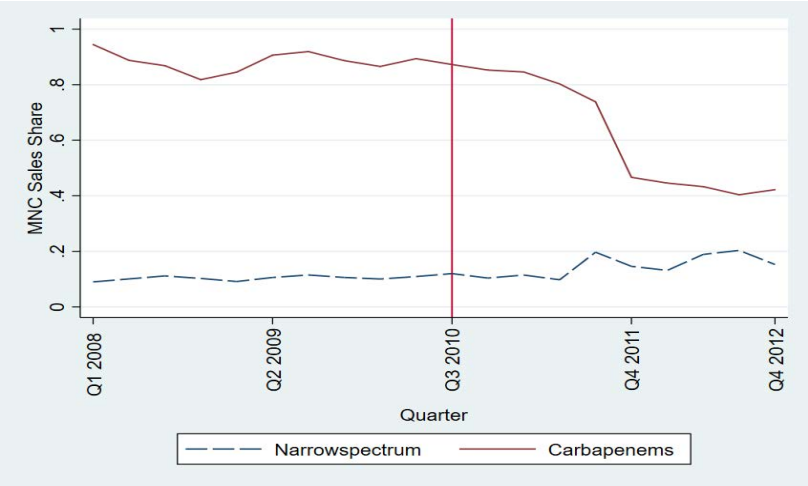

Figure 4. Synthetic control results for multinational sales share: Multinational market share in sales during pre- and post-treatment periods (separated by the vertical line) in the carbapenems (treated) market. Using the synthetic control method, we assign weights to narrow-spectrum molecules to create an artificial matched sample (control) of carbapenem molecules The y-axis denotes multinational market share while the x-axis denotes the number of quarters from Q1:2008 to Q4:2012.

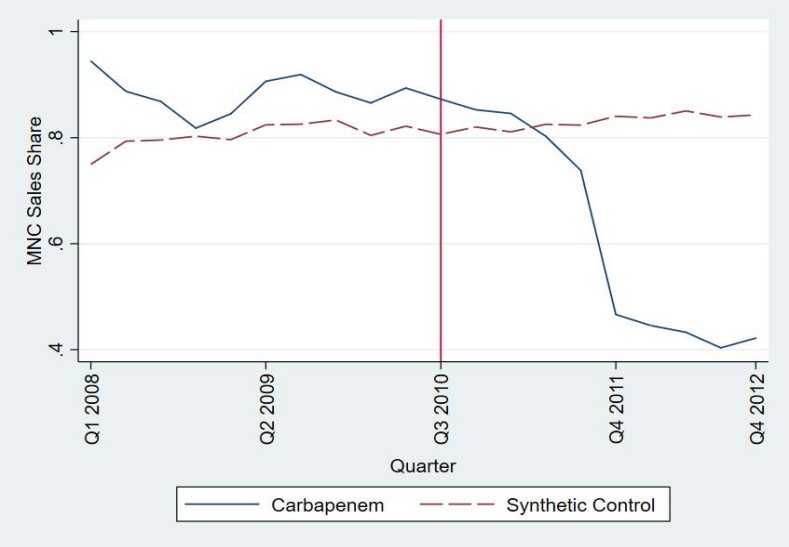

Table 1. Variable definition, description, and source.

Dependent variables	Description	Data Source
MNCshare	This variable is defined as aggregated market share (based on sales) of multinational firms for a focal molecule in time *t.* Time is defined in quarters and sales are defined as "defined daily dosages" (DDD).	AIOCD Pharmatrac
Log (Sales)	Logarithm of sales in DDD for a focal firm and molecule at time *t.* Time is defined in quarters.	AIOCD Pharmatrac
MNC-RXshare	Aggregated market share (based on the number of prescriptions) of multinational firms for a focal molecule in time *t*. Time is defined in quarters.	IQVIA Prescription Audit Database-India
Bonus Dose	Inverse sine transform of bonus doses for a focal firm and molecule in time *t.* Time is defined in quarters and dose in DDD.	AIOCD Pharmatrac
Log (RX per Doctor)	Logarithm of prescriptions per physician for a focal firm and molecule in time *t*. Time is defined in quarters.	IQVIA Prescription Audit Database-India
Log (Sales: US)	Logarithm of focal molecule sales in time *t.* Time is defined in quarters and sales are in standard units, defined by IQVIA.	IQVIA MIDAS
Log (Revenue: US)	Logarithm of focal molecule revenues in time *t.* Time is defined in quarters.	IQVIA MIDAS

Independent variables	Description	Data Source
NDM-1	Dummy equal to zero for quarters before August 2010 (*i.e.*, Q2:2010) and equal to one after.	
Carbapenem	Dummy variable equal to one if a molecule is a carbapenem (ATC code J01DH), 0 otherwise.	
NDM-1 × Carbapenem	Interaction term between variables NDM-1 and Carbapenem.	
MNC	Dummy variable equal to one if a firm had majority foreign ownership as of Q3:2010, 0 otherwise.	IQVIA Prescription Audit Database-India and CMIE Prowess
MNC × NDM-1 × Carbapenem	Interaction term between variables: MNC, NDM-1 and Carbapenem.	
Year	Dummy variable for each year defined from one (2008) to five (2012).	
Placebotreatment	Dummy variable equal to zero for quarters before Q2:2009 and one after Q2:2009 in pre-treatment sample.	
Placebotreatment × Carbapenem	Interaction term between variables Placebotreatment and Carbapenem.	

Control variables	Description	Data Source
Total Revenue	Total aggregate revenue of a focal molecule, across firms, at time *t.* Time is defined in quarters and revenue in millions of Indian Rupees.	AIOCD Pharmatrac
Log (Price)	Logarithm of average maximum retail price in Indian Rupees per DDD of molecule.	AIOCD Pharmatrac
Time	Dummy variable for each quarter *t* where *t* ranges from 1 (Quarter 1: 2008) to 20 (Quarter 4: 2012).	
Molecule	Dummy variable for each molecule *m.*	AIOCD Pharmatrac
Firm	Dummy variable for each firm, *f.*	AIOCD Pharmatrac
Molecule × Firm	Interaction between Molecule and Firm dummies.	AIOCD Pharmatrac
Geography	Dummy variable for each geographical region *g* covering 23 geographical markets in India.	AIOCD Pharmatrac
Molecule × Geography	Interaction between Molecule and Geography dummies.	AIOCD Pharmatrac
Geography × Time	Interaction between Geography and Time dummies.	AIOCD Pharmatrac

Table 2. NDM-1 Timeline. A listing of important events that took place after the publication of the focal NDM-1 paper in *Lancet Infectious Diseases* in August 2010.

Month	Event
August 2010	NDM-1 paper published in *Lancet Infectious Diseases*.
August 2010	Countries such as Bahrain and Thailand issue alerts about possible superbug spread from the Indian subcontinent.
August 2010	Indian parliament debates the naming of the superbug.
September 2010	Indian government forms a committee to draft guidelines for antibiotic prescriptions.
January 2011	Dr. Richard Horton (The editor of Lancet) acknowledges that naming NDM-1 after New Delhi unnecessarily stigmatised a single country or city.
April 2011	Second NDM-1 paper published in *Lancet Infectious Disease*.
April 2011	India announces a national policy for containment of antimicrobial resistance.
June 2011	First case of NDM-1 identified in Canada without any Indian travel history.
August 2012	Symposium by medical societies in India to discuss antimicrobial resistance and Chennai Declaration intended to curb antimicrobial resistance.

Table 3. Analysis of pre-trends. To quantitatively test the parallel trends assumption more formally we follow the approach adopted in (Higgins *et al.*, 2021) and take our pre-trend data and split it in half, defining the midpoint as an arbitrary treatment (*Placebotreatment*) event and estimating our main diff-in-diffs specification (Equation 8). A constant term is included in all the specifications. Time horizon is Q1:2008 to Q2:2010. The placebo treatment time is Q2:2009. To account for the presence of zeroes and the bounded nature of the dependent variable (between 0 to 1), we include a Fractional Probit model (Papke and Wooldridge, 2008). Standard errors in parenthesis are clustered at the molecule level. * p<0.1, ** p<0.05, *** p<0.01.

	(1) **MNCshare** **(OLS)**	(2) **MNCshare** **(Fractional Probit)**
Placebotreatment	0.0000	0.0526
	(.)	(0.0680)
Carbapenem	0.0000	6.4693***
	(.)	(0.4258)
Placebotreatment × Carbapenem	-0.0338	-0.2163
	(0.0200)	(0.1527)
Total Revenue	0.0002***	0.0008
	(0.0001)	(0.0005)
Time	Yes	Yes
Molecule	Yes	Yes
R^2	1.00	
Log pseudo likelihood		-20.51
N	164	165

Table 4. Summary Statistics. This table presents summary statistics of the narrow-spectrum and carbapenem antibiotics for the pre- and post-treatment period. We note that during the post-treatment period, market share of carbapenem sold by multinationals decreased in terms of sales and prescriptions compared to narrow-spectrum antibiotics. Nominal quantities are in Indian rupees.

	Panel (1) Narrow spectrum pre-treatment			**Panel (2) Narrow spectrum post-treatment**		
	Mean	Max	Min	Mean	Max	Min
MNCshare	0.1858	0.1972	0.1576	0.1995	0.2241	0.1843
Number of firms	118.70	137.00	103.00	81.00	105.00	71.00
Total Revenues	1,165.59	1,345.04	1,045.78	1.273.14	1,456.38	1,073.25
Sales (Local, million DDD)	35.00	719.00	0.0001	53.50	1050.00	0.0001
Sales (MNC, million DDD)	153.00	443.00	0.0094	166.00	529.00	0.0011
Price (Local)	0.3535	4.1600	0.0448	0.3577	4.0800	0.0506
Price (MNC)	0.3890	0.6562	0.0943	0.4303	0.7812	0.0807
Bonus Dose (Local, million DDD)	0.8306	31.0000	0.0000	2.1286	46.5000	0.0000
Bonus Dose (MNC, million DDD)	1.8461	9.2873	0.0000	2.9366	11.1000	0.0000

	Panel (3) Carbapenem pre-treatment			**Panel (4) Carbapenem post-treatment**		
	Mean	Max	Min	Mean	Max	Min
MNCshare	0.8402	0.9445	0.7579	0.7227	0.7884	0.6361
Number of firms	12.00	14.00	9.00	22.10	27.00	15.00
Total Revenues	620.06	992.25	389.43	668.95	902.39	514.92
Sales (Local, million DDD)	2.2379	7.9793	0.0018	1.9618	16.4000	0.0003
Sales (MNC, million DDD)	25.8000	92.2000	0.9525	16.7000	66.2000	0.0007
Price (Local)	4.1233	4.8320	2.9720	5.1676	9.6960	2.8500
Price (MNC)	5.1712	8.7162	4.2869	6.2808	9.7500	4.4505
Bonus Dose (Local, million DDD)	0.0091	0.1973	0.0000	0.0419	0.5570	0.0000
Bonus Dose (MNC, million DDD)	0.0335	0.4318	0.0000	0.0100	0.1700	0.0000

Table 4. Summary Statistics. (continued)

	(5) Narrow spectrum pre-treatment (prescription)			(6) Narrow spectrum post-treatment (prescription)		
	Mean	Max	Min	Mean	Max	Min
MNC-RXshare	0.0019	0.0035	0.0011	0.0015	0.0047	0.0004
Number of firms	5,734.50	6382.00	3754.00	2451.70	3690.00	1724.00
Total prescriptions	11,100,000	12,300,000	10,400,000	9,192,247	10,900,000	8,354,308
RX per Doctor (Local)	34.5618	440.1207	5.5385	77.5288	771.6631	5.5000
RX per Doctor (MNC)	25.4958	47.1186	14.3784	57.0003	137.9153	7.5714

	(7) Carbapenem pre-treatment (prescription)			(8) Carbapenem post-treatment (prescription)		
	Mean	Max	Min	Mean	Max	Min
MNC-RXshare	0.3055	0.6857	0.0000	0.0494	0.1483	0.0000
Number of firms	3.50	7.00	1.00	1.33	2.00	1.00
Total prescriptions	686.25	1868.00	45.00	217.33	472.00	67.00
RX per Doctor (Local)	11.7150	21.9643	6.2093	7.9669	6.7000	9.4961
RX per Doctor (MNC)	22.9127	38.8636	9.0619	7.0000	7.0000	7.0000

Table 5. Impact of the upstream NDM-1 publication research shock on downstream product markets. We estimate the impact of the NDM-1 publication on multinational market share (Equation 8) in Models 1 and 2. Given the nature of the dependent variable, Model 1 utilizes OLS while Model 2 utilizes Fractional Probit. Model 3 redefines the dependent variable as the aggregated market share (based on the number of prescriptions) of multinational firms for a focal molecule at time *t*. Model 3 utilizes a Fractional Probit model to test Equation 10 for RXshare. A constant term is included in all the specifications but not reported. Time horizon is Q1:2008 to Q4:2012. Standard errors in parenthesis are clustered at the molecule level. * p<0.1, ** p<0.05, *** p<0.01.

	(1) MNCshare (OLS)	**(2) MNCshare (Fractional Probit)**	**(3) MNC-RXshare (Fractional Probit)**
NDM-1	0.0000	0.5210	0.6942
	(.)	(0.5069)	(1.6218)
Carbapenem	0.0000	4.3554***	6.0669***
	(.)	(0.4709)	(0.6687)
NDM-1 × Carbapenem	-0.1693**	-0.7283**	-4.8282***
	(0.0622)	(0.3355)	(0.7088)
Total Revenue	0.0002***	0.0012	
	(0.0001)	(0.0008)	
Time	Yes	Yes	Yes
Molecule	Yes	Yes	Yes
R^2	0.96		
Log pseudolikelihood		-51.97	-8.38
N	320	320	181

Table 6. Impact of the upstream NDM-1 publication research shock on sales, prescriptions, and bonus quantities. We estimate the impact of the NDM-1 publication (Equation 9) on firm level sales (Model 1), average MNC prescriptions per physician (Model 2) and bonus dose quantities (Model 3). Price is instrumented in Model 1. A constant term is included in all the specifications but not reported. Time horizon is Q1:2008 to Q4:2012. Remaining explanatory variables from Equation 9 are not estimated due to collinearity with fixed effects and thus not reported. Standard errors in parenthesis are clustered at the molecule-firm level. * p<0.1, ** p<0.05, *** p<0.01.

	(1)	(2)	(3)
	Log (Sales) (OLS)	**Log (RX per Doctor) (OLS)**	**Bonus Dose (OLS)**
Log (Price)	-0.1063		
	(0.1923)		
MNC × NDM-1	0.4393	0.1935	0.5785
	(0.3768)	(0.3106)	(0.5533)
NDM-1 × Carbapenem	0.6996***	-0.8450***	1.3715
	(0.2524)	(0.1956)	(1.3236)
MNC × NDM-1 × Carbapenem	-0.9391**	-0.8324**	-5.0279***
	(0.4414)	(0.3609)	(1.7498)
Time	Yes	Yes	Yes
Molecule	Yes	Yes	Yes
Firm	Yes	Yes	Yes
Molecule × Firm	Yes	Yes	Yes
R^2	0.01	0.61	0.80
First-stage F	470.12		
N	3523	1892	3523

Table 7. Vintage effect in our baseline results: Old versus new Carbapenems. We split our sample into 'new' and 'old carbapenems and estimate the impact of the NDM-1 publication on multinational market share (Equation 8). Given the nature of the dependent variable, Models 1 and 2 utilizes OLS while Models 3 and 4 utilizes Fractional Probit. A constant term is included in all the specifications but not reported. Time horizon is Q1:2008 to Q4:2012. Standard errors in parenthesis are clustered at the molecule level. * p<0.1, ** p<0.05, *** p<0.01.

	(1) **New: MNCshare (OLS)**	(2) **Old: MNCshare (OLS)**	(3) **New: MNCshare (Fractional Probit)**	(4) **Old: MNCshare (Fractional Probit)**
NDM-1	0.0000	0.0000	0.7659	0.6212
	(.)	(.)	(0.6797)	(0.4811)
Carbapenem	0.0000	0.0000	11.8255***	3.9213***
	(.)	(.)	(0.3106)	(0.1923)
NDM-1 × Carbapenem	-0.2711***	-0.1021***	-5.3106***	-0.4461***
	(0.0076)	(0.0122)	(0.1936)	(0.1411)
Total Revenue	0.0001	0.0002***	-0.0009	0.0008
	(0.0001)	(0.0001)	(0.0016)	(0.0005)
Time	Yes	Yes	Yes	Yes
Molecule	Yes	Yes	Yes	Yes
R^2	0.95	0.97		
Log pseudolikelihood			-40.69	-45.76
N	295	305	295	305

Table 8. Robustness accounting for regional heterogeneity. We estimate the impact of the NDM-1 publication on multinational market share (Equation 8) accounting for regional heterogeneity in demand for antibiotics in India. We define *Geography* as a dummy variable for the 23 separate regions in India corresponding to state boundaries. Given the nature of the dependent variable, Models 1, 2 and 3 utilizes OLS while Models 3, 4 and 5 utilizes Fractional Probit. A constant term is included in all the specifications but not reported. Time horizon is Q1:2008 to Q4:2012. Standard errors in parenthesis are clustered at the molecule-geography level. * p<0.1, ** p<0.05, *** p<0.01.

	(1) **MNCshare (OLS)**	(2) **MNCshare (OLS)**	(3) **MNCshare (OLS)**	(4) **MNCshare (Frac. Probit)**	(5) **MNCshare (Frac. Probit)**	(6) **MNCshare (Frac. Probit)**
NDM-1	0.0000	0.0000	0.0000	0.1351	0.0215	0.0282
	(.)	(.)	(.)	(0.1067)	(0.1168)	(0.2093)
Carbapenem	0.0000	0.0000	0.0000	4.5392	0.9738**	1.0798*
	(.)	(.)	(.)	(.)	(0.3791)	(0.6207)
NDM-1 ×	-0.1941***	-0.1869***	-0.1861***	-0.7179***	-0.7735***	-0.7567***
Carbapenem	(0.0357)	(0.0352)	(0.0342)	(0.1261)	(0.1442)	(0.1310)
Total Revenue	0.0031***	0.0023***	0.0023***	0.0152***	0.0213***	0.0202***
	(0.0008)	(0.0009)	(0.0008)	(0.0056)	(0.0038)	(0.0038)
Geography	Yes	Yes	Yes	Yes	Yes	Yes
Molecule x Geography	No	Yes	Yes	No	Yes	Yes
Geography x Time	No	No	Yes	No	No	Yes
R^2	0.82	0.90	0.91			
Log pseudolikelihood				-1152.95	-989.72	-953.89
N	5403	5389	5389	5403	5403	5403

Table 9. Robustness: Alternative control groupings. We re-estimate the impact of the NDM-1 publication on multinational market share (Equation 8) using three alternative sets of controls. First, we use all other broad-spectrum antibiotics as control group, excluding carbapenems (Models 1 and 2). Second, we use all other antibiotics as control group, excluding carbapenems (Models 3 and 4). Our treated group remains carbapenems. Finally, using the synthetic control method, we assign weights to narrow-spectrum molecules to create an artificial matched sample of carbapenem molecules (Models 5 and 6). Given the nature of the dependent variable both OLS and Fractional Probit specifications are estimated. A constant term is included in all the specifications but not reported. Time horizon is Q1:2008 to Q4:2012. Standard errors in parenthesis are clustered at the molecule level. * p<0.1, ** p<0.05, *** p<0.01.

	(1) **MNCshare (OLS)**	(2) **MNCshare (Fractional Probit)**	(3) **MNCshare (OLS)**	(4) **MNCshare (Fractional Probit)**	(5) **MNCshare (OLS)**	(6) **MNCshare (Fractional Probit)**
Control Type:	**Broad spectrum**	**Broad spectrum**	**All antibiotics**	**All antibiotics**	**Synthetic control**	**Synthetic control**
NDM-1	0.0000	-0.0170	0.0000	0.0074	0.0000	-0.2066
	(.)	(0.1042)	(.)	(0.1079)	(.)	(0.5251)
Carbapenem	0.0000	-1.2580***	0.0000	4.3639***	0.0000	0.3372***
	(.)	(0.3536)	(.)	(0.3705)	(.)	(0.0062)
NDM-1 × Carbapenem	-0.1626***	-0.6287*	-0.1621***	-0.6334**	-0.2801***	-0.9587***
	(0.0567)	(0.3242)	(0.0564)	(0.3225)	(0.0000)	(0.0141)
Total Revenue	-0.0000	-0.0001	-0.0000	-0.0001		
	(0.0001)	(0.0002)	(0.0001)	(0.0002)		
Time	Yes	Yes	Yes	Yes	Yes	Yes
Molecule	Yes	Yes	Yes	Yes	Yes	Yes
R^2	0.97		0.96		0.70	
Log pseudo likelihood		-311.60		-551.41		-19.25
N	1539	1539	2668	2668	40	40

Table 10. Robustness: Alternative global antibiotic markets, US sample. We re-estimate the impact of the NDM-1 publication on aggregate sales (Model 1) and aggregate revenues (Model 2) for the U.S. antibiotic market. Sales are in standard units as defined by IQVIA and revenues are in U.S. dollars. A constant term is included in all the specifications but not reported. Time horizon is Q1:2008 to Q4:2012. Standard errors in parenthesis are clustered at the molecule level. * p<0.1, ** p<0.05, *** p<0.01.

	(1) **Log (Sales: US)**	**(2)** **Log (Revenue: US)**
NDM-1	0.0000	0.0000
	(.)	(.)
Carbapenem	0.0000	0.0000
	(.)	(.)
NDM-1 × Carbapenem	-0.2573	0.0955
	(0.5642)	(0.5179)
Time	Yes	Yes
Molecule	Yes	Yes
R^2	0.94	0.91
N	153	153

Online Appendix

Figure A1. Robustness: Alternative global antibiotic markets. Sales in millions of standard units as defined by IQVIA MIDAS during pre- and post-treatment periods (separated by the vertical line) in the U.S. carbapenems (treated) and narrow-spectrum (control) antibiotic markets. The x-axis denotes the number of quarters from Q1:2008 to Q4:2012. Source: IQVIA MIDAS.

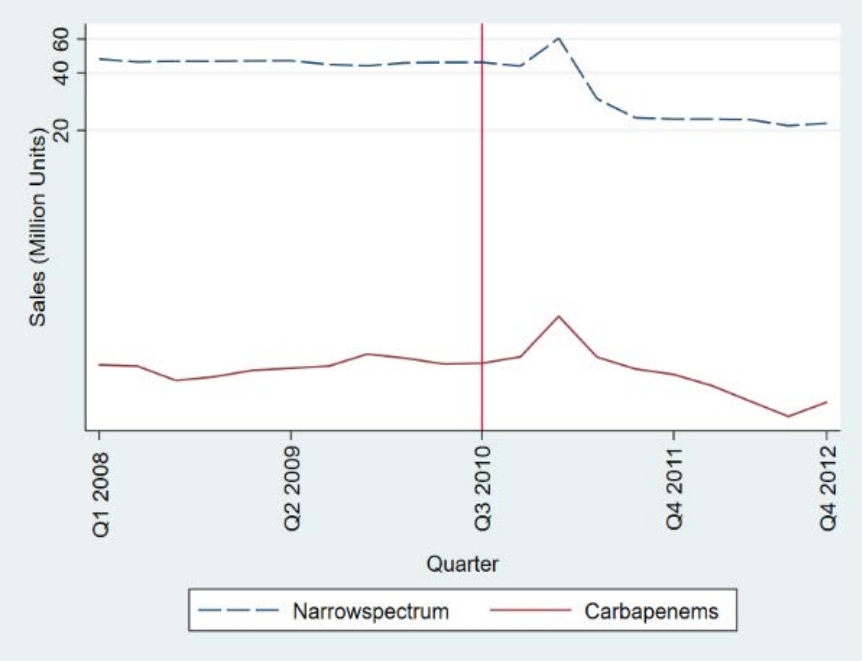

Table A1. Molecule classification based on ATC code

Molecule	ATC code	Classification	U.S. FDA approval year	U.S. patent year	Structure
AMBROXOL + CEFADROXIL	J01DB05	narrow-spectrum	Before 1982	1978	First-generation cephalosporins
CEFADROXIL + CLAVULANIC ACID	J01DB05	narrow-spectrum	Before 1982	1978	First-generation cephalosporins
CEFADROXIL + LACTOBACILLUS ACIDOPHILUS	J01DB05	narrow-spectrum	Before 1982	1978	First-generation cephalosporins
CEFADROXIL + PROBENECID	J01DB05	narrow-spectrum	Before 1982	1978	First-generation cephalosporins
CEFADROXIL COMBINATIONS	J01DB05	narrow-spectrum	Before 1982	1978	First-generation cephalosporins
CEFADROXIL	J01DB05	narrow-spectrum	Before 1982	1978	First-generation cephalosporins
CEFALEXIN + BROMHEXINE	J01DB01	narrow-spectrum	Before 1982	1975	First-generation cephalosporins
CEFALEXIN + CARBOCISTEINE	J01DB01	narrow-spectrum	Before 1982	1975	First-generation cephalosporins
CEFALEXIN + PROBENECID	J01DB01	narrow-spectrum	Before 1982	1975	First-generation cephalosporins
CEFALEXIN	J01DB01	narrow-spectrum	Before 1982	1975	First-generation cephalosporins
CEFAZOLIN	J01DB04	narrow-spectrum	Before 1982	1967	First-generation cephalosporins
CLOXACILLIN	J01CF02	narrow-spectrum	Before 1982	1962	First-generation cephalosporins
DICLOXACILLIN	J01CF01	narrow-spectrum	Before 1982	1971	Beta-lactamase resistant penicillin
DORIPENEM	J01DH04	carbapenem	2007	1994	Carbapenems
ERYTHROMYCIN	J01FA01	narrow-spectrum	1985	1966	Macrolides
IMIPENEM + CILASTATIN	J01DH51	carbapenem	1985	1975	Carbapenems
MEROPENEM + SULBACTAM	J01DH02	carbapenem	1996	1983	Carbapenems
PENICILLIN G	J01CE01	narrow-spectrum	Before 1982	NA	Beta-lactamase sensitive penicillin
PENICILLIN V	J01CE02	narrow-spectrum	Before 1982	NA	Beta-lactamase sensitive penicillin

Table A2. Robustness: Baseline results with wild cluster bootstrap error. We estimate the impact of the NDM-1 publication on multinational market share (Equation 8) in Models 1 and 2 with wild cluster bootstrap standard errors. Given the nature of the dependent variable, Model 1 utilizes OLS while Model 2 utilizes Fractional Probit. A constant term is included in all the specifications but not reported. Time horizon is Q1:2008 to Q4:2012. Standard errors in parenthesis are clustered at the molecule level. * p<0.1, ** p<0.05, *** p<0.01.

	(1) MNCshare (OLS)	(2) MNCshare (Fractional Probit)
NDM-1	0.0333	0.4975
	(0.0591)	(0.5822)
Carbapenem	0.1747**	4.3292***
	(0.0690)	(0.4135)
NDM-1 × Carbapenem	-0.1578**	-0.6826**
	(0.0581)	(0.3450)
Total Revenue	0.0002***	0.0012
	(0.0001)	(0.0007)
Number of Firms	-0.0011	-0.0034
	(0.0019)	(0.0161)
Time	Yes	Yes
Molecule	Yes	Yes
R^2	0.96	
Log pseudolikelihood		-51.9607
wildbootpvalue	0.0000	
N	320	320

Table A3. **Robustness: High versus low bonus quantities.** We split our sample into markets with 'high' (Models 1 and 3) and 'low' (Models 2 and 4) bonus quantities by aggregating over our entire sample period and estimate the impact of the NDM-1 publication on multinational market share (Equation 8). Given the nature of the dependent variable, Models 1 and 2 utilizes OLS while Models 3 and 4 utilizes Fractional Probit. A constant term is included in all the specifications but not reported. Time horizon is Q1:2008 to Q4:2012. Standard errors in parenthesis are clustered at the molecule level. * p<0.1, ** p<0.05, *** p<0.01.

	(1) High Bonus Dose (OLS)	(2) Low Bonus Dose (OLS)	(3) High Bonus Dose (Fractional Probit)	(4) Low Bonus Dose (Fractional Probit)
NDM-1	0.0000	0.0000	0.7659	0.6212
	(.)	(.)	(0.6797)	(0.4811)
Carbapenem	0.0000	0.0000	11.8255***	3.9213***
	(.)	(.)	(0.3106)	(0.1923)
NDM-1 × Carbapenem	-0.2711***	-0.1021***	-5.3106***	-0.4461***
	(0.0076)	(0.0122)	(0.1936)	(0.1411)
Total Revenue	0.0001	0.0002***	-0.0009	0.0008
	(0.0001)	(0.0001)	(0.0016)	(0.0005)
Time	Yes	Yes	Yes	Yes
Molecule	Yes	Yes	Yes	Yes
R^2	0.95	0.97		
Log pseudolikelihood			-40.6887	-45.7615
N	295	305	295	305