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Research and Market Structure: Evidence from A Pathogenic Outbreak
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ABSTRACT

Do upstream research shocks directly and contemporaneously impact related but disconnected downstream product markets? We explore this question using a natural experiment involving the New Delhi Metallo-Beta-Lactamase 1 superbug pathogenic outbreak in India. Using a difference-in-differences strategy, we find that this upstream research shock caused multinational firms selling antibiotics in India to reduce their market exposure. Surprisingly, this void was filled by domestic Indian firms. These results are bolstered by a concurrent decline in multinational prescriptions of focal products by Indian physicians relative to prescriptions for domestic firm products. We present a stylized model building on a Cournot differentiated duopoly model to explain these heterogeneous responses. Results are robust to alternate control groups, including synthetic controls, as well as placebo testing. Implications for 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 as exemplified by the adage "yesterday's research becomes today's development and tomorrow's products". In the pharmaceutical industry, for example, university technologies are often commercialized by small, research-intensive firms and ultimately licensed or acquired by larger, downstream 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 this kind of system ripple, for example, from (yesterday's) research through (today's) development before impacting (tomorrow's) product market. But what if the innovation process is not linear (*e.g.*, Higgins *et al.*, 2014)? Would this imply that shocks to one aspect of R&D could directly impact some other non-connected part of the innovation ecosystem?

It is not surprising that shocks to research will impact future development activities. Prior research has explored the impact of development shocks on future development activities (*e.g*, Krieger *et al.*, 2018; Hermosilla and Wu, 2018; Higgins and Rodriguez, 2006; Danzon *et al*., 2005) development shocks on product markets (*e.g*., Higgins *et al.*, 2021); and, product market shocks on development activities (*e.g.*, Agarwal and Gaule, 2021; Manso *et al*., 2019; Branstetter *et al*., 2014; Blume-Kohout and Sood, 2013; Dranove *et al.*, 2013; Dubois *et al*., 2013; Acemoglu and Linn, 2004; Finkelstein, 2004). The relationships from these more demand-pull (*e.g.*, Mowery and Rosenberg, 1979) studies, however, are not unexpected as the focal shocks occur between connected parts of the R&D process. More recently researchers have considered the impact of downstream product market shocks on disconnected but related upstream research activities (*e.g.*, Byrski *et al*, 2021). Missing from the literature is a clear understanding whether a causal relationship exists in the opposite direction; do upstream research shocks directly and contemporaneously impact related but disconnected downstream product markets?

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 a plausibly exogenous shock to research, coupled with unique and disaggregate data from the pharmaceutical industry, we are able to examine the direct and contemporaneous impacts of this event on unconnected but related downstream antibiotic

product markets. Importantly, we are able to 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 start with a theoretical model to hypothesize about *ex post* strategic behavior of multinational and domestic firms in reaction to the NDM-1 research shock. 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). Using this model, we are able to ask important research questions that contribute to the literature. First, we find that the effects of the NDM-1 research shock were dramatic and immediate in the downstream Indian antibiotic 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 decreases to expected revenues coupled with increases in marginal costs. The lost revenues are driven by the withdraw from the market while the increase in marginal cost is driven by changes to reputational costs faced by multinational firms.

The behaviors observed by these multinational firms 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 (*e.g.*, Cheah *et al.,* 2007; Rhee and Haunschild, 2006). Relatedly, multinationals also face 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 given the reputational costs multinationals potentially face by selling "dodgy" products in host markets, in this case India, once a shock credibly reveals negative information about a product. Since multinationals may not have the same institutional backing as domestic firms, they will need a higher rate of responsiveness to scientific evidence to avoid possible sanction by regulators (Kostova *et al.*, 2008).

Corresponding to this withdraw from the market, we find that the average number of prescriptions for multinational firm drugs in the affected markets also declines 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. Moreover, we are able to track 'bonus 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 within newer classes of drugs in order to protect them. Dividing drugs in affected markets by vintage (*e.g.*, Chahine *et al*., 2010; Papp-Wallace *et al.*, 2011), we find that multinational firms reacted 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, the intuition is that given the demand function from the unit mass of consumers and a given degree of substitutability, 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.[1]

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

[1] For example, in 2011the 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.

Gonzales, 2012; Davies *et al.*, 2013) and is even more acute in India (*e.g.*, Thakolkaran *et al.*, 2017).[2] 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.[3] 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 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 provide a new, plausible channel – increased reputational costs in the face of negative upstream research shocks - 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, our results are robust with respect to pre-trends; both synthetic control analysis and event-study plots show that pre-trends do not exist. We have also tested for placebo treatment in April 2008 to rule out pre-trend due to the diagnosis of the first-ever patient with NDM-1, which is also insignificant. Second, our findings are robust with respect to an alternate control group comprising all broad-spectrum antibiotic molecules,

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

[3] To contrast with our focal analysis on the Indian market, we have estimated the market impact using data from the U.S. as well; 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.

excluding carbapenems. Third, our results are robust to controlling for regional heterogeneity within India. Fourth, we truncated our sample of molecules by excluding Ertapenem which was sold only by an Indian domestic firm; results remain robust. Fifth, 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 antibiotic markets.

Finally, our findings also have important policy implications given the *Red Queen Effect* in antibiotics resistance (Baquero *et al.,* 2009; 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*.[4] 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's an ongoing problem. It's not like we can fix it, and it's over. We have to fight continued resistance with a continual pipeline of new antibiotics and continue with the perpetual challenge*".[5]

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).[6] 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

[4] The *Red Queen Effect* is aptly pulled from Lewis Carroll's *Through the Looking Glass*, a sequel to *Alice's Adventures in Wonderland*.
[5] 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
[6] See: https://www.nytimes.com/1945/06/26/archives/penicillins-finder-assays-its-future-sir-alexander-fleming-says.html

was a long development gap until the oxazolidinones in the early 2000s (see 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 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, per 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.[7,8]

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.[9] 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.[10] 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).

[7] See: https://www.who.int/news-room/detail/17-01-2020-lack-of-new-antibiotics-threatens-global-efforts-to-contain-drug-resistant-infections
[8] See: https://www.theguardian.com/business/2020/jan/17/big-pharma-failing-to-invest-in-new-antibiotics-says-who
[9] See: https://www.downtoearth.org.in/blog/health/india-the-antibiotic-capital-of-the-world-63097
[10] 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/

With respect to India, antibiotic consumption has dramatically outpaced the growth in global consumption, expanding by 103 percent over the same 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).[11] Fourth, some antibiotics are available over-the-counter allowing patients easy (and often uninformed) access to drugs (Laxminarayan 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 The supply side of the Indian pharmaceutical industry

From the supply side, the Indian pharmaceutical industry is marked by over-dependence on antibiotics as the 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).[12]

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).[13] 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

[11] 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.

[12] See: https://www.livemint.com/news/india/dcgi-moves-to-curb-sales-of-antibiotics-without-prescriptions-11577380637918.html

[13] Based on AIOCD reports, we find that anti-infective accounts for 17 percent of sales in 2012.

enough attention to the brewing problem of drug-resistance. Luckily, rationalizing drug usage in India has slowly started to take hold (Pulcini *et al*., 2012). In 2014, the Indian government instructed pharmacists to set up registers to maintain detailed record of drug sales and also implemented other comunnity surveillance programs to monitor medically irrational prescribing behavior.[14]

Adding to the complexity of the problem, the Indian pharmaceutical industry is highly fragmented with over 5,000 (multinational and domestic) firms operating in the market (Adbi *et al*., 2019; Adbi *et al.*, 2018). 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 of The Drug Price Competition and Patent Term Restoration Act (otherwise known as the "Hatch-Waxman Act") in 1984, 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).

3.0 Theoretical Model

We use a theoretical model to help explain and illustrate possible firm-level reactions in downstream product markets to upstream research shocks. Fundamentally, the main mechanism involves strategic behavior between domestic and multinational firms in the presence of an adverse event. For this purpose, we adopt a duopoly model with differentiated goods and linear demand, and we will apply the solution concept from Cournot competition in terms of quantity choice.[15] The baseline framework is built on Dixit (1979). For simplicity and to retain tractability, we treat the multinational firms as one composite set of firms and the domestic firms as another composite set of firms. This assumption not only simplifies the model considerably, but is also consistent with our econometric approach. We denote the

[14] See: http://origin.searo.who.int/india/topics/antimicrobial_resistance/amr_containment.pdf
[15] Product differentiation can either be real or perceived.

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:

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

where α and β are shape parameters of the utility function. The parameter δ represents the degree of product differentiation. As δ goes up, the products become more identical. All parameters are positive and, in particular, δ has a magnitude between 0 and 1. The parameter 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 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:

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

On the producer side, we assume that the marginal cost of production is constant for both the multinational and domestic firms. 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: [16]

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

By maximizing profits, we can write

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

where $\alpha_f = \alpha - c_f$ and $\alpha_d = \alpha - c_d$.[17]

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

[16] 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.
[17] The second-order conditions are satisfied.

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

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

$$q_f^* = \frac{2\alpha_f - \delta\, \alpha_d}{\beta(4-\delta^2)} \qquad \text{and} \qquad q_d^* = \frac{2\alpha_d - \delta\, \alpha_f}{\beta(4-\delta^2)} \, . \tag{6}$$

It is important to analyze equilibrium quantity choices and their relationships. We note that the equilibrium quantity choices for both the multinational and domestic firms arise from the strategic interactions in a duopoly set up. In particular, the cost of production as well as the degree of product differentiation is embedded in the equilibrium quantity choices. In order to understand the dynamics of the model we engage in a series of simulations. We start by assuming α = 1 and β = 2 throughout. Three panels in Figure 2 describe the firm-level response functions.

In Panel (a), we further assume that the degree of substitutability is δ = 0.5, marginal costs for domestic firms are fixed at c_d = 0.5, and the marginal costs for the multinational firms, c_f, vary from 0 to 1. On the y-axis we plot the equilibrium output of the multinational firms, q_f^*. As marginal costs, c_f, increase the decrease in the output by multinational firms, q_f^*, is evident. Importantly, beyond a threshold of approximately 0.85, multinational firm equilibrium output falls to zero (*i.e.*, q_f^* = 0).

In Panel (b), we fix the marginal costs for both multinational and domestic firms at 0.5 (*i.e.*, c_f and c_d = 0.5) and we vary δ from 0 (complete product differentiation) to 1 (zero product differentiation). As can be seen, low product differentiation is associated with smaller output in equilibrium as the products compete closely against each other, whereas high product differentiation reduces competition across firms and therefore leads to higher output.

Finally, in Panel (c), we plot the multinational firm's output in equilibrium as a function of marginal cost, c_f, as well as the degree of product differentiation, δ. The shade of the color (color online) is scaled with respect to the quantity; a lighter shade indicates higher output. As can be seen for very high marginal cost and high product substitutability, the equilibrium output is zero (as is indicated by the flat region).

We posit that the NDM-1 research shock leads to two major changes for these firms' strategic choices. First, the reputational cost for multinational firms go up for selling a

potentially controversial product in a foreign market (*i.e.*, the domestic market of India is a foreign market for the multinational firms), reflected by an increase in marginal costs, c_f. Our model generates a clear prediction for such a change. If c_f goes up, then α_f goes down (since $\alpha_f = \alpha - c_f$). Thus, the output of multinational firms, q_f^*, goes down and simultaneously the output of the domestic firms, q_d^*, goes up. We note that the first part of the result is intuitively obvious that if the marginal cost of production goes up for multinational firms, it is natural to expect that they will produce and sell less.

The less-obvious result, however, arises from the response by domestic firms, who increase sales by producing more. The intuition is that given the demand function from the unit mass of consumers and a given degree of substitutability, any reduction in one firm's output, due to their strategic interaction, creates an opportunity for the other firm to step in and increase their own output. For multinational firms, reducing production is perfectly consistent with exiting the market. In terms of the model, we see both the reduction in output (intensive margin) and market exit (extensive margin) as inducing effectively the same downward adjustment in equilibrium output, q_f^*. The opposite is true for the domestic firms. These observations lead to our first research question: *Will an upstream research shock cause multinational firms to abandon downstream product markets and induce domestic firms to fill this void?*

Next, it is important to note that the NDM-1 research shock alters the degree of product substitutability between the antibiotics produced by multinational and domestic firms. In the presence of a reputational cost, multinational firms may behave differently than domestic firms with respect to the demand side. Since markets can be reciprocal, it is conceivable that there will be differences from the demand side in terms of how domestic and multinational firm antibiotics are treated. Upon publication of the article in *Lancet*, there were multiple high-profile discussions among policymakers and within the relevant medical community in India. As such, it is natural to expect the degree of substitutability between the focal antibiotic (*i.e.*, carbapenems) produced by domestic and multinational firms to go down.

This mechanism can be modelled by a fall in δ and the resulting effect can be readily seen by considering the signs of the cross-partial derivatives $\frac{\partial^2 q_f}{\partial \alpha_f \partial \delta}$ (the sign is positive) and

$\frac{\partial^2 q_d}{\partial \alpha_f \partial \delta}$ (the sign is negative).[18] The intuition is as follows. A fall in substitutability will positively impact both firms' output. However, the direct effect of a rise in marginal cost is much larger for multinational firms and hence, the net impact will be negative. Domestic firms, on the other hand, gain on both counts due to higher product differentiation as well as an increase in competitor marginal cost. This observation leads to our second research question: *To what extent do upstream research shocks induce differential impacts on supply- and demand-side factors that shift the composition of downstream product markets?*

4.0 Data

For this study, we utilize two 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 and includes price at which drugs are supplied to the retailer, maximum retail price and quantity sold. This dataset has become the standard source of sales data to study the Indian pharmaceutical market (*e.g.*, Adbi *et al.*, 2019; Adbi *et al.*, 2018; Bhaskarabhatla *et al.*, 2016). Our time frame covers the period from April 2007 to October 2013, with monthly data consisting of a total of five carbapenems and sixteen narrow-spectrum antibiotics sold by more than 100 firms.

In our baseline specification, the treatment group consists of the carbapenem antibiotics (ATC codes J01DH03, J01DH04, J01DH02 and J01DH51) and the control group consists of narrow-spectrum antibiotics.[19] 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), the narrow spectrum antibiotics consist of: (1) β-lactamase sensitive penicillin (J01 CE with suffix 01, 02); (2) β-lactamase resistant penicillin (J01CF with suffix 01, 02); (3) first-generation cephalosporins (J01DB with suffix 01, 04, 05; and,

[18] The function is continuous in both δ and α_f (along with having first and second derivatives). Thus, differentiating with respect to α_f and then with respect to δ makes the calculations easier. One can change the order and check that the result is identical.

[19] ATC is Anatomical Therapeutic Code, a standard code used in the pharmaceutical economics literature specified by the World Health Organization. For details see: https://www.whocc.no/atc_ddd_index/

(4) macrolides (J01FA with suffix 01). All molecules along with their corresponding ATC classification are given in Appendix Table A1.[20]

Second, we are also interested in physician prescribing behavior. For this purpose, we utilize a unique dataset drawn from the IQVIA Prescription Audit Database that consists of approximately 1 million physician prescriptions, at a monthly frequency, covering all of India. IQVIA is a well-recognized, global provider of pharmaceutical data. As before, this dataset has been used in prior work (Adbi *et al.*, 2019; Bhaskarabhatla and Chatterjee, 2017; Dutta, 2011; Farooqui *et al.*, 2019).

In our robustness analysis we examine whether the NDM-1 research shock impacted market structures outside India. For this analysis we picked the U.S., which has a low level of reported carbapenem-resistance (see Figure 3). Thus, we obtain additional sales data from IQVIA for the U.S. market. More specifically, we obtain sales data at the molecule-time level for the antibiotics market for the period April 2007 to October 2013. The antibiotics cover 10 molecules; four of them are carbapenems and the remaining are six narrow spectrum antibiotics.

Finally, a detailed listing of all of our variables along with a description of how they were constructed are given in Table 1. We also identify the data source for each variable.

5.0 Identification and Empirical Strategy

5.1 Multinational shares in the downstream carbapenem product market

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

$$MNCshare_{mt} = \beta_0 + \beta_1 Carbapenem_m + \beta_2 NDMdummy_t + \beta_3 NDMdummy_t \times Carbapenem_m + \beta_4 Total\ monetary\ sales_{mt} + \beta_5 Molecule_m + \beta_6 Time_t + \epsilon_{mt} \quad (7)$$

The dependent variable, $MNCshare_{mt}$, is defined as multinational firm market share at the molecule (m) and monthly time unit (t) level. The variable C*arbapenem*$_m$ is defined as a dummy variable equal to one if a molecule belonging to the treatment group, zero otherwise. *NDMdummy*$_t$ 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

[20] As a robustness check we have also tested all other broad-spectrum antibiotics (*i.e.*, other than carbapenems) as an alternate control group. All results hold qualitatively and quantitatively.

multinational firm market share in the carbapenem market (*i.e.*, treated group) relative to narrow spectrum antibiotics (*i.e.*, control group). We anticipate this coefficient of interest to be negative based on our theoretical discussion in Section 3.0.

Next, $Total\ monetary\ sales_{mt}$ represent monthly molecule sales and controls for molecule-time varying effects, like variation in market sizes and any associated firm-level incentives to enter and exit. Molecule specific idiosyncrasies are accounted for by incorporating molecule-level fixed effects, $Molecule_m$. In order to account for time-specific variations in our data we also control for time specific fixed effects, $Time_t$. We use both OLS and fractional probit methods for estimation (Papke and Wooldridge, 2008) and standard errors are clustered at the molecule level.

In order to capture inter-firm heterogeneity, we follow Dutta (2011) and estimate firm sales based on Defined Daily Dosages (DDD).[21] Our unit of observation changes to the firm-molecule-month level and we estimate the following triple differences specification:

$$\log(Sales_{fmt}) = \alpha_0 + \beta_1 Carbapenem_m + \beta_2 NDMdummy_t + \beta_3 MNC_f + \beta_4(NDMdummy_t \times Carbapenem_m) + \beta_5(MNC_f \times Carbapenem_m) + \beta_6(MNC_f \times NDMdummy_t) + \beta_7(MNC_f \times NDMdummy_t \times Carbapenem_m) + \beta_8 \log(Price_{fmt}) + \beta_9 Time_t + \beta_{10} Molecule_m + \beta_{11} Firm_f + \beta_{12}(Molecule_m \times Calendermonth_t) + \beta_{13}(Molecule_m \times Firm_f) + \epsilon_{mft} \quad (8)$$

where the dependent variable, $Sales_{fmt}$, corresponds to the sales of a particular firm, *f*, in molecule, *m*, in period *t*. The interpretations of the dummy variables remain identical to those in Equation (7), 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_7, provides the estimate of change of multinational sales in carbapenems post-NDM-1 research shock.

In Equation (8) 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 retailer price and margin. Retailer margin influences the profit of the manufacturer and their marketing expense (Lal and Narasimhan, 1996; Sudhir,

[21] While computing the Defined Daily Dosage (DDD) in the paper, we followed the recommendation of the World Health Organisation (WHO). For example, as per WHO, 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.

2001) and thus acts as a cost shifter (Ellison *et al.*, 1997; Nevo, 2001).[22] Hence, retail margin influences the price but not sales thereby satisfying the exclusion criteria. Building on this insight, we use it as an instrumental variable for prices.[23]

We also control for unobserved heterogeneity at the month, molecule and firm level with respective fixed effects. We account for any seasonal changes in molecule sales (*e.g.*, due to weather) with a control for seasonality using an interacted fixed effect, ($Molecule_m \times Calendarmonth_t$), where $Calendarmonth_t$ is a representation of calendar month (January, February, etc.). 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 behavior*

In order 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 behavior. Physicians are a major stakeholder in this phenomenon as they directly influence patients (Guan *et al.*, 2019; Ahmadi and Zarei, 2017; 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 companies 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. In order to understand if and how physicians prescribing behavior changed in reaction to the NDM-1 research shock, we test the following specification:

$$Prescriptionshare_{mt} = \beta_0 + \beta_1 Carbapenem_m + \beta_2 NDMdummy_t + \beta_3 NDMdummy_t \times Carbapenem_m + \beta_4 Molecule_m + \beta_5 Time_t + \epsilon_{mt} \quad (9)$$

Equation (9) is the same as Equation (7) except we replace the dependent variable with $Prescriptionshare_{mt}$, defined as share of prescriptions written for molecule (m) in month (t). As before, our coefficient of interest is β_3 which captures the impact of the treatment on

[22] The demand of a particular product is directly related to the price paid by consumer. The final price consists of two factors, price at which the drug is procured by the retailer and retailer margin which includes the retailer profit along with marketing, distributional and other expenses borne by the retailer. This variable represents a cost shifter for the firm, as the consumer will be unaware of the mark-up but the firm needs to incorporate this margin in their profit maximising exercise as this represents a cost for them to distribute and sell their product.
[23] The first stage F-statistic was 520 which is substantially more than recommended value of 10 (Staiger and Stock, 1994) in our instrumental variable estimations.

the prescription share for multinationals in the post-treatment period. To account for the presence of excess zeroes and the bounded nature of the dependent variable (between 0 to 1), we use a fractional probit model (Papke & Wooldridge, 2008).

Next, we consider an analogue of the quantity model described in Equation (8) but at the prescription level:

$$\log(Prescriptions_{fmt}) = \beta_0 + \beta_1 Carbapenem_m + \beta_2 NDMdummy_t + \beta_3 MNC_f + \beta_4(NDMdummy_t \times Carbapenem_m) + \beta_5(MNC_f \times Carbapenem_m) + \beta_6(MNC_f \times NDMdummy_t) + \beta_7(MNC_f \times NDMdummy_t \times Carbapenem_m) + \beta_8 Time_t + \beta_9 Molecule_m + \beta_{10} Firm_f + \beta_{11}(Molecule_m \times Calendarmonth_t) + \beta_{12}(Molecule_m \times Firm_f) + \epsilon_{mft} \quad (10)$$

Equation (10) is the same as Equation (8) except we replace the dependent variable with $Prescriptions_{fmt}$ defined as prescriptions of a particular firm, *f*, in molecule, *m*, in period *t*. We take the natural log of this variable and add one. As before, our coefficient of interest is β_7,which provides the estimate of change of multinational prescriptions in carbapenems post-NDM-1 research shock.

5.3 Analysis of pre-trends

Following Angrist and Pischke (2008), we check for the existence of pre-trends using the following derivative of Equation 7:[24]

$$MNCshare_{mt} = \beta_0 + \beta_1 Carbapenem_m + \beta_2 Year_{2008} + \beta_3 Year_{2009} + \beta_4 Year_{2010} + \beta_5 Year_{2011} + \beta_6 Year_{2012} + \beta_7 Year_{2013} + \beta_{8(} Carbapenem_m \times Year_{2008}) + \beta_9(Carbapenem_m \times Year_{2009}) + \beta_{10}(Carbapenem_m \times Year_{2010}) + \beta_{11}(Carbapenem_m \times Year_{2011}) + \beta_{12}(Carbapenem_m \times Year_{2012}) + \beta_{13}(Carbapenem_m \times Year_{2013}) + \beta_{14} Total\ monetary\ sales_{mt} + \beta_{15} Molecule_m + \beta_{16} Time_t + \epsilon_{mt} \quad (11)$$

[24] A question arises about the correct timing of the NDM-1 shock as the super-bug was first discovered in 2008 (Kumarasamy *et al.*, 2010). While correct, its discovery did not get public attention until the *Lancet* paper was published 2010. This pattern is clear from Google search data (Figure 1) and is also supported by Saliba *et al.* (2016). To further ensure our pre-treatment period is not contaminated, we conduct the same estimation with a placebo treatment in 2008. Results are presented in Appendix Table A7 and show no evidence of pre-trends. We thank Philippe Gorry for insightful comments on this issue.

Insignificant coefficients in the pre-trend periods (*i.e.*, β_8, β_9, β_{10}) would signify the absence of pre-trends between our treatment and control markets in our estimated results. We find that the coefficients in the pre-treatment period are near zero and insignificant. We also plot the coefficients β_8 to β_{13} in Figure 6. In the post-treatment period, the coefficients are negative and significant. As a robustness check, we introduce placebo treatment in 2008 (prior to the true shock). There is no significant effect due to this placebo treatment (see Appendix Tables A7). We perform a second robustness check with a subsample of data for the 36 month period April 2009 to March 2012.[25] Our results are qualitatively similar and reported in Appendix Table A3.

6.0 Empirical Findings

6.1 Descriptive analysis

We start by examining the overall market trends over our sample period, 2007-2013. Figure 4 plots sales in DDDs over this period.[26] We note that even after the NDM-1 research shock (*i.e.*, paper publication) in August 2010, the overall market for carbapenems expanded in India.[27] However, in Figure 5, we observe that the multinational market share both in terms of quantity sold (from 71.5 percent in April 2007 to 29.5 percent in October 2013) and monetary sales (from 74.4 percent in April 2007 to 33.8 percent in October 2013) declined in the post NDM-1 research shock period.[28] In the market for narrow spectrum antibiotics, however, multinational firms maintained their presence with a relatively stable market share of approximately 10 to 20 percent, both in quantity and monetary sales.

In Table 2, we provide descriptive statistics. We see that in terms of the narrow spectrum antibiotic market (Panels 1 and 2), fewer firms were operating in the market after the research shock, while the size of the market substantially expanded in terms of share and monetary sales. Changes in the level of competition (measured by a Hirschman-Herfindahl

[25] Due to introduction of Doripenem by multinationals firms in June 2009, there is an upward bump in Figure 4. We try to address this issue by focussing on a sample with a smaller time period, and find our results to be consistent. It may also be noticed that Ertapenem was introduced in 2010 and this drug was sold only by domestic firms, which might bias the MNC shares downward in the post-treatment period. We have estimated the main model after taking out Ertapenem. The results continue to hold (see Appendix Figure 2 and Appendix Table A6).

[26] The observe cyclicality in sales due to monsoon season which is strongly associated with infections.

[27] Sales of carbapenems in our data in April 2007 were 57.3 million DDDs which amounted to around $7.4 million USD whereas in October 2013, the combined sales were 113.5 million DDD resulting in sales of around $9.5 million USD.

[28] We also observe a bump in the pre-treatment period, which is attributable to introduction of Doripenem in early 2009 followed by Lupin's introduction of Ertapenem.

index computed over sales in DDD) were minor. In contrast, in the carbapenem market (Panels 3 and 4), we see that the multinational share declines and monetary sales decrease. The level of competition, however, remains stable. A complementary analysis in terms of prescribing behaviour of physicians, indicates a very similar scenario. In Panels 5 and 6, the market share for narrow spectrum antibiotics increases while in Panels 7 and 8, the market share for carbapenems declines.

6.2 Impact of the upstream research shock on downstream product markets

We start by estimating Equation (7). In Model 1, Table 3 we report OLS regression results with multinational market share as the dependent variable. Model 2 reports results using a fractional probit specification. Models 3 and 4 report corresponding results using a second dependent variable, monetary market share, using OLS and fractional probit specifications. In short, 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 13.9 percent in multinational firm market share for an average carbapenem molecule. Given average sales of 20.29 million DDD per month for an average carbapenem molecule, this 13.9 percent reduction in market share translates into a 2.63 million DDD reduction per month, per carbapenem molecule.

Along similar lines, in Model 3, we observe a market share reduction of 11.42 percent in terms of monetary share, which translates into a reduction of Indian Rs. 9.35 million or about $128,000 USD per carbapenem molecule, per month. In order to test the effects at the intensive margin, we redefine the dependent variable as the multinational share of prescriptions by physicians. The results are presented in Model 5 and the effect is even stronger. We will discuss this physician behavior more fully below.

Finally, we present the results from Equation (8) in Model 1, Table 4. Here the dependent variable is firm level sales measured in DDD and prices are instrumented. In this triple difference setting, we observe a sharp drop in the quantity of carbapenems sold by multinationals in the post-treatment period. Collectively, and consistent with theory, the results across Tables 3 and 4 point to a causal decline in terms of sales and market shares of carbapenems by multinational firms in the post NDM-1 research shock period.

6.3 Unpacking underlying heterogeneous mechanisms

6.3.1 Impact on physician prescribing behavior

As noted above, in Table 3, Model 5, we find a decline in the share of multinational firm prescriptions by physicians. This result holds in a quantity-model specification, Model 3, Table 4. In this triple difference setting, our coefficient of interest is again negative and significant. Combined, these results provide convincing evidence that the total number of prescriptions for carbapenems went down in the post-treatment period for multinational firms compared to domestic firms. We can conjecture on why this occurs. First, it is probable that fewer physicians were prescribing carbapenems after the shock. Second, on average, physicians may have written fewer prescriptions after the shock.

Unfortunately, our dataset does not allow us to track individual physician prescriptions. However, we can extract the average number of carbapenem prescriptions, per physician, for a particular firm. In Model 4, Table 4 we estimate Equation (8) but with a dependent variable defined as the log of prescriptions per physician. In this triple difference setting, we see that the average number of multinational firm carbapenem prescriptions, per physician, declined significantly compared to domestic firms. This suggests that the shift in physician behavior occurred through the intensive margin.

To summarize our results so far, we have established two major points. First, in the post-treatment period, multinational firms were significantly reducing their market presence. Second, physicians exhibited a complementary response, they prescribed fewer carbapenems produced by multinationals relative to domestic firms. These findings are consistent with the predictions of our theoretical model and also clearly demonstrate that upstream research shocks can have contemporaneous impacts on downstream product markets.

6.3.2 Vintage: Old versus new carbapenems

Thus far in our investigation we have considered carbapenems as one homogeneous group of molecules that belong to the same class. But there are generational differences within carbapenems in terms of vintage of the active ingredient. Broadly, we can divide carbapenems into "old" versus "new" following prior work (*e.g.*, Chahine *et al.*, 2010; Papp-Wallace *et al.*, 2011; Shah and Isaacs, 2003). We divide our treatment group into two sub-groups consisting of newer carbapenems (*Ertapenem* and *Doripenem*) and older carbapenems (combination of *Imipenem* and *Cilastatin*, combination of *Meropenem* and *Sulbactam*, and

only *Meropenem*) and examine which sub-group within carbapenems saw higher reduction of market shares for multinationals.[29]

This division is important for a number of reasons. Newer drugs are more likely to still be under patent protection and hence may be more valuable to a firm. Because of this they would likely want to protect newer drugs from exposure to drug resistant bacteria. If bacteria indeed became resistant to newer drugs then there are fewer incentives left at the margin, especially for global multinational innovator firms. This is highly problematic given that antibiotic innovation is already limited (Spellberg and Gilbert, 2014). On the flip side, older drugs will be more stable in the sense that their side-effects are known. It is also more likely that older drugs are generics, thus the reputational costs for selling them should be muted, at least with respect to newer drugs.

In order to explore whether multinational firms react more aggressively with respect to their newer drugs we estimate Equation (7) with this split sample in Table 5. Models 1 and 2 present results for multinational sales share in newer carbapenems, while Models 3 and 4 show the same for older carbapenems. Models 5 and 6 present results for prescription-level regressions for newer and older carbapenems, respectively. Across all models, we find that multinational firms reacted more sharply with respect to their newer carbapenems. In all cases, they actively reduced their sales. Similarly, in Model 5 physicians reduced prescriptions for newer carbapenems.

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

So far, our analyses have focused on firm choices and physician behavior. 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 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 100 strips of drugs they are able

[29] See Appendix Table A1 for the set of molecules along with the ATC classification. Ertapenem and Doripenem were introduced after 2000 whereas Imipenem and Meropenem were patented in the 1970s and 1980s and marketed long before 2000. Appendix Table A2 lists the introduction dates of carbapenem in the U.S. Imipenem and Meropenem were introduced before 2000 and Ertapenem and Doripenem were introduced after 2000.

to sell within a fixed time period. We examine this issue using Equation (8) in Model 2, Table 4. 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.

6.3.4 Is there regional heterogeneity in India?

Previous studies (*e.g.*, Adbi *et al.*, 2019; 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 (7): (1) *Geography*; (2) *Molecule-Geography*; and, (3) *Geography-Time*. *Geography* is defined as 23 regions in India as per AIOCD database broadly corresponding to state boundaries in India. Results are presented in Table 6a for sales and Table 6b for monetary sales. Across Models 1 to 6, we find that our baseline results hold both qualitatively and quantitatively. In summary, after controlling for regional heterogeneity sales of carbapenems by multinational firms declined in the post-treatment period.

6.4 Robustness

6.4.1. Alternative control groupings

Our current control group consists of narrow spectrum antibiotics. In an effort to ensure that our results are not driven by this choice, we re-examine our core results using an alternate control group comprised of other broad spectrum antibiotics, excluding carbapenems. The rationale for considering this alternate control group 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 (7) using the rest of the broad spectrum antibiotics, excluding carbapenems (eighty six broad spectrum molecules barring five carbapenems) as the control group and present results in Table 7.[30] Results are robust in Models 1 and 2 when

[30] As an alternate specification we took all the antibiotic molecules (more than 150 molecules) minus carbapenems as control group. Results are reported in Appendix Table A4 and are quantitatively and qualitatively robust.

we consider multinational market share. However, in Models 3 and 4 when we consider multinational monetary market share, results are negative but not significant. This result is not entirely unexpected because this control group is closer to our treatment group, *i.e*, they are all broad spectrum antibiotics.

Next, we explore a second alternate control group based on the synthetic control method (Abadie *et al.*, 2010; Abadie and Gardeazabal, 2003). The synthetic control method is a matching technique, which creates an artificial control group matched to the characteristic of the treated group in the pre-treatment period. This data-driven approach makes the synthetic control method a more objective way to create a counterfactual, as opposed to more subjective choices. The advantages of the synthetic control method had led to wide-spread use in recent studies (*e.g.*, Adbi *et al.*, 2019; Peng *et al.*, 2018; Greene *et al.*, 2014). 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. Our new synthetic control group along with our treatment group is plotted in Figure 7. As can be seen from this non-parametric analysis our core results are supported; there is a negative and significant effect on our treatment sample in the post-shock period.

6.4.2. Did the research shock spill over to other markets?

Given that antibiotics are globally available; one can reasonably ask whether the structural shift in the Indian market spilled over into other countries. To answer this question, we obtain data for the U.S. as it represents a lower antibiotic resistant market (see Figure 3). 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 US antibiotics markets.

To better understand this we use IQVIA data for the U.S. market. Our treatment group matched with the Indian sample, consists of four carbapenem molecules sold in US while our control group consists of six narrow spectrum molecules. These are plotted in Appendix Figure 1. From this plot there is no visual evidence of any impact from the NDM-1 research shock. Regression results are reported in Appendix Table A8 and are consistent with the lack of visual evidence, our interaction term of interest is not significant in either model. While we do not have access to global antibiotic data, it is not a stretch to conjecture that we would

anticipate similar non-responses in other low-antibiotic resistant markets, such as Canada or the European Union. From a policy perspective, this non-response suggests that U.S. regulators do not (yet) appear concerned that this particular antibiotic resistance will spread to the U.S. or at least the concern does not rise to the level of trying to protect these particular antibiotics.

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 contemporaneous, 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 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)) to the potential adverse impact on medical tourism in India (Saliba *et al*., 2016), and what this finding 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. Using this model, 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 their 'liability of foreignness' (Zaheer and Mosakowski, 1997). This in turn increases a firm's marginal cost leading them to exit the downstream product market. This result contributes to the abandonment literature by providing a new channel by which firms may choose to exit 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 meant to be. 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 contemporaneous 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 know 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. First, while we test and find that there were no effects of the Indian NDM-1 shock in 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, our results suggest a more detailed analysis on upstream innovation is warranted. Given the public welfare importance of antibiotics, more fully understanding possible disincentives for innovation is critical. Finally, it may be worthwhile for future work to understand more deeply the speed of exit between heterogeneous firms. As with all research, more is left to be done.

References

Abadie, A., Diamond, A., & Hainmueller, J. (2010). Synthetic control methods for comparative case studies: Estimating the effect of California's tobacco control program. *Journal of the American Statistical Association*, *105*(490), 493–505.

Abadie, A., & Gardeazabal, J. (2003). The economic costs of conflict: A case study of the Basque Country. *American Economic Review*, *93*(1), 113–132.

Acemoglu, D., & Johnson, S. (2007). Disease and development: the effect of life expectancy on economic growth. *Journal of Political Economy*, *115*(6), 925–985.

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

Ackerman, S., & Gonzales, R. (2012). The context of antibiotic overuse. *Annals of Internal Medicine*, *157*(3), 211–212.

Adbi, A., Bhaskarabhatla, A., & Chatterjee, C. (2018). Stakeholder Orientation and Market Impact: Evidence from India. *Journal of Business Ethics*, 1–18.

Adbi, A., Chatterjee, C., Drev, M., & Mishra, A. (2019). When the Big One Came: A Natural Experiment on Demand Shock and Market Structure in India's Influenza Vaccine Markets. *Production and Operations Management*, *28*(4), 810–832.

Adbi, A., Chatterjee, C., & Mishra, A. (2019). Nations within a Nation: Pandemic, Regional Heterogeneity, and MNC Share of Vaccine Uptake. In *Academy of Management Proceedings* (Vol. 2019, p. 12668).

Agarwal, R., & Gaule, P. (2021). *What drives innovation? lessons from covid-19 r&d*. International Monetary Fund.

Ahmadi, F., & Zarei, E. (2017). Prescribing patterns of rural family physicians: a study in Kermanshah Province, Iran. *BMC Public Health*, *17*(1), 908.

Angrist, J. D., & Pischke, J.-S. (2008). *Mostly harmless econometrics: An empiricist's companion*. Princeton university press.

Bahar, D., Choudhury, P., & Rapoport, H. (2020). Migrant inventors and the technological advantage of nations. *Research Policy*, 103947.

Baquero, F., Alvarez-Ortega, C., & Martinez, J. L. (2009). Ecology and evolution of antibiotic resistance. *Environmental Microbiology Reports*, *1*(6), 469–476.

Basu, S., Chatterjee, M., & Chandra, P. K. (2008). Antibiotic misuse in children by the primary care physicians-an Indian experience. *Nigerian Journal of Clinical Practice*, *11*(1), 53–58.

Bayus, B. L., & Agarwal, R. (2007). The role of pre-entry experience, entry timing, and product technology strategies in explaining firm survival. *Management Science*, *53*(12), 1887–1902.

Bellemare, M. F., & Wichman, C. J. (2020). Elasticities and the inverse hyperbolic sine transformation. *Oxford Bulletin of Economics and Statistics*, *82*(1), 50–61.

Bhaskarabhatla, A., & Chatterjee, C. (2017). The role of physicians in prescribing irrational fixed-dose combination medicines in India. *Social Science & Medicine*, *174*, 179–187.

Bhaskarabhatla, A., Chatterjee, C., Anurag, P., & Pennings, E. (2016). Mitigating regulatory impact: the case of partial price controls on metformin in India. *Health Policy and Planning*, *32*(2), 194–204.

Bhaskarabhatla, A., Chatterjee, C., & Karreman, B. (2016). Hit where it hurts: cartel policing using targeted sales and supply embargoes. *The Journal of Law and Economics*, *59*(4), 805–846.

Blume-Kohout, M. E., & Sood, N. (2013). Market size and innovation: Effects of Medicare Part D on pharmaceutical research and development. *Journal of Public Economics*, *97*, 327–336.

Branstetter, L., Chatterjee, C., & Higgins, M. J. (2014). Starving (or fattening) the golden goose?: Generic entry and the incentives for early-stage pharmaceutical innovation (NBER Working Paper No. w20532).

Branstetter, L., Chatterjee, C., & Higgins, M. J. (2016). Regulation and welfare: evidence from paragraph IV generic entry in the pharmaceutical industry. *The RAND Journal of Economics*, *47*(4), 857–890.

Byrsiki, D., Gaessler, F., Higgins, M.J., (2021). Market size and research: Evidence from the pharmaceutical industry. Working paper, Max Planck Institute for Innovation and Competition

Burnet, M., Burnet, F. M., & White, D. O. (1972). *Natural history of infectious disease*. CUP Archive.

Campbell, J. T., Eden, L., & Miller, S. R. (2012). Multinationals and corporate social responsibility in host countries: Does distance matter? *Journal of International Business Studies*, *43*(1), 84–106.

Centers for Disease Control and Prevention, 2016. Newly reported gene, mcr-1, threatens last resort antibiotic. https://www.cdc.gov/drugresistance/mcr1.html (Accessed 19 April 2017)

Chahine, E. B., Ferrill, M. J., & Poulakos, M. N. (2010). Doripenem: a new carbapenem antibiotic. *American Journal of Health-System Pharmacy*, *67*(23), 2015–2024.

Chatterjee, C. (2009). *New Suppliers & New Markets: Essays on the Global Pharmaceutical Industry*. Carnegie Mellon.

Chatterjee, C., Kubo, K., & Pingali, V. (2015). The consumer welfare implications of governmental policies and firm strategy in markets for medicines. *Journal of Health Economics*, *44*, 255–273.

Chaudhuri, Shubham, Goldberg, P. K., & Gia, P. (2006). Estimating the effects of global patent protection in pharmaceuticals: a case study of quinolones in India. *American Economic Review*, *96*(5), 1477–1514.

Chaudhuri, Sudip. (2005). *The WTO and India's pharmaceuticals industry: Patent protection, TRIPS, and developing countries*. Oxford University Press, USA.

Cheah, E. T., Chan, W. L., & Chieng, C. L. L. (2007). The corporate social responsibility of pharmaceutical product recalls: An empirical examination of US and UK markets. *Journal of Business Ethics*, *76*(4), 427–449.

Conly, J. M., & Johnston, B. L. (2005). Where are all the new antibiotics? The new antibiotic paradox. *Canadian Journal of Infectious Diseases and Medical Microbiology*, *16*(3), 159–160.

Crilly, D., Ni, N., & Jiang, Y. (2016). Do-no-harm versus do-good social responsibility: Attributional thinking and the liability of foreignness. *Strategic Management Journal*, *37*(7), 1316–1329.

Dandona, L., Dandona, R., Kumar, G. A., Shukla, D. K., Paul, V. K., Balakrishnan, K., … others. (2017). Nations within a nation: variations in epidemiological transition across the states of India, 1990--2016 in the Global Burden of Disease Study. *The Lancet*, *390*(10111), 2437–2460.

Danzon, P. M., Wang, Y. R., & Wang, L. (2005). The impact of price regulation on the launch delay of new drugs—evidence from twenty-five major markets in the 1990s. *Health Economics*, *14*(3), 269–292.

Datta, A., & Dave, D. (2017). Effects of physician-directed pharmaceutical promotion on prescription behaviors: longitudinal evidence. *Health Economics*, *26*(4), 450–468.

Davies, J., & Davies, D. (2010). Origins and evolution of antibiotic resistance. *Microbiology and molecular biology reviews*, *74*(3), 417–433.

Davies, K. J., Walters, J. H., Kerslake, I. M., Greenwood, R., & Thomas, M. J. C. (2013). Early antibiotics improve survival following out-of hospital cardiac arrest. *Resuscitation*, *84*(5), 616–619.

Dieckmann, U., Marrow, P., & Law, R. (1995). Evolutionary cycling in predator-prey interactions: population dynamics and the Red Queen. *Journal of Theoretical Biology*, *176*(1), 91–102.

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

Dixit, A. (1979). A model of duopoly suggesting a theory of entry barriers. *The Bell Journal of Economics*, 20–32.

Dranove, D., Garthwaite, C., & Hermosilla, M. (2014). *Pharmaceutical profits and the social value of innovation* (No. w20212).

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

Duggan, M., Garthwaite, C., & Goyal, A. (2016). The market impacts of pharmaceutical product patents in developing countries: Evidence from India. *American Economic Review*, *106*(1), 99–135.

Dutta, A. (2011). From free entry to patent protection: Welfare implications for the Indian pharmaceutical industry. *The Review of Economics and Statistics*, *93*(1), 160–178.

Ellison, S. F., Cockburn, I., Griliches, Z., & Hausman, J. (1997). Characteristics of demand for pharmaceutical products: an examination of four cephalosporins. *The RAND Journal of Economics*, 426–446.

Eswaran, M., & Gallini, N. (2019). Can competition and Patent Policies Avert the Antibiotic crisis? *Canadian Public Policy*, *45*(1), 74–92.

Farooqui, H. H., Mehta, A., & Selvaraj, S. (2019). Systemic antibiotic prescription rates and patterns in private sector in India: Evidence from medical audit data. *International Journal of Infectious Diseases*, *79*, 41–42.

Finkelstein, A. (2004). Static and dynamic effects of health policy: Evidence from the vaccine industry. *The Quarterly Journal of Economics*, *119*(2), 527–564.

Finkelstein, S. N., & Gilbert, D. L. (1985). Scientific evidence and the abandonment of medical technology: A study of eight drugs. *Research Policy*, *14*(4), 225–233.

Goff, D. A., Kullar, R., Goldstein, E. J. C., Gilchrist, M., Nathwani, D., Cheng, A. C., … others. (2017). A global call from five countries to collaborate in antibiotic stewardship: united we succeed, divided we might fail. *The Lancet Infectious Diseases*, *17*(2), e56--e63.

Green, C. P., Heywood, J. S., & Navarro, M. (2014). Did liberalising bar hours decrease traffic accidents? *Journal of Health Economics*, *35*, 189–198.

Guan, X., Tian, Y., Song, J., Zhu, D., & Shi, L. (2019). Effect of physicians' knowledge on antibiotics rational use in China's county hospitals. *Social Science & Medicine*, *224*, 149–155.

Hafner, T., & Popp, D. (2011). China and India as suppliers of affordable medicines to developing countries. *National Bureau of Economic Research*, *No. w17249*.

Haraguchi, J., & Matsumura, T. (2014). Price versus quantity in a mixed duopoly with foreign penetration. *Research in Economics*, *68*(4), 338–353.

Hermosilla, M., & Wu, Y. (2018). Market size and innovation: The intermediary role of technology licensing. *Research Policy*, *47*(5), 980–991.

Higgins, M. J., & Rodriguez, D. (2006). The outsourcing of R&D through acquisitions in the pharmaceutical industry. *Journal of Financial Economics*, *80*(2), 351–383.

Higgins, M. J., Thursby, J., & Thursby, M. (2014). Bench-to-bench bottlenecks in translation. *Science Translational Medicine*, *6*, 250.

Higgins, M. J., Yan, X., & Chatterjee, C. (2021). Unpacking the effects of adverse regulatory events: Evidence from pharmaceutical relabeling. *Research Policy*, *50*(1), 104126.

Hu, Z., Yang, Z., Li, Q., & Zhang, A. (2020). The COVID-19 Infodemic: Infodemiology Study Analyzing Stigmatizing Search Terms. *Journal of Medical Internet Research*, *22*(11), e22639.

Kapczynski, A. (2009). Harmonization and its discontents: a case study of TRIPS implementation in India's pharmaceutical sector. *California Law Review.*, *97*, 1571.

Klein, E. Y., Van Boeckel, T. P., Martinez, E. M., Pant, S., Gandra, S., Levin, S. A., … Laxminarayan, R. (2018). Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proceedings of the National Academy of Sciences*, *115*(15), E3463--E3470.

Klepper, S., & Simons, K. L. (1997). Technological extinctions of industrial firms: an inquiry into their nature and causes. *Industrial and Corporate Change*, *6*(2), 379–460.

Kostova, T., Roth, K., & Dacin, M. T. (2008). Institutional theory in the study of multinational corporations: A critique and new directions. *Academy of Management*

Review, *33*(4), 994–1006.

Kotwani, A., Wattal, C., Katewa, S., Joshi, P. C., & Holloway, K. (2010). Factors influencing primary care physicians to prescribe antibiotics in Delhi India. *Family Practice*, *27*(6), 684–690.

Krieger, J., Li, D., & Papanikolaou, D. (2018). *Developing novel drugs* (No. w24595). National Bureau of Economic Research Cambridge, MA.

Kristensen, P. K., Johnsen, S. P., & Thomsen, R. W. (2019). Decreasing trends, and geographical variation in outpatient antibiotic use: a population-based study in Central Denmark. *BMC Infectious Diseases*, *19*(1), 337.

Kumarasamy, K. K., Toleman, M. A., Walsh, T. R., Bagaria, J., Butt, F., Balakrishnan, R., … others. (2010). Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. *The Lancet Infectious Diseases*, *10*(9), 597–602.

Lal, R., & Narasimhan, C. (1996). The inverse relationship between manufacturer and retailer margins: A theory. *Marketing Science*, *15*(2), 132–151.

Laxminarayan, R., & Chaudhury, R. R. (2016). Antibiotic resistance in India: drivers and opportunities for action. *PLoS Medicine*, *13*(3), e1001974.

Laxminarayan, R., & Heymann, D. L. (2012). Challenges of drug resistance in the developing world. *BMJ*, *344*.

Manchanda, P., & Honka, E. (2005). The effects and role of direct-to-physician marketing in the pharmaceutical industry: an integrative review. *Yale J. Health Pol'y L. & Ethics*, *5*, 785.

Manso, G., Balsmeier, B., & Fleming, L. (2019). Heterogeneous innovation and the antifragile economy. *Unpublished Working Paper*.

Masters-Waage, T. C., Jha, N., & Reb, J. (2020). COVID-19, Coronavirus, Wuhan Virus, or China Virus? Understanding How to "Do No Harm" When Naming an Infectious Disease. *Frontiers in Psychology*, *11*.

Mowery, D., & Rosenberg, N. (1979). The influence of market demand upon innovation: a critical review of some recent empirical studies. *Research Policy*, *8*(2), 102–153.

Murmann, J. P., & Frenken, K. (2006). Toward a systematic framework for research on dominant designs, technological innovations, and industrial change. *Research Policy*, *35*(7), 925–952.

Nevo, A. (2001). Measuring market power in the ready-to-eat cereal industry. *Econometrica*, *69*(2), 307–342.

O'neill, J. I. M. (2014). Antimicrobial resistance: tackling a crisis for the health and wealth of nations. *Review on Antimicrobial Resistance 20*, 1–16.

Papke, L. E., & Wooldridge, J. M. (2008). Panel data methods for fractional response variables with an application to test pass rates. *Journal of Econometrics*, *145*(1–2), 121–133.

Papp-Wallace, K. M., Endimiani, A., Taracila, M. A., & Bonomo, R. A. (2011). Carbapenems: past, present, and future. *Antimicrobial Agents and Chemotherapy*,

55(11), 4943–4960.

Peng, L., Meyerhoefer, C., & Chou, S.-Y. (2018). The health implications of unconventional natural gas development in Pennsylvania. *Health Economics*, *27*(6), 956–983.

Pulcini, C., Bush, K., Craig, W. A., Frimodt-Møller, N., Grayson, M. L., Mouton, J. W., … for Antibiotic Policies, E. S. G. (2012). Forgotten antibiotics: an inventory in Europe, the United States, Canada, and Australia. *Clinical Infectious Diseases*, *54*(2), 268–274.

Rhee, M., & Haunschild, P. R. (2006). The liability of good reputation: A study of product recalls in the US automobile industry. *Organization Science*, *17*(1), 101–117.

Rogers, E. M. (2003). *Diffusion of innovations*. *Free Press of Glencoe*. Simon and Schuster.

Roy, N., Madhiwalla, N., & Pai, S. A. (2007). Drug promotional practices in Mumbai: a qualitative study. *Indian Journal of Medical Ethics*, *4*(2), 57–61.

Saliba, V., Washer, P., Pett, P., Kakkar, M., Abbas, S., Raghuvanshi, B., & McKee, M. (2016). A comparative analysis of how the media in the United Kingdom and India represented the emergence of NDM-1. *Journal of Public Health Policy*, *37*(1), 1–19.

Sampat, B.N. & Shadlen, K. (2021). The COVID-19 innovation system. *Health Affairs*, 40(3), 400-409.

Shah, P. M., & Isaacs, R. D. (2003). Ertapenem, the first of a new group of carbapenems. *Journal of Antimicrobial Chemotherapy*, *52*(4), 538–542.

Singh, N., & Vives, X. (1984). Price and quantity competition in a differentiated duopoly. *The Rand Journal of Economics*, 546–554.

Spellberg, B., & Gilbert, D. N. (2014). The future of antibiotics and resistance: a tribute to a career of leadership by John Bartlett. *Clinical Infectious Diseases*, *59*(suppl_2), S71--S75.

Staiger, D., & Stock, J. H. (1994). Instrumental variables regression with weak instruments. *National Bureau of Economic Research., No. t0151*.

Sudhir, K. (2001). Structural analysis of manufacturer pricing in the presence of a strategic retailer. *Marketing Science*, *20*(3), 244–264.

Thakolkaran, N., Shetty, A. V., D'Souza, N. D. R., & Shetty, A. K. (2017). Antibiotic prescribing knowledge, attitudes, and practice among physicians in teaching hospitals in South India. *Journal of Family Medicine and Primary Care*, *6*(3), 526.

Trajtenberg, M. (1989). The welfare analysis of product innovations, with an application to computed tomography scanners. *Journal of Political Economy*, *97*(2), 444–479.

Van Boeckel, T. P., Brower, C., Gilbert, M., Grenfell, B. T., Levin, S. A., Robinson, T. P., … Laxminarayan, R. (2015). Global trends in antimicrobial use in food animals. *Proceedings of the National Academy of Sciences*, *112*(18), 5649–5654.

Wang, L.-F., Anderson, D. E., Mackenzie, J. S., & Merson, M. H. (2020). From Hendra to Wuhan: what has been learned in responding to emerging zoonotic viruses. *The Lancet*, *395*(10224), e33--e34.

Younkin, P. (2016). Complicating abandonment: how a multi-stage theory of abandonment clarifies the evolution of an adopted practice. *Organization Studies*, *37*(7), 1017–1053.

Zaheer, S., & Mosakowski, E. (1997). The dynamics of the liability of foreignness: A global study of survival in financial services. *Strategic Management Journal*, *18*(6), 439–463.

Figure 1. Patterns in Google Search: Cumulative frequency of Google searches within India for NDM-1 from April 2007 to October 2013. The sudden surge around August 2010 (NDM-1 paper's publication) illustrates increased public awareness about NDM-1. The vertical bar denotes the treatment (*i.e.*, publication of NDM-1 article in *The Lancet Infectious Diseases*) in August 2010.

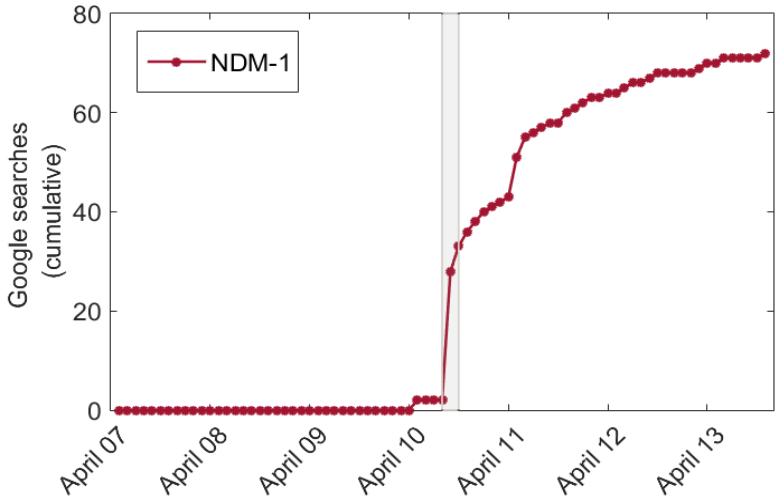


Figure 2. Firm-level Reactions: Firm-level reaction functions in a market characterized by Cournot competition with multinational and domestic firms. Panel (a): Optimal quantity choice (q_f) of the multinational firm decays as a function of increasing marginal cost (c_f). Panel (b): Optimal quantity choice of the multinational and domestic firms (q_f and q_d) decay as a function of increasing product differentiation (δ). Panel (c): Optimal quantity choice for the multinational firms as a function of the degree of product substitutability and cost.

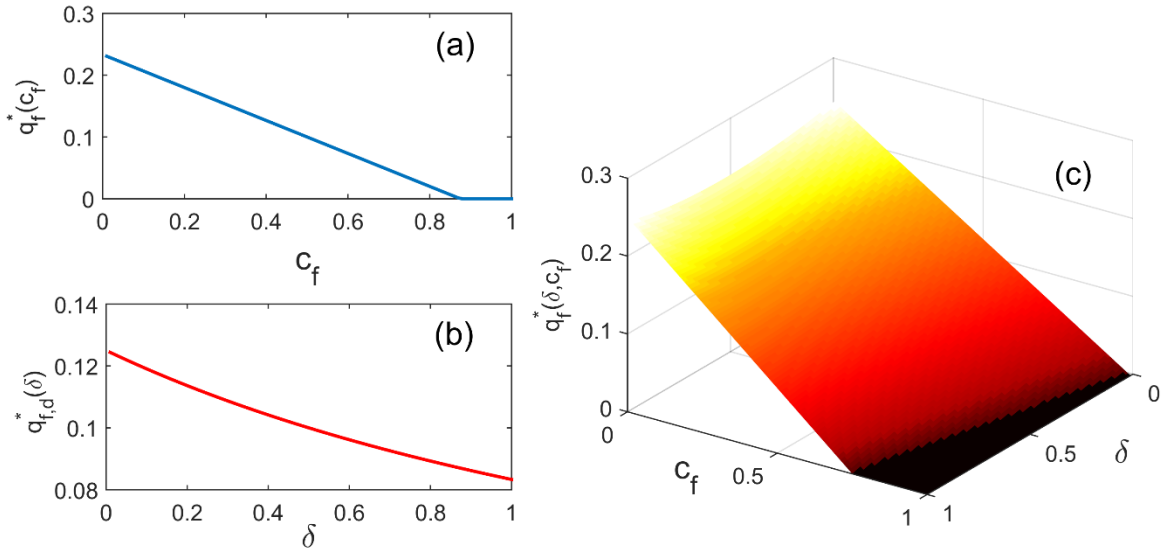


Figure 3. Resistance to Carbapenems across Countries all over the World: India has the highest resistance. Resistance has been measured by randomly testing bacteria with respect to treatment in carbapenems and noting the frequency of resistant bacteria. Used with permission from The Center for Disease, Dynamics Economics & Policy. Resistance Map: Antibiotic resistance. 2019. Source: https://resistancemap.cddep.org/AntibioticResistance.php. Date accessed: Dec 30, 2019

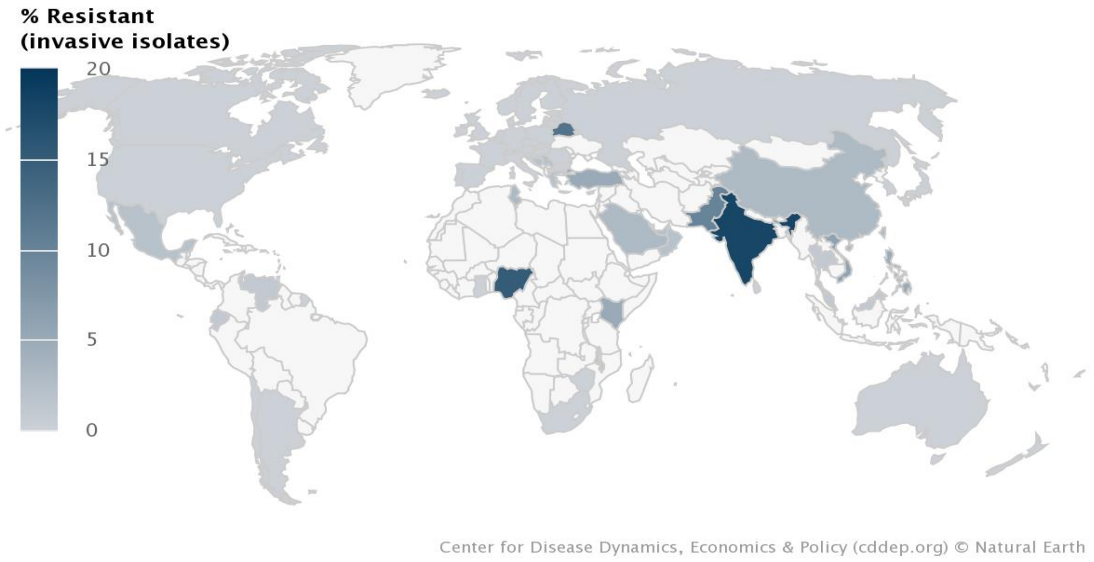


Figure 4. Total Sales of Carbapenems in India from April 2007 to October 2013, in terms of log of Defined Daily Dosages (DDD): The total sales time series shows an increasing trend in the post-treatment period. The vertical bar denotes the treatment (*i.e.*, publication of NDM-1 article in *The Lancet*) in August 2010. Source: AIOCD Pharmatrac.

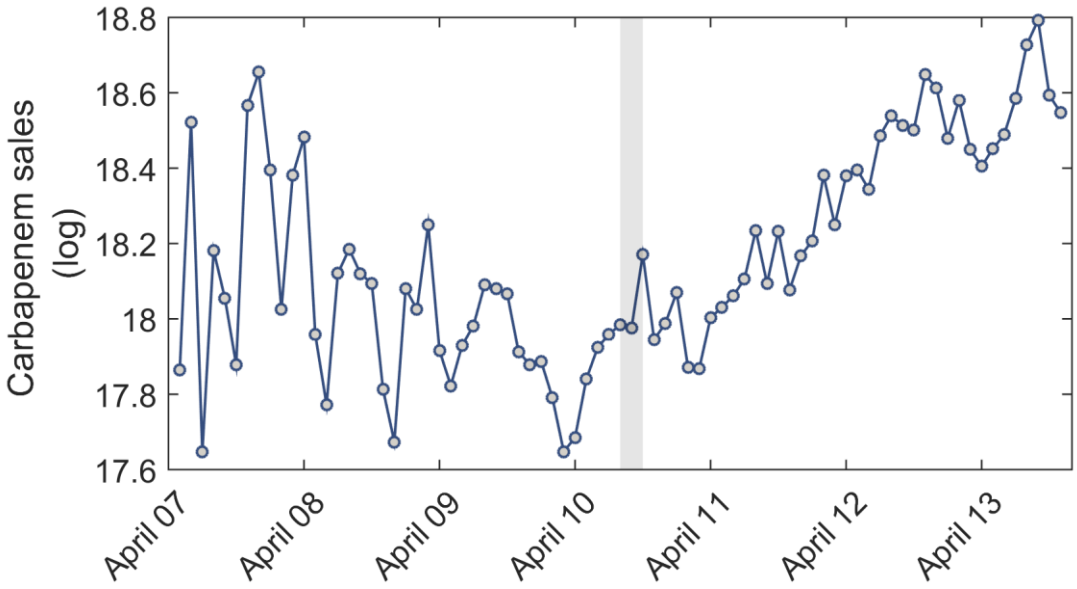


Figure 5. Multinational Share in Sales and Monetary terms during pre- and post-treatment periods (separated by the vertical line) in the Carbapenems and Narrow-spectrum Antibiotics Markets. Multinational market shares show a steep decline both in terms of sales (left panel) and monetary sales (right panel) in the post-treatment period while the corresponding share in the market for narrow spectrum antibiotics remain stable. The x-axis denotes the number of months (data spans over 79 months from April 2007 to October 2013). Source: AIOCD Pharmatrac.

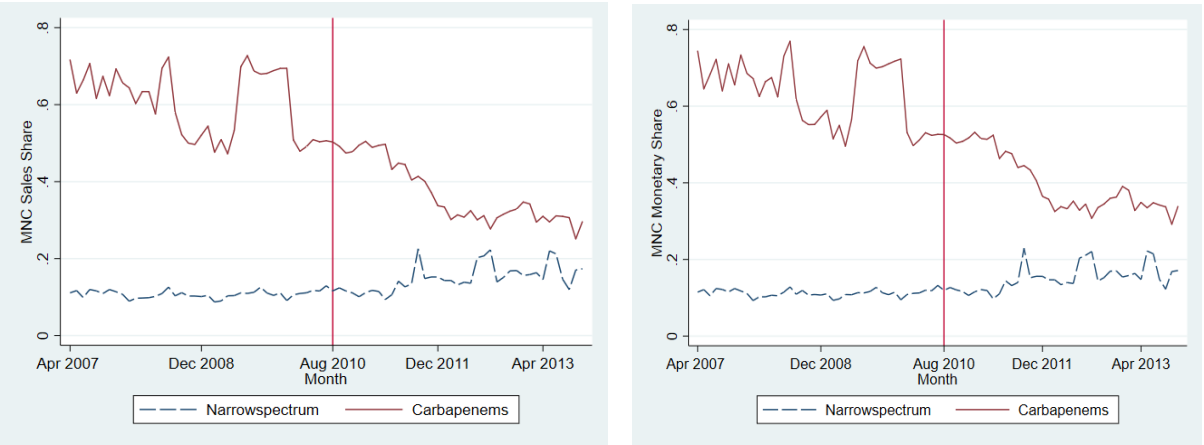


Figure 6. Coefficient Estimates from Equation 11 of year-Carbapenem Interaction Dummies: In the pre-treatment period, the coefficients are statistically zero and in the post-treatment period, they are negative. We conclude an absence of pre-trends in multinational sales (left panel) and monetary shares (right panel).

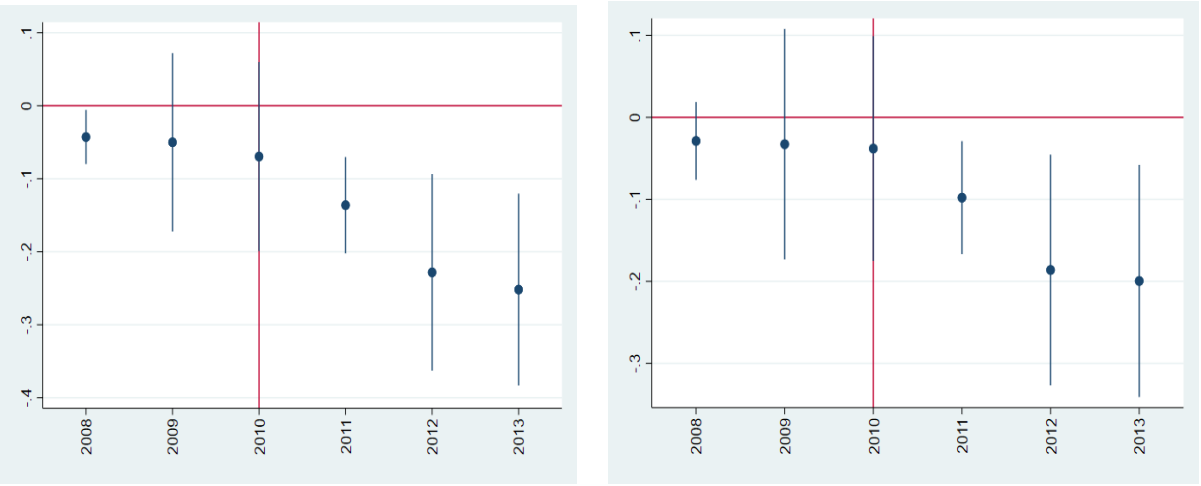


Figure 7. Synthetic Control Results for Multinational Sales Share (left panel) and Monetary Share (right panel). In both cases, the simulated series (synthetic control) is substantially above the realized sales path, indicating a substantial decay in sales in the multinational share in the post-treatment period (treatment period is indicated by the vertical line) compared to the counterfactual of no treatment.

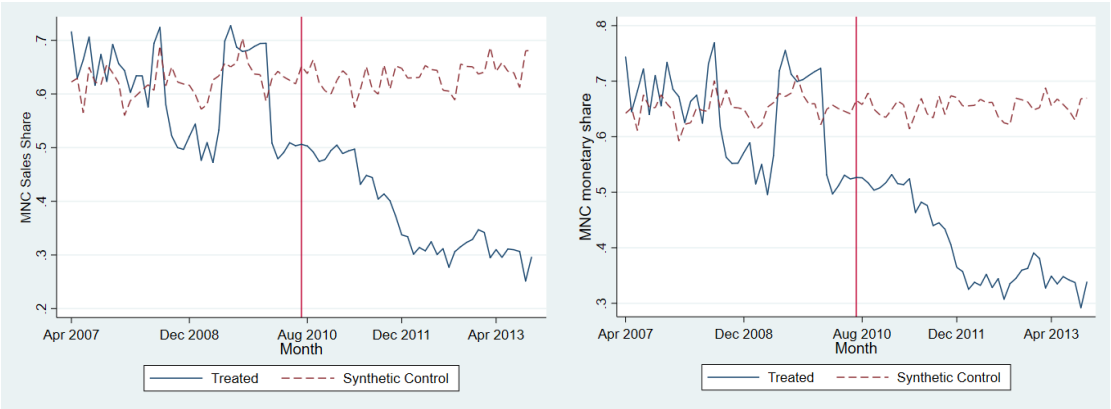


Table 1. Variable description

Dependent variables	**Description**	**Data Source**
MNCshare	We measure MNCshare in two different ways. (a) sales:-Aggregated market share of multinational firms in a particular molecule in particular month in terms of sales in Defined Daily Dosage (DDD). (b) monetary sales:-Aggregated market share of multinational firms in a particular molecule in particular month in terms of sales revenue (Rs).	AIOCD Pharmatrac
log (Sales)	Logarithm of sales in Defined Daily Doses (DDD) of a particular firm for a particular molecule in a particular month.	AIOCD Pharmatrac
Prescriptionshare	Aggregated market share of multinational firms in a particular molecule in particular month in terms of prescriptions written.	IQVIA Prescription Audit Database-India
Invsine (Bonus)	Inverse sine transform of Bonus in Defined Daily Doses (DDD) of a particular firm for a particular molecule in a particular month.	AIOCD Pharmatrac
log (Prescriptions)	Logarithm of prescriptions of a particular firm for a particular molecule in a particular month.	IQVIA Prescription Audit Database-India
log (Prescription per Physician)	Logarithm of prescriptions per physician of a particular firm for a particular molecule in a particular month.	IQVIA Prescription Audit Database-India
log (Sales (US))	Logarithm of focal molecule sales in standard units in a particular month.	IQVIA US drug sales database
log (Revenue (US))	Logarithm of focal molecule revenue (US $) in a particular month.	IQVIA US drug sales database
Independent variables	**Description**	
NDMdummy	0 for months before August 2010 and 1 after August 2010 (*NDM-1 article appeared online in August 2010*).	
Carbapenem	Molecules belonging to the carbapenem (ATC code J01DH) have a value of 1, otherwise 0.	
NDMdummy × Carbapenem	Interaction term between variables NDMdummy and Carbapenem. It takes the value one for carbapenem from August 2010.	
MNC	1 if a firm had majority foreign ownership as on August 2010, otherwise 0.	IQVIA Prescription Audit Database-India and CMIE Prowess
MNC × NDMdummy × Carbapenem	Interaction term between variables, MNC, NDMdummy and Carbapenem. It takes the value one for carbapenem molecules sold by MNC from August 2010.	
Year	Dummy variable for each year from 1 (2007) to 7(2013).	
Placebotreatmentapril2008	0 for months before April 2008 and 1 after April 2008.	

Placebotreatmentapril2008 × Carbapenem	Interaction term between variables Placebotreatmentapril2008 and Carbapenem. It takes the value one for carbapenem from April 2008.	
Control variables	**Description**	
Total monetary sales	Total revenue of a particular molecule in a particular month aggregated over all the firms (in Rs. million).	AIOCD Pharmatrac
log (Price)	Logarithm of average maximum retail price in Rs. per DDD of molecule.	AIOCD Pharmatrac
Time	Dummy variable for each month *t* where *t* ranges from 1 (April 2007) to 79 (October 2013).	
Molecule	Dummy variable for each molecule *m.*	AIOCD Pharmatrac
Firm	Dummy variable for each firm.	AIOCD Pharmatrac
Molecule × Firm	Interaction between molecule dummies and firm dummies.	AIOCD Pharmatrac
Molecule × Calendar month	Interaction of calendar month with molecule to account for seasonality.	AIOCD Pharmatrac
Geography	Dummy variable for each geographical region *g* covering 23 geographical markets in India.	AIOCD Pharmatrac
Molecule × Geography	Interaction between molecule dummies and geography dummies.	AIOCD Pharmatrac
Geography × Time	Interaction between geography dummies and time dummies.	AIOCD Pharmatrac

Table 2. 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 carbapenems sold by multinationals decreased in terms of sales, monetary sales and prescriptions compared to narrow-spectrum antibiotics.

	(1)			**(2)**		
	Narrow spectrum pre-treatment			**Narrow spectrum post-treatment**		
	mean	sd	Count	mean	sd	Count
MNCshare (sales)	0.1076	0.2487	591	0.1471	0.2865	461
MNCshare (monetary sales)	0.1119	0.2646	591	0.1498	0.3016	461
HHI (sales)	0.6843	0.2986	591	0.7030	0.3172	461
Number of firms	11.5296	19.9636	591	9.0868	13.0937	461
Total monetary sales (Rs. million)	26.4	55.0	591	34.8	63.7	461

	(3)			**(4)**		
	Carbapenem pre-treatment			**Carbapenem post-treatment**		
	mean	sd	Count	mean	sd	Count
MNCshare (sales)	0.5992	0.3447	100	0.3636	0.3263	179
MNCshare (monetary sales)	0.6280	0.3317	100	0.3948	0.3304	179
HHI (sales)	0.4496	0.3273	100	0.4777	0.3527	179
Number of firms	15.3100	11.3464	100	14.2011	12.9165	179
Total monetary sales (Rs. million)	148.0	102.0	100	106.0	109.0	179

	(5)			**(6)**		
	Narrow spectrum pre-treatment (prescription)			**Narrow spectrum post-treatment (prescription)**		
	mean	sd	Count	mean	sd	Count
Prescriptionshare	0.0260	0.1324	353	0.0673	0.2483	258
Number of firms	10.9518	19.0459	353	8.5271	11.6566	258
HHI (Prescriptions)	0.5956	0.2974	353	0.5718	0.2968	258
Total prescriptions	438897	900373	353	431824	682620	258

	(7)			**(8)**		
	Carbapenem pre-treatment (prescription)			**Carbapenem post-treatment (prescription)**		
	mean	sd	Count	mean	sd	Count
Prescriptionshare	0.2628	0.4069	56	0.1544	0.3401	41
Number of firms	2.3929	1.3028	56	1.4390	0.7433	41
HHI (Prescriptions)	0.5794	0.2641	56	0.4485	0.2808	41
Total prescriptions	687.3036	615.1142	56	528.1951	519.7750	41

Table 3. Multinational Shares in Sales, Monetary Sales and Prescriptions fall in Carbapenems after NDM-1 publication. We estimate impact of NMD-1 publication on Multinationals' market shares as per Equation 7 in terms of sales (Models 1 and 2) and monetary sales (Models 3 and 4) and find that market share decreased significantly in the post-treatment period compared to the pre-treatment period, in both OLS and fractional probit estimation. Quantitatively and qualitatively similar effects are seen in physicians' prescribing pattern (Equation 9) as well (Model 5). Constant term is included in all the specifications but not reported. Time horizon is April 2007- October 2013.

	(1) **MNCshare (sales) (OLS)**	(2) **MNCshare (sales) (fractional probit)**	(3) **MNCshare (monetary sales) (OLS)**	(4) **MNCshare (monetary sales) (fractional probit)**	(5) **Prescription Share (fractional probit)**
NDMdummy	0.0000	-0.5292*	0.0000	-0.6089**	4.5358***
	(.)	(0.2771)	(.)	(0.2660)	(1.4715)
Carbapenem	0.0000	4.5050***	0.0000	4.7591***	4.2116***
	(.)	(0.3514)	(.)	(0.3820)	(1.0533)
NDMdummy × Carbapenem	-0.1391***	-0.6501***	-0.1142**	-0.5655**	-4.7347***
	(0.0463)	(0.2174)	(0.0530)	(0.2389)	(1.4736)
Total monetary sales	0.0006***	0.0040***	0.0007***	0.0047***	
	(0.0001)	(0.0013)	(0.0002)	(0.0016)	
Time dummies	Yes	Yes	Yes	Yes	Yes
Molecule dummies	Yes	Yes	Yes	Yes	Yes
R^2	0.96		0.97		
Log pseudo likelihood		-244.77		-231.32	-35.23
N	1331	1331	1331	1331	708

Note: Robust clustered standard errors at the molecule level in parentheses; * p<.1, ** p<.05, *** p<.01.

Table 4. Decline in Multinational Sales, Bonus Quantity, Prescriptions & Prescriptions per Physician in Carbapenems after NDM-1 discovery. We estimate impact of NDM-1 publication on firm sales according to Equation 8 and find significantly negative coefficient for the triple interaction term indicate that in the post-treatment period sales of carbapenems decreased for multinational firms in absolute value (Model 1). In our model we instrumented price with retailer margin. Model 2 shows multinational firms offered lesser bonus quantity to retailers compared to local firms, in the post-treatment period. We also estimated impact of NDM-1 publication on prescriptions as per Equation 9 and find that number of prescriptions of carbapenems produced by multinationals decreased in the post-treatment period (Model 3). Similarly, average number of prescriptions per physician (Model 4) also decreased for carbapenems produced by multinationals in the post-treatment period. Constant term is included in all the specifications but not reported. Time horizon is April 2007- October 2013.

	(1) **log (Sales)**	(2) **Invsine (Bonus)**	(3) **log (Prescriptions)**	(4) **log (Prescription per Physician)**
Log (Price)	-0.3228**			
	(0.1452)			
MNC × NDMdummy	0.8045**	1.2301	0.0455	0.2301
	(0.3380)	(0.8980)	(0.2761)	(0.2107)
NDMdummy × Carbapenem	0.7105***	0.8314	0.9073***	-0.3711
	(0.1835)	(0.5208)	(0.2335)	(0.2744)
MNC × NDMdummy × Carbapenem	-1.0394***	-4.0140***	-1.4791***	-1.2693***
	(0.3908)	(1.4190)	(0.5657)	(0.3288)
Time dummies	Yes	Yes	Yes	Yes
Molecule dummies	Yes	Yes	Yes	Yes
Firm dummies	Yes	Yes	Yes	Yes
Molecule × Calendarmonth dummies	Yes	Yes	Yes	Yes
Molecule × Firm dummies	Yes	Yes	Yes	Yes
R^2	0.02	0.01	0.86	0.51
First stage F	520.24			
N	15047	15050	6232	6232

Note: Robust clustered standard errors at the molecule-firm level in parentheses; * p<.1, ** p<.05, *** p<.01.

Table 5. Vintage Effect - Multinational Shares in Sales, Monetary sales and Prescriptions fall more in newer Carbapenems after NDM-1 discovery. We estimate multinationals' market shares as per Equation 7 for with subsample of newer and older carbapenems in terms of sales and monetary sales and find that the market share decreased significantly post the publication of NDM-1 article more in newer carbapenems (Models 1 and 2) compared to older carbapenems (Models 3 and 4). The same feature is seen more aggressively in prescription patterns (Models 5 and 6). Constant term is included in all the specifications but not reported. Time horizon is April 2007- October 2013. All models have been estimated via fractional probit specification.

	(1) **MNCshare (sales) (newer carbapenems)**	(2) **MNCshare (monetary sales) (newer carbapenem)**	(3) **MNCshare (sales) (older carbapenems)**	(4) **MNCshare (monetary sales) (older carbapenems)**	(5) **Prescription share (newer carbapenems)**	(6) **Prescription share (older carbapenems)**
NDMdummy	-0.2923	-0.3870	-0.3072	-0.3694**	2.2926***	3.4384***
	(0.3114)	(0.2925)	(0.2063)	(0.1726)	(0.7679)	(0.7670)
Carbapenem	0.4832*	0.5243**	4.1933***	4.3066***	13.2898***	2.1961**
	(0.2602)	(0.2660)	(0.2076)	(0.2136)	(0.9205)	(0.8948)
NDMdummy × Carbapenem	-5.3337***	-5.2912***	-0.4342***	-0.3149**	-12.1298***	-1.7108
	(0.1818)	(0.1817)	(0.1273)	(0.1278)	(0.9489)	(1.0545)
Total monetary sales	0.0015	0.0013	0.0026***	0.0030***		
	(0.0018)	(0.0016)	(0.0005)	(0.0004)		
Time dummies	Yes	Yes	Yes	Yes	Yes	Yes
Molecule dummies	Yes	Yes	Yes	Yes	Yes	Yes
Log pseudo likelihood	-156.29	-139.93	-218.49	-204.69	-17.65	-28.82
N	1150	1150	1233	1233	629	690

Note: Robust clustered standard errors at the molecule level in parentheses; * p<.1, ** p<.05, *** p<.01.

Table 6a. Robustness of Baseline Results for sales after accounting for Regional Heterogeneity. Even after accounting for regional heterogeneity expanding the unit of observation at the regional level within India, multinationals' market share in carbapenems is seen to be significantly reduced in the post-treatment period in both OLS (Models 1 to 3) and fractional probit estimation (Models 4 to 6) with respect to sales. Constant term is included in all the specifications but not reported. Time horizon is April 2007- October 2013.

	(1) **MNCshare (sales) (OLS)**	(2) **MNCshare (sales) (OLS)**	(3) **MNCshare (sales) (OLS)**	(4) **MNCshare (sales) (fractional logit)**	(5) **MNCshare (sales) (fractional logit)**	(6) **MNCshare (sales) (fractional logit)**
NDMdummy	0.0000	0.0000	0.0000	-0.2423**	-0.2698**	-0.5988*
	(.)	(.)	(.)	(0.1111)	(0.1284)	(0.3236)
Carbapenem	0.0000	0.0000	0.0000	5.0376**	0.6827*	0.5116
	(.)	(.)	(.)	(1.9969)	(0.3616)	(0.4294)
NDMdummy	-0.1490***	-0.1406***	-0.1393***	-0.5633***	-0.5856***	-0.5825***
× Carbapenem	(0.0247)	(0.0241)	(0.0241)	(0.0992)	(0.1102)	(0.1037)
Total monetary sales	0.0056***	0.0035*	0.0037*			
	(0.0016)	(0.0021)	(0.0020)			
Geography dummies	Yes	Yes	Yes	Yes	Yes	Yes
Molecule-Geography dummies	No	Yes	Yes	No	Yes	Yes
Geography-Time dummies	No	No	Yes	No	No	Yes
R^2	0.78	0.86	0.87			
Log pseudo likelihood				-5464.03	-4783.45	-4608.88
N	22540	22528	22528	22540	22540	22540

Table 6b. Robustness of Baseline Results in terms of monetary sales after accounting for Regional Heterogeneity. Even after accounting for regional heterogeneity expanding the unit of observation at the regional level within India, multinationals' market share in carbapenems is seen to be significantly reduced in the post-treatment period in both OLS OLS (Models 1 to 3) and fractional probit estimation (Models 4 to 6) with respect to monetary sales. Constant term is included in all the specifications but not reported. Time horizon is April 2007- October 2013.

	(1) **MNCshare (monetary sales) (OLS)**	(2) **MNCshare (monetary sales) (OLS)**	(3) **MNCshare (monetary sales) (OLS)**	(4) **MNCshare (monetary sales) (fractional logit)**	(5) **MNCshare (monetary sales) (fractional logit)**	(6) **MNCshare (monetary sales) (fractional logit)**
NDMdummy	0.0000	0.0000	0.0000	-0.2973***	-0.3332**	-0.9559***
	(.)	(.)	(.)	(0.1140)	(0.1319)	(0.2841)
Carbapenem	0.0000	0.0000	0.0000	4.8518	0.5215	0.4141
	(.)	(.)	(.)	(.)	(0.3643)	(0.4383)
NDMdummy × Carbapenem	-0.1209***	-0.1122***	-0.1112***	-0.4278***	-0.4325***	-0.4227***
	(0.0257)	(0.0251)	(0.0252)	(0.1039)	(0.1153)	(0.1099)
Total monetary sales	0.0056**	0.0037*	0.0039*			
	(0.0019)	(0.0024)	(0.0023)			
Geography dummies	Yes	Yes	Yes	Yes	Yes	Yes
Molecule-Geography dummies	No	Yes	Yes	No	Yes	Yes
Geography-Time dummies	No	No	Yes	No	No	Yes
R^2	0.79	0.87	0.88			
Log pseudo likelihood				-5260.68	-4611.71	-4429.51
N	22540	22528	22528	22540	22540	22540

Note: Robust clustered standard errors at the Molecule-Geography level in parentheses; * p<.1, ** p<.05, *** p<.01. All models include time and molecule fixed effects

Table 7. Robustness of Baseline Results with Alternate Control Group of Other Broad Spectrum Antibiotics. Instead of narrow spectrum antibiotics, here we consider broad spectrum antibiotics (86 molecules) other than carbapenem itself, to constitute the control group and estimate impact of NDM-1 publication on MNCshare (Equation 7) Since this is a within group comparison, the effects are expected to be muted. We see that multinationals' sales share in carbapenem has decreased significantly (Models 1 and 2), the results for monetary sales share are negative but insignificant (Models 3 and 4). Constant term is included in all the specifications but not reported. Time horizon is April 2007- October 2013.

	(1) **MNCshare (sales) (OLS)**	(2) **MNCshare (sales) (fractional probit)**	(3) **MNCshare (monetary sales) (OLS)**	(4) **MNCshare (monetary sales) (fractional probit)**
NDMdummy	0.0000	-0.3928	0.0000	-0.3532
	(.)	(0.2427)	(.)	(0.2357)
Carbapenem	0.0000	-1.0567***	0.0000	-1.0789***
	(.)	(0.2583)	(.)	(0.2840)
NDMdummy × Carbapenem	-0.1146**	-0.4040*	-0.0933	-0.3309
	(0.0533)	(0.2235)	(0.0606)	(0.2491)
Total monetary sales	0.0000	0.0003	0.0000	0.0004
	(0.0001)	(0.0006)	(0.0001)	(0.0006)
Time dummies	Yes	Yes	Yes	Yes
Molecule dummies	Yes	Yes	Yes	Yes
R^2	0.94		0.95	
Log pseudo likelihood		-1299.14		-1343.92
N	6057	6057	6057	6057

Note: Robust clustered standard errors at the molecule level in parentheses; * p<.1, ** p<.05, *** p<.01.

Online Appendix

Figure A1. Carbapenems and Narrow-spectrum Antibiotics Sales during pre- and post-treatment periods (separated by the vertical line) in the US market. The quantity difference between carbapenems and narrow spectrum remain stable, apart from a dip in the carbapenem sales

in the beginning of the observed time period. However, there is no visible impact of the NDM-1 shock on the US market. The x-axis denotes the number of months (data spans from April 2007 to October 2013 i.e. over 79 months) and y-axis denotes sales in standard units (logarithm). Source: IQVIA US drug sales database.

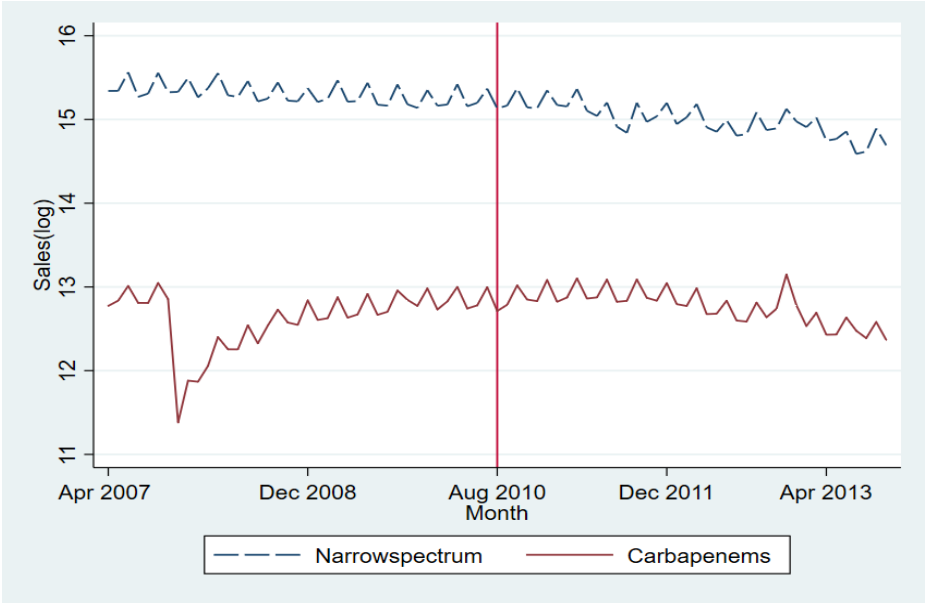
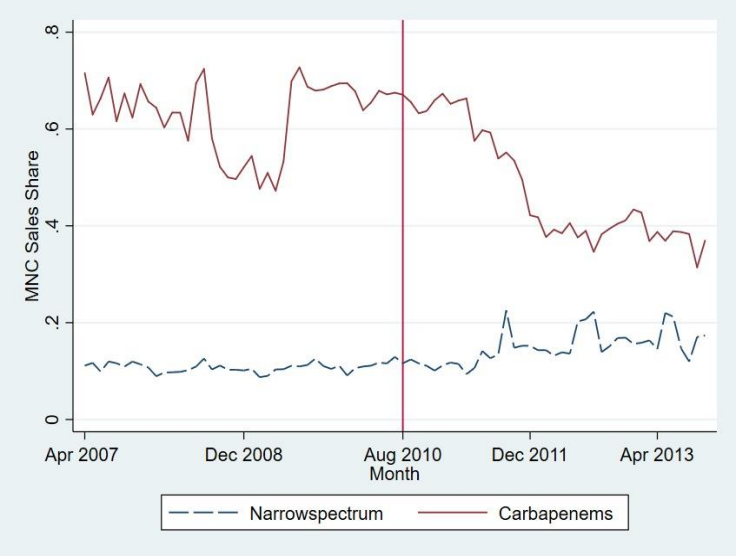


Figure A2. Multinational Share in Sales and Monetary terms during pre- and post-treatment periods (separated by the vertical line) in the Carbapenems and Narrow-spectrum Antibiotics Market, without the newly introduced molecule (Ertapenem). As in the full sample, multinational market shares show a steep decline both in terms of sales (left panel) and monetary sales (right panel) in the post-treatment period while the corresponding share in the market for narrow spectrum antibiotics remain stable. The x-axis denotes the number of months (data spans from April 2007 to October 2013 i.e. over 79 months). Source: AIOCD Pharmatrac.



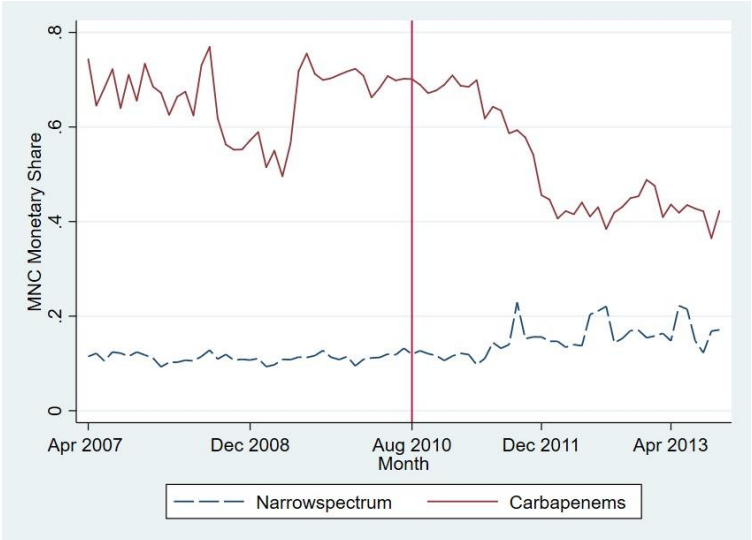


Table A1. Molecule Classification based on ATC-code

Molecule	ATC_code	Classification	US FDA Approval year	US 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 penicillins
DORIPENEM	J01DH04	carbapenem	2007	1994	Carbapenems
ERTAPENEM	J01DH03	carbapenem	2001	1993	Carbapenems
ERYTHROMYCIN	J01FA01	narrow-spectrum	1985	1966	Macrolides
IMIPENEM + CILASTATIN	J01DH51	carbapenem	1985	1975	Carbapenems
MEROPENEM + SULBACTAM	J01DH02	carbapenem	1996	1983	Carbapenems
MEROPENEM	J01DH02	carbapenem	1996	1983	Carbapenems
PENICILLIN G	J01CE01	narrow-spectrum	Before 1982	NA	Beta-lactamase sensitive penicillins
PENICILLIN V	J01CE02	narrow-spectrum	Before 1982	NA	Beta-lactamase sensitive penicillins

Table A2: Antibiotic Classification (orange denotes Broad-spectrum, blue denotes Carbapenems and yellow denotes Narrow-spectrum)

J01A TETRACYCLINES	J01AA Tetracyclines (1950s)					
J01B AMPHENICOLS	J01BA Amphenicols (1950s)					
J01C BETA-LACTAM ANTIBACTERIALS, PENICILLINS	J01CA Penicillins with extended spectrum (1950s)	J01CE Beta-lactamase sensitive penicillins (1940s)	J01CF Beta-lactamase resistant penicillins (1960s)	J01CG Beta-lactamase inhibitors (1970s)	J01CR Combinations of penicillins, incl. beta-lactamase inhibitors	
J01D OTHER BETA-LACTAM ANTIBACTERIALS	J01DB First-generation cephalosporins (1960s)	J01DC Second-generation cephalosporins (1970s)	J01DD Third-generation cephalosporins (1980s)	J01DE Fourth-generation cephalosporins (1980s)	J01DF Monobactams (1980s)	J01DH Carbapenems (1980s)
J01E SULFONAMIDES AND TRIMETHOPRIM	J01EA Trimethoprim and derivatives (1960s)	J01EB Short-acting sulfonamides 1940s)	J01EC Intermediate-acting sulfonamides (1960s)	J01ED Long-acting sulfonamides (1960s)	J01EE Combinations of sulfonamides and trimethoprim, incl. derivatives	
J01F MACROLIDES, LINCOSAMIDES AND STREPTOGRAMINS	J01FA Macrolides (1950s)	J01FF Lincosamides (1960s)	J01FG Streptogramins (1990s)			
J01G AMINOGLYCOSIDE ANTIBACTERIALS	J01GA Streptomycins (1960s)	J01GB Other aminoglycosides				

J01M QUINOLONE ANTIBACTERIALS	J01MA Fluoroquinolones (1960s)	J01MB Other quinolones				
J01R COMBINATIONS OF ANTIBACTERIALS	J01RA Combinations of antibacterials					
J01X OTHER ANTIBACTERIALS	J01XA Glycopeptide antibacterials (1980s)	J01XB Polymyxins (1970s)	J01XC Steroid antibacterials (1960s)	J01XD Imidazole derivatives (1960s)	J01XE Nitrofuran derivatives (1950s)	J01XX Other antibacterials

Table A3: Robustness of Baseline Results in Truncated Sample. This table provides the findings from a truncated sample with an 18 months pre and 18 months post truncated sample as per Equation 7. Results are consistent with our baseline findings in Table 3, where there continues to be decrease in multinationals' market share both in terms of sales and monetary sales. Constant term is included in all the specifications but not reported. Time horizon is April 2009 to March 2012, i.e. 3 years in total.

	(1) MNCshare (sales) (OLS)	**(2) MNCshare (sales) (fractional probit)**	**(3) MNCshare (monetary sales) (OLS)**	**(4) MNCshare (monetary sales) (fractional probit)**	**(5) Prescription share (fractional probit)**
NDMdummy	0.0000	-0.0386	0.0000	-0.0379	1.9746
	(.)	(0.1357)	(.)	(0.1402)	(1.5489)
Carbapenem	0.0000	0.5642	0.0000	0.5392	4.3304**
	(.)	(0.4417)	(.)	(0.4725)	(1.8183)
NDMdummy × Carbapenem	-0.0728**	-0.3573*	-0.0615	-0.3125	-5.1442***
	(0.0325)	(0.2139)	(0.0365)	(0.2290)	(1.7228)
Total monetary sales	0.0008*	0.0051	0.0009*	0.0056	
	(0.0005)	(0.0032)	(0.0005)	(0.0036)	
Time dummies	Yes	Yes	Yes	Yes	Yes
Molecule dummies	Yes	Yes	Yes	Yes	Yes
R^2	0.98		0.99		
Log pseudo likelihood		-105.73		-99.24	-10.19
N	601	602	601	602	311

Note: Robust clustered standard errors at the molecule level in parentheses; * p<.1, ** p<.05, *** p<.01.

Table A4: Robustness of Baseline Results with wild cluster bootstrap error. We have replicated the same model estimation with wild clustered bootstrap error. P-value for coefficient of interest NDMdummy × Carbapenem are reported separately for OLS model. Overall our results are robust even with wild cluster bootstrap error (p-value .001 and .036). We have also controlled for number of firms and our results remain consistent and significant. Constant term is included in all the specifications but not reported. Time horizon is April 2007-October 2013.

	(1) **MNCshare (sales) (OLS)**	(2) **MNCshare (sales) (fractional probit)**	(3) **MNCshare (monetary sales) (OLS)**	(4) **MNCshare (monetary sales) (fractional probit)**	(5) **Prescription share (fractional probit)**
NDMdummy	-0.0643	-0.0636*	-0.6016**	-0.6667**	4.5358***
	(0.0379)	(0.0363)	(0.2669)	(0.2654)	(1.4715)
Carbapenem	0.1484***	0.1434**	4.3801***	4.6481***	4.2116***
	(0.0495)	(0.0571)	(0.2904)	(0.3120)	(1.0533)
NDMdummy × Carbapenem	-0.1133**	-0.0920*	-0.3865*	-0.3324*	-4.7347***
	(0.0408)	(0.0462)	(0.2020)	(0.1900)	(1.4736)
Total Monetary Sales	0.0007***	0.0007***	0.0041***	0.0048***	
	(0.0001)	(0.0002)	(0.0013)	(0.0017)	
Number of firms	-0.0023	-0.0020	-0.0168*	-0.0150	
	(0.0015)	(0.0014)	(0.0102)	(0.0101)	
Time dummies	Yes	Yes	Yes	Yes	Yes
Molecule dummies	Yes	Yes	Yes	Yes	Yes
R^2	.96	.97			
Log pseudo likelihood			-244.10	-230.82	-32.66
wildbootpvalue	0.0010	0.0360			
N	1331	1331	1331	1331	708

Note: Robust clustered standard errors at the molecule level in parentheses; * p<.1, ** p<.05, *** p<.01.

Table A5: Robustness Of Baseline Results with Alternate Control Group of all other Antibiotics (WHO ATC J01 class). Instead of narrow spectrum antibiotics, we consider all other antibiotics other than carbapenems itself, to constitute the control group. Since this is a within group comparison, the effects are expected to be muted. We see that multinationals' sales share in carbapenems has decreased significantly (Models 1 and 2), the results for monetary sales share (Model 3 and 4) and Prescriptionshare (Model 5) are negative but insignificant. Constant term is included in all the specifications but not reported. Time horizon is April 2007- October 2013.

	(1) MNCshare (sales) (OLS)	**(2) MNCshare (sales) (fractional probit)**	**(3) MNCshare (monetary sales) (OLS)**	**(4) MNCshare (monetary sales) (fractional probit)**	**(5) Prescription share (fractional probit)**
NDMdummy	0.0000	-0.3104**	0.0000	-0.2961*	-0.3034***
	(.)	(0.1559)	(.)	(0.1519)	(0.1173)
Carbapenem	0.0000	4.6156***	0.0000	4.7825***	0.5484***
	(.)	(0.2785)	(.)	(0.3005)	(0.1483)
NDMdummy × Carbapenem	-0.1142**	-0.4076*	-0.0917	-0.3260	-1.4535
	(0.0527)	(0.2217)	(0.0601)	(0.2475)	(1.1067)
Total monetary sales	0.0000	0.0004	0.0001	0.0006	
	(0.0001)	(0.0005)	(0.0001)	(0.0005)	
Time dummies	Yes	Yes	Yes	Yes	Yes
Molecule dummies	Yes	Yes	Yes	Yes	Yes
R^2	0.93		0.93		
Log pseudo likelihood		-2246.52		-2321.69	-1963.14
N	10426	10426	10426	10426	8785

Note: Robust clustered standard errors at the molecule level in parentheses; * p<.1, ** p<.05, *** p<.01.

Table A6: Robustness of Baseline Results without Ertapenem (the molecule with zero presence of MNCs). In this exercise, we replicate the main estimation (Equation 7) exercise by taking out Ertapenem from the group of molecules. The reason is that Ertapenem was introduced in 2010 and were sold exclusively by domestic firms, thereby potentially biasing the MNC shares. All results continue to hold in the truncated sample. Constant term is included in all the specifications but not reported. Time horizon is April 2007- October 2013.

	(1) **MNCshare (sales) (OLS)**	(2) **MNCshare (sales) (fractional probit)**	(3) **MNCshare (monetary sales) (OLS)**	(4) **MNCshare (monetary sales) (fractional probit)**
NDMdummy	0.0000	-0.5292*	0.0000	-0.6089**
	(.)	(0.2775)	(.)	(0.2663)
Carbapenem	0.0000	4.5051***	0.0000	4.6638***
	(.)	(0.3518)	(.)	(0.3833)
NDMdummy × Carbapenem	-0.1538***	-0.6500***	-0.1266**	-0.5656**
	(0.0504)	(0.2177)	(0.0589)	(0.2392)
Total monetary sales	0.0007***	0.0040***	0.0007***	0.0047***
	(0.0001)	(0.0013)	(0.0002)	(0.0016)
Time dummies	Yes	Yes	Yes	Yes
Molecule dummies	Yes	Yes	Yes	Yes
R^2	0.96		0.97	
Log pseudo likelihood		-244.77		-231.32
N	1286	1286	1286	1286

Note: Robust clustered standard errors at the molecule level in parentheses; * p<.1, ** p<.05, *** p<.01.

Table A7: Robustness of Baseline Results with respect to Placebo Treatment date (before the actual treatment). In this exercise, we replicate the main estimation (Equation 7) with an additional alternate placebo treatment dated April 2008, to rule out pre-trends. The first appearance of the NDM-1 was in April 2008 which may potentially create a treatment effect before the Lancet publication, resulting in a pre-trend. The results are pre-dominantly insignificant with the OLS estimates (Models 1 and 3) or marginally significant with the fractional probit estimates (Models 2 and 4). Constant term is included in all the specifications but not reported. Time horizon is April 2007- October 2013.

	(1) **MNCshare (sales) (OLS)**	(2) **MNCshare (sales) (fractional probit)**	(3) **MNCshare (monetary sales) (OLS)**	(4) **MNCshare (monetary sales) (fractional probit)**
Placebotreatmentapril2008	0.0000	-0.0726	0.0000	-0.1243
	(.)	(0.1670)	(.)	(0.1802)
Carbapenem	0.0000	4.7091***	0.0000	4.9197***
	(.)	(0.3436)	(.)	(0.3636)
Placebotreatmentapril2008 × Carbapenem	-0.0547	-0.2734	-0.0316	-0.2159
	(0.0395)	(0.1986)	(0.0432)	(0.1728)
NDMdummy	0.0000	-0.3904*	0.0000	-0.4307*
	(.)	(0.2308)	(.)	(0.2413)
NDMdummy × Carbapenem	-0.1253**	-0.5859**	-0.1062	-0.5162**
	(0.0580)	(0.2428)	(0.0651)	(0.2634)
Total monetary sales	0.0006***	0.0041***	0.0006***	0.0048***
	(0.0002)	(0.0014)	(0.0002)	(0.0017)
Time dummies	Yes	Yes	Yes	Yes
Molecule dummies	Yes	Yes	Yes	Yes
R^2	.96		.96	
Log pseudo likelihood		-244.60		-231.22
N	1331	1331	1331	1331

Note: Robust clustered standard errors at the molecule level in parentheses; * p<.1, ** p<.05, *** p<.01.

Table A8: Discovery of NDM-1 does not Impact US Markets for Antibiotics. We estimate the main model with the US data with impact on overall sales (in standard units) and revenue (US $) for the matched list of four carbapenem molecules and six narrow-spectrum molecules. The results are insignificant indicating there is no response to NDM-1 publication in the US market. Constant term is included in all the specifications but not reported. Time horizon is April 2007- October 2013.

	(1) **log (Sales (US))**	(2) **log (Revenue (US))**
NDMdummy	0.0000	0.0000
	(.)	(.)
Carbapenem	0.0000	0.0000
	(.)	(.)
NDMdummy × Carbapenem	-0.2404	0.0754
	(0.4015)	(0.3636)
Time dummies	Yes	Yes
Molecule dummies	Yes	Yes
R^2	0.93	0.86
N	779	780

Note: Robust clustered standard errors at the molecule level in parentheses; * p<.1, ** p<.05, *** p<.01.