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Product patents and access to innovative medicines

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ABSTRACT

Enacted in 1995, the Agreement on Trade-Related Aspects of Intellectual Property Rights of the World Trade Organisation makes it obligatory for member states to protect pharmaceutical product patents, which has great impacts on global access to medicines. This paper analyses the impact of patents on the availability and affordability of new and innovative medicines in a post-TRIPS era. Our data from IQVIA covers 578 molecules in 70 countries. Using launch data from 1980 to 2017, we find that introducing product patents is important for innovative medicines by speeding up their launch by 14 percent. Innovative medicines are launched sooner than non-innovative ones irrespective of patent regimes. However, we find little evidence that either patentability or innovativeness improves drug availability in low-income countries. With regard to differential pricing, a firm-level strategy to achieve affordable prices for patented medicines, we find that overall, from 2007 to 2017, originator medicine prices are adjusted to local income levels by only 11 percent and generic medicine prices by 26 percent. Prices of generic HIV/AIDS, malaria, and tuberculosis medicines are much better adjusted to local income—by 69 percent—suggesting that disease-specific global policy responses have led to more affordable prices benefiting people with these diseases in poor countries. Also, brand competition in the molecule market can effectively drive down prices of both originator and generic medicines, implying that multiple generic entry is crucial to achieving drug affordability.

1. Introduction

Enacted in 1995, the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) of the World Trade Organisation (WTO) makes it obligatory for WTO members to protect pharmaceutical product patents. Despite the transition periods for implementation, this obligation of product patents for pharmaceuticals has been the most controversial in the context of access to new, innovative medicines. Access to medicines generally includes two distinct components: availability and affordability. While patent protection may promote the availability of new medicines by speeding up launches, such protection may also lead to unaffordable prices of patented medicines ('t Hoen, 2002). One market-based mechanism that pharmaceutical firms could adopt is voluntary differential pricing. However, whether—and to what extent—differential pricing can achieve the affordability of new medicines is open to empirical examination. In response to debates over the impacts of patents on access to medicines, this study comprehensively investigates both availability and affordability of new and innovative medicines and poses two questions in this context:

(1) How does allowing pharmaceutical product patents affect the time lag between the first introduction of the medicine anywhere in the world and in the country under study or launch speed of new and innovative medicines across countries?
(2) For those launched medicines, how much do firms adjust their prices to local income levels to make these products affordable (i.e. differential pricing)?

A drug launch refers to the first appearance of a new molecule on a market (Cockburn et al., 2016). Note that in order to launch new medicines that show promise at the laboratory stage in any market, their safety and efficacy generally need to be tested by originator companies on humans in progressively costly phased clinical trials with a view to obtaining regulatory approvals. Launch by originator brands makes the same medicine available in markets other than where it was originally launched. Launch in a market after first launch anywhere in the world, could mean submission of additional clinical trials to obtain regulatory approvals or could just mean reliance on the regulatory approvals given elsewhere. Launch by original brand is theoretically more likely where

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there is patent protection enabling monopoly and high prices; whereas launch by a generic will most likely be where no patent for that product has been filed or granted and is likely to be delayed as despite no patent barrier, it takes time to imitate original medicines that have launched anywhere in the world.

While building on the previous literature, our paper adds to the literature in many important ways (Cockburn et al., 2016). First, we study how drug innovativeness affects the launch speed and pricing strategies of new medicines. Throughout this paper, we rely on the classification of drug innovativeness defined in Lanthier et al. (2013), where innovative medicines are USFDA-approved medicines either being first in class or having received a priority review. Second, we measure affordability by accounting for competition in the molecule market in addition to that in the therapeutic group market used in previous studies (Danzon et al., 2015), which has shown to be effective in driving down drug prices. Third, we distinguish between medicines that treat different diseases as well as countries' income levels, which enables us to investigate access to new medicines in heterogeneous populations, especially those living in poor countries and those with diseases of global concern, such as HIV/AIDS.

Our empirical analyses are based on pharmaceutical data from IQVIA (previously IMS Health and Quintiles) for 578 molecules in up to 70 country markets. In our dataset, a market refers to a country in most cases (66 out of 70), while in a few cases, a market refers to a territory with a high degree of autonomy (i.e. Hong Kong and Puerto Rico), or a country group in which member states are located in the same region and have a similar legal tradition (i.e. French West Africa and Central America). For easier understanding, we use country instead of market throughout the paper. The detailed market information is presented in Appendix. Our launch data is from 1980 to 2017 and price data from 2007 to 2017. In summary, we find that pooling over all countries, introducing pharmaceutical product patents increases the launch likelihood of innovative medicines by 14 percent. Innovative medicines are launched sooner than non-innovative ones irrespective of the patent regime in high- and middle-income countries. However, neither patentability nor innovativeness matters for the availability of new medicines in low-income countries. With regard to drug affordability and differential pricing, we find that on average, originator drug prices differentiate by only 11 percent and generic drug prices by 26 percent relative to local income levels. Thus, differential pricing of originator medicines alone is unlikely to achieve drug affordability in low- and middle-income countries (LMIC). Prices of generic medicines that treat HIV/AIDS, malaria, and tuberculosis (TB) are much better adjusted to local income—by 69 percent—suggesting that by promoting access to cheaper generics, disease-specific global response has benefitted greatly to people with these disease in poor countries. Last, brand competition within a molecule market can effectively drive down drug prices of both originator and generic products, implying that the generic entry of new, innovative medicines is critical to achieving drug affordability.

This paper is organised as follows. **Introduction** provides the background and relevant literature for this study. The section **Data and Method** introduces data and empirical methods for analyses. The section **Results** presents our findings on drug launch and differential pricing. We discuss limitations in **Discussion.** The last section concludes this paper.

1.1. Pharmaceutical product patents and TRIPS

Product patent protection is crucial to the R&D-based pharmaceutical industry. Among multiple patents associated with a new medicine, the originator firms file primary patent applications, i.e. the most important patent to protect new compounds, at an early stage in the R&D process, and as the R&D process advances, secondary patents, e.g. patents on forms, dosages, formulations, are filed following the primary patent (Sampat and Shadlen, 2015). This study focuses on the primary patent on pharmaceutical products given the strong relevance to market exclusivity. Although the drug development timeline varies case by case (Sampat and Shadlen, 2015), on average, it takes 8–12 years from filing the primary molecule patent to commercialisation of a new medicine (European Commission, 2009; Grabowski and Kyle, 2007; Mestre-Ferrandiz et al., 2012; Office of Technology Assessment, 1993; Sternitzke, 2010; Wagner and Wakeman, 2016). Given the high cost of each new medicine (DiMasi et al., 2016; Mestre-Ferrandiz et al., 2012), patent rights are critical to the originator seeking to maximise profits by ruling out generic competitors. Conversely, in the absence of patent rights, once the originator launches its new medicine anywhere in the world, other manufacturers could easily copy it accurately through reverse engineering and sell those resulting generics at a lower price to capture a large market share. Therefore, in countries where quality generic copies can easily enter the market due to lack of patent protection, originators may choose not to launch their new medicines as they may not be willing to compete at such low prices.

Since the 1990s, a number of countries have introduced patent protection for pharmaceutical products, which is largely attributed to the requirement in TRIPS. Before this, the decision to introduce such protection or not was the preserve of sovereign decision making in each jurisdiction. Since the establishment of the WTO in 1995, WTO Members, and those seeking accession, had to generally accept the provisions of all WTO agreements, including TRIPS. TRIPS requires WTO Members to make available patent protection for any inventions, whether products or processes, for a minimum duration of 20 years from the date of filing of the patent application, in all fields of technology. Given the transition periods, developing country members had to introduce product patents in fields of technology previously excluded, such as pharmaceuticals, by 2005 (under the so-called mailbox system, developing countries were required to accept pharmaceutical product patent filing from 1995, but not all developing countries invoked this system), while least developed countries (LDCs) have been given time up to 2033. Therefore, by 2005, pharmaceutical product patents were meant to be available for all WTO members, except LDCs.

The public health debate over pharmaceutical patents focuses on the lack of access to patented medicines in LMICs. Although the patent regime is not the only barrier for access to medicines in the real world, and some countries still suffer from insufficient supply of off-patent medicines due to poverty, small market size, the absence of generic substitution regulations, and low local production capacity for pharmaceuticals (Attaran, 2004; Chaudhuri et al., 2010; Kaplan et al., 2012), patent protection is considered the most critical institutional factor that determines the drug availability and affordability in LMICs. During the patent term, if the originator does not launch its patented product in the country or if the launched product is too expensive to be affordable, patients in need of this medicine may be undertreated or left untreated; whereas in the absence of patents, these patients' healthcare needs could be met through locally produced or imported low-priced generics.

1.2. Economic studies on patents and access to medicines

For availability of new medicines, previous studies have found that price control policies, firm characteristics, and the regulatory environment matter for launch decisions of originators (Danzon et al., 2005; Kyle, 2006, 2007; Varol et al., 2012). The importance of the patent regime on global drug diffusion has been studied by Cockburn et al. (2016). Using launch data from 1983 to 2002 in 76 countries, they find that while price regulation delays drug launch, longer and more extensive patent rights accelerate it.

With respect to differential pricing or tiered pricing, the segmentation of pharmaceutical markets enables pharmaceutical firms to sell their products at lower prices in LMICs as compared to high-income countries, yielding improvement in drug affordability despite patent rights (Batson, 1998). The extent to which drug prices are adjusted to local income levels by producers is open to empirical study. Danzon and Furukawa (2008) present the stylistic facts on price differentiation

across 12 countries in 2005. Compared to the prices in the United States, originator products are cheaper in other countries, while generics are cheaper in the United States. Flynn, Hollis, and Palmedo (2009) hypothesise that the R&D-based pharmaceutical firms set prices of their products based on local income distribution. In markets with high income inequality, such firms have no interest in tiered pricing but tend to sell a small quantity to the very rich at a high price. This positive association between income inequality and drug prices has been empirically verified in Danzon et al. (2015).

2. Data and Method

We briefly describe our data in this section. Details of data sources, caveats, and the adjustments made to data are presented in the online Appendix.

2.1. Pharmaceutical data and IQVIA database

Inspired by previous work where a distinction was made between the USFDA-approved drugs and others (Cockburn et al., 2016), we distinguish between innovative medicines and non-innovative ones based on a previous classification for 645 new molecular entities (NMEs) approved by the USFDA from 1987 to 2011 (Lanthier et al., 2013). Three distinct sub-categories of NMEs are provided according to drug innovativeness: first-in-class drugs are drugs presenting a new pathway for treating a disease and being the first drug approved in the respective drug class; advance-in-class drugs, not being first in class but receiving a priority review designation from the USFDA, suggesting a potential of major advances in treatment; addition-to-class drugs (i.e. the remainder of drugs), providing modest additional benefit relative to other drugs. In this study, we define NMEs classified in first-in-class and advance-in-class sub-categories as innovative medicines, and those in the addition-to-class sub-category are non-innovative medicines. We assume that the United States, being one of the most important markets for new medicines, is likely to see the earliest introduction of innovative (be they first-in-class or advance-in-class) medicines. We understand that this is a reasonable—though not exact—proxy for innovativeness.

Our pharmaceutical data is provided by IQVIA (2018Q1 version), which covers 70 country markets. Among the 645 NMEs examined in Lanthier et al. (2013), 578 molecules are or were protected by product patents in at least one country based on the product classification used in IQVIA, so we restrict our sample to these 578 molecules, consisting of 307 innovative ones (of which 180 are first-in-class and 127 are advance-in-class) and 271 non-innovative ones. We present these new medicines by innovativeness and by disease category in Table 1.

2.1.1. Launch data

Of these 578 molecules, we have the launch data for only 556 molecules whose global launch took place from 1980 to 2011. Among the 578 molecules approved by the USFDA from 1987 to 2011, 22 molecules were launched in countries other than the USA before 1980. We dropped these molecules as we were unsure whether this counterintuitive launch data could be considered to be unreliable.

A launch date is defined as the date when a new medicine is first sold in a country, irrespective of whether it is marketed by the originator or a generic firm; the global launch date is the earliest launch date of the molecule anywhere in the 70 countries for which we have data (Cockburn et al., 2013). By the end of 2017, 64 percent of possible launch opportunities were fulfilled. As shown in Figs. 1 and 2, originator products entered markets before generic entry in most cases; whereas in a few exceptional cases, such as India and Bangladesh, it was generics that were launched first, since these two countries have a strong domestic generic industry, and for a long period in our observation period, product patents were not available for pharmaceuticals.

Table 1
Distribution of 578 molecules by innovativeness and by disease category.

Disease category	Count	By innovativeness		Share in sample (%)	WHO GHE code
		Innovative	Non-innovative		
A. Infectious diseases	**95**	**59**	**36**	**16.4**	**-**
Other infectious diseases	38	15	23	6.6	40, 370
HIV/AIDS	25	22	3	4.3	100
Respiratory infections	11	6	5	1.9	380
Hepatitis	8	5	3	1.4	185
Neglected tropical diseases	5	5	0	0.9	210, 330 (excl. 220)
Diarrheal diseases	4	2	2	0.7	110
Tuberculosis (TB)	2	2	0	0.3	30
Malaria	2	2	0	0.3	220
B. Non-communicable diseases (NCD)	**467**	**247**	**220**	**80.8**	**-**
Cancers (neoplasms)	111	89	22	19.2	610, 790
Cardiovascular diseases	84	33	51	14.5	1100
Neurological conditions	39	19	20	6.7	940
Sense organ diseases	37	19	18	6.4	1020
Mental and behavioural disorder	36	12	24	6.2	820
Musculoskeletal diseases	25	12	13	4.3	1340
Respiratory diseases	23	6	17	4.0	1170
Endocrine, blood, immune disorders	22	14	8	3.8	810
Skin diseases	20	10	10	3.5	1330
Diabetes	19	8	11	3.3	800
Genitourinary diseases	19	3	16	3.3	1260
Digestive diseases	18	8	10	3.1	1210
Congenital anomalies	12	12	0	2.1	1400
Nutritional deficiencies	2	2	0	0.3	540
C. Others					
Anaesthetics, contraceptive means, or antidotes	**16**	**1**	**15**	**2.8**	–
Sum	**578**	**307**	**271**	**100**	**-**

2.1.2. Price data

We use the IQVIA estimated ex-manufacturer prices per standard unit in US dollars from 2007 to 2017. The standard unit is defined as the smallest dose of each presentation of pharmaceutical products, e.g., 5 ml liquid, 1 tablet or 1 vial. For products having more than one strength per pill or per vial, we use the smallest one as the standard unit.

We distinguish between originator products and generics, because originators and generic firms may have different pricing strategies due to their different costs of manufacture, regulatory approvals, sale, and distribution. Among the 578 molecules, 573 had originator products and 504 had one or more generic versions sold somewhere in the world during our study period.

2.1.3. Anatomical Therapeutic Chemical (ATC) classes and competition indicators

Consulting the IQVIA database, we link each molecule to a unique Anatomical Therapeutic Chemical (ATC) code. In the ATC classification

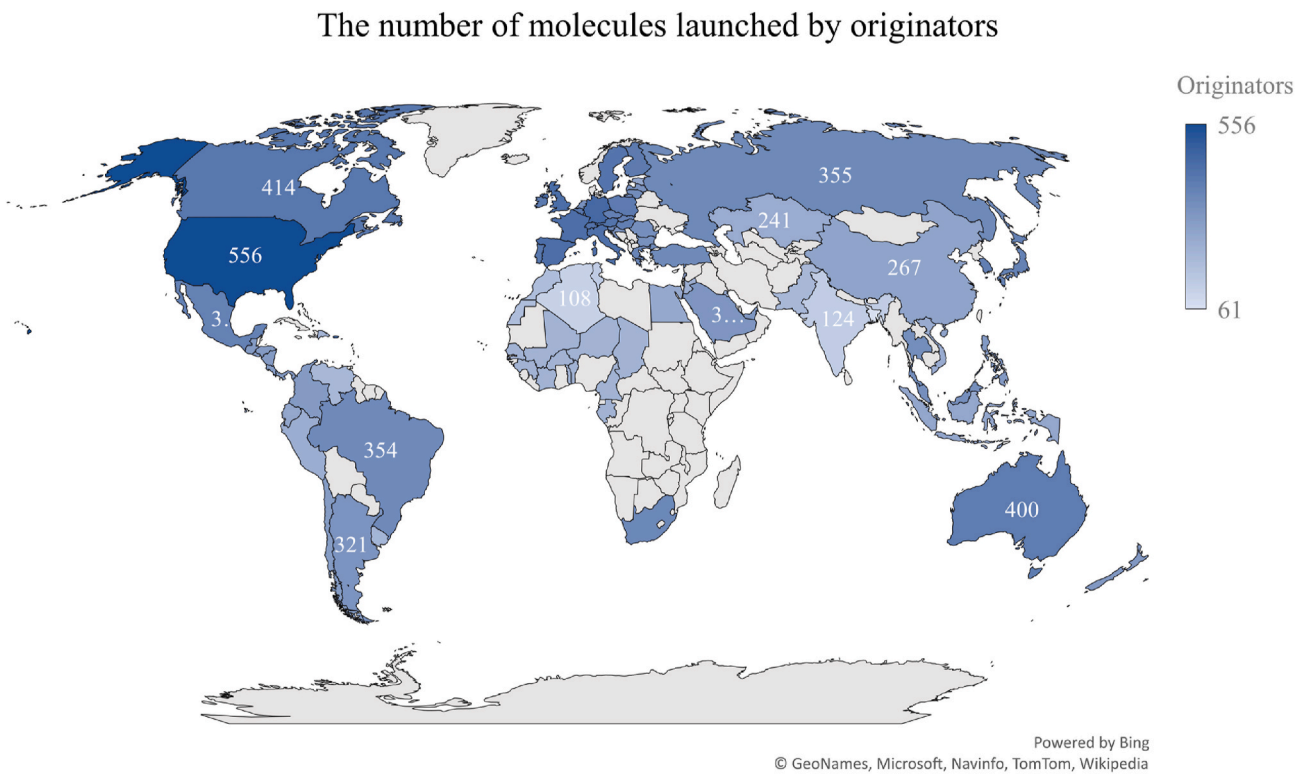

Fig. 1. The number of molecules first launched by originators. Notes: This graph is based on 22,772 launches made by originators or licensees of our sampled 556 molecules in 70 markets from 1980 to 2017.

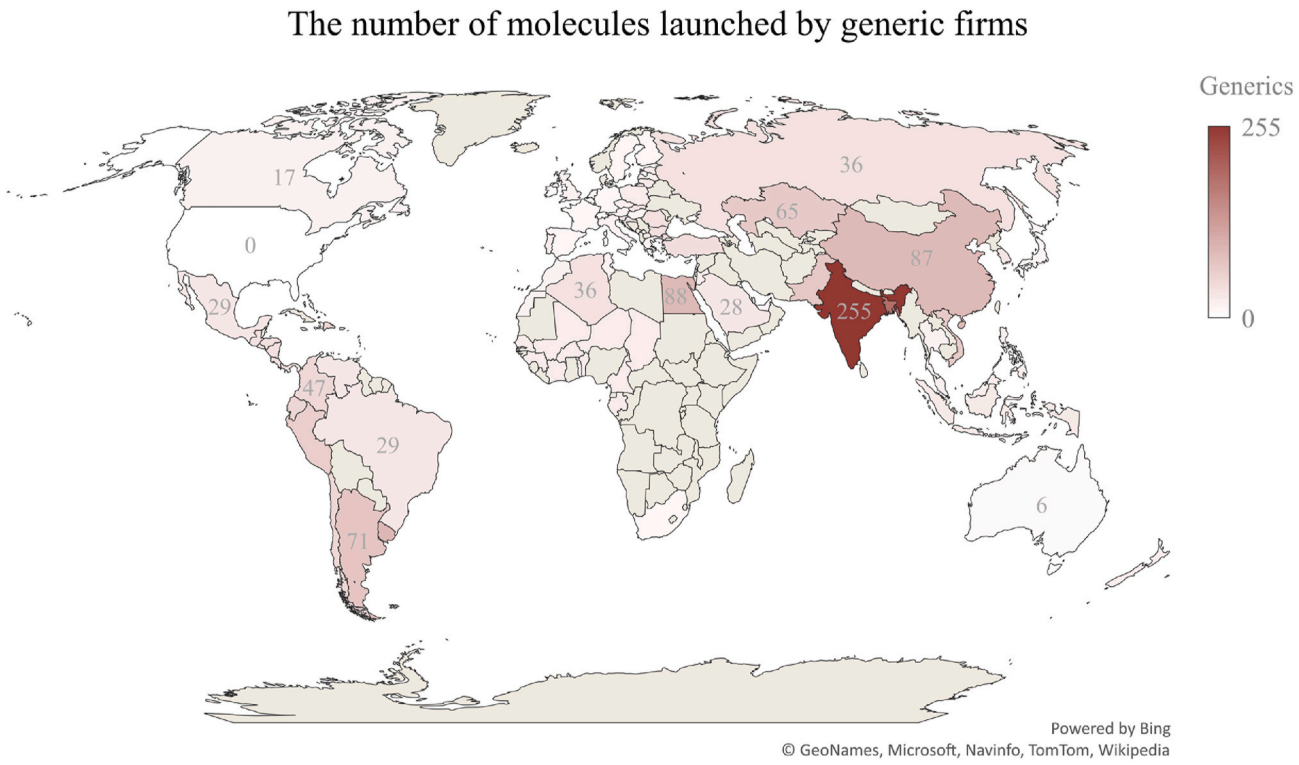

Fig. 2. The number of molecules first launched by generic firms. Notes: This graph is based on 2,321 launches made by generic firms of our sampled 556 molecules in 70 markets from 1980 to 2017. Map disclaimer: Maps are for graphical purposes only. The designations employed and the presentation of the materials on the maps do not imply the expression of any opinion concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries.

system, active substances are classified in groups at five different levels, where ATC1 is the most aggregated level, and ATC5 is the active substance or molecule itself.

We count the number of brands in the molecule market and in the respective ATC4 group for each molecule in each country from 2007 to 2017, which serve as alternative measures of competition intensity for the molecule in question. For each molecule, the brands can be original brands, licensed brands, or other brands (i.e. branded generic medicines) according to the IQVIA database. Within a molecule, branded products are expected to be close substitutes. Also, since ATC4 has the next lowest level of aggregation, molecules in the same ATC4 group are expected to treat the same or similar disease conditions and so be able to substitute each other to some extent.

2.2. Patentability data

In the launch analysis, we track the changes in pharmaceutical patent regime in each country from publicly available sources and construct a binary indicator of patentability based on our own research (results available in online Appendix). We take the date when the product patent application can be filed on pharmaceutical inventions in the country as the date from which product patents are available for pharmaceuticals. We only consider product patents for pharmaceuticals, because process patents cannot guarantee market exclusivity. Also, the patent term is not considered, given that WTO members have to provide 20-year protection from the date of patent filing when they extended patent coverage to pharmaceutical products.

We do not have the actual data on patents filed or granted in each of our 70 countries and hence we use a reasonable approximation. We match our launch data and patent information in the following way: a molecule is patentable in the country if pharmaceutical product patents have been available there for at least 10 years prior to the global launch of the molecule. We use the 10-year lag here, because it takes 10 years on average from the date of primary patent filing to commercialisation of a new medicine (European Commission, 2009; Grabowski and Kyle, 2007; Mestre-Ferrandiz et al., 2012; Office of Technology Assessment, 1993; Sternitzke, 2010; Wagner and Wakeman, 2016). Notably, due to variability of such lag around 10 years across new molecules (Sampat and Shadlen, 2015), this patentability variable is an approximation in the absence of country-level data on the molecule basis. Also, we recognise that in some countries, such as Brazil, it could take much longer than ten years for patents to be granted. For example, supposing that pharmaceutical product patents have been available in Country A since 1995 and in Country B since 2000, and the global launch of molecule x took place in 2008: we presume that patents of x were filed in 1998 which was 10 years prior to its global launch, and thus, x is patentable in Country A but not in Country B, given that patent application for pharmaceutical products could not be filed in Country B until 2000.

2.3. Socio-economic variables and disease burden

We control for socio-economic variables in this study, including population, GDP per capita (measured in current USD), Gini coefficient, life expectancy, and health expenditure as a percentage of GDP. We do not have data on availability, quantity and quality of medical insurance in the 70 countries and use GDP per capita as a proxy for capacity to pay for medicines. The data for these variables are obtained from the *World Development Indicators* (World Bank). Since launches in our sample took place from 1980 to 2017, we take income classification in 2000 as roughly being in the middle of this period. We capture the disease burden in each molecule market using the Disability-Adjusted Life Years (DALY) (World Health Organisation, 2018). As shown in Table 1, we classify disease conditions into 22 categories and assign each molecule to one of them.

For the missing values of these six variables mentioned above, we use backward filling to fill missing observations (Cockburn et al., 2016). Table 2 presents summary statistics of socio-economic variables and DALY without backward filling.

Table 2
Summary statistics.

Variables	(1)	(2)	(3)	(4)	(5)
	N	mean	sd.	min	max
World Development Indicators 1980–2017					
Population (millions)	2,660	70.94	190.5	0.36	1,379
GDP per capita (1,000 USD)	2,505	14.56	17.23	0.09	119.2
Gini coefficient (%)	1,540	38.37	9.07	21	64.80
Life expectancy	2,660	72.78	6.18	46.54	84.28
Health expenses/GDP (%)	1,224	6.71	2.54	1.93	16.84
Disability Adjusted Life Year (1,000 years [DALY])					
DALY 2000	1,496	996.8	4,024	0.00	64,161
DALY 2010	1,496	1,022	4,144	0.00	81,459
DALY 2015	1,496	1,048	4,413	0.00	95,098
Originator drug price equation (2007–2017)					
Price (USD per standard unit)	186,647	139.2	580.6	0.00	12,409
Brands in molecule	186,647	4.26	8.61	1	230
Brands in ATC4	186,647	30.34	58.15	1	2,719
Generic drug price equation (2007–2017)					
Price (USD per standard unit)	89,657	16.24	86.46	0.00	2,007
Brands in molecule	89,657	8.14	11.87	1	230
Brands in ATC4	89,657	49.97	85.49	1	2,719

2.4. Empirical methods

2.4.1. Launch data analysis

We use the Cox proportional hazard model to study the impact of introducing product patents for pharmaceuticals on launch likelihood of new medicines. The advantage of Cox model is that estimation of coefficients is possible without making any assumption on the shape of the hazard function, thus ruling out the risk of misspecification (Cleves et al., 2010). Since only the first launched product matters for availability, we define that launch as the first entry of a new medicine in the country without distinguishing between originator products and generics. In Eq. (1), the hazard function $h(t|\mathbf{X})$ represents the launch likelihood for molecule j in country i, year y, after time t which is the time elapsed since the global launch of molecule j, conditional on all right-hand-side variables **X**. The baseline hazard $h_{i0}(t)$ is the value of hazard function for country i when all independent variables are equal to zero (by stratification). For right-hand-side variables, the patentability dummy is equal to one if product patent application for pharmaceuticals could be filed in country i 10 years before the global launch of molecule j. We also include an innovativeness dummy, the interaction term of innovativeness and patentability, and socio-economic variables as well as disease burden (**x**) in Eq. (1). We do not include the number of launched molecules (or brands) in drug class in the launch equation, as this data is only available from 2007 to 2017, which is too short to be aligned with our launch dataset.

$$h\left(t|X_{ijy}\right) = h_{i0}(t)\cdot\exp\left(\alpha_0 + PAT_{ij}\alpha_1 + INNOV_j\alpha_2 + PAT_{ij}\times INNOV_j\alpha_3 + x_{ijy}\alpha_x + \eta_{ATC1} + \mu_y + u_{ijy}\right) \quad (1)$$

We control for unobservables in the following way: first, we introduce ATC1 (i.e.14 therapeutic groups) fixed effects to capture heterogeneity in launch hazard across medicines, because the approval time of medicines may differ by its therapeutic group and condition that the medicine treats (Cockburn et al., 2016). Second, we add year fixed effects to control for time trend and changes in international regulatory environment (such as the establishment of European Medicines Agency in 1995 as analysed in Varol et al., 2012). Third, to address time-invariant institutional heterogeneity in each country that influences both patent regimes and the launch speed, we apply country fixed effects by stratification. Thus, the effects of time-invariant variables, including geography, legal origins, colonisation history, and ethnolinguistic factors are controlled by stratification, leaving our estimation unbiased. The stratification also addresses other factors that affect local pharmaceutical markets to some extent, such as lack of enforcement, levels of corruption, and the availability of substandard and substitute products, which are important in how people in LMICs access drugs. All analyses were performed in STATA 15.

2.4.2. Pricing and affordability analysis

Turning now to the second aspect of access to medicine, namely affordability, we estimate the extent of differential pricing across countries of different income levels. Theoretically, differential pricing can improve drug affordability in LMICs despite patent protection. We use specification in Eq. (2) to study differential pricing, where i indexes country; j, molecule; and y, year. By introducing molecule × year fixed effects, we rule out price variation across molecule-year combinations, and thus we only study price variation within the same molecule in each given year across countries. We use price per standard unit in our regressions, but given the molecule-by-year fixed effects, the measurement unit (either per standard unit or per kilogram) of drug prices does not affect regression results. We do not use country fixed effects, as it would wipe out variation between countries.

In Eq. (2), δ represents the degree to which drug prices are adjusted to local income levels. Competition indicators **z** are the total number of brands in a molecule market and that in ATC4 group. Instead of directly considering patent protection, we control for brand competition in each molecule market, because it is not patent protection per se but the degree of competition that matters for pricing strategies of drugs. $\tilde{\mathbf{x}}$ includes socio-economic variables and disease burden except per capita income. The retail dummy is equal to one if sales data was exclusively collected from the retail sector in the country.

$$\ln(p_{ijy}) = \ln\left(GDPPC_{iy}\right)\delta + \mathbf{z_{ijy}}\boldsymbol{\gamma} + \tilde{\mathbf{x}}_{\mathbf{ijy}}\boldsymbol{\varphi} + Retail_i\pi + \lambda_{jy} + e_{ijy} \quad (2)$$

We conduct regressions of originator drug prices and generic drug prices separately, because originators and generic firms may adopt different pricing strategies even in the same market environment given their differences in launch cost, distribution cost, regulatory screening, and other factors. Competition between originator and generic products is considered in both regressions as we control for the total number of brands in each molecule market, including original brands, licensed brands, and brands of generic medicines. All analyses were performed in STATA 15.

3. Results

3.1. Results of launch analysis

While including a broad range of socioeconomic controls and DALY in all regressions, we only present results of major coefficients. Table 3 presents our baseline regression of the launch analysis and regressions by countries' income level. In column (1), pooling over all molecules and countries, we find that the patentability variable is insignificant, but the interaction term of it and innovativeness is positively significant, meaning that introducing product patents for pharmaceuticals only facilitates the diffusion of innovative medicines but has no effect on non-innovative ones. This could be explained that the originators particularly value patent protection when making the decision to launch their innovative medicines, as innovative medicines have no close competitors once generic copies are blocked. After introducing product patents, these countries are 14 percent more likely than before to have innovative medicines. Also, innovative medicines are launched sooner than non-innovative ones by 10 percent, irrespective of the local patent regime.

Table 3
Launch regressions using Cox model.

Variables	(1)	(2)	(3)	(4)
			By income level	
	Baseline	High	Middle	Low
Patentability (PAT)	0.024	0.196***	0.095**	0.122
(lag 10)	(0.034)	(0.059)	(0.048)	(0.116)
Δ hazard ratio	*0.02*	*0.22*	*0.10*	*0.13*
Innovative	0.097***	0.314***	0.083***	−0.099
	(0.020)	(0.046)	(0.025)	(0.065)
Innovative × PAT	0.128***	−0.038	0.109**	−0.216*
	(0.029)	(0.053)	(0.043)	(0.112)
Δ hazard ratio	*0.14*	*−0.04*	*0.12*	*−0.19*
ln(GDP per capita)	0.265***	0.047	0.426***	0.420**
	(0.034)	(0.110)	(0.045)	(0.189)
Observations	356,410	89,820	224,692	41,898
Socioeconomic controls and DALY	Y	Y	Y	Y
Country FE	Y	Y	Y	Y
ATC1 FE	Y	Y	Y	Y
Year FE	Y	Y	Y	Y

Notes: Standard errors clustered on molecule-country in parentheses. Socioeconomic controls and DALY included in all columns. Original coefficients reported. The change in hazard ratio is calculated as *Δ hazard ratio* = exp (coefficient)−1. We use the World Bank income classification in 2000. *p < 0.1. **p < 0.05. ***p < 0.01.

The effects of patentability and innovativeness, however, vary with local income levels. In high-income countries, patentability and therapeutic innovativeness are associated with faster launches: patentability increases launch likelihood of new medicines by 22 percent; innovativeness, by 37 percent. Regression for middle-income countries in column (3) also finds positive results: both patentability and innovativeness facilitate drug diffusion, along with an additional effect on innovative medicines. Column (4) presents results for low-income countries, showing neither patentability nor innovativeness enhances the availability of new medicines. There are two explanations for this. After patent protection was introduced, first, these countries where patients cannot afford most new medicines are still not attractive enough to originator firms. Second, despite possible increases in drug launch by originators, the overall drug availability may not be improved given the offset of the ban on generic drugs. Across columns in Table 3, income growth is found to benefit drug availability in LMICs, as it improves drug affordability and makes drug launches more profitable. Using income level as a proxy for capacity to pay, we find that only in middle-income countries do both increasing capacity to pay and patentability facilitate launch; whereas no effect is found for income growth in high-income countries or for patentability in low-income countries. Thus, we attribute fewer new medicines launched in low-income countries to low capacity to pay rather than lack of patent protection. However, as income increases, patent protection plays an increasingly important role in drug availability.

We analyse the same question by disease category in Table 4. For medicines to treat non-communicable diseases (NCDs), introducing product patents facilitates launches of these drugs by 7 percent, and the impact is greater for innovative ones (by 17 percent). As patients with many NCDs rely on medication for the rest of their lives, patent

Table 4
Launch regressions by disease category of medicines (Cox model).

Variables	(1)	(2)	(3)	(4)
	Non-communicable	Infectious	HIV/AIDS, malaria, TB	Cancer
Patentability (PAT)	0.072**	−0.258***	1.271***	0.139
(lag 10)	(0.036)	(0.097)	(0.322)	(0.092)
Δ hazard ratio	*0.07*	*−0.23*	*2.56*	*0.15*
Innovative	0.009	0.474***	1.592***	−0.044
	(0.022)	(0.059)	(0.290)	(0.061)
Innovative × PAT	0.092***	0.365***	−1.060***	−0.114
	(0.031)	(0.081)	(0.313)	(0.082)
Δ hazard ratio	*0.10*	*0.44*	*−0.65*	*−0.11*
ln(GDP per capita)	0.265***	0.205**	0.680***	0.273***
Observations	283,944	72,466	19,893	66,013
Socioeconomic controls and DALY	Y	Y	Y	Y
Country FE	Y	Y	Y	Y
ATC1 FE	Y	Y	Y	Y
Year FE	Y	Y	Y	Y

Notes: Standard errors clustered on molecule-country in parentheses. Socioeconomic controls and DALY included in all columns. Original coefficients reported. The change in hazard ratio is calculated as $\Delta\ hazard\ ratio = \exp(\text{coefficient}) - 1$. *p < 0.1. **p < 0.05. ***p < 0.01.

protection is important for originators to secure long-term profits accruing to these NCD medicines. In particular, originators are more willing to launch their innovative products delivering therapeutical advances and potentially being more profitable in markets with patent protection.

In column (2), we present results for medicines to treat infectious diseases (including HIV/AIDS, malaria, and TB). Compared to their non-innovative counterpart, treatments providing breakthrough or advanced therapies are more likely to be launched. Also, though the marginal effect of patentability is insignificant for innovative medicines, introducing product patents alone is found to delay launches of non-innovative medicines. This finding could be explained by the fact that the demand for medicines to treat infectious diseases is concentrated in lower-income countries, which used to rely primarily on generics to meet their healthcare needs. After introducing product patents, generic entry is hindered but originators are not interested in these lower-income markets, thus worsening the availability of new, but non-innovative medicines. Meanwhile, originators may be less motivated to launch non-innovative medicines, because these countries may already have similar and cheaper medicines available on the market. Thus, we find the availability of new, non-innovative medicines to treat infectious diseases is significantly lower after introducing product patent protection.

In column (3), we present the results for HIV/AIDS, malaria, and TB medicines, where the global diffusion of innovative treatment is not affected by patentability, because irrespective of local patent regimes, these innovative medicines are procured and launched in high-burden countries with donor money.

For cancer medicines in column (4), neither patentability nor innovativeness matters for the launch decisions of such medicines, probably because cancer medicines generally involve complex technologies and thus difficult to copy and hence originators do not have to worry about generic drugs' entry, irrespective of local patent regimes.

3.2. Results of differential pricing analysis

Table 5 presents regressions of originator medicine prices. We include socioeconomic controls and DALY in all regressions based on Eq. (2), and only major coefficients are presented. We start from findings on differential pricing. In column (1), the income elasticity of price is 0.11 for all originator products. Prices of innovative medicines are slightly less adjusted to local income compared to non-innovative ones (0.102 vs. 0.119), indicating a two percent price premium charged by originators for therapeutic innovativeness of medicines. Turning to disease category, prices of originator medicines to treat infectious diseases, especially HIV/AIDS medicines, are better adjusted than NCD medicines to income differentials (0.126 vs. 0.106); the prices adjustment of cancer medicines is smaller than the average of NCD medicines (0.066 vs. 0.106). Results represented by standardised coefficients are mostly consistent with our findings on income above. Apart from income levels, we find that income inequality drives up drug prices as theorised by Flynn et al. (2009), with an exception of HIV/AIDS, malaria, and TB medicines.

Besides, brand competition is found to drive down originator medicine prices. On average, increasing the number of brand competitors in molecule by one percent leads to a price reduction by 0.08 percent, which is twice as effective as brand competition in ATC4 group (0.082 vs. 0.041).

Table 6 presents regressions of generic drug prices. Compared to originator products, prices of generic medicines are better adjusted to local income levels whether measured by income elasticity (0.109 vs. 0.256) or standardised coefficient (0.160 vs. 0.311). As for the effect of innovativeness, generic firms are more flexible about pricing strategies of innovative medicines, which are adjusted to local income levels by 31 percent compared to non-innovative medicines adjusted by 20 percent. Similar to originator products, the income elasticity of generic drug

Table 5
Differential pricing analysis of originator medicines.

Variables	(1)	(2)	(3)	(4)	(5)	(6)	(7)
	All molecules	By Innovativeness		NCD vs. Infectious		HIV/AIDS, malaria, and TB	Cancer
		Innovative	Non-innovative	NCD	Infectious		
ln(GDP PC)	0.109***	0.102***	0.119***	0.106***	0.126***	0.140***	0.066***
	(0.003)	(0.005)	(0.005)	(0.003)	(0.012)	(0.035)	(0.007)
Standardised coef. of ln(GDP PC)	*0.160*	*0.150*	*0.174*	*0.158*	*0.171*	*0.167*	*0.099*
ln(Gini coefficient)	0.592***	0.377***	0.837***	0.658***	0.247***	−0.189***	0.039
	(0.017)	(0.023)	(0.026)	(0.019)	(0.039)	(0.067)	(0.026)
ln(# brands in molecule)	−0.082***	−0.071***	−0.080***	−0.078***	−0.110***	−0.095***	−0.088***
	(0.005)	(0.007)	(0.007)	(0.006)	(0.013)	(0.028)	(0.009)
ln(# brands in ATC4)	−0.041***	−0.026***	−0.077***	−0.046***	−0.004	0.002	−0.015
	(0.007)	(0.008)	(0.011)	(0.007)	(0.017)	(0.020)	(0.011)
Observations	186,647	98,900	87,747	159,935	26,712	7888	33,020
Adj. within R-squared	0.131	0.117	0.167	0.124	0.197	0.415	0.070
Socioeconomic controls and DALY	Y	Y	Y	Y	Y	Y	Y
Molecule × year FE	Y	Y	Y	Y	Y	Y	Y

Notes: Standard errors clustered on molecule-year in parentheses. Socioeconomic controls and DALY included in all columns. Standardised coefficients are calculated as $\text{coef.}(x) \times \text{sd.}(x)/\text{sd.}(y)$, where standard deviations are based on the within variation in the corresponding regression subsamples. *p < 0.1. **p < 0.05. ***p < 0.01.

Table 6
Differential pricing analysis of generic medicines.

Variables	(1)	(2)	(3)	(4)	(5)	(6)	(7)
	All molecules	By Innovativeness		NCD vs. Infectious		HIV/AIDS, malaria, and TB	Cancer
		Innovative	Non-innovative	NCD	Infectious		
ln(GDP PC)	0.256***	0.311***	0.201***	0.244***	0.343***	0.690***	0.311***
	(0.006)	(0.009)	(0.007)	(0.006)	(0.018)	(0.048)	(0.017)
Standardised coef. of ln(GDP PC)	*0.311*	*0.363*	*0.253*	*0.301*	*0.377*	*0.576*	*0.351*
ln(Gini coefficient)	1.065***	0.633***	1.488***	1.198***	0.163**	−1.129***	0.219***
	(0.025)	(0.036)	(0.029)	(0.026)	(0.067)	(0.196)	(0.065)
ln(# brands in molecule)	−0.146***	−0.135***	−0.135***	−0.143***	−0.152***	−0.157***	−0.062*
	(0.009)	(0.013)	(0.011)	(0.010)	(0.019)	(0.044)	(0.034)
ln(# brands in ATC4)	0.005	0.033**	−0.051***	−0.014	0.149***	0.301***	0.048
	(0.009)	(0.015)	(0.011)	(0.010)	(0.023)	(0.041)	(0.034)
Observations	89,657	42,480	47,177	78,760	10,897	1511	12,382
Adj. within R-squared	0.158	0.158	0.183	0.148	0.261	0.557	0.074
Socioeconomic controls and DALY	Y	Y	Y	Y	Y	Y	Y
Molecule × year FE	Y	Y	Y	Y	Y	Y	Y

Notes: Standard errors clustered on molecule-year in parentheses. Socioeconomic controls and DALY included in all columns. Standardised coefficients are calculated as $\text{coef.}(x) \times \text{sd.}(x)/\text{sd.}(y)$, where standard deviations are based on the within variation in the corresponding regression subsamples. *p < 0.1. **p < 0.05. ***p < 0.01.

prices is much stronger for infectious disease medicines than NCD medicines (0.343 vs. 0.244). In particular, adjusted by two thirds to income differentials across countries, prices of generic medicines to treat HIV/AIDS, malaria, and TB are much better adjusted than other generics. For the impact of income inequality, Gini coefficient is positively associated with generic drug prices. Compared to originators, generic firms take better advantage of income inequality in their pricing strategies (1.065 vs. 0.592). Again, as an exception, prices of HIV/AIDS, malaria, and TB medicines are negatively correlated with income inequality, which may also be explained by special donor financing models for medicines to treat global epidemics.

For competition indicators, again within-molecule brand competition can effectively reduce generic drug prices. Increasing brands in a molecule market by one percent contributes to decline in generic drug prices by 0.15 percent, which is almost twice as large as the effect on originator products (0.146 vs. 0.082), presumably because despite generic competition, originator products tend to maintain a high price as a signal of quality (Bate et al., 2011). We also find that controlling for within-molecule competition, having a larger number of potential substitutes in the ATC4 group does not drive down prices of generic medicines in general.

4. Discussion

In this section, we discuss four limitations in this study. First, we do not directly control for firm-level factors, price controls, reimbursement schemes (e.g. Managed Entry Agreements), and patent enforcement due to data unavailability, despite their influence on the launch speed and drug pricing (Cockburn et al., 2016; Danzon et al., 2005; Kyle, 2007). To address this omitted variable issue, we have used the most stringent fixed effects as robustness check, and our results still hold: in our differential pricing study, molecule × year fixed effects can largely eliminate the effects of firm-level factors on drug prices; for the launch study, we perform regressions using country × ATC1 fixed effects that can capture price controls, and the results are aligned with our baseline findings (robustness checks shown in Appendix). Also, we control for patent enforcement in the price analysis using competition indicators. However, the remaining unobservables may still be correlated with regressors, thus biasing our results, although we do not believe this issue will change our results in any dramatic way.

Second, attributing changes in patent regimes to TRIPS, we assume that introducing product patents for pharmaceuticals is exogenous and we do not instrument patentability in our launch analysis. Owing to country fixed effects, effects of geography, legal origins, colonisation, and ethnolinguistic diversity, which have greatly influenced the formation of the legal systems, have been controlled leaving our estimation results unbiased, and all country-invariant factors are ineligible for instrumental variables (IVs). Although fixed effects can control for time- and country-invariant heterogeneity, endogeneity would rise if other factors, such as lobbying of the pharmaceutical industry, were correlated with changes in patent regimes as well as the launch decisions. For example, as the results of negotiations of international trade agreements, including TRIPS, can be affected by industrial lobby groups (Grossman and Helpman, 1994; Sell, 2003), the impact of patentability on the launch likelihood may be overestimated if introducing pharmaceutical patents in a country resulted from lobbying of the originators on a country-by-country basis, based on profitability. Future research should certainly take these factors into account to improve our understanding of these variables in answering the research questions posed in this study.

Third, we would like to recognise two important policy issues which call for further studies. To begin with, we acknowledge that parallel imports (where the same original brand could be imported and sold at a lower price) policy could play a role in the dynamics of pricing decisions but, not having data on each country's policy and actual imports molecule-wise, we are unable to differentiate according to the provenance of the original brand to study this aspect. Also, we recognise that competition analysis of this kind is important because competition policy is often not as well understood in immature regulatory markets, and much more work needs to be done to support government in managing the regulatory environment. In the differential pricing analysis, we address product competition by controlling for the number of brand competitors within molecule or ATC4 class instead of competition per se, and the effect of having more brand competitors on drug prices would be under-estimated if brand competition is inadequate due to policy or behavioural reasons, such as kick back of certain brands for pharmacists. In other words, policies promoting fair competition may further drive down drug prices after generic entry. Future studies on pricing strategies should incorporate these policy and behavioural factors that determines actual competition intensity into analysis.

Finally, we recognise that the interplay between patent protection, drug launch, and drug prices is a critical issue, but while controlling for market competition, this study does not explicitly address how patent protection affects drug prices within a country due to data unavailability. To estimate the impact of patent protection on drug prices, we will need information not only on patentability, but also on grant and renewal for each molecule across 70 countries (this cannot be directly inferred by brand competition data), which is unavailable. Previous literature has found that countries without product patents such as India may be trading off slower launch for lower prices (Berndt and Cockburn,

2014), and further research should definitely follow to shed light on this important topic.

5. Concluding remarks

In the launch analysis, we find that pooling over all countries, introducing product patents for pharmaceuticals facilitates launches of new medicines to some extent, and this effect to facilitate launches is stronger for innovative medicines. Also, innovative medicines are launched sooner than non-innovative ones in high- and middle-income countries irrespective of local patent regimes. However, neither patentability nor innovativeness is found to speed drug launches in low-income countries, suggesting that in terms of drug availability, these countries barely profit from introducing patent protection until their income levels reach a certain level at which these countries become profitable for innovators to launch new medicines. Notably, the availability of innovative HIV/AIDS, malaria, and TB medicines is not subject to variations in patent regimes, because special policies and funding by donors (e.g. the Global Fund) enable these innovative treatments to be distributed to various countries based on local healthcare needs.

With regard to differential pricing, we find that neither the originator nor the generic firms appear to be engaging in this type of pricing strategies as, on average, originators adjust drug prices to local income levels by only 11 percent and generic firms by 26 percent. Prices of infectious disease medicines are better adjusted to local income levels than NCD medicines. In particular, prices of generic HIV/AIDS, malaria, and TB medicines take account of income differentials by 69 percent, suggesting that patients with these diseases in lower-income countries benefit greatly from generic entry. Apart from income levels, income inequality is also positively associated with drug prices, implying that patients need to pay more for medicines in countries where income are unequally distributed, with an exception of HIV/AIDS medicines. In addition, we find that competition within the molecule can effectively drive down prices of both originator and generic medicines. We conclude that despite efforts made by pharmaceutical firms to differentiate drug prices, without competition in molecule markets or special price regulation policies, differential pricing alone is unlikely to achieve drug affordability in LMICs.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.socscimed.2021.114479.

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